Ventilation/perfusion lung scintigraphy. Multiple applications besides pulmonary embolism [(*)]

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Abstract

Ventilation/perfusion scintigraphy is the diagnostic tool of choice for detection and monitoring of pulmonary embolism. However, the knowledge on its value for other or concurrent pathologies is poor. In this review scintigraphic characteristics of the main pathologies, interpretation and artefacts are described. Together with the understanding of pathophysiology of the lung, the potential gain of information derived from ventilation/perfusion scintigraphy is much higher than generally believed. *In conclusion*, ventilation/perfusion scintigraphy not only in PE but also in other lung diseases is underused, its value and clinical potential underestimated.

Introduction

Radionuclide lung imaging studies two essential functions: lung perfusion and ventilation. Lung scintigraphy most commonly involves the demonstration of pulmonary perfusion employing usually a limited capillary blockade through injected radioactive particles as well as the evaluation of ventilation (gas exchange) using inhaled inert gas or aerosols. The information gained from these studies may be used to diagnose and determine treatment of lung diseases. While radionuclide lung studies are essentially qualitative, they have an advantage over most quantitative tests of global lung function in distinguishing between diffuse and regional lung disease with the option of loco-regional semi quantitation.

Ventilation/perfusion scintigraphy is the diagnostic tool of choice for the detection and follow-up of pulmonary embolism (PE). The display of regional airway and vascular integrity forms the basis for the scintigraphic diagnosis of this entity which has been for long the major clinical indication for lung scintigraphic studies [1, 2]. Lung scintigraphy has advantages as compared to spiral computed tomography (CT), in particular pertaining to the detection of more peripheral and smaller pulmonary emboli and lower radiation dose [3-5]. During ventilation/perfusion scintigraphy for the diagnosis of PE, hints for other pathologies such as chronic obstructive pulmonary disease (COPD), pneumonia and left heart failure, among others may be discovered incidentally. Commonly, abnormalities in ventilation cause redistribution of pulmonary perfusion. Hypoventilation leads to regional hypoxia and reflex redistribution of perfusion away from the hypoventilated regions [6, 7]. It should be stressed, that a routine chest x-ray of the patient in two planes should be available at the time of scintigraphy in order to define or exclude infiltrations, pleural effusion, pneumothorax or place–occupying lesions within the chest. Furthermore, a simple lung function test (spirometry with forced ventilatory parameters), whenever possible, should be added.

While guidelines extensively describe the indication of lung scintigraphy for PE, the information about the value of this method in other pathologies of the lung until now is quite limited.

Radiopharmaceuticals

The two most common agents used for lung perfusion are macroaggregated albumin (MAA) and human albumin microspheres (HAM) which localize by the mechanism of capillary blockade. The intravenous injection should be while the patient is lying in the supine or close-to supine position [2, 6]. Perfusion scintigraphy has a low rate of artefacts. However, particle aggregation induced by drawing blood into the syringe containing the radiopharmaceutical or incomplete resuspension of particle aggregates may mimic a positive finding on perfusion scintigraphy [2, 6, 7].

For ventilation studies, the inert gas [81m]Kr and the aerosols ^{99m}Tc-diethylenetriaminepentaacetate (DTPA) and an ultrafine dispersion of ^{99m}Tc-labeled carbon (Technegas;

Cyclomedica Ltd., Salzgitter, Germany) are currently recommended [1, 8]. [81m]Kr is of limited use because of its high cost and short half-life. Previously, ^{133}Xe was also used for ventilation studies, but this is no longer recommended according to the guidelines of the European Association of Nuclear Medicine [1].

Patient position

Gravidity and patient position may have a significant impact on both ventilation and perfusion. However, the alteration of blood flow throughout the lungs with positional change is much more marked than accompanying changes in ventilation; this can result in a mismatched ventilation/perfusion pattern. In the upright patient, both ventilation and perfusion increase progressively from the lung apex to bases, although this gradient is more pronounced for perfusion, which results in a ventilation/perfusion ratio in the apex of about 0.5 and at the base of about 2.0. In the supine position, both ventilation and perfusion gradients are less pronounced, resulting in more ventilation and perfusion throughout the lungs; perfusion becomes more uniform, but there is still a relative increase in blood flow in the dependent portions of the lung. In patients who demonstrate more blood flow to the upper lobes, pulmonary hypertension, congestive failure, or increased left atrial pressure should be suspected [6, 7]. Basal emphysema due to alpha-1-antitrypsin deficiency would also show this redistribution of relative bloodflow towards the apex, even in the absence of pulmonary hypertension.

Chronic obstructive pulmonary disease (COPD)

This term encompasses nowadays several phenotypes relative to prevailing symptoms and findings like dyspnoea, mucus production, frequent exacerbations, rapid decline of lung function and rate as well as regions developing emphysema.

Patients with a chronic bronchitic phenotype may temporarily show ventilation defects due to mucous plugging of bronchi. They suffer from >1 acute exacerbations/year, where ventilation and accompanying perfusion abnormalities in ventilation/perfusion scintigraphy are common [7]. These abnormalities usually affect both lungs.

In patients with a phenotype defined by predominant emphysema with loss of respiratory bronchioles ventilation scintigraphy is sensitive to even early changes, when "slow paces" delayed washout of inhaled xenon or "hot spots" (accumulation of the tracer at the branching site of airways) is encountered. It is an additional, though not official tool for the characterization as to mild, moderate and severe COPD, according to the international GOLD-classification. Although there is no strict correlation between hot spots with the clinical stage, a correlation between ventilation abnormality and pulmonary function, in particular using aerosol ventilation, has been claimed. In earlier stages, usually the aerosol exhibits enhanced central deposition with normal peripheral ventilation, while in more severe stages areas of little or even absent aerosol transportation to the periphery of the lung are seen [1, 2, 6-8].

In patients with early or mild COPD, the perfusion scan may be normal or near normal. However, as the destruction of lung parenchyma progresses, it characteristically produces multiple nonsegmental perfusion defects, which may be relatively focal and discrete or diffusely scattered throughout the lungs. Perfusion defects may also be caused by regional hypoxia producing reflex vasoconstriction and by bullae themselves or their compression of adjacent lung (Table 1). Large apical bullae may render reduced or absent perfusion to the upper lung zones [6, 7]. COPD is thus characterized by matched ventilation and perfusion defects. A phenomenon named "reverse mis-match" is encountered when perfusion exceeds in the same area ventilation (low ventilation/perfusion-ratio) [9, 10].

In acute bronchial constriction (asthma, acute exacerbation of COPD), bronchodilator therapy before lung scintigraphy may decrease ventilatory defects and thereby improve the accuracy of the study. Perfusion defects are often reversed

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Table 1. *Diagnostic data from defects in lung ventilation perfusion scintigraphy*

Pulmonary embolism – with preserved ventilation:	mismatch +++
Pneumonia – with ventilation defect:	match +
Granulomatous disease affecting vessels (pulmonary sarcoidosis, tuberculosis):	(-)
Localized hypoxia due to asthma, bronchitis or emphysema:	match +++
Bronchial plugging:	match +++, cave reversed mis-match!
Bulla or cyst:	match +
Atelectasis:	(-)
Lung resection:	(-)
Pleural effusion:	match +, reversed mis-match?
Lung fibrosis (postinflammatory, postradiation, pleural tickening):	match +
Vascular compression (by tumor, metastases, hilar adenopathy, fibrosing mediastinitis	mismatch +++
Lymphangitis carcinomatosa	(-)
Pulmonary edema	(-)
Pulmonary artery atresia or hypoplasia	mismatch +
Vasculitis:	mismatch +

+++: diagnostic, +: helpful, (-): better incidental finding

as acute obstruction resolves [2]; therefore, the patients´ findings are less biased when bronchospasm has resolved. However, another confounding effect in this setting is hyperperfused areas (low ventilation/perfusion-ratio) due to the circulatory stimulus of the beta-adrenergic bronchodilator, which also can be responsible for a reversed mismatch.

It is important to consider that PE is quite frequent in COPD. In spite of the presence of clinical symptoms, the chest x-rays are often negative, and excluding the presence of superimposed PE may be difficult [7]. On the contrary, in patients referred under the suspected diagnosis of PE, ventilation/perfusion scintigraphy is sensitive in discovering co-existing COPD, while areas with preserved ventilation (high ventilation/perfusion-ratio, classical mis-match) strengthen the suspicion of PE and might give rise to further investigations (CT-angiogram), if justified by at least an intermediate clinical suspicion of PE.

Emphysema

Ventilation imaging is most helpful in characterizing the regional distribution of abnormalities and to a lesser extent in delineating the clinical severity.

Emphysema is likely if in the perfusion scan all the defects are small, subsegmental, and have matched ventilation defects. However, widely differing patterns of regional ventilation are seen, ranging from predominantly upper lobe involvement (smokers) and predominantly lower lobe disease (emphysema in alpha-1-antitrypsin deficiency) to diffuse involvement [7, 11, 12]. Besides CT, perfusion scans help in the assessment of the type of regional involvement, which is crucial for the indication of procedures for reducing lung volume by surgery [13] or bronchial interventions causing atelectasis [14].

[133]Xenon has been found useful for the assessment of interaction between intra-bullous and surrounding lung ventilation which is difficult to judge by CT. Occasionally, in patients with emphysema particles may be trapped by the bullae ("slow spaces"), an image which might be misinterpreted as "normally ventilated" [11, 12].

Bronchiectasis and cystic fibrosis

Patients with bronchiectasis show perfusion defects that are constant in location and generally restricted to the lung bases; they are mainly related to reflex vasoconstriction secondary to local hypoxia [7].

A less common form of COPD, cystic fibrosis, with its onset in early childhood is characterized by regionally irregular ventilation and perfusion, with patchy nonsegmental defects in perfusion and markedly disturbed ventilation. In general, both lungs are affected to a similar, though rarely identical, degree. Usually, the upper parts of the lung are more severely involved, the involvement mostly being not symmetrical. The prominent delineation of the interlobar fissures, often called the "fissure sign", is seen frequently in this disease. The extent of scintigraphic abormalities is related to the severity of the disease. As differentiation from other clinical problems such as asthma is not possible, lung scintigraphy plays no role in either diagnosis or monitoring [6, 7, 15].

Airway inflammation plays a critical role in progression of cystic fibrosis and the destruction of parenchyma. Enhanced ^{18}F-fluorodeoxyglucose ([18]FDG) accumulation in inflammatory foci, cleared after antibiotic therapy, has been reported. Calculating of the [18]FDG influx rate has been claimed to be useful as a quantitative measure of the inflammatory burden [16]. Radiolabelling of white blood cells with ^{111}In-oxine or ^{99m}Tc-HMPAO for imaging inflammation is of poor diagnostic value in the lung.

Alpha-1-antitrypsin deficiency

As mentioned above, this condition carries an autosomal recessive inherited risk for the development of premature emphysema with predominant abnormalities of ventilation and perfusion in the lower lungs [9, 17]. This pattern is a clear contraindication against volume reduction surgery, because the remaining upper lobes would be too small to expand into the empty space. As a consequence, these patients represent a large fraction of all lung transplantations in COPD.

Bronchial asthma

Acute bronchospasm may cause segmental perfusion defects resolving on treatment, whereby the ensuing decrease of perfusion might mimic PE. Therefore, bronchospasm should be excluded (remember the advantage of a spirogram prior to the examination!). Otherwise, in presence of perfusion defects an additional ventilation study is mandatory. Often, during episodes of asthma the defects in ventilation are local and more severe than the accompanying perfusion defects (reverse mis-match) [7, 9].

Some asthmatic patients show normal ventilation and perfusion between attacks, but others, mainly with a long history and/or COPD, even when asymptomatic, may continue to show matching defects of ventilation and perfusion. In patients with unstable bronchoconstriction the topographic location of these scintigraphic abnormalities changes during the same or subsequent attacks, giving an altered pattern of ventilation/perfusion abnormalities [7, 18]. This provides a scintigraphic distinction from chronic parenchymal damage (emphysema), which results in a fixed location of the abnormalities. Monitoring 45 asthmatic children before and 4 weeks after corticosteroid treatment with semiquantitative ventilation scintigraphy revealed an excellent correlation to clinical symptoms, better than the one to peak expiratory flow [19].

Bronchial obliteration

The defects in ventilation and perfusion due to bronchial obstruction (often caused by a foreign body, mucus plug or a tumor) correspond to the anatomic distribution of the involved segment or lobe. Complete lobar obstruction is usually followed by atelectasis, with absent ventilation and markedly diminished perfusion [7, 20].

Depending on the nature of a foreign body or tumor, it may either cause a ventilation defect by mechanical plugging or, in case of biologically irritating material, a chemical reaction, resulting in localized inflammation. The ventilation is often more affected than the perfusion.

Bronchoscopic removal of the obstructing material is followed by return of ventilation and perfusion within several days. It should be pointed out, however, that there are cases with preserved collateral ventilation preventing atelectasis. Then the perfusion defect does not match the x-rays, mimicking PE [21].

Sarcoidosis

[67]Gallium scintigraphy has been used since long for diagnosis and staging of sarcoidosis. Diffuse as well as focal radionuclide uptake has been reported in this entity. However,

^{18}F-FDG positron emission tomography (PET), which is useful in assessing inflammatory activity in sarcoidosis, seems to be more suitable for evaluating the mediastinum and mediastinal lymph nodes as well as posterior regions of the lung and non-thoracic lesions [22]. ^{18}F-FDG PET/CT allows to obtain complete morphofunctional cartography of inflammatory active localizations and to follow treatment efficacy in patients with sarcoidosis, particularly in atypical, complex, and multisystemic forms [23]. Similar findings have been obtained using cationic tracers

Infectious diseases of the lungs

Viral and other infections of the respiratory tract may result in the production of more mucus, inflammation and secondary infection of the bronchial walls, and sometimes bronchospasm, which leads to abnormalities of regional ventilation.

Lung scans in patients with pulmonary tuberculosis commonly show absent ventilation with significantly reduced perfusion in the affected parts; its extent usually exceeds the one seen in chest x-rays [7]. PET scans using ^{18}F-FDG or ^{11}C-choline can sometimes help to differentiate tuberculous granuloma from lung malignancy [24].

Pneumonia is characterized by matched ventilation/perfusion defects. However, the ventilation defects are usually larger than the perfusion defects [6, 7]. Furthermore, ventilation and perfusion abnormalities often persist for some time after an infiltrate has resolved on the chest radiograph, when hyperemia of inflammation resolves more slowly than the infiltration of the airspaces.

Lung tumors

Lung tumors, if large enough, whether benign, malignant, or metastatic, may alter both ventilation and perfusion. Usually, defects in ventilation predominate and depend on the degree of bronchial obstruction and/or parenchymal involvement. They are confined to the affected segment or lobe, or the whole lung when the tumor is located in a mainstream bronchus. If the lesion is endobronchial, there may be distal hypoxia with a reflectory decrease in perfusion [2, 7], regardless whether atelectasis has developed or not (see above, "bronchial obliteration").

Tumors less than 2cm in diameter usually are not detected in the perfusion scan unless they involve vessels at the hilus. Such involvement may be due to metastatic spread to lymph nodes, direct invasion of the mediastinum, or less commonly, invasion and thrombosis of the pulmonary veins, more rarely of the pulmonary arteries (Table 1). Larger tumors produce perfusion defects that correspond to the size of the tumor, to the involved segment or lobe, or even to the entire lung [6, 7, 25]. In patients with bronchoalveolar carcinoma, focally increased perfusion has been rarely observed, which is thought to be caused by intrapulmonary venoarterial shunting [26].

Pulmonary embolism with or without tumor invasion may be seen as a consequence of paraneoplasia, associated thrombophilia and disturbances in haemostatic balance.

Lymphangitis carcinomatosa

Patients suffering from lymphangitis carcinomatosa may show multiple small linear defects in the perfusion scan that outline the bronchopulmonary segments, a finding called "contour mapping". Often, regional ventilation is normal [7, 21, 27]. The combination of perfusion defects and normal ventilation may lead to the false diagnosis of pulmonary embolism [27]. However, in PE the perfusion defects usually occupy entire segments or subsegments.

Lung transplantation

Lung transplantation became a therapeutic option for patients with obstructive or interstitial lung disease at a terminal stage. If a single lung is to be transplanted, perfusion scintigraphy allows evaluating and quantifying the relative function of both lungs in order to select the more compromised lung. Once transplanted, perfusion scan is a useful diagnostic method to study the functional status of the organ [2, 7, 28].

In the immediate post-transplantation setting, perfusion imaging documents the patency of the vascular anastomoses. Perfusion is inhomogeneous immediately after transplantation, normalizing with time. In a retrospective study [29] performed in 41 patients with lung transplants, the ventilation was found to be more homogenously distributed in the transplanted lung as compared to the perfusion in the same organ. However, in this study primary graft dysfunction defined at 72h post-transplantation did not lead to recognizable changes in ventilation/perfusion scintigraphy at 3 months, and scintigraphy did not correlate with the development of lung dysfunction during the initial 12 months. These data are in contrast to earlier findings [28] that quantitative lung scintigraphy predicts the development of chronic rejection. In single-lung transplantation, the ratio of right-to-left lung perfusion and the change in this ratio were found to correlate with rejection [2, 7, 28].

Analysis of regional changes in ventilation and perfusion scintigraphy may also be useful. The development of matched ventilation/perfusion abnormalities often reflects rejection [2].

Effect of radiation therapy

Pneumonitis and pulmonary fibrosis secondary to irradiation may present as non-segmental process. These effects depend on the radiation dosage, fractionation schedule, lung volume irradiated, and biological factors. Optimization of the radiation therapy plan for lung carcinoma can be supported by a lung perfusion scintigraphy [7, 21, 30].

A quantitative ventilation/perfusion scintigraphy giving regional and functional information that morphological methods cannot provide, allows for a better prediction of the effects of radiation upon the pulmonary tissue [30]. Furthermore, information based on perfusion can help to prevent radiation damage to the remaining functioning lung parenchyma, especially in patients with major perfusion deficiencies [31]. The best predictors of pulmonary function following radiation therapy are variables obtained from lung perfusion scintigraphy such as the "predicted perfusion reduction" and the "mean perfusion weighed lung dosage" [32].

Acquired heart disease

Uncomplicated congestive heart failure is characterized by diffuse, nonsegmental perfusion defects throughout both lungs; however, these defects may occasionally be focal. Cardiac enlargement, reversal of the perfusion gradient in the lungs producing a redistribution of blood flow to the upper lung zones (due to secondary pulmonary hypertension), and "fissure signs" due to pleural effusions may also be present [6, 7, 25].

Pulmonary embolism in the presence of congestive heart failure can present as the usual segmental ventilation/perfusion mismatch [7], but also hide behind matching lesions due to early infarction, which should manifest in chest x-rays, too.

Congenital heart disease

Lung perfusion scintigraphy is a simple and cheap procedure with high specificity for detection and quantification of a right-to-left shunt and for estimating the consecutive right ventricular strain. The presence of a right-to-left shunt is identified by the deposition of injected particles in systemic, extra pulmonary vascular beds, mainly in the brain, the liver and the kidneys [33, 34]. The absence of tracer accumulation in the brain virtually excludes a significant right-to-left shunt [33].

The fraction of right-to-left shunting can be approximated by comparing the activity in the lungs to the activity in the rest of the body [2].

Other lung diseases

Abnormalities in ventilation and perfusion scans can occur in several conditions such as pneumoconiosis, pneumothorax, pleural disease, bronchopleural fistula, drug addiction and kyphoscoliosis, but the indication for scans as an additional diagnostic tool remain facultative.

Paediatric use of lung scintigraphy

In children and adolescents, lung perfusion scintigraphy is indicated in cases of worsening of lung function by cystic fibrosis or suspected bronchiolectasis, and for assessment of lung perfusion before and after surgery for congenital heart defect or anomalies of central extra- or intrapericardial blood vessels, right-left shunt quantification, diagnosis and exclusion of possible pulmonary embolism and monitoring lung perfusion after PE [35].

Quantitative aspects of ventilation/perfusion studies

Quantitative measures of relative lung perfusion (comparing lungs or dividing each lung into thirds and calculating the percentage of total counts in each region) may be useful in preoperative lung assessment and evaluation of post-lung transplant patients [6, 36]. Preoperative lung imaging is often performed to assess the regional lung function to predict expected residual function after surgery [7, 21, 37] in order to prevent unexpected postoperative respiratory failure (assessment of functional inoperability). Quantitation of perfusion (right to left, upper to lower lung fields) is indicated when spirometric measurements are borderline (forced expiratory volume in first second, FEV1 < 1,5L) and serves as the basis for calculation of postoperative ventilation. These studies are particularly important in patients with lung cancer since coexistence of COPD is frequent in these patients. On the other hand, after surgical removal of large cysts, intrathoracic upside-down-stomach or other space occupying lesions the resulting improvement can be documented by quantitation of perfusion and ventilation scans pre- and postoperatively [38].

Aerosol deposition and mucociliary transport

The inhalation of ^{99m}Tc-labelled microspheres is the classical method for investigation of regional distribution and deposition, but also dynamics of clearance by mucociliary transport. This is in agreement with the information derived from radioactive gases (^{81m}Krypton, ^{127}Xenon) and pertains also to medications, thus bearing the potential of clinical application [39]. The pattern of deposition of the particles (central, bronchial, alveolar) can give additional clues for diagnosis (e.g., "hot spots" pathognomonic for COPD) and therapeutic efficacy of inhaled drugs [40].

Sources of error

Perfusion scan may show hot spots in the lung if clotting of blood occurs in the syringe during the injection or if the injection is made through an indwelling catheter that is not well flushed. Injection of ^{99m}Tc-MAA through a central line can result in inadequate mixing of activity in the pulmonary artery, especially if the activity is injected through a pulmonary artery line [2, 6, 7]. In rare cases of former unknown situs inversus and concomitant pathologies this may be overlooked.

Ventilation scintigraphy may be obtained with the patient upright, while the radiopharmaceutical for perfusion scintigraphy typically is injected with the patient supine. These changes in position may result in mis-matched patterns between ventilation and perfusion scan [1, 2]. Accordingly, any nonstandard patient positioning should be recorded and considered during subsequent interpretation of the studies.

In conclusion, this review of findings in pulmonary diseases other than PE clearly outlines the widely ignored great potential of ventilation/perfusion scintigraphy. The fact that in many even larger units it is not available all around the clock may be one of the major reasons.

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