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ABSTRACT

Objectives: A balanced comparison between single photon emission computed tomographic (SPECT) lung scintigraphy with the planar imaging and multislice (MS) spiral computed tomography (CT) and correlating the outcomes with the clinical probabilities.

Background: Pulmonary embolism (PE) is a potentially lethal serious problem with a confusing clinical database to diagnose. In the majority of the studies, the clinical probabilities were always in the scope of the secondary consideration, although they are the gates, patients step through to the investigatory zone.

Methods: 68 patients suspected for PE (66% females and 34% males, mean age 43.5±15.3) were evaluated for pretest clinical probability score (PCPS) and investigated with ventilation/perfusion lung scintigraphy (planner & SPECT) and MS spiral CT.

Results: 63% and 45.5% were positive for dyspnoea and deep venous thrombosis, respectively. They have low, intermediate and high PCPS of 47.1, 17.6 and 35.3%, respectively. Planner and SPECT studies were positive in 28/68 and 33/68 cases, respectively. SPECT showed 25 % more positives in the high clinical probability group (p-value 0.02). MS spiral CT was positive in 9/25 and negative in 16/25, with 2/25 false positive with SPECT and 4/25 disagreement with planner scans. Sensitivity, specificity, positive and negative predictive values were (100%, 87.5%, 81.8% and 100%) and (77.8%, 87.5%, 77.8% and 87.5%) for planner and SPECT, respectively.

Conclusion: SPECT scintigraphy potentiates the diagnostic power of the clinical probability of the suspected cases with PE. It detects more positives and changes the planner based PIOPED categories, so we advise its routine use.

INTRODUCTION

Pulmonary embolism (PE) is a highly lethal condition that is among the major leading causes of death in all age groups. Its incidence is difficult to determine, however, post-mortem studies have indicated that 65% of hospitalised patients have PE and about 7% of them die as a result of PE as the sole cause. Symptoms and clinical signs allow the clinician to determine the clinical probability but are insufficient to diagnose or exclude the condition.

Among the starting points for assessment of pretest probability is the relative risk of deep venous thrombosis (DVT) as the association between DVT and PE is well established. The clinical conditions associated with venous stasis or intimal injury include pelvic or lower extremity trauma, surgery, burns, pregnancy, post partum state, immobility, cancer and many others.

Several clinical prediction have been developed to categorised such patients as Geneva or Well’s scores; however the ability to accurately determine the pretest probability of PE appears to increase with clinical experience.

Accurate diagnosis of acute PE may be difficult on these bases, because of non-specificity of not only the clinical, but also laboratory, and radiographic findings, and although acute PE is a complication of DVT, many patients with PE have no DVT signs (subclinical form).

Since the introduction of the ventilation/perfusion (V/Q) lung scans, it is usually used to evaluate pulmonary perfusion and ventilation and globally it is used in patients with suspected PE. Although planner V/Q lung scintigraphy is the well-accepted, still frequently performed procedure, there is a growing controversy about its relevance, particularly due to increasing use of computed tomography (CT), however comparative studies with large number of patients between both modalities is essential to achieve the probable cost effective diagnostic method for PE.
It is important to say that in recent years, CT has become important in PE diagnosis, mainly because of the advent of fast scanning techniques. It demonstrated high accuracy in the pulmonary emboli at the segmental arterial level, with a lower capability to depict sub-segmental emboli. Besides, CT can evaluate the mediastinum and lung parenchyma, so potentially life-threatening pathologic entities can be identified.

The ethical scientific committee of Kasr El-Einy Center of Radiation Oncology and Nuclear Medicine (NEMROCK), Cairo University has approved our study aiming to determine the pretest clinical probability score (PCPS) for the PE suspected patients and investigating them with V/Q lung scanning (planar & SPECT) and MS spiral CT. To analyse SPECT diagnostic ability of segmental and sub-segmental PE, in comparison with planar and MS spiral CT in correlation with PCPS.

**METHODS**

68 patients suspected for PE (45 females (66%) and 23 males (34%), mean age 43.5±15.3) were included. All underwent full clinical questioner evaluation and V/Q scan (planar & SPECT). 25/68 patients underwent MS spiral CT. The clinical questioner was based on the Well's PCPS (Table 1). [8] A maximum interval of three days was chosen between V/Q scan and MS spiral CT, because the endogenous lyses of even small pulmonary clots takes at least 2–3 days, whereas larger clots cannot be lysed endogenously in less than a week. Chest radiography was done the same day of scintigraphy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current DVT</td>
<td></td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart beats ≥ 100 beats/ minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilisation or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/ PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (treatment ongoing or within previous 6 months or palliative)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>PCPS</strong></td>
<td><strong>Total points</strong></td>
</tr>
<tr>
<td>High</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Moderate</td>
<td>2-6</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

**V/Q lung scan protocols (Planar and SPECT)**

Ventilation scan was first performed using 25-50 mCi of Tc99m DTPA (Di-ethylene-penta-acetic acid) activity, placed in a special nebuliser system, and the patient is asked to breathe for 10-15 minutes aiming to deliver enough radio-aerosol to the lungs that 150.000- 250.000 count for good quality imaging can be obtained. Four hours later, perfusion scintigraphy was done using 15 mCi of Technetium 99m Macro-aggregated Albumin (Tc99m MAA) for Planar and SPECT acquisitions. Planar was acquired first, then a 360° SPECT acquisition starts (dual-headed gamma camera (Philips Medical Systems), a 180° rotation per head, 32 steps, 30 second/step, 64 X 64 matrix). SPECT images were processed with filtered back-projection (Third-order Butterworth filter, cutoff frequency 0.65). The V/Q scintigrams were interpreted in conjunction with the chest radiograph using the modified prospective investigation of pulmonary embolism diagnosis probability (PIOPED) [9], without knowledge of the CT findings.

**MS spiral CT protocol**

MS Spiral CT for 25 patients was obtained with use of 16 multi-detector row (GE Medical Systems), with intravenous infusion of 120 ml of iodo-hexol (3-5 ml/ second) with a computed injector, then MS Spiral CT of the pulmonary arteries was performed 10 seconds after commencing infusion. A 3mm slice thickness thoracic images were obtained, during a single breath hold with a pitch of 1.8-2.0. The 43/68 patients in whom no MS spiral CT was not done, 11 patients had contraindication for the use of intravenous contrast material [renal impairment [7], history of allergy (2), unstable haemodynamic status [2]]. The remaining 32 patients had a low clinical risk with normal V/Q scan or not accessible for CT within 72 hours or refused to perform CT angiography. CT scans were interpreted without knowledge of the V/Q scans findings.

**STATISTICAL ANALYSIS**

Statistical analysis was done using Epi 6 and Excel 2007 for Windows. Significance was tested using the non-parametric X2 test and McNemar. P-value < 0.05 is statistically significant. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for planar and SPECT were obtained in the 25/68 sub-group.

**RESULTS**

**I- Clinical data base**

**Frequency of the Presenting Symptomatology**

The most common presenting symptom in our study population was dyspnoea (63%) either alone or associated with others. The classic triade (Dyspnoea+Chest pain+ Hemoptysis) was gathered only in four patients. (Table 2)
Table 2. Frequency of the presenting symptoms for the study population.

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>No.(n=68)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>43</td>
<td>63.0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>36</td>
<td>52.0</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>44.0</td>
</tr>
<tr>
<td>Wheeze</td>
<td>14</td>
<td>20.0</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>6</td>
<td>9.0</td>
</tr>
<tr>
<td>Syncope</td>
<td>4</td>
<td>6.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Frequency of the predisposing factors

DVT was the most frequently found risk factor 31/68 (45.5%). The others are detailed in Table 3, however more than one risk factor were seen in the same patient. The hyper-coagulopathy was observed in five patients (7.4%), all were systemic lupus erythematosis.

Table 3. Frequency of the predisposing risk factors to thromboembolic venous

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No.(n=68)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>31</td>
<td>45.5</td>
</tr>
<tr>
<td>Immobility</td>
<td>21</td>
<td>30.9</td>
</tr>
<tr>
<td>Heart disease</td>
<td>13</td>
<td>19.1</td>
</tr>
<tr>
<td>Trauma</td>
<td>12</td>
<td>17.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
<td>16.2</td>
</tr>
<tr>
<td>History of PE</td>
<td>6</td>
<td>8.8</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>5</td>
<td>7.4</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Pretest clinical probability score

Based on the Well’s PCPS, our patients were belonging to the high (35.3%), intermediate (17.6%) and low (47.1%) PCPS. (Table 4)

Table 4. Pretest clinical probability categorisation of the study population.

| Pretest clinical probability | No. (n=68) | %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>24</td>
<td>35.3</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>12</td>
<td>17.6</td>
</tr>
<tr>
<td>Low probability</td>
<td>32</td>
<td>47.1</td>
</tr>
</tbody>
</table>

II- Imaging tools

Chest X-ray findings

The chest x-ray features were classified into normal, with PE features, and non embolic features associated. 39/68 (57.3%), 1/68 (1.5%) and 38/68 (55.9%) were belonging respectively to this classification. Among the later (18/38 (47.4%)) were having pleural effusion (10/18 PE negative & 8/18 PE positive).

The Prevalence of PE in the study population based on V/Q lung scans

We have analysed the diagnostic outcomes regarding all the clinical-diagnostic aspects:

1-Age
The mean age was 43.5±15.3, being above forty in the positive and below forty in the negative cases respectively with statistically insignificant difference.

2-Sex
The male to female ratio was about 1:2 (23:45). In the females 26/45 (57.8%) were PE positive; the males was 12/23 (52.2%) with statistically insignificant difference.

3- Pretest clinical probability score

Planner outcome
The positivity rate was 12/24 (50%), 3/12 (25%) and 13/32 (40.6%) of the high, intermediate and high PCPS with overall positivity agreement of 41.2%.

SPECT outcome
A higher positivity rate was elicited: six more cases were added in the high PCPS (18/24(75%)), one in the intermediate PCPS (4/12 33.3%), and two less in the low PCPS (11/32(34.4%)), with overall positivity agreement of 48.5%. Statistically significant difference was found between planner and SPECT in the high PCPS (p-value 0.02). The added six cases were belonging to the intermediate and high modified PIOPED categories, three for each (were normal on planner), while two cases from the intermediate and low PCPS were transformed to the normal category (were positive on planner).
4- Modified PIOPED probabilities

Positive cases
In the planner: 2/28(7.1%), 4/28(14.3%) and 22/28(78.6%) were low, intermediate and high PIOPED, respectively. In SPECT 4/33 (12.1%), 10/33 (30.3%) and 19/33 (57.6%) were low, intermediate and high PIOPED, respectively. The term probability change [PC] was used with the analytic aim of the SPECT induced exchanges in-between the planner PIOPED probabilities. SPECT PC was: 3/22 high PIOPED changed to normal (13.6% PC), 2/4 intermediate PIOPED changed to one normal and one low probability (50% PC) and 2/2 low PIOPED changed to normal and intermediate probability (100% PC). The overall PC was about 18%.

Negative cases
40/68 cases were negative with planner. SPECT transformed 10/40 to positive (seven low and three intermediate) representing 25% overall PC.

Negative and positive cases
To intermingle the positive and negative scan outcomes, we have used what we called clinical probability change [CPC] regarding only the cases transformed from positive to normal or from normal to positive with SPECT, being 10 negative planner cases transformed to positive with SPECT (three low and seven intermediate) and five positive planner cases (three, one and one in the high, intermediate and low PIOPED) transformed to negative with SPECT. The SPECT based CPC was 22% (15/68).

4- Number of segmental and sub-segmental defects
The total defect number detected with planner and SPECT was 113 and 142, respectively. They were 86 and 96 segmental and 27 and 46 sub-segmental defects by the planner and SPECT methods respectively. SPECT detected additional 29 perfusion defects (10 segmental & 19 sub-segmental) with statistically significant difference (p-value 0.04).

The Prevalence of PE in the 25/68 Patient Sub Group
9/25 and 16/25 were positive for PE by MS spiral CT. Among the nine positive cases, seven were high PIOPED and two were normal using the planner method, while all the nine cases were positive by using the SPECT (seven high, one intermediate and one low PIOPED). In the negative 16 patients, planner and SPECT were negative in 14/16 and falsely positive in 2/16. By considering MS spiral CT as a gold standard; sensitivity, specificity, PPV and NPV of planner and SPECT were (77.8%, 87.5%, 77.8% and 87.5%) and (100%, 87.5%, 81.8% and 100%), respectively.

DISCUSSION
We are going to present our discussion in partitions stepping the same sequence we have used in the results. The points, regarding the study design and technical aspects, that may be questioned, we have tried to clarify in the methods section.

Clinical database
The most striking clinical presentations were dyspnoea, chest pain and cough as seen in 63%, 52% and 44%, respectively (Table 2). A difference of around 10% in between each of these numeric figures was noted, so we re-analyse the patient with a simple enquiry about any possible useful combination. We found no useful combination. The real problem is in an emergency situation, as the patient may be too confused to determine what their complaint is. Dyspnoea was the most frequent and we considered dyspnoea an important item in the PE symptomatic portrayal.

In a published report, they concluded; although the clinical presentation of PE has many different faces with a different face coming with each subject, dyspnoea is the most frequent. [10] Among patients with confirmed PE without preexisting cardiac or pulmonary disease, either dyspnoea or tachypnoea occurring in 96%. [3] Based on our and the other aforementioned reports, we suggest a modification in the Well's PCPS by adding dyspnoea to the score variables giving it 1-1.5 point.

It is known that there is a 90% association between PE patients and DVT. The DVT is precipitated by predisposing factors as immobilisation, traumatic crashes and others. We focused on that point guided by the PIOPED study, where a 92% incidence of at least one predisposing factor was recorded, so a 90% incidence in our PE included subjects was not a surprise. However, these conditions are non sensitive and non specific as they are frequently present in patients proved to be PE negative.

So, objective testing for PE is crucial, because clinical assessment alone is unreliable and the consequences of misdiagnosis are serious. [11] We can partially agree with this statement, although we have encountered a similar behaviour in more than 50% of the PE negatives, because this can lead to underestimation of the clinical aspects and subsequently PCPS. We have found 24/68 (35.3%), 12/68 (17.6%) and 32 (47.1%) belonging to the high, intermediate and high PCPS, respectively (Table 5).

The planner proved that 50% of the high PCPS suffer with PE; then SPECT increases the predictive power of the high PCPS to 75% (p-value 0.02). About 10% similar increment is noted in the intermediate PCPS (planner 25%, SPECT 33.3%). In the low, PCPS SPECT showed less positive cases (34.4%) than planner (40.6%). It is worth mentioning that there is good evidence that clinical assessment, either empirical or standardised, can stratify a patient’s probability of PE using the Well's PCPS with an expected prevalence 10% in low, 25% in the intermediate and 60% in the high PCPS. [8] So, from a clinical point of view, we notice a higher PCPS predictability regarding the SPECT outcomes than the planner. Put differently, SPECT potentiates PCPS especially in the high PCPS group.

II- Imaging tools
Chest X-ray findings
It is a global practice to make the V/Q lung scan interpretation with a recent chest x-ray, so in our study, this was the routine to correlate the non-embolic V/Q features with the radiological state. Among the sources of discrepancy between the planner and SPECT are the associated non-embolic changes as they influence the interpretation capability in the planner especially in the neighbouring segments and sub segments, and this is much less pronounced with SPECT. As published: radiograph is especially valuable in excluding other conditions mimicking PE, but PE may coexist with other cardiopulmonary processes. [8]
V/Q lung scans

V/Q lung scan is a safe non-invasive technique used worldwide since more than two decades for diagnosis of PE. On the other hand SPECT is a routine methodology in all the modern nuclear medicine diagnostics; however in the recent years it comes in the routine practice of V/Q lung scintigraphy. In our study 86 and 96 segmental and 27 and 46 sub-segmental defects were detected by the planner and SPECT, respectively. SPECT detected additional 29 perfusion defects (10 segmental and 19 sub-segmental) with statistically significant difference (p-value 0.04). In the 25/68 sub-group, considering MS spiral CT as a gold standard, the sensitivity, specificity, PPV and NPV of planner and SPECT modalities were (77.8%, 87.5%, 77.8% and 87.5%) and (100%, 87.5%, 81.8% and 100%), respectively.

This was not surprising, when you refer to global publications. For example, I- The Planner technique has been widely used for the evaluation of patients with suspected PE. Despite imaging in multiple projections, the perfusion scan may underestimate perfusion abnormalities. II- Our data support better sensitivity of SPECT over planar. III- At the sub segmental level, the detectable defect number by SPECT could be significantly increased up to 82.6% compared with that of planar (P = 0.01), while at the segmental level, the increase was still considerable 12.8% but statistically insignificant (P = 0.4) . The reason for this upper hand is SPECT owns a higher resolution power of the lung segments and more important sub segments whether they are in the centre or periphery and the ability of overcoming any interference from associated non embolic changes.

Now, we will move to the point considered by our group as the main core in our study i.e. probability change (PC) and clinical probability change (CPC). Based on these points, SPECT proves a higher and more accurate diagnostic power than planner and subsequently potentiates the predictive power of the PCPS. When we see the transfer of a patient probability from an extreme to the opposing extreme (normal to high PIOPED or high PIOPED to normal) with no doubt this is remarkably important. This was presented as CPC being 22% (among them 2/3 were negative in planner and PCPS positive).

This is simply because the treatment policy has turned from anti-clockwise to a clockwise direction. Now, we will focus on the low and intermediate PIOPED categories. 10/40 negative planner changed to positive SPECT (seven low and three intermediate) with an overall PC 25%. While in the positive planner, there were two cases, one goes from intermediate to low and the other has done the opposite. We will start with a question: what is the clinical significance of low probability of PE? The answer comes in the following published facts in the PE research community. Hull et al., 1994 wisely stated that the low probability interpretation of V/Q scan has been characterised as misleading because unacceptably high prevalence of PE associated with this interpretation. Worsley and Alavi, 2003 claimed that a high rate of false negatives may occur with low probability and should not be considered as an entirely normal lung scan. Therefore, clinical correlation and follow-up for this group is very important.

In patients with low probability V/Q scan plus no history of immobilisation, recent surgery, trauma to the lower extremities or central venous instrumentation, the PE prevalence is only 4.5%, while in those with low probability interpretations plus only one risk or more than one risk, the PE prevalence is 12% and 21%, respectively. They have focused on the risk factors or what we called PCPS.

They also stated: patients with false-negative lung scan interpretations tend to have non-occlusive sub segmental thrombi, with low pulmonary clot burden and in recent years, concern has been raised that a low probability lung scan interpretation could be a misleading and result in unnecessary morbidity or mortality in patients with PE and were not anticoagulated. Garg et al claimed, in many studies patients with low-probability V/Q scan obtained a positive spiral CT scan. So, when planner says no PE while PCPS is positive and SPECT says low probability, this is very critical. By referring to the aforementioned publications, low probability is stating that we are confronted with a clinically critical and potentially lethal situation.

Especially if we have high PCPS, and it is the to go to the end of the light button volume, using CT angiography, and if this is the situation in the low PIOPED, it is an expected issue to be more exaggerated in the intermediate PIOPED when SPECT and PCPS are pointing to it, while planner is not. Also, this means a combination of negative or low PIOPED planner with positive PCPS, SPECT is a must, to be able to judge properly the PCPS positivity.

We will conclude with a few points. First, we have mentioned the gray zone in to which the patient steps with clinical suspicions and here the tools are working to focus the light and solve what has been missed. The clinical suspicion is PCPS and our results have showed their relevant importance when SPECT is used, potentiation its diagnostic importance. Second, SPECT is not a new imaging modality but recently added to the classical planar lung technique with no added cost or efforts except for several additional minutes. We recommend its use on routine basis, or at least under guidance by PCPS. Third, CT and lung scans are not competitors but complementary.

Lung scan is a functional modality showing the clinical significance of an embolus in a probability mode (embolus effect) while CT see the embolus itself. Fourth, the interpretation abilities of SPECT lung scans must increase, to be more familiar (the clinicians and nuclear medicine) with SPECT and possible associated pitfalls. The more practice; the more experience gained. Finally, the PE diagnostic dilemma is not only an investigatory portrayal, but a clinico-investigatory portrayal, and it is the time to put the PCPS in its normal place of importance as the clinicians, especially the less experienced, must be fully briefed about its importance in guiding the investigatory tools and giving the green light for each modality to be activated for diagnosis of PE.
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