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PET/CT Lung Ventilation and Perfusion Scanning using Galligas and Gallium-68-MAA

Pierre-Yves Le Roux, MD, PhD,* Rodney J. Hicks, MBBS, FRACP, MD,†,‡ Shankar Siva, MBBS, FRANZCR, PhD,‡,§ and Michael S. Hofman, MBBS, FRACP, FAANMS, FICIS†,‡

Ventilation/Perfusion (V/Q) positron emission tomography computed tomography (PET/CT) is now possible by substituting Technetium-99m (^{99m}Tc) with Gallium-68 (^{68}Ga), using 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. Perfusion imaging can be performed with ^{68}Ga-macroaggregated albumin. Similar physiological processes can therefore be evaluated by either V/Q SPECT/CT or PET/CT. However, V/Q PET/CT is inherently a superior technology for image acquisition, with higher sensitivity, higher spatial and temporal resolution, and superior quantitative capability, allowing more accurate delineation and quantification of regional lung function. Additional advantages include reduced acquisition time, respiratory-gated acquisition, and a lower impact on human resources. V/Q PET imaging offers an opportunity to improve the accuracy and utility of V/Q imaging in various pulmonary conditions. For pulmonary embolism, V/Q PET/CT scan may improve the diagnostic performance of the test owing to a better characterization of the pattern of defects and allow an accurate quantification of the extent of vascular obstruction. Establishing an accurate functional map of the regional ventilation and perfusion in the lungs may be relevant in many other clinical situations, including preoperative assessment of the lung cancer patients, radiotherapy planning, or presurgical evaluation of patients undergoing lung volume reduction surgery.
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Introduction

The principle underlying Ventilation/Perfusion (V/Q) scintigraphy is very attractive for lung function assessment as it offers the unique opportunity to concurrently assess and compare the regional distribution of the two major determinants of gas exchange in the lungs. Macroaggregated albumin (MAA) particles are trapped in the lung capillaries so that local concentration is related to the regional pulmonary blood flow at an arteriolar level. Inert gases or radiolabeled aerosols reach alveolar regions or terminal bronchiolar levels, respectively, proportional to regional ventilation.

The main clinical application of V/Q scintigraphy is pulmonary embolism (PE) diagnosis. V/Q scanning was introduced in the 1960s and became the first noninvasive test validated for PE diagnosis.[2-4] Probabilistic criteria were defined for interpretation of planar images but yield a significant rate of nondiagnostic scans. Since that time, imaging equipment and radiotracers for ventilation have greatly evolved,[5,6] allowing the introduction of SPECT and more recently SPECT/CT imaging, which have improved diagnostic performance[7,8] enabling a binary interpretation,[9,10] and reducing the proportion of nondiagnostic scans. Nevertheless, SPECT V/Q has technical limitations, including relatively low spatial and temporal resolution, limited count statistics, and blurring effect resulting from breathing, which may limit the diagnostic performances of the test in some cases. Inherent limitations of SPECT images also prevent accurate quantification of the

*Nuclear Medicine Department, Brest University Hospital, Brest, France.
†Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne Australia.
‡Sir Peter MacCallum Department of Oncology, the University of Melbourne, Melbourne, Australia.
§Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne Australia.
Address reprint requests to Michael S. Hofman, MBBS, FRACP, FAANMS, FICIS, Centre for Cancer Imaging, Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne 3000, Australia. E-mail: michael.hofman@petermac.org

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extent of vascular obstruction, where a relationship with PE recurrence has been demonstrated.[12,13]

Besides PE, there are many other pulmonary conditions in which an accurate imaging of regional lung function has the potential to change patients' management and improve outcomes. This includes assessment of pulmonary reserve in lung cancer patients before surgery, radiotherapy planning to maximize dose to the tumor while minimizing the dose to the surrounding lungs, or presurgical evaluation of patients undergoing lung volume reduction surgery. Accurate delineation and quantification of regional lung function, however, remains a challenge because of the inherent technical limitations of SPECT imaging.[14] As a consequence, SPECT V/Q has not been widely translated to routine clinical use and is not presented as a reference modality in clinical guidelines.[15,16] With advancements in competing modalities including dual-source CT and MRI it is imperative that nuclear medicine techniques continue to improve if this modality is going to remain clinically relevant.

Nuclear medicine and molecular imaging have undergone a technologic revolution with the development of multimodality hybrid imaging and an increasing array of new PET tracers. Technical advantages of PET compared to SPECT include higher sensitivity for detecting radioactive decay, higher spatial resolution, higher temporal resolution, and superior quantitative capability.[18,19] Several PET tracers that can substitute for existing SPECT radionuclides have been developed and have rendered some SPECT applications obsolete, eg, for imaging somatostatin receptor expression on neuroendocrine tumors.[20] For lung imaging, V/Q PET/CT is now possible by substituting ^{99m}Tc with ^{68}Ga, using the same carrier molecules as conventional V/Q imaging.[21] Ventilation imaging can be performed with ^{68}Ga-labeled carbon nanoparticles using the same synthesis device as Technegas (Cyclopharm Ltd, Australia), yielding "Galligas." Perfusion imaging can be performed with ^{68}Ga-MAA. Similar physiological processes are therefore evaluated using V/Q SPECT/CT or V/Q PET/CT. However, V/Q PET/CT is inherently a superior technology for image acquisition. As a consequence, V/Q PET imaging offers an opportunity to improve the accuracy and utility of V/Q imaging in various clinical indications.

V/Q Imaging With ^{68}Ga

^{68}Ga Radiotracer Production

^{68}Ga is an extremely convenient PET radiotracer for clinical use.[14] It is produced in a long-lived (6-8 months) generator based on germanium-68, allowing the production of ^{68}Ga on demand in a nuclear medicine department. Physical half-life (68 minutes) is sufficient to allow radiolabeling but limits the radiation dose for patients while allowing a relatively short interval between ventilation and perfusion imaging. It is increasingly available in nuclear medicine departments from ^{68}Ge-generators owing to its use in tracers used in assessing neuroendocrine tumors[1] and prostate cancer.[11]

^{68}Ga perfusion PET imaging was first reported in 1976.[22,23] Chesler et al injected albumin microspheres radiolabeled with ^{68}Ga into dogs to obtain three-dimensional reconstructed images of lung perfusion. Various techniques have been used for the radiolabeling of ^{68}Ga to MAA, using commercial MAA kits.[24,25] Several teams proposed to wash commercial MAA kits with deionized water in order to remove the Sn(II) associated with the MAA.[21,26,27] ^{68}Ga was buffered with acetate buffer before being added to the MAA. The suspension mixture was then incubated for 5-15 minutes at 70°C-75°C after the addition of ^{68}Ga. Radiolabeling efficiency of more than 90% was demonstrated.[21,26] More recently, Mueller et al reported an automated synthesis of ^{68}Ga-MAA using MAA commercial kits.[28] This method did not require removing $SnCl_2$ from the kits. The lyophilisate of the MAA labeling kit was suspended with the buffer. After a purification step on a SCX cartridge, the ^{68}Ga eluate was introduced in the MAA suspension. The vial was heated for 10 minutes at 90° and neutralized with sodium phosphate buffer. A labeling efficiency of more than 99% was demonstrated.

^{68}Ga ventilation PET imaging was first described in 2010 by Kotzerke et al[29] ^{68}Ga-labeled equivalent of Technegas, termed "Galligas" can be produced using an unmodified commercially available Technegas generator (Cyclopharm Ltd, Australia). With this device, Galligas is prepared using the same technique as for Technegas production with substitution of ^{68}Ga for ^{99m}Tc. Approximately 50 MBq of ^{68}Ga in the form of gallium chloride is placed in the carbon crucible of the synthesis unit. Of note is that the lead shielding in the Technegas generator is designed for ^{99m}Tc (140 keV), which may lead to the need for additional radiation precautions for staff using the device due to the higher energy of the annihilation photons arising from positron decay of ^{68}Ga.[14]

^{68}Ga V/Q PET/CT Acquisition Protocol

Similar to a SPECT V/Q procedure using aerosols, imaging starts with the ventilation scan followed by the perfusion scan.[30] Patients inhale Galligas using the standard ventilation technique as for Technegas. A Geiger counter can be used to assess the amount of inhaled gas. The patient is imaged supine, with arms up and resting behind the neck. Generally, the ventilation PET acquisition can be performed as a two bed position scan of 3 minutes for each bed.

Without moving the patient, approximately 40-50 MBq of ^{68}Ga-MAA is subsequently injected as a slow intravenous bolus. This dose allows a minimum 1:4 activity ratio between ventilation and perfusion imaging. Lung perfusion PET is performed using the same axial coverage; however the acquisition can be reduced 2 minutes per bed position.

In free-breathing PET there can be significant misregistration between PET and CT due to effects of respiratory motion resulting in inaccurate attenuation correction and consequent artifact, most marked at the lung bases. With free breathing, the position of the diaphragm is periodic and spatially variable and therefore the amount of misregistration is unpredictable. Furthermore, respiratory motion reduces

quality elsewhere due to blurring of the radiopharmaceutical distribution. Modern PET/CT scanners allow acquisition of multiple bed position respiratory-gated (4D) PET and CT scans. We now routinely acquire V/Q PET/CT with 4D CT, 4D ventilation, and 4D perfusion. We utilize the a respiratory tracking system (RPM, Varian Medical Systems, Palo Alto, CA) and reconstruct data into five or ten bins based on a percentage of the respiratory cycle with the first phase representing the end-inspiration position. We utilize automatic phase matching reconstruction software (GE Advantage 4D processing package), which matches each CT and PET bin. Adding 4D acquisition is feasible without additional scan time but does slightly increase the CT dose. For both ventilation and perfusion the best image coregistration is seen with either free-breathing PET/4D average CT or expiratory-phase PET/CT (Fig. 1). Other groups have additionally used audiovisual biofeedback to further standardize patient breathing, which may further improve image quality.[31]

A summary of reasons to transition from SPECT to PET for V/Q imaging is outlined in Table 1 while Table 2 lists factors that may limit implementation.

Table 1 Advantages of Transitioning From SPECT to PET for V/Q Imaging

Superior imaging characteristics: higher sensitivity of the ring detector, better count statistics, higher spatial, and temporal resolution.
Reduction of the acquisition time (approximately 10 min with current PET/CT scans, likely less than 5 min with new digital PET/CT scans).
Commercially available respiratory-gated acquisition reducing artifact particularly at lung bases.[29]
Allows multiple ventilation studies (eg, prebronchodilator and postbronchodilator) on the same day owing to the short half-life of ^{68}Ga.[12]
Remains a simple and noninvasive test, with no contraindication, or side-effects related to the injection of contrast media (allergy, renal dysfunction).
Relatively simple radiopharmacy requirements utilizing existing Technegas equipment and modified MAA synthesis.
^{68}Ge generator increasingly available potentially enabling widespread adoption.
Radiation dose approximately the same than the radiation dose of a conventional V/Q SPECT/CT scan.[31]

Pulmonary Embolism

Suspected PE is currently the main indication of V/Q imaging. The introduction of SPECT/CT has already improved the diagnostic performance of the test and reduced the proportion of nondiagnostic scans.[17] In the same way, V/Q PET/CT may further improve the detection and the characterization of regional lung dysfunction. Higher spatial resolution and better count statistics may allow better assessment of the size, shape, location, and V/Q relationship of defects. It may also allow better correlation with morphologic abnormalities on coregistered CT, especially with respiratory-gated acquisition. Some may argue that increased detection of perfusion defects may lead to the risk of over-diagnosing/over-treating PE, while planar and SPECT techniques has been shown to be sensitive enough to safely rule out PE.[7,32] Future research will have to pay attention to this risk and interpretation criteria may be different with PET imaging. However, from our perspective, the main benefit of better appreciation of the pattern of defects would be to decrease the risk of false positive results. There are many situations in which V/Q SPECT images are heterogeneous because of non-PE conditions, which may lead to false positive conclusions, especially with the fear of missing a potentially life-threatening diagnosis.

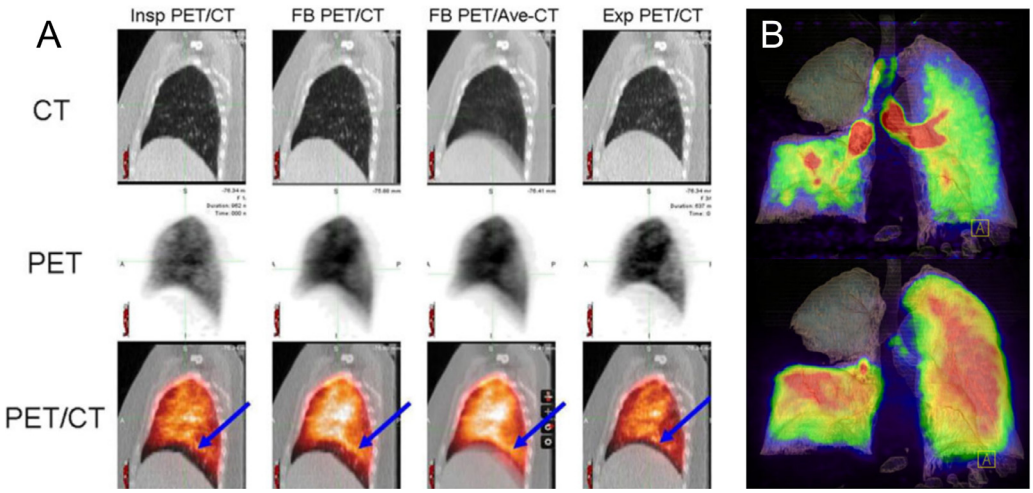

Figure 1 Respiratory-gated (4D) PET and CT acquisition enabling phase-matched attenuation correction. (A) Perfusion PET/CT showing effects of respiratory motion on image coregistration around the lung bases in (1) inspiratory-phase PET/CT, (2) free-breathing (FB) PET/CT, (3) FB PET / 4D CT average (Ave-Ct), and (4) expiratory-phase PET/CT. The best result is achieved with expiratory phase bin. (B) Volume-rendered PET/CT images showing large areas of aerated lung in the right upper lobe with no evident ventilation (top) or perfusion (bottom). Precise coregistration of PET and CT datasets is provided with respiratory gated acquisition. Modified with permission from Callahan et al.[30]

Table 2 Perceived Limitations in the Development and Implementation of V/Q PET/CT

V/Q PET requires a ^{68}Ge generator; this, however, is increasingly available in the nuclear medicine departments owing to use of ^{68}Ga tracers for neuroendocrine [1] and prostate cancer [11] imaging.
Radiolabeling of the MAA is logistically less straightforward with ^{68}Ga as compared with ^{99m}Tc as commercial kits are not yet available. Automated kit or synthesis device radiolabelling of ^{68}Ga-MAA would be useful.
It may be difficult to respond to acute request given the low availability of PET/CT cameras, which are often busy with whole body scans for cancer patients. The development of digital PET/CT cameras should increase the accessibility of the cameras.
A potential physical limitation is related to the range of the positron before annihilation.[14] The ^{68}Ga positron has a relatively high energy (E_{max}: 1.898 MeV as compared with 0.633 MeV for the ^{18}F positron) and the density of the lungs is low. This may potentially limit the spatial resolution although this disadvantage is largely offset by others technical advantages
Similar to the transition from planar V/Q to SPECT and to SPECT/CT imaging, some may not see an interest in improving a test that already performs well. However, the technical advantage of PET imaging is significant and the test only has few drawbacks. As for any imaging test, it is difficult to assert or reject the superiority and utility of a new technology before it has been formally evaluated.
As for any new imaging modality, validation studies will be needed to convince clinicians of the utility of the test for patient management.[17]

There are currently very few published studies on this topic. In a pilot study including 10 patients, we showed the feasibility of performing V/Q PET/CT in a routine clinical setting in patients with suspected acute PE.[21] ^{68}Ga-labeled V/Q PET/CT image quality was equivalent or superior to SPECT in all patients, with more homogeneous radiotracer distribution for both ventilation and perfusion studies (Fig. 2). A study comparing CTPA and V/Q PET/CT for PE diagnosis in cancer patients has just been completed (ACTRN12614001170617) and will provide additional data about the potential of the test for the management of patients with suspected PE. In this setting of suspected acute PE, formal diagnostic accuracy studies using an independent reference standard will be needed.

Another application of V/Q imaging for PE is the quantification of the extent of vascular obstruction, at diagnosis or at completion of anticoagulant therapy, which has been described as an independent risk factor of PE recurrence,[12,13] and may be used to adapt the duration of anticoagulant therapy. In that respect, the clear technical superiority of PET technology may be of value to accurately quantify the pulmonary vascular obstruction index. Finally, improved performance may also allow an accurate multimodal approach by combining the anatomical information imaged with CTPA (ie, the clot itself) and the functional information provided by V/Q PET (ie, the consequences of the clot on lung perfusion).[5]

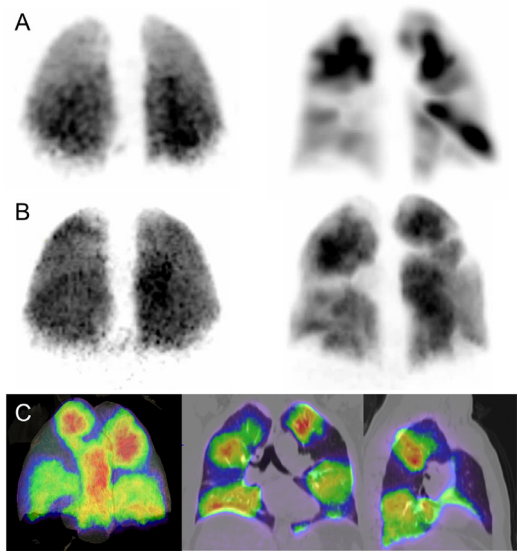

Figure 2 V/Q SPECT/CT compared to PET/CT in the same patient with diagnosis of acute pulmonary embolism. (A) Maximum intensity projection (MIP) ventilation (left) and perfusion (right) SPECT demonstrates normal ventilation with multiple large unmatched perfusion defects consistent with acute pulmonary embolism. (B) MIP PET findings mirror the SPECT/CT findings. The unmatched defects are more clearly defined on PET with sharper cutoff. (C) Perfusion PET fused with volume rendered lung CT (left), coronal (middle), and sagittal (right) PET/CT clearly demonstrates large segmental perfusion defects.

Assessment of Regional Lung Function

The management of patients with lung disease is mainly based on pulmonary function tests (PFTs). However, these only provide reliable information about global lung function and not spatial information about regional pulmonary function, the heterogeneity of which is well known. Establishing a functional map of the regional ventilation and perfusion in the lungs may be highly relevant in many clinical situations.

Comparing PET V/Q to Pulmonary Function Tests

To support the validity of using regional measures of lung function derived using ^{68}Ga V/Q PET in predicting the consequences of therapies that affect regional function, such as surgery or radiotherapy, our group assessed the correlation between ^{68}Ga V/Q PET/CT functional volumes and PFTs indices in a series of 30 lung cancer patients.[33] The percentage of lung volume with normal and abnormal function was computed for four physiologic patterns: areas with normal ventilation and perfusion, reversed mismatched defect, mismatched defects, and matched defects, respectively (Fig. 3). Overall, a percentage of lung volume with normal ventilation and perfusion higher than 90% correctly identified lung function impairment (defined by chronic obstructive pulmonary disease or DLCO <55%) in 93% of patients. A high

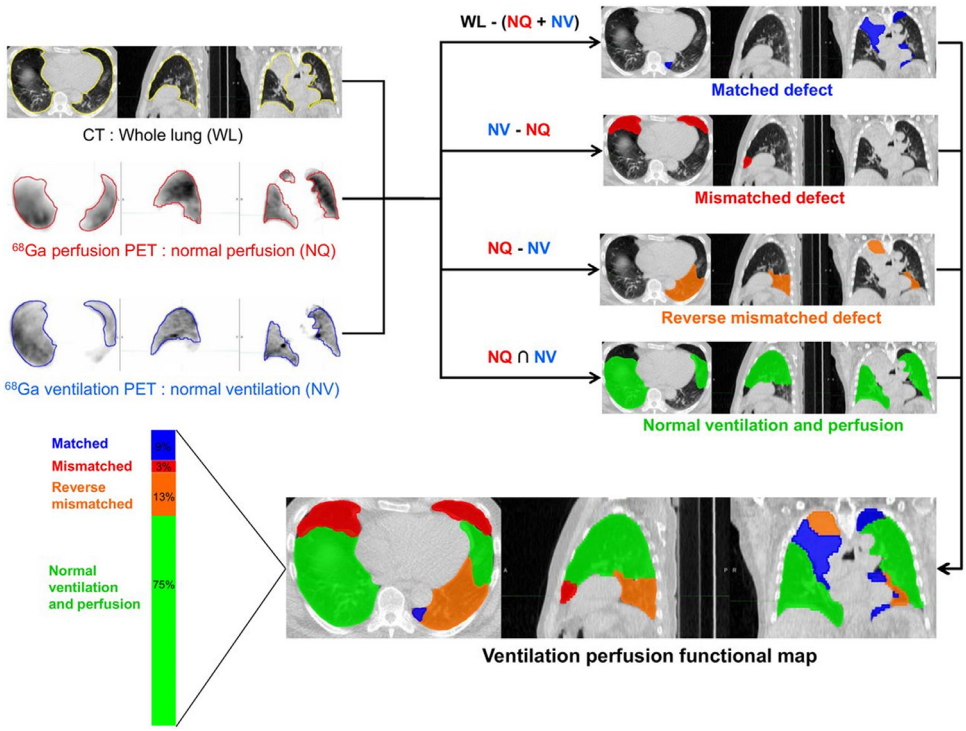

Figure 3 Lung functional volume calculation. WL volume, areas with normal perfusion (NQ), and areas with normal ventilation (NV) were delineated on CT, perfusion PET, and ventilation PET images, respectively. Lungs were then mapped according to relationship between ventilation and perfusion distribution in four physiologic conditions: matched defects, reverse mismatched defects, mismatched defects, or normal ventilation and perfusion (NVQ). Functional volumes were expressed as percentage of WL. Used with permission from Le Roux et al.[33]

degree of correlation was shown between all functional lung volumes on V/Q PET/CT and lung function as assessed by PFTs (Fig. 4). The high correlation between global measures of lung V/Q concordance with PFT supports the concept of using ^{68}Ga V/Q PET/CT to predict the consequences of therapies that affect regional function.

A further challenge is the validation of an automatic segmentation method to facilitate delineation of functional volumes. A simple method consists of applying a fixed threshold value expressed as a percentage of the maximal value was proposed.[34] The best cutoff that provided highest correlation with PFTs was 15% of maximum for both ventilation and perfusion images. However, using this unique threshold systematically provided unacceptable errors in some patients. A visually adapted semiautomatic method remains the method of choice. Future research may focus on

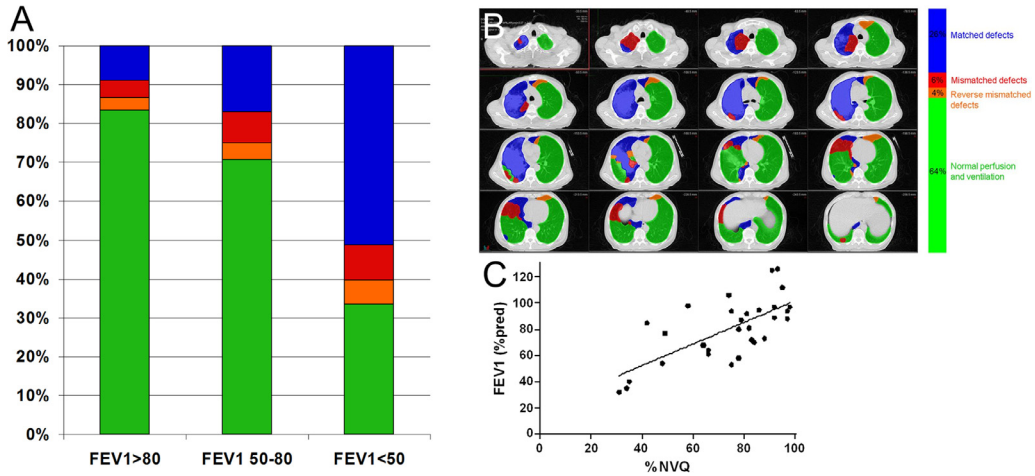

Figure 4 (A) Declining normal V/Q (%NVQ) derived from V/Q PET/CT lung functional volume calculation with decreasing FEV1. (B) Example of lung functional map and quantification with V/Q PET/CT. (C) High correlation between FEV1/FVC and percentage of lung volume with normal ventilation and perfusion (%NVQ). Adapted from Le Roux et al.[33]

other reference value to determine the cutoff. An approach based on an absolute quantification or voxel-based V/Q subtraction may also become a reality with PET/CT technology, possibly using a machine-learning approach.

Quantitative V/Q for Determining Suitability for Surgery or Other Interventions

The first clinical application of regional lung function assessment with V/Q PET/CT imaging may be the prediction of postoperative lung function after lung resection in lung cancer patients. Most patients with lung cancer are former or current smokers resulting in chronic obstructive pulmonary disease, which increases operative risk. In patients with poor lung function, the dilemma may arise whether to perform potentially life-saving surgery in a patient with increased risk of operative mortality or significant postoperative dyspnoea. Therefore, accurate evaluation of preoperative lung function is imperative to estimate the risk of both short and long-term postoperative adverse events, and to select patients who will derive maximum benefit with minimal risk from surgery.

The American College of Chest Physicians guidelines recommend that both FEV1 and DLCO be measured and that both predicted postoperative (PPO) FEV1 and PPO DLCO are calculated in all patients with lung cancer being considered.[15] To compute PPO many centers still perform planar [^{99m}Tc]-MAA scintigraphy and perform quantification by dividing the lungs into three zones (see paper by Wechalekar in this issue). This provides inaccurate results with overestimation of the right middle lobe/lingula split function and underestimation of the left lower lobe. Lung PET imaging can provide a more accurate assessment of regional lung function. In a series of 22 patients planned for curative surgical resection,[35] lobar split PPO lung function was calculated using perfusion PET/CT and the current recommended method before lobectomy, ie, calculation based on anatomical segments for lobar function.[15] Lobes were delineated on CT and segmentation subsequently applied to the PET imaging using MIM Software (Cleveland); similar tools to assist with rapid three-dimensional contours are now available from multiple vendors (Fig. 5). There was variation on an individual level between perfusion PET/CT and the anatomical method, with absolute difference over 5 % and 10 % in 37 % and 11 % of patients, respectively. In addition, while anatomic estimation provided "fixed" results, split lobar functions computed with perfusion PET/CT varied widely, reflecting the intra and interindividual variability of regional lung function. Similarly, Eslick et al showed low correlation between lobar lung function computed with ventilation PET/CT imaging and the anatomical segment counting ($r < 0.45$).[36] Further larger studies are now needed to assess if lung PET/CT allows better prediction of short and long-term outcome and may influence management of lung cancer patients undergoing surgery.

Another application of regional lung function assessment with V/Q PET/CT may be the evaluation of patients with severe emphysema undergoing bronchoscopic lung volume reduction surgery. Baseline evaluation may be of value to

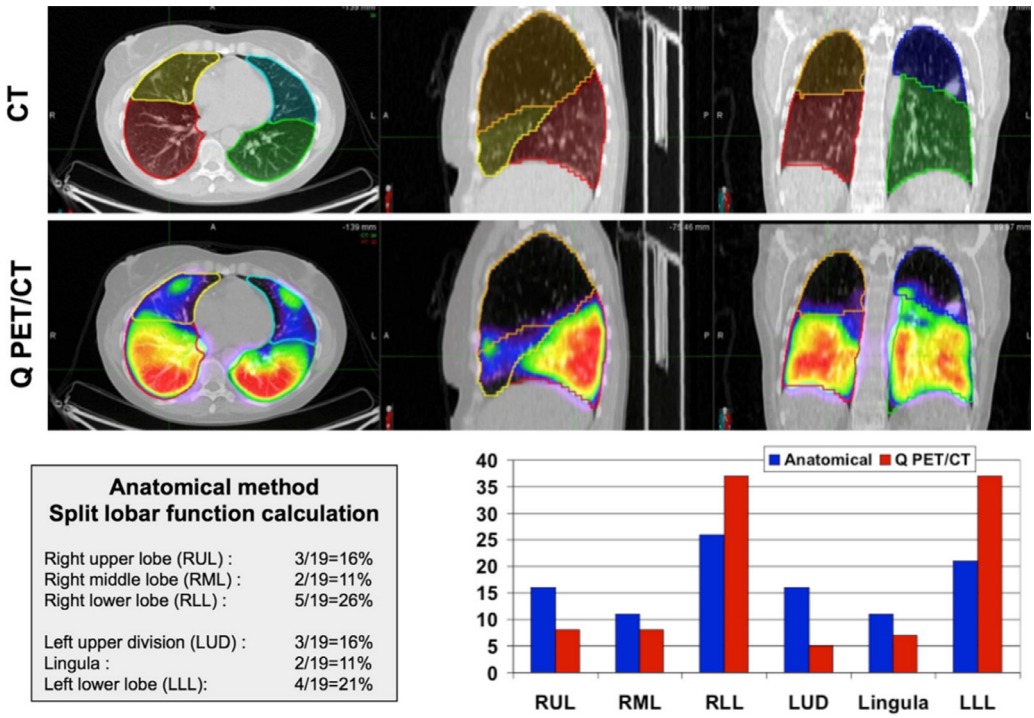

Figure 5 Two regional lung quantification analyses using ^{68}Ga-MAA PET/CT. In this example, there is significant discordance between lobar split function derived from volumetric CT analysis and functional perfusion analysis owing to emphysematous changes in the upper lobes. Planar three-zone scintigraphy (not shown) was also significantly discordant. The high-resolution images provided by perfusion PET/CT provide confidence to the cardiothoracic surgeon to enhance decision making.

select the lobe to target (Fig. 6). Postvalve scan may be useful to confirm the efficacy of the procedure in the targeted lobe and to assess the improvement of V/Q relationship in the others lobes.[37]

PET V/Q for Individualizing Radiotherapy Treatment

In patients with nonsmall cell lung cancer (NSCLC) being treated with curative-intent radiotherapy, loco-regional failures still occur in approximately one-third of patients resulting in mortality and morbidity. However, efforts to increase the intensity of radiotherapy are tempered by the need to constrain dose to the surrounding normal lung in order to preserve lung function and limit the risk of pneumonitis. Current constraints applied in radiotherapy planning are based on population-based volumetric measurements of total irradiated lung irrespective of regional variation in pulmonary physiology. Advanced imaging techniques allow functional information to be derived and integrated into treatment planning.[38] In particular, accurate assessment of regional lung function with V/Q PET imaging may be useful for individualizing radiotherapy treatment plans.[39,40] Our group has undertaken a large prospective observational study of V/Q PET/CT to evaluate the pattern of regional V/Q changes before, during, and after a course of radiotherapy in patients with NSCLC.[41] A secondary objective of this study was to simulate administration of biologically adapted radiotherapy techniques personalized to regional lung function in individual patients based on information gained from V/Q PET/CT at baseline and midtreatment. The latter scan is to assess for possible reventilation or reperfusion of obstructed lung due to tumor shrinkage, which may impact regional lung function.

In a cohort of patients with NSCLC being treated with curative-intent radiotherapy, we simulated a radiotherapy plan based on perfusion 4D PET/CT.[40] These patients were planned to receive 60 Gy in 30 fractions of radiotherapy using 3D conformal techniques. We defined "perfused" or "well-perfused" lung on ^{68}Ga-MAA using an automated contour encompassing any ^{68}Ga-MAA uptake or maximum standardized uptake value (SUV_{max}) cutoff of 30%, respectively. Automated contours were visually adjusted to exclude any areas of clumping or other artifacts. Plans optimized for well-perfused lung improved functional V30, V40, V50, and V60 metrics (all P values <0.05) and functional mean lung dose was improved by a median of 0.86 Gy ($P < 0.01$; Fig. 7). We also investigated the role of ventilation in addition to perfusion for functional lung avoidance when using intensity modulated radiotherapy. Intensity modulated

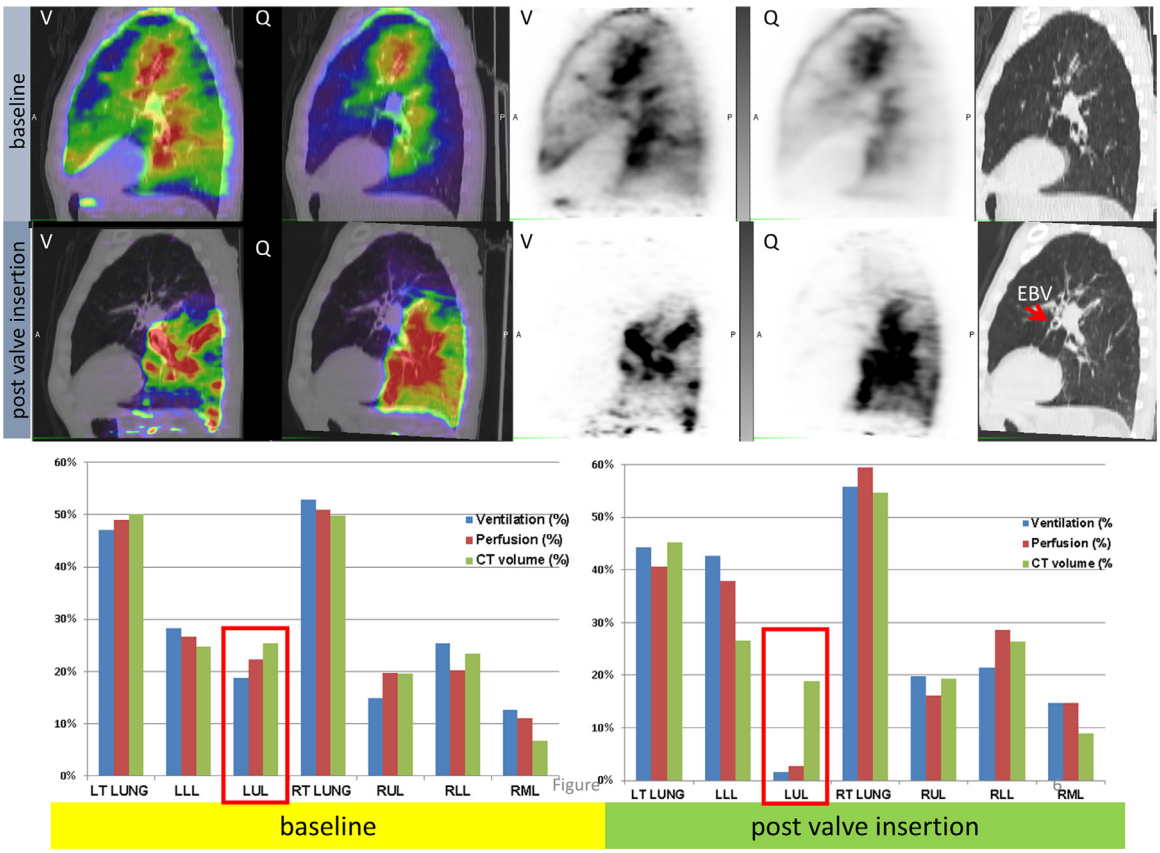

Figure 6 Baseline V/Q in patient with severe emphysema demonstrated expected marked heterogeneous radiotracer distribution. Based on conventional imaging assessment including hyper-expansion of the left upper lobe, the patient underwent endoscopic insertion of a valve in the LUL. Postprocedural reassessment demonstrated near total diminishment of V/Q in the LUL associated with more minor volume reduction. Postprocedure, the patient's shortness of breath worsened which, in retrospect, may have been predicted by the preserved V/Q in the lobe undergoing intervention.

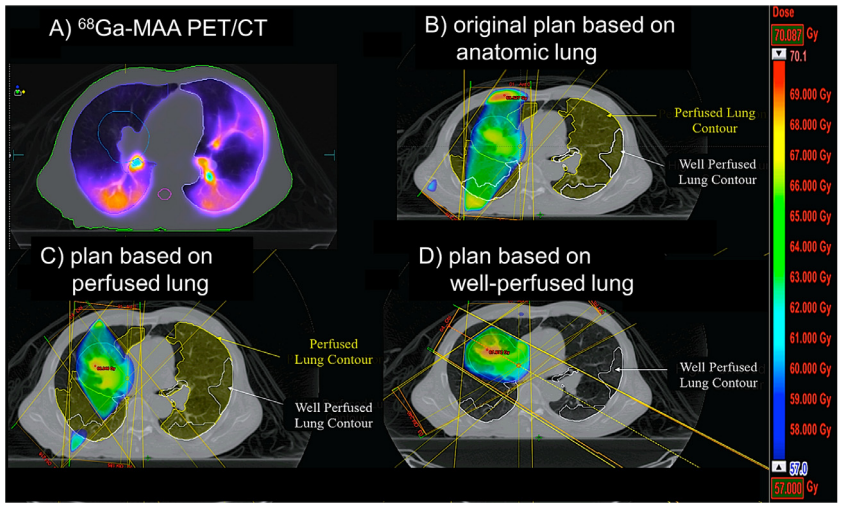

Figure 7 Using ^{68}Ga-MAA Perfusion 4D PET/CT for functionally-adapted radiotherapy planning. (A) Perfusion PET showing the PTV contoured in cyan. (B) The conventional plan based on anatomical lung. (C) Modified plan adapted for "perfused" and (D) "well-perfused" lung contours demonstrating avoidance of contralateral anatomical lung. Adapted with permission from Siva et al.[40]

radiotherapy plans adapted to perfuse but not ventilation lung allowed for reduced dose functional lung while maintaining consistent plan quality.[42]

Our current understanding of the relationship between toxicity, radiation dose, and volume of irradiated lung is incomplete. We investigated changes in perfusion, ventilation and CT lung density changes in the same group of patients with NSCLC.[43] Functional images were registered to the RT planning using deformable registration[39] (Fig. 8) and isodose volumes were averaged into 10 Gy bin intervals. Within each dose bin, relative loss in SUV was analyzed for ventilation and perfusion. An almost perfectly linear negative dose-response relationship was observed for perfusion ($r^2 = 0.99$, $P < 0.01$) with a strongly negative correlation for ventilation ($r^2 = 0.95$, $P < 0.01$). In some patients, peritumoural reperfusion/reventilation occurred (Fig. 9). This may indicate that postradiotherapy effects are closely correlated to deficiencies in perfusion more so than ventilation, and efforts prioritize functional sparing of perfused lungs may be warranted.

Using PET V/Q to Develop and Optimize Other Methods

Other techniques could also offer high-resolution replacement or complement to nuclear medicine techniques. This includes a variety of CT and MRI techniques. These are of interest as these imaging technologies are widely available, may be cheaper and more convenient for patients especially if existing scans used for radiotherapy planning or other purposes can be reprocessed to provide this information.

CT ventilation imaging is a promising new functional imaging modality that computes regional air-flow in the lung from regional lung formation using deformable image registration. PET. CT ventilation images are generated in three steps (Fig. 10a): (1) acquisition of respiratory-correlated

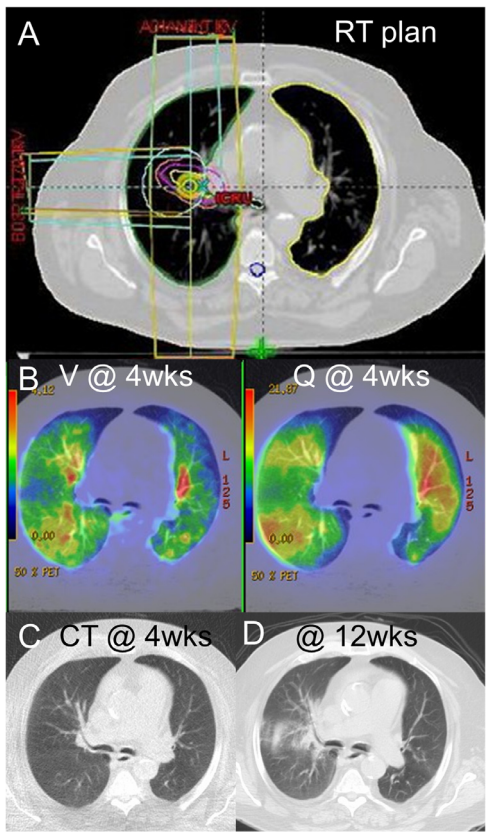

Figure 8 "High resolution" 4D PET V/Q identifies pneumonitis early during a course of radiotherapy for lung cancer. Baseline V/Q (not shown) was normal. (A) Radiotherapy (RT) treatment plan. (B) Ventilation (left) Perfusion (right) 4D PET/CT 4 weeks after commencing RT demonstrates horizontal and vertical band of decreased function congruent with the RT-plan. (C) CT at same time point demonstrates no abnormality. (D) At 12 weeks CT demonstrates band of pneumonitis. In summary, clear changes on functional imaging were identifiable before anatomic changes were visible.

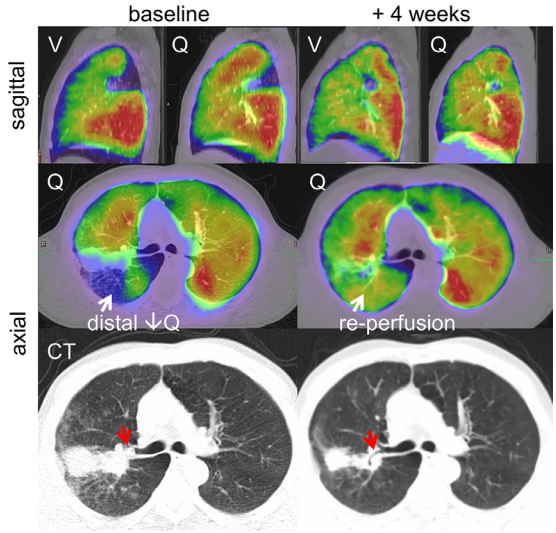

Figure 9 Baseline and 4-week PET V/Q in patient undergoing curative-intent RT for lung cancer. At baseline, there is a large area of decreased ventilation and perfusion owing to tumor obstructing bronchus. Following tumor regression, reventilation and reperfusion of the distal lung segment is evident.

4D-CT lung images, (2) deformable image registration of the inhale to exhale phase, and (3) quantitative analysis of the resulting deformation vector field. They can be visualized using a color map analogous to Galligas PET. Our protocol of acquiring Galligas PET/CT using 4D CT enabled us to retrospectively perform CT Ventilation on acquired scanned and performed a correlation study.[44] We found that standard CT ventilation using Jacobian-based metrics performed poorly in areas of bulla formation. Areas of bulla formation represent nonfunctioning lung with no ventilation seen on Galligas PET. As the bulla expands and contracts by surrounding lung with breathing, standard CT ventilation can demonstrate erroneous ventilation in these regions. This was clearly evident when performing intraindividual comparison of Galligas PET to CT Ventilation (Fig. 10b). With this knowledge, we found that modified CT Ventilation could be improved by adding density Hounsfield unit (HU)-based metric that downscaled calculated ventilation in areas of low HU bullous formation. In further research, we found that simple time-averaged 4D-CT HU improved voxel-wise correlations compared to more complex deformation vector field-derived ventilation.[45]

Conclusions

V/Q PET/CT imaging offers a unique opportunity to provide high quality functional lung imaging and to improve the usefulness of V/Q imaging in the management of patients with various pulmonary conditions. In nuclear medicine departments equipped with a ^{68}Ge/^{68}Ga generator and a Technegas device, its implementation is feasible. The high-resolution images obtained can provide referrers with the diagnostic confidence required to potentially improve management in a range of pulmonary diseases. Further validation studies are now needed to assess the performance of this new imaging modality and its impact on patient' management.

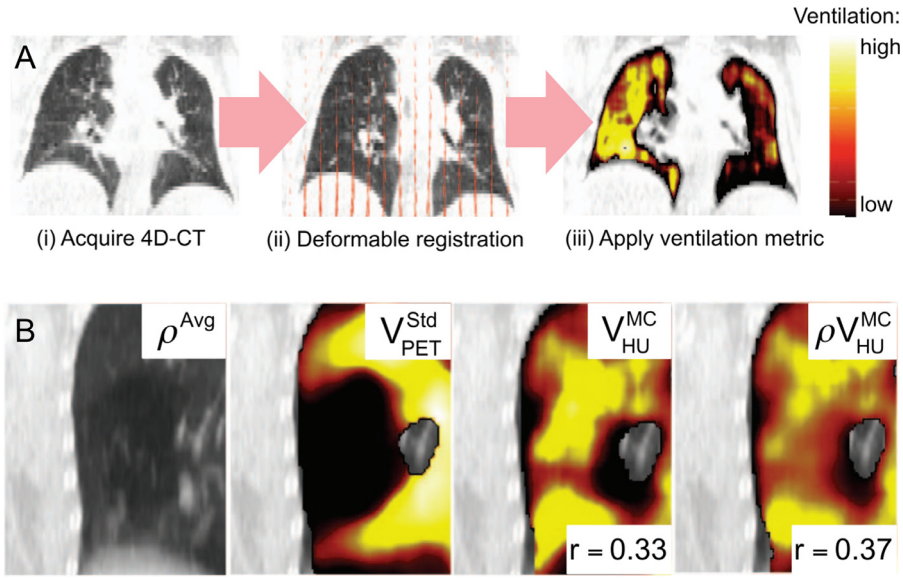

Figure 10 Using Galligas Ventilation PET to validate and improve CT Ventilation. (A) CT ventilation image generation in three steps. (B) Coronal slices of an emphysematous bulla in the right lung. From left to right: (a) Time-averaged 4D-CT image ρAvg, (b) standard PET image V Std PET with σ m = 3 mm, (c) the HU based motion-compensated CT ventilation without density-scaling, and (d) HU based motion-compensated CT ventilation with density scaling. The Spearman *r* refers to the correlation of the CT and PET ventilation images. Note that in the three right-most images a small region was excluded from the lung volumes as a result of our threshold-based segmentation algorithm. Used with permission Kipritidis et al.[44]

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