Using Clinical Evaluation and Lung Scan to Rule Out Suspected Pulmonary Embolism

Is It a Valid Option in Patients With Normal Results of Lower-Limb Venous Compression Ultrasonography?

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Background: In patients with a low clinical probability of pulmonary embolism (PE) and a nondiagnostic lung scan, the prevalence of PE is theoretically very low. We assessed the safety and usefulness of this association for ruling out PE.

Methods: We analyzed data from 2 consecutive cohort management studies performed in 2 university hospitals (Geneva University Hospital, Geneva, Switzerland, and Hôpital Saint-Luc, Montreal, Quebec), which enrolled 1034 consecutive patients who came to the emergency department with clinically suspected PE. All patients were submitted to a sequential diagnostic protocol of lung scan, D-dimer testing, lower-limb venous compression ultrasonography (US), and pulmonary angiography in case of inconclusive results of noninvasive workup.

Results: The prevalence of PE was 27.6%. Empirical assessment was accurate for identifying patients with a low likelihood of PE (8.2% prevalence of PE in the low clinical probability category). One hundred eighty patients had a low clinical probability of PE and a nondiagnostic lung scan. Among these patients, US showed deep vein thrombosis in 5. Hence, PE could be ruled out by a low clinical probability, a nondiagnostic lung scan, and a normal US in 175 patients (21.5%). The 3-month thromboembolic risk in these patients was low (1.7%; 95% confidence interval, 0.4%-4.9%).

Conclusions: Anticoagulant treatment could be safely withheld in patients with a low clinical probability of PE and a nondiagnostic lung scan, provided that the US is normal. This combination of findings avoided pulmonary angiography in 21.5% of patients with suspected PE in this series.

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Suspected pulmonary embolism (PE) is a frequent and vexing clinical problem. Pulmonary angiography, although the criterion standard, is costly, invasive,1 and not available in many clinical settings. Lung scans are diagnostic (high-probability lung scan establishes diagnosis of PE and low-probability lung scan [normal or near-normal] rules out PE) in only 30% to 50% of patients.2-4 Newer diagnostic instruments, such as plasma D-dimer measurement5,6 and lower-limb venous compression ultrasonography (US),4,7,8 have increased the options for noninvasive diagnosis. Nevertheless, even when combining all these tests, a significant proportion of patients still require an angiogram if clinical assessment is left out (36% in a recent study by our group9).

Clinical evaluation of patients with suspected PE has long been considered unreliable due to poor sensitivity and specificity of individual symptoms and signs.10-13 However, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study1 showed that clinicians could accurately distinguish between patients with a low, intermediate, or high probability of PE. In that study, clinical assessment was empirical and based on clinical elements (history, presence of risk factors for venous thromboembolism, and physical examination) and widely available tests (blood gases, chest x-ray, and electrocardiography). The proportion of patients with PE in the low clinical probability category was 9% and decreased to only 4% in patients with both a low clinical probability of PE and low-probability lung scan,3 suggesting that this combination might be used in clinical practice to rule out PE. Recently, the British Thoracic Society14,15 published guidelines that incorporated clinical evaluation in a practical approach to the diagnosis and management of PE.
PATIENTS AND METHODS

PATIENTS

One thousand three hundred thirteen consecutive patients admitted to the emergency department of the Geneva University Hospital between October 1, 1992, and October 31, 1997, or to the emergency department of the Hôpital Saint-Luc, Montreal, Quebec, between November 1, 1996, and October 31, 1997, for clinically suspected PE were included in 2 successive trials on the diagnosis of PE. Patients were excluded if they met the following criteria: suspected PE during hospital stay (15); symptoms of deep vein thrombosis (DVT) (4); DVT or PE in the previous 3 months (10); refusal or inability to consent to care (21); contraindication or impossible to undergo pulmonary angiography (14); ongoing anticoagulant treatment at study entry (16); expected survival less than 3 months (5); unavailable for follow-up (11); and lung scan read in comparison to a previous examination (37). Patients in whom the diagnostic protocol was not strictly applied (104) or in whom the diagnostic workup was incomplete (no clinical probability assessment in 26, no D-dimer measurement in 4, no lung scan in 11, and no US in 1) were also excluded. Therefore, 1034 patients were available for analysis.

METHODS

In both trials, diagnosis of PE rested on a sequence of noninvasive instruments, such as clinical assessment, lung scan, plasma D-dimer measurement using enzyme-linked immunosorbent assay (ELISA), and US. An angiogram was performed in patients with inconclusive results of the noninvasive workup. In the second study, the diagnostic sequence was modified: the plasma D-dimer level and US were obtained before instead of after the lung scan. Pulmonary embolism was ruled out by a normal lung scan, a plasma D-dimer level less than 500 µg/L, the combination of low clinical probability and a nondiagnostic lung scan, or a normal angiogram. Pulmonary embolism was established by a high-probability lung scan, DVT shown on US, or an abnormal angiogram. Moreover, in the first series, PE was also diagnosed in patients with a high clinical probability and an abnormal, though nondiagnostic, lung scan (15).

Clinical probability was assessed by the physicians in charge (more than 90 residents in internal medicine, with a median of 2 years of postgraduate training) after filling out a standard checklist, including risk factors for venous thromboembolism, symptoms and signs frequently encountered in PE, blood gases, electrocardiogram, and a description of chest x-ray findings (Table). The checklist served as a reminder of useful information to the clinician, who then integrated it on an empirical basis (ie, without using a score or prediction rule). In the first study, clinical probability was rated between 0% and 100%. In the second study, it was rated low (≤20%), intermediate (21%-79%), or high (≥80%).

OUTCOMES

The usefulness of clinical probability was evaluated in terms of the proportion of patients in whom PE could be ruled out by the combination of a low clinical probability and a nondiagnostic lung scan. The safety of this combination was assessed by the upper limit of the 95% confidence interval (CI) for the 3-month thromboembolic risk.20,21

THREE-MONTH FOLLOW-UP

Venous thromboembolic events (DVT or PE) were recorded during the 3-month follow-up. Patients were followed up by their family physicians and were interviewed by telephone by one of the study coordinators at the end of the follow-up period. The family physician was contacted whenever a possible event was disclosed in the interim history, and the medical charts were reviewed if a patient was readmitted to a hospital for any cause. The death registries of the city of Geneva and the province of Quebec were consulted for patients who could not be traced after checking with the family physician. For patients who died, the cause of death was ascertained by either the autopsy or the death certificate.

DIAGNOSTIC STUDIES

The techniques for performing and interpreting lung scan and pulmonary angiography have been described elsewhere.4,22

In both studies, plasma D-dimer levels were measured using the ELISA technique (Asserachrom D-Di enzyme immunoassay kit; Diagnostica Stago, Asnières-sur-Seine, France)4,16 and a rapid ELISA (Vidas DD; bioMérieux, Lyon, France)9 by a technician unaware of the clinical probability, the lung scan result, and the final diagnosis. The result of the blood test was transmitted to the physician in charge of the patient within approximately 1 hour following the reception of the blood sample to the laboratory. Ultrasonography was done by trained staff within 24 hours in all cases. The examination consisted of a real-time B-mode venous compression test of the common femoral and popliteal veins. The criterion for diagnosing DVT was noncompressibility of the vein.23

STATISTICAL ANALYSIS

The exact 95% CIs for incidence of thromboembolic and bleeding events during follow-up were calculated from the binomial distribution using computer software.24

In 2 recent trials at Geneva University Hospital, Geneva, Switzerland, on noninvasive diagnosis of PE, empirical clinical probability of PE was systematically assessed by internal medicine trainees before any specialized tests were performed. The combination of low clinical probability and a low-probability lung scan ruled out PE. These patients did not undergo anticoagulant therapy and were followed up for 3 months because untreated PE will result in a high frequency of recurrences.17,18 Because the proportion of such patients in each of these individual trials was too small to allow a definitive assessment of the safety of this potentially cost-saving diagnostic criterion, we performed a pooled analysis of both studies. Moreover, since the distinction between the low- and intermediate-probability lung scan categories is difficult and fraught with substantial interobserver disagreement,19 we merged these results into a single nondiagnostic category in this article. Hence, this article reports the efficacy and safety of a low clinical probability combined with a nondiagnostic lung scan to rule out PE.
One thousand thirty-four patients with suspected PE were included in the 2 trials and were available for assessing the accuracy of clinical probability. In 197 patients from the second trial, a lung scan was not performed because the diagnosis was already established by plasma D-dimer level or US, which were performed before the lung scan. Therefore, the usefulness and safety of combining clinical and lung scan probability for ruling out PE were evaluated in the subset of 837 patients who had undergone a lung scan. The prevalence of PE was similar in the entire cohort and this subset of patients (27.6% and 28.9%, respectively).

**ACCUACY OF CLINICAL PROBABILITY OF PE**

Physicians had a high accuracy for identifying patients with a low likelihood of having PE (8.2% observed prevalence of PE in that category; Figure). Conversely, in the high clinical probability category, physicians tended to overestimate the likelihood of PE (Figure). To avoid incorporation bias, this analysis was also done in the subset of patients in whom clinical probability did not intervene in the final diagnosis (so-called certified diagnosis, which relied solely on lung scan, D-dimer level, US, or angiogram). The results were unchanged.

**USEFULNESS AND SAFETY OF CLINICAL PROBABILITY OF PE**

Of the 1034 patients, 428 had a low clinical probability; of those, 309 underwent a lung scan. In 180 (58.2%) of these patients, both a low clinical probability and a nondiagnostic lung scan ruled out PE. In 5 of these patients US showed DVT. Therefore, the combination of a low clinical probability and a nondiagnostic scan ruled out PE in 175 (20.9%) of 837 patients. The D-dimer level was normal in only 28 of these 175 patients vs 202 of the patients with lung scan. There were 3 false-negative results assessed by further testing (1 patient with an abnormal pulmonary angiogram or by follow-up (1 with DVT and 1 with PE). Finally, a young female patient with no risk factors for PE and a normal D-dimer level was lost to follow-up. Hence, the proportion of thromboembolic events missed by the combination of clinical and lung scan probability was 3 (1.7%) of 175 patients (95% CI, 0.4%-4.9%) after US. This rate would have been higher if US had not been performed in all patients (4.4%; 95% CI, 1.9%-8.6%).

**COMMENT**

This pooled analysis shows that empirical assessment of clinical probability of PE is accurate in identifying patients with a low clinical likelihood of the disease. Moreover, it confirms that ruling out PE in patients in the emergency department with a low clinical probability of PE and a nondiagnostic lung scan is both effective, avoiding pulmonary angiography in 21.5% of patients, and safe, provided US shows no DVT.

The main limitation of empirical clinical probability assessment is potentially poor interobserver agreement, since different clinicians may attribute different weights to the same clinical elements. Several observations suggest that this is seldom a problem. First, a previous trial showed that residents and senior residents had a high level of agreement in establishing the clinical probability of PE. Second, the Figure shows that the accuracy of clinical assessment in our series was remarkably similar to that observed in the PIOPED study, despite the fact that the latter study was conducted in several centers in North America. The only difference was a higher proportion of patients with a low clinical probability in
our series (40% vs 20%), probably due to inclusion of a significant proportion of inpatients in the PIOPED study. Indeed, hospitalization is by itself an important risk factor for venous thromboembolism. Therefore, clinical probability is more often high in that patient population. Third, clinical probability was assessed by more than 90 physicians throughout the study, all of whom were internal medicine residents in the second or third year of training. It is unlikely that this fair accuracy would have been observed if interindividual variability of empirical assessment were very important.

Admittedly, disagreement between physicians on clinical probability occurred occasionally. In our institutions, patients were treated by different teams in the emergency department and in the ward. Therefore, in 104 patients (7.9% of the entire cohort), clinical probability was either raised or, more often, lowered by the second team. Since physicians in the ward generally knew the results of the lung scan, D-dimer testing, or US when they modified the clinical probability and were likely to be influenced by that knowledge, such cases were excluded from our trials. Interestingly, the 3-month follow-up could be completed in the 74 patients who did not undergo angiography because their clinical probability was lowered by the ward physicians, and none had a thromboembolic event. Still, in case of a disagreement about clinical probability, it would be cautious to classify the patient in the higher clinical probability category and proceed to further tests. Obviously, a clinical prediction rule or score would allow a standardized estimate of clinical probability. However, existing scores are cumbersome and have not been prospectively validated in patient cohorts distinct from those in which they were established.

The 3-month thromboembolic risk was only 1.7% (95% CI, 0.4%-4.9%), comparable to that in patients who did not undergo anticoagulant therapy based on a normal lung scan. The 95% CI is still wide, due to the small size of this particular subset of patients. Studies by other groups to confirm our findings would verify the reliability of clinical assessment and increase the sample size to definitively ensure the safety of the strategy. Further study would be especially worthwhile, considering the potential contribution of clinical probability to noninvasive diagnosis of PE. In this study, the combination of a low clinical probability and a nondiagnostic lung scan was found in 21.5% of patients consecutively admitted to the emergency department, while in the PIOPED study, which included both inpatients and outpatients, this association was present in 18% of the cohort. This combination was associated with a normal US in 21.5% of patients in our series, allowing us to rule out PE. Admittedly, in institutions using ELISA to measure D-dimer levels and have not been prospectively validated in patient cohorts distinct from those in which they were established.

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