Pulmonary embolism: advances in diagnosis and prognosis
Douma, R.A.

Chapter 11

An alternative diagnostic strategy in young women with suspected pulmonary embolism

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ABSTRACT

Background
Because younger women have an increased risk of cancer following radiation exposure with CT scanning, they might benefit from an alternative diagnostic strategy for suspected pulmonary embolism (PE).

Methods
We investigated the safety and efficacy of a diagnostic strategy consisting of clinical probability, D-dimer assay, chest X-ray and perfusion-scintigraphy in women aged <50 years with suspected PE, in order to reduce the number of CT-scans. This strategy was analyzed in two cohorts of consecutive patients with suspected PE, in which perfusion-scans and chest X-rays were combined (X/Q-scan). We calculated the predictive accuracy and the proportion of women in whom CT could be avoided.

Results
The prevalence of PE was 20% and 19% for the first and second cohort, respectively. In the first cohort, 44% (95% confidence interval (CI), 33-55%) of the women with either a likely Wells score or an abnormal D-dimer had a normal X/Q-scan; 40% (95%CI, 30-51%) had a non-high X/Q-scan and 14% (95%CI, 8-24%) a high-probability X/Q-scan. In the second cohort, these percentages were 58% (95%CI, 44-70%), 17% (95%CI, 9-30%) and 25% (95%CI, 15-38%) respectively. The positive predictive value of a high probability X/Q-scan was high in both cohorts: 82% (95%CI, 52-95%) and 100% (95%CI, 77-100%), respectively. CT could theoretically be avoided in 60% and 83% of women.

Conclusions
A strategy consisting of clinical decision rule, D-dimer testing, perfusion scintigraphy and chest X-ray seems promising to reliably exclude or diagnose PE. Further prospective evaluation in a larger population of young women is warranted.
INTRODUCTION

In the diagnostic management of patients with suspected pulmonary embolism (PE), an algorithm consisting of clinical probability, D-dimer, and computed tomography (CT) has been shown to be safe and efficient (1). However, concerns have been raised recently regarding the risk of cancer following radiation exposure with CT scanning (2,3). The lifetime attributable risk of cancer is considerable for young women, particularly for breast cancer (3). In an average woman weighing 60 kg, breast irradiation with CT angiography is 10-20 mGy per breast (4,5), up to 190 mGy in a woman with large breasts (6). In contrast, breast irradiation with a ventilation-perfusion scan is approximately 0.28 mGy (4). Hence, young women might benefit from an alternative diagnostic strategy to avoid CT and the associated radiation to the breasts.

Although ventilation-perfusion (V/Q) scintigraphy is an established diagnostic test in patients with suspected PE, ventilation scintigraphy is expensive and not available daily in most hospitals. Also, large studies have shown that V/Q scanning is often non-diagnostic, i.e. unable to exclude or confirm PE (7,8). If the ventilation scan could be omitted, this would reduce both costs and radiation. Previously, two 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) (9,10). Although the positive predictive values of a high probability X/Q scan were high (86% compared to V/Q (10) and 93% compared to pulmonary angiography (9), respectively), the proportions of non-diagnostic test results were still considerable (40% and 49%, respectively). However, these studies assessed patients with suspected PE, without stratification according to pre-test clinical probability, D-dimer or age. Young women, in whom irradiation from CT scanning is most harmful, will have less co-morbidity compared to elderly patients. Consequently, this may improve the diagnostic yield of an X/Q scan in this subgroup (11).

We therefore investigated the safety and efficiency of a diagnostic strategy consisting of clinical probability, D-dimer assay, chest X-ray and perfusion scintigraphy in women aged <50 years with suspected PE, in order to reduce the number of CT scans.

METHODS

We tested a diagnostic strategy with chest X-ray and perfusion scintigraphy in women less than 50 years of age in two study cohorts. The strategy was first analyzed retrospectively in a large diagnostic accuracy study (the ANTELOPE study (12)) to evaluate how patients were distributed among the various outcome categories and to assess diagnostic accuracy. Because the original scans were not available for re-examination, we validated the strategy in another diagnostic management study cohort (Leventas study, PW Kamphuisen, AJM Rijnders, EF Ullmann, unpublished).
The ANTELOPE study was a large multi-centered accuracy study, performed in six teaching hospitals in Amsterdam, Leiden, The Hague and Utrecht, the Netherlands, which assessed various diagnostic methods for pulmonary embolism. The Leventas study was a diagnostic management study, performed in the Rijnstate Hospital, a teaching hospital in Arnhem, the Netherlands, in which a combination of clinical probability, D-dimer testing, and ventilation-perfusion scintigraphy in consecutive patients with suspected pulmonary embolism was assessed. For both studies, the Institutional Review Boards of the participating centers approved the study protocol and informed consent was obtained from all participants. Predefined exclusion criteria were: pregnancy, indication for thrombolytic therapy, already undergone objective testing for venous thromboembolism, and inability to complete the diagnostic protocol within 48h of presentation. Upon referral, clinical probability and risk factors were assessed allowing calculation of the Wells score (13). After assessing the clinical probability, a rapid whole blood D-Dimer test (SimpliRED D-Dimer assay, Agen Biomedical Ltd., Brisbane, Australia) or enzyme-linked immunosorbent assay (ELISA, Tinaquant D-dimer assay, Roche Diagnostica, Mannheim, Germany) were used in the first and second cohort, respectively. The D-dimer was normal when below 500 μg/L.

**Imaging studies**

In both studies, a six-view perfusion lung scintigraphy was performed within 24h of referral using 50-100 MBq of 99mTechnetium-labeled macroaggregates of albumin. If at least one segmental or larger perfusion defect was seen, ventilation scintigraphy, using 81mKrypton gas, was performed. Lung scans were interpreted and categorized according to previously described criteria (14). PE was ruled out in case of a normal perfusion scan (i.e. no perfusion defects) and confirmed in case of a high-probability ventilation-perfusion scan (i.e. at least one segmental perfusion defect with normal ventilation). In all other cases, the scans were categorized as non-diagnostic and pulmonary angiography was performed, using standard techniques and interpreted according to accepted criteria (15,16). V/Q or pulmonary angiography were the reference standard for the analyses in both cohorts.

**X/Q-scan**

A chest X-ray was performed in all patients and interpreted by a radiologist unaware of the results of the V/Q scan. For our analysis we used the results of the chest X-ray combined with perfusion scintigraphy. In case of abnormalities on the perfusion scan, the findings were combined with the result of the chest X-ray (“X/Q scan”). Perfusion scans with at least one segmental defect and a normal chest X-ray were defined as high probability scans for PE (see Table 1, criteria adapted from Hull et al. (14)). In all other cases (i.e. defects smaller than segmental or segmental defects but abnormal chest X-ray) the X/Q scan was considered non-diagnostic. These patients would, in theory, require additional testing.
Table 1. X/Q criteria

<table>
<thead>
<tr>
<th></th>
<th>ANTELOPE</th>
<th>Leventas</th>
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<tr>
<td>Normal Q scan</td>
<td>Normal perfusion scan</td>
<td>Normal perfusion scan</td>
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<td></td>
<td></td>
<td>Near normal perfusion scan:</td>
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<td></td>
<td></td>
<td>- Small irregularities</td>
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<td></td>
<td></td>
<td>- Perfusion defects smaller or equal in size</td>
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<tr>
<td></td>
<td></td>
<td>and shape to the following chest X-ray</td>
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<tr>
<td></td>
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<td>abnormalities:</td>
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<td>cardiomegaly, enlarged aorta, hila and</td>
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<td></td>
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<td>mediastinum, elevated diaphragm, blunting of</td>
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<td></td>
<td>the costophrenic angle, pleural thickening,</td>
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<tr>
<td></td>
<td></td>
<td>intrafissural collection of liquid</td>
</tr>
<tr>
<td>High probability X/Q</td>
<td>≥ 1 segmental defect and a normal chest X-ray</td>
<td>≥ 1 segmental defect and a locally normal chest X-ray</td>
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<tr>
<td>scan</td>
<td></td>
<td></td>
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<tr>
<td>Non-diagnostic X/Q</td>
<td>All other cases</td>
<td>All other cases</td>
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</table>

In the ANTELOPE cohort, the outcome of the perfusion scan and chest X-ray were used according to the reports and as documented in the database. The abnormalities on chest X-ray had not been specified to location; therefore, in case of an abnormal Q scan and an ‘abnormal’ chest X-ray, the X/Q-scan was classified as non-diagnostic.

In the Leventas cohort, two experienced nuclear medicine physicians blinded for outcome separately re-evaluated the perfusion scans of all women less than 50 years with a likely clinical decision rule and/or an abnormal D-dimer, to calculate predictive values of the X/Q-scan more accurately. In case of abnormalities, the scans were locally compared with the chest X-ray for a matched or mismatched abnormality (for the X/Q criteria, see Table 1). Disagreement between the two readers was solved by consensus reading.

**Diagnostic management with X/Q**

In our analysis, pulmonary embolism was regarded absent in patients with an “unlikely” clinical probability (Wells score ≤4) and a normal D-dimer test (see Figure 1), as previously described (1). In patients with a “likely” clinical probability or an abnormal D-dimer, a normal perfusion scan ruled out pulmonary embolism. In case of abnormalities on the perfusion scan, the findings were combined with the result of the chest X-ray (X/Q scan).

**Statistical analysis**

The proportion of patients in each X/Q category was calculated, as well as the positive and negative predictive values, with 95% confidence intervals (CI). The positive predictive value was defined as the proportion of patients with a high probability X/Q scan, who had PE as defined by the reference standard. The negative predictive value was defined as the proportion of
patients with a normal perfusion scan, who did not have PE according to the reference standard. Exact 95% confidence limits were calculated using Confidence Interval Analysis (CIA, version 1.0; Gardner MJ). To assess the interobserver variability between the two readers in the Leventas cohort kappa statistics were used (calculated with SPSS statistical software).

RESULTS

Step One – ANTELOPE cohort

In the ANTELOPE study, a total of 517 patients with clinical suspicion of pulmonary embolism were included from May 1997 through March 1998 (12), of whom 165 (32%) were women aged <50 years. The D-dimer test result was missing in 6 women, leaving 159 women for the present analysis (see Figure 2). Of these 159 women, 32 (20%) were diagnosed to have pulmonary embolism. The diagnosis was made by pulmonary angiography in 9 women and by high probability ventilation-perfusion scan in 23 women. Eighty-one women (51%) had an “unlikely” clinical probability and a normal D-dimer test. Figure 2 shows the distribution of women with a “likely” clinical probability and/or an abnormal D-dimer test result among the X/Q categories. Of these 78 women, 34 (44%; 95% CI, 33-55%) had a normal perfusion scan.
The perfusion scintigraphy result was missing in two women. There were 42 women (58%) with an abnormal perfusion scan, of whom 11 (14%; CI, 8-24%) were categorized as high probability X/Q and 31 (40%; CI, 30-51%) as non-diagnostic X/Q.

The negative and positive predictive values of the X/Q scan in the ANTELOPE cohort were high, see Table 2. The proportion of women with a non-diagnostic test result was 31/159 (19%) based on the total cohort, and 31/78 (40%) in women with a “likely” clinical probability or an abnormal D-dimer test. Theoretically, CT would be avoidable in 60% of women requiring an imaging test.
Table 2. X/Q-scan results compared with reference standard (V/Q-scan or pulmonary angiography) results in two cohorts.

<table>
<thead>
<tr>
<th>Index</th>
<th>ANTELOPE cohort</th>
<th>Leventas cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90.0% (9/10)</td>
<td>100.0% (13/13)</td>
</tr>
<tr>
<td>95% CI</td>
<td>59.6% - 98.2%</td>
<td>77.2% - 100.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.3% (33/35)</td>
<td>100.0% (30/30)</td>
</tr>
<tr>
<td>95% CI</td>
<td>81.4% - 98.4%</td>
<td>88.6% - 100.0%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>81.8% (9/11)</td>
<td>100.0% (13/13)</td>
</tr>
<tr>
<td>95% CI</td>
<td>52.3% - 94.9%</td>
<td>77.2% - 100.0%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>97.1% (33/34)</td>
<td>100.0% (30/30)</td>
</tr>
<tr>
<td>95% CI</td>
<td>85.1% - 99.5%</td>
<td>88.6% - 100.0%</td>
</tr>
<tr>
<td>Non-diagnostic results</td>
<td>39.7% (31/78)</td>
<td>17.3 % (9/52)</td>
</tr>
<tr>
<td>95% CI</td>
<td>29.6% - 50.8%</td>
<td>9.4% - 29.7%</td>
</tr>
</tbody>
</table>

V/Q-scan, ventilation-perfusion scan; X/Q-scan, perfusion scan combined with chest X-ray; CI, confidence interval.

Step Two - Leventas

In the Leventas cohort, a total of 228 patients with clinically suspected pulmonary embolism were included, of whom 78 were women aged <50 years. The reference standard was missing in one woman, leaving 77 women for this analysis (see Figure 3). Of these women, the prevalence of PE was 19% (15/77). PE was confirmed by pulmonary angiography in 3 women and by high probability V/Q scan in 12 women. In this cohort, 25 women (32%; 95% CI, 23-44%) had an unlikely clinical probability and a normal D-dimer test (see Figure 3). Thirty of the 52 women with a likely clinical probability and/or an abnormal D-dimer test result had a normal perfusion scan (58%; 95% CI, 44-70%). Thirteen women (25%; 95% CI, 15-38%) had a high probability X/Q scan; 9 women (17%; 95% CI, 9-30%) had an X/Q scan classified as non-diagnostic.

The predictive accuracy of the X/Q scan in the Leventas cohort was high: 100% (95% CI, 89-100%) and 100% (95% CI, 77-100%) for the negative and positive predictive value, respectively (see Table 2). The proportion of women with a non-diagnostic test result was 9/77 (12%) of the total cohort and 9/52 (17%) of the women with a likely clinical probability or an abnormal D-dimer test. Hence, CT would be avoidable in 83% of women requiring an imaging test.

The kappa statistic of agreement between the two readers in the Leventas cohort was 0.92.

DISCUSSION

Our findings indicate that an alternative diagnostic strategy in patients with suspected PE that consists of perfusion scintigraphy combined with chest X-ray seems promising to reduce CT
scanning in young women. One third of the patients in both cohorts were women aged less than 50 years, the subgroup of patients who are most vulnerable to the adverse effects of radiation from CT scanning. In 129 young women with suspected PE with either a “likely” clinical probability or an abnormal D-dimer, the combination of a perfusion scan and chest X-ray reliably categorized segmental perfusion defects as non-high or high probability for the
presence of PE. The positive predictive value was 82% (95% CI, 52-95%) in the retrospective database analysis (step one), but increased to 100% (77-100%) in the re-evaluation of the scans with local comparison to the chest X-ray (step two). The evaluation of the scans using these X/Q criteria resulted in an almost perfect interobserver agreement.

Even though we focused on patients with a “likely” clinical probability for PE or an abnormal D-dimer test result, our findings are in agreement with two previous studies that report comparable predictive accuracies. De Groot and colleagues performed an analysis similar to our approach in 389 consecutive patients, in which they prospectively classified abnormal perfusion scans and chest X-rays as either mismatched or matched. The positive predictive value of a segmental mismatched X/Q (high probability for PE) test result was 86% compared to V/Q scan (10). Stein et al. compared the diagnostic accuracy of V/Q and X/Q scanning in 98 randomly selected patients. The positive predictive value of the X/Q scan compared to the reference diagnostic standard pulmonary angiography was high: 93% (9).

The notion of using only perfusion scanning instead of ventilation-perfusion scanning is also supported by studies by the PISAPED group, in which abnormal perfusion scans were classified as positive for PE based on the presence or absence of single or multiple wedge-shaped perfusion defects. Compared to pulmonary angiography, the sensitivity and specificity were 92% and 87%, respectively (17), and 80% and 97%, respectively, compared to CT scanning (18). The results from these four studies, however, are based on patients without discrimination according to pre-test clinical probability, D-dimer test result, and age (in three studies).

In young patients, less co-morbidity is expected compared to older patients and consequently, the number of non-diagnostic test results will be smaller. The analysis of the first cohort showed non-diagnostic test results in 40% of the women in whom diagnostic imaging testing was required. This proportion was only 17% in the second cohort, where chest X-ray and Q scan were compared together, meaning a similar defect was seen on both X-ray and Q scan. Excluding the patients with an unlikely clinical probability and a normal D-dimer from imaging testing, and selecting only young women in this analysis rendered a very small proportion of non-diagnostic test results. This shows that CT-scan could be avoided in a large proportion of young women when perfusion scintigraphy is performed first: 60% in the first cohort and 83% in the second cohort.

It should be noted that analyses were based on retrospective data, in a small population of young women. Therefore, although the positive predictive value of a high-probability X/Q scan was 100%, the 95% confidence interval was wide. Further validation in a larger study is necessary to confirm our findings. In addition, the perfusion scans and X-rays were irretrievable for the ANTELOPE cohort. In this study the predictive accuracy compared to V/Q scanning was lower than in the Leventas study, because local matching of the abnormalities on chest X-ray
and perfusion scintigraphy was not possible, and any abnormality on chest X-ray resulted in a non-diagnostic test, irrespective of the location of this abnormality. Finally, we could not compare the X/Q findings to CT, which is nowadays regarded as the gold standard. However, even with a positive predictive value of 85-90% compared to pulmonary angiography, a segmental mismatched V/Q scan defect is generally accepted to indicate the presence of PE and justifies anticoagulant treatment (19). The accuracy of a normal perfusion scan is also well accepted (17,20,21).

Replacing CT scan for perfusion scintigraphy as a first diagnostic imaging test to exclude or diagnose PE in young women means less radiation and as a result a lower risk of developing cancer. Our study suggests that a strategy consisting of clinical decision rule, D-dimer testing, perfusion scintigraphy and chest X-ray may reliably exclude or diagnose PE. Further prospective evaluation in a larger population of young women is warranted.

REFERENCE LIST