Diagnosing pulmonary embolism: establishing and consolidating the role of spiral CT

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Helical CT and alternative diagnosis in patients with excluded pulmonary embolism

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Abstract

Background: *A clinical diagnosis of pulmonary embolism (PE) is confirmed objectively in 20 - 30% of patients. Helical CT can allow an alternative diagnosis to be made. The frequency and validity of alternative diagnoses on helical CT in consecutive patients presenting with clinically suspected PE was assessed.*

Methods: In all 512 prospectively analyzed patients helical CT scan was performed, and apart from presence or absence of pulmonary embolism, pathologic changes in lung parenchyma, mediastinum, cardiovascular system, pleura and skeleton were recorded. When possible an alternative diagnosis was given and compared with the final diagnosis after 3 months follow-up.

Results: *In 130 patients (25,4%) PE was excluded and an alternative diagnosis considered likely. In 123 of the 130 patients (94,6%) this diagnosis was unchanged at three months follow-up. The diagnoses included pneumonia (n=67), malignancy (n=22), pleural fluid (n=10), cardiac failure (n=10), COPD (n=6) and a variety of other causes (n=15). The diagnosis changed at follow-up in seven patients (5,4%). An initial diagnosis of pneumonia changed to malignancy in two patients and to pleuritis and cardiac failure in one patient each. In two other patients malignancy and COPD were ruled out and the diagnosis changed to pneumonia. In one patient the final diagnosis remained unknown after an initial suspicion of malignancy.*

Conclusion: *In clinically suspected PE helical CT allows a reliable alternative diagnosis to be made in 25,4% of patients. This feature is an unique advantage in comparison to other diagnostic tests and supports the decision of taking helical CT as first line test in suspected PE.*

Introduction

Helical computed tomography (CT) is increasingly used as the first line imaging test in patients clinically suspected of pulmonary embolism (PE).[1-5] A noninvasive and quick procedure, helical CT can be used to detect PE by displaying the intravascular thrombus. Recent studies have shown overall sensitivities ranging from 64% to 100% and specificities from 89% to100% [6-9]. A potential advantage of helical CT is its capability of providing information on all thoracic structures including lung parenchyma. It can therefore, after exclusion of PE, allow an alternative diagnosis to be made that explains the patient's signs and symptoms. Prospective data on these alternative diagnoses in large patient series are, however, lacking.[10-12] Providing a possible alternative diagnosis that can explain the patients complaints and symptoms, is clinically relevant because approximately 60-70 % of patients with clinically suspected PE actually do not have PE.[1,13,14] Ventilation perfusion scintigraphy and pulmonary angiography have been widely used methods for detecting pulmonary emboli but these techniques provide little information on the other anatomical structures of the chest.

The purpose of the current study is to assess the role of CT in making an alternative diagnosis in patients referred to CT for a clinically suspected pulmonary embolism.

Materials and methods

Study design

The data of this study were obtained as a part of the ANTELOPE multicenter initiative (Advances in New Technologies Evaluating the Localization Of Pulmonary Embolism). The analysis was performed on a subset of patients without PE. The details of this study have been described before.[1] Patients were recruited in three unaffiliated participating hospitals. The study protocol was approved by the ethics committees of the participating centers and the study was designed as a prospective clinical management trial. All patients had a helical CT scan performed within 24 hours after inclusion.

Patients

All 512 consecutive in- and outpatients (median age of 55.1 years (range 18-96 years),who presented with clinically suspected PE in one of the three participating centers during the inclusion period (April 1999 – May 2000) were eligible. The diagnosis PE was considered in patients with sudden onset of dyspnea or (pleuritic) chest pain on respiration, sudden deterioration of existing dyspnea (for instance in patients with chronic obstructive pulmonary disease (COPD)) or with unexplained

dyspnea for a prolonged period of time (median duration of symptoms three days). Exclusion criteria were diagnostic testing for PE/deep vein thrombosis (DVT) in the preceding week, oral anticoagulant medication or heparin for more than 24 hours, age < 18 years, probable pregnancy as indicated by the patient, CT not performed or not of diagnostic quality and/or failure to obtain written informed consent. Further demographic characteristics of included patients are summarized in table 1.

Table 1. Clinical and demographic characteristics of included and eligible patients.

Number	512
History of VTE	67 (13,1%)
Known malignancy	100 (19,5%)
COPD	74 (14,5%)
Congestive heart failure	48 (9,4%)

Percentages are between brackets
VTE: venous thromboembolism COPD: chronic obstructive pulmonary disease

All patients without a diagnosis of PE and with findings on CT allowing an alternative explanation for the complaints at inclusion, were evaluated in this study.[1] The scans were analyzed for signs suggesting an alternative diagnosis to explain the clinical signs and symptoms. The diagnostic strategy is schematically depicted in Figure 1. No anticoagulant therapy was given when CT was negative for PE. If an alternative diagnosis was made, specific treatment was started when appropriate. The safety of withholding anticoagulant therapy in patients in whom the diagnosis of PE was ruled out on the basis of a normal CT has been previously reported.[1] In all patients with no PE on CT and no possible alternative diagnosis serial compression ultrasonography was performed on day 1, day 4 and day 7 after inclusion.

Imaging studies

The helical CT scanners used in this study were all of the single detector type (Siemens Somatom plus 4 and Somatom 6, Siemens Medical Systems, Erlangen, Germany; Philips Tomoscan AV, Philips, Best, The Netherlands). The protocol was targeted for the detection of PE (5 mm/s table feed, 5 mm-thick collimation (pitch of 1, 120 kV, 210 mAs, 16 cm volume during 32 sec breath hold, intravenous injection of contrast medium after 15-20 sec imaging delay, 2 mm interval reconstructions). The contrast protocol was standardized in all institutions (either 100 ml of 35% iodine (Iomeron 350, Bracco Byk Gulden, Konstanz, Germany) injection rate of 2.5 ml/s, or 120 ml of 30% contrast agent

(Ultravist 300, Schering, Berlin, Germany) rate of 3.0 ml/s).

CT-Image analysis

All CT-examinations were read by one of nine available experienced radiologists on a viewing station using standard window and level settings (mediastinal setting: window width 350 HU, window level 50HU; lung setting: window width 1500HU, level –500HU). The observer was allowed to change these settings. Overlapping images (reconstructed every 3 millimeters) were also printed on hard-copy film at the two standard settings. All clinical data were available at the time of interpretation, including clinical presentation (onset, dyspnoea, presence and aspect of pain, left or right localization of complaints). The clinical presentation was used by the radiologist to find a possible alternative explanation for the complaints in cases with excluded PE. A CT-scan was considered to be not of diagnostic quality and therefore inconclusive for PE if there was insufficient opacification (subjective interpretation of available contrast in the pulmonary arteries, no definite HU cut off value used) of the vessels or in case of major imaging artifacts. Since PE could not be excluded in these patients, they were also not included in the analysis for an alternative diagnosis.

Initial alternative diagnosis at baseline

The radiologist had to indicate if PE was present or absent. A standard scoring form was used by the interpreting radiologist to systematically describe and localize abnormalities in skeleton, soft tissues and pleura, mediastinum, cardiovascular system, and lung parenchyma. Subsequently the radiologist also had to indicate an alternative diagnosis he considered when appropriate in case of absence of PE. The established diagnoses were categorized in 6 groups: pneumonia, malignancy, on conventional chest X-ray underestimated amounts of pleural fluid, heart failure, COPD or other. The diagnosis of pneumonia was based on patchy consolidations, parenchymal opacities, air bronchograms, and/or thickened interstitium, with or without atelectasis and hilar and mediastinal lymph node enlargement. Malignancy was considered when tumor in the lung, parenchymal metastasis, metastatic lymph node enlargement with known primary tumor or mediastinal tumor was depicted. Diagnosis of cardiac failure was based on enlargement of the heart with increased pulmonary circulation, interstitial fluid and pleural fluid. COPD was based on well defined areas of increased lucency, reduction in number and caliber of pulmonary vessels, and fibrotic parenchymal changes (emphysema). A number of separate diagnoses such as pneumothorax, aortic dissection, pericarditis and compression atelectasis secondary to pleural

effusion were diagnosed based on previously described criteria.[15] In accordance with usual care, additional tests initiated by CT findings were allowed. (e.g. laboratory tests, cardiac ultrasound etc.). The results of these tests were not separately recorded, but instead the treating physicians were asked to indicate a final, clinical diagnosis based on all available information (history, clinical findings, lab tests, CT and other diagnostic tests performed etc.). In addition, with the complete set of diagnostic tests and their results available the treating physician was asked to indicate which test or finding had been most helpful in making a diagnosis.

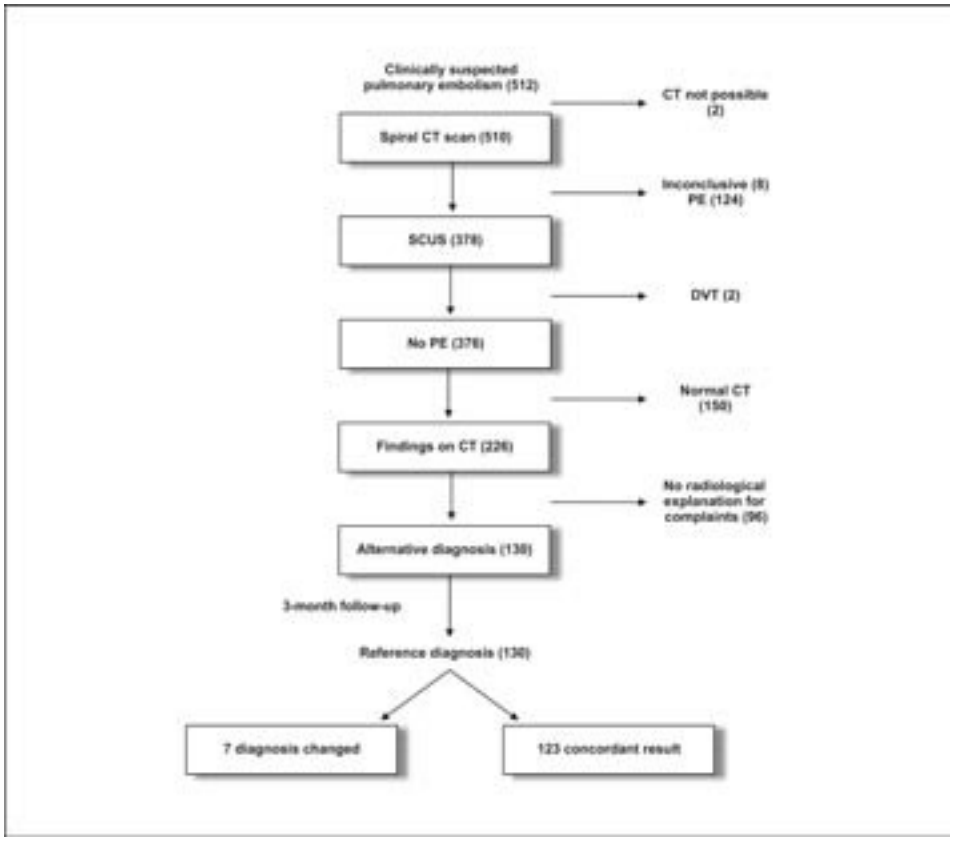
Follow-up and reference diagnosis

All patients were followed during three months after completion of the diagnostic work-up at baseline. During follow-up all patients received routine clinical care from their treating physicians aimed at treating the alternative diagnosis determined at baseline. In addition, patients were instructed to report to the physician or to the local study coordinator immediately in case signs or symptoms suggesting PE or DVT became apparent. If, at any time during follow-up, venous thromboembolism (VTE) was suspected by the treating physician, patients were investigated using objective tests, in particular compression ultrasonography (CUS) or contrast venography for suspected DVT and pulmonary angiography for suspected PE. After 6 weeks and at the end of the 3-months follow-up period the patients were seen by one of the study coordinators for an interview and a physical examination, aimed to assess the incidence of VTE. Also at the end of follow-up the diagnosis determined at initial presentation was re-evaluated to see if this initial diagnosis had changed. In the case record form, any additionally performed tests during follow-up, as well as recurrence of complaints, hospital admissions and mortality in this three month' period were also recorded.

Data collection and adjudication

The data collection was centralized. All instances of morbidity and relevant mortality during follow-up were recorded and adjudicated by an independent committee. The committee had full access to medical charts including results of laboratory and imaging tests, and autopsy reports, when performed. For the purpose of this study it was of particular interest if a patient death should be attributed to PE, hemorrhage or to a PE unrelated cause.

Figure 1. Result of the diagnostic algorithm.



SCUS: serial compression ultrasonography
PE: pulmonary embolism
DVT: deep vein thrombosis
Numbers between brackets indicate number of patients

Results

Results of the diagnostic algorithm (Figure 1)

During the recruitment period, 704 patients presented with suspected pulmonary embolism, of whom 611 patients were eligible based on the inclusion (clinical suspicion of PE) and exclusion criteria (objective diagnostic testing for PE/DVT in the preceding week, treatment with anticoagulants or heparin for more than 24 hours prior to inclusion, age < 18 years, pregnancy). Ninety-nine of these eligible patients refused (or were not able) to give written informed consent.

512 patients with a clinical suspicion of PE were included. In 510 of 512 included patients a helical CT scan was performed. In two patients a CT scan could not be performed because the use of contrast agents was contraindicated in one patient

and supine positioning in the CT gantry was not possible in another patient. In both patients a ventilation perfusion scintigraphy was performed with a high probability result in one and a normal result in the other. In eight of the 510 patients (1,6%) CT was not of diagnostic quality. In three of these patients pulmonary embolism could not be excluded, additional pulmonary angiography did not show pulmonary embolism but these three patients were still treated with oral anticoagulants. The remaining five patients did not receive anticoagulant treatment. In two of these five patients serial compression ultrasonography was performed with normal results. The other three patients were treated for alternative diagnoses (pneumonia and chronic obstructive pulmonary disease).
PE was found in 124 patients (24,2%) and DVT in another two patients after serial compression ultrasonography in 378 patients. In 150 patients (29,3%) there were no abnormalities seen on CT. In 130 patients (25,4% of all suspected patients, 34,4% of all patients with excluded PE) CT findings allowed an alternative explanation for the complaints.

Table 2. Overview of various uncategorized explanations for complaints at inclusion

Aortic dissection (Debakey type A)	1
Pleural fluid and consolidations, postoperative changes after splenectomie	1
Pneumomediastinum	1
Liver hematoma in HELLP	1
Hydropneumothorax	1
Respiratory insufficiency	1
Pulmonary oedema	1
Sarcoidosis	1
Pneumothorax	2
Pleuritis in SLE	1
Lung abcesses	1
Subphrenic abcess with reactive pleural effusion	1
Pericarditis and splenomegaly	1
Aspecific pleural reaction	1
Total	**15**

HELLP: high bloodpressure, elevated liver enzymes and low platelets (pregnancy)
SLE: systemic lupus erythematosus

In 96 of 226 patients the radiologist indicated that the minor pathologic findings had no relevance to the current complaints leading to the clinical suspicion of PE. These findings included minimal and insignificant parenchymal findings (scarring, fibrosis, aspecific small isolated nodules and small bullae), anatomic variants (vascular anatomy, fissures), pleural adhesions, lymphadenopathy, postoperative changes and degenerative skeletal changes, and tiny collections of pleural fluid that were considered no explanation for complaints of dyspnea, During follow-up

there were no deaths attributable to PE in these 96 patients and no patient was treated with anticoagulants.

Alternative diagnosis at the time of inclusion (baseline) and most conclusive test

The distribution of diagnoses over the six defined groups was as follows: pneumonia in 67 patients (51,5%), malignancy in 22 patients (16,9%; in 19 patients progression of known malignancy, in 3 patients new malignancy), pleural fluid and compression atelectasis in 10 patients (7,7%), heart failure in 10 patients (7,7%), COPD in 6 patients (4,6%) or other various diagnoses in 15 patients (summarized in table 2) (11,5%).

The treating physicians indicated that the helical CT scan was most conclusive in establishing an alternative diagnosis in 112 patients (86,2%) in the 130 patients with an alternative diagnosis . In 3 of the other 18 patients (2,3 %) fine needle aspiration (FNA) cytology /histology (malignancy, pleuritis and lung abscesses),

Table 3. Overview of alternative diagnoses and most conclusive test.

	Alternative diagnosis found						
Most conclusive test	Pneu-monia	Malig-nancy	Pleural fluid	Cong. cardiac failure	COPD	Other	Total
CT	62	18	10	6	6	10	112
FNA/histology	-	1	-	-	-	2	3
Clinical findings	1	1	-	-	-	1	3
CT + abdominal US	-	-	-	-	-	1	1
CT + chest X-ray	-	-	-	1	-	-	1
CT + clinical findings	2	-	-	2	-	-	4
CT + echocardiography	1	-	-	1	-	-	2
All tests combined	1	-		-	-	1	2
Missing	-	2*	-	-	-	-	2
Total	67	22	10	10	6	15	130

**The designation of the most conclusive test was missing in 2 patients (1,5%).*

and in 3 patients (2,3%) the findings at clinical examination were considered to be most informative. In these three patients CT was considered to be primarily useful for excluding PE. The initial diagnoses before completion of the CT considered to be most likely by the clinicians in charge of the patient were in fact confirmed by the CT diagnoses: flank trauma with fractured rib, pleural effusion and atelectasis; pneumonia; and malignancy. In 10 patients (7,7%) CT in combination with another test was used for determining the baseline diagnosis. (chest CT and abdominal ultrasound in one patient (pericarditis and splenomegaly), chest CT and chest X-ray in one patient (cardiac failure), CT in combination with clinical findings in four patients (pneumonia in two, cardiac failure in two), CT and echocardiography in two patients (cardiac failure and bilateral pneumonia). The designation of the most conclusive test was missing in 2 patients with malignancy (1,5%). In all of these 10 patients, the CT diagnosis was in agreement with the suggested final diagnosis after conclusion of the diagnostic process (table 3).

Comparison between diagnosis at baseline and final diagnosis after three months follow-up

In 123 patients the alternative diagnosis established at inclusion was confirmed by the final diagnosis after three months follow-up. In 7 patients (5,4%) the diagnosis had changed: in two patients the initial diagnosis pneumonia was changed to malignancy. In one patient, pneumonia was changed to pleuritis and in another patient pneumonia was changed to cardiac failure. In two patients malignancy and COPD were ruled out and changed to pneumonia. In the last patient the final diagnosis remained unknown after the initial suspicion of malignancy. In this patient all further investigations did not confirm the baseline diagnosis of pleuritis. In the other six patients the initial diagnosis was mainly based on the results of the CT scan. In six of seven patients the change in diagnosis was based on repeat CT during follow-up.

During follow-up a DVT, demonstrated by abnormal CUS, was diagnosed 14 days after initial presentation in one patient with the baseline diagnosis pneumonia that was later changed to malignancy at follow-up. This patient was treated with anticoagulants. Three other patients returned after 13, 26 and 76 days with recurrent complaints. Three patients complained of pain on breathing and one patient also of dyspnea. None of these patients complained of hemoptysis or signs of symptomatic deep vein thrombosis. On further questioning the patients with pain, this pain was not considered to be of a pleuritic nature, but was qualified as of musculoskeletal origin. In neither of these three patients additional diagnostic tests were considered necessary by the treating physician: the minor complaints

Table 4. Reasons for re-admission during follow-up.

	Baseline alternative diagnosis			
Reason for re-admission during follow-up	Pneumonia	Malignancy	Congestive heart failure	Other
Pneumonia	7* +			
Malignancy and comorbidity		5*		
Congestive heart failure		1	2*	
Complications of renal/ pancreatic transplant				1*
Exacerbation COPD				1*
Surgery for abdominal adhesions	1			
Chemotherapy for leukemia	1			
Splenic rupture	1			
Removal of ileostoma	1			
Surgery for urethral stricture	1			
Abdominal pain	1			
Pyelonephritis, renal colic	1			
Hepatocellular Carcinoma			1	
Treatment for ovarian cancer			1	
Total	14	6	4	2

**Reason for re-admission during follow-up equal to initial diagnosis after completion of diagnostic work-up*
+5 patients readmitted within 2 weeks after discharge, in 2 patients readmission was because of a new episode of pneumonia due to recurrent aspiration in one patient (51 days) and fibrotic changes and recurrent infections in the other (66 days).

were attributed to sequelae of the pneumonia in one patient (returned after 13 days), while in the other patient (who came back after 76 days) a recurrent pneumonia was considered the most likely explanation for the complaints. In the third patient the reason for the short episode of pain remained unclear. These patients were not treated with anticoagulants and at further follow-up none of the three patients developed PE.
When asked at the three-month follow-up appointment, another two patients

indicated their initial symptoms had recurred briefly and disappeared spontaneously. These two patients had found it unnecessary to report back to their responsible physician. One of these patients had been diagnosed with metastasized breast carcinoma 10 months prior to inclusion and had showed progression to pleuritis carcinomatosa on the CT scan at initial presentation. The other patient had been initially treated for pneumothorax and COPD. None of the above mentioned patients returned with pulmonary complaints a second time.
Twenty-six patients were re-admitted during follow-up (table 4), for reasons unrelated to suspected PE. In 16 patients readmission was necessary for the initial alternative diagnosis (mostly pneumonia and malignancy), in 10 patients there was a different reason for re-admission.
During follow-up 28 patients died. The causes of death and time interval with inclusion are listed in table 5. In one patient with an extensive mediastinal tumor mass (small cell lung carcinoma), who died suddenly 22 days after inclusion, the cause of death was not clear. The adjudication committee could not rule out PE as a contributing cause of death (table 5).

Table 5. Summary and details of deaths during follow-up

No. of patients	Cause of death	Days after inclusion
18	Progression of malignancy	Mean 32 days
3	Pneumonia	1, 7 and 42 days*
3	Cardiac causes (myocardial infarction, multi-organ failure with mitral valve insufficiency, and cardiac failure)	2, 46 and 72 days
2	Respiratory failure	14 and 99 days*
1	Dissection of ascending aorta	1 day
1	Sudden death, death to PE could not be confidently ruled out. Extensive mediastinal tumor mass	22 days
Total 28		Mean 32 days

**these 2 patients died of respiratory failure and pneumonia in a new disease episode, after initial improvement of the diagnosis at baseline.*

Discussion

CT allows an alternative diagnosis to be made in 25,4% of patients presenting with clinically suspected PE (34,4% of patients with excluded PE), that does not change in almost all cases (94,6% of patients) after three months follow-up. This fraction of patients with an alternative diagnosis is as large as the fraction of patients in which the initial clinical diagnosis of PE is confirmed (24,6%). This finding is especially relevant considering the direct consequences for treatment.

The role of ultrasound with only 2 diagnoses (0,4%) of DVT is in comparison, very limited.

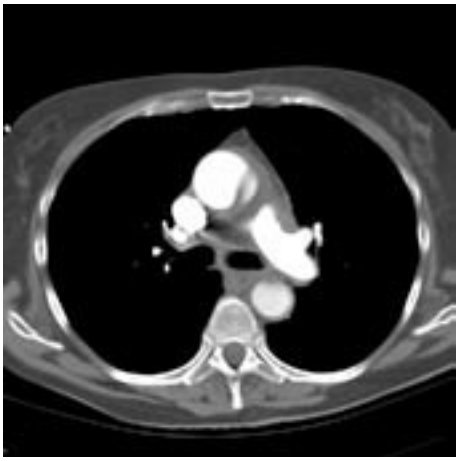
We emphasize that in the work-up of a patient clinically suspected of PE, diagnosis of or exclusion of PE is the first step in the reading of a CT. Only following this diagnosis an alternative diagnosis in patients in whom PE has been excluded can be entertained. The presence of pathologic changes suggesting an alternative diagnosis should not be used as the sole basis to exclude PE [16], especially not in CT scans that are of limited diagnostic quality for the diagnosis PE. The study by Shah et al. showed that parenchymal abnormalities can be found in 86% of patients with PE and 88% of patients without PE. Similar results were found for atelectasis (71% and 64% respectively) and pleural effusion (57% and 56% respectively). The study by Coche et al. also describes these findings with similar results.[17] It is still possible that changes, in particular parenchymal changes, are present in combination with smaller PE (e.g. parenchymal changes indicating infarction, right cardiac enlargement in pulmonary hypertension with PE, or malignancy). In our study we also used the 3 month follow-up for confirming accurate exclusion of PE. In one of the 130 patients with an alternative diagnosis fatal pulmonary embolism could not be excluded.[1]
As far as we know only five studies are available that have reported on alternative findings and diagnosis in patients with clinically suspected PE. The first study from 1999 to describe alternate findings on CT in patients suspected of PE found in 57 patients of 110 patients (51%)suspected of PE alternate findings. [18] In the second study an alternative diagnosis was described in 24 of 77 patients (31%) with a CT scan. CT was performed in 77 of 249 patients screened for inclusion.[19] Cross et al[20] described alternative findings in 23 of 59 (39 %) patients with CT, but 12 patients had no CT scans and VQ scans were used to exclude PE. In the fourth study [21] non-PE diagnoses were described in 9 patients (32 %) in a subgroup of 28 patients (32%) with low-probability V/Q-scan result. In the other subgroup of patients in this study non-PE diagnoses were not mentioned. In the last study in 19 of 66 patients without PE an alternative diagnosis was suggested or supported by CT.[22] In none of these studies follow-up was available to check for consistency of the diagnosis or the assessment of the most conclusive tests in these alternative diagnosis. Atelectasis, pneumonia and emphysema were most often found.
CT has an important advantage when compared to perfusion scintigraphy and pulmonary angiography. Perfusion scintigraphy gives an indirect depiction of the arteries in low-resolution formed by the distribution of the injected isotope, but

with this technique adequate and reliable assessment of alternative diagnosis is not possible. Van Beek et al described an alternative diagnosis in 44,7% of patients with excluded PE in a study evaluating potential additional information in pulmonary angiography.[23] These diagnostic techniques are however used less as a first line test in suspected PE nowadays.
Spiral CT is an attractive first line test since it visualises all thoracic structures. Instead of having to perform multiple diagnostic tests for each different item on the differential diagnostic list of pulmonary embolism, one can perform a single helical CT. CT continues to play an important role after the initial phase as is illustrated by the fact that CT was instrumental in change of diagnosis in six of the seven patients that had a change of diagnosis during follow-up. CT is furthermore a robust technique since it was not of diagnostic quality in only eight (1,6%) patients, which is considerably lower than some of the older studies, but is comparable to the recent study by Perrier et al (1,9% [24]). This is probably a result of the improved experience, and the improvements in scanning protocols and equipment.

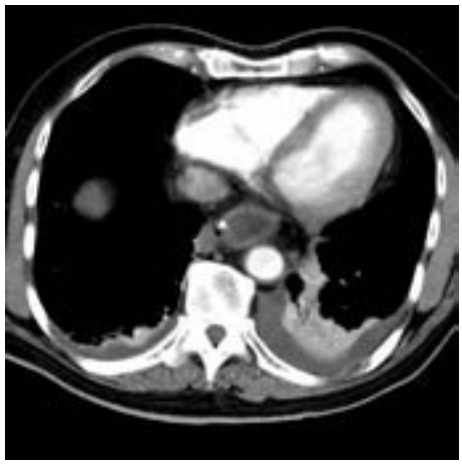
A limitation of this study is that it was not possible to obtain a standard reference test for every suggested alternative diagnosis This was in our view overcome by performing routine follow-up in all patients, for possible changes in the alternative diagnosis determined at baseline when compared to the reference diagnosis, in which the diagnosis was unchanged in 95% of patients.
A second limitation is that during the period of our study multi detector CT scanners were not yet available. With the introduction of multi-detector scanners the improvement of scan quality may lead to improved visualization of small thrombi and therefore more confident exclusion of PE.

We conclude that the use of helical CT in patients clinically suspected of PE can lead to a reduction of further diagnostic testing by combining the ability to exclude PE safely [1,2,9] and at the same time providing information that can lead to establishing an alternative diagnosis in 25,4% of patients who initially were referred for suspected PE.

Examples of alternative diagnoses (included patients)

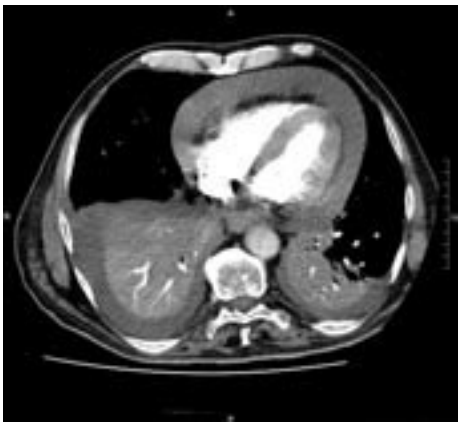


Dissection and pericardial effusion

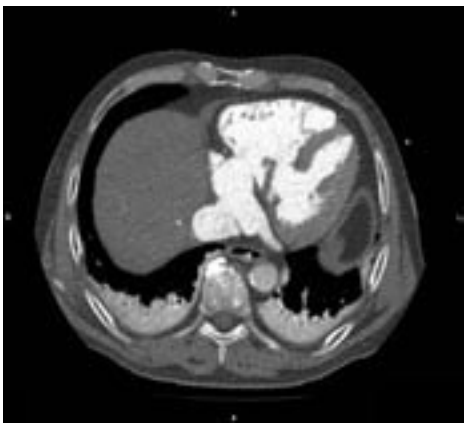


Pleura fluid and compression atelectasis

Examples of alternative diagnoses (recent studies)



Severe case of pericarditis



Rupture of the interventricular septum

References

1. Van Strijen, MJL, De Monyé W, Schiereck J, Kieft GJ, Prins MH, Huisman MV, Pattynama PMT.
Single detector CT as the primary diagnostic test in suspected pulmonary embolism: a multicentre clinical management study in 510 patients.
Ann Intern Med 2003; 138:307-314.

2. Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, Revel MP, Carette MF, Laurent M, Charbonnier B, Laurent F, Mal H, Nonent M, Lancar R, Grenier P, Simonneau G.
Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study.
Lancet 2002, Dec 14;360 (9349): 1914-20.

3. Kauczor HU, Heussel CP, Thelen M.
Update on diagnostic strategies of pulmonary embolism.
Eur Radiol 1999, 9:262-275.

4. Schibany N, Fleischman D, Thallinger C, Schibany A, Hane J, Ba-Ssalamah A, Herold CJ.
Equipment availability and diagnostic strategies for suspected pulmonary embolism in Austria.
Eur Radiol 2001, 11: 2287-2294.

5. Remy-Jardin M, Remy J, Wattinne L, Giraud F.
Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique-comparison with pulmonary angiography.
Radiology 1992;185:381-7.

6. Rathbun SW, Raskob GE, Whitsett TL.
Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review.
Ann Intern Med 2000; 132:227-232.

7. Mullins MD, Becker DM, Hagspiel KD, Philbrick JT.
The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism.
Arch Intern Med 2000; 160:293-298.

8. De Monyé W, Pattynama PMT.
Contrast-enhanced spiral computed tomography of the pulmonary arteries: an overview.
Semin Thromb Hemostas 2001; 27:32-39.

9. Goodman LR, Lipchik RJ, Kuzo RS, Liu Y, McAuliffe TL, O'Brien DJ.
Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram--prospective comparison with scintigraphy.
Radiology 2000; 215:535-542.

10. Ferretti GR, Bosson JL, Buffaz PD, Ayanian D, Pison C, Blanc F, Carpentier F, Carpentier P, Coulomb M.
Acute pulmonary embolism: Role of helical CT in 164 patients with intermediate probability at ventilation-perfusion scintigraphy and normal results at duplex US of the legs.
Radiology 1997; 205:453-458.

11. Van Rossum AB, Pattynama PMT, Mallens WM, Hermans J, Heijerman HG.
Can helical CT replace scintigraphy in the diagnostic process in suspected pulmonary embolism? A retrolective-prolective cohort study focusing on total diagnostic yield.
Eur Radiol 1998; 8:90-96.

12. Baghaie F, Remy-Jardin M, Remy J, Artaud D, Fribourg M, Duhamel A.
Diagnosis of peripheral acute pulmonary emboli: optimization of the spiral CT acquisition protocol.
Radiology 1998; 209 (p): 299.

13. PIOPED investigators.
Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators.
JAMA 1990; 263: 2753-27599.

14. Van Strijen MJ, De Monyé W, Kieft GJ, Pattynama PM, Huisman MV, Smith SJ, Bloem JL.
Diagnosis of pulmonary embolism with spiral CT as a second procedure following scintigraphy.
Eur radiology 2003; 13 (7): 1501-1507.

15. Prokop M, Galanski M, van der Molen AJ, Schaefer-Prokop CM.
Spiral and multislice computed tomography of the body.
Book chapter ISBN 0865778701.

16. Shah AA, Davis SD, Gamsu G, Intriere L.
Parenchymal and pleural findings in patients with and patients without acute pulmonary embolism detected at spiral CT.
Radiology 1999; 211: 147-153.

17. Coche EE, Müller NL, Kim KI, Wiggs BR, Mayo JR.
Acute pulmonary embolism: ancillary findings at spiral CT
Radiology 1998; 207: 753-758.

18. Kim KI, Müller NL, Mayo JR.
Clinically suspected pulmonary embolism: utility of spiral CT
Radiology 1999; 210: 693-697.

19. Van Rossum AB, Treurniet FEE, Kieft GJ, Smith SJ, Schepers-Bok R.
Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion lung scan.
Thorax 1996; 51: 23-28.

20. Cross JJL, Kemp PM, Walsh CG, Flower CD, Dixon AK.
A randomized trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism.
Clin Radiol 1998; 53: 177-182.

21. Garg K, Welsh CH, Feyerabend AJ, Subber SW, Russ PD, Johnston RJ, Durham JD, Lynch DA.
Pulmonary embolism: diagnosis with spiral CT and ventilation perfusion scanning-correlation with pulmonary angiographic results or clinical outcome.
Radiology 1998; 202: 201-208.

22. Coche E, Verschuren F, Keyeux A, Goffette P, Goncette L, Hainaut P, Hammer F, Lavenne E, Zech F, Meert P, Reynaert MS.
Diagnosis of acute pulmonary embolism in outpatients: comparison of thin-collimation multi-detector row spiral CT and planar ventilation-perfusion scintigraphy.
Radiology 2003; 229: 757-765.

23. van Beek EJ, Reekers JA.
The value of pulmonary angiography for the differential diagnosis of pulmonary embolism.
Eur Radiol 1999;9(7):1310-6.

24. Perrier A, Roy P-M, Aujesky D, Chagnon I, Howard N, Gourdier A-L, Leftheriothis G, Barghouth G, Cornuz J, Hayoz D, Bounameaux H.
Diagnosis pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound and helical computed tomography: a multicenter management study.
Am J med 2004; 116: 291-299.

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