The value of 64-detector row computed tomography for the exclusion of pulmonary embolism

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Summary

Recently, a diagnostic strategy using a clinical decision rule, D-dimer testing and spiral computed tomography (CT) was found to be effective in the evaluation of patients with clinically suspected pulmonary embolism (PE). However, the rate of venous thromboembolic complications in the three-month follow-up of patients with negative CT was still substantial and included fatal events. It was the objective to evaluate the safety of withholding anticoagulants after a normal 64-detector row CT (64-DCT) scan from a cohort of patients with suspected PE. A total of 545 consecutive patients with clinically suspected first episode of PE and either likely pre-test probability of PE (using the simplified Wells score) or unlikely pre-test probability in combination with a positive D-dimer underwent a 64-DCT. 64-DCT scanning was inconclusive in nine patients (1.6%), confirmed the presence of PE in 169 (31%), and ruled out the diagnosis in the remaining 367. During the three-month follow-up of the 367 patients one developed symptomatic distal deep-vein thrombosis (0.27%; 95%CI, 0.0 to 1.51%) and none developed PE (0%; 95%CI, 0 to 1.0%). We conclude that 64-DCT scanning has the potential to safely exclude the presence of PE virtually in all patients presenting with clinical suspicion of this clinical disorder.

Keywords

Pulmonary embolism, CT scan, diagnosis management, diagnostic strategy

Introduction

Spiral computed tomography (CT) is the reference diagnostic test in patients with suspected acute pulmonary embolism (PE) (1). In a recent prospective cohort study conducted in a large series of patients with suspected PE – the Christopher study – a diagnostic strategy using a clinical decision rule, D-dimer test and CT scanning was found to be both accurate and safe (2). However, the rate of thromboembolic complications in the three-month follow-up of patients with negative CT scan was still substantial (1.3%) and included fatal events. This figure is consistent with those obtained in previous smaller studies (3–13) and in a recent meta-analysis of most available investigations (14). The single-slice or low-multidetector row CT scanners (MDCT) (4-, 8-, or 16-detector row) used in those studies have variable sensitivity, partly due to their relative inaccuracy in identifying the small sub-segmental pulmonary emboli. Unlike older generation CT, the recently introduced high-definition MDCT scanners (64 detectors and over) reach sub-millimetre spatial resolution, thus allowing the identification of small, sub-segmental emboli (15–19). The clinical significance of such small emboli is controversial but cannot be ruled out (20, 21), and failure to initiate anticoagulation therapy when they remain undiagnosed might promote recurrence of disease, especially in subjects with congenital or acquired thrombophilic states (22). Therefore, in order to establish the value of the newer generation high-definition MDCTs in the diagnostic strategies for PE, we evaluated the safety of withholding the anticoagulant therapy after a normal 64-detector row CT (64-DCT) scan in a cohort of patients with suspected PE.

Methods

Study objective

We designed a prospective study that assessed the prevalence of PE in a cohort of patients with clinical suspicion of the first episode of PE who underwent a 64-DTC lung scan as well as the incidence of venous thromboembolic events (VTE) after three months of follow-up in those with negative findings. The ethical board of the University Hospital of Padua, Italy approved the study, and written or oral informed consent was obtained from all participants.
Patients

Consecutive out- and in-patients with suspected PE were eligible for this investigation provided that they had “likely” pre-test clinical probability of PE, according to the simplified PE Wells score (23, 24) or “unlikely” pre-test clinical probability associated with positive D-dimer. All consecutive subjects who were admitted to the emergency department of our Institution and suspected of having PE were defined as out-patients. All consecutive subjects already admitted in a hospital ward, usually for different diseases, who were suspected of having PE were defined as in-patients. The clinical suspicion of PE was based on the following findings lasting less than 30 days: acute onset of new shortness of breath, sudden deterioration of existing dyspnoea, sudden onset of chest pain without another apparent cause.

Patients with previous episodes of PE were excluded, as were those with concomitant deep-vein thrombosis (DVT) of the upper or lower extremities, those with indication for preventive or therapeutic doses of anticoagulant drugs for reasons other than VTE, those with contraindications to the contrast medium (i.e. allergy or severe renal insufficiency, defined in the presence of a creatinine clearance < 30 ml/minute), those with a life expectancy shorter than three months, pregnant patients, patients younger than 18-years-old, patients who showed poor compliance and/or were unavailable for long-term follow-up, patients with lack of an accessible vein for the infusion of the radiological contrast medium, and those who refused to sign the informed consent.

Recruitment took place from June 2007 to September 2009.

D-dimer assay

In patients with “unlikely” pre-test clinical probability of PE, D-dimer concentration was measured, using the Biopool Autodimer assay (Trinity Biotech, Bray, Ireland) (25). A D-dimer concentration of 225 ng/ml or less was defined as normal/negative.

Imaging test

The radiological evaluation was performed using Siemens SOMATOM® Definition 64-detector row CT scanner.

The patients were usually examined at the top of inspiration.

Using automatic bolus tracking collimated to the main pulmonary artery, 40–60 ml of non-ionic, low osmolarity contrast medium was injected with a flow of 3–5 ml/second (s). Image acquisition began from caudal to cranial direction about 3–5 s after the trigger was achieved (usually 60 HU) with collimation of 0.6 mm, 120 KV and mAs depending on care dose. Images were reconstructed with a thickness of 0.7–1.2 mm and 0.5–1.0 mm increments. The pulmonary arteries were examined in caudal-cranial direction with the z-axis coverage and the fields of view chosen to include the entire thorax, from the apex to the base of the lungs, including sub-segmental pulmonary arteries.

A team of skilled radiologists performed the procedure and interpreted the images obtained. CT scanning was considered inconclusive in the presence of artifacts from either the heart or movement of the patient, inadequate contrast enhancement of the pulmonary arteries, poor visualisation of sub-segmental arteries or unclear findings in them.

Diagnostic criteria of PE were an intraluminal filling defect outlined by contrast medium or total vessel occlusion by low-attenuation material in at least two adjacent layers. In patients without PE, an attempt was systematically made to identify alternative diagnoses.

Three independent senior-staff radiologists who were unaware of patients’ details later reviewed all CT images.

Follow-up

All patients in whom diagnosis of PE was excluded were left without anticoagulants and were instructed to contact the study staff or their general practitioner immediately in case of symptoms suggestive of DVT or PE. An outpatient visit or a telephone interview was scheduled at three months. On the occasion of each visit, information was collected on signs or symptoms suggestive of VTE, including acute onset or acute worsening of existing dyspnoea, acute chest pain, unilateral leg swelling and/or pain. If DVT or PE were suspected, an objective diagnostic procedure was required, including compression ultrasound or venography for suspected DVT, ventilation-perfusion lung scan, CT scan or pulmonary angiography in case of suspected PE. In the event of death, every effort was made to obtain information about its causes from autopsy, hospital records, general practitioner or from the patient’s relatives.

Deaths were interpreted as induced by PE in case of confirmatory autopsy whenever preceded by symptomatic proven DVT or PE or in case of sudden otherwise unexplained event.

An independent adjudication committee, whose members were unaware of the patients’ details and study aims, evaluated all suspected VTE events and deaths.

Statistical analysis

We calculated the prevalence of PE as well as the incidence and 95% confidence intervals (CIs) of symptomatic VTE after the three-month follow-up.

Assuming a prevalence of PE of approximately 30% and an incidence of VTE events of 1.3% in the follow-up of patients with negative CT scan (2), we estimated that a sample size of approximately 500 patients with suspected PE would make it possible to demonstrate with sufficient confidence (upper limit of the 95% CIs lower than 3.0 %) the safety of withholding anticoagulant treatment from patients with negative CT findings.
Results

Patients

Of the 911 eligible patients with clinically suspected PE, 107 were excluded because of the need for preventive or therapeutic doses of anticoagulant drugs for conditions other than VTE (45), concomitant DVT (24), contraindications to contrast media (11), previous PE (10), known or highly suspected pregnancy (7), life expectancy shorter than three months (3), lack of vein access (3), unavailability for long-term follow-up (2), patient’s poor compliance or refusal (2). Of the remaining 804 patients, 259 (28.4%) were excluded because of “unlikely” pre-test clinical probability and negative D-dimer.

Accordingly, 545 patients were included in the current investigation and underwent 64-DCT scanning. Of these, 338 (62%) were out-patients and the remaining 207 in-patients. Table 1 shows the main demographic and clinical characteristics of the patients included.

CT scanning

The CT scanning confirmed the presence of PE in 169 patients (31.0%; 95% CI, 27.1 to 34.9), was inconclusive in nine patients (1.6%), and ruled out the diagnosis in the remaining 367 patients. In the 169 patients whose diagnosis of PE was confirmed, the embolic material was localised in the main pulmonary arteries in 28 (16.6%) patients and in the segmental arteries in 120 (71.0%). Isolated sub-segmental PE was detected in 21 patients (12.4%). The prevalence of PE was 24% in patients with “unlikely” pre-test clinical probability and a positive D-dimer test, while it was 38.2% in those with “likely” clinical probability.

Of the 367 patients with negative CT scanning, an alternative diagnosis was shown by the radiological test in 108: pneumonia in 50, pleural effusion in 27, malignancy in 11, and other findings in 20.

Follow-up

Of the 367 patients in whom the anticoagulant treatment was withheld following a negative 64-DCT scan, 40 (10.9%) died during follow-up. As shown in Table 2, no deaths were attributed to PE. Table 2 lists the causes of death during the three-month follow-up. Of note, in one patient a fatal episode of acute renal failure occurred during the third month of follow-up. Considering the time of onset of complication, we believe that a direct correlation between renal damage and the previous administration of radiological contrast media is unlikely.

Six patients presented with clinical symptoms suggestive of DVT or PE, which were excluded in all but one presenting with calf complaints and isolated calf-vein thrombosis, as shown by ultrasonography. The incidence of overall VTE events during the three-month follow-up of the 367 patients was 0.27% (95% CI, 0.0 to 1.51 %) and the incidence of PE was 0 % (95%CI, 0 to 1.0%). Figure 1 illustrates the diagnostic flow-chart and summarises the results.

Table 1: Baseline demographic and clinical characteristics of included patients (N = 545)*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>69 ± 14 years</td>
</tr>
<tr>
<td>Outpatients</td>
<td>338 (62.0)</td>
</tr>
<tr>
<td>Male</td>
<td>218 (40.0)</td>
</tr>
<tr>
<td>Recent surgery or trauma</td>
<td>28 (5.1)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>110 (20.2)</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>78 (14.3)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>47 (8.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pts with PE</th>
<th>Pts without PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>124 (73.4)</td>
<td>230 (62.7)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>112 (66.3)</td>
<td>193 (52.6)</td>
</tr>
<tr>
<td>Syncope</td>
<td>37 (21.9)</td>
<td>68 (18.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>25 (14.8)</td>
<td>80 (21.8)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>16 (9.5)</td>
<td>21 (5.7)</td>
</tr>
<tr>
<td>Heart rate &gt; 100 bpm</td>
<td>38 (22.5)</td>
<td>81 (22.1)</td>
</tr>
<tr>
<td>Shock/hypotension</td>
<td>7 (4.1)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

*Data are presented as number and percentage unless otherwise indicated. PE, pulmonary embolism.

Table 2: Causes of death during follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant disease</td>
<td>19</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
</tr>
<tr>
<td>Stroke after CEA*</td>
<td>1</td>
</tr>
<tr>
<td>End-stage respiratory failure from chronic lung silicosis</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory failure from acute exacerbation of severe COPD**</td>
<td>1</td>
</tr>
<tr>
<td>Spinal cord hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1</td>
</tr>
<tr>
<td>Overall</td>
<td>40</td>
</tr>
</tbody>
</table>

*CEA, carotid endarterectomy **COPD, chronic obstructive pulmonary disease.
Subsequent independent reading of CT images

The three senior-staff radiologists who subsequently reviewed all CT images disagreed on the results of two tests. In the first of the two tests they did not confirm the initial diagnosis of sub-segmental PE; the related patient was treated with anticoagulant therapy for three months during which neither symptomatic VTE nor bleeding occurred. In the second test, which was considered negative for PE, a consensus was reached on the actual presence of a small sub-segmental PE; under the initial findings the patient was allocated in the group of those with negative CT scanning and was followed up for three months during which no symptomatic VTE occurred.

Discussion

This prospective cohort study shows that the use of 64-detector row CT scanning in patients with suspected PE has the potential to safely exclude the presence of PE virtually in all subjects with high clinical suspicion of this disorder.
In the last decade, several prospective studies have assessed the efficacy and safety of algorithms for the diagnosis of PE, including a clinical decision model combined with D-dimer test and an instrumental diagnostic procedure (2, 9, 10, 14, 23, 27–31). The safety of withholding anticoagulant treatment in subjects with suspected PE and especially in those with low pre-test clinical probability and a normal D-dimer test was definitively confirmed, even using a dichotomous clinical decision rule based on Wells score (32). In patients showing higher risk of PE, the diagnostic efficacy of CT varies within certain limits depending on the number of detectors available. In the PIOPED II study, most patients underwent 4-detector row CT scanning and its negative predictive value (NPV) was 89% in subjects with intermediate pre-test clinical probability of PE and only 60% in those with high clinical probability (12). The addition of virtual CT venography improved only marginally the overall diagnostic performance in these categories of patients (NPV of 92% and 82%, respectively).

In the Christopher study, patients underwent single slice CT or MDCT scan collimated at 1.25-mm with a 1.2-mm reconstruction interval.

The incidence of overall VTE in patients with PE ruled out by CT/MDCT scanning was 1.3% after a three-month follow-up, an outstanding result when compared with that of pulmonary angiography. However, the incidence of fatal PE was 0.5%, a low though not negligible value (2). Interestingly, in a subsequent "post-hoc" analysis of the same cohort the patients with high clinical probability (Wells score higher than 6 points) and PE ruled out by MDCT scan had a three-month rate of overall VTE of 5.3% and of fatal PE of 1.7%. In this subgroup of patients most thromboembolic events were detected within the first 10 days of the index MDCT scan, so we can speculate that they might already have been present at the time of the initial diagnosis (33).

Recently, Righini et al. randomised 1819 patients with suspected PE to receive two different diagnostic strategies based on a clinical decision model, D-dimer test, MDCT scan and which differ in that one envisaged a systematic venous ultrasonographic test and the other did not (13). MDCTs adopted in that study were 16- and 64- detector row, with 0.625 mm to 1.25 mm slice thickness. The three-month incidence of VTE was 0.3% for both strategies adopted but, unlike both Christopher and our study, a negative result of the MDCT scan was not considered adequate in subjects with high pre-test clinical probability and the protocol required further diagnostic objective procedures in order to definitively rule out PE. Moreover, a MDCT scan showing only an intraluminal sub-segmental defect was considered inconclusive and further diagnostic procedures were required.

Overall, these studies show that even though it is generally safe to rule out PE based on a negative CT scan there is still a subgroup of about one patient in 20 with suspected PE in whom a less refined CT scan is not sufficient to safely rule out the diagnosis.

Unlike previous studies, we adopted a diagnostic algorithm including the systematic use of 64-DCT scanning. The results of our study could be considered generalisable: the algorithm adopted had been extensively validated in previous studies (2, 30), it was designed to be used in everyday clinical practice, patients were consecutive, only a few were excluded and the incidence of PE was comparable to that observed in previous studies.

Our study has some potential limitations: firstly, it is a single-centre "clinical management" study; therefore, the radiological procedure was not compared with the "gold standard" reference test, i.e. pulmonary angiography, in order to confirm its diagnostic accuracy. Nevertheless, the alternative method of assessing the incidence of thromboembolic events during a strict three-month follow-up is widely accepted (30). The potential weakness of the results obtained from a single-centre study is largely offset by a high-level ability to keep adhesion to the protocol under control.

Secondly, we excluded patients with previous PE; therefore, the results of our study cannot apply to these categories of patients, though they represent a minority of patients with suspected PE.

Thirdly, in almost half of the observed deaths the cause was attributed to malignant disease. Cancer patients are at high risk of VTE events but in case of death they are seldom investigated by autopsy, especially those at an advanced stage. Thus, we cannot exclude an underestimation of fatal PE in this fraction of our cohort. However, the comparability of both the prevalence of cancer and the incidence of death with those observed in previous studies (2, 12) is reassuring.

Fourthly, the adoption of 64-DCT might lead to increased radiological hazard. Though it is difficult to make a direct comparison between the radiation exposure of newer and older generation CT scanning there is substantial agreement that the multi-slice CT scanners increase radiation doses from 20% to over 100% compared to the older scanners. The radiation dose delivered to superficial radiosensitive organs, such as the breast, may be relevant (from 20 mGy for a woman of medium weight up to 190 mGy for a woman with large breasts) (34). Considering the irreplaceable diagnostic value of multi-slice CT examinations in several clinical situations, a number of methods have been implemented in order to reduce the radiation dose to the patients undergoing multi-slice CT examinations. The most common method is to modulate CT acquisition parameters such as milliampere, kilovolt peak, and cranio-caudal (z-axis) extent of acquisition, all of them without a substantial decrease in diagnostic accuracy. Dose reduction methods unrelated to the CT imaging parameters include the use of bismuth breast shields and lead shielding (35, 36). Interestingly, the more recent multi-slice CT scanners, built mainly for coronary studies, are characterised by a signal to noise ratio high enough to significantly reduce the radiation dose, down to only a few mGy, in order to obtain the same or even a greater diagnostic performance.

Fifthly, the systematic adoption of 64-DCT, which is not yet widely available, might reduce the generalisability of our results and lead to higher costs due to over-diagnosed PE events, mainly characterized by small sub-segmental emboli, whose prognostic value and actual need for anticoagulation are still unclear (20, 22, 37). The prevalence of overall PE in our study population (31%) is slightly higher than that observed in previous studies (2, 13, 19) and is associated with a higher fraction of isolated sub-segmental thromboemboli (12.4%). The proportion of in-patients in our study (38.0%) was higher than in some previous studies, possibly leading to higher prevalence of PE.
The patients with isolated sub-segmental pulmonary emboli did not undergo a confirmatory pulmonary angiography so that we cannot assess the false positive rate of 64-DCT scans and some patients might have been over-treated.

There are scarce and mostly indirect data addressing the outcome of subjects with isolated sub-segmental PE. In a recent meta-analysis of the previous management outcome studies, the risk of VTE in untreated patients with suspected PE and a negative CT scanning was low, irrespective of both the number of slices used and the increased rate of sub-segmental emboli observed when MDCTs were used (risk of 0.9% and 1.1% for single and multiple detector CT scanning, respectively) (38). A few small studies based on an overall sample of 116 subjects with isolated sub-segmental PE showed the absence of VTE recurrences after a three-month follow-up (20, 39). In a recent retrospective analysis of 93 patients with isolated sub-segmental PE, 76% of whom treated with anticoagulants, Donato et al. (39) observed an incidence of recurrent non-fatal PE equal to 1.05% and of major non-fatal haemorrhages equal to 5.3%. Of note, in almost 17% of the treated patients a caval filter was inserted, which suggests a previous high risk of bleeding in several of them. Overall considered, these data seem to show that isolated sub-segmental PE has a benign prognosis and that its overtreatment leads to an increased hazard without a clear clinical benefit. These results, albeit interesting, should be treated with some caution: studies using single-slice CT scanner had been performed several years before those using MDTC scanners and often had not adopted the same diagnostic algorithm; many studies were not included in the pooled analyses; no head-to-head comparison was made between older and newer generation CTs; very few studies used 64 detector CT scanners; the clinical features of the subjects enrolled were often heterogeneous and both asymptomatic and symptomatic sub-segmental PE were brought together in some retrospective studies.

What is known about this topic?
- In patients with suspected pulmonary embolism (PE) a diagnostic strategy using a clinical decision rule, D-dimer test and computed tomography (CT) scanning was found to be both accurate and safe. However, the rate of thromboembolic complications in the group of patients with negative CT scan was still substantial and included fatal events.
- Unlike older generation CTs the recently introduced high-definition multidetector row CTs reach submillimetre spatial resolution thus allowing the systematic identification of even subsegmental pulmonary emboli.
- The clinical significance of such small emboli is largely unknown.

What does this paper add?
- The systematic exclusion of even small emboli adopted in this study was associated with the absence of PE during the three-month follow-up.
- The use of 64-detector row CT scanning in patients with suspected PE has the potential to safely exclude the presence of PE virtually in all subjects with high clinical suspicion of this disorder.

It may be worthy of note that the systematic exclusion of even small emboli adopted in our study, was associated with the absence of PE during the three-month follow-up. We believe that a proper identification of PE, regardless of its size, can effectively constitute a warning for the clinician about the need to quantify the individual patient’s thromboembolic risk, which could have a number of consequences in terms of preventing possibly fatal recurrences. Moreover, the natural course of PE and one of its major late complications, chronic thromboembolic pulmonary hypertension, is still unknown and the latter apparently occurs without PE in a large minority of patients affected; we cannot exclude the presence of occult, possibly sub-segmental recurrent and often misdiagnosed PE in these patients. Diagnostic strategies using older generation CT scanners are still associated with a small number of fatalities, which are probably even more frequent in common medical practice, where the strict application of such strategies is far from obvious. Finally, technological progress is an irreversible process and the outstanding potential of high definition MDCTs in several fields of medicine is rapidly leading to the widespread dissemination of this diagnostic equipment.

In conclusion, the adoption in a large fraction of patients with clinical suspicion of PE of a diagnostic strategy including the combined use of a simple clinical decision rule, D-dimer test and 64-detector row CT scan can definitively rule out the presence of PE.

References


