Pre-surgical Evaluation of Lung Function

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Chronic obstructive pulmonary disease affects 400 million individuals worldwide and is predicted to be the third leading cause of death by 2020 with a projected economic cost of 4.8 trillion US dollars by 2030. Lung volume reduction surgery is an established means of targeting hyperinflation in patients with severe emphysema, optimizing ventilator mechanics, and reducing the work of breathing. Preoperative evaluation of regional lung function is essential to planning and predicting the outcomes of surgery. The traditional planar approach is inaccurate for lobar contribution since it is not based on anatomy. We developed a novel approach combining single photon emission tomography (SPECT) with CT, offering accurate quantitative characterization of ventilation and perfusion at a lobar level. The utility of this hybrid imaging technique has been demonstrated in preoperative disease profiling, surgical planning, and predicting of postoperative outcomes in patients undergoing Lung volume reduction surgery, affording superior results to conventional planar imaging modalities. In this article, we describe the methodological development of this technique with technical validation.
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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow limitation caused by repeated inhalation of noxious particles or gases.[1] Cigarette smoking is the most important preventable cause. COPD affects 400 million individuals worldwide[2] and is predicted to be the third leading cause of death by 2020[3] with a projected economic cost of 4.8 trillion US dollars by 2030.[4] The natural history of the condition varies greatly: in individuals with severe disease, 5-year mortality approaches 70%.[5] The airflow limitation in COPD is caused by a combination of small airways disease[6-8] and parenchymal destruction (emphysema),[9,10] which ultimately progresses to gas entrapment and hyperinflation.[11] Despite optimal medical therapy using inhaled and oral drugs, many patients remain symptomatic and functionally limited.

Lung volume reduction surgery (LVRS) is an established means of targeting hyperinflation in patients with severe emphysema,[12] optimizing ventilator mechanics, and

reducing the work of breathing.[13] Preoperative evaluation of regional lung function is essential to planning and predicting the outcomes of surgery. Traditionally, planar ventilation and perfusion imaging has provided a semiquantitative evaluation of regional lung function according to arbitrarily defined geometric zones, which, however, imprecisely reflect lobar anatomy. A novel approach combines single photon emission tomography (SPECT) with low-dose CT (LDCT), offering accurate quantitative characterization of ventilation (V) and perfusion (Q) at a lobar level. The utility of this hybrid imaging technique has been demonstrated in preoperative disease profiling, surgical planning, and predicting of postoperative outcomes in patients undergoing LVRS, affording superior results to conventional planar imaging modalities.[14,15] At our institution, we routinely employ this multimodality imaging protocol in the work-up of individuals for surgery and for the developing field of bronchoscopic lung volume reduction procedures.

Thoracic surgeons have also adopted SPECT/CT in their imaging armamentarium to refine the surgical resection margin and to better evaluate regional lung function reserve, pertinent to a cohort of individuals who will frequently have compromise in lung function from accompanying emphysema. In a study of 69 longstanding smokers, 55 with COPD and 14 healthy, Jögi et al showed that SPECT/CT hybrid imaging is better at defining emphysema and identifying

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lung malignancy as well as other complications compared with either imaging modality individually.[16] In those with early lung cancer, sentinel lymph node activity can be detected by lymphoscintigraphy using SPECT/CT providing optimal staging of disease.[17] Ohno et al showed that fused SPECT/CT was superior in predicting postoperative lung function in 229 individuals with non−small cell lung cancer who underwent lung resection surgery compared with traditional planar imaging or SPECT alone.[18] Furthermore, the detailed functional-morphologic correlation of SPECT/CT can be used to assess the effects of chemoradiotherapy and predict those who will best respond to treatment.[19-21] Moreover, interpretation of SPECT/CT is easy to perform and reproducible with excellent inter- and intraobserver agreement.[22] We describe our stepwise transition from planar to SPECT/CT in this article.

Methodological Development

Conventionally, differential and regional lung function has been measured from the geometrical mean of anterior and posterior planar images of lung perfusion and ventilation, using whole lung and upper, middle, and lower zones. These were then used to estimate the likely postoperative reduction in respiratory capacity. However, a limitation of this technique is that subdividing the lung parenchyma into rectangular zones does not represent the true anatomical lobes as shown in Figure 1.

V/Q SPECT imaging has improved image contrast and helps to identify smaller defects more easily than planar imaging wherein overlapping lung regions make interpretation difficult. The addition of CT helps with attenuation correction to improve image quantification, but also helps to show the structural detail of lung parenchyma to correlate its effect on perfusion as well as ventilation. This is important in presurgical patients with COPD or lung cancer where CT is almost always performed. It could be done near simultaneously on the same scanner or can be performed days apart on a dedicated, diagnostic CT scanner. In the latter situation, although attenuation correction from CT is not possible due to the separate acquisitions, in our experience, this does not cause significant difference in lobar quantification. The reason for this is likely to be the fairly large size of the organs.

With this knowledge and the introduction of hybrid multimodal imaging using SPECT and SPECT/CT, we developed software for three-dimensional (3D) lobar quantification in collaboration with a nuclear medicine software vendor (Hermes Medical Solutions, Stockholm, Sweden).

Image Acquisition

Following administration of 200 MBq of [^{99m}Tc]MAA, both planar and SPECT/CT V/Q (^{81m}Kr) images were acquired (Fig. 2) using a general purpose dual head gamma camera (Infinia Hawkeye, General Electric, Milwaukee, WI) with extended low energy general purpose collimators.

Anterior and posterior planar perfusion and ventilation images (256 × 256 matrix) were followed by SPECT (128 × 128 matrix), with ventilation and perfusion being performed sequentially. The reconstructed ventilation and perfusion images were accurately aligned in all three planes
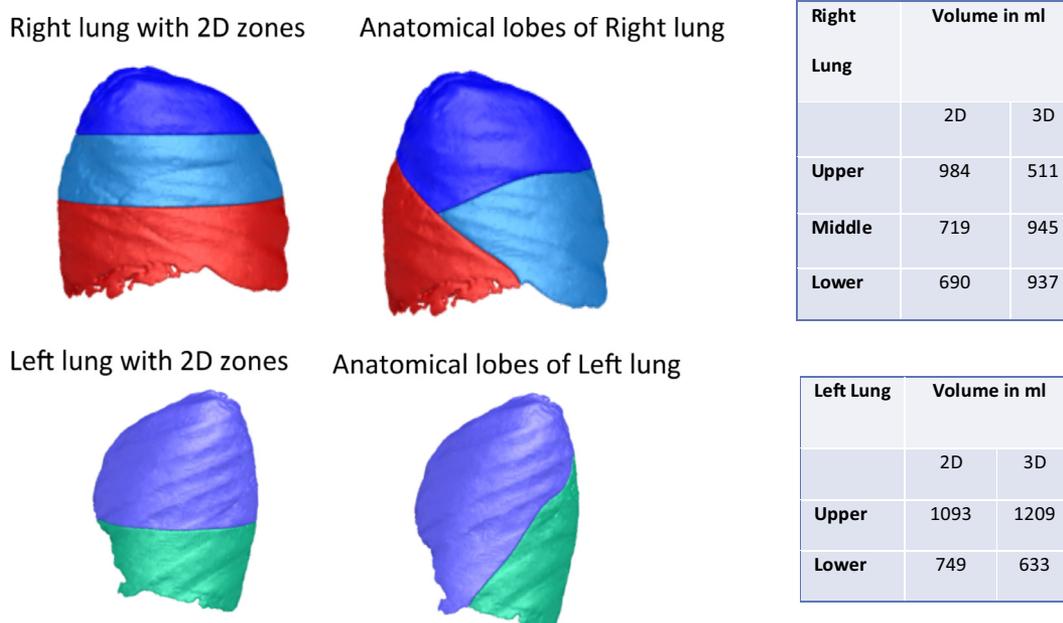

Right Lung	Volume in ml	
	2D	3D
Upper	984	511
Middle	719	945
Lower	690	937

Left Lung	Volume in ml	
	2D	3D
Upper	1093	1209
Lower	749	633

Figure 1 Schematic diagram (left) demonstrating the difference between zones as defined by 2D planar method and true lobes defined by 3D SPECT/CT method. Also, the difference in volumes (right) of the lung regions between the two methods is shown.
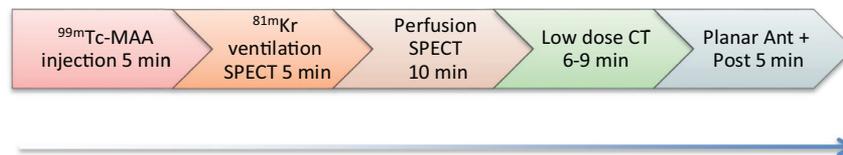
Figure 2 Time-line demonstrating the SPECT acquisition protocol of 35 minutes including planar imaging.

(transverse, sagittal, and coronal) in order to be able to correctly compare. Therefore, both perfusion and ventilation studies were acquired in one session while maintaining consistent body position.

As shown in Figure 2, the perfusion SPECT is followed by a LDCT scan (140 kV_p tube voltage, 2.5 mA beam current) of the thorax tailored to the area of the lungs to facilitate attenuation correction and anatomical visualization of the thorax. The patients raised their arms above their heads to allow optimum camera-patient distance Hands-free straps were used to secure the krypton breathing mask over the patient's face to minimize the leakage of gas, which may contaminate the gamma camera, degrading the image. A fan was positioned to blow any leaked krypton away from the camera heads. To minimize patient movement between SPECT scans (important for image registration), ventilation was performed first as the fitting of the mask was likely to result in patient movement during setup.

Tomographic acquisition employs 120 projections over 360° at 10 seconds per projection for perfusion (20% energy window centered on 140 keV) and 5 seconds per projection for ventilation (20% window centered on 159 keV), although for ventilation this served as a guide only as the radioconcentration of krypton output from the rubidium generator decreases over the course of the day, and acquisition times may need to be extended to acquire adequate ventilation events. If CT imaging was not available then scatter windows below the ^{81m}Kr and ^{99m}Tc photopeaks at 162 keV and 120 keV $\pm$ 5%, respectively, were employed to permit the construction of a "synthetic" attenuation correction (μ) map.

The radiation estimates of Effective Dose were 2 mSv for the ^{99m}Tc perfusion study, 1 mSv for the LDCT scan, and 0.2 mSv for ^{81m}Kr ventilation study.
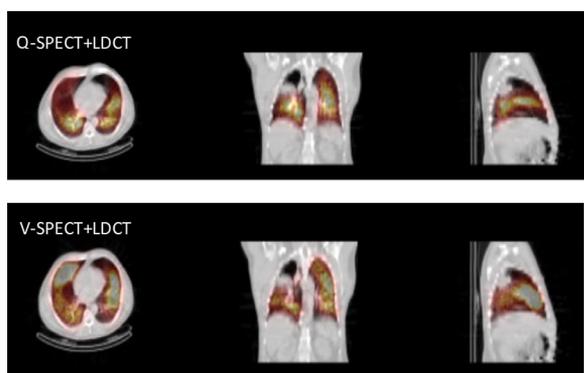

Figure 3 Coregistration of LDCT with SPECT perfusion (upper) and ventilation (lower) scans. LDCT, low-dose CT.

SPECT-LDCT

The application software *Hybrid Recon for Lung* (Hermes Medical Solutions) was used to reconstruct the perfusion and ventilation attenuation-corrected SPECT images. A cine display of raw data was used to check for patient movement, krypton leakage, and Macro-aggregated albumin (MAA) clumping. SPECT reconstruction was performed using an iterative algorithm (ordered subset expectation maximization with four iterations and four subsets; 3D Gaussian postreconstruction filter—Full width at half maximum (FWHM) = 1.3 cm). For attenuation correction, the perfusion and ventilation images were registered to the LDCT attenuation map (μ map; Fig. 3). This also facilitated the registration of perfusion and ventilation images to each other. If LDCT was not available then a synthetic μ map was produced by acquiring an additional scatter energy window (108 keV $\pm$ 12.5%) simultaneously with the emission window (140 keV $\pm$ 10%) during SPECT acquisition. The synthetic μ map was used to generate an attenuation corrected transverse reconstructed SPECT dataset.

Q + SPECT

A separate application was used for the 3D lung lobar quantification (Hermes Medical Solutions). Three observers (clinician, radiographer, and physicist) independently performed semiautomatic registration of LDCT to a diagnostic CT (performed separately) as it is easier to register CT to CT than perfusion and ventilation SPECT images to diagnostic CT. As the perfusion and ventilation SPECT data were already registered to LDCT on reconstruction for attenuation correction, by registering LDCT to diagnostic CT, we were effectively registering the Diagnostic CT to SPECT perfusion and ventilation data. Mis-registration was inevitable as the diagnostic CT is acquired on a separate scanner and with breath-hold whereas the LDCT is acquired during tidal breathing. To correct for this we used translation, rotation and elastic registration.

The right and left lungs were then segmented semiautomatically from the diagnostic CT, minimizing operator variability. Each observer defined lobar boundaries by marking anatomical fissures on sample slices. These were interpolated for all the slices in three planes (sagittal, coronal, transverse) and a volume of interest was created for each lobe and mapped onto the SPECT ventilation and perfusion images (Fig. 4). We used the sagittal plane to mark the fissures as the fissures were better visualized in this orientation. The lobar volumes were used to assess to lobar radioactivity contained in the SPECT ventilation and perfusion images and the relative percent contribution of each lobe to total lung
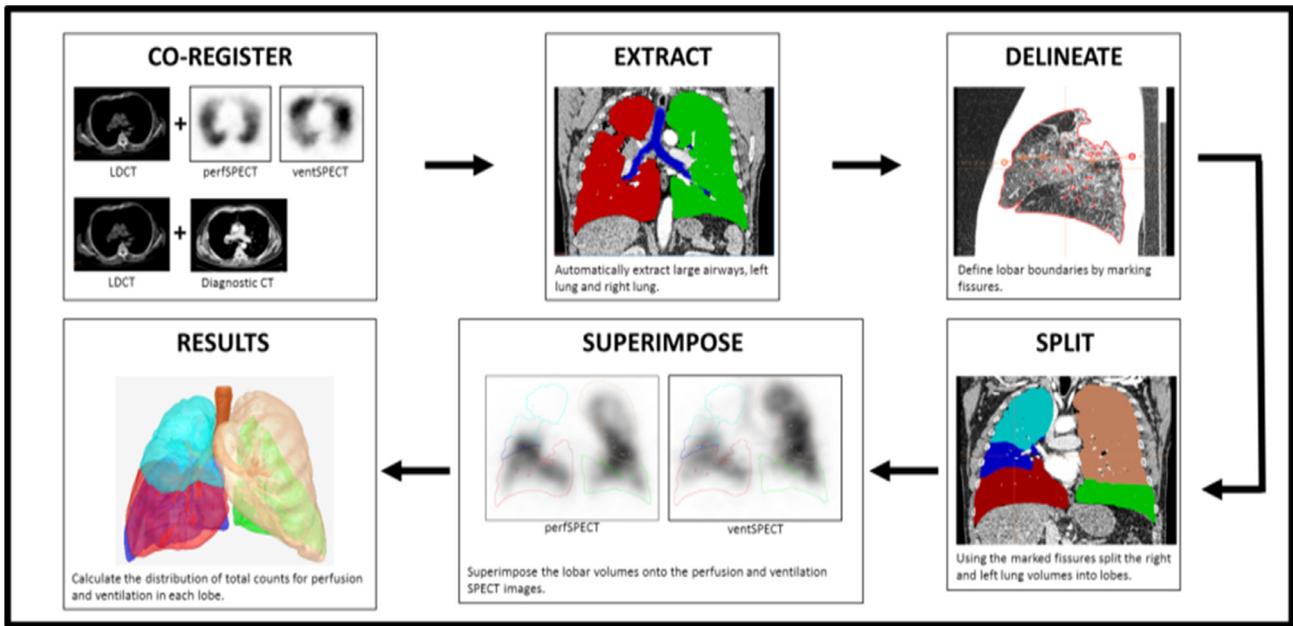
Figure 4 SPECT/CT quantification workflow.

function was measured (Fig. 5). These were compared with the planar method (Fig. 6).

robustness of this technique in the clinical setting by measuring the interobserver agreement in assessment of lobar function with 3D SPECT/CT and observer confidence in coregistration of diagnostic CT with ventilation and perfusion images and lobar definition.

Comparison With Planar Quantification

A retrospective study was conducted on 75 patients (48 male, mean age 64, range 29-85 years) who underwent perfusion and ventilation planar and SPECT/CT in a routine clinical setting for preoperative quantification of lobar lung function for lung volume resection surgery. The primary objective was to compare the percentage lobar function determined by planar scintigraphy with corresponding results from SPECT/CT. Furthermore, we assessed the

Data Analysis

Relative lung function for each lung, per zone (two-dimensional; 2D) or per lobe (3D) were estimated and compared using both ventilation and perfusion planar and SPECT scans. Planar (2D) quantification software (Hermes Medical Solutions) was used to determine the percentage contribution from each zone to total lung function. Differential and regional lung function was measured from the geometric mean of anterior and posterior planar V/Q images using
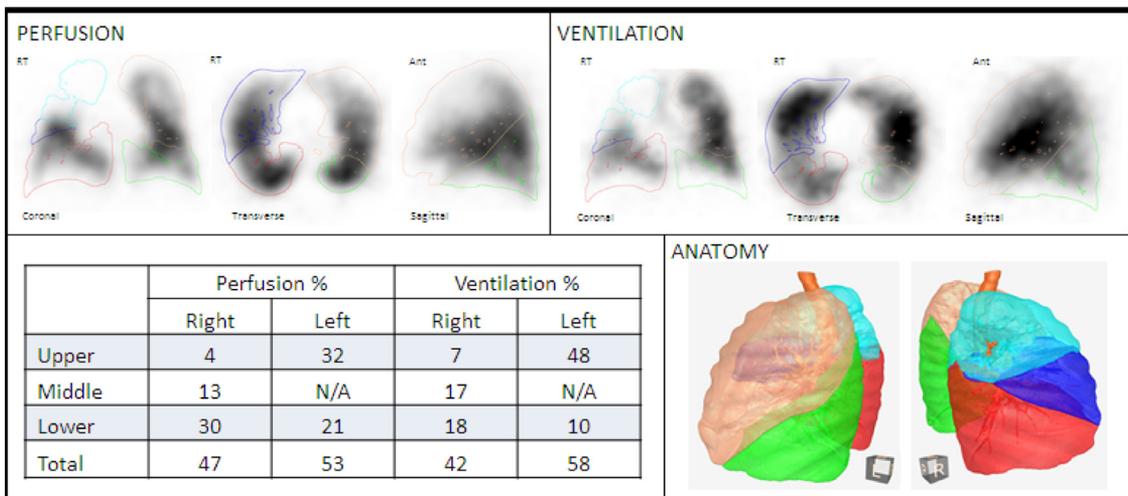

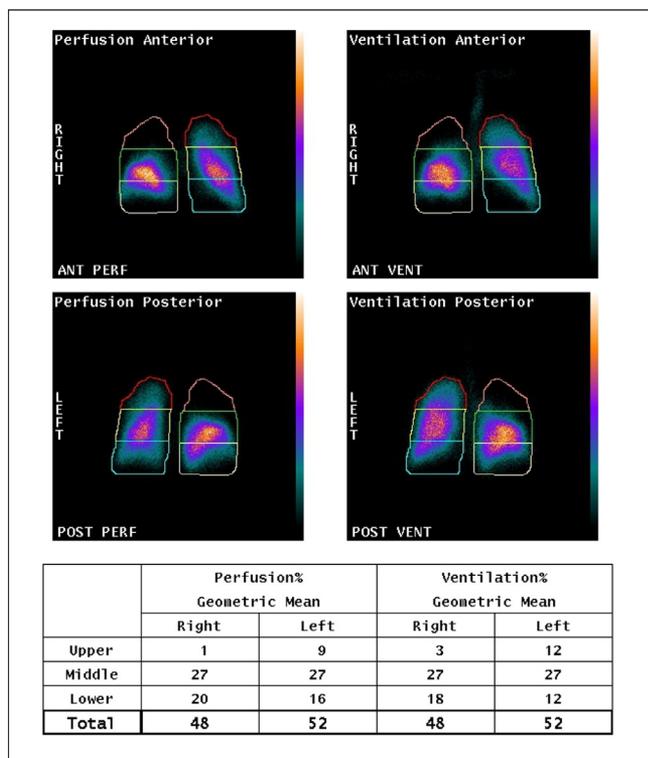**Figure 5** Example of SPECT/CT quantification results.

Figure 6 Example of quantification of regional perfusion and ventilation using the planar method. For comparison with SPECT method, the upper and middle zones for the left lung were combined.

whole lung and upper, middle, and lower zones of equal area. The percentage contribution of each zone to total lung activity was determined.

The quantification results for the left upper and left middle zones from planar scintigraphy were summed for the left lung to enable comparison with left upper and left lower lobes for SPECT/CT method. For the right lung right upper, right middle and right lower zones from the planar method were compared directly with right upper lobe, right middle lobe, and right lower lobe from the 3D SPECT/CT method. Comparison of the results for whole left and right lungs as well as lobar quantification achieved by planar and SPECT/CT studies was performed using Bland-Altman plots for both ventilation and perfusion.

Results: Planar vs SPECT Quantification

Three-dimensional lung lobar quantification was feasible for all patients in this study. The whole lung contribution by planar and SPECT showed good correlation which suggests that SPECT is as equally applicable as the planar method. However, as expected, there was a difference in regional contributions due to differences in lobar definitions.

The Bland-Altman plots for the agreement between planar and SPECT for perfusion and ventilation for the whole lung function (Fig. 7 A and B) shows the difference between 2D and 3D estimation methodologies against

the mean of the two techniques. As might be expected, there was a good agreement between planar and SPECT techniques for the assessment of differential whole lung function and correlation was good ($r = 0.9$, $P < 0.0001$). The Bland-Altman plots for the agreement between the lobes for the two techniques (Fig. 7 C and D) show poor agreement between 2D and 3D for the lobes for both ventilation and perfusion due to differences in region definition between the techniques. The mean contribution of individual lobes by both V and Q SPECT differed significantly from the corresponding zones on planar imaging (median SPECT-planar difference ranged from 17.4% [−0.6%, 34%] to −11.8% [−28.6.5%, +1%]; $P < 0.05$) with correlation being poor ($r = 0.3$, $P < 0.01$) for all lobes. The correlation between the methods for whole lungs and individual lobes is shown in Figure 8.

Interobserver Variability in 3D Lobar Quantification and Observer Confidence in SPECT/diagnostic CT Coregistration

A further 20 patients (eight male, mean age 66, range 40-83 years) were assessed for interobserver variability (three observers) in 3D lung lobar quantification results. In addition, a subjective assessment was carried out on overall observers confidence in coregistration of diagnostic CT with SPECT perfusion and ventilation studies. As shown in Figure 9, the coregistration confidence was rated good by all observers (77%) and only moderate for about 26% of the studies, with only one study scoring poorly for coregistration.

Bland-Altman plots for the assessment of lobar function demonstrate very good agreement between observers for both perfusion and ventilation for all lobes (−1.21 to +3.27, bias = 1.03 for perfusion and −1.02 to +3.42, bias = 1.2 for ventilation; Fig. 10 A and B). Also, the limits of agreement for right and left lung were very good between observers (−0.66 to +0.55, bias = 0.62 for perfusion and −0.94 to +0.91, bias = 0.95 for ventilation.

Variations, Modifications, and Future Technical Developments

Having demonstrated the value of improved regional definition based on anatomical boundaries for the lung lobes, we look forward to further improvements, some of which are detailed below.

- **CT**—The newer generation CTs (16 slice or 64 slice) are now attached to SPECT scanners which will allow faster sequential acquisition with improved fissure definition. New automatic fissure detection algorithms are also being developed to make the image processing faster and automated.
- **Dual nuclide imaging**—With the reasonable energy difference which exists between ^{81m}Kr and ^{99m}Tc photon energies, it is possible to perform dual nuclide
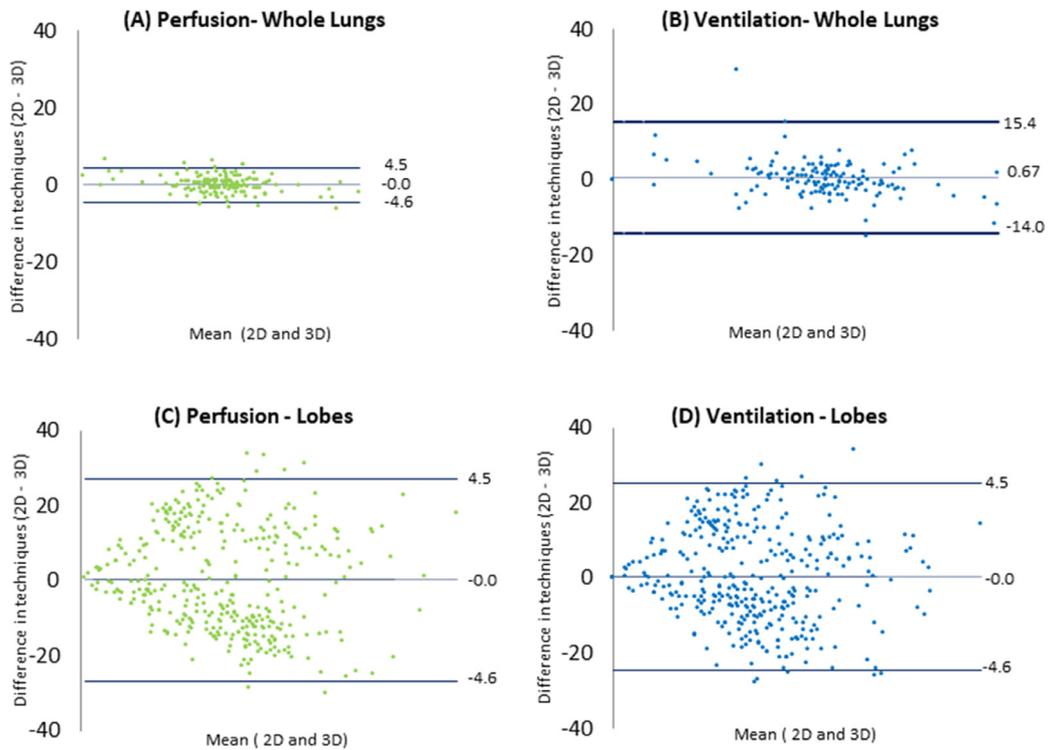
Figure 7 Bland-Altman plot for Planar and SPECT/CT quantification comparison for whole lungs (upper row—A and B) and lobes (lower row—C and D) for both perfusion and ventilation.

simultaneous V/Q SPECT to reduce imaging further. However, some crosstalk that could potentially contaminate the data may remain. With new solid-state SPECT cameras with higher energy resolution, this crosstalk may be minimized.

- **Respiratory Gating**—CT imaging takes seconds but SPECT imaging requires minutes making it impossible

to do breath-hold imaging. Respiration induces motion artifacts, especially near the diaphragm and heart motion introduces anterolateral mis-registration artifacts with CT. This could be mitigated to some extent with respiratory gating but at the cost of increased acquisition time. Once again, this could be minimized by solid-state SPECT cameras with higher sensitivity.
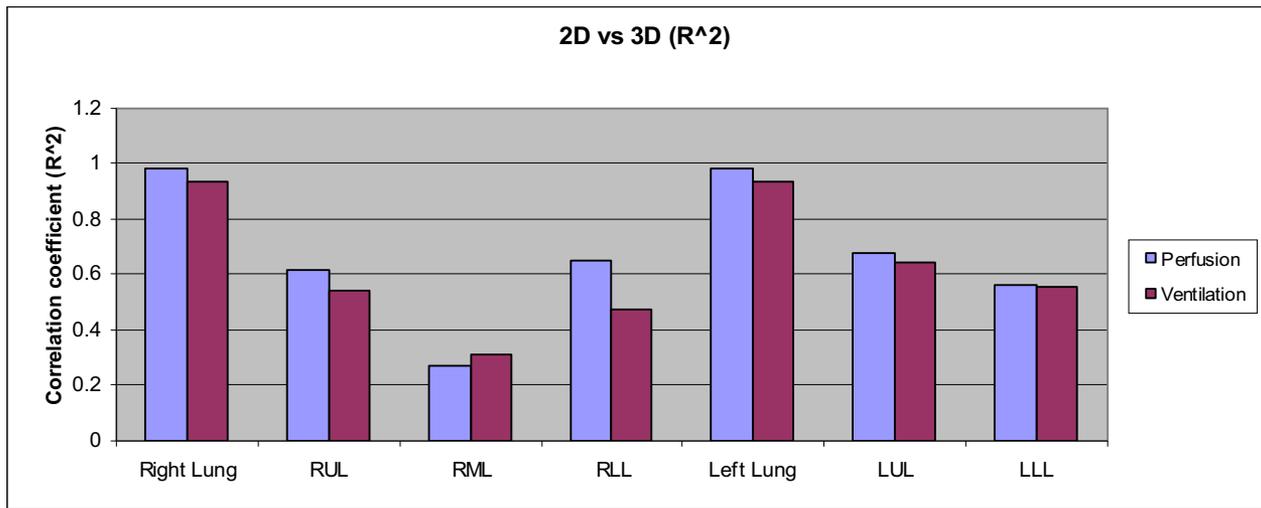

Figure 8 Comparison of 2D vs 3D region definitions. Whole lungs estimates are in good agreement for whole lung contribution, but poorer for regional assessments. Correlation is worse for the middle lobe than for the rest of the lobes likely due to the fact that it is bound by two separate fissures introducing more variability.
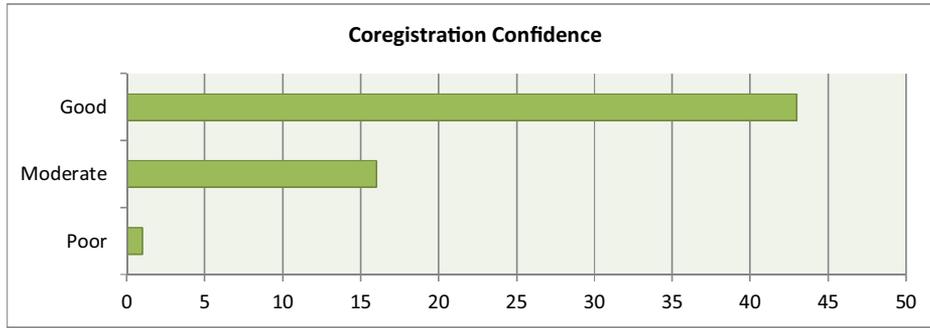
Coregistration Confidence

Figure 9 Coregistration confidence score for all observers based on the following technical observations during coregistration: Registration not possible, Translation & stretching in two planes, Translation and stretching in one plane, Translation only, no intervention (despite minor mis-registration), no intervention(excellent coregistration)

Discussion

The joint guidelines from *European Respiratory Society and European Society of Thoracic Surgeons—Clinical Guidelines* on fitness for radical therapy in lung cancer patients (surgery and chemoradiotherapy) in 2009 mentioned that the role of scintigraphy is not widely employed in assessing patients for lobectomy, because of the difficulty in interpreting the contribution of individual lobes to the overall ventilation or perfusion.[25] This new method for lobar quantification of perfusion and ventilation with SPECT/CT using anatomically accurate lobar definitions should reinstate the place for scintigraphic imaging in preoperative evaluation of lung function for COPD and lung cancer patients. The presence of intact interlobar fissures and absence of collateral ventilation in heterogeneous emphysema patterns on CT helps to identify
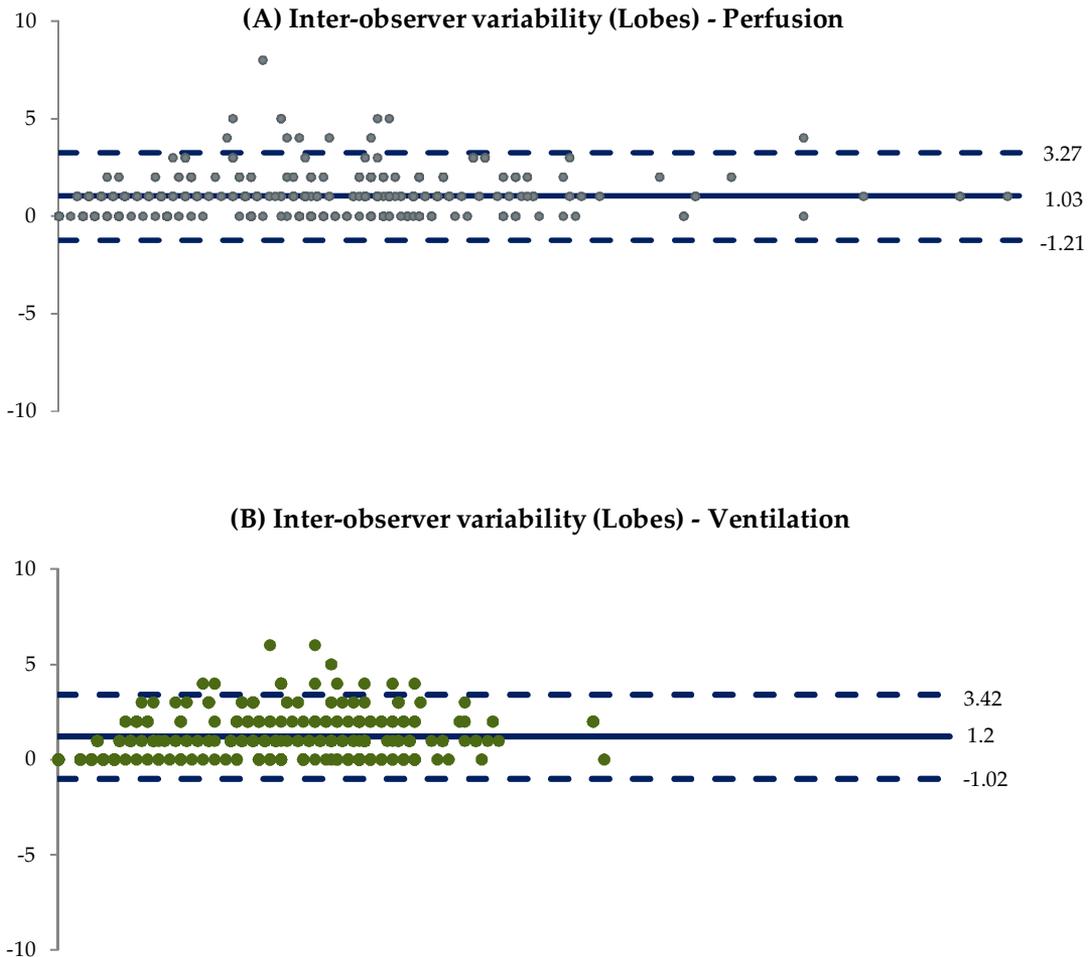

(A) Inter-observer variability (Lobes) - Perfusion

(B) Inter-observer variability (Lobes) - Ventilation

Figure 10 Bland-Altman Plots showing interobserver variability between the three observers for all the lobes for perfusion (A) and ventilation (B).
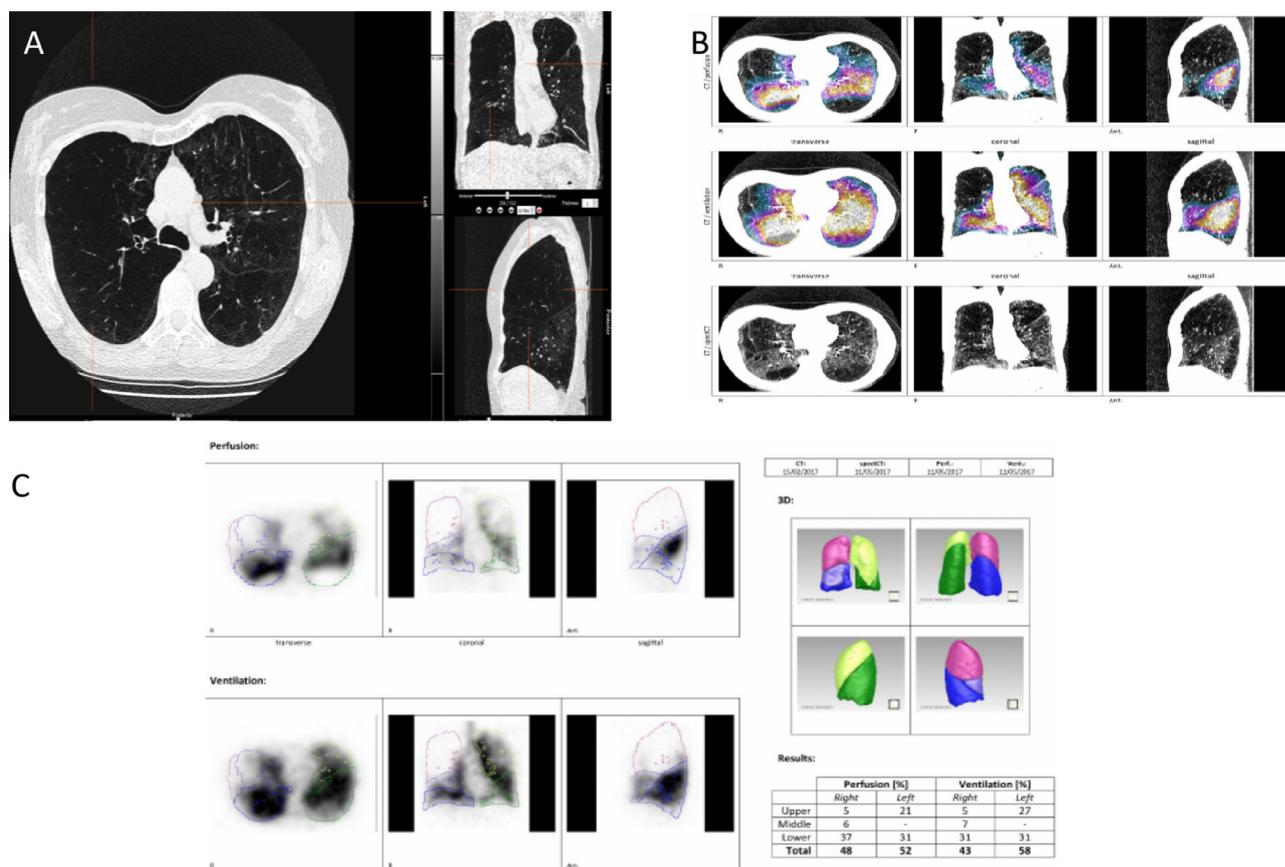
Figure 11 Example of an ideal case for LVRS—a 63-year-old female, ex-smoker, GOLD III COPD with upper lobe predominant emphysema on CT and normal Alpha 1 antitrypsin levels. FEV1 = 33.7% predicted, FVC = 2.96 L, K_{CO} = 44.2% predicted. (A) CT demonstrating destruction of right lobe architecture and hyperinflation, (B) Coregistration with V/Q SPECT, and (C) analysis demonstrating reduced contribution of right upper lobe to function. These data helped to confirm the right upper lobe as a target for LVRS.

ideal patients for LVRS procedure, and V/Q imaging helps to target the location for LVRS by quantifying function (Fig. 11). The method is now fully validated and tested for interobserver variability and user confidence.

Recently, Provost et al also reported excellent reproducibility of lobar perfusion and ventilation quantification using SPECT/CT segmentation software in lung cancer patients using [^{99m}Tc]Technegas.[22]

More work needs to be focused on reducing the duration of imaging to improve patient compliance, especially in COPD patients who are often breathless. With further technical advances, it should be possible to bring the imaging time and processing time to less than 10 minutes each. With growing reporter confidence, planar imaging is no longer performed in our institution, unless the patient is unable to lie supine or severely claustrophobic.

Conclusion

V/Q SPECT/CT is a reliable and robust technique in preoperative assessment of lobar function in patients with COPD and lung cancer. The new SPECT/CT method has improved structure-function information to help define target areas for LVRS and resection margins in lung cancer.

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