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Can helical CT replace scintigraphy in the diagnostic process in suspected pulmonary embolism? A retrolective-prolective cohort study focusing on total diagnostic yield

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Abstract. The aim of our study was to compare the diagnostic value of helical CT vs that of ventilation–perfusion (V/Q) scintigraphy as a first-line test in a diagnostic strategy in patients suspected of pulmonary embolism (PE). In a retrolective–prolective cohort study we tested the accuracy of helical CT vs V/Q scintigraphy in 123 patients suspected of PE. A diagnostic panel was asked to formulate the presumptive diagnosis on the presence or absence of PE, or of alternative disease by using two competing diagnostic strategies. These consisted of the patient history, laboratory tests and chest X-ray (together baseline tests) in combination with either helical CT or V/Q scintigraphy (CT strategy and V/Q strategy, respectively). The results were compared with the final diagnosis in each patient that was established from various reference tests (which included V/Q scintigraphy, pulmonary angiography and clinical follow-up). The CT and V/Q strategies were compared with regard to the accuracy for PE, for alternative diseases and with regard to the proportion of conclusive diagnoses that were made. The CT strategy was more accurate than the V/Q strategy for detecting or excluding PE. Sensitivity and specificity were 49 and 74 % for the V/Q strategy and 75 and 90 % for the CT strategy, respectively ($P = 0.01$). The CT strategy provided a conclusive diagnosis in a significantly larger proportion of patients than the V/Q strategy, 92 vs 72 % ($P < 0.001$). The CT strategy detected more alternative diagnosis than the V/Q strategy, 93 vs 51 %, respectively ($P < 0.001$). Helical CT seems more useful than V/Q scintigraphy as a first-line test in patients suspected of PE.

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Introduction

Diagnostic imaging in patients suspected of pulmonary embolism (PE) remains an important clinical issue. Five years ago, Remy-Jardin et al. introduced contrast-enhanced helical CT of the pulmonary arteries as a potential diagnostic test for pulmonary embolism (PE) [1]. Since then several validation studies have attested to the accuracy of helical CT to detect or exclude PE, with claimed values of sensitivity and specificity ranging 54–100 % and 78–100 %, respectively [1–10]. Helical CT appears to be a robust method that yields a conclusive diagnosis in the vast majority of patients. It has thus been suggested that helical CT should be incorporated in the diagnostic algorithm for PE. [2, 8, 11] At present, there are no studies that indeed use helical CT for this purpose. Only validation studies of helical CT for PE have been published, but no studies that have directly compared the diagnostic accuracy of helical CT vs that of V/Q scintigraphy.

It was the aim of this study, then, to compare the diagnostic accuracy of helical CT vs that of ventilation/perfusion (V/Q) scintigraphy in combination with clinical findings in a diagnostic strategy in patients suspected of PE. We were particularly interested in what would happen in daily clinical practice if helical CT is actually used in the workup for PE.

This would be ideally tested in a randomized clinical trial (RCT). But at the start of this study there were no data that supported use of helical CT alone (an RCT with an isolated CT arm seemed unethical). To simulate such a clinical trial, we created an experimental clinical setting in which we used clinical data from an already existing patient group. These data were used previously in a validation study [7]. The diagnostic accuracy of helical CT vs V/Q scintigraphy were thus tested in a so-called retrolective–prolective cohort study design. In such a study design, a patient cohort is identified (retrolectively) from existing medical data and this cohort is then analysed in a (prolective) manner by observers who are unaware of the imaging studies and patients' diagnosis [12].

Materials and methods

Characteristics of the existing patient group

Two strategies were tested in a single, well-defined already existing group of 123 consecutive patients suspected of PE patients (44 males and 79 females; age range 19–91 years, mean age 59 years) with clinically suspected PE. Most patients were outpatients, without relevant underlying diseases. All patients had undergone V/Q scanning and helical CT. The mean period between first clinical symptoms and the first imaging test was 14 h (range 2–24 h). In two patients the CT scan was non-diagnostic because of suboptimal image quality. Forty-nine patients who either had non-diagnostic V/Q scans ($n = 44$) or CT findings that contradicted the V/Q scan (which means negative CT and high probability V/Q scan, $n = 1$, or positive CT and normal V/Q scan, $n = 2$, or inconclusive CT with normal V/Q scan, $n = 2$) had undergone additional pulmonary angiography. All examinations were done within a 48-h time window. Four patients could not be included in this study because of contrast allergy ($n = 1$) and renal insufficiency ($n = 3$). Informed consent was obtained in all patients and the study protocol was approved by the ethics committee of the hospital.

Final diagnosis of PE

The final diagnosis in each patient was established by using the opinion of multiple expert readers on the imaging studies. The 49 pulmonary angiograms were re-evuluated in a blinded fashion by two independent radiologists. The 123 V/Q scintigrams were re-evaluated independently by two specialists in nuclear medicine who used the modified PIOPED criteria [13, 14]. Third observers were used whenever the first two observers disagreed. These results served to establish the presence or absence of PE as follows: pulmonary angiography, whenever available, was the definite gold standard (PE in 11 of 49, normal in 38 of 49). In the remainder of patients, a high-probability V/Q scan ($n = 42$) was taken as evidence for presence of PE (chance of not having PE = 12 %) [15–17]. It is currently accepted that a high-probalitity V/Q scan is convincing enough evidence of PE to warrant the start of anticoagulant treatment. Of 123 patients, 53 (43 %) had PE. A normal perfusion scan (in 32 patients) was taken as evidence for absent PE (chance of having PE < 0.2 %) [18, 19]. In all 70 patients without PE, clinical follow-up of more than 1 year showed no clinical sequelae consistent with PE as revealed by medical records.

Table 1. Patient group: final diagnosis according to reference studies ($n = 123$). PE pulmonary embolism

PE present	53 (43 %)
Positive pulmonary angiography	11
High-probability V/Q scan	42
PE absent, alternative diagnosis	41 (33 %)
Pneumonia	17
Chronic obstructive pulmonary disease	13
Ischaemic heart disease	4
Pleuritis carcinomatosa	2
Malignant tumour	2
Oesophageal rupture	1
Osteoporotic vertebral collapse	1
aortic dissection	1
PE absent, no alternative diagnosis	29 (24 %)

Alternative diagnoses were made in 41 of the 70 patients in whom imaging modalities did not indicate PE. Pneumonia ($n = 17$) was proved by bacterial culture, malignancy ($n = 4$) by histology or cytology, ischaemic heart disease ($n = 4$) by electrocardiographic changes, enzymatic markers and follow-up, and chronic obstructive pulmonary disease ($n = 13$) by resolution of clinical symptoms after treatment with specific pulmonary medication. One case of aortic dissection was proven by post-mortem correlation and one case of esophageal rupture, by esophagography. One case of an verterbral collaps was proved by conventional roentgenography (Table 1).

Study design

In this study we evaluated the clinical impact of using either helical CT or V/Q scintigraphy as a part of diagnostic strategies. Two strategies were compared in a cohort of 123 patients suspected of PE. From each patient the clinical history, a physical examination, laboratory findings, electrocardiogram and a chest X-ray were considered together as what we termed "baseline studies". These baseline studies together with either helical CT or V/Q scintigraphy formed the two tested strategies: (a) baseline studies + V/Q scintigraphy (V/Q strategy); and (b) baseline studies + CT (CT strategy).

We assembled "patient cases" out of the existing patient group. Two matching cases were made: one case consisting of baseline studies plus V/Q scan and the other consisting of baseline studies plus the CT scan. The $2 \times 123 = 246$ cases were presented in random order to a panel consisting of two experienced physicians: a pulmonary physician (H. H.) and a radiologist (W. M.), who were unaware of patient identity. The radiologist had a more than 20-year working experience with CT of the chest and also with nuclear medicine studies. (In The Netherlands a radiologist can have additional board certification to read nuclear medicine studies.) This panel was chosed as it simulates daily clinical practice, in which a physician and a radiologist discuss patient cases.They were asked to formulate in consensus a presumptive diagnosis for each of the 246 patient cases, using the information provided in the strategy, and to score them as follows: 1 = PE present or very likely; 2 = PE; 3 = alternative disease; 4 = inconclusive examination. We assumed that the two panel members, because of the large number of patient cases and the randomization process, would be unable to recognize matching case pairs. The cases were reviewed during ten sessions over a 2-month period. The panel's answers allowed direct comparison of the performances of the V/Q and CT strategies with the final diagnosis known from the reference studies.

Statistical analysis

For each strategy 3 × 2 tables were constructed, relating the strategy outcome to the final diagnosis. From these tables sensitivity and specificity were calculated. The proportions of inconclusive examinations were recorded. Percentages of strategies were compared with McNemar's chi-squared tests at $P = 0.05$.

Results

The performance of the two strategies are listed Tables 1 and 2. The helical CT strategy was more accurate in diagnosing PE than the V/Q strategy ($P = 0.007$). The overall values for the sensitivity and specificity in the helical CT strategy were 75 and 90 %, and in the V/Q strategy 49 and 75 %, respectively.The positive and negative predictive values were 93 and 90 % in the CT strategy, and 96 and 85 % in the V/Q strategy.

The proportion of inconclusive examinations were 35 of 123 (28 %) and 10 of 123 (8 %) for the V/Q and CT strategies, respectively; thus, the strategy that contained CT showed significantly less inconclusive examinations than the V/Q strategy ($P < 0.001$).

In the 35 cases, where the V/Q strategy results were inconclusive, the CT strategy correctly identified the final diagnosis in 29 patients (13 PE, 11 alternative diagnoses, 5 normal); in one case the CT strategy was also inconclusive and in the remaining 5 patients the outcome of the CT strategy was incorrect (one false-positive PE, four false-negative). In the ten cases, where the CT strategy was inconclusive, the V/Q strategy detected correctly three PEs, three alternative diagnoses and one normal case; the V/Q strategy was also inconclusive in one case. In the remaining two cases the V/Q strategy was incorrect (two false-negative cases).

The V/Q strategy detected 21 of 41 (51 %) alternative diagnosis vs 38 of 41 (93 %) with the CT strategy ($P < 0.001$). Some alternative diagnoses, such as pneumonia or chronic obstructive pulmonary disease, were detected by both strategies (because the chest X-ray was part of both strategies). But important findings, such as aortic dissection and mediastinitis in esophageal rupture, were detected with CT only, as were the two cases of malignancy. For examples see Figs. 1–3.

Table 2. Outcome of the two strategies related to the final diagnosis for 123 patients suspected of PE

	Final diagnosis		
	PE present	Alternative diagnosis	Normal
V/Q strategy			
PE	26	0	1
Alternative diagnosis	0	21	0
Normal	9	9	22
Inconclusive	18	11	6
Total	53	41	29
CT strategy			
PE	40	0	3
Alternative diagnosis	0	38	0
Normal	7	0	25
Inconclusive	6	3	1
Total	53	41	29

Table 3. Diagnostic indices of the two strategies

	V/Q strategy (%)	CT strategy (%)
Inconclusive	28 (35 of 123)	8 (10 of 123)
Diagnostic indices		
Sensitivity	49 (26 of 53)	75 (40 of 53)
Specificity	74 (52 of 70)	90 (63 of 70)
Positive predicted value	96 (26 of 27)	93 (40 of 43)
Negative predicted value	85 (52 of 61)	90 (63 of 70)

Discussion

Initial validation studies suggest a high sensitivity and specificity of helical CT in detection of PE. [1, 3–10], despite the fact that helical CT seems limited for detecting small PEs that may be present in isolation in the smaller, subsegmental branches of the pulmonary vascular tree [5, 7, 8]. On the basis of these results it has been argued that helical CT should be incorporated into the diagnostic algorithm for PE [2, 5, 8]. Until know, to our knowledge, validation studies of helical CT have focused on the accuracy of this method in isolation. However, it is probably more appropiate to test the diagnostic accuracy of helical CT in the context of a diagnostic algorithm, as this more accurately reflects routine clinical practice. In this study we compared the clinical impact of helical CT vs V/Q scintigraphy as a first-line test as part of diagnostic strategies.

The main finding of the current study is that the CT strategy more accurately detects or excludes PE than the V/Q strategy. The overall sensitivity and specificity values for CT strategy were 75 and 90 %, and for V/Q strategy 49 and 74 %, respectively (Tables 2, 3). Helical CT thus seems a safe substitute for V/Q scintigraphy as a primary diagnostic test in suspected PE. These results are in accordance with a previous study by Mayo et al. [9]. In a recent abstract they reported 51 patients who all underwent helical CT and V/Q scintigraphy and concluded that CT was more accurate than V/Q scintigraphy in diagnosing PE.

The use of helical CT proved also to be advantageous as a larger proportion of examinations were conclusive

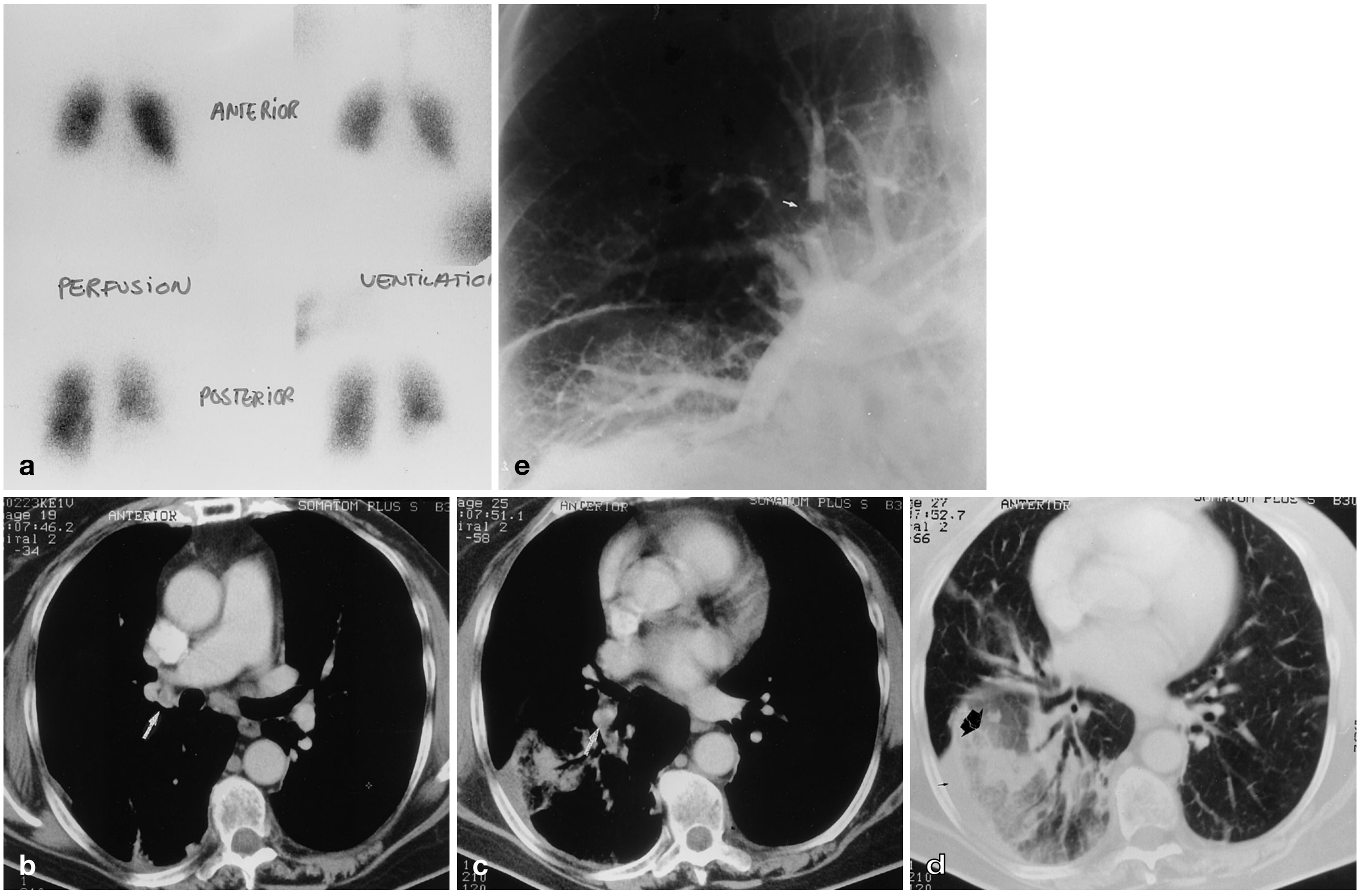

Fig. 1a–e. A 71-year-old woman with sudden onset of shortness of breath. Laboratory findings showed no abnormalities and the chest X-ray showed area of air-space consolidation in the right lower lobe (not shown here). **a** The V/Q scan shows matching defect of the right lower lobe on the anterior and posterior view. The panel scored the V/Q strategy as inconclusive. **b** The CT scan shows a filling defect in a right upper lobe segmental artery *(arrow)*. **c, d** A CT scan at the level of the right lower lobe shows another filling defect in a lower lobe artery *(white arrow)* with an area of parenchymal consolidation *(black arrow)* and some pleural effusion *(small black arrow)*. Panel scored this patient with CT strategy as present PE with pulmonary infarction. **e** Pulmonary angiography of the same patient confirmed CT findings, embolus in the right upper lobe *(arrow)*

than in the V/Q strategy, 92 vs 72 % ($P < 0.001$) That helical CT increases the number of conclusive examinations is relevant. V/Q scintigraphy is often non-diagnostic in most patients (28 % in the current analysis and 73 % in the PIOPED study [19]), whereby the proportion of non-diagnostic V/Q scans varies considerably among different institutions and patient population being studied. It is generally held that these patients should undergo subsequent pulmonary angiography to guide treatment decisions. But in the majority of cases pulmonary angiography is not performed [17, 21]. An important advantage of CT, our results suggest, is that it will reduce the need for additional pulmonary angiograms: the proportion of conclusive examinations increased from 72 to 92 %.

A further advantage of helical CT relates to its ability to detect or rule out alternative diagnosis. As only one third of patients suspected of PE will actually have this condition, other diseases should be looked for in the remaining two thirds. In this analysis the CT strategy was significantly better in this respect than the V/Q strategy (93 vs 51 % detection rate of alternative disease, $P < 0.001$).

Some limitations of the present study should be considered. Firstly, the retrolective–prolective study design with assembled patient cases provides less conclusive evidence when compared with a randomized clinical trial (RCT). At the start of this study, there were only few data in the literature that support using CT as a first-line test in a diagnostic strategy without pulmonary angiography [2, 8, 9]. An isolated CT arm seemed unethical at that time. On the other hand, the used study design has the advantage that the two competing strategies are challenged with a single independent set of patients: first to decrease the number of patients necessary (123 in the current study vs $2 \times 123 = 246$ patients in an RCT) and, second, to ascertain an identical patient mix with the same spectrum of PE and comorbidity.

Another limitation may be that our results represent the diagnostic acumen of a panel of two observers only. One may rightly argue, for example, the expertise of the panel members to interpret the imaging studies, or to make clinical decisions based on the available information. The panel's accuracy for diagnosing PE with scintigraphy, however, was better than the values in the PIOPED study with reported sensitivity of 41 % and

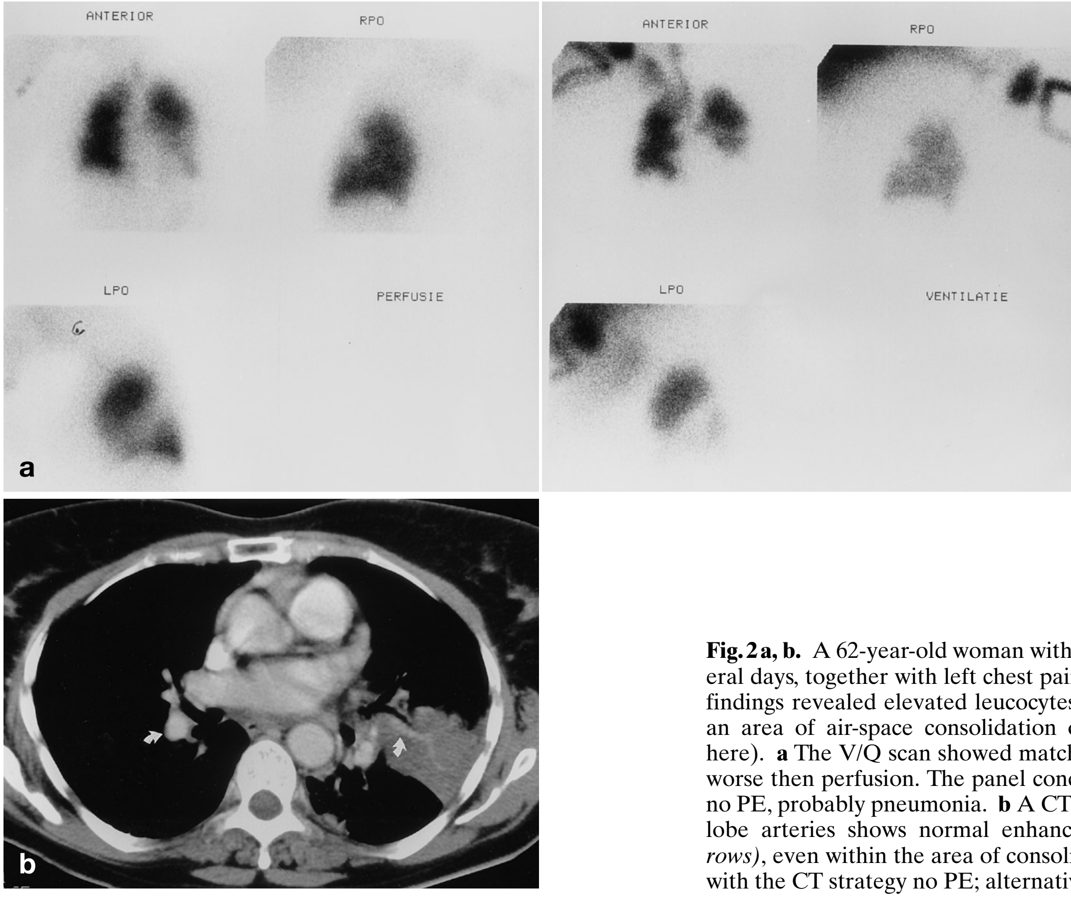

Fig. 2 a, b. A 62-year-old woman with cough and dyspnoea for several days, together with left chest pain and mild fever. Laboratory findings revealed elevated leucocytes count. Chest X-ray showed an area of air-space consolidation on the left side (not shown here). **a** The V/Q scan showed matching defects, ventilation even worse then perfusion. The panel concluded with the V/Q strategy no PE, probably pneumonia. **b** A CT scan at the level of the lower lobe arteries shows normal enhancing pulmonary arteries *(arrows)*, even within the area of consolidation. The panel concluded with the CT strategy no PE; alternative diagnosis: pneumonia

specificity 52 %, respectively [19]. The accuracy with helical CT was within the range of the figures reported in the literature.

A point of critism might be that the V/Q scintigram is part of the diagnostic strategy under consideration and also part of the reference studies. The V/Q scan, however, when used as part of the reference studies was scored by independent observers using the modified PIOPED criteria. This seems a valid gold standard, because it is generally accepted that a normal perfusion scan rules out PE and that a high probability V/Q scan warrants the start of anticoagulant therapy. On the other hand, in the diagnostic strategy under consideration, the V/Q scan was scored by the diagnostic panel incombination with the baseline studies in a more clinical setting. That this has led to discrepancy in interpretation of the V/Q scan is explained in more detail below.

It is of interest that the diagnostic panel scored nine V/Q cases as normal, whereas the reference studies indicated that PE was present in these cases (based on positive pulmonary angiograms in 5 patients, and high probability V/Q scan plus positive CT scan in 4 patients). This discrepancy in interpretation of the V/Q scan alone and the V/Q strategy in our opinion reflects the known observer variability for indeterminate V/Q scans (25–30 % disagreement between expert readers in the PIOPED study) [17]. Another factor is that V/Q scan interpretation may differ depending on whether or not clinical data are taken into account. In fact, the PIOPED investigators have recommended that a low-probability V/Q scan (as were these nine V/Q scans according to the diagnostic panel) obviates further testing in a patient with a low pretest probability of PE.

Given the limitations in study design, this study cannot provide conclusive proof about the use of helical CT vs V/Q scintigraphy. Nevertheless, this study provides strong arguments favoring a prominent role for helical CT in the diagnostic workup of suspected PE. Helical CT appears to provide more conclusive diagnoses than V/Q scintigraphy and its diagnostic accuracy for PE seems at least as good as that of the V/Q scan. Helical CT also appears to detect more alternative disease, which could explain patients complaints. Confirmation of these results by other investigators is needed. Perhaps, bearing the current results in mind, one may now seriously consider RCT using helical CT as a replacement test for V/Q scintigraphy in suspected PE.

Appendix

Technique

Helical CT

Helical CT scans were obtained using a Somatom Plus S scanner (Siemens, Erlangen, Germany). If possible, scanning was performed during a single breath hold.

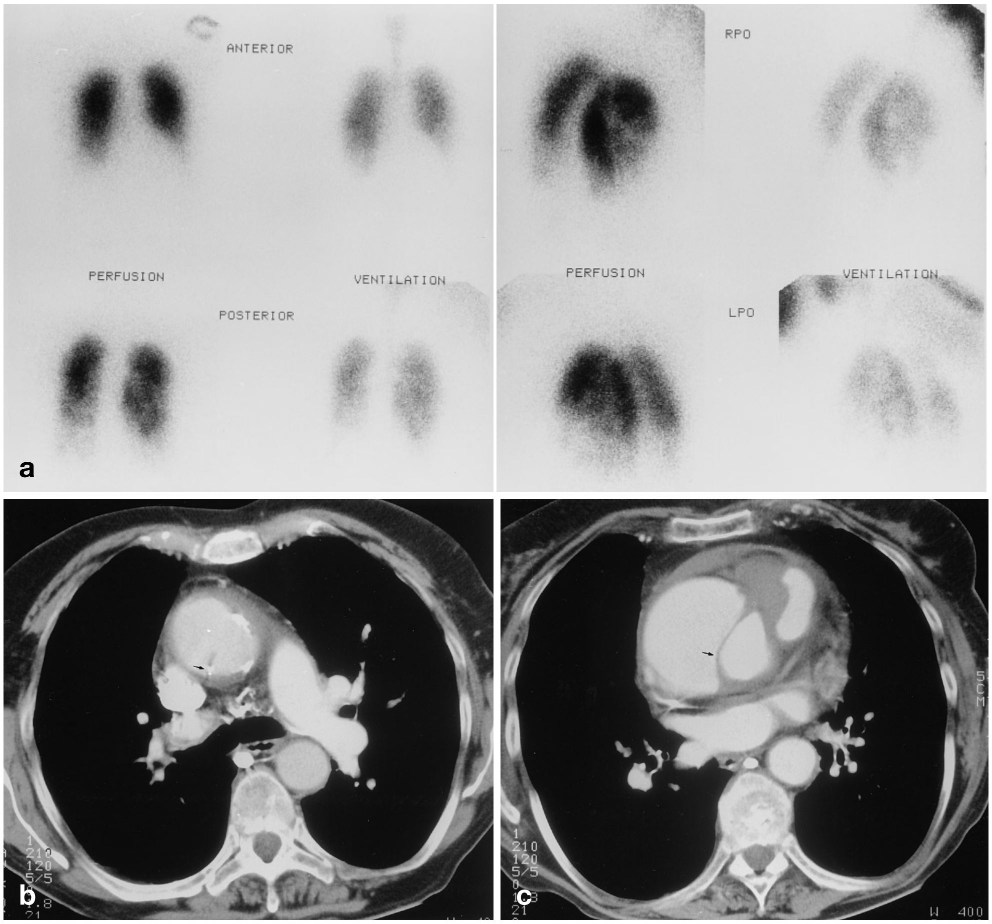

Fig. 3a–c. A 69-year-old with acute sharp anterior chest pain and shortness of breath. **a** The V/Q scan shows diffuse nonsegmental matching defects. Panel scored the V/Q strategy as inconclusive. **b, c** The CT scan showed no PE, but found another diagnosis: dissection of the ascending aorta (*arrow* points at intima tear)

Dyspnoeic patients were asked to breathe gently. The CT scans were obtained using 210 mA and 120 kV. Scanning time was 32 s, with a 5-mm/s table feed and collimation of 5 mm (pitch of 1). Data were reconstructed with a 360° linear interpolation algorithm and images were reconstructed at 4-mm interval. A scanning volume of 16 cm was obtained in craniocaudal direction starting immediately above the aortic knob. One hundred millilitres of a low-osmolarity, 30 % iodinated non-ionoic contrast agent (Iopamiro 300, Bracco, Milan, Italy) was administrated via an antecubital vein using a power injector. We used a biphasic contrast injection with a flow of 3 ml/s during the first 15 s, then a flow of 2 ml/s up to 100 ml, with a 15-s scanning delay.

Computed tomography images were viewed on lung (window width 1500 HU; window centre –500 HU) and mediastinal (window width 400 HU; window centre 40 HU) settings. Lung window settings are used for the interpretation of the normal anatomy and for detection of alternative diagnosis. The diagnosis of PE was based on a centrally filling defect within pulmonary artery, or if there was a complete occlusion of a pulmonary artery. [3]

V/Q lung scan

Technetium-99m-labelled macroaggregated albumin (75–80 MBq) was used for perfusion lung scanning. Six views were obtained: anterior, posterior, right and left lateral, and right and left posterior oblique. Ventilation scintigraphy was performed with Krypton-81 m and the same six views were obtained. Diagnosis of PE was made according to the modified PIOPED criteria [13–14].

Pulmonary angiography

Pulmonary angiograms were made using conventional Roentgen-film technique with a Grollman catheter (Cordis, Roden, The Netherlands) positioned in the main left or right pulmonary artery. Anterior–posterior and 30° contralateral views were obtained using 40-ml injections of 30 % nonionic contrast agent at a flow rate of 20 ml/s. The angiographic criteria defined by Sagel and Greenspan were used for diagnosis of PE. [20]

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