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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

Wim A.M. Lucassen [a,*], Ludo F.M. Beenen [b], Harry R. Büller [c], Petra M.G. Erkens [d], Cornelia M. Schaefer-Prokop [e], Inge A.H. van den Berk [b], Henk C. van Weert [a]

[a] Academic Medical Centre, Department of General Practice, Amsterdam, The Netherlands
[b] Academic Medical Centre, Department of Radiology, Amsterdam, The Netherlands
[c] Academic Medical Centre, Department of Vascular Medicine, Amsterdam, The Netherlands
[d] University of Maastricht, Department of General Practice, Maastricht, The Netherlands
[e] Meander Medical Centre, Department of Radiology, Amersfoort, The Netherlands

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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.

* Corresponding author at: Department of General Practice, AMC, J2-218, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 5667956; fax: +31 20 5669186.
E-mail address: w.a.lucassen@amc.uva.nl (W.A.M. Lucassen).

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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