Pulmonary embolism: advances in diagnosis and prognosis
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Chapter 9

False normal results on multidetector-row spiral computed tomography in patients with high clinical probability of pulmonary embolism

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INTRODUCTION

Over the past years, CT scanning has gained a prominent role in the diagnostic management of pulmonary embolism (PE), especially with the introduction of multi-detector row CT scanning. Recently, Righini and colleagues (1) performed a study which convincingly showed that venous compression ultrasonography of the legs is not needed to rule out pulmonary embolism (PE) when a clinical decision rule, D-dimer testing and multidetector-row CT (MDCT) scan are used in patients with suspected PE. With this conclusion, this well designed and large prospective study seems to have given an answer to the question whether a normal CT scan alone is sufficient to exclude the diagnosis. What has remained debatable, however, is whether a normal CT scan is also safe to exclude PE in the subgroup of patients with a high clinical pretest probability for PE, i.e. an apparent discrepancy between the clinical pretest probability and the normal findings on the CT scan. Of note, in the PIOPED II study (2) six of the 15 patients with a high clinical probability and a negative MDCT had PE demonstrated by a composite reference standard. Contrary to these results, additional testing with ventilation-perfusion lung scan or pulmonary angiography in the study by Righini et al. (1) did not demonstrate PE in seven patients with a high clinical pretest probability and a normal CT scan. Furthermore, physicians were reluctant to follow the protocol and perform further testing in another 19 patients with also a high clinical probability and a normal MDCT scan result. Eighteen of these patients were not treated with anticoagulants and had an uneventful follow-up. The authors therefore concluded that they could not make a firm statement for the best diagnostic algorithm for patients with a high clinical probability of PE. To gain more insight in the negative predictive value of a normal CT scan in patients with a high clinical pretest probability, we have re-analyzed our data obtained in the Christopher study (3).

METHODS

In this large prospective diagnostic management study, 3306 consecutive in- and outpatients with clinically suspected pulmonary embolism from 12 hospitals in the Netherlands were included. PE was excluded based on an unlikely clinical probability (Wells score ≤ 4 points) combined with a normal D-dimer (≤ 500 μg/L), or a normal CT scan. False normal MDCT scans were defined as objectively confirmed venous thromboembolism (VTE) during the 3-month follow-up in patients in whom PE was excluded based on a normal MDCT scan and who were not treated with anticoagulants. For this analysis the cut-off for a low-intermediate or high clinical probability was a Wells score ≤ 6; the cut-off for ‘unlikely’ or ‘likely’ clinical probability was a Wells score ≤ 4.
**RESULTS**

In total, a MDCT scan was performed in 1938 patients with a “likely” clinical probability or an abnormal D-dimer. The diagnosis was confirmed in 591 patients (30.5%). The incidence of a false normal MDCT scans during follow-up in the 1266 who patients who were not treated with anticoagulants is displayed in the Table. This rate was slightly higher in patients with a “likely” clinical probability (Wells score > 4) compared to an “unlikely” probability, although not statistically significant (p=0.11) nor clinically relevant. The failure rate regardless clinical probability was 1.1% (95% CI, 0.6-1.9%). Of the 1266 patients with a normal MDCT, 57 (4.5%) had a “high” clinical pretest probability. Three of these patients had VTE during follow-up (5.3%; 95%CI, 1.8-14.4%). This included one death attributable to PE in a woman with metastasized breast cancer, who died one day after the initial diagnostic workup for PE, in the two others PE and deep vein thrombosis were discovered 10 and 2 days after the normal CT scan, respectively. This CT-scan failure rate is significantly higher compared to patients with a “low-intermediate” score (Wells score ≤ 6; p=0.02).

<table>
<thead>
<tr>
<th>Clinical Probability</th>
<th>Incidence of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>14/1266 1.1, 0.6-1.9</td>
</tr>
<tr>
<td>“Unlikely” (Wells score ≤ 4)</td>
<td>5/721 0.7, 0.3-1.6</td>
</tr>
<tr>
<td>“Likely” (Wells score &gt; 4)</td>
<td>9/545 1.7, 0.9-3.1</td>
</tr>
<tr>
<td>“Low-intermediate” (Wells score ≤ 6)</td>
<td>11/1209 0.9, 0.5-1.6</td>
</tr>
<tr>
<td>“High” (Wells score &gt; 6)</td>
<td>3/57 5.3, 1.8-14.4</td>
</tr>
</tbody>
</table>

CT, computed tomography; VTE, venous thromboembolism; CI, confidence interval.

**DISCUSSION**

How should these findings be interpreted? As the present analysis confirms, a normal multidetector-row CT scan safely excludes PE, regardless the clinical probability. The observed failure rate of 1.1% compares favorably with other modalities such as angiography to exclude PE. Hence, physicians should be reassured that this is an adequate strategy to follow in their patients. However, in the rare case of a high clinical suspicion combined with a normal CT (which occurred in approximately 1 of 20 patients with a normal CT), the physician could consider additional testing, although at present it is unclear which method should be used. Given the observed failure rate of 5.3% in our series, treating all these patients appears also not to be the right strategy.
To our knowledge, this is the largest number of patients with a high clinical probability for PE and a normal MDCT result reported to date. As mentioned, in the PIOPED II study, six of the 15 patients with a high clinical probability and a normal MDCT had PE (2), whereas there were no failures during follow up or additional testing in patients with a high clinical probability and normal MDCT in the study by Righini et al (1). Further data on this subject is limited, since most recent diagnostic outcome or accuracy studies did not disclose specific information for the subgroup of patients with a high clinical probability, or because both single slice and MDCT were used (4,5).

It can be argued that our definition of a false normal test result, which is based on a VTE event during follow-up, is not optimal. It is possible that patients developed VTE during follow-up while this was truly not present at the time of initial diagnostic workup. However, the time between the diagnostic testing and the VTE events in the three patients with a high clinical pre-test probability we defined as having had a false normal test result suggests the thromboembolism was already present at the time the CT scan was made.

In conclusion, as long as we can not resolve the above mentioned dilemma, a normal MDCT is a safe strategy to exclude pulmonary embolism.

REFERENCE LIST