Longterm Follow-Up of Patients with Suspected Pulmonary Embolism and a Normal Lung Scan*

Perfusion Scans in Embolic Suspects

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There is widespread acceptance of the thesis that in a patient with suspected embolism, a normal perfusion lung scan excludes the diagnosis of acute pulmonary embolism. However, limited published data exist which validate this thesis. We have explored this question by longitudinal follow-up of 68 patients who were referred for lung scanning to rule out embolism and proved to have normal perfusion lung scans. Risk factors for venous thromboembolism among these patients were similar to those reported in prior series of patients with pulmonary embolism. Our data support the widely-held views that: 1) a normal perfusion lung scan excludes the diagnosis of clinically significant pulmonary emboli; 2) the diagnostic work-up for suspected pulmonary embolism need not extend beyond a normal perfusion scan; 3) anticoagulant therapy can be discontinued after a normal perfusion scan, except in the presence of documented venous thrombosis; and 4) a normal lung scan has the same value in ruling out embolism in man as does a normal pulmonary angiogram.

The management of patients suspected of having a pulmonary embolism presents a decision-making challenge. On the one hand, pulmonary thromboembolism is a relatively common disorder which, if left untreated, carries a high morbidity and mortality, both acutely and chronically. On the other hand, treatment of thromboembolism is not without risk, and such therapy is not appropriate for the many disorders which mimic embolism. The pulmonary perfusion scan has been proposed as a procedure which can help direct this difficult decision-making sequence.

There is general agreement that perfusion scanning is a safe procedure and, more important, that a normal scan, performed properly, essentially excludes the diagnosis of embolism. In practice, this agreement translates into a therapeutic decision: namely, to discontinue, or not initiate, anticoagulant therapy in the patient with suspected embolism in whom a normal scan is obtained. If "false negative" scans do occur, such a decision would expose patients to a significant risk of recurrence and death.

Despite the widespread agreement that a normal perfusion scan excludes the diagnosis of pulmonary embolism, definitive data validating this decision-making sequence are not available. Furthermore, both theoretic considerations and experimental data suggest that a normal scan may not detect very small emboli or larger emboli which do not completely occlude a pulmonary artery.

Two approaches could be used to assess the validity of the decision not to treat suspected patients with embolism with a normal perfusion scan: (1) pulmonary angiography could be performed in a series of such patients with normal perfusion scans; or (2) the outcome, over time, among such patients not given anticoagulant therapy, could be studied. In this study, we exercised the second option. The clinical course of 68 patients suspected of having pulmonary emboli, but with normal findings on perfusion lung scans, was followed. Only one patient (who had active venous thrombosis) received anticoagulant therapy after the scan. We attempted to identify any subsequent event which could be attributed to pulmonary embolism.

**Materials and Methods**

The data of all patients who had had an imaging procedure at the San Diego Veterans Hospital between 1976 and 1980 were reviewed. If the data noted a perfusion lung scan, the requisition and scan report were examined to determine whether two criteria were met: (1) the patient had been...
referred for the scan to rule out clinically-suspected pulmonary embolism; (2) findings on the perfusion scan were reported as normal. The scans were then reviewed independently by two of us (MSK and KEK). Each study consisted of a minimum of four views (anterior, posterior, both laterals) and most included six views (both posterior obliques). All studies were performed with technetium-labeled macroaggregates, utilizing a standard large field of view gamma camera. Our review confirmed that the findings on scans were normal, defined as showing no focal perfusion defects (lobar, segmental, or subsegmental), in any projection. Ventilation studies, if performed, were not included in this retrospective analysis.

Seventy-two patients meeting these criteria were identified. The medical records of 68 patients were available. Despite an exhaustive search, records of four patients (all referred from the emergency room) could not be found. Thus, this report is based upon follow-up of 68/72 (94 percent) of the patients who fit the study criteria. Of these 68 patients, the reference lung scan in the folder had been obtained prior to 1976 in 11.

The medical records were reviewed to document risk factors for pulmonary embolism at the time of the reference perfusion scan, as well as symptoms, signs and laboratory data suggesting that diagnosis. The patient’s subsequent course was then reviewed, seeking any evidence suggesting pulmonary embolism. All post-mortem examinations were performed at the San Diego VA Hospital. Pulmonary arterial dissection was carried out to the subsegmental vessels.

Statistical analyses of the data were performed according to standard methods by Dr. Charles Berry of the UCSD Department of Mathematics.

RESULTS

Of the 68 patients, 63 (93 percent) were men. They ranged in age from 22 to 80 years (average 51.0 years). Thirty-three (49 percent) had documented heart disease; 12 (18 percent) had a history of surgery and/or immobilization less than one month prior to the time of the reference perfusion scan; and more than half (38) were smokers. Other documented risk factors included a previous history of lower extremity thrombophlebitis in six and a current malignancy in three (Table 1).

Chest pain, usually pleuritic, was the most frequent symptom suggesting the diagnosis of pulmonary embolism. Dyspnea and/or cough were common complaints. Hemoptysis was reported by four patients. Arterial blood gas analyses were performed in most cases, and mild to moderate hypoxemia was present in the majority.

Sixty-seven patients received no anticoagulant therapy after the perfusion scan. One, shown by contrast venography to have deep vein thrombosis at the time of his perfusion scan, received a ten-day course of intravenous heparin.

All patients survived the hospitalization during which their reference scan was obtained. All were subsequently followed-up in the VA system, approximately 90 percent of them at the San Diego VA Hospital. All had been observed for a minimum of two months at the time of this study, with the range of follow-up from 2.97 months after the reference scan; the average, 30.2 months.

Of the 68 patients, 60 have been followed-up exclusively as outpatients. In none of these did the record reveal a note raising the clinical suspicion of subsequent embolism, a request for a lung scan or the initiation of anticoagulant therapy. Eight patients were hospitalized at least once after the reference scan, all at the San Diego VA Hospital. Two patients were admitted for noncardiopulmonary diagnoses, did not receive anticoagulants and had no lung scan. Six patients who were admitted died during or after readmission. These deaths occurred at six, nine, 14, 36, 47 and 67 months after the reference scan. While none of these deaths was attributed to embolism by the attending physician, the details surrounding these deaths are provided here.

CASE REPORTS

CASE 1

This 74-year-old man had been treated for congestive heart failure of unknown cause during his initial admission. A normal perfusion lung scan was obtained during this admission. Despite intensive therapy, severe, unremitting dyspnea led to readmission six months later. Chest roentgenogram on admission disclosed cardiomegaly, pulmonary congestion and bilateral pleural effusions. A perfusion lung scan now disclosed bilateral basilar defects. He failed to respond to treatment. Postmortem examination revealed extensive cardiac amyloidosis, pulmonary amyloidosis and two recent, small right subsegmental basilar pulmonary infarctions.

CASE 2

This 30-year-old man died 36 months after a normal perfusion scan, following a long course of progressive heart failure secondary to cardiomyopathy. Postmortem examination revealed no gross or microscopic evidence of pulmonary emboli.

CASE 3

This 83-year-old man succumbed 47 months after a nor-
mal perfusion scan. He had a history of documented myocardial infarctions and recurrent heart failure. He died at home four days after an extended hospitalization for congestive heart failure. A postmortem examination was not performed.

CASE 4

This 25-year-old man, on chronic hemodialysis for renal failure, was seen in the emergency room nine months after his normal perfusion scan, with cardiorespiratory arrest. He had been seen as an outpatient two days prior to this admission and was without cardiac or pulmonary symptoms. Serum potassium was found to be 10 mEq/L in the emergency room. He failed to respond to resuscitative measures. Autopsy was denied.

CASE 5

This 75-year-old man was readmitted with a severe cerebrovascular accident, 67 months after a normal perfusion scan. He died several days after admission. Autopsy revealed laryngeal carcinoma, bladder carcinoma, severe coronary and cerebral atherosclerosis, extensive cerebral infarction and mild emphysema, but no gross or microscopic evidence of recent or remote pulmonary embolism.

CASE 6

This 61-year-old woman had a long history of progressive multiple sclerosis. She was admitted 14 months after her normal perfusion scan with massive aspiration pneumonia. She died soon after admission; autopsy was not obtained.

Only one of these six patients had received anticoagulant therapy since the reference scan; case 2 was started on therapy with heparin after the positive lung scan obtained during the last admission.

Statistical Analyses

These data were analyzed statistically in two ways. In the first analysis, it was assumed that: (1) the four patients for whom no records could be located could be excluded, since the loss of the record was unrelated to the presence of embolism; and (2) that all reference scans were true negatives. Based upon the 68 patients actually followed-up, the 95 percent confidence interval for the probability of a false negative perfusion scan result extends from 0 to 5.3 percent.

In the second analysis, the 95 percent confidence interval was based upon all 72 patients, and on a "worst case" concept that all four patients not observed actually had emboli. Under these assumptions, the probability of a false negative scan is 2-14 percent.

DISCUSSION

The accurate and prompt diagnosis of pulmonary embolism remains a challenge to the clinician, radiologist, and specialist in nuclear medicine. Two major questions are faced in defining the most appropriate diagnostic sequence in patients with suspected embolism: (1) how can the diagnosis be excluded? and (2) if it cannot be excluded, how can the diagnosis be established? In this study, we focused on the first question. Our data indicate that, based upon patient outcome, a normal perfusion scan does effectively exclude the diagnosis of pulmonary embolism.

Exclusion of the diagnosis of pulmonary embolism requires a clinical or laboratory finding which rarely provides false negative results. Previous studies have demonstrated that in the patient with suspected embolism, symptoms and physical signs,19-21 "typical" biochemical abnormalities,22,23 blood gas analysis,18,24 electrocardiographic changes,25 and chest x-ray film findings26,27 do not qualify as exclusionary approaches.

Pulmonary angiography with selective catheterization and opacification of segmental pulmonary arteries remains the definitive procedure for diagnosing pulmonary emboli. However, despite the many useful investigations dealing with angiography in the patient with suspected emboli,28-33 only one has dealt specifically with the question of potential "false negative" angiographic findings, ie, the power of a negative angiogram in ruling out the diagnosis. Novelline et al34 are the only workers who have directly addressed this question. They attempted a six-month follow-up of 207 patients who were referred for pulmonary angiography and in whom the angiogram proved negative. Twenty-seven patients were lost to follow-up; and another 13 received anticoagulant therapy. Therefore, their report dealt with 167 patients (81 percent of the initial group) who had not been treated and in whom follow-up data were available. Twenty of these patients (12 percent) had died at various intervals prior to six months. Of the ten who had autopsy, three had small pulmonary emboli. The authors state that these "small new or old pulmonary emboli were... incidental findings... [and]... none were... thought to be the cause of death." As they noted, it could not be determined whether this 30 percent incidence of embolism occurred before or after the negative angiography (a problem common to our study and any others which involve longterm follow-up). Of the 147 nontreated patients who were alive at six months, none had "evidence of embolism." They concluded that a "selective pulmonary arteriogram with superselective magnification views [when necessary]... performed within 24-48 hours of the onset of symptoms, can effectively rule out clinically-significant pulmonary embolism...[and render] anticoagulant therapy unnecessary..."

However, because of its cost, potential risk and, particularly, logistic constraints, pulmonary angiography cannot be regarded as an ideal screening test for the exclusion of pulmonary embolism. Pulmonary perfusion scanning, on the other hand,
is an extremely low-risk, essentially noninvasive and widely accessible procedure. Again, as in the case of angiography, virtually all prior reports regarding this procedure have dealt with its sensitivity and specificity, rather than with the frequency of "false negative" results.18,14,16,17,36,38 Greenspan12 solicited input from his colleagues regarding "false negative" scans and reached the conclusion that the frequency of false negative studies must be extremely low. McNeil et al,13 in a study designed to answer other questions, reported on a subgroup of 42 young patients (ages 18-40) who had normal findings on perfusion scan. All patients had been referred for pleuritic chest pain. A follow-up of 6-18 months after the initial scan disclosed that all subjects were alive and none had had "recurrent pleuritic chest pain after the first attack." Whether anticoagulant therapy was applied to any of these patients was not reported. Thus, these and other reports infer that the normal scan has a frequency of "false negative" reports comparable to that for pulmonary angiography. This is an important inference because it translates into a decision to discontinue, or not initiate, anticoagulant therapy for embolism, a translation that has become generally accepted.

Our data provide additional support for the validity of this important decision. Only one of our patients, who had documented venous thrombosis, received anticoagulant therapy beyond a normal perfusion scan. If, contrary to consensus, small or large emboli were present in these patients with normal perfusion scans, follow-up should have documented the error of this assumption. Untreated pulmonary embolism, according to the available literature, is associated with an appreciable frequency of mortality and recurrence, although precise estimates are not available.1,4 Our follow-up disclosed no deaths attributable to embolism and only one patient who, during the follow-up period, had suspected or documented pulmonary embolism. This patient died six months after his normal scan, and his small infarcts were recent. Obviously, a normal perfusion scan does not protect against future venous thromboembolism in patients with continuing risk factors. This excellent outcome among these 68 patients does not appear to be related to the absence of known risk factors among them; indeed, these patients had an array of risk factors (Table 1) similar to those reported in other series of patients with proven embolic disease.5,6,8

Thus, in a population of patients clearly at risk for pulmonary embolism, with a clinical presentation suggesting that diagnosis, failure to apply anticoagulant therapy after a normal perfusion scan was not associated with increased morbidity or mortality due to pulmonary embolism during the follow-up period. None of the six deaths encountered appears attributable to emboli; and these deaths occurred at 6, 9, 14, 36, 47 and 67 months after the "no anticoagulant therapy decision" was made. In addition, all patients were spared the risks of empirical anticoagulation. Indeed, estimates of the risks of anticoagulation would appear to exceed even our "worst case" estimates of diagnostic error based upon a normal scan.9-11

In view of the unequivocal evidence, in animals, that perfusion scanning may fail to detect small and nonocclusive emboli,16,17 our data raise interesting speculations. For example, if a normal scan "misses" small emboli, perhaps such failure is of no clinical significance. Stated another way, if withholding anticoagulant therapy after a normal scan is not associated with a subsequent risk of death, hospitalization or morbidity due to embolism, then perhaps emboli below the resolving capability of the scan are of pathologic-epidemiologic—but not clinical—importance. Perhaps such speculations will be validated. However, our data indicate only that, whatever the explanation, a favorable long-term outcome can be anticipated when patients with suspected embolism with a normal scan are not given anticoagulant drugs.

Our data provide additional support for the widely-held views that: 1) a normal perfusion scan does effectively exclude the diagnosis of clinically significant emboli; 2) the diagnostic work-up for suspected pulmonary embolism need not extend beyond a multiple-view, well-performed perfusion scan that is interpreted as normal; and 3) anticoagulant therapy is not required after normal perfusion scan except in the presence of documented venous thrombosis. Our data, compared to those of Novelline et al,44 indicate that a well-performed multiple-view perfusion scan which is negative appears to have the same value as does an appropriately-performed and interpreted pulmonary angiogram: namely, it allows one to decide that anticoagulant therapy can be withheld without a negative effect on the patient's outcome.

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