Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism
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The accuracy of chest X-ray in combination with perfusion scanning as an alternative for CTPA in young patients with a high risk of pulmonary embolism

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**ABSTRACT**

**Background:** Computed tomography pulmonary angiogram (CTPA) has become the standard test in the diagnostic workup of patients with suspected pulmonary embolism (PE). However, especially young patients have an increased risk of cancer due to radiation exposure with CTPA and may benefit from an alternative diagnostic modality. Perfusion scanning combined with chest X-ray result (X/Q) by using the PISAPED criteria seems an adequate alternative, but has never been prospectively validated. We therefore directly compared this strategy with CTPA in patients aged < 50 years with suspected PE.

**Methods:** Consecutive patients with a likely clinical probability or an abnormal D-dimer level were included, in whom both CTPA and X/Q were performed. X/Q-scans were independently analyzed by two trained nuclear physicians. The accuracy of X/Q according to the PISAPED criteria in terms of sensitivity, specificity positive predictive value (PPV) and negative predictive value (NPV) was calculated.

**Results:** A total of 76 patients were included. The prevalence of PE was 33%. The interobserver agreement for X/Q-scan reading was high (κ=0.89). After consensus reading, 21 patients (28%, 95% confidence interval (CI) 19-38%) were categorized as 'PE present', 54 (71%, 95% CI 60-80%) as 'PE absent', and two (2.6%, 95% CI 0.8-9.0%) as 'non-diagnostic'. In 17 cases (22%, 95% CI 14-32%) was a discrepancy between CTPA and the X/Q result. The PPV and NPV were 71% (95% CI 50-86%) and 83% (95% CI 71-91%), respectively.

**Conclusion:** Although the X/Q-strategy seems promising in literature to reduce CTPA in young patients, its diagnostic accuracy was limited in our cohort.
**INTRODUCTION**

A diagnostic algorithm based on clinical probability, D-dimer, and computed tomography pulmonary angiogram (CTPA) has been shown to be a safe and efficient strategy in the management of patients with suspected pulmonary embolism (PE) (1). However, concerns have been raised regarding the risk of cancer following radiation exposure with CTPA, especially among young women (2;3). In this group of patients, the lifetime risk of cancer incidence is considerable, particularly the risk of breast cancer (2;3). Compared to CTPA, breast irradiation with ventilation/perfusion scintigraphy is approximately 50-100 times lower (4-6).

Although ventilation/perfusion scintigraphy (V/Q-scan) is an established diagnostic test, ventilation scintigraphy is expensive and not available in many hospitals. Also, the proportion of non-diagnostic scan results is around 50%, which limits its use in clinical practice. Previously, several studies have evaluated whether ventilation lung scanning could be replaced by the chest X-ray in defining a segmental perfusion defect to be matched or mismatched in patients with suspected PE (X/Q-scan) (7-9). Although the positive predictive value (PPV) of a high probability X/Q-scan was high (86%), the proportions of non-diagnostic test results were still considerable (ranging from 21% to 49%). The use of only perfusion scanning instead of the V/Q-scan is also supported by a prospective study by the PISAPED group (Prospective Study of Acute Pulmonary Diagnosis) (10). A retrospective validation (9), showed a sensitivity and specificity of 80% and 97%, respectively, compared to CTPA (9). However, because of the retrospective design, the Q-scans were performed without following the PISAPED protocol. These studies assessed patients without stratification according to pre-test clinical probability combined with the D-dimer test. Moreover, young patients have less co-morbidity than elderly patients. Consequently, this may improve the diagnostic yield of an X/Q scan in this subgroup of patients (11;12).

The aim of this study was to prospectively investigate the sensitivity, specificity, PPV and the negative predictive value (NPV) of the X/Q-scan according to the PISAPED criteria in comparison to CTPA in patients aged < 50 years, and with a likely clinical probability of PE or an abnormal D-dimer result. Furthermore, we assessed the proportion of perfusion scans classified as ‘non-diagnostic’ according to the PISAPED criteria, requiring CT-scanning.


METHODS

Patients
The study was a prospective, multi-center cohort study of consecutive in- and outpatients younger than 50 years old with suspected PE, who had either a likely clinical probability (according to Wells and/or Revised Geneva Score) (13,14) or an abnormal D-dimer test result (1). The D-dimer test was considered normal when below 500 µg L\(^{-1}\). Next to the CTPA, a chest X-ray and Q-scan were performed within 24 hours in all participants.

Patients were included in seven academic and non-academic medical centers in the Netherlands and Belgium between October 2008 and June 2011. Participants were managed according to the outcome of the CTPA, and according to local hospital practice. Exclusion criteria were age below 18 years or above 50 years, pregnancy, use of therapeutic dose LMWH or unfractionated heparin for longer than 48 hours prior to eligibility assessment and inability to perform a perfusion scan within 24 hrs after CTPA. Demographic data and additional relevant information were collected on a Case Record Form. Institutional ethical review board of all participating centers approved the study protocol and informed consent was obtained from all included patients.

Although three months follow-up was not performed, we retrospectively evaluated whether PE occurred in patients with a discrepancy between the CTPA and the X/Q scan result.

CTPA
CTPA was the reference standard in this study. All CTPAs were assessed by the radiologist on-call. Standard contrast enhanced CTPAs were performed using a multi-detector row CT-scanner according to state-of-the-art protocols for the diagnosis and evaluation of PE (15). Patients were scanned during a single breath-hold, in caudocranial direction, from the upper level of the diaphragm to a level slightly above the aortic arch (pitch of 1, 120 kV, 150-200 mAs). One hundred milliliters of contrast was administered intravenously. An imaging delay of 20 seconds was used and overlapping images were reconstructed every 3 mm. PE was confirmed by the presence of a constant intraluminal defect in (sub) segmental or more proximal branches of a pulmonary artery.

Perfusion scintigraphy
Six-view perfusion lung scintigraphy was performed within 24h of referral following the guidelines of the Society of Nuclear Medicine (SNM 2004) (16). Images were
obtained immediately after the administration of 148-155 MBq of technetium-99m macroaggregated albumin particles (MAA) after several deep breaths. According to the PISAPED protocol, care was taken to inject the radioactive bolus with the patient positioned as closely as possible to the sitting position in order to preserve the effect of gravity on the regional distribution of pulmonary blood flow (10). The effective radiation dose varied per MBq dose, ranging from 0.55-1.1 mSv.

Chest radiographs (X)
In examining the chest radiographs, the PISAPED readers considered the size and shape of the heart and hilar arteries, position of the diaphragm, presence or absence of pulmonary parenchymal abnormalities (consolidation, atelectasis, edema), and pleural effusion. Chest radiographs were rated as abnormal if one or more of the following were present: enlargement of the heart or hilar vessels; elevated diaphragm (unilateral or bilateral); pleural effusion (including intrafissural liquid); increased lung density (focal or diffuse); pulmonary edema; oligemia with or without pleonemia in the contralateral lung; consolidation suggestive of infarction; emphysema; or fibrothorax.

X/Q-scan
The X/Q-scans were centrally adjudicated according to the PISAPED criteria (10) (Table 1) and compared with the CTPA. For our analysis we used the results of the chest X-ray combined with Q-scan (X/Q-scan). All images at time of the diagnosis were stored on CD-Rom or comparable storage. All X/Q-scans were analyzed by two trained nuclear physicians, who were blinded of clinical information or CTPA result. In case of disagreement, a consensus reading was carried out with a third reviewer. In case of abnormalities on the perfusion scan, the findings were combined with the result of the chest radiograph (X/Q-scan).

The readers interpreted the Q-scans according to PISAPED criteria (Table 1). Abnormal perfusion scans were classified as 'PE present' when single or multiple wedge-shaped perfusion defects were present, irrespective of abnormalities on the chest X-ray, aiming to reduce the number of non-diagnostic scans. PE was considered as 'PE absent' in case of either no perfusion defects of any kind or perfusion defects which are smaller or equal in size and shape to the following chest radiograph abnormalities: cardiomegaly, enlarged aorta, hilar and mediastinum, elevated diaphragm blunting of the costophrenic angle, pleural thickening, intrafissural collection of pleural effusion. Also, if the perfusion defects were not wedge-shaped regardless matching chest
radiograph abnormalities, X/Q-scan was considered as 'PE absent'. Wedge-shaped areas of overperfusion are usually not seen. In all other cases the X/Q-scan was considered non-diagnostic. These patients would, theoretically, require additional testing (Table 1, criteria adapted from Miniati et al (10)).

**Table 1.** PISAPED Scintigraphic Criteria (Prospective Study of Acute Pulmonary Diagnosis) (10).

<table>
<thead>
<tr>
<th>PE present</th>
<th>Abnormal: PE</th>
<th>One or more wedge-shaped perfusion defects, with or without matching chest X-ray abnormalities. Wedge-shaped areas of overperfusion usually coexist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE absent</td>
<td>Normal:</td>
<td>No perfusion defects of any kind</td>
</tr>
<tr>
<td></td>
<td>Near normal:</td>
<td>Perfusion defects smaller or equal in size and shape to the following chest X-ray abnormalities:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- cardiomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- enlarged aorta, hila and mediastinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- elevated diaphragm blunting of the costophrenic angle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pleural thickening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- intrafissural collection of liquid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-diagnostic</th>
<th>Abnormal: no PE</th>
<th>Perfusion defects not wedge-shaped with or without matching chest X-ray abnormalities. Wedge-shaped areas of overperfusion are usually not seen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cannot classify as PE+ or PE-</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical analysis**

Normally distributed variables are presented as mean and standard deviations (SD) and non-normally distributed variables are expressed as medians with (interquartile-) ranges. The proportion of patients in each X/Q category was calculated, as well as the sensitivity, specificity and positive and negative predictive values, with 95% confidence intervals (CI). To express inter-reader agreement the multi-reader kappa (κ) coefficient was calculated. Sensitivity, specificity, positive and negative predictive values of X/Q were calculated in comparison to CTPA. All analyses were performed using SPSS, version 19.0 (SPSS, Chicago il. USA).
RESULTS

A total of 78 patients with suspected PE and a likely clinical probability or abnormal D-dimer test result were included. The Q-scan result was missing in one patient and in another patient the timeframe between the CTPA and Q-scan was > 24 hours. Consequently, these patients were excluded. Table 2 shows the baseline characteristics of the 76 participants, who underwent CTPA and X/Q-scan. Twenty-six patients (34%) had a likely clinical decision rule, 68 patients (90%) had an abnormal D-dimer test result. Twenty-five patients (33%) were diagnosed with PE based on the CTPA.

Table 2. Clinical characteristics of patients with suspected PE (likely clinical probability or abnormal D-dimer test result), who underwent CTPA and X/Q-scan.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>48 (64)</td>
</tr>
<tr>
<td>Age, years, median (IQR)</td>
<td>40 (29-45)</td>
</tr>
<tr>
<td>Body Mass Index, mean (SD)</td>
<td>27 (5.9)</td>
</tr>
<tr>
<td>Duration of complaints in days, median (IQR)</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Use of estrogen containing drugs, n (%)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Clinical symptoms of DVT, n (%)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Tachycardia, n (%) #</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Hemoptysis, n (%)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Immobilization or surgery in last 4 weeks, n (%)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Active cancer, n (%)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td>Previous episode of VTE, n (%)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Likely Wells score or Revised Geneva Score</td>
<td>26 (34)</td>
</tr>
<tr>
<td>D-dimer level &gt; 500 µg L⁻¹, n (%)</td>
<td>68 (90)</td>
</tr>
</tbody>
</table>

COPD chronic obstructive pulmonary disease, CTPA computed tomography pulmonary angiogram DVT deep venous thrombosis, N number, SD standard deviation, VTE venous thromboembolism, X/Q-scan chest X-ray combined with perfusion scintigraphy.
The interobserver agreement was almost perfect ($\kappa = 0.89$). After consensus reading, 21 patients (28%, 95% CI 19-38%) were categorized as ‘PE present’ with X/Q, 53 patients (70%, 95% CI 64-84%) were categorized as ‘PE absent’ and in two patients (2.6%, 95% CI 0.8-9.0%), the scan was classified as non-diagnostic (Table 3).

Overall agreement for the diagnosis of PE between the CTPA and the X/Q-scan was present in 59 of 76 patients (78%, 95% CI 67-86%) (Table 3). The sensitivity and specificity of the X/Q-scan were 60% (95% CI 41-77%) and 86% (95% CI 74-93%), respectively. The PPV of X/Q was 71.4% (95% CI 50-86%) and the NPV was 83.0% (95% CI 71-91%), respectively (Table 3).

In nine patients, PE was detected with CTPA whereas X/Q-scan scored ‘PE absent’. Eight of these cases had segmental or more proximal PE and one patient had subsegmental PE. All these patients received anticoagulant therapy. On the other hand, PE was ruled out by CTPA, but classified as ‘PE-present’ on X/Q-scan, in six patients. Three months follow-up in those patients was uneventful despite the fact that anticoagulant therapy had not been started.

**Table 3.** Overall agreement of the CTPA and Chest X-ray/perfusion scan (X/Q) according to PISAPED (10).

<table>
<thead>
<tr>
<th>X/Q</th>
<th>PE present, n (%)</th>
<th>PE absent, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTPA</td>
<td>PE</td>
<td>No PE</td>
<td>total</td>
</tr>
<tr>
<td>PE present, n (%)</td>
<td>15 (20)</td>
<td>6 (8)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>PE absent, n (%)</td>
<td>9 (12)</td>
<td>44 (58)</td>
<td>53 (70)</td>
</tr>
<tr>
<td>Non diagnostic, n (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>25 (33)</td>
<td>51 (67)</td>
<td>76 (100)</td>
</tr>
</tbody>
</table>

CI confidence interval, CTPA computed tomography pulmonary angiogram, PE pulmonary embolism, PISAPED Prospective Study of Acute Pulmonary Diagnosis

Sensitivity: 60% (95% CI 41-76%)
Specificity: 86% (95% CI 74-93%)
Positive predictive value: 71% (95% CI 50-86%)
Negative predictive value: 83% (95% CI 71-90%)


**Discussion**

In our cohort of young patients suspected of PE with likely clinical probability or abnormal D-dimer, X/Q-scans read according to PISAPED criteria did not reliably categorize segmental perfusion defects as ‘PE absent’ or ‘PE present’ for PE. The PPV was 71% (95% CI 50-86%), and NPV of 83% (95% CI 71-91%) by using CTPA as standard. Therefore, X/Q-scan as a diagnostic test for PE was not accurate enough to either confirm or exclude PE.

Our results differ from previous reports. Sostman and colleagues compared both the PISAPED criteria and the PIOPED II criteria with CTPA, using data of 889 perfusion scans (9). Compared to CTPA, they found a sensitivity of the PISAPED criteria of 83.3% (95% CI, 76.0-88.7%) and a specificity of 97.0% (95% CI, 95.5-98.0%) among patients less than 50 years. The PPV and NPV were 96% and 95 %, respectively. There were no patients with a non-diagnostic scan in this cohort. The reason why we cannot reproduce these data on our cohort is unclear. However, since they have validated the PISAPED criteria retrospectively in scans using the PIOPED II protocol, there was no care taken that the patients received the radioactive bolus while they were positioned in a sitting position, according to the PISAPED protocol (10). Besides, in this study, patients were stratified according to their pre-test probability by using the Wells score, but not in combination with a D-dimer test-result. However, whether this explains the large difference between the accuracy of the PISAPED criteria is not known.

Previous studies, investigating the efficiency of a chest radiograph and Q-scan showed, high levels of the PPV, ranging from 82-100% (7;8;17). In these studies, the chest X-ray was also used as a substitute for ventilation scintigraphy, and was interpreted in a similar fashion when it was combined with the Q-scan. PE was considered present in case of one or more segments of X/Q mismatches, regardless the shape of the perfusion defect. Although adequate predictive values were obtained in these studies, the number of non-diagnostic results was also high (ranging from 31-49% (7;8;17)).

PISAPED criteria classified patients as ‘PE present’ or ‘PE absent’ based on the shape of the perfusion defect, irrespective of the presence of chest X-ray abnormalities. Therefore fewer non-diagnostic test results were to be expected, which is confirmed by our results (2 out of 77). However, the wedge shape perfusion defect that had to be specifically present for the Q-scan being classified as ‘PE present’ may have caused the high number of false negative test results (9 of 53 patients with ‘PE absent’ were diagnosed with PE by CTPA).
The near perfect interobserver agreement of the X/Q-scans using the PISAPED criteria ($\kappa=0.89$), which is in line with the literature (Sostman et al. reported $\kappa=0.903$) (9), suggests a good consistency in the evaluation, which strengthens our results. Among patients diagnosed with PE on the X/Q-scan and with a negative CTPA result ($n=6$), none had a suspected or recurrent PE during the next 3 months, despite the lack of anticoagulant therapy. Additionally, among patients classified as ‘PE absent’ by the X/Q, and having PE on CTPA, all but one patient had segmental or larger PE with a CTPA. One of these patients had central PE, which leads to large areas of hypoperfusion and makes wedge-shaped perfusion defects harder or even impossible to detect.

Our finding that CTPA detects more PE than the Q-scan, is in line with the literature (18). The proportion of patients with PE was comparable to other management studies on the diagnostic work-up of PE (36% and 45%) (1;19). Our study has implications regarding the role of the Q-scans in patients with suspected acute PE. The advantages of CTPA secure a place for CTPA as a first-line diagnostic imaging test in appropriately selected patients (1). However, the advantages of Q-scanning, which are in addition to the lower radiation dose and avoidance of iodinated contrast material, lower costs, can also be considered. Despite an increased use of Q-scans appears warranted, especially in a young and healthy population (20), our data show that the PISAPED criteria seem neither a safe nor an accurate alternative for CTPA. However, the accuracy of X/Q-scan strategy, prospectively assessed and using other criteria (i.e. modified PIOPED II criteria), remains to be shown. If in a prospectively conducted investigation X/Q-scan shows a high sensitivity and specificity, clinical care might be enriched by X/Q-scan next to the CTPA. Currently, however, CTPA is the gold standard for detecting or excluding PE, regardless the patients’ age.

The conclusions of this study are strengthened by its prospective and multicenter design, in patients with a risk stratification including a clinical decision rule and a D-dimer, which enhance the extrapolation of our findings. Some limitations of our study warrant consideration. First is the moderate sample size. We discontinued this study after the first 78 included patients, since it appeared from the analysis that further continuation of the study was futile. This was on the basis of the NPV and PPV of the X/Q-scan, which seemed to fall short compared to CTPA. We believe that the conclusions of the diagnostic accuracy of the X/Q-scan according to the PISAPED criteria would not change with a larger sample size. In addition, we did not perform follow-up in all participants. However, since the event rate of VTE after a negative CTPA results is negligible (1), we consider this strategy as safe. Besides, in the patients with a negative CTPA result and
‘PE present’ on the X/Q-scan, we did perform follow-up retrospectively. None of these patients experienced (suspected) VTE within three months after inclusion.

In conclusion, our results demonstrate that in patients aged < 50 years with a likely clinical probability of PE or abnormal D-dimer test result, a diagnostic strategy of X/Q-scan according to the PISAPED criteria is insufficient to reliably exclude or confirm the diagnosis of PE.

**Reference List**


(20) Freeman LM. Don't bury the V/Q scan: it's as good as multidetector CT angiograms with a lot less radiation exposure. J Nucl Med 2008 Jan;49(1):5-8.