Original Article

Use of D-dimer and Lower Extremity Doppler Ultrasound Results to Obviate the Need for Computerised Tomographic Pulmonary Angiography

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Abstract

Introduction: We hypothesise that correct interpretation of other diagnostic tests could reduce the use of computerised tomographic pulmonary angiogram (CTPA) examinations in patients with suspected pulmonary embolism (PE). Materials and Methods: We carried out a retrospective analysis of 158 patients in a 928-bed university hospital. These consecutive patients were investigated for suspected PE from May 2001 to February 2002 using CTPA. Results: There were 74 men and 84 women with a mean (±SD) age of 57 (±19) years. Overall, 56% of patients (89/158) showed clinically significant abnormalities on the CTPA examination. The overall prevalence of PE was 15% (24/158). The D-dimers were assayed in 40% (63/158) and lower limbs were scanned with Doppler ultrasound (US) in 22% (35/158) of patients. None of the 19 patients with negative D-dimer assays had PE. Of the patients who were positively tested on Doppler US, 4 were positive and 1 was negative for PE on the CTPA. None of the patients with positive Doppler US had negative D-dimer test. In retrospect, patient management based on negative D-dimer assays and positive lower extremity Doppler US studies could have reduced the need for further investigation with CTPA by 15% (24/158). Conclusion: In patients with suspected PE, correct interpretation of D-dimer and leg Doppler US tests may reduce the demand for CTPAs.

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Introduction

The diagnosis of pulmonary embolism (PE) can be a challenging problem. It depends on clinical suspicion and the interpretation of a combination of clinical and radiological presentations. Pulmonary angiogram (PA) is the gold standard for the diagnosis of PE but it requires special expertise and is not available in all centres. It is also invasive and can be difficult to interpret.[1] Ventilation perfusion (V/Q) scans have been used extensively and validated in large prospective studies against PA.[2,3] However, most studies report that only a minority of the patients with suspected acute PE have a definitive diagnosis following V/Q scanning. A large proportion of patients return intermediate probability V/Q scans and these usually require further testing. In the past decade, computerised tomographic pulmonary angiogram (CTPA) has emerged as a major tool of investigation for PE. It has definite advantages over PA in being non-invasive and easier to arrange out of the hours, particularly in ill patients.[4] However, the CTPA examination has its own drawbacks; it requires rapid injection of a high volume of radiographic contrast agent, which may not be suitable for patients with renal impairment. Also, the sensitivity (53% to 100%) and specificity (81% to 100%)[5] of CTPAs in the detection of PE vary in different studies. This variable accuracy is mostly dependent upon the extent of the thrombo-embolic disease and the CT technique employed. Moreover, in contrast to the V/Q scan, the accuracy of CTPAs has not been rigorously validated against PA. Nevertheless, the CTPA has become the diagnostic test of choice for PE in many centres around

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the world, including our hospital.

Other screening and diagnostic tests for thrombo-embolic disease such as plasma D-dimer, which is a degradation product of fibrin,[6-8] and the different techniques of Doppler ultrasound (US) examining deep veins of the leg[7,8] have also been subjected to formal evaluation in clinical trials and are widely used in routine practice. D-dimer has poor positive predictive value[6] and elevated levels alone are not useful because of the low specificity. D-dimer may also be elevated in other conditions including surgery, trauma, malignancy, pregnancy, severe infection, liver disease and disseminated intravascular coagulation (DIC).[9]

The purpose of this study was to assess if the interpretation of the results of the D-dimer tests and the Doppler US of the lower limbs could have reduced the number of requests for the CTPA examinations and to evaluate the utility of the CTPA in routine clinical practice.

Materials and Methods

We included all adult inpatients above the age of 18 years who had had CTPA scan of the thorax for suspected PE between 5 May 2001 and 14 February 2002. Patient's details were retrieved from clinical notes. Patients who had spiral CT of the thorax for reasons other than suspected PE were not included. Two experienced radiologists reviewed all CTPAs and any disagreement was resolved either by consensus or independent review by another radiologist. D-dimer levels, which were measured in the 24 hours before the CTPAs, were included. Details of Doppler US examination of veins, which were done in the 72 hours before the CTPAs, were collated.

The CTPAs were performed with multi-detector CT (Volume Zoom, Siemens, Erhlangen, Germany). Scanning of the thorax was performed either in a craniocaudal or caudocranial direction, from just above the level of aortic arch to the level of domes of the diaphragm. The scan delay was performed with the bolus tracking method after the start of injection of intravenous contrast administered at 3 to 4 mL/sec from a peripheral vein. A total of 100 mL of contrast was administered to ensure adequate enhancement of the pulmonary vessels throughout the scanning period, which lasted for 12 to 20 seconds. The trigger point was maintained at 180 HU in the main pulmonary artery. Scans were acquired using 4 x 1 mm collimation and a pitch of 1.5. Axial 3-mm scans were reconstructed in both the mediastinal window (width, 400 HU to 450 HU; level, 40 HU to 50 HU) and the lung window (window width, 1200 HU; level, 750 HU).

Acute emboli were diagnosed when the filling defects were seen to completely or partially occlude the vessels. Pulmonary arteries down to the subsegmental levels were evaluated. Identification of the segmental and subsegmental branches was performed with both sets of images and using bronchi as landmarks. The presence of other abnormalities was also identified on both sets of images.

The level of D-dimer, a degradation product from fibrin, rises during the coagulation-activated states due to fibrinolysis. We used D-di test (Diagnostica Stage, France), which is a rapid latex agglutination slide test using mouse monoclonal antibodies for the qualitative and semi-quantitative determination of D-dimer in plasma. The latex particles provided in the D-di test are coated with mouse anti-human D-dimer monoclonal antibodies. The test sample containing D-dimer, when mixed with the latex particle suspension, makes the particle agglutinate. At the predetermined concentration of D-dimers that the D-di test is designed for, the agglutination of the latex particles produces macroscopic clumps that can be visualised by the naked eye. The D-di test is designed to have a positive cut-off at 0.5 mg/mL expressed in fibrinogen equivalent unit (FEU). An FEU is the quantity of fibrinogen initially present that leads to the observed level of D-dimer.

Data were analysed with SPSS software (version 11.0, SPSS BI, Chicago, IL). Summary data were expressed as mean (±SD).

Results

A total of 160 patients were subjected to CTPA examination during the study period. The case records were incomplete for 2 patients and thus, they were excluded from this study. The results of the remaining 158 patients were available for analysis. Of these, 74 were men and 84 women. The average age of the patients was 57 ± 19 years. Eighty per cent of the referrals for CTPAs were made within the first 2 weeks of hospital admission.

The overall prevalence of PE was 15% (24/158). After reviewing all scans, 1 patient was found to have a doubtful subsegmental PE in the initial consultation. She also had leg Doppler US and D-dimer tests performed, both of which were negative. On further review, this was thought to be an artifact and this patient was considered negative for PE by CTPA.

D-dimer

Sixty-three (63/158, 40%) patients had D-dimer assays. Of these, 44 (44/158, 28%) were positive and 19 (19/158, 12%) were negative. Among the patients with positive D-dimer tests, CTPAs were positive in 13 cases and negative in 31 cases. Of the 19 with negative D-dimer results all were negative for PE by CTPAs. Therefore, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for D-dimer in this study are 96% (95% CI, 73-99.6), 38% (95% CI, 26.2 -51.9), 30% (95% CI, 18.6-44.5) and 98 % (95% CI, 80-99.7), respectively, taking CTPA as the reference standard.

Doppler US of the Legs

Thirty-five (35/158, 22%) patients had their legs veins examined by Doppler US. Of these, 30 were negative and 5 examinations were positive for deep vein thrombosis (DVT). Among the patients who had normal leg examinations, the CTPA was positive for PE in 8 and negative in 22 cases. Of the 5 patients who had positive leg examinations, 4 were positive and 1 was negative for PE on the CTPA scan. Thus, the sensitivity, specificity, PPV and NPV for Doppler US of the leg in relation to PE were 33% (95% CI, 13.8-61), 96% (95% CI, 79-99.8), 80% (95% CI, 37.6-99) and 73% (95% CI, 55.6-85.8), respectively, compared to CTPA.

Polyvalency of the CTPA

Abnormalities other than PE were detected on CTPA in 41% (65/158) of patients. They are shown in Table 1. The most common abnormality was pulmonary consolidation, often with pleural effusions. Of these, 34 (52%) were visible in the chest radiography and 15% (24/158) were clinically significant, leading to a change in clinical management.

Correct Interpretation of Collaborative Tests for PE

Analysis of the above data showed that 5 patients had DVT detected on US Doppler while another 19 patients had negative D-dimer tests. None of the patients with positive Doppler US had negative D-dimer, thus these 2 groups did not overlap. Patients with positive US Doppler who also had CTPA were haemodynamically stable and did not have massive or submassive PE either clinically or radiologically. Analysis of records suggests that for both groups of patients, the CTPA did not result in any changes in clinical management. Therefore, in retrospect, we could have avoided the CTPA in 15% (24/158) patients if the results of the leg Doppler and D-dimer tests had been interpreted correctly.

Table 1. Abnormalities Detected by Computerised Tomographic Pulmonary Angiogram

Pulmonary	
Pulmonary embolism	24
Consolidation ± pleural effusion	58*
Mediastinal lymphadenopathy ± lung nodule	10*
Lung mass	6
Emphysema ± bullae	5*
Interstitial fibrosis	4*
Pneumothorax	1
Pulmonary lymphangitic carcinomatosis	1*
Extrapulmonary	
Enlarged thyroid ± thyroid nodule	2*
Fatty liver	1
Adrenal cyst	1
Aortic aneurysm	1
Pneumomediastinum	1
Pericardial effusion	1
Normal	69

* Some patients had these abnormalities in addition to pulmonary embolism. Thus, the total number of abnormalities was above 158.

Discussion

We found in this study that, with a correct interpretation of the leg Doppler US and the D-dimer results, we could have avoided the CTPA examination in 15% (24/158) patients. The D-dimer test has a very high NPV (99% to 100%),[6] and a negative result, in the correct clinical context, may be an indication for the clinician not to proceed with further testing. In other words, D-dimer will help to rule out rather than include PE as a possible diagnosis. However, some authors have raised the concern that D-dimer may not be able to help in the diagnosis of small subsegmental PE, where its sensitivity remains low.[10] Burkill et al[11] had shown that a negative semiquantitative latex agglutination D-dimer test is highly predictive of a negative CTPA and the inclusion of such a test reduced the need for CTPAs by 36%. A negative D-dimer at the end of anticoagulation also has a high NPV for recurrence of venous thromboembolism.[12] On the other hand, the indiscriminate use of D-dimer may increase the number of requests for further confirmatory tests. In a study in Christchurch Hospital, New Zealand, Iles et al[13] had shown that after the introduction of the D-dimer test, the number of requests for CTPA and V/Q scanning rose without any substantial increase in PE diagnoses.

The CTPA could also have been avoided in another 5 patients who already had DVT detected on leg US Doppler examination. This is because these patients did not show any evidence of significant PE, either clinically or radiologically, and the CTPA examination would not have made any difference to the immediate management of these patients, who required therapeutic anticoagulation anyway. Importantly, as haemodynamics and oxygenation were stable in all these 5 patients, none of them were considered for further measures, including thrombolysis. The lower than expected incidence of PE is this study is also consistent with the notion that the CTPA has been utilised more often than is necessary.

To our knowledge, this is one of the few descriptions of the utility of CTPAs in a routine clinical setting. In contrast, most recent reports of CTPA have been undertaken by experts and researchers within the setting of formal clinical trials.[14,15] In this regard, the 15% incidence of PE reported in this study is in the lower range of reported studies of CTPA (18% to 44.5%).[16-18] This suggests that there might have been a degree of over-investigation for PE in using the CTPA in our centre during the study period.

Until recently, most evidence-based guidelines on the approach to patients suspected of acute PE, including that published by the American Thoracic Society,[17] have recommend V/Q scanning as the first screening test. This is because radionuclide lung scans have been validated against the gold standard of PA in prospectively blinded studies and thus, are considered pivotal tests in the diagnosis of acute PE by many expert reviewers. However, in the clinical practice setting of suspected acute PE, V/Q scanning may have limited usefulness. A large proportion of patients return intermediate probability scans for PE and these usually demand further testing. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,[2] the incidence of intermediate-probability scans was 13% even in patients with normal chest radiograms, and this increased to 43% in those patients with any form of cardiopulmonary disease. As the extent of parenchymal lung abnormality increases, it is more likely that the scan will be non-diagnostic. The anticipation that the lung scans will be non-diagnostic in hospitalised patients with pre-existing cardiorespiratory illness is probably a major reason for its infrequent use in this study. Only 1 patient had V/Q scan in the present study, which revealed a low probability of PE.

In many centres, including ours, the CTPA is becoming increasingly popular for the diagnosis of PE and is the first choice of investigation for this purpose. In a previous published study[18] from our centre, we have shown that CTPA was the investigation of choice in breathless patients suspected to have PE. Some investigators suggest that it is superior to V/Q scanning and may obviate the necessity for further testing.[19,20] A CTPA scoring system reported by Mastora et al[21] also correlates well with the severity of PE. Newer multislice CT offers further technical advantages, including fewer motion artifacts, visualisation of subsegmental arteries[22] and the possibility of imaging the leg veins at the same time.

The British Thoracic Society guidelines for the diagnosis of PE[23] acknowledge the advantages of the CTPA examination and recommend this as the first test for clinically suspected submassive and massive PE. While V/Q scans help to diagnose PE, CTPA provides additional information on why the patient is unwell rather than simply excluding the diagnosis of PE. Moreover, the CTPA is relatively easy to perform, particularly in ill patients, and may be considered a polyvalent test in acutely breathless patients. In this study, the CTPA was helpful in diagnosing PE and other abnormalities in the majority of patients (Table 1). In a retrospective analysis of 92 patients with suspected PE, Shah et al[24] showed that parenchymal abnormalities are common (90%), atelectasis being the commonest. Coche et al[4] analysed CTPA scans of 88 patients with suspected PE and found that 37.5% had wedge-shaped consolidations. Linear band of atelectasis was found in 28.4%. Given the ease of performing this examination in an acutely ill patient and the array of potentially useful information it reveals, it is not surprising that the clinicians are more inclined to request for a CTPA rather than a V/Q scan.

A recent meta-analysis suggests that it may be safe to withhold anticoagulation if the CTPA is negative.[25] A study by Musset et al[14] suggested that, in the presence of low to intermediate clinical probability of PE, it is safe to withhold anticoagulation if the CTPA and leg USs are negative. Earlier studies[15,26,27] included CTPAs in conjunction with other diagnostic modalities, but recent studies[28-30] using CTPAs alone found the incidences of subsequent PE at 3 month's follow-up to be low.

There has been a trend of analysing the accuracy of the CTPA using clinical outcome measures instead of comparing it with conventional angiography. The ongoing prospective investigation of pulmonary embolism diagnosis II (PIOPED II)[31] will use a composite reference test for venous thrombo-embolism that is based on the V/Q lung scan, venous compression US of the lower extremities, digital subtraction PA and contrast venogram in various combinations to establish the PE status of the patient. However, CTPA involves the administration of large doses of radiographic contrast material and may not be suitable in patients with impaired renal function. It is important to note that of all patients in the PIOPED II trial, 3% were pregnant, 4% were allergic to iodinated contrast material and 19% had elevated serum creatinine levels.[31] Magnetic resonance angiography of the pulmonary artery may be useful in these circumstances[32] but large randomised trials are lacking.

The strength of this study is the evaluation of outcomes of CTPAs performed in a large multidisciplinary teaching hospital. In our hospital, CTPA examinations are available on demand, including out of hours, at the discretion of the attending physician, who could be of any specialty. In this "real world" setting, which, we suspect, would be similar to many other institutions, appropriate use of other simple, cost-effective and potentially less harmful investigations like D-dimer and Doppler US of the legs may reduce the additional costs and side-effects associated with the CTPA. However, the decision to avoid CTPA in a patient who is already positive for DVT should be taken after considering other factors, including inpatient versus outpatient management, type of injected anticoagulant, focusing attention on oxygenation, consideration of thrombolytic therapy and plan for follow-up regarding assessment for thrombo-embolic pulmonary hypertension. Conversely, in the situation where another clear indication for further pulmonary imaging is present, such as hilar or mediastinal abnormalities on plain radiographs, it might be more

expedient to proceed directly to the CTPA examination and omit the other indirect tests for PE.

This study has a few limitations. We evaluated a relatively small population, the data were retrospective in nature and every patient did not undergo all 3 tests. The attending physician did not adhere to any uniform protocol in the diagnosis of PE or request for the CTPA and no patient underwent PA, the gold standard test. Most importantly, due to the retrospective nature of the data, no assessment of the pretest probability of PE was possible. Estimation of pre-test risk of PE is a key step in the diagnostic process, which has been incorporated, in most clinical trials and practice guidelines on the diagnosis of PE. This differentiation of patients into different risk categories facilitates interpretation of the test results and further management especially when the test results are equivocal. Finally, patients were not followed up in a consistent way; we therefore have incomplete information regarding the recurrence of PE and mortality.

We would also like to stress that a decision to proceed to CTPA when a DVT is found is clinical and depends on multiple factors, including inpatient versus outpatient management, type of injected anticoagulation, focusing attention on oxygenation, consideration of thrombolytic therapy and plan for follow-up regarding assessment of thrombo-embolic pulmonary hypertension.

In conclusion, we have shown that the correct interpretation of D-dimer and, where appropriate, prior leg Doppler US tests, may reduce the demand for CTPAs in the detection of PE.

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