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Original Research

PULMONARY VASCULAR DISEASE

Noninvasive Diagnosis of Pulmonary Embolism

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Background: **We designed a simple and integrated diagnostic algorithm for acute pulmonary embolism (PE). Diagnosis was based on clinical probability assessment, plasma D-dimer testing, then sequential testing to include lower limb venous compression ultrasonography, ventilation perfusion lung scan, and chest multidetector CT (MDCT) imaging.**

Methods: **We included 321 consecutive patients presenting at Brest University Hospital in Brest, France, with clinically suspected PE and positive D-dimer or high clinical probability. Patients in whom VTE was deemed absent were not given anticoagulants and were followed up for 3 months.**

Results: **Detection of DVT by ultrasonography established the diagnosis of PE in 43 (13%). Lung scan associated with clinical probability was diagnostic in 243 (76%) of the remaining patients. MDCT scan was required in only 35 (11%) of the patients. The 3-month thromboembolic risk in patients not given anticoagulants, based on the results of the diagnostic protocol, was 0.53% (95% CI, 0.09-2.94).**

Conclusions: **A diagnostic strategy combining clinical assessment, D-dimer, ultrasonography, and lung scan gave a noninvasive diagnosis in the majority of outpatients with suspected PE and appeared to be safe.**

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Abbreviations: CTPA = CT pulmonary angiography; CUS = compression ultrasonography; ELISA = enzyme-linked immunosorbent assay; MDCT = multidetector CT; PE = pulmonary embolism; $\dot{V}/\dot{Q}$ = ventilation perfusion ratio

Pulmonary embolism (PE) is a common and serious disease. Clinical signs and symptoms are insufficient to diagnose or rule out the condition. Laboratory tests and imaging are, thus, required in all patients with suspected PE to reach a definitive diagnosis. Current diagnostic strategies rely on the sequential use of noninvasive diagnostic tests, such as plasma D-dimer measurement, lower limb proximal deep vein compression ultrasonography (CUS), ventilation perfusion ratio ($\dot{V}/\dot{Q}$) lung scan, and chest multidetector CT (MDCT) scan. In recent years, CT pulmonary angiography (CTPA) tended to replace $\dot{V}/\dot{Q}$ scan in diagnostic strategies for PE. Indeed, strategies using CTPA or $\dot{V}/\dot{Q}$ have shown similar safety in excluding PE.[1] However, CTPA is associated with significantly

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higher radiation exposure than V̇/Q̇, which might lead to an increased risk of secondary malignancies, especially breast cancer in young women.[2] Moreover, CTPA cannot be used in patients with iodinated contrast agents allergy or impaired renal function. Therefore, assessing the use of V̇/Q̇ in diagnostic strategy for PE remains of utmost importance. In fact, V̇/Q̇ scan is a robust and well-established diagnostic test for suspected PE. Results are usually classified according to criteria established in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study into four categories: normal or near-normal, low, intermediate, and high probability of PE. The validity of a normal perfusion lung scan has been evaluated in several prospective clinical outcome studies that observed low event rates, suggesting that it is a safe practice to withhold anticoagulant therapy in patients with a normal perfusion scan.[3] However, patients with a normal V̇/Q̇ scan only represented 14% of patients with suspected PE included in the PIOPED study. The high frequency of nondiagnostic probability scans has been a source of criticism because they indicate the necessity of further diagnostic testing.[4] Strategies to overcome this problem have been proposed, in particular, the combination of V̇/Q̇ scan results with clinical probability assessment and with lower limb veins CUS results. The 2008 European Society of Cardiology Guidelines on the diagnosis and management of acute PE consider that it is safe to rule out PE in low clinical probability patients with nondiagnostic lung scans (ie, either low or intermediate probability V̇/Q̇ scans) as well as in patients with an intermediate clinical probability, but only if they also have a negative proximal CUS.[5] However, few management outcome studies have validated such a strategy.[6] Therefore, we analyzed the outcome of consecutive patients with suspected PE managed according to a simple diagnostic algorithm that combined clinical probability assessment, enzyme-linked immunosorbent assay (ELISA) D-dimer measurement, single proximal lower-limb venous CUS, V̇/Q̇ lung scan, and chest MDCT scan.

Materials and Methods

Study Population and Enrollment

The eligible study population consisted of consecutive patients aged 18 years or older who were inpatients and outpatients seen at Brest University Hospital in Brest, France, between April 2004 and September 2006 with symptoms suggestive of PE. The hospital is a tertiary care center for a 300,000 population area. Clinical probability of PE was assessed by the physicians in charge according to the clinical model described by Wells et al[7] on the basis of risk factors for VTE, symptoms and signs commonly encountered in PE, and the likelihood of an alternative diagnosis to that of PE. Clinical probability of PE was rated as low, intermediate, or high.

All patients with either a high clinical probability of PE or a non-high clinical probability but abnormal plasma ELISA D-dimer concentration (> 500 μg/mL) were considered for inclusion. Exclusion criteria were pregnancy, breastfeeding, life expectancy of < 3 months, impossible follow-up, patients who were receiving long-term anticoagulant treatment or who started receiving anticoagulant treatment of > 48 h at the time of screening, and patients with already confirmed or massive PE. The protocol was approved by the ethics committee of our institution, and written informed consent was obtained from all patients and registered with institutional review board authorization number 04.036.

Diagnostic Strategy

All included patients underwent a standardized diagnostic strategy (Fig 1). First, patients underwent CUS (Acuson 128XP 7MHz linear probe; Siemens USA; Washington, DC) performed by a vascular ultrasonography specialist physician. No indirect venography was performed. The diagnostic criterion for DVT was a lack of compressibility of a proximal deep vein. PE was considered present in patients with proximal DVT. Patients with no DVT on CUS underwent V̇/Q̇ planar lung scan. Dual isotope (^{99m}Tc macroaggregated /^{81m}Kr gas) V̇/Q̇ planar lung scans were acquired in six standard views (anterior, posterior, both lateral and both posterior oblique) and classified based on the revised PIOPED criteria (normal, low, intermediate, or high).[8] PE was diagnosed in patients with an intermediate or high clinical probability and a high probability V̇/Q̇ scan. PE was ruled out in patients with (1) a normal V̇/Q̇ scan, (2) a low or intermediate clinical probability of PE and a low probability V̇/Q̇, or (3) a low clinical probability and an intermediate probability V̇/Q̇ scan. All other patients underwent a chest MDCT scan (Philips MX 8000 IDT 16-slice CT scanner; Philips Healthcare; Eindhoven, The Netherlands) interpreted by a vascular radiologist. The protocol for chest MDCT scan consisted of an evaluation of the pulmonary arteries up to and including the subsegmental vessels. Patients were examined during a breath hold or shallow breathing, depending on the degree of dyspnea. PE was considered present if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low attenuation material. PE was ruled out in patients with negative chest MDCT scan.

Study Analysis

The safety of the diagnostic strategy was assessed by monitoring the risk of thromboembolic events during the 3-month follow-up period in patients deemed not to have PE. 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, using a semi-structured questionnaire. We contacted the family physician whenever a possible event was disclosed by the interim history, and charts were reviewed if a patient was readmitted to hospital for any cause. For patients who died, the cause of death was ascertained either by necropsy or by the death certificate. All suspected recurrent VTEs were reviewed by an independent adjudication committee.

We calculated the rate of confirmed symptomatic thromboembolic events during the 3-month follow-up as the ratio of the number of confirmed thromboembolic events over the total number of patients in whom PE was ruled out by the diagnostic strategy and who were left untreated during the follow-up period. To be considered as a safe diagnostic exclusion strategy, the upper limit of the 95% CI for the 3-month thromboembolic risk should not exceed 3%—a risk similar to what is observed after a negative gold standard test for PE (ie, pulmonary angiography).[9]

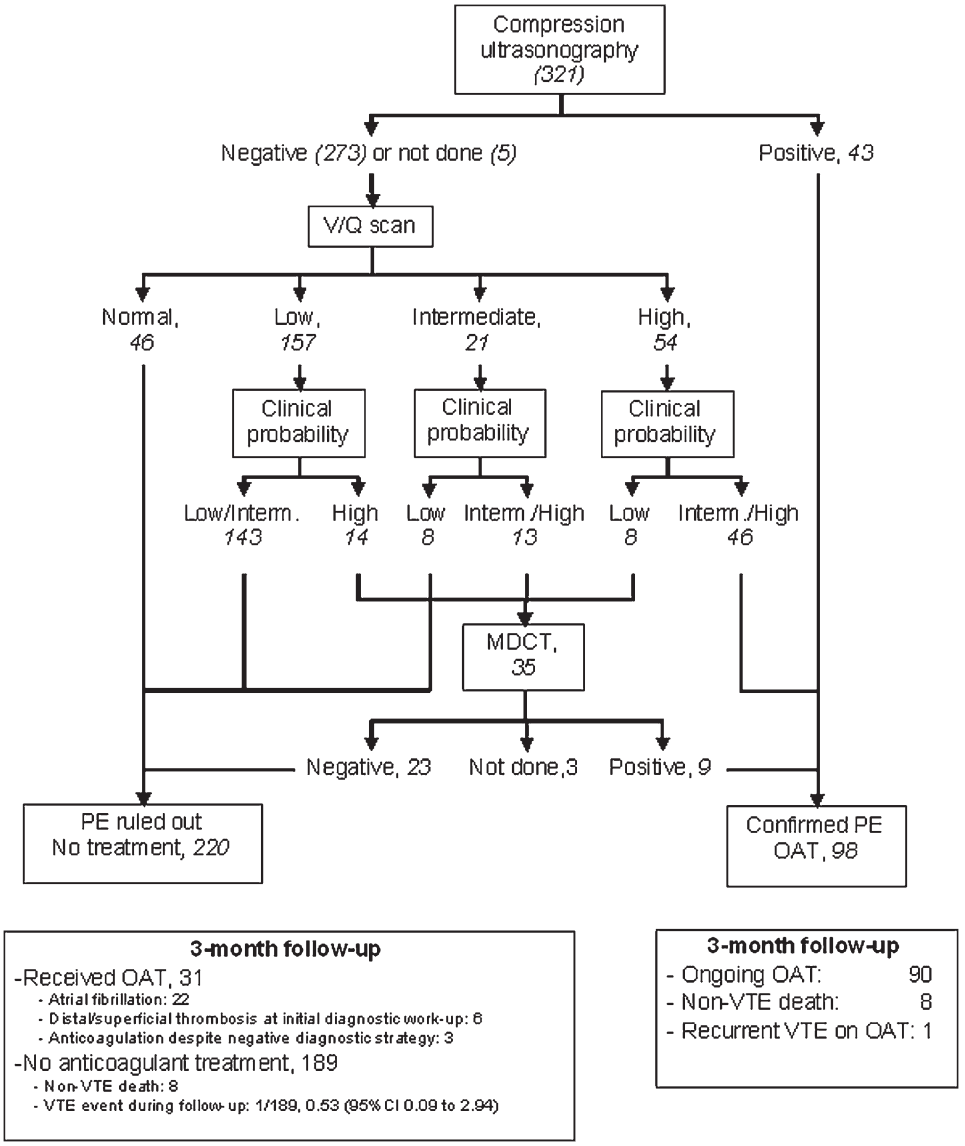

FIGURE 1. Study flowchart. Interm = intermediate; MDCT = multidetector CT; OAT = oral anticoagulant therapy; PE = pulmonary embolism; V/Q = ventilation perfusion ratio.

RESULTS

We included 321 patients with a median age of 72 years (range, 18-95 years). General characteristics of included patients are shown in Table 1.

Diagnosis of VTE

Figure 1 summarizes the results of the diagnostic strategy. CUS showed a proximal DVT establishing VTE in 43 (13%) patients. V̇/Q̇ scan was, therefore, required in 278 (87%) patients. PE was ruled out by a normal V̇/Q̇ scan, whatever the clinical probability, in 46 (14%) patients; by a low probability V̇/Q̇ scan combined with a low (n = 81) or intermediate (n = 62) clinical probability in 143 (45%) patients; and by an intermediate probability V̇/Q̇ scan combined with a low clinical probability in eight (3%) patients. A high-probability V̇/Q̇ scan combined with an intermediate or high clinical probability established the diagnosis in 46 (14%) patients. Chest MDCT scan was required in 35 (11%) patients with either a low clinical probability but a high probability V̇/Q̇ scan (n = 8), an intermediate or high clinical probability in patients with an intermediate probability V̇/Q̇ scan (n = 13), or a high clinical probability but a low probability V̇/Q̇ scan (n = 14). It was negative in 23 patients and positive in nine: one out of the eight patients with a low clinical probability but a high probability V̇/Q̇ scan, six out of the 13 patients who had an intermediate or high clinical probability and an intermediate V̇/Q̇ scan, and two out of those 14 with a high clinical probability but a low V̇/Q̇ scan. Finally, there were three protocol violations: Chest MDCT scan was not performed in three patients with an otherwise inconclusive diagnostic

Table 1—*General Characteristics of the 321 Included Patients*

Characteristics	No. (%)
Age, mean ± SD, y	68 ± 16
Female sex	165 (51)
Risk factors	
History of VTE	82 (26)
Recent surgery, plaster cast, or immobilization (< 3 mo)	63 (20)
Active malignancy	39 (12)
Current estrogen use	19 (6)
COPD	52 (16)
Chronic heart failure	59 (18)
Inpatients	51 (16)
Clinical signs and symptoms	
Chest pain	165 (51)
Shortness of breath	253 (79)
Hemoptysis	20 (6)
Clinical signs of DVT	84 (26)

strategy. All three patients were treated with anticoagulant therapy on the basis of the finding of a distal DVT. Overall, the diagnosis of PE was confirmed in 98 patients (31%): six out of 107 (6%) patients classified as having a low clinical probability according to Wells' model,[7] 32 out of 132 (24%) intermediate clinical probability patients, and 60 out of 79 (73%) high clinical probability patients.

Follow-up

Follow-up was completed successfully for all patients. All 98 patients with PE received anticoagulant therapy during the 3-month follow-up period. One of them had a recurrent VTE while on treatment, and eight patients died during the follow-up period. None of these deaths was ruled to be related to PE. Of the 220 patients in whom PE was deemed absent according to the diagnostic strategy, 31 patients (14%) received anticoagulant therapy at some point during follow-up for an indication other than PE, mainly atrial fibrillation (n = 22) and distal or superficial vein thrombosis at initial diagnostic strategy (n = 6). Therefore, we calculated the 3-month thromboembolic risk in the 189 patients who did not receive anticoagulant therapy during follow-up. None of the eight deaths during follow-up in this group was ruled as due to PE. Deaths were due to cancer in five patients, terminal heart failure in two, and ruptured abdominal aorta aneurism in one. One 46-year-old patient with cancer had an acute venous thromboembolic event during the 3-month follow-up period. The diagnosis of PE had initially been ruled out on the combination of a low clinical probability, negative CUS, and low probability V̇/Q̇ scan. Initial diagnostic conclusion was bacterial pneumonia. She was discharged on antibiotic therapy. One month later, she presented with persistent shortness of breath and new onset of calf pain. CUS revealed a proximal DVT, and a high probability of PE was observed on V̇/Q̇ scan. Hence, the 3-month thromboembolic risk was 1 out of 189 or 0.53% (95% CI, 0.09-2.94).

Discussion

In this study, we found that using diagnostic strategy based on V̇/Q̇ lung scan as the main imaging test safely excluded PE in inpatients and outpatients with suspected PE. The 3-month thromboembolic risk in patients in whom PE was ruled out on the basis of this diagnostic strategy was 0.53% (95% CI, 0.09-2.94). This 3-month thromboembolic risk is in line with what is observed after a negative pulmonary angiography[9] and with the thromboembolic risk observed in recently published diagnostic strategies for the diagnosis of PE.[1,10,11]

Our study leads to a more accurate prognosis in patients in whom a suspicion of PE is discarded on the combination of clinical probability, CUS, and V̇/Q̇ scan results. Although the safety of ruling out PE on the basis of a normal V̇/Q̇ is well established, limited data from management outcome studies exist on patients with inconclusive V̇/Q̇ scans. Indeed, in a systematic review, Roy et al[6] found only few studies that evaluated strategies to rule out PE included the use of lung scintigraphy. Most of them used V̇/Q̇ scans classified only as conclusive or inconclusive results, without the help of the four categories validated by PIOPED study. Perrier et al[12] proposed, in a study including 444 patients with suspected PE, a strategy combining pretest clinical probability (as assessed by the physician in charge on the basis of risk factors, symptoms, and signs commonly encountered in PE and likelihood of an alternative diagnosis) and D-dimer testing before lower limb CUS, and V̇/Q̇ scan in case of negative CUS. In patients with a low or intermediate V̇/Q̇ scan, PE was ruled out only if the clinical probability was low, whereas in our study, PE was also ruled out in the 62 patients (that is, 19% of our study population) with an intermediate clinical probability. However, despite this difference in the noninvasive diagnostic pathway, both rates of requirement for further invasive test (11%) and of prevalence of PE (23%) fall close to our findings. In the study by Wells et al,[13] including 930 patients with suspected PE, the diagnostic strategy was based on clinical probability, D-dimer, and V̇/Q̇ scan, performed previous to lower limbs CUS. This latter examination was repeated 1 week later in patients with an inconclusive diagnostic pathway (7%), thus enabling requirement of invasive tests in few patients (1%). Interestingly, four out of the five patients who developed PE or DVT during follow-up after withdrawal of anticoagulation had not undergone the proper diagnostic pathway.

Some limitations of our study deserve comment. First, the proportion of confirmed PE seems higher in our study than what is reported in most recent PE diagnostic studies. This is likely because we did not include all patients with suspected PE but only those with either a high clinical probability of PE or a non-high clinical probability but positive D-dimer test. Indeed, the safety of ruling out the diagnosis of PE in patients with a non-high clinical probability of PE and a negative ELISA D-dimer test has already been strongly established.[12] Second, at the time our study was designed, we chose to assess the clinical probability of PE using the clinical model developed by Wells et al.[7] Admittedly, this model did not receive large clinical validation, and it was later proposed to replace it with clinical prediction rules.[14-16] However, our study demonstrates the accuracy of the Wells model: The proportion of confirmed PE in patients categorized as having a low, intermediate, or high probability was 6%, 24%, and 73%, respectively. Third, this study was performed in a single center, which could limit generalizability of our results. However, $\dot{V}/\dot{Q}$ scans were interpreted on a daily basis by one out of the six physicians from the Department of Nuclear Medicine on duty in order to stick to real-life clinical practice. In conclusion, our study proposes a diagnostic strategy combining clinical assessment, D-dimer, ultrasonography, and lung scan that allows safe and noninvasive exclusion of the diagnosis in the vast majority of outpatients with suspected PE without the use of chest MDCT scan.

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Dr Couturaud: contributed to designing the study, ensuring inclusion and follow-up of patients, analyzing the data, and redacting the manuscript.
Dr Le Duc-Pennec: contributed to designing the study, managing imaging procedures, and redacting the manuscript.
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Dr Le Roux: contributed to managing imaging procedures, analyzing the data, and redacting the manuscript.
Dr Guillo: contributed to designing the study, managing imaging procedures, and redacting the manuscript.
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Dr Cornily: contributed to ensuring inclusion and follow-up of patients and redacting the manuscript.
Dr Leroyer: contributed to designing the study, ensuring inclusion and follow-up of patients, analyzing the data, and redacting the manuscript.
Dr Le Gal: contributed to designing the study, analyzing the data, and redacting the manuscript.
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