The prevalence of COPD among patients suspected for pulmonary embolism using V/P SPECT

Author: Abir Nasr
Supervisor: Marika Bajc
PhD, Senior consultant, associate professor, Skåne University Hospital and Lund University
ABSTRACT

Background: Chronic Obstructive Lung disease (COPD) is a major cause of morbidity and mortality globally. The methods used to detect and classify COPD in the early stages are insufficient. Today, V/P SPECT is a method used primarily to identify and follow-up of pulmonary embolism (PE). However, it is also a useful tool in identifying other cardio-pulmonary diseases such as COPD. The clinical diagnosis of pulmonary embolism (PE) in COPD patients is often difficult due to non-specific and similar symptoms of the two conditions.

Aim: The first aim of the study was to determine the prevalence of COPD among patients with suspected PE using V/P SPECT. The second aim was to investigate the extent and ability to diagnose PE in patients with COPD.

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

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

Conclusion: The prevalence of COPD was frequent among patients with suspected PE, being present in more than half of the referred patients. COPD is not a contraindication to use V/P SPECT for PE diagnosis even in the most severe grade of COPD.

Keywords: V/P SPECT, COPD, Pulmonary embolism (PE).
Abbreviations

PE Pulmonary embolism

COPD Chronic Obstructive Lung disease

GOLD Global Initiative for Chronic Obstructive Lung disease

V/P SPECT Ventilation/Perfusion Single Photon Emission Computed Tomography

FEV1 Forced Expiratory Volume in 1 second

FVC Forced Ventilation Capacity

HRCT High Resolution Computed Tomography

DTPA DiethyleneTriaminePentaAcetic acid

CTPA Computed Tomography Pulmonary Angiography
Background

Chronic Obstructive Lung disease (COPD) is an increasing global health problem and one of the major causes of morbidity and mortality. It is predicted to be the 3rd leading cause of death and the 7th leading contributor to the global burden of disease by 2030. COPD involves at least two pathological features, emphysema and small airway disease. Pathologic changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. It is a heterogeneous disease and quite complex to diagnose and stage. The Global Initiative for Chronic Obstructive Lung disease (GOLD) has recommended a global strategy for the diagnosis, management and prevention of COPD, to inspire international and local guidelines to manage this disease (1, 2). According to GOLD´s latest revision, there are four main points that should be determined in the assessment of COPD:

1) Evaluation of the severity of the airflow limitation using forced expiratory volume (FEV) in 1s, measured by spirometry.
2) Assessment of current symptoms using validated questionnaires.
3) The risk of exacerbations and
4) The presence of comorbidities (2, 3).

The measurements of the pulmonary function are weak descriptors of status of the disease as they mainly reflect impairment of large and intermediate airways. However, it is the changes in small airways that are considered to be among the earliest signs of COPD (4, 5). A just published study by Woodruff and colleagues has shown that current and former smokers, with the normal spirometry values have actually chronic respiratory symptoms of clinical significance (6).

HRCT High Resolution Computed Tomography (HRCT) is a generally used imaging method to visualize the morphology of the lungs. It enables characterization and measurement of the extent of emphysema usually present in patients with COPD and other morphological changes such as a tumor. However, measurements of the small airways are not satisfactory(5). Thus the methods used to diagnose and grade COPD are insufficient. Early detection of changes in the small airways is crucial to manage this disease.

Ventilation/Perfusion Single Photon Emission Computed Tomography (V/P SPECT) is a functional imaging method visualizing ventilation and perfusion distribution in the lungs. It is
primarily used for diagnosing pulmonary embolism (PE) and is recommended as an initial examination for diagnosing PE as well as for follow-up according to European guidelines (7). The method is applicable to all patients and has no contraindications, low radiation exposure and less than 4% of non-diagnostic findings. However, the old technique using planar imaging was validated in the biggest prospective study for investigation of pulmonary embolism (PIOPEDI) during the 90s showing high sensitivity and specificity but high number of non-diagnostic findings (69%) (8, 9). This was mainly due to other pulmonary pathology. Since then, COPD was considered a contraindication to use as a method for diagnosing PE. On the contrary, recent studies have shown that the method can indeed be used to diagnose COPD. Moreover, it was shown that V/P SPECT is more sensitive than CT in detecting early changes in small airway disease. Further, it was possible to grade the degree of COPD (10-12). However, grading of COPD with V/P SPECT is still not implemented in clinical routine and needs to be evaluated in large cohorts.

**V/P SPECT**

The examination starts with the patient inhaling an ultra-fine carbon nano-particles labeled by $^{99m}$Tc, Technegas (Cyclomedica Ltd, Lucas Heights, NSW, Australia) in supine position until approximately 30 MBq has reached the lungs. That is achieved by placing a calibrated radiation protection monitor above the patient. The administration of Technegas is finished when the desired count rate for the camera is reached.

Imaging is performed by a large field-of-view dual-head gamma camera with low energy all-purpose collimators and 64x64 matrix with 128 projections over 360°. Each projection takes 10 seconds. Subsequently 120MBq of $^{99m}$Tc-MAA (Macro Aggregated human Albumin, Technescan Lyo MAA; Mallinckrodt Medical, Petten, the Netherlands) is administrated intravenously without any patient movement. Imaging starts immediately with the same rate of images as the ventilation study but each image takes 5 seconds. The entire acquisition time is 20 minutes, which is a comfortable time period for the patient to lie still.

Iterative reconstruction was used for processing of the acquired images by ordered-subset expectation maximization (OSEM) with 8 subsets and 2 iterations. Ventilation background is subtracted from the perfusion tomogram and a normalized image, V/P quotient, is calculated. The ventilation and perfusion patterns of the SPECT images were interpreted according the criteria of the European Guidelines (13, 14).
The effective dose for V/P SPECT is 1.2 - 2.0 millie Sievert (mSv), 0.015 mSv/MBq Technegas and 0.017 mSv/MBq MAA. According to the Swedish Radiation Safety Authority (SSI), the average radiation for the non-smoking part of the Swedish population is estimated to be 2.4 mSv/year (15).

**Interpretation of PE**

In lung scintigraphy, emboli are seen as perfusion defects on lobar, segmental or sub-segmental levels as a result of the thrombus. In PE, ventilation is typically normal since tissue viability is maintained by the bronchial circulation. Diagnosis of PE is therefore based on absent perfusion conforming vascular anatomy with preserved ventilation in these areas, so-called mismatch (Figure 1). Most other lung diseases cause ventilation and perfusion abnormalities in the affected region, so-called matched defects (7).

**Aim**

The first aim of the study was to determine the prevalence of COPD among patients with suspected PE using V/P SPECT. The second aim was to investigate the extent and ability to diagnose PE in patients with COPD.

**Methods and material**

Totally 1485 consecutive patients were identified for V/P SPECT retrospectively from the database and referred to 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.
Subsequent analysis of the referrals and the final reports led to exclusion of 211 patients. 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 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. 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 (Table1). Inclusion criteria were all patients referred for V/P SPECT for suspected PE or control of previous PE. 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.

Table1. Exclusion criteria

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

**Classification of ventilation impairment – grading of airway obstruction**

For the purpose of the study, classification of the ventilation impairment was based on the routine description of ventilation images in accordance with recent grading as follows (16). Slightly uneven distribution of the aerosol was classified as mild airway obstruction- grade 1. Uneven and diminished penetration of Technegas to the periphery with deposition of aerosols in small airways were classified as a moderate airway obstruction-grade 2. Severe airway obstruction, grade 3, was identified as central deposition in large airways is identified with
severely impaired penetration of Technegas to the periphery and usually major areas with reduced/absent ventilation (Figure 2).

In patients with both PE and COPD, V/P SPECT findings were reviewed again by a skilled physician to control that the grading of COPD based on the description from the routine reports was in agreement with the latest classification (16).

![Figure 2. Ventilation patterns of different grades of COPD. Bajc et al. (16)](image)

**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.

**Ethical consideration**

The study was approved by the regional ethics committee in Lund (324/2006). All procedures performed in this study were in accordance with the clinical standards and the Declaration of Helsinki.
Results

COPD-grading
More than a half of the patients (55%) showed signs of airway obstruction (from the sign of uneven ventilation to deposition of Technegas in small and large airways as well as areas of absent ventilation, mild-severe).

- Grade 1 was identified in 348 of 697 (50%): Patients with impaired ventilation pattern.
- Grade 2 was identified in 151 of 697 (22%): Patients having an uneven and diminished penetration of Technegas to the periphery, with deposition of aerosols in small airways,
- Grade 3 was identified in 198 of 697 (28%): Patients, having deposition of the aerosol in the large and small airways with areas of reduced/absent ventilation.

No gender related difference was found between all groups. Grade 1-2 of COPD was found predominantly in elderly patients (Table2).

Table 2. Characteristics for patients with COPD-findings

<table>
<thead>
<tr>
<th>Gender</th>
<th>Grade 1 (n=348)</th>
<th>Grade 2 (n=151)</th>
<th>Grade 3 (n=198)</th>
<th>All COPD (n=697)</th>
<th>All patients (n=1274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160</td>
<td>188</td>
<td>65</td>
<td>86</td>
<td>321 (46%)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>102</td>
<td>30</td>
<td>125</td>
<td>376 (54%)</td>
</tr>
<tr>
<td></td>
<td>321</td>
<td>376</td>
<td>206</td>
<td>491 (70%)</td>
<td>559 (44%)</td>
</tr>
<tr>
<td></td>
<td>559</td>
<td>715</td>
<td>472</td>
<td>802 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

Age

<60

150 26 30 206 (30%) 472 (37%)

>60

198 125 168 491 (70%) 802 (63%)

PE
353 patients (28%) were detected with PE. 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, 10 patients (11%) had medium size PE (<50 %) and 2 (2%) had extensive PE (>50%) (Table3).

All examinations were diagnostic even in the most severe grade of obstruction which was identified in 28% of these patients.

Table 3. Characteristics for patients with detected PE and COPD
<table>
<thead>
<tr>
<th>PE-extent</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>All patients with PE (n=353)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>37</td>
<td>21</td>
<td>20</td>
<td>78 (87%)*</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>10 (11%)*</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (2%)*</td>
</tr>
</tbody>
</table>

Figure 3. V/P SPECT images for a COPD patient with extensive PE (red arrows). Bajc et.al(17)

**Discussion**

In the current study more than half of the patients (697) had various degrees of airway obstruction as in COPD. This indicates in turn that COPD is a frequent disease and that the patients have similar symptoms to the patients with clinical suspicion of PE. Hence it is important to raise clinical suspicion of PE; the clinical diagnosis is not sufficient and always needs to be diagnosed with imaging technique. Importantly, all findings were diagnostic, regardless of obstruction. In addition, V/P SPECT has also shown to be a useful method to differentiate and diagnose the two conditions.
Different grades of airway obstruction can be identified by different patterns of ventilation which reveals pathophysiological changes as was presented in this study. Jögi 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 decreased FEV in 1s or ventilation capacity (11). This is in agreement with the results of just published study by Woodruff and colleagues. They showed that current and former smokers, with normal spirometry values have chronic respiratory symptoms, of clinical significance, exacerbations activity, lower exercise tolerance, and imaging evidence of inflammation in the small airways (6).

Jobse et al 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. 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. The authors suggest that V/P SPECT can be applied clinically to diagnose the early stages of COPD (12).

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. 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 4th and 14th 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 (5).

Man and women were equally represented among COPD patients. The results are in accordance with the World Health Organization. The reason are mainly due to increased tobacco use among women in both developed and developing countries (18). Majority (84%) of COPD 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 (2). The number of patients with diagnosed PE was 28% of all included patients which is in line with the results in previous studies (13, 19, 20).

The most important finding however is that as many as 90 (25%) patients with PE had COPD and that all of them were diagnostic regardless of the degree of airway obstruction (Figure 3). This result breaks previous advice and still generally current thinking, that COPD is contraindication to perform V/P study in patients with suspected PE. This myth originates from the results of the largest prospective study (PIOPED I), that had 69% of the non-diagnostic findings (8, 9). The reasons were many; first, the technique was mainly based on planar imaging technique and for the ventilation study Xenon gas was used in only one projection. Furthermore, the interpretation criteria were stiff and not taking into account ventilation and perfusion patterns conforming pulmonary vascular anatomy and third, it is not possible to interpret the 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. The small size of Technegas particles with a diameter less than 0.1 µm enables the penetration of this aerosol to the periphery of the lung. It behaves as a gas and has become a preferred agent among other aerosols (7).

The prevalence of COPD in patients with PE was (25%) which is higher than results from the study by Begic et.al (7%) (20). 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.

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 prevalence of 18% of COPD patients hospitalized for an acute exacerbation. The result supports the fact that these patients are more prone to get PE and should be evaluated for PE systematically during their hospitalization (21, 22). Nevertheless, CTPA has limitations in diagnosing patients with history of COPD and suspected for PE. Walen et al. have shown in their study that it is less likely to achieve a diagnostic outcome by CTPA in patients with COPD (23). Therefore the prevalence of PE in COPD patients may be underestimated when CTPA is used.
We should take into consideration that V/P SPECT is a source of ionized radiation even if the doses are low but they must be justified. In case that V/P SPECT will be used routinely to diagnose COPD, the radiation exposure should be taken into consideration. A suggestion is to perform V/P SPECT initially at baseline, and use the ventilation study to assess the effects of treatments in the follow-up examinations of COPD. That will decrease the radiation dose to a minimal level.

The power 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 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 (16). Therefore the results presented in table 2 may represent adequate classification. Other limitations are that the smoking habits of the participants were unknown in most cases. This information is important in studies of COPD-patients as smoking is the main cause of COPD. Information about asthma among the included patients was also 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
The prevalence of COPD was frequent among patients with suspected PE, being present in more than half of the referred patients. COPD is not a contraindication to use V/P SPECT for PE diagnosis even in the most severe grade of COPD.
Acknowledgments

This study was performed at the Department of Clinical Physiology at Skåne University Hospital in Lund, Sweden and supported by grants from the research Funds at Skåne University Hospital (SUS fonder). I would like to dedicate my gratitude to my supervisor associate professor Marika Bajc for her supervision, help, support and all the great discussions that we had. Thank you for introducing me to the world of research.

References:


