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Review article

Ventilation perfusion pulmonary scintigraphy in the evaluation of pre-and post-lung transplant patients

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ABSTRACT

Lung transplantation is an established treatment for patients with a variety of advanced lung diseases. Imaging studies play a valuable role not only in evaluation of patients prior to lung transplantation, but also in the follow up of patients after transplantation for detection of complications. After lung transplantation, complications can occur as a result of surgical procedure, pulmonary embolism and ultimately chronic lung allograft dysfunction. Lung scintigraphy, which includes physiologic assessment of lung ventilation and perfusion by imaging, has become an important procedure in the evaluation of these patients, assuming a complementary role to high resolution anatomic imaging (computed tomography [CT]), as well as spirometry.

The purpose of this atlas article is to demonstrate the uses of ventilation perfusion scintigraphy in the pre-transplantation setting for surgical planning and in the evaluation of complications post-lung transplantation based upon experience at our institution.

Contents

1. Introduction

The number of lung transplant procedures for advanced lung disease has steadily increased over the last three decades, with >55,000 lung transplants performed worldwide, with a median survival of 6 years [1]. Lung transplant is performed in patients with advanced lung disease, namely, obstructive (such as chronic obstructive lung disease), restrictive (such as interstitial lung disease), vascular (such as pulmonary hypertension) and suppurative (such as cystic fibrosis). With the increase in the number of lung transplants being performed, the transplant evaluation techniques have continued to evolve for potential transplant recipients and novel modalities or indications for existing technologies have been developed. Further, patients need continued monitoring and assessment after lung transplant, as the allograft function can be affected by a variety of complications, which limit longevity [2]. High resolution computed tomography (HRCT), spirometry and ventilation perfusion (V/Q) scintigraphy are mainstays of such evaluations, with HRCT demonstrating anatomical alterations in lung allografts as well as air trapping on expiratory images [3], while spirometry offers physiologic information with regard to the type of ventilatory abnormality, such as airway obstruction or restriction, either of which may indicate allograft dysfunction [4]. However, anatomic evaluation of the transplanted lungs using CT may have limited sensitivity for detection of early signs of allograft dysfunction [5]. Alternatively, functional evaluation using spirometry is not specific, as a variety of

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extra-pulmonary causes can affect it, such as physical deconditioning, which makes the interpretation challenging especially among patients with single-lung transplant [6]. Since V/Q scintigraphy can demonstrate early changes in lung perfusion and ventilation, there has been an increase in appreciation of their value in the evaluation of lung transplants in recent times [7].

Ventilation and perfusion scintigraphy is most commonly associated with evaluation for pulmonary embolism (PE) and is used widely for this purpose [8–10]. The use of V/Q scintigraphy for specific applications related to lung transplant (other than PE), although not widespread, has gained more importance lately. It is therefore important to recognize that useful information, beyond the presence of ventilation and perfusion mismatches indicative of PE, can be gleaned from these scans.

The purpose of this article is to describe and show examples of how V/Q scintigraphy can be used for pre lung transplant planning and for post lung transplant evaluation, not only for the detection of complications but also as a surveillance tool to detect early subclinical signs of allograft dysfunction. Clinical material is drawn from our institution which is a major lung transplant center.

2. Ventilation perfusion lung scintigraphy technique

At our institution, ventilation scans are performed with Xenon-133 gas (Xe-133) (10–20 mCi, 370–740 MBq via inhalation). Images are acquired with the patient in a supine position, in both posterior oblique projections during single initial breathing, equilibrium (normal breath for 3 min) and washout. These images allow for demonstration of ventilation defects as well and retention on the washout images, which are indicative of air trapping.

Ventilation images are followed by a perfusion scan performed with Tc-99 m macro-aggregated albumin (MAA) (5 mCi, 185 MBq intravenous). Perfusion scans are performed in anterior, posterior, lateral and anterior and posterior oblique projections. For all patients in the pre or post lung transplant setting, quantification of perfusion is performed

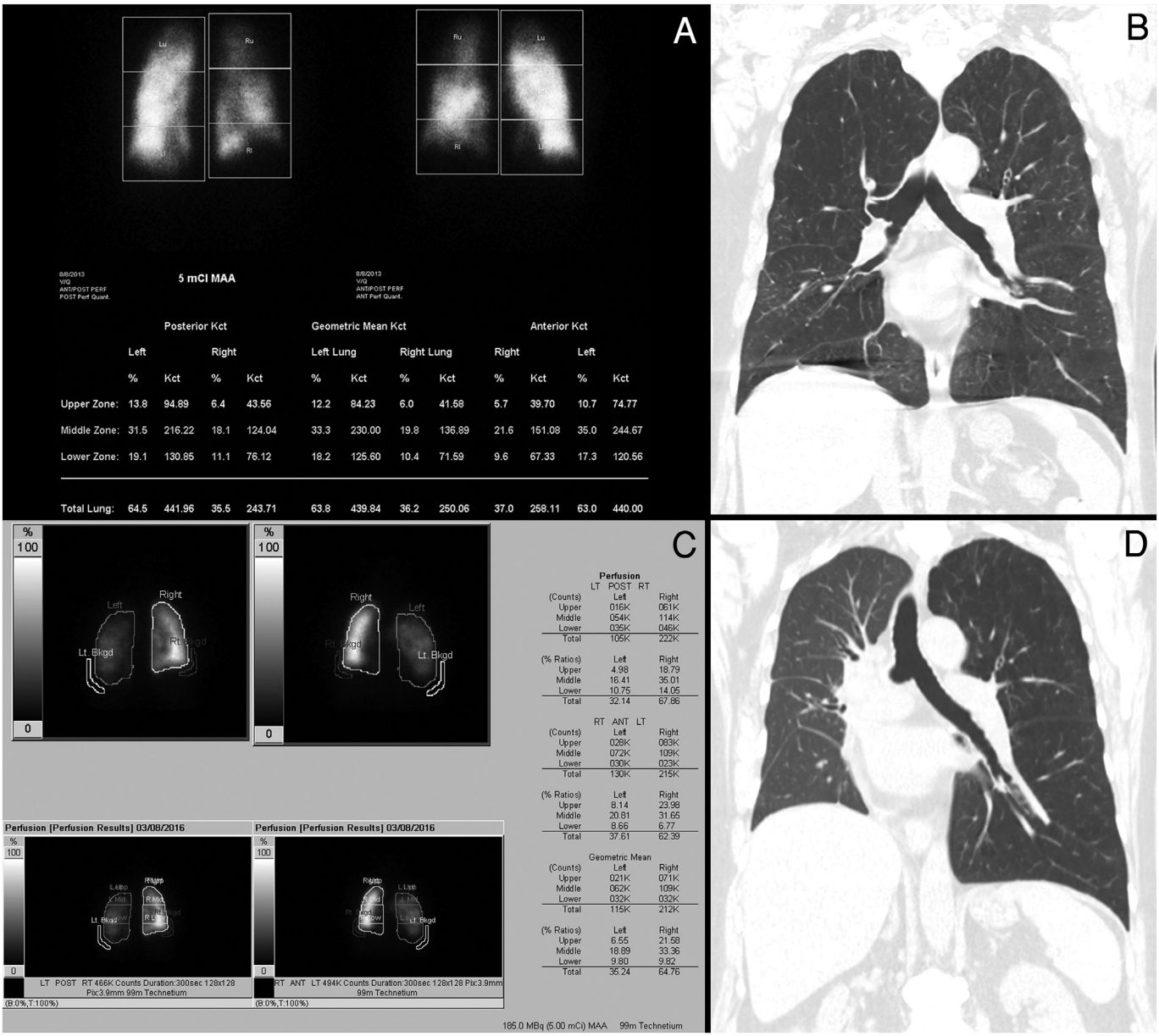


Fig. 1. 59 y/o female with chronic obstructive pulmonary disease. (A) Pretransplant quantitative perfusion lung scintigraphy showed decreased perfusion to the right lung (36.2%) compared to the left (63.8%), which prompted a single right lung transplantation. (B) Pretransplantation coronal CT image shows severe bilateral emphysema. (C) Post transplantation quantitative perfusion lung scintigraphy shows increased perfusion to the transplanted right lung, compared to the left, as expected. (D) Post transplantation coronal CT image shows a normal transplanted right lung and persistent diffuse hyperinflation and emphysema of the left lung.

in the anterior and posterior projections, using the geometric mean, by an automated software. Additionally, in patients with pulmonary arterial hypertension (PAH), images over the brain and kidneys are obtained to assess for right to left shunt [11].

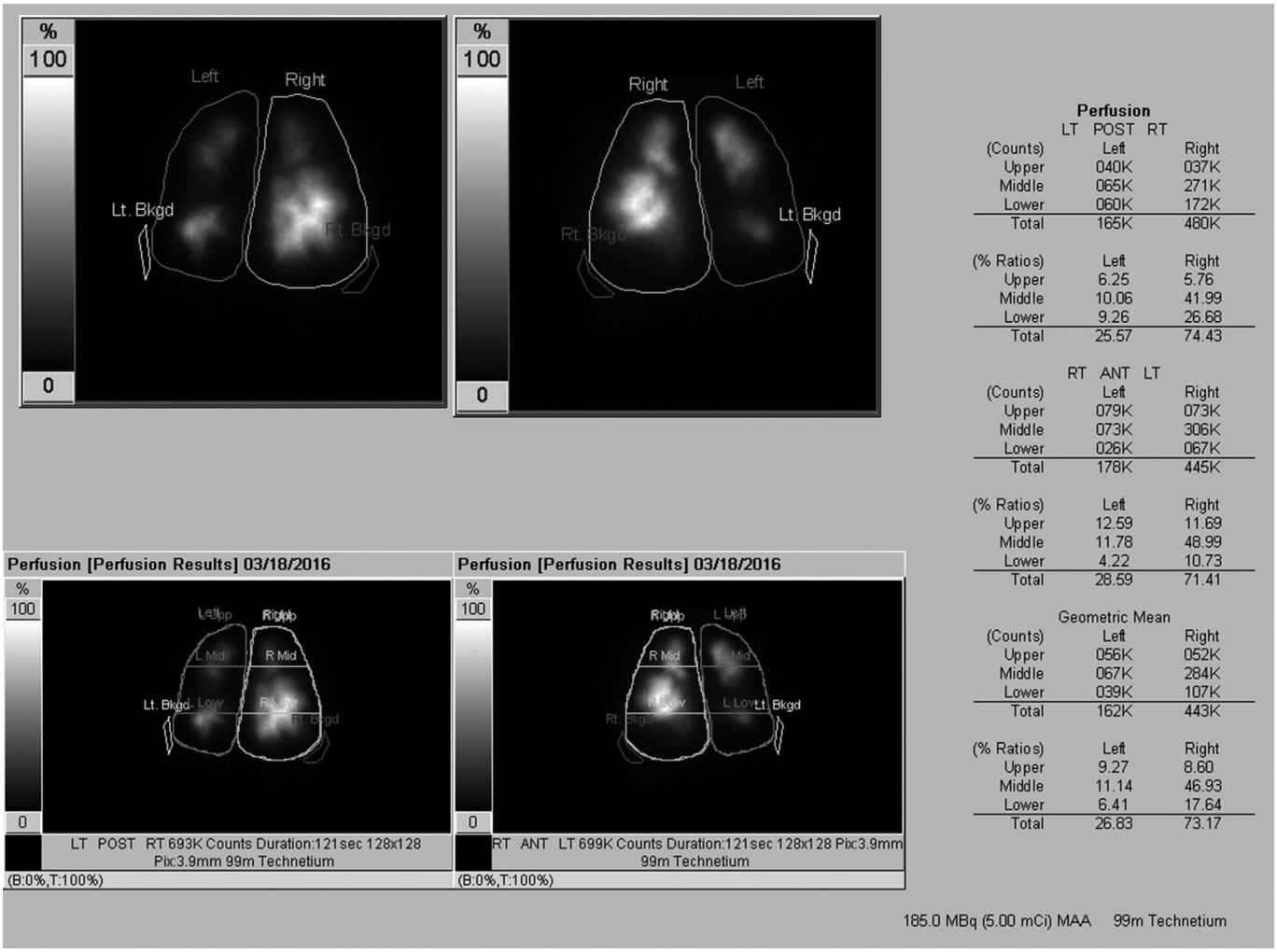
3. Role of V/Q Scintigraphy in the Pre -Transplant Patient

In the pre-transplant setting, the main value of V/Q scintigraphy is to provide quantitative analysis of perfusion and to detect the more dysfunctional lung, to guide the surgical planning. In cases of single-lung transplant, the more dysfunctional lung should be the one transplanted. In cases of bilateral lung transplant, it will help determine which lung should be the one to be transplanted first (the more dysfunctional), in order to avoid cardiac bypass during the lung transplant procedure (Fig. 1).

Single lung transplants (SLT) may be considered in cases of pulmonary fibrosis and COPD. A recent large retrospective study showed that since implementation of a medical need-based lung allocation system, there was no survival difference at 5 years between SLT and bilateral lung transplant (BLT) in patients with COPD. However, patients with pulmonary fibrosis showed better graft survival with BLT than SLT in this same study [12]. SLT is favored in patients older than 70 years of age and those with comorbidities, such as significant coronary artery disease, where right SLT may be performed to avoid cardiac manipulation that is required during implantation of left lung. Right SLT is also preferred among patients with significant emphysema as it is associated with lower risk of post- operative complication of hyperinflation of the native lung. SLT may also be performed when there is history of previous pulmonary surgery or significant pleural space abnormalities [14,15].

In the case of suppurative conditions such as cystic fibrosis and bronchiectasis, as well as pulmonary hypertension, bilateral lung transplant (BLT) tends to be the procedure of choice. It may be associated with longer post-transplant survival as compared to SLT in general [16]. Among patients with cystic fibrosis, Stanchina et al. in a 2002 study (17) concluded that a pre transplant differential lung perfusion (difference of percentage perfusion between the right and the left lung) >31% may be predictive of poorer prognosis in patients while on lung transplant waiting list, while ventilation differential abnormalities were not predictive of poor outcome(Fig. 2) [17]. However, interpretation of these findings should be taken with care, given that the management of patients with cystic fibrosis has improved greatly in the last years.

Due to the presence of anatomic changes related to chronic lung disease, the majority of V/Q scans performed in the pre transplant setting will show marked perfusion changes. This may be a problem if radiologists, who are unfamiliar with the findings of V/Q scintigraphy among patients with advanced lung disease in the lung transplant setting, misinterpret the studies as high probability scans for pulmonary embolism rather than chronic changes. This is one of the reasons why ventilation scans are always acquired in the pre-transplant patients in our



Perfusion

LT POST RT

(Counts)	Left	Right
Upper	040K	037K
Middle	065K	271K
Lower	060K	172K
Total	165K	480K

(% Ratios)	Left	Right
Upper	6.25	5.76
Middle	10.06	41.99
Lower	9.26	26.68
Total	25.57	74.43

RT ANT LT

(Counts)	Left	Right
Upper	079K	073K
Middle	073K	306K
Lower	026K	067K
Total	178K	445K

(% Ratios)	Left	Right
Upper	12.59	11.69
Middle	11.78	48.99
Lower	4.22	10.73
Total	28.59	71.41

Geometric Mean

(Counts)	Left	Right
Upper	056K	052K
Middle	067K	284K
Lower	039K	107K
Total	162K	443K

(% Ratios)	Left	Right
Upper	9.27	8.60
Middle	11.14	46.93
Lower	6.41	17.64
Total	26.83	73.17

Fig. 2. 33 y/o female with cystic fibrosis being considered for lung transplant. Lung scintigraphy shows bilateral reduction of perfusion to the left lung and to the upper right lung. The differential perfusion is 27% to the left lung and 73% to the right lung. These large differential perfusion has been shown to correlate with increased risk of death of these patients while on the transplant list.

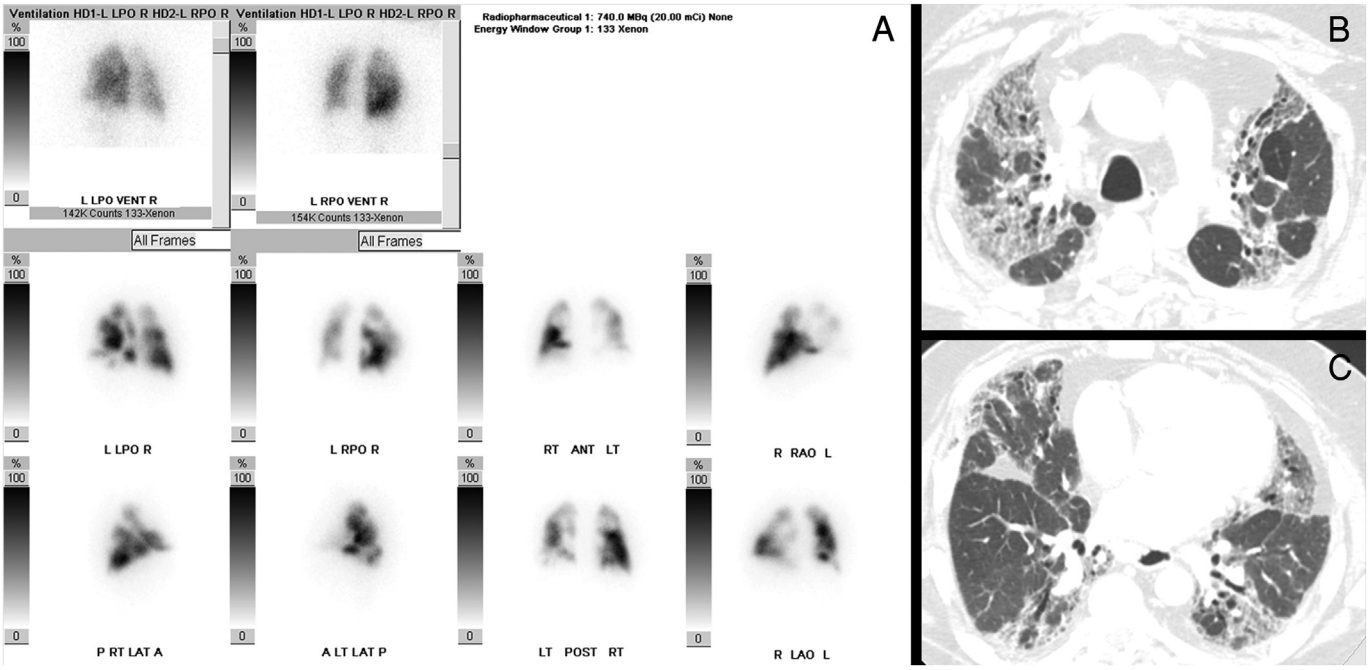


Fig. 3. 51 y/o female with interstitial disease, with a pre-transplant lung scintigraphy(A) showing heterogeneous ventilation (upper row) and heterogeneous perfusion (two bottom rows), with multiple perfusions defects matched with the ventilation and/ interstitial abnormalities seen on axial images from the CT of the chest performed concurrently (B and C).

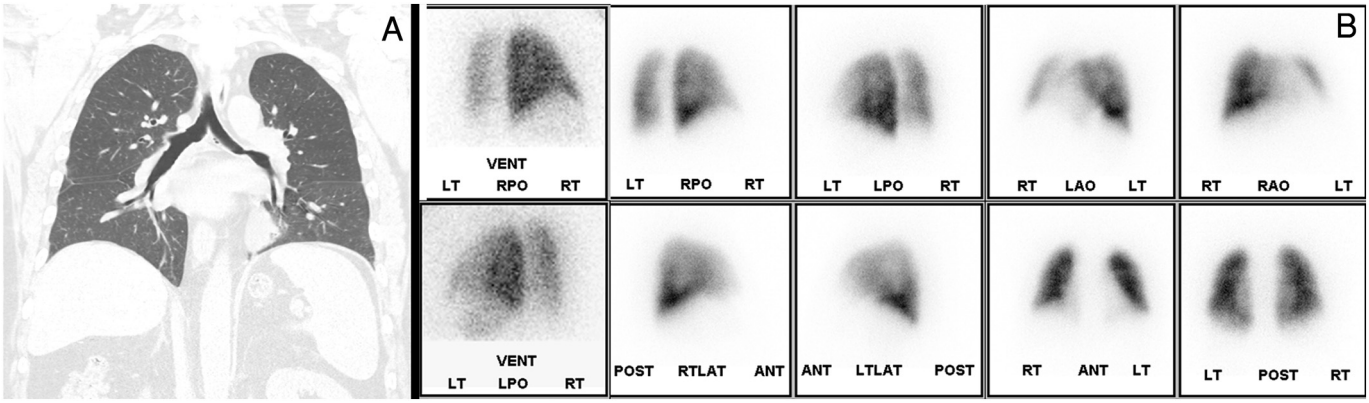


Fig. 4. 49 y/o male status post bilateral lung transplant underwent a follow up CT of the chest (A), that showed anastomotic narrowing of the left mainstem bronchus (arrow). Lung scintigraphy (B) was performed to evaluate the functional impact of such stenosis, and demonstrated normal ventilation (first column) and perfusion (other columns) with symmetric ventilation and perfusion for both lungs. This patient has been followed up for >3 years, without symptoms related to the stenosis.

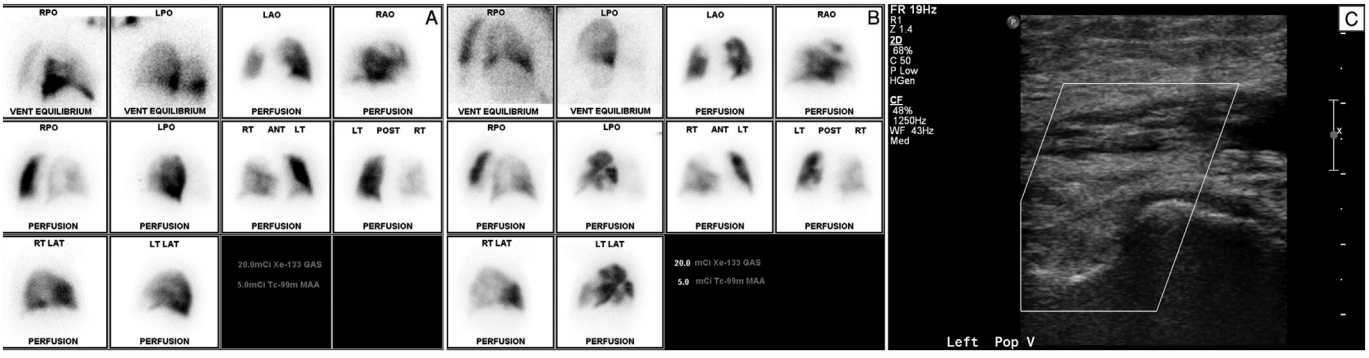


Fig. 5. 69 y/o male underwent single left lung transplant for COPD. Post transplant lung scintigraphy 11 months after transplant (A) shows heterogeneous and reduced ventilation and perfusion to the native right lung. The perfusion and ventilation to the left transplanted lung is slightly heterogeneous, with no segmental or subsegmental defects. Patient had another lung scintigraphy performed a month after the first study (B), due to shortness of breath. The study shows grossly unchanged findings in the native right lung and multiple new areas of unmatched segmental defects in the left lung, including the anterior segment of the left upper lobe, superior segment of the left lower lobe and some basal segments of the left lower lobe, consistent with a high probability scan for pulmonary embolism. A doppler ultrasound of the lower extremities (C) showed left deep venous system thrombosis.

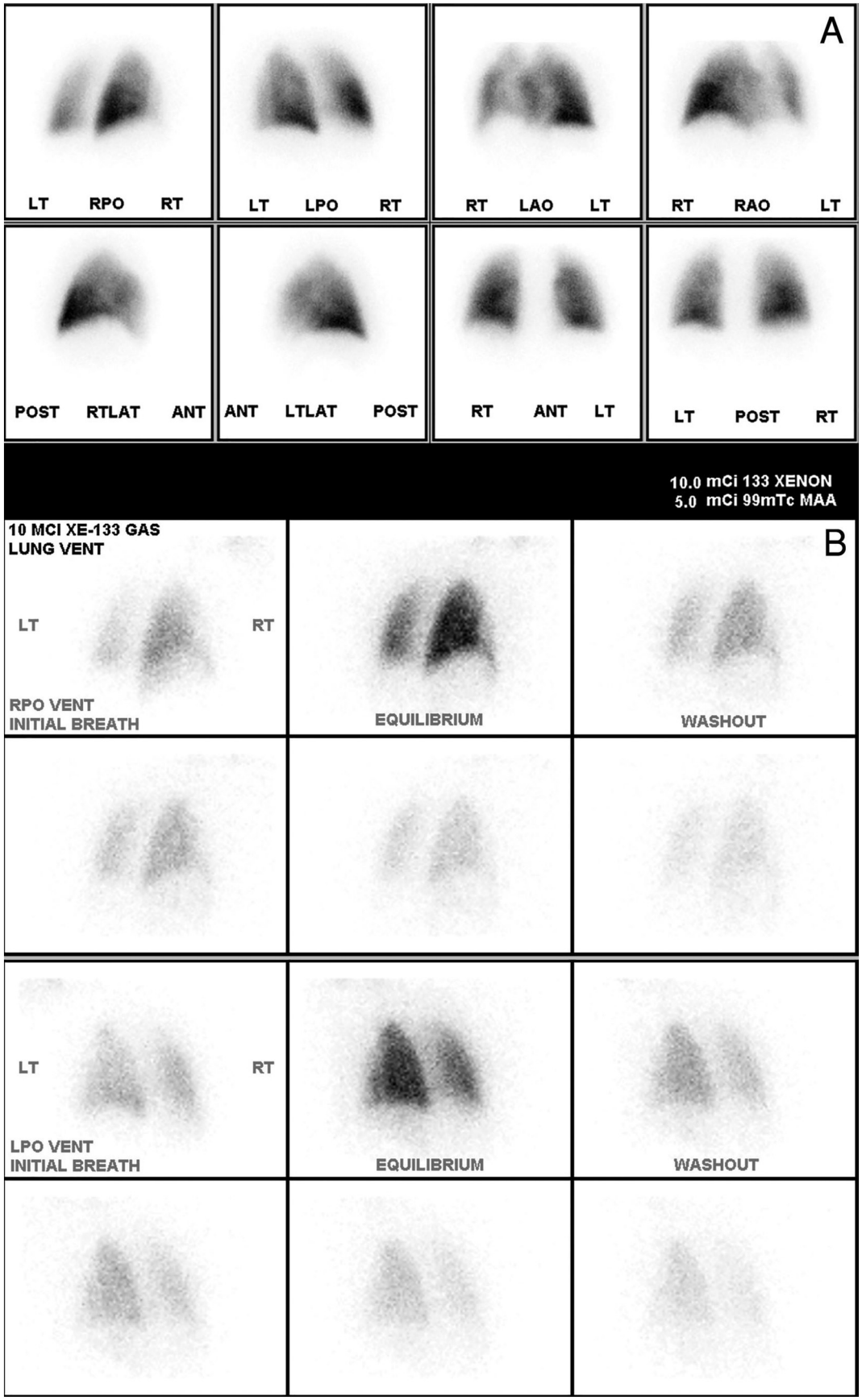


Fig. 6. 67 y/o male status post bilateral lung transplant for interstitial disease, had a routine ventilation perfusion scan at 1 year post transplant. Patient had normal concurrent CT of the chest (not shown) and a normal perfusion on lung scintigraphy (A). There was marked air trapping on ventilation images (B), which has been gaining importance in the early evaluation of air trapping in post transplant patients.

institution, in addition to the perfusion images. The ventilation images help classify the perfusion defects as matching abnormalities, decreasing the suspicion for pulmonary embolism, which are classically suspect when there are unmatched segmental defects (Fig. 3).

4. Role of V/Q scintigraphy in the post-transplant patient

There are multiple complications which can occur after lung transplant, which are broadly categorized into early and late complications. Some of the complications such as infections and pulmonary embolism can occur virtually any time in the post lung transplant period. The early complications that occur exclusively within few weeks after lung transplant include ischemia reperfusion injury or primary graft dysfunction and acute rejection. Anastomotic complications are more commonly seen in the early post-surgical period, but can occur any time point post-transplant. Chronic lung allograft dysfunction (CLAD) is a key post-transplant complication that limits long-term survival.

High resolution chest CT is critical for early detection, evaluation and follow up of patients in the post-transplant period and have an established role in diagnosis of some complications [18–27]. However, as a surrogate for lung perfusion and ventilation, V/Q scintigraphy can potentially detect functional changes that may manifest before anatomic changes, although literature is sparse in this topic.

Bronchial stenosis is the most common airway complication after lung transplant, with an incidence of 4 to 24%, typically occurring within 2 to 9 months of transplantation [28–30]. The bronchial stenosis is likely caused by a combination of mucosal ischemic necrosis, infection and dehiscence [31,32]. A large series showed that the most common site of bronchial stenosis requiring dilation was the bronchus intermedius (31%), followed by the right (20%) and left (22%) mainstem bronchus

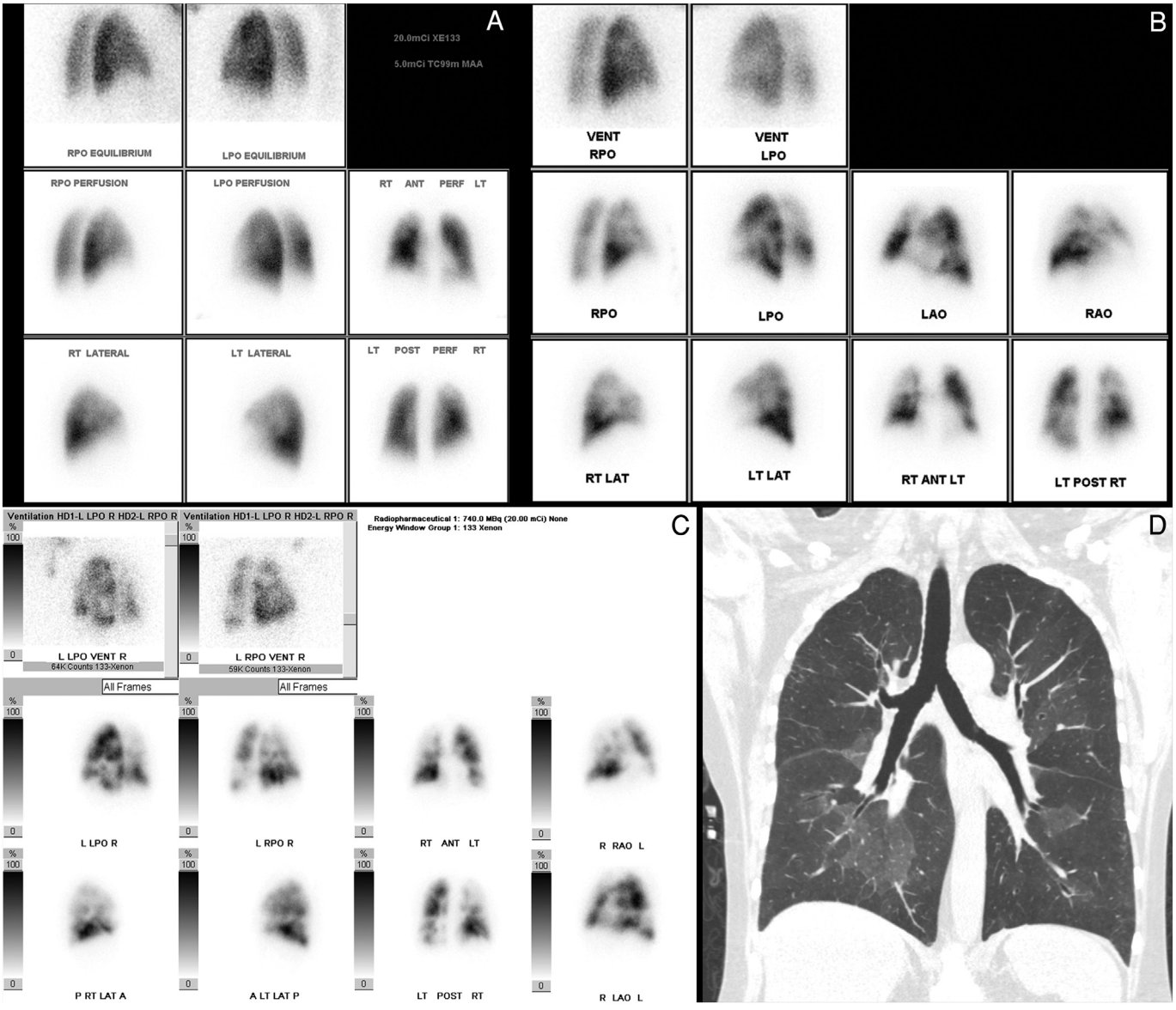


Fig. 7. 37 y/o female status post bilateral lung transplant for cystic fibrosis. (A) Lung scintigraphy 4 years after transplant shows normal ventilation and normal perfusion. (B) Lung scintigraphy 2 years after first study shows progression to a more heterogeneous perfusion, however with no evidence for segmental perfusion defects to suggest pulmonary embolism. (C) Lung scintigraphy 1 year later again shows progressive non-segmental heterogeneous perfusion predominantly matched to the ventilation findings. (D) CT of the chest performed at the same time of study (C) showed peribronchovascular ground glass opacities and no pulmonary embolism. Biopsy showed severe bronchiolitis obliterans / chronic rejection.

[33]. The gold standard for diagnosis and treatment (with balloon bronchoplasty) is broncoscopy, but CT is usually the initial study to detect stenosis based on a diameter < 8 mm and findings of post obstructive pneumonia in a symptomatic patient [31]. Although not an established indication per published literature, V/Q scintigraphy can be performed in patients with anatomic stenosis without complications or symptoms to reassure that no functional impact on ventilation is present, favoring a conservative follow up without intervention, as shown on Fig. 4.

Patients with lung transplants are at increased risk of venous thromboembolism (VTE), which includes pulmonary embolism and deep vein thrombosis. It may occur at any stage after transplant, but most frequently in the first 4 months after surgery. Either preexisting conditions or transplant-related causes can be the causative factor for thromboembolic events. Deep vein thrombosis occurs in 9–64% [34–39] and pulmonary embolism occurs in 1.7–15.3% [34–41] of the lung transplant patients. Cardiopulmonary bypass [37], older age, diabetes, pneumonia, hypercoagulable states [36], sirolimus therapy post lung transplant [34], prior history of DVT, days in intensive care and use of extracorporeal membrane oxygenation [42] have been described as a significant predictors for venous thromboembolic events. Most recently, VTE was shown to be independently associated with worse survival. Although PE can be detected with CT angiography, it cannot be obtained among patients with contraindications to iodine contrast and patients with poor renal function, which is a common comorbidity among lung transplant patients due to calcineurin inhibitor use. In such situations, V/Q scintigraphy may be used in its more familiar role for detection of PE (Fig. 5).

Chronic lung allograft dysfunction (CLAD) is a clinico-pathologic syndrome often associated with histological development of bronchiolitis obliterans (BO) and was until recently thought to be the only cause of CLAD. New research has demonstrated several subtypes of CLAD, of which obstructive CLAD (previously referred to as bronchiolitis obliterans syndrome, a surrogate for BO) is one of the major ones [43,44]. Obstructive CLAD is defined as a > 20% persistent decline in lung functions with an obstructive ventilatory defect from the best post-transplant measurement [45,46]. Accurate imaging diagnosis of BO can be challenging with HCRT as mosaic pattern and hyperinflation have low sensitivity for diagnosis of BO. Air trapping is an important variable reflecting small airway disease seen with BO, but can only be assessed reliably with inspiratory / expiratory CT [43] or alternatively on Xe-133 ventilation scintigraphy. Lung volume assessment via body plethysmography or helium dilution method is used for the detection of air trapping but can be of limited utility in SLT in presence of COPD native lung. Similarly, the fluctuating contribution of the native lung among SLT patients can make the spirometry based definition of CLAD unreliable. Previous studies have shown that the perfusion component of the V/Q scintigraphy can aid in assessing the functional contribution of the native lung and can, therefore, be used to correct the FEV1 measurements [47]. In addition the early development of Xe-133 retention in lungs, an indication of air trapping (Fig. 6), can have prognostic value in subsequent development of BO which in late stages can demonstrate both ventilation and perfusion abnormalities (Fig. 7).

5. Conclusion

Ventilation perfusion lung scintigraphy is an important imaging modality in assessing patients prior to lung transplant and for following patients post lung transplant. It is important for individuals interpreting V/Qs in the setting of lung transplant to understand the manifestations of V/Q patterns in the various end stage lung diseases, which may differ from each other, as well as from the patterns more familiarly associated with PE. It is also important that an erroneous diagnosis of PE not be made in patients with findings that are due to the onset of CLAD. There is increasing recognition that the development of air trapping in post- transplant V/Q scans, even in the presence of normal lung perfusion, may indicate early stage BO and may have prognostic significance for overall allograft survival.

Conflict of interest

The authors have no conflicts of interest.

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