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Concerns in using multi-detector computed tomography for diagnosing pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion as reference standard

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ABSTRACT

Introduction: Multi-detector computed tomography (MDCT) is considered to be the reference standard in diagnosing pulmonary embolism (PE). However, two concerns remain. Firstly, with the introduction of MDCT the prevalence of (sub)segmental emboli increased but the clinical implications of these small clots are uncertain. Secondly, we are not well informed about the number of false-positive CT-scans due to the lack of a gold standard.
Patients and Methods: We used data from a prospective primary care study including patients suspected of pulmonary embolism. CT-scan-reading by the local radiologist in daily care was retrospectively compared with expert reading as reference standard. Final diagnosis was categorized as central/lobar, segmental or subsegmental PE.
Results: A total of 79 patients were included. In 3 of 30 patients (10%) diagnosed with PE by the local radiologist the experts refuted the diagnosis. In 7 of 49 patients (14%) not diagnosed with PE by the local radiologist the experts confirmed the presence of PE. The experts diagnosed 17 of 32 PE-patients (53%) with a central or lobar PE. All these 17 patients were also diagnosed with PE by the local radiologist. The experts diagnosed 15 patients with (sub)segmental PE. In 7 of these 15 patients (47%) the local radiologist refuted PE.
Conclusions: Accuracy of MDCT using the expert radiologist as reference standard is not optimal. On the one hand it shows 10% false-positives exposing patients to anticoagulant treatment unnecessarily. On the other hand small emboli seem to be missed although the clinical implications of this finding are not fully clear.

Introduction

In the work-up of patients with suspected pulmonary embolism (PE) it has been demonstrated that PE can be safely excluded with a negative clinical decision rule and a negative D-dimer test both in primary care and in secondary care [1,2]. In patients having a high clinical probability or a positive D-dimer test computed tomography pulmonary angiography (CTPA) is currently the preferred diagnostic test. The negative predictive value (NPV) for symptomatic venous thrombo-embolism in 3 months following a CTPA without signs for embolism in this population approaches 99% [3].

However, in the diagnosis of pulmonary embolism using CTPA two major concerns remain.

Firstly, with the introduction of multi-detector CT (MDCT) visualization of (sub)segmental arteries improved significantly [4]. The rate of subsegmental PE was 4.7% and 9.4% in patients examined with single-and multiple-detector CTPA, respectively, without showing a difference in the 3-months follow-up rate of thrombo-embolism, suggesting that subsegmental PE not detected by single detector CT might not be clinically important [5]. In addition it has to be noted that currently available mortality rates from PE are derived from earlier studies, when small emboli could have been easily missed [6–8]. Therefore diagnosis of small (sub)segmental emboli creates a therapeutic dilemma. Treatment of a possibly clinically not-important small embolus might cause bleeding from anticoagulant treatment [9], which in the worst case can be fatal whereas no treatment might have severe consequences as well. Moreover diagnosing PE poses a weight on the future of patients, who might experience difficulties in obtaining life insurances and mortgages.

Abbreviations: MDCT, multi-detector computed tomography; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; NPV, negative predictive value; PCP, primary care physician; SSPE, subsegmental pulmonary embolism.

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Secondly, we are not well informed about the number of false-positive CT-scans due to the lack of a gold standard. False-positive scans result in patients unnecessarily exposed to anti-coagulant treatment. The interobserver agreement for interpretation of MDCT for PE is resulting in less agreement with increasing number of detectors, probably due to the less reliable detection beyond the segmental level [10–12]. In PIOPED II, using a composite reference standard, the positive predictive value of MDCT for pulmonary embolism in the main or lobar artery was 97%, for segmental PE 68% and for subsegmental PE 25%. The authors recommended to take the clinical assessment into consideration and to perform additional testing when clinical probability is inconsistent with the imaging results [13]. The results of the quantitative D-dimer test could be used with the same purpose as there is a strong correlation between plasma D-dimer concentrations and embolus location, with the highest concentrations in patients with emboli in the pulmonary trunk and the lowest in the subsegmental arteries [14,15].

In this study performed in primary care patients with suspected PE, we retrospectively assessed the accuracy of the local reading of the CT in daily practice with a radiology expert reading as the reference standard (i). We investigated whether this accuracy was dependent on thrombus localization (ii) and related the presence of pulmonary embolism and thrombus localization to the quantitative D-dimer results (iii).

Patients and Methods

For the present study we used data from a prospective cohort study including 598 primary care patients with suspected pulmonary embolism (PE). This study, executed in the Netherlands between July 1, 2007 and December 31, 2010, evaluated a diagnostic strategy consisting of the Wells PE-rule and a qualitative point-of-care D-dimer test [1]. Eligible for inclusion were consecutive adult (≥18 years) patients in whom the primary care physician (PCP) suspected PE. The PCP obtained written informed consent and systematically documented information on the patient's history and physical examination. The PCP calculated the score of the Wells-rule and performed a qualitative D-dimer test. Regardless of the outcome of the Wells PE-rule and the D-dimer test, we asked PCPs to refer all patients to secondary care for reference testing. In secondary care, the diagnostic strategy was based on current guidelines and routine care practice. In the Netherlands this mostly is a combination of probability estimation and quantitative laboratory based D-dimer testing (either an ELISA or a latex assay), followed by CT-scanning when indicated. CT-scanning was performed according to local CTPA protocols as used in regular patient care. No limitations were set on scanning technique and equipment. In addition to the results of the qualitative point-of-care D-dimer testing, we obtained the results of this quantitative laboratory based D-dimer testing. During 3 months of follow-up, PCPs were asked to document the final diagnosis of every patient.

The protocol was approved of by the medical ethical committee of the University Medical Center Utrecht, the Netherlands.

Selection of Patients

A total of 224 out of 598 patients (37%) underwent CT pulmonary angiography. In 175 of these 224 patients the result of a quantitative D-dimer test was available. From these 175 patients we included all patients diagnosed with PE with a negative Wells decision rule and a negative qualitative D-dimer test (n = 4). We saturated our sample to 80 patients with a proportional sample out of the three other probability groups: (i) patients diagnosed with PE with a positive Wells decision rule and/or positive qualitative D-dimer test (n = 26), (ii) patients in whom PE was refuted, with a negative Wells-rule and a negative qualitative D-dimer test (n = 16), (iii) patients in whom PE was refuted with a positive Wells rule and/or a positive qualitative D-dimer test (n = 34).

Assessment of CT-scans

For the assessment of the CT-scans the local radiologists had access to all clinical information as usual in daily care. Pulmonary embolism was either diagnosed or refuted.

Participating local radiologists sent us the selected CT-scans on CD-ROM. All scans were imported into a PACS reading system (Agfa Gevaert Impax 5.2, Mortsel, Belgium).Two expert radiologists (IvdB and LB), board certified and experienced in reading PE-CT-scans for 5 and 7 years, respectively, independently reassessed the CT scans. Due to differences in the image quality and the design of the image display (due to the different scanner types) the readers were not completely blinded to the type of MDCT. The readers were unaware of prior interpretation and of any clinical information, except of date of birth and sex. They interpreted the CT-scans for image quality (range 1 (inadequate, no diagnosis of PE possible)-5 (excellent)), confidence of diagnosis (range 1 (definitive no PE)-5 (definitive PE)) and either diagnosed or refuted pulmonary embolism or evaluated the CT-scan as indeterminate. CT-scanning was considered indeterminate if the image quality was too bad to diagnose or refute pulmonary embolism. Diagnosis of pulmonary embolism was categorised as central/lobar, segmental or subsegmental by the thrombus' most proximal end.

In cases of disagreement of diagnosis of pulmonary embolism between the two expert radiologists (n = 5), in cases one or both readers evaluated the CT-scan as indeterminate (n = 9) or in cases for which there was disagreement with respect to thrombus localization (n = 11) a consensus reading (total n = 25) was conducted by a third experienced chest-radiologist (CSP). In case of full discordance between the three readers (n = 4) a consensus reading was conducted by the three readers together.

Statistical Analysis

Statistical analyses were performed by using IBM statistical packages for the social sciences software (version 16.0; SPSS).

Clinical characteristics of study patients were compared using a chi-2 test for categorical variables and a student t-test for continuous variables. Quantitative D-dimer test results of different patient groups were compared using a student t-test. To assess the rate of agreement between local and expert radiologists the kappa-coefficient was calculated.

Results

The CT-scans of the 80 patients were performed according to local protocols in 21 different hospitals geographically distributed throughout the Netherlands. A wide variety of CT scanner generations and techniques were used for the examinations (see Table 1).

One patient had to be excluded because the date of CT-examination was not in accordance with the study-inclusion date. The final study population of 79 patients ranged in age from 21 to 91 years old. Baseline characteristics of these 79 patients are shown in Table 2.

The local radiologists diagnosed 30 of 79 patients (38%) for having pulmonary embolism. None of the 49 patients, in whom pulmonary embolism was refuted, had venous thrombo-embolism in the 3-months follow-up period.

The expert radiologists rated 32 of 79 patients (40.5%) as having pulmonary embolism. One of 32 PE-patients (3%) was diagnosed with subsegmental PE. The experts rated 6 of 79 CT-scans (8%) as indeterminate.

In 3 of 30 patients (10%) diagnosed with PE by the local radiologist the experts refuted the diagnosis. In two more patients the experts rated the CT-scan as indeterminate. Hence in 5 of 30 patients (17%) diagnosed locally with PE the experts could not confirm the diagnosis. In 7 of 49 patients (14%) not diagnosed with PE by the local radiologist the experts diagnosed PE. In four more patients the experts rated the

Table 1
Number of CT-slices and number of included patients in participating hospitals.

No. of CT-slices	No. of hospitals	No. of included patients
1	1	1
4	8	30
16	8	19
40	2	19
64	2	10
	Total: 21	Total: 79

CT-scan as indeterminate. Hence in 11 of 49 patients (22%), originally diagnosed as being negative for PE, the expert radiologists disagreed. The experts diagnosed 17 of 32 PE-patients (53%) with a central or lobar pulmonary embolism. All these 17 patients were diagnosed with pulmonary embolism by the local radiologist as well. The experts diagnosed 15 patients with either segmental or subsegmental PE. In 7 of these 15 patients (47%) the local radiologist refuted PE (see Table 3).

Quantitative D-dimer-result and Thrombus Localization

The quantitative D-dimer value of one patient was missing. This was the only patient diagnosed by the experts with subsegmental PE. The average quantitative D-dimer result of the other 78 patients was 1868 ng/ml. Only 10 patients had a D-dimer value below the cut-off value (either 400 or 500 ng/ml). In 8 of those 10 patients pulmonary embolism was refuted by both expert and local radiologists. One patient was diagnosed with segmental PE by the experts whereas the local radiologist refuted PE. The other patient was diagnosed with a (central/lobar) pulmonary embolism by both local and expert radiologists. In 3 patients in whom the experts refuted PE but who were diagnosed with PE by the local radiologist as compared to 38 patients in whom both local and expert radiologists refuted the diagnosis PE the average D-dimer values were 593 ng/ml and 1277 ng/ml respectively ($p = 0.44$).

In 17 patients diagnosed with a central or lobar PE as compared to 14 patients diagnosed with a segmental PE the average D-dimer values were 3504 ng/ml and 1767 ng/ml, respectively ($p = 0.09$) (See Fig. 1).

Table 2
Baseline characteristics included patients.

	Total study-population n = 79
Mean age (SD)	50 years [15]
range	21–91 years
Female patients	n = 60 (76%)
Acute complaints	n = 56 (71%)
Acute dyspnoea	n = 44 (56%)
Pain on inspiration	n = 60 (76%)
Unexplained cough	n = 25 (32%)
Duration of symptoms (SD)	5.8 (5.7) days
range	1–28 days
Items Wells-rule	
Signs and symptoms suggestive of deep venous thrombosis	n = 10 (13%)
PE most likely diagnosis	n = 51 (65%)
Heart rate >100 beats/min	n = 18 (23%)
Immobilisation or surgery in last month	n = 22 (28%)
Previous deep vein thrombosis or pulmonary embolism	n = 17 (22%)
Haemoptysis	n = 2 (3%)
Active malignancy (treatment<6 months)	n = 5 (6%)
Wells-score PCP mean (SD)	3.50 (2.4)
Wells-score PCP ≤4	n = 43 (54%)
Simplify D-Dimer test negative patients	n = 27 (34%)
D-dimer quantitative mean (SD) in ng/ml	1868 (2227)

SD=standard deviation, PE=pulmonary embolism, PCP=primary care physician.

Table 3
Assessment of CT-scans for PE by local radiologist versus expert radiologists.

	Expert no PE	Expert central or lobar PE	Expert segmental PE	Expert subsegmental PE	Expert Indeterminate	Total
Local PE	3	17	7	1	2	30
Local no PE	38	0	7	0	4	49
Total	41	17	14	1	6	79

Kappa: 0.72 (for dichotomous categories no PE versus PE present, without n = 6 indeterminate).

Discussion

In this retrospective study performed in primary care patients with suspected pulmonary embolism in at least 10% of patients diagnosed with PE and treated with anticoagulants, academic experts refuted the diagnosis by second reading (false-positives). In at least 14% of patients not diagnosed with PE by the local radiologist and not treated with anticoagulants the experts diagnosed PE (false-negatives). The readings of CT by local radiologists in suspected PE patients appeared accurate for patients diagnosed with central or lobar PE. The reading appeared less accurate in patients with segmental PE as in 50% of patients diagnosed by the experts with segmental PE the local radiologist refuted the diagnosis and patients were not treated with anticoagulants.

To appreciate the present results several aspects require comment.

Although we included a small number of patients the results are in line with previously published accuracy-studies using expert radiologists as reference standard. The interobserver agreement is high in central or lobar emboli and is lower for more peripheral emboli [12]. In reviewing CT-scans with an index diagnosis subsegmental pulmonary embolism (SSPE) a total of 11% of the patients were diagnosed without evidence of PE by a second expert radiologist (false-positives) [16]. In assessing the precision of (64-slice) CT-scanning 12% of scans read as positive at the clinical site were subsequently read as negative or indeterminate upon second reading conducted by an independent expert radiologist causing patients to be treated with anti-coagulation unnecessarily (false-positives). In case the reference radiologist detected PE contrary to the clinical site reading, the diagnosis was based on very small clots (false-negatives) [17]. In 20 not-anticoagulated patients retrospectively diagnosed with pulmonary embolism in segmental or smaller arteries one patient died of the effects of the original pulmonary embolism [7]. In our study none of the 7 patients with a false negative diagnosis (and hence not treated with anticoagulants) suffered from venous thrombo-embolism-sequelae during the three months follow-up.

With the introduction of MDCT the incidence of pulmonary embolism increased significantly [18]. It is likely that the increasing incidence

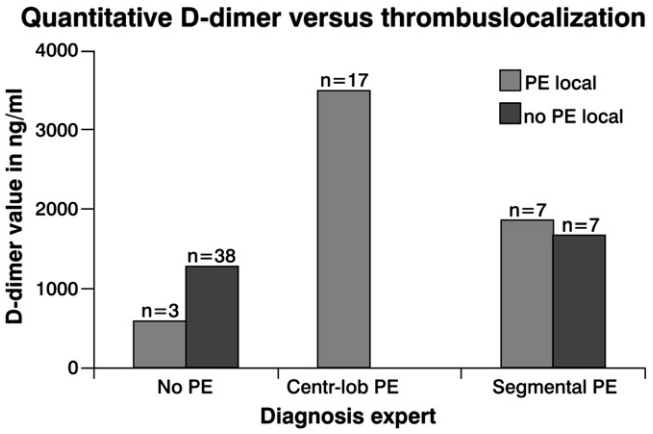

Fig. 1. 6 patients rated as indeterminate and 1 patient diagnosed with subsegmental PE are not listed in the table, PE local: diagnosis of PE by local radiologist, Centr-lob: Central-lobar.

of pulmonary embolism corresponds to an increase in true-positive results, detecting more small emboli [19]. Although we still do not know the clinical significance, physicians tend to treat these emboli [20]. The increasing incidence might be due to an increase in false-positive results as well due to the significant lower interobserver agreement in diagnosing (sub)segmental emboli.

In the present study in 15 patients diagnosed with (sub)segmental PE by the expert radiologists the local radiologist had refuted the diagnosis in 7 patients. Although both expert radiologists diagnosed pulmonary embolism in all those 15 patients they disagreed about the exact localization of the thrombus in 7 patients showing that the interobserver agreement for small emboli even for expert radiologists is substantial (data not shown). In a previous study 37% of patients with an index diagnosis of SSPE were re-interpreted as having a more proximal filling defect (segmental) [16].

We have circumstantial evidence indicating that the experts indeed gave the right diagnosis. Firstly, both expert radiologists independently diagnosed pulmonary embolism in all 15 patients with (sub)segmental PE. Secondly, correlating the diagnosis of pulmonary embolism and thrombus localization with quantitative D-dimer results as measure for clot burden [15] we found that the average D-dimer value in false-positive patients as compared to D-dimer values in true positive patients was 593 and 3023, respectively ($p = 0.19$), suggesting that the expert radiologists were right with refuting the diagnoses of pulmonary embolism in these patients. In patients diagnosed with segmental PE the mean D-dimer values in patients diagnosed with PE in comparison with patients not diagnosed with PE by the local radiologist didn't differ much and were 1857 and 1678 respectively, but were considerably higher as in patients in whom both experts and local radiologists refuted the diagnosis (mean D-dimer 1277) ($p = 0.24$) suggesting that the experts were right in diagnosing segmental PE.

In the present study only one patient (3%) was diagnosed with subsegmental PE. The prevalence of subsegmental PE in studies using MDCT varies between 5% and 14% [20–22]. It is likely that the triage of patients with a low clinical probability and a negative D-dimer test is reducing the proportion of patients with subsegmental defects selected for CT [19].

Six of 79 scans (7.6%) were rated as indeterminate, which is higher as compared to the 1–2% observed in clinical outcome studies [2,21] but is comparable with studies using expert radiologists as reference standard [17,23], showing that CTPA is not always producing a binary, positive or negative result. Of course evaluating scans in a research setting without management consequences is different from daily clinical practice suggesting that in daily practice treatment decisions might be based upon inconclusive CT-scans in a subset of patients [23].

In this study we observed a huge variation in used CT-technology reflecting current clinical practice. In assessing CT-scans using 4 or less slices ($n = 31$) versus CT-scans using 16 or more slices ($n = 48$) we found no differences in number of detected (sub)segmental PE neither in number of indeterminate scans (data not shown).

Clinical implications and implications for further research.

In case the radiologist is diagnosing central or lobar pulmonary embolism the diagnosis seems accurate. However in case of a negative CT-scan or in case the CT-scan is assessed as (sub)segmental pulmonary embolism we recommend radiologists to perform a non-urgent second opinion. Further research should be focused on the clinical implications of (sub)segmental emboli. To diminish the number of false-positive CT-scans research is needed to investigate the additional role of quantitative D-dimer levels or compression ultrasonography in the assessment of non-central/lobar pulmonary embolism.

Conclusion

There is no true gold standard for diagnosing or refuting pulmonary embolism. CTPA is currently the preferred imaging test because of the high negative predictive value in outcome-studies using the thromboembolic rate in the follow-up period as the outcome-measure. However in accuracy-studies using the expert radiologist as reference standard the accuracy of the CT-scan is less optimal. On the one hand this study shows 10% false-positives exposing patients to treatment unnecessarily. On the other hand small emboli seem to be missed although the clinical implications of this finding are yet unknown. In our study no patient, diagnosed as suffering from (sub)segmental embolism and not anticoagulated experienced clinical consequences during three months follow-up.

Conflict of Interest Statement

None of the authors have any financial or other potential conflicts of interest relative to the data in this manuscript.

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