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Research Article

Ventilation Defect Typical for COPD is Frequent among Patients Suspected for Pulmonary Embolism but Does Not Prevent the Diagnosis of PE by V/P SPECT

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Abstract

Background: V/P SPECT is today primarily used to diagnose and follow-up pulmonary embolism (PE). The clinical diagnosis of pulmonary embolism (PE) in chronic obstructive pulmonary disease (COPD) patients is considered challenging because the symptoms of both PE and COPD are non-specific and quite alike.

Aim: The first aim of the study was to evaluate how frequent COPD is among patients with suspected PE using V/P SPECT. The second aim was to investigate the ability of V/P SPECT to diagnose PE in patients who have simultaneously airway obstruction.

Methods and Materials: 1274 consecutive patients clinically suspected for PE were retrospectively investigated for PE and signs of obstruction with V/P SPECT. All patients with signs of obstruction were classified into 3 groups according to the grade of severity of obstruction mentioned in the final reports.

Results: PE was diagnosed in 353 (28%) patients. Mild, moderate or severe airway obstruction were shown in 697 patients (55%). Among patients with PE, 90 patients (25%) were also diagnosed as obstructive. All examinations in patients with both PE and COPD were diagnostic.

Conclusion: Mild, moderate or severe airway obstruction typical for COPD is frequent among patients with suspected PE, and more than half of the patients referred with clinical suspicion of PE have signs of COPD. With V/P SPECT it is possible to diagnose both conditions fast and accurately. COPD is not a contraindication to use pulmonary ventilation/perfusion tomography for PE diagnosis even in the most severe grade of COPD.

Keywords: *V/P SPECT; COPD; Pulmonary Embolism (PE)*

Background

The clinical diagnosis of pulmonary embolism (PE) in COPD patients is often difficult due to non-specific and similar symptoms of the two conditions. It is of high importance to make a fast and accurate diagnosis of PE. Patients with COPD are prone to suffer from PE [1]. Pulmonary scintigraphy is one of the objective methods used to confirm or deny a clinical suspicion of pulmonary embolism (PE). Due to limited planar imaging technique and probabilistic PIOPED interpretation criteria, planar pulmonary scintigraphy was assumed to be a contraindication in patients with COPD. In the big prospective PIOPED study from 1990, planar V/P scintigraphy had a high number of non-diagnostic findings (69%) in spite of high sensitivity and specificity. Since then, planar V/P scintigraphy was considered a contraindication for diagnosing PE in COPD patients [2]. Since that time, the planar technique has evolved to the tomographic ventilation/perfusion technique, and the interpretation criteria have evolved from probabilistic to holistic.

The tomographic technique, Ventilation/Perfusion Single Photon Emission Computed Tomography (V/P SPECT) is a functional imaging method visualizing ventilation and perfusion distribution in the lungs. The method is recommended as an initial examination for diagnosing PE as well as for follow-up according to European guidelines [3]. The method is applicable to all patients and has no contraindications, it has a low radiation exposure and it results in less than 4% of non-diagnostic findings. Ventilation imaging is often performed using (99m)Tc-DTPA or Technegas, an ultrafine dispersion of (99m)Tc-labeled carbon. Technegas, hydrophobe aerosol, size of 0.01 micrometer has shown to have better properties than DTPA aerosols, size 1.2 - 2 micrometer. Jogi *et al*. showed, in a head to head study, the overall unevenness of radiotracer deposition and the degree of central deposition were more pronounced in (99m)Tc-DTPA than Technegas studies in both obstructive and non-obstructive disease [4]. The authors conclude that Technegas is the preferred radioaerosol, particularly in obstructive disease [4]. Gruning., *et al*. also showed that V/P mismatch areas are clearly revealed when using Technegas [5].

Moreover, recent studies with V/P SPECT have shown that the method can indeed be used to diagnose COPD and grade the degree of COPD [6-8] as well as diagnose other pulmonary co-morbidities such as pneumonia and left heart failure [9,10]. Still, grading of COPD with V/P SPECT and diagnosing other pulmonary co-morbidities are not yet implemented in clinical routine and needs to be evaluated in large cohorts.

Aim

The first aim of the study was to evaluate the frequency of COPD among patients with suspected PE using V/P SPECT. The second aim was to investigate the diagnostic ability to diagnose PE in patients with the airway obstruction.

Patients and Methods

Totally 1485 consecutive patients with a V/P SPECT examination were identified retrospectively from the database at the department of Clinical Physiology and Nuclear Medicine at Skåne University Hospital in Lund, Sweden, between 1 January 2005 and 31 December 2005. Searching words in the final reports were obstruction, uneven distribution of aerosol, areas of absent ventilation, deposition of aerosol in airways and other related synonyms.

Inclusion criteria were all patients referred for V/P SPECT for suspected PE or control of previous PE and using Technegas (Cyclomedica Ltd, Kingsgrove, NSW, Australia) as an inhalation agent. Exclusion criteria were the follow up examinations in case patients did the examination twice during 2005, examinations when ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid; SmartVent; Diagnostic Imaging Ltd, Welford, UK) was used as a ventilation agent in case the Technegas generator was not available due to planned maintenance of the generator or due to equipment malfunction. Examinations where the referring indication was not suspicion for PE were also excluded: such as control of transplanted patients, pre-operative pulmonary surgery and congenital pulmonary disease and examinations with only a perfusion study or when scans where judged to be technically inadequate. In one examination, there was no available information about the referral or final report in the database (Table 1). Subsequent analysis of the referrals and the final reports led to exclusion of 211 patients. The total number of patients that were enrolled in the study was 1274 (86%) of referred patients, 559 men and 715 women. The mean age was 64 ± 18; range 16-95.

Criteria	Number of patients
	n = 211
Patients with control examinations after PE	105
Ventilation with administration with DTPA	31
Control of lung transplanted patients	40
Pre-operative pulmonary surgery	14
Only perfusion scan (Pregnancy n = 3, Other reasons n = 4)	7
Technically inadequate	4
Children under 16 years	9
Patient with missing information	1

Table 1: *Exclusion criteria.*

Ethical Consideration

The study was approved by the regional ethics committee in Lund.

Grading of ventilation impairment and degree of airway obstruction typical for COPD

Ventilation impairment was based on penetration and distribution of Technegas to the periphery. For the purpose of the study, classification of the ventilation impairment was based on the routine description of ventilation images in accordance with grading as published earlier [6].

- **Grade 1:** An uneven distribution of the aerosol through lung. This is typical for a mild airway obstruction in COPD.
- **Grade 2:** An uneven distribution of the aerosol and diminished penetration of Technegas to the periphery, with deposition of aerosols in small airways, seen as hot spots. This is typical for a moderate airway obstruction in COPD.
- **Grade 3:** A severely impaired penetration of Technegas to the periphery and a central deposition of Technegas in large airways, usually with large areas of reduced/absent ventilation. This is typical for a severe airway obstruction in COPD.

We have previously shown that this grading based on Technegas ventilation SPECT correlates to spirometric airway obstruction in COPD and GOLD stages of the COPD [6]. In patients with both PE and COPD, V/P SPECT findings were reviewed again by a skilled physician to control if the grading of airway obstruction typical for COPD based on the description from the routine reports was in agreement with the classification by Bajc., *et al* [6].

Statistical analysis

Descriptive analyses are presented as frequencies and percentages for categorical data as means and standard deviations for numerical data. All statistical calculations were performed using Microsoft Excel 2013.

Results

Abnormal ventilation typical for airway obstruction in COPD

In more than a half of the patients (55%) a ventilation pattern typical for airway obstruction in COPD was found: Grade 1 was identified in 348 of 697 (50%), Grade 2 was identified in 151 of 697 (22%). Grade 3 was identified in 198 of 697 (28%).

No gender related difference was found between groups. Grade 2-3 ventilation defect was found predominantly in elderly patients (Table 2).

	Grade 1 (n = 348)	Grade 2 (n = 151)	Grade 3 (n = 198)	All COPD (n = 697)	All patients (n = 1274)
Gender					
Male	160	65	96	321 (46%)	559 (44%)
Female	188	86	102	376 (54%)	715 (56%)
Age					
< 60	150	26	30	206 (30%)	472 (37%)
> 60	198	125	168	491 (70%)	802 (63%)

Table 2: *Characteristics for patients with graded ventilation defect typical for COPD.*

Pulmonary embolism

PE was diagnosed in 353 patients (28%). Among these patients, 90 (25%) patients also had signs of airway obstruction. In the group of obstructive patients, majority (87%) had small PE, < 25% of the total pulmonary perfusion. Ten patients (11%) had a medium size PE (< 50 %) and two patients (2%) had an extensive PE (> 50%) (Table 3). All examinations were diagnostic even in the severe grade of obstruction which was identified in 28% of these patients (Figure 1).

	Grade 1	Grade 2	Grade 3	All patients with PE (n = 353)**
PE	39 (43%)*	26 (29%)*	25 (28%)*	90*(25)**
PE-extent				
< 25%	37	21	20	78 (87%)*
< 50%	1	4	5	10 (11%)*
> 50%	1	1	0	2 (2%)*

Table 3: *Characteristics of detected PE and graded ventilation defect typical for airway obstruction in COPD.*

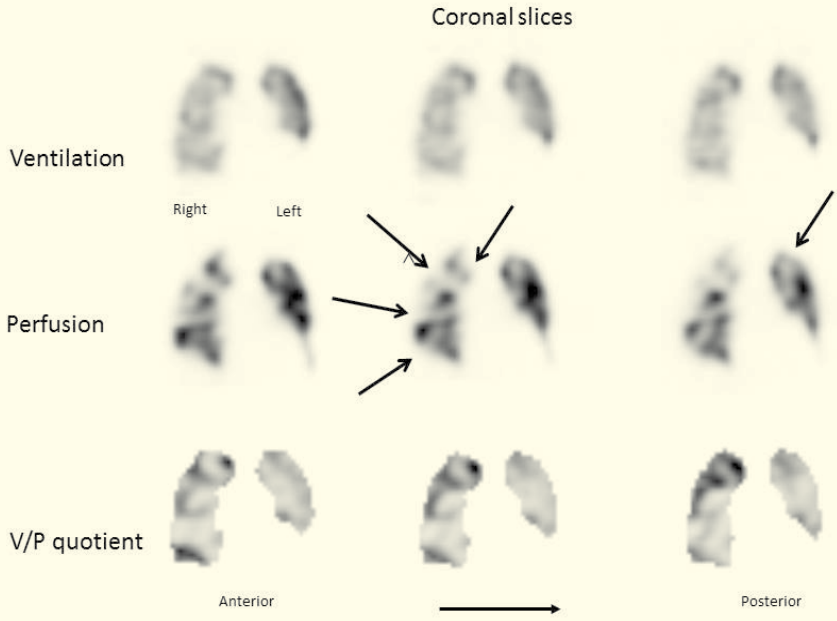

Figure 1: *Patient with PE and COPD.*

Frontal slices: V/P SPECT: bilaterally reduced ventilation (V) with of a deposition of Technegas as seen in obstructive airways. Corresponding perfusion images showed multiple peripheral segmental/sub-segmental perfusion defects. Absent perfusion (arrows), and V/P mismatch are clearly seen in V/P quotient images.

Discussion

In the current study, more than half of the patients (697) suspected of having PE also had a pattern typical for an airway obstruction. The degree of ventilation defect varied demonstrating varying severity of small airway disease typical for COPD [6]. This in turn indicated that the small airway disease typical for COPD was frequent among patients with clinical suspicion of PE and that symptoms of airway obstruction and PE were similar. For detecting a PE it is important to raise a clinical suspicion of PE. But a clinical suspicion is not sufficient for a diagnosis of PE. An imaging technique is always needed for a PE diagnosis. An important result of this study was that all V/P findings were diagnostic, regardless of airway obstruction. In addition, V/P SPECT appeared to be a useful method to differentiate and diagnose both PE and airway obstruction.

The most important finding was that as many as 90 (25%) patients with a PE had also a small airway obstruction typical for COPD and that all of them could be diagnosed by V/P SPECT regardless of the degree of airway obstruction (Figure 1). This result overturns the previous recommendations and still general thinking, that COPD is a contraindication to performing a V/P examination in patients with a suspected PE. This myth originates from the results of the largest prospective study investigation of pulmonary embolism (PIOPED I), that had 69% of the non-diagnostic findings [2,11]. The reasons were many. First, the technique was mainly based on planar imaging technique and xenon gas was used for a ventilation study in only one projection. Secondly, the interpretation criteria were stiff and they were not taking into account ventilation and perfusion patterns conforming to pulmonary vascular anatomy. Thirdly, it is not possible to interpret a ventilation study with only one projection. The introduction of the tomographic technique in 1990s and the implementation of Technegas as a novel ventilation agent facilitated imaging of PE in comparison with planar imaging in all patients and particularly in COPD patients together with the new interpretation criteria [3]. The small size of Technegas particles with a diameter less than 0.01 μm enables the penetration of this aerosol to the periphery of the lung. It behaves like a gas and it has become a preferred agent among other aerosols [3]. In the present study, the prevalence of COPD in patients with PE was similar with the results from the recently published multicenter study from China [12]. The results in the study by Begic., *et al*. showed a lower incidence (7%) [9]. The reason for this difference might be that they have not interpreted all ventilation studies in detail, but were rather focused to diagnose perfusion defects typical for PE only.

Jogi., *et al*. found that even so called "healthy" smokers show various grades of airway obstruction by V/P SPECT, although spirometry did not show any sign of airway obstruction or limitation in expiratory flow, (FEV1) [13]. Woodruff and colleagues showed that current and former smokers, with a normal spirometry have chronic clinically significant respiratory symptoms, exacerbation activity, declined exercise tolerance, and imaging evidence of inflammation in the small airways [14]. Jobse., *et a*l. induced an inflammatory process in mice by exposing them to cigarette smoking and studied the early structural changes in the lungs by imaging with both CT and V/P SPECT [15]. CT could not discriminate controls from cigarette exposed animals at any time of the trial while V/P detected early changes to the lungs caused by cigarette exposure. V/P SPECT might be applied clinically to diagnose also early stages of COPD [15].

CTPA (Computed Tomographic Pulmonary Angiography) is an alternative method to detect PE and is used more frequently than V/P SPECT due to its availability. In a study by Shapira-Rootman., *et al*. patients with acute exacerbation of COPD were evaluated for PE using CTPA. The study showed a PE in 18% of COPD patients hospitalized for an acute exacerbation and suggested that patients with a COPD exacerbation are more prone to get a PE and should be evaluated for a PE systematically during their hospitalization [16,17]. Nevertheless, CTPA has limitations in diagnosing patients with a history of COPD and suspected for PE. Walen., *et al*. have shown in their study that it is less likely to make a diagnostic outcome of PE by CTPA in patients with COPD [18]. Therefore, the prevalence of PE in COPD patients may be underestimated when CTPA is used.

COPD is a heterogeneous disease usually occurring with a combination of two different diseases, chronic bronchiolitis and emphysema. Milne., *et al*. described the advantages and disadvantages of different imaging methods in COPD patients [19]. HRCT is commonly used as a reference method in the detecting and characterizing of emphysema and it also enables quantification as to the extent of emphysema. However, HRCT is not ideal in classifying the airway obstruction due to several reasons. According to Milne., *et al*. airway branching is asymmetrical (in terms of length and caliber of bronchi) and 'functional' classification of individual airways cannot be made by simple counting of generations as the small airways (0 - 2 mm in diameter) can be found anywhere between the 4^{th} and 14^{th} generations the measurable parameters of airway geometry (such as airway wall thickness and luminal area) vary greatly by anatomical location. Finally, since the major site of airflow obstruction in COPD is in airways with dimensions less than 2 mm , the primary area of pathology is generally below the resolution of conventional HRCT [19].

Men and women were equally represented among COPD patients.

Majority (84%) of patients with moderate to severe grade of obstruction were elderly patients. This was also an expected result based on the fact that the onset of COPD occurs usually in mid-life [20]. The number of patients with a diagnosed PE was 28% of all included patients which is in line with the results in previous studies [9,21,22].

The strength of this study is the large number of patients and that it was performed at a hospital where V/P SPECT is the recommended method by many referring clinicians. Therefore, the physicians reviewing the images of V/P SPECT are well educated and skilled to interpret this examination in their daily routine.

A limitation of our study is that the staging of small airway obstruction on the basis of V SPECT and typical for COPD was based on the descriptive analysis in the final reports to the referring clinicians. However the group of patients with both PE and COPD has been re-read according to the latest classification and it was found to be in accordance with them [6]. Therefore, the results presented in figure 1 represent adequate classification. Other limitations are that the smoking habits of the participants were unknown in most cases. Information about asthma among the included patients was lacking in most referrals and the clinical outcome was not confirmed by follow-up of patients. Further studies are required to compare the grade of airway obstruction between V/P SPECT and spirometry measurements, particularly in "healthy smokers" and relate the results to the GOLD grading.

Grading of COPD should be added routinely in the final report of V/P SPECT to the referring clinicians. This additional finding may provide crucial information to the referring physician in detecting early signs of airway obstruction.

Conclusion

In patients studied with V/P SPECT, small airway obstruction typical for COPD was frequent among patients with suspected PE, being present in more than half of the referred patients. With V/P SPECT it was possible to diagnose PE regardless of the degree of airway obstruction. Thus, COPD is not a contraindication to use V/P SPECT.

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Disclosure

The authors declare to that no conflicts of interest exist in this work.

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