Clinical Validity of Helical CT Being Interpreted as Negative for Pulmonary Embolism: Implications for Patient Treatment

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OBJECTIVE. The purpose of our study was to assess the clinical usefulness of helical CT findings that are interpreted as negative for pulmonary embolism.

MATERIALS AND METHODS. One hundred twenty-six patients underwent 132 helical CT examinations and 352 patients underwent ventilation–perfusion scanning for suspected acute pulmonary embolism over a 17-month period at a single institution. Findings from clinical follow-up at a minimum of 6 months were assessed, with a special focus on the presence of recurrent thromboembolism and mortality in 78 consecutive patients in whom helical CT findings were interpreted as negative for pulmonary embolism and anticoagulant therapy was not administered (group I). During the same 17-month period, 46 patients underwent ventilation–perfusion scanning that was interpreted as normal (group II), and 132 patients underwent ventilation–perfusion scanning that was interpreted as showing a very low to low probability for pulmonary embolism (group III). Patients in groups II and III did not undergo helical CT or pulmonary angiography and did not receive anticoagulant therapy. However, clinical follow-up was solicited. Patients from groups II and III were used as control subjects.

RESULTS. Nine patients in group I died, one of whom was found to have a microscopic pulmonary embolism at autopsy. In group II, four patients died, none of whom were shown to have a missed or recurrent pulmonary embolism. Of the 18 patients in group III who died, three had a recurrent or missed pulmonary embolism (mean interval, 9 days), and two were found to have deep vein thrombosis on sonography of the leg (mean interval, 12 weeks). Negative predictive values for helical CT, normal lung scanning, and low-probability ventilation–perfusion scanning were 99%, 100%, and 96%, respectively (p = .299). CT provided either additional findings or an alternate diagnosis in 42 (53.8%) of the 78 patients in whom helical CT findings had been interpreted as negative for pulmonary embolism.

CONCLUSION. A helical CT scan can be effectively used to rule out clinically significant pulmonary emboli and may prevent further investigation or unnecessary treatment of most patients.

Investigators have reviewed the sensitivity, specificity, and accuracy of helical CT in the diagnosis of pulmonary embolism [1–7]. However, only a few studies mention the negative predictive value of this diagnostic test [1–3]. We have observed that clinicians have more confidence in CT when CT shows emboli than when a CT scan is interpreted as negative for pulmonary embolism. When presented with negative findings on CT, clinicians in many centers tend to investigate further or may still treat the patient with anticoagulant therapy on the basis of clinical criteria. The lack of data to support the clinical validity of a helical CT scan interpreted as negative for pulmonary embolism and the fear that peripheral vessels will be inadequately depicted—resulting in missing subsegmental emboli—remain two of the important factors in the reluctance to use helical CT for the diagnosis of pulmonary embolism. Recently, two studies have shown that diagnostic testing is underused in the evaluation of pulmonary embolism and that scintigraphy remains the most accepted imaging test [8, 9]. Pulmonary angiography is frequently not performed because of its limited availability and because of concerns about safety, patient acceptance, and cost. Despite excellent spatial resolution of small vessels on pulmonary angiograms, poor interobserver agreement makes angiography less reliable in diagnosing emboli in subsegmental arteries than in diagnosing emboli in central arteries [10].

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If helical CT could reliably exclude a diagnosis of pulmonary embolism and serve as a clinically valid test, then helical CT would have the potential to be the ideal single diagnostic test for the evaluation of pulmonary embolism. Two approaches could be used to assess the validity of the decision not to treat patients with suspected pulmonary embolism and negative findings on CT: Pulmonary angiography could be performed in a series of such patients, or the outcome, over time, of such patients who also did not receive anticoagulant therapy could be studied. In this study, we exercised the second option. The clinical course of 78 patients with suspected pulmonary embolism, but in whom no embolus had been detected by CT and no treatment had been administered, was followed at a minimum of 6 months and compared with the clinical course of age- and sex-matched subjects.

Materials and Methods

Patients

Approval was obtained from the institutional review board to perform a retrospective review of patient records and to interview study patients. Between November 1996 and March 1998, 126 consecutive patients underwent 132 contrast-enhanced helical CT examinations for suspected acute pulmonary embolism. Subjects who had a diagnostic lung scan or positive findings on sonography for deep vein thrombosis did not undergo helical CT. Forty-eight CT scans showed positive findings for pulmonary emboli, and two CT scans revealed indeterminate findings. Eighty-two CT scans were prospectively interpreted by two chest radiologists independently or by consensus, who did not have prior knowledge of scintigraphic results, as being negative for emboli. Two of these 82 patients were treated with anticoagulant therapy for stroke prophylaxis and one for atrial fibrillation. One patient was excluded because of incomplete follow-up. The remaining 78 patients (72 men and six women), who ranged in age from 36 to 86 years (mean, 65 years), were not treated. These patients underwent clinical follow-up at a minimum of 6 months and constituted group I of the study population.

Patients with normal findings on a lung scan who did not undergo anticoagulant therapy were used as control subjects because normal findings on a perfusion lung scan have the same value in ruling out embolism as do normal findings on a pulmonary angiogram [11, 12]. Select patients with low-probability ventilation–perfusion scans were also used as control subjects because, for the purposes of patient treatment, results of these scans were considered negative for pulmonary embolism. Of the 352 ventilation–perfusion lung scans obtained during the same 17-month period, normal findings were revealed on 57 lung scans. Five of these 57 patients were treated with anticoagulant therapy for deep vein thrombosis or atrial fibrillation, and six were lost to follow-up. The remaining 46 patients (44 men and two women), who ranged in age from 38 to 78 years (mean, 63 years), constituted group II of the study population. Of the 158 patients with very low– to low-probability ventilation–perfusion scans, 26 patients were excluded from the study either because they were lost to follow-up ($n = 18$) or because they were receiving anticoagulant therapy ($n = 8$). The remaining 132 patients (128 men and four women), who ranged in age from 31 to 83 years (mean, 64 years), constituted group III. None of the patients entered in the study as control subjects (groups II and III) underwent CT, pulmonary angiography, or anticoagulant therapy.

Clinical Follow-Up and Outcome

Patients were interviewed by telephone at least once at a minimum of 6 months after CT or ventilation–perfusion scintigraphy. A standard interview form containing questions based on diagnosing pulmonary embolism using clinical criteria [13] was used to assess recurrent or missed thromboembolic disease. Twenty-two patients who could not be contacted by telephone were contacted by mail and responded. The medical records of all study patients were reviewed. In cases of death, the cause of death was found from the medical record, autopsy results, or discussion with the clinician treating the patient at the time of death. Autopsies were performed according to the standard hospital protocol using the macroscopic and microscopic criteria for diagnosis of pulmonary embolism, as described by Freiman et al. [14]. Pulmonary artery ramifications to each lobe were dissected as far out as the branches with an external diameter of 2–3 mm. If suspected to contain emboli, small arterial branches were routinely examined under the microscope in only two to five sections of the peripheral portions of the parenchyma. If an embolus was seen only microscopically (microembolus), it was considered subsegmental for the purpose of this study. A large embolus detected during the dissection was considered central or segmental. The vena cava and deep veins of the legs were routinely checked for venous thrombosis at autopsy. In cases of subsequent admission, an attempt was made to ascertain the reason for the admission and the results of imaging tests if performed. A pulmonary embolism was considered to be absent if during a 6-month interval no clinical evidence of pulmonary embolism was discovered, an embolus was absent at autopsy, or death or subsequent admission was associated with an unrelated cause. A pulmonary embolism was considered to be present if clinical evidence of pulmonary embolism was seen, signs and symptoms suggestive of pulmonary embolism caused death, or an embolus was found at autopsy. An attempt was also made to detect deep vein thrombosis using clinical evidence or sonography.

Statistical analysis was performed using a software program (Statistical Analysis System 6.11; SAS Institute, Cary, NC). Negative predictive values were calculated by standard methods for proportions (negative predictive value = true-negatives / [true-negatives + false-negatives]). To assess whether the difference between the different groups was statistically significant, results were analyzed using Fisher's exact test.

Imaging Studies

CT scans were obtained with a model 2000 unit (Picker International, Cleveland, OH). Thin-section CT performed to evaluate lung parenchyma and airways was followed by contrast-enhanced helical CT (200 mA; 130 kV; pitch, 2; mean z-axis coverage, ≥12 cm; acquisition time, 17–23 sec; collimation, 3 mm) to evaluate the pulmonary vessels. In 18 patients, CT venography was performed by acquiring 10-mm-thick slices at 20-mm intervals from the level of the pubic symphysis to that of the diaphragm, with CT venography starting 2 min after CT angiography. None of the CT venograms revealed any venous thrombosis. Iodinated contrast material was administered as a bolus with an automated injector (MCT Plus; Medrad, Pittsburgh, PA). The injection was carefully monitored by either a registered nurse or a physician. A total of 100–140 ml of a dilute 30% iopromide solution (Ultravist 300; Berlex Imaging, Wayne, NJ) or of iothalamate meglumine (Conray 60; Mallinckrodt Medical, St. Louis, MO) was injected at a rate of 4–5 ml/sec, with a delay of 10–15 sec before scanning. The criterion used for diagnosis of acute pulmonary embolism on CT was an intraluminal filling defect as has been described [1]. We interpreted a CT scan as revealing positive findings for an embolus only if a definite filling defect was seen on more than one contiguous axial image.

Pulmonary perfusion imaging was performed after IV injection of 1–2 mCi (37–74 MBq) of ^{99m}Tc macroaggregated albumin followed by ventilation imaging after administration of 4–5 mCi (148–185 MBq) of ^{99m}Tc diethylenetriaminepentaacetic acid aerosol [3]. Images were recorded in eight projections for both perfusion and ventilation scanning. Each ventilation–perfusion scan was interpreted by a single nuclear medicine physician during the course of clinical work, using the standard modified diagnostic criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis study [12].

Venous sonography was performed with a 5- or 7-MHz linear array transducer (HDI 3000; Advanced Technology Laboratories, Bothell, WA, and 128 XP; Acuson, Mountain View, CA). The main diagnostic criterion for positive sonographic findings in the leg was the loss of venous compressibility. Changes in venous spectral waveforms or color Doppler were considered as evidence supporting the diagnosis of thrombosis.

Pulmonary angiography was performed using standard techniques, with an intraluminal filling defect being considered as a positive finding.

A prospective comparison between CT scans and chest radiographs was not performed. Chest radiographs were reviewed retrospectively only for those patients in whom CT provided an alternate diagnosis or additional findings. Additional information provided by CT was further characterized as new or not new on the basis of the patient's clinical history before undergoing CT and whether findings were visible on retrospective review of radiographs. If the diagnosis provided by CT had not been considered clinically before the CT results were available or if a pulmonary embolism had not been shown on chest radiographs, then the diagnosis was considered new and a truly alternate diagnosis.

TABLE 1 Results of 6-Month Follow-Up in 256 Patients with Suspected Acute Pulmonary Embolism and Negative Findings on CT or Scintigraphy

Outcome	No. (%) of Patients		
	Negative Findings on Helical CT Scan	Ventilation–Perfusion Scan	
		Normal Findings	Findings of Low Probability
Alive without pulmonary embolism	69	42	114
Died	9 (12)	4 (9)	18 (14)
Autopsy	2	1	4
No pulmonary embolism	1	1	2
Microscopic pulmonary embolism	1	0	1
Macroscopic pulmonary embolism	0	0	1
Deep vein thrombosis	0	0	0
No autopsy	7	3	14
No pulmonary embolism	7	3	13
Pulmonary embolism	0	0	1
Deep vein thrombosis	0	0	2
Total no. of patients	78	46	132

Results

Results are summarized in Table 1. Of the 78 patients in group I, nine had died by the time of follow-up. Autopsy results were available for two patients: One patient had negative findings for pulmonary emboli, and the other patient, who had parkinsonism and obstructive sleep apnea, was found to have aspiration pneumonia, pulmonary arterial hypertension, and right ventricular hypertrophy at autopsy. This patient also had a microembolus measuring 1–2 mm in the right middle lobe that may have developed in situ but more likely originated from nonbacterial vegetations found in his right heart. The patient died 7 days after undergoing CT; death was likely caused by pneumonia. The CT scan of this patient was suboptimal in quality because he could neither hold his breath nor move his arms above his head as a result of arm contractures. Bilateral pulmonary angiography performed on the same day was also interpreted as negative for an embolus and was also limited by motion artifact. Causes of death for the other seven patients in group I included prostate carcinoma with bone metastasis (n = 3), lung cancer with sepsis (n = 2), esophageal cancer (n = 1), and multiorgan failure on the second postoperative day after laparotomy for small-bowel obstruction (n = 1).

TABLE 2 Alternate Diagnoses or Significant Additional Findings Revealed by Helical CT in 42 Patients

Diagnoses	No. of Patients	
	New Diag.	Prev. Known Diag.
Emphysema	6	6
Aspiration pneumonia	4	2
Pulmonary edema	2	5
Interstitial lung disease	4	4
Lung cancer	4	1
Esophageal cancer	2	1
Hypersensitivity pneumonitis	2	0
Bronchiolitis obliterans with organizing pneumonia	2	0
Radiation pneumonitis	1	1
Drug toxicity	1	0
Invasive aspergillosis	1	0
Total no. (%) of patients	31 (40)	20 (26)

Note.—New diag. = new diagnosis, prev. known diag. = previously known diagnosis. Nine patients had more than one diagnosis.

The causes of death in patients with normal findings on ventilation–perfusion scans (group II) included one case each of cerebral edema and tonsillar herniation proven at autopsy, end-stage renal disease, severe emphysema and right heart failure, and severe coronary artery disease. Autopsy results of four patients in the low-probability group (group III) revealed one case each of subsegmental embolism (4 days after ventilation–perfusion scanning), segmental embolism (14 days after ventilation–perfusion scanning), aspiration pneumonia in a patient with cerebrovascular accident, and rapidly progressive scleroderma with fibrosis of the cardiac conduction system in another patient. Causes of death in the 14 other patients in group III included the following: pulmonary embolism (n = 1), which was diagnosed on the basis of a positive D-dimer test, results of blood gases, and signs and symptoms (13 days after ventilation–perfusion scanning); cerebrovascular accident with tonsillar herniation or aspiration pneumonia (n = 3); lung cancer and respiratory failure (n = 3); end-stage renal disease (n = 2); acute myocardial infarction (n = 2); and unknown entities that were considered unrelated to pulmonary embolism (n = 3).

Eighty-five (33.2%) of the 256 study patients had at least one subsequent admission during the 6-month follow-up for reasons unrelated to pulmonary embolism. Most patients were on multiple drug regimens for a variety of illnesses.

Additional findings were discovered or an alternate diagnosis was made from CT examinations of 42 (53.8%) of the 78 patients (Table 2). In 20 patients, the findings were also shown on chest radiography, but CT helped to better characterize the findings. The findings that were better depicted by CT included consolidation in the dependent portions of the lung parenchyma with or without esophageal dilatation as an indication of aspiration pneumonia; smooth, thin septal lines in patients with pulmonary edema; and unsuspected loculated pleural fluid collections (detected only by CT in two patients with pulmonary edema). The severity and extent of pulmonary fibrosis and of emphysema were also better shown on CT.

The negative predictive values for a helical CT scan, a normal lung scan, and a low-probability ventilation–perfusion scan were 99% (95% confidence interval [CI], 93–100%), 100% (95% CI, 92–100%), and 96% (95% CI, 91–99%), respectively (p = .299).

Discussion

The negative predictive value for helical CT in our cohort of patients is higher than that reported previously. In their comparison of pulmonary angiography and CT, Remy-Jardin et al. [1] reported a negative predictive value of 89% based on 32 of 36 CT examinations with negative findings for emboli including seven suboptimal studies. Only one false-negative CT study of 26 technically optimal examinations was reported. This false-negative occurred in a patient with a history of right middle and right lower lobectomy for lung carcinoma. Intraluminal filling defects seen on CT in the anterior segmental artery were falsely interpreted as partial volume averaging. In another prospective study, one of the two false-negative interpretations was caused by the failure to recognize a filling defect in the anterior basal segmental artery of the right lower lobe [3]. A prospective negative predictive value of 82% (36/44 pa-

tients) for electron-beam CT was reported when compared with pulmonary angiography by Teigen et al. [2]. The negative predictive value in this study approached 100% for clinically important pulmonary emboli, after further review of eight false-negative cases. In their study, four patients with subsegmental emboli missed on electron-beam CT were not treated. We think the sensitivity and specificity of helical CT in the evaluation of pulmonary embolism has improved at our institution because we have gained more experience in interpreting these studies and have become more familiar with the appearances of small emboli. Improvement in our own learning curve in the later part of our study may be one of the factors resulting in our high negative predictive value. The only false-negative CT scan was one that was of suboptimal quality because of motion artifact. The same limitation with the corresponding pulmonary angiogram also resulted in a false-negative interpretation. Using clinical follow-up rather than pulmonary angiography as the standard of reference may be the other explanation for the high negative predictive value in our study. Pulmonary angiography has better spatial resolution and has the potential to show more subsegmental emboli especially in nonvertical vessels than CT [1, 3]. However, despite excellent resolution, the difficulty of evaluating subsegmental artery segments results in poor interobserver agreement (mean, 45%) [10]. In addition, the clinical significance of subsegmental emboli is not clear.

In spite of studies reporting greater sensitivity, specificity, and accuracy for CT than scintigraphy [3, 4], scintigraphy remains the most widely used initial study and often the only imaging test used by clinicians [8, 9]. Therefore, we obtained scintigrams from two groups of patients for comparison. Patients with normal findings on lung scans were selected because a normal finding on a perfusion scan excludes the presence of clinically important pulmonary embolism [11]. Select patients with low-probability scintigrams were also used as control subjects (group III) because for patient treatment the scintigram was considered by clinicians as a definite negative study influencing them to either withhold anticoagulation therapy or not investigate further for suspected pulmonary embolism. When both the clinical suspicion for pulmonary embolism and the probability of seeing pulmonary embolism on scintigraphy are low, pulmonary embolism is excluded in as many as 90% of patients [12]. This practice still leads to a substantial false-negative rate.

One of the reasons for the underuse of CT is the lack of confidence, because of the concern of subsegmental emboli being missed, in a CT scan with negative findings for pulmonary emboli.

The results of our study show that a CT scan is as good as a normal lung scan in excluding a diagnosis of pulmonary embolism. Although the negative predictive values for low-probability scans and CT scans were not statistically different in our study, we found additional reasons to consider CT more useful. CT often provides an alternate diagnosis or shows significant additional findings that help explain the patient's signs and symptoms. For instance in our series, CT provided an alternate diagnosis that helped to direct appropriate follow-up and treatment for 31 (39.7%) of the 78 patients. Even in the other 11 patients in whom chest radiographs showed an abnormality, CT not only characterized the abnormality better but, in some cases, showed additional unsuspected findings. This additional information increases the level of clinical confidence of a negative diagnosis of pulmonary embolism. Whether the detection of additional findings introduces bias or influences interpretation of the negative predictive value is debatable.

A substantial number of patients, 57 (73.0%) of the 78 patients in group I, underwent scintigraphy before CT, although most patients ($n = 37$) underwent scintigraphy during a period when we required ventilation–perfusion scanning of all patients who underwent helical CT for pulmonary embolism assessment. The remaining patients had either nondiagnostic findings on scintigraphy or findings from ventilation–perfusion scans that were discordant with clinical findings; in these patients, the clinicians subsequently chose to perform CT. It would have been cost-effective if CT had been used as the initial screening examination in these patients rather than ventilation–perfusion scintigraphy. In a patient in whom findings on a chest radiograph are abnormal, findings on a scintigram will likely be nondiagnostic; thus, screening for suspected pulmonary embolism could reasonably start with helical CT. Although investigators have used a combination of ventilation–perfusion scanning and CT (normal- to low-probability ventilation–perfusion scintigram and a helical CT scan without findings of pulmonary embolism) to exclude a diagnosis of pulmonary embolism [3, 4], our results show that CT alone can effectively rule out a diagnosis of pulmonary embolism.

No significant difference was seen in the mortality rates of our three groups of patients in spite of a higher clinical probability of pulmonary emboli and comorbid conditions in group I (CT) patients. Most of the deaths were caused by underlying diseases, a finding that is reported even in patients with a diagnosis of pulmonary embolism [15]. All the patients in whom autopsy results were available were hospitalized at the time of death, which probably explains the high rate of pulmonary embolism (3/7, 42.8%) in unselected autopsies in our study. The incidence of pulmonary embolism at autopsy has varied from 10% of the general population to 30–65% of hospitalized patients [14, 16].

Our study has important limitations. It was a retrospective analysis based on findings from clinical follow-up at a minimum of 6 months. One can only speculate that more thromboembolic events would have been discovered if a prospective follow-up had been performed. Incidental findings of pulmonary embolism or deep vein thrombosis in patients without symptoms, although rare, have been reported [17]. The follow-up in this study reflects what actually happens in clinical practice. The tests to assess for pulmonary embolism are not performed unless clinically indicated, although sonography of the leg has been proposed in asymptomatic patients at high risk for pulmonary embolism [18]. Although it can be argued that a pulmonary angiogram would have been a more objective standard of reference, subjecting a large number of patients with negative findings on CT scans to this costly and invasive test would have been unethical. Another limitation of our study was the small number of autopsies.

Using clinical outcome instead of pulmonary angiography, we conclude that a helical CT scan is as valuable as a normal lung scan in excluding a diagnosis of pulmonary embolism and may be used as a basis to prevent unnecessary treatment or further investigation in most patients. CT may be more helpful than scintigraphy in the treatment of patients, because CT often provides significant additional information or an alternate diagnosis. Large prospective studies should be performed to further assess whether helical CT does effectively exclude clinically significant pulmonary emboli.

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