Correlation of $^{68}$Gallium ventilation-perfusion PET/CT with pulmonary function test indices for assessing lung function

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Running foot line: V/Q PET/CT for assessing lung function
ABSTRACT

Pulmonary function tests (PFT) 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: 30 patients underwent V/Q PET/CT and PFT. Respiratory-gated images were acquired following inhalation of \(^{68}\)Gallium-carbon nanoparticles and administration of \(^{68}\)Gallium-macroaggregated albumin. Functional volumes were calculated by dividing the volume of normal ventilated and perfused (%NVQ), unmatched and matched defects from the total lung volume. These functional volumes were correlated with forced expiratory volume in 1 second (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 (COPD) (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 cut-off value of 90% correctly categorized 28/30 patients with or without significant pulmonary function impairment.

Conclusion: Our study demonstrates strong correlations between V/Q PET/CT functional volumes and PFT parameters. Since V/Q PET/CT is able to assess regional lung function, these data support the feasibility of its use in radiation therapy, 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
INTRODUCTION

Pulmonary function tests (PFTs) are simple, non-invasive and well-established physiological 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). Whilst 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 physiological 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 in predicting clinical outcomes after lung volume reduction surgery in patients with emphysema (8).

The principle underlying Ventilation/Perfusion (V/Q) scintigraphy is very attractive for lung function assessment as it simultaneously assesses and compares the regional distribution of the two major determinants of gas exchange in the lungs. Ventilation is imaged following inhalation of inert gases or radiolabelled aerosols, such as $^{99m}$Tc-labelled aerosol (Technegas, Cyclopharm, Sydney, Australia), that reach terminal bronchioles in proportion to regional distribution of ventilation (9). Perfusion is imaged following intravenous administration of $^{99m}$Tc-labelled-macroaggregated albumin (MAA) 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 positron emission tomography (PET) technology for V/Q imaging (12). 

$^{99m}$Technetium can be substituted by $^{68}$Gallium, 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-MAA. As with others areas of nuclear medicine, PET offers a unique opportunity to dramatically improve the diagnostic performances of V/Q imaging due to its higher sensitivity, spatial resolution, speed of acquisition, and quantitative capability in comparison to conventional V/Q scan (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.

**MATERIAL AND METHODS**

**Patients**

Thirty consecutive patients (19 males, 11 females; mean age 65 years, range 46-89 years) were prospectively recruited. All had locally advanced or inoperable non-small-cell lung cancer and were planned to have 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 pre-treatment 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.
Pulmonary function tests

Spirometry was quality controlled according to the European Respiratory Society and American Thoracic Society guidelines (19). Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and diffusing capacity for carbon monoxide, corrected for the patient’s haemoglobin (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 <55% predicted (21).

V/Q PET/CT protocol

All patients underwent a respiratory-gated V/Q PET/CT scan acquired on a GE Discovery 690 PET/CT scanner (GE Medical Systems Milwaukee, WI, USA) using a procedure that we have previously described (18). Ventilation images were acquired following inhalation of Galligas prepared using a Technegas generator (Cyclopharm, Sydney, Australia). Perfusion images were acquired following intravenous administration of $^{68}$Ga-MAA.

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, Cleveland, OH, USA).

1. Whole lung volume delineation

The phase of the respiratory cycle where 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 whole lung (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.

2. Ventilation and Perfusion volumes 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 reading V/Q imaging.

3. Combined Ventilation/Perfusion lung volumes calculation

The percentage of lung volume with normal and abnormal function was computed for several parameters including: (a) normal ventilation and perfusion, (b) normal perfusion but abnormal ventilation (reverse mismatched), (c) normal ventilation but abnormal perfusion (mismatched), (d) abnormal ventilation and perfusion (matched). Accordingly, the sum of (a), (b), (c) and (d) 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 carried out using GraphPad Prism 5 (La Jolla, CA, USA). The Spearman rank correlation test was used to calculate correlations between V/Q PET/CT functional volumes and PFTs indices. The two-tailed Mann-Whitney U and Kruskall-Wallis tests were used for comparison of differences between groups. The null hypothesis was rejected when p<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 29/30 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 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.

**FEV1/FVC**

The percentage of lung volume with normal perfusion and ventilation (%NVQ) correlated most strongly with FEV1/FVC (r =0.82) (Figure 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) (see FIGURE 4A).

**FEV1**

%NVQ also demonstrated the highest correlation with FEV1 (r =0.64) (Figure 3B). Figure 4B shows 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 ($r=0.55$) (FIGURE 3C). All V/Q PET/CT functional volumes were significantly different in patients with severe impairment of DLCO (DLCO<55% predicted) (p<0.05) (See FIGURE 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**

Considering %NVQ only, a cut-off value of 90% correctly categorized 28 of 30 patients (93%) with or without significant pulmonary function impairment (defined by confirmed chronic obstructive pulmonary disease or severe impairment of DLCO) (see FIGURE 5). Eight patients had more than 90% of lung volume with normal ventilation and perfusion and all were free from significant pulmonary disease. Out of the 22 patients demonstrating less than 90% of lung volume with normal ventilation and perfusion, 20 (91%) had COPD and/or DLCO<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 physiological 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 four physiological patterns: areas with functional ventilation and perfusion, reversed mismatched defect, mismatched defects...
and matched defects, respectively. Results were expressed as percentage of whole lungs. 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 impact of 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 diagnostic performances of the test especially in pulmonary embolism diagnosis (23,24), and also in lung functional assessment (25,26). However, 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 physiological, biological 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).
The majority of patients studied in this cohort had underlying 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 indicates that physiologic impairment due to matched or unmatched defects are associated with the pathologic changes related to COPD and are 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 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.

Whilst PFTs enable 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 four physiological patterns which give information which 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. This includes radiotherapy planning to minimise dose to functional lung in order
decrease the risk of radiation pneumonitis (5,29), pre-surgical evaluation of patients undergoing bronchoscopic or surgical lung volume reduction surgery (8,30), and assessment of pulmonary reserve prior to pulmonary resection surgery (7). Several imaging techniques have been proposed in that purpose (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 physiological process. As an example, FEV1/FVC which represents the volume of air expired in the first second expressed as a percent of FVC was compared to the percentage of the whole lungs volumes with normal perfusion and ventilation. In addition, PFTs are routinely interpreted as a multiparametric exam and isolated values such as FEV1 or DLCO, whilst directly impaired by local therapies, only have limited significance (33,34). Nevertheless, a cut-off 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 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, which may limit its use in clinical practice. Further research would be of value to assess automated or semi-automated contouring methods that would provide reproducible and quick methodology.
Beside these promising findings in relation to regional and global lung function assessment, V/Q PET/CT technology offers many additional advantages. It is a non-invasive 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 minutes with our protocol, and could probably be reduced due to 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 months versus 1-2 weeks for $^{99m}$Tc generator. The $^{68}$Ga generator is increasingly available owing to 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 a novel-imaging tool that allows high-resolution measurement of ventilation and perfusion distribution in the lungs. It allows regional quantification of the relationship between the two 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 lungs volumes and PFTs parameters, suggesting significant potential in 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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FIGURE 1: Lung functional volumes calculation.

Whole lung volume (WL), 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 the relationship between ventilation and perfusion distribution in four physiological conditions: matched defects, reverse mismatched defects, mismatched defects, or normal ventilation and perfusion (NPQ). Functional volumes were expressed as percentage of WL.
FIGURE 2: Example of lung functional map and quantification with V/Q PET/CT
FIGURE 3: Relations between: (A) FEV1/FVC and the percentage of lung volume with normal ventilation and perfusion (%NVQ), (B) FEV1 and %NVQ, (C) DLCO and the percentage of lung volume with unmatched defects (%Unmatch). Inserted lines represent regression line.
FIGURE 4: V/Q PET/CT functional profile in relation with (A) FEV1/FVC, (B) FEV1, and (C) DLCO.

Upper graphs show mean functional volumes according to the pulmonary function test parameter. Lower graphs show minimal, maximal, median, 25% and 75% quartiles for the most discriminant functional volume, i.e. the percentage of whole lung with normal ventilation and perfusion (%NVQ) for FEV1/FVC and FEV1, and the percentage of whole lung with unmatched defects (%unmatch), i.e. 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 the 30 patients. Below is mentioned the presence and grade of COPD, and the presence of severe DLCO impairment. A cut-off value of 90% normal ventilation and perfusion correctly identified significant pulmonary disease in 28 of 30 patients (93%).
TABLES

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**TABLE 1**: Spearman correlation results between V/Q PET/CT functional volumes and PFTs parameters. *indicates p value <0.05
Correlation of $^{68}$Gallium ventilation-perfusion PET/CT with pulmonary function test indices for assessing lung function

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