Spiral computed tomography for the diagnosis of acute pulmonary embolism

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Summary

The accuracy of computed tomography (CT) imaging for the diagnosis of acute pulmonary embolism (PE) was reviewed. Single detector CT, based on pooled data, showed a sensitivity of 73% and multidetector CT, mostly 4-slice, showed a sensitivity of 83%. Respective specificities were 87% and 96%. Among patients with suspected PE evaluated with single slice CT, 20% of patients found to have venous thromboembolic disease were diagnosed on the basis of a positive CT venous phase venogram. With multislice CT, 14% were diagnosed on the basis of a positive CT venogram. The positive likelihood ratio with single detector CT was 5.7 and with multidetector CT it was 19.6. Respective negative likelihood ratios were 0.31 and 0.18. Calculations of post-test probability using pretest probability and likelihood ratios according to Bayes' theorem showed that even with multidetector CT, false positive and false negative images are not uncommon when clinical assessment is discordant with the CT interpretation. Outcome studies showed recurrent PE in only 1.7% or fewer untreated patients with negative CT pulmonary angiograms.

Keywords
Pulmonary embolism, deep venous thrombosis, venous thromboembolism, computed tomography

Introduction

The diagnosis of acute pulmonary embolism (PE) by computed tomographic (CT) pulmonary angiography, sometimes in combination with CT venous phase imaging of the veins of the pelvis and lower extremities has evolved since contrast enhanced single detector spiral CT was first compared with pulmonary angiography in 1992 (1). In this review we trace the development of advances in imaging, the relevance and additional diagnostic value of venous phase imaging and most recent use of 64-slice electrocardiographic gated CT for an angiographic protocol for simultaneous assessment of the pulmonary arteries, coronary arteries, and aorta in patients with acute chest pain.

Methods

Reviews of investigations of diagnostic accuracy of CT were based on inclusion criteria recommended by Lijmer et al. for avoidance of bias in studies of diagnostic tests (2). Tier 1 was defined as those that met the following requirements: i) The diagnosis of PE was made on the basis of objective tests; ii) Patients were studied consecutively; iii) The study was performed prospectively; iv) The CT was read without knowledge of the results of the reference test; v) All patients studied were suspected of having PE; vi) The study included patients with and without PE; vii) The decision to perform the reference diagnostic test was made independently of the result of the spiral CT; viii) Descriptions of the CT methods were sufficiently detailed to permit replication; ix) Patients with a broad spectrum of demographics were investigated; x) Patients with all severities of PE were evaluated, with no restriction on the results of preliminary diagnostic tests. Prospective investigations that did not meet all of these criteria were defined as Tier 2. Retrospective investigations were defined as Tier 3.

Tier 1 studies

Diagnostic accuracy

One Tier 1 investigation of diagnostic accuracy was with a 2-slice scanner (3) the others prior to the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) used single detector scanners (1, 4–9), and in PIOPED II, multidetector CT was used (10) (Table 1). Pooled data from Tier 1 studies that used single detector or in some 2-slice CT showed a sensitivity of 255 of 335 (76%) and specificity of 380 of 429 (89%) (3–6, 10).
Table 1: Tier 1 sensitivity and specificity of individual investigations.

<table>
<thead>
<tr>
<th>First author (Ref)</th>
<th>Detector #</th>
<th>Collimation (mm)</th>
<th>Reference standard</th>
<th>Sensitivity n/N (%)</th>
<th>Specificity n/N (%)</th>
<th>Sensitivity n/N (%)</th>
<th>Specificity n/N (%)</th>
<th>Sensitivity n/N (%)</th>
<th>Specificity n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drucker (4)</td>
<td>1</td>
<td>5</td>
<td>Angio</td>
<td>9/15 (60)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nilsson (5)</td>
<td>1</td>
<td>3</td>
<td>Angio</td>
<td>30/33 (91)</td>
<td>55/57 (96)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perrier (6)</td>
<td>1</td>
<td>3</td>
<td>V-Q or Angio</td>
<td>51/74 (69)</td>
<td>88/98 (90)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Qanadli (3)</td>
<td>2</td>
<td>5</td>
<td>Angio</td>
<td>56/62 (90)</td>
<td>89/95 (94)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Remy-Jardin (1)</td>
<td>1</td>
<td>5</td>
<td>Angio</td>
<td>-</td>
<td>-</td>
<td>18/18 (100)</td>
<td>23/24 (96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Remy-Jardin (7)</td>
<td>1</td>
<td>3 or 5</td>
<td>Angio</td>
<td>-</td>
<td>-</td>
<td>39/43 (91)</td>
<td>25/32 (78)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ruiz (8)</td>
<td>1</td>
<td>3</td>
<td>Angio</td>
<td>21/23 (91)</td>
<td>31/38 (82)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Van Strien (9)</td>
<td>1</td>
<td>5</td>
<td>V-Q or Angio</td>
<td>88/128 (69)</td>
<td>92/109 (84)</td>
<td>80/93 (86)</td>
<td>-</td>
<td>6/28 (21)</td>
<td>-</td>
</tr>
<tr>
<td>Stein (10)</td>
<td>4, 8, 16</td>
<td>Composite ^</td>
<td>150/181 (83)</td>
<td>567/592 (96)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism, Angio = angiography, V-Q = ventilation-perfusion. *Main, lobar or segmental pulmonary artery. ^Specificity not stated. See text.

Table 2: Tier 1 investigations pooled data.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity n/N (%)</th>
<th>Specificity n/N (%)</th>
<th>Positive pred value n/N (%)</th>
<th>Negative pred value n/N (%)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single and 2-slice CT</td>
<td>255/335 (76)</td>
<td>380/429 (89)</td>
<td>255/304 (84)</td>
<td>380/460 (83)</td>
<td>6.7</td>
<td>0.27</td>
<td>3–6, 8, 9</td>
</tr>
<tr>
<td>Single-slice CT</td>
<td>199/273 (73)</td>
<td>291/334 (87)</td>
<td>199/244 (82)</td>
<td>291/365 (80)</td>
<td>5.7</td>
<td>0.31</td>
<td>4–6, 8, 9</td>
</tr>
<tr>
<td>Single-slice CT 3 mm collimation</td>
<td>102/130 (78)</td>
<td>174/193 (90)</td>
<td>102/121 (84)</td>
<td>174/202 (86)</td>
<td>8.0</td>
<td>0.24</td>
<td>5, 6, 8</td>
</tr>
<tr>
<td>Single-slice CT 5 mm collimation</td>
<td>97/143 (68)</td>
<td>117/141 (83)</td>
<td>97/121 (80)</td>
<td>117/163 (72)</td>
<td>4.0</td>
<td>0.38</td>
<td>4, 9</td>
</tr>
<tr>
<td>4, 8, 16-Slice</td>
<td>150/181 (83)</td>
<td>567/592 (96)</td>
<td>150/175 (86)</td>
<td>567/598 (95)</td>
<td>19.6</td>
<td>0.18</td>
<td>10</td>
</tr>
</tbody>
</table>

Pred = predictive.
higher sensitivities, specificities, positive and negative predictive values than in Tier 1 investigations (13–24) (Tables 3 and 4).

**Tier 3 investigations**

Two retrospective investigations (Tier 3), both with single slice CT and 3 mm collimation (29) or either 3 or 5 mm collimation (30) were reported. Sensitivity for all PE was 18 of 21 (86%), and specificity was 12 of 12 (100%) (29). Pooled data for proximal PE showed a sensitivity of 43 of 46 (93%) and specificity 32 of 35 (91%) (29, 30).

**4-slice CT**

Only two investigations of diagnostic accuracy prior to PIOPED II evaluated multidetector CT, and both were with 4-slice CT (25, 26). Pooled data from these Tier 2 studies showed a sensitivity of 45 of 46 (98%) and specificity 132 of 141 (94%) (25, 26) (Table
4). With 4-slice CT, visualization of the pulmonary arteries in the middle and peripheral lung zones has been shown to be significantly higher than with single-slice CT, although visualization the central lung zone was ranked equally with single-slice CT and 4-slice CT (31). Thin collimation (1.25 mm) with 4-slice CT showed improved small pulmonary artery visualization compared with single-slice CT (32).

In PIOPED II, a composite reference standard was used to diagnose or exclude PE (10). Diagnosis of PE according to the composite reference standard required one of the following:

1. High probability ventilation/perfusion (V/Q) lung scan in a patient with no history of prior PE.
2. Positive pulmonary digital subtraction angiogram (DSA).
3. Positive venous ultrasound in a patient without prior DVT at that site and a non-diagnostic V/Q scan (not normal and not high probability without prior PE). This was interpreted as a surrogate for the diagnosis of PE.

Exclusion of PE according to the composite reference standard required one of the following:

- Negative DSA
- Normal V/Q scan
- Low or very low probability V/Q scan, clinical score by the Wells criteria <2 (32), and negative venous ultrasound.

Scanners with four detector arrays were used in 691 patients, 8-detector scanners were used in 37 patients, and 16 detector scanners were used in 45 patients. Low osmolar non-ionic contrast material (135–150 ml) was injected through an arm vein at 4 ml/second. Patients were scanned from the diaphragm to the apex of the lung. For patients <250 pounds scanned on 4-slice equipment, collimation was 1.25 mm, table speed 7.5 mm/rotation, pitch 1.5 (usually between 1.0–2.0), voltage 120 kVp, current 400 mA, and rotation time approximately 0.8 seconds. Minor protocol modifications were made for heavier patients and for newer scanners.

The CT angiogram was of insufficient quality for conclusive interpretation in 46 of 824 patients (5.6%) (10). Among patients with an interpretable CT angiogram, the sensitivity for PE was 150 of 181 (83%) and specificity was 567 of 592 (96%). The likelihood ratio for a positive test was 19.6 and the likelihood ratio for a negative test was 0.18. The positive predictive value was 150 of 175 (86%) and the negative predictive value was 567 of 598 (95%).

Positive predictive values were 116 of 120 (97%) for PE in a main or lobar artery, 32 of 47 (68%) for a segmental vessel, and 2 of 8 (25%) for a subsegmental branch (10).

CT in combination with clinical assessment

Single-slice CT

The apparent objectivity of CT may lull physicians into a sense of complacency (34). A positive CT in patients with a low probability clinical impression is often falsely positive, and a negative CT in combination with a high probability clinical impression is often falsely negative (34). Calculations of post-test probability using pretest probability and likelihood ratios according to Bayes’ theorem showed that for single-slice CT (based on Tier I pooled data), the post-test probability of PE would be < 84% after a positive single-slice CT in patients with a clinical probability of PE < 40%. In patients with a negative single-slice CT, if the clinical probability of PE was >70%, there would be more than a 36% post-test probability of PE.

4-slice CT

Pooled data of only two investigations of multidetector CT prior to PIOPED II showed that in patients with a positive 4-slice CT and discordantly low clinical probability of <30%, the post-test probability of PE is <90% (25, 26). Conversely, with a negative 4-slice CT, if the clinical probability of PE is discordantly high, >90%, the calculated post-test probability of PE is >17%.

In PIOPED II (10) among patients with a positive CT angiogram and high or intermediate probability prior clinical assessment, the respective positive predictive values for PE were 22 of 23 (96%) and 93 of 101 (92%). Among patients with a positive CT angiogram and discordantly low clinical probability, the positive predictive value was only 22 of 38 (58%); 42% of the CT angiogram readings were falsely positive.

In patients with a negative CT angiogram, and low or intermediate probability prior clinical assessment, the negative predictive value for exclusion of PE was 158 of 164 (96%) and 121 of 136 (89%), respectively (10). Among patients with a negative CT angiogram and discordantly high clinical probability, the negative predictive value was only 9 of 15 (60%); 40% of the CT angiogram readings were falsely negative. To avoid bias (35), negative predictive values in patients with a low clinical probability were based entirely on a DSA or V/Q scan as the reference test.

Calculations of post-test probability using pretest probability and likelihood ratios according to Bayes’ theorem showed that even with multislice CT, with a discordantly low clinical assessment and positive CT angiogram, there is a high proportion of false positive images. Conversely with a discordantly high probability clinical assessment and negative CT angiogram there is a high proportion of false negative images. Multislice CT angiograms alone would require additional testing to diagnose or exclude PE if the prior clinical probability were discordant with the imaging results.

Increased sensitivity for venous thromboembolism (VTE) using venous phase imaging in patients with suspected acute PE

Patients with suspected PE in whom the diagnosis of venous thromboembolic disease was made by CT venography are shown in Table 5 (10, 36–46). Among patients in whom single-slice CT was used for the diagnosis of suspected PE, 73 of 436 (17%) patients with VTE were diagnosed on the basis of a positive CT venous phase venogram (37–39). Among those in whom multislice CT was used, 66 of 456 (14%) with VTE were diagnosed on the basis of a positive CT venogram (10, 40–44). Studies that used single- and multislice CT showed VTE on the basis of CT venous phase imaging in 73 of 436 (17%) (45, 46) (Table 5). Some evaluated veins of the pelvis and thighs (10, 37, 40, 45) and some evaluated the calf veins as well (36, 38, 39, 42–44, 46). One investigator evaluated only the thighs and calves unless the patient was older than 65 years or had a low cardiac output, in which case the pelvic veins were also evaluated (41).

In PIOPED II the sensitivity for detection of patients with suspected PE increased from 83% to 90% by using CT ve-
nography in combination with CT pulmonary angiography. The CT angiogram/CT venogram combination was of insufficient quality for a conclusive interpretation in 87 of 824 patients (11%). Among the 737 with an adequate CT angiogram/CT venogram combination, the sensitivity for PE was 164 of 183 (90%) and specificity was 524 of 554 (95%) (10). The likelihood ratio for a positive test was 16.5 and the likelihood ratio for a negative test was 0.11. The positive predictive value was 164 of 194 (85%) and the negative predictive value was 524 of 543 (97%).

**Clinical assessment, CT angiography with CT venography**

Among patients in PIOPED II with either a positive CT angiogram or positive CT venogram and high or intermediate probability prior clinical assessment, the respective positive predictive values for PE were 27 of 28 (96%) and 100 of 111 (90%) (10). Among patients with a positive CT angiogram or CT venogram and discordantly low clinical probability, the positive predictive value was only 24 of 42 (57%); 43% of the CT angiogram or CT venogram readings were falsely positive (10). Causes of misdiagnosis of PE on CT angiograms include low-attenuation abnormality, image noise, beam hardening artifact, flow-related artifact, inappropriate window width and level settings, partial volume averaging effect in lymph nodes, mucus plugs, perivascular edema, localized increased vascular resistance, pulmonary artery stump with in-situ thrombosis, primary pulmonary artery sarcoma and tumor emboli (47).

Among patients with a negative CT angiogram and negative CT venogram, and low probability prior clinical assessment, the negative predictive value for exclusion of PE was 146 of 151 (97%) and with an intermediate probability assessment it was 114 of 124 (92%) (10). Among patients with a negative CT angiogram and negative CT venogram and discordantly high clinical probability, the negative predictive value was only nine of 11 (82%); 18% of the readings were falsely negative (10). Negative predictive values in patients with a low clinical probability were based entirely on a digital subtraction angiography or ventilation-perfusion lung scans as the reference test (10). With an intermediate probability clinical assessment, which typically is about a 30% to 40% clinical probability of pulmonary embolism (33, 48–54), CT angiography with CT venography gives a somewhat better post-test probability than CT angiography alone (10).

The PIOPED II investigators recommended that most patients with suspected acute PE have imaging with multidetector spiral CT combined with venous phase venography providing PE is not excluded by a negative D-dimer in combination with a low or intermediate probability clinical assessment (55). Compression ultrasound in the diagnostic strategy may make the diagnosis of PE without further testing (55–57). The additional radiation to which the patient is exposed with CT venography is a concern (55, 58), and compression ultrasound is preferred by some over CT venography (58).

Since PIOPED II, 64-slice CT has become available. Some have used electrocardiographic-gated 64-slice CT in the differential diagnosis of acute chest pain, by evaluating the pulmonary arteries, coronary arteries, and aorta (59, 60). Both groups reported that 64-slice CT of the entire thorax is technically feasible and enables rapid triage of patients to determine cardiac and non-cardiac reasons for chest pain.

Even though in PIOPED II patients with an intermediate probability clinical assessment, negative multidetector CT angiograms failed to identify 11% with PE (10), well-performed outcome studies showed recurrent PE in only 1.7% or fewer untreated patients with negative CT pulmonary angiograms (42, 61–66) (Table 6). Follow-up period in most was three months (42, 61, 63, 64, 66), but in some six or nine months (62, 65). The

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**Table 5: Distribution of positive findings on CT angiograms and CT venograms in patients with suspected pulmonary embolism.**

<table>
<thead>
<tr>
<th>First author (Ref)</th>
<th>Number slice CT</th>
<th>Pos CT Angio only</th>
<th>Pos CT Angio and CTV</th>
<th>Pos CT Angio ± Pos CTV</th>
<th>Pos CTV only</th>
<th>Pos CTV only/ VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richmond (41)</td>
<td>4</td>
<td>31</td>
<td>42</td>
<td>88</td>
<td>15</td>
<td>15/88 (17)</td>
</tr>
<tr>
<td>Coche (36)</td>
<td>2</td>
<td>9</td>
<td>13</td>
<td>25</td>
<td>3</td>
<td>3/25 (12)</td>
</tr>
<tr>
<td>Loud (38)</td>
<td>1</td>
<td>27</td>
<td>58</td>
<td>116</td>
<td>31</td>
<td>31/116 (27)</td>
</tr>
<tr>
<td>Garg (37)</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>0</td>
<td>0/12 (0)</td>
</tr>
<tr>
<td>Cham (45)</td>
<td>1, 2, 4</td>
<td>62</td>
<td>29</td>
<td>107</td>
<td>16</td>
<td>16/107 (15)</td>
</tr>
<tr>
<td>Revel (42)</td>
<td>4</td>
<td>33</td>
<td>21</td>
<td>59</td>
<td>5</td>
<td>5/59 (8)</td>
</tr>
<tr>
<td>Nicolas (39)</td>
<td>1</td>
<td>18</td>
<td>29</td>
<td>52</td>
<td>5</td>
<td>5/52 (10)</td>
</tr>
<tr>
<td>Begemann (40)</td>
<td>4</td>
<td>7</td>
<td>13</td>
<td>31</td>
<td>11</td>
<td>11/31 (35)</td>
</tr>
<tr>
<td>Stein (10)</td>
<td>4, 8, 16</td>
<td>71</td>
<td>79</td>
<td>164</td>
<td>14</td>
<td>14/164 (9)</td>
</tr>
<tr>
<td>Ghaye (43)</td>
<td>16</td>
<td>15</td>
<td>38</td>
<td>73</td>
<td>20</td>
<td>20/73 (27)</td>
</tr>
<tr>
<td>Ghaye (43)</td>
<td>1</td>
<td>55</td>
<td>164</td>
<td>256</td>
<td>37</td>
<td>37/256 (14)</td>
</tr>
<tr>
<td>Johnson (44)</td>
<td>4, 8</td>
<td>30</td>
<td>10</td>
<td>41</td>
<td>1</td>
<td>1/41 (2)</td>
</tr>
<tr>
<td>Nchim (46)</td>
<td>1, 16</td>
<td>70</td>
<td>202</td>
<td>329</td>
<td>57</td>
<td>57/329 (17)</td>
</tr>
</tbody>
</table>

CT = computed tomography, Pos = positive, Neg = negative, CTV = CT venogram, Angio = angiogram, VTE = venous thromboembolic disease.
Christopher Group, for example, showed PE on three-month follow-up of untreated patients with a negative CT angiogram in only 10 of 1,436 (0.7%) (66). An additional eight of 1,436 (0.6%) had deep venous thrombosis on follow-up. Perrier et al., among untreated patients with a negative multidetector CT angiogram and negative venous ultrasound, showed fatal pulmonary embolism at three months in two of 292 (0.7%) patients with low or intermediate probability clinical assessments, and an additional three of 292 (1.0%) had non-fatal VTE (64). The overall three-month risk of thromboembolism in patients without PE would have been 1.5% if the D-dimer assay and multidetector CT had been the only tests to rule out PE and ultrasonography had not been performed (64). The reason that outcome studies show a lower incidence of symptomatic recurrent PE than predicted by accuracy studies, is that small pulmonary emboli show a lower incidence of symptomatic recurrence (67). Results of outcome studies give entirely different information than results of accuracy studies (67). Outcome studies provide appropriate data for clinical management.

Conclusion
A systemic review showed that with single-slice CT angiography, 3 mm collimation gave better results than 5 mm collimation. Even with single-slice CT, the sensitivity for detection of proximal PE was high, but the sensitivity for distal PE was inadequate. Sensitivity and specificity for PE with multislice CT are higher than single slice CT. Still, the sensitivity of multislice CT alone is only 83%. The high positive likelihood ratio and low negative likelihood ratio of multislice CT indicate, however, that discordant clinical findings and CT angiographic findings will give a high post-test probability for making or excluding the diagnosis of PE.

Venous phase imaging in combination with CT angiography increased the sensitivity for the detection of venous thromboembolic disease. In patients evaluated by multislice CT, 14% of those with VTE were diagnosed on the basis of a positive CT venogram. The sensitivity for the detection of PE in PIOPED II increased from 83% to 90% by use of CT venous phase venography in combination with CT angiography. A high probability clinical assessment with CT angiography in combination with CT venography in PIOPED II gave a positive predictive value for PE of 96% and with an intermediate probability clinical assessment, the positive predictive value was 90%. If clinical assessment and CT angiography/CT venography were discordant, further testing was needed unless the PE was in a main or lobar pulmonary artery. Even though multidetector CT may fail to identify as many as 11% of patients with PE, such missed PE presumably is in small vessels, and outcome studies showed recurrent PE in 1.7% or fewer untreated patients who had negative CT angiograms.

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