

Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in hospitalized patients

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ABSTRACT: The effectiveness of new diagnostic tools for suspected pulmonary embolism (PE), such as clinical probability assessment, plasma D-dimer (DD) measurement and lower limb venous compression ultrasonography (US), has not been specifically studied in patients with a suspected PE occurring during hospital stay.

This study applied a sequential, decision analysis-based strategy adding these instruments to a ventilation/perfusion lung scan in a cohort of 114 consecutive inpatients clinically suspected of PE in order to establish in how many patients a pulmonary angiogram could thereby be avoided.

A definitive diagnosis could be established by the noninvasive protocol in 61% of these patients: normal/near-normal lung scan, 14%; high probability lung scan, 19%; clinical probability combined with lung scan result, 18%; and US, 8%. Specificity of DD was only 7% and contributed to the exclusion of PE in only two patients. Pulmonary angiography was required in 39% of patients. The 3-month thromboembolic risk in patients in whom PE was excluded by the diagnostic process was 0% (95% confidence interval 0–4.9%).

In conclusion, a noninvasive work-up for suspected pulmonary embolism is effective in hospitalized patients, allowing to forego angiography in 61% of them, and it appears to be safe, although this should be further investigated. In contrast to outpatients, D-dimer measurement appears to be useless in hospitalized patients.

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The clinical picture of pulmonary embolism (PE) is non-specific and sometimes misleading [1, 2], and the frequency of clinically unsuspected PE at autopsy has not varied over the past three decades [3], which points to sustained underdiagnosis of this condition. The ventilation/perfusion lung scan is often the first test to be performed, but it is diagnostic in only 30–50% of patients [4]. Nevertheless, physicians are usually reluctant to proceed to pulmonary angiography in case of a nondiagnostic lung scan [5].

Various strategies have been proposed to meet this diagnostic challenge with a view toward minimizing the requirement for pulmonary angiography in patients with nondiagnostic lung scans [6–8]. These strategies include lower limb venous compression ultrasonography (US), which is highly sensitive and specific for the diagnosis of proximal deep vein thrombosis (DVT) [9, 10], and plasma measurement of D-dimer (DD), a degradation product of cross-linked fibrin. In patients with suspected PE, proximal DVT can be detected in 10–20% of cases, hence obviating the need for further testing and warranting anticoagulant treatment [6, 7, 11]. On the other hand, DD is able to rule out venous thromboembolism (VTE) because of its high sensitivity to the presence of acute PE and/or DVT [12–14]. Various assay techniques are available, of which the most reliable is the enzyme-linked immuno-

sorbent assay (ELISA) technique [15, 16] which now exists as a rapid, automated test that is more suited for emergency use [17].

In addition, clinical evaluation of a patient suspected of PE can be combined with a lung scan result, to lower or increase the probability of PE. Although such a clinical assessment cannot confirm or exclude PE by itself, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study [4] has shown that the combination of a low clinical probability and a low probability lung scan renders PE very unlikely.

These modern, cost-effective [18] diagnostic tools were mostly developed in outpatient or mixed populations, and their performances have not been specifically studied in a population of patients in whom PE was suspected during the hospital stay, although strategies targeting outpatients may not necessarily apply to inpatients. Indeed, in the latter, the comorbidities, including the cause of hospital stay, may interfere with the interpretation of the tests; in particular, DD concentrations can be nonspecifically elevated in many clinical conditions unrelated to VTE [19].

Therefore, this study applied to a population of hospitalized, surgical and medical patients, a sequential, decision analysis-based strategy previously validated in outpatients, including clinical probability, DD level and US, in order to

evaluate the performance of these noninvasive instruments in the work-up of suspected PE in this population. Patients with a negative work-up did not receive anticoagulant treatment and all patients were followed up for 3 months.

Patients and methods

Patients

Consecutive patients admitted for a surgical or a medical condition other than VTE at the University hospital of Geneva (Switzerland), and clinically suspected of PE during the course of their hospital stay (at least 24 h after admission), were studied between June 1, 1995 and June 30, 1997. Exclusion criteria included: symptoms suggestive of PE or DVT at admission, age <16 yrs; occurrence of PE or DVT <3 months before inclusion; patients already on therapeutic anticoagulation; contra-indication to pulmonary angiography; survival estimated to be <3 months; refusal or inability to give an informed consent; lung scan interpreted in function of a previous scan, a situation in which the PIOPED criteria cannot be applied; follow-up impossible; and nonadherence to the study diagnostic algorithm by the managing physician. Patients were recruited in both medical and surgical wards. For the purpose of the study, patients hospitalized in a surgical ward but who had not undergone any operation when PE was clinically suspected, were considered medical in the analysis.

The protocol had been approved by the Ethics Committee of the Department of Internal Medicine, University of Geneva, Switzerland.

Study design

The study was designed as a prospective management trial with a formalized 3-month follow-up. Patients admitted for ≥ 24 h and presenting symptoms suggesting PE that were not present at the time of admission, underwent clinical evaluation. The clinical probability was assessed empirically by the physician in charge in the ward prior to lung scan, on the basis of familial and personal history; risk factors for VTE; physical examination; arterial blood gas analysis; chest radiograph; and electrocardiogram. The clinical probability was rated low ($\leq 20\%$), intermediate (21–79%) or high ($\geq 80\%$). All patients were then managed according to the protocol described in figure 1.

Noninvasive testing started with a ventilation/perfusion lung scan. A normal or near-normal lung scan excluded PE and a high probability lung scan established the diagnosis. In the presence of a nondiagnostic lung scan (so-called low or intermediate probability), clinical probability was combined to the lung scan result. Patients were classified as having PE if a high clinical probability was combined with a nondiagnostic lung scan; PE was considered to be ruled out by a low clinical probability combined with a nondiagnostic lung scan. For other combinations, a blood sample was taken to measure plasma DD level, and compression US of the proximal leg veins was performed. A DVT shown by US confirmed acute VTE, and a DD $< 500 \mu\text{g}\cdot\text{L}^{-1}$ along with a negative US excluded PE. Pulmonary angiography was carried out in all patients in whom a definitive diagnosis had not been reached at that point.

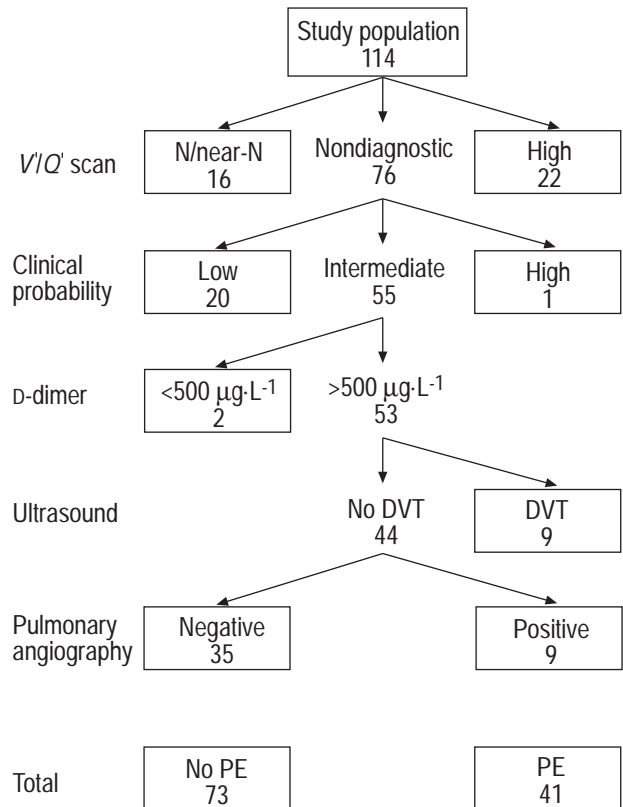


Fig. 1. – Flow chart summarizing the diagnostic process in the study. The numbers in each box represent the absolute number of patients in which a final diagnosis has been made at each stage through a diagnostic lung scan, clinical probability combined with lung scan result, d-dimer, ultrasound or a pulmonary angiogram. *V/Q*: ventilation/perfusion; N: normal; DVT: deep vein thrombosis; PE: pulmonary embolism.

For the purpose of the study, however, all patients were submitted to clinical assessment, DD measurement, US and lung scan, regardless of the other test results. Patients were followed up during 3 months to evaluate the risk of thromboembolic events or treatment complication (major haemorrhage).

Outcome

The principal outcome measure was the proportion of patients in whom a definitive diagnosis could be reached by the noninvasive strategy. This was compared to the percentage of necessary angiograms: 1) in a reference strategy in which all patients with a nondiagnostic lung scan would undergo an angiogram, and 2) in a cohort of outpatients submitted to the same diagnostic strategy [7].

Three-month follow-up

Patients were instructed to report haemorrhagic and suspected recurrent thromboembolic events occurring after hospital discharge without delay to their general practitioner and the study physician. A formal follow-up was performed by an interview of the patients by one of the study coordinators at the end of the follow-up period. At that time, the general practitioner was contacted, and the patient asked about any symptoms suggestive of PE or

DVT during the interim history. Information about any examination or testing made to diagnose a thromboembolic event was recorded. Lastly, the charts of the hospitalization or any subsequent hospital stay were reviewed for more complete information.

Diagnostic studies

The technique for performing lung scan, pulmonary angiography and for assaying plasma DD have been described previously [13, 17]. Lung scans were classified as normal, near-normal (or very low), low, intermediate or high probability, according to the PIOPED interpretation criteria [4]. Plasma DD measurements were performed with a rapid ELISA assay (Vidas DD®, bioMérieux, Marcy-L'Étoile, France) as soon as the samples arrived in the laboratory, by a technician unaware of the clinical probability, the lung scan result and the final diagnosis. The results of the blood tests were forwarded to the physician in charge of the patient within 1 h following the reception of the blood sample to the laboratory.

Lower-limb B-mode venous compression US was performed in all patients by trained staff within 24 h of suspicion of PE. It consisted of a real-time B-mode examination of the common femoral and popliteal veins. The criterion for diagnosing DVT was noncompressibility of the vein [9].

Statistical analysis

Sensitivity and specificity of DD dosage and US were calculated in reference to the discharge diagnosis. The Chi-squared test for proportions, with Yates correction for small numbers, was used to compare the sensitivity and specificity of DD and US in the surgical and nonsurgical populations as well as the proportion of patients with a low clinical probability, and the percentage of pulmonary angiograms and PE in the two groups. The Mann-Whitney test was used to compare age in surgical and medical patients. When appropriate, 95% confidence intervals (CI) were computed by means of the exact method (Confidence Interval Analysis® software, BMJ, 1989).

Results

One hundred and forty-five consecutive patients admitted for a surgical or a medical condition other than VTE at the University hospital of Geneva (Switzerland), and clinically suspected of PE during their hospital stay, were studied during the study period. Thirty-one (21%) patients were excluded for the following, predefined reasons: patients already on therapeutic anticoagulation (n=4); contra-indication to pulmonary angiography (n=3); survival estimated to be <3 months (n=4); refusal or inability to give an informed consent (n=7); lung scan interpreted in function of a previous scan, situation in which the PIOPED criteria could not be applied (n=2); follow-up presumably impossible (n=2); and nonadherence to the study diagnostic algorithm by the managing physician (n=9). Thus, 114 patients were effectively included in the trial, coming from surgical (n=55) or medical wards (n=59). The overall prevalence of PE in the study population

Table 1. – Demographic and clinical characteristics of the study population

	All	Surgical patients	Nonsurgical patients	p-value
Subjects n	114	55	59	
Age yrs	72 (19–94)	64 (19–87)	74 (28–94)	<0.01
Male %	46 (40)	25 (45)	21 (36)	NS
Risk factors for PE				
History of DVT or PE	18 (16)	3 (5)	15 (25)	<0.01
Cancer	34 (30)	18 (33)	16 (27)	NS
Surgery or trauma	60 (53)	55 (100)	5 (8)	<0.01
Immobilization >48 h	84 (74)	47 (85)	37 (63)	NS
DVT prophylaxis	86 (75)	51 (93)	35 (59)	NS

Data presented as n (%) or as median (range). PE: pulmonary embolism; DVT: deep vein thrombosis.

was 36% (41/114) and was not significantly different in surgical and medical patients ($p=0.15$). The demographic and clinical characteristics of the patients are summarized in table 1.

Clinical probability of PE

Overall, clinical probability of PE was low in 33% of patients (n=38). In this category, the observed prevalence of PE was 13%. Clinical probability was high in 9% of patients (n=10) with an observed prevalence of PE of 70%. Hence, the majority of patients had an intermediate clinical probability, a category in which the prevalence of PE was 44% (29/66) (fig. 2). The proportion of patients with a low clinical probability was significantly smaller in the surgical group than in the medical group (18 versus 47%, $p<0.05$). As was already demonstrated [4], clinicians were better at predicting a low probability of PE than a moderate or high clinical probability.

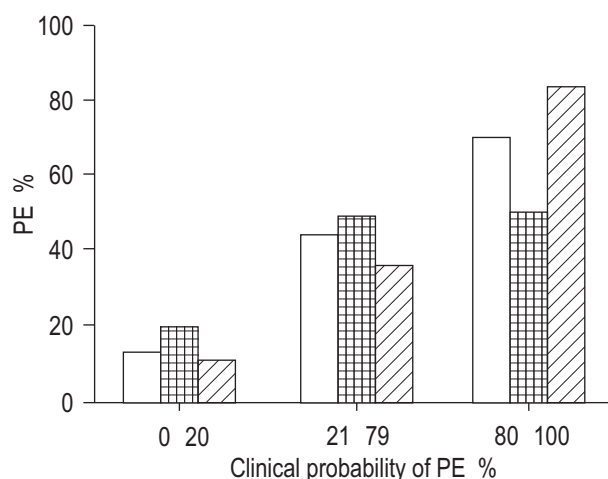


Fig. 2. – Association between empirically assessed clinical probability of pulmonary embolism (PE) and final diagnosis. □: all; ▨: surgical; ▩: nonsurgical.

Diagnostic work-up

A final diagnosis could be achieved by noninvasive tools in 70 (61%) patients (table 2). Lung scan was diagnostic in 33% of patients (high probability, 22; normal or near-normal lung scan, 16), and the diagnostic yield of lung scan was similar in the medical and surgical groups. The combination of a low clinical probability of PE and a low probability lung scan allowed excluding PE in 20 additional patients (17 in the medical group and three in the surgical group). In one case, a high clinical probability associated with a non-normal albeit nonhigh probability lung scan was considered indicative of PE. Therefore, the combination of lung scan with clinical probability of PE yielded a noninvasive diagnosis of PE in 51% of patients (58/114).

Leg vein US was positive in nine patients with a non-diagnostic lung scan (8% of the entire cohort). However, DVT was also diagnosed in five patients who had a high probability lung scan. Thus, the overall sensitivity of US was 38% (14/37), but it was significantly lower in the surgical (18%; 4/22) than in the medical group (67%; 10/15) ($p < 0.01$).

Only five patients had a DD $< 500 \mu\text{g}\cdot\text{L}^{-1}$ (specificity 7% (5/73)), of whom two had a normal lung scan, and one had a low clinical probability combined with a low probability lung scan. There was no false negative DD in this cohort.

In 44 (39%) patients, no definitive diagnosis could be reached by the noninvasive strategy, and a pulmonary angiography was required. This test was needed more frequently in the surgical (28/55) than in the medical group (16/59) ($p = 0.016$). This was mainly due to the higher proportion of patients in whom PE was ruled out by the combination of a low clinical probability and a low probability lung scan in the medical group (38 versus 10%).

Follow-up

Follow-up data could be obtained for all 114 patients. Overall, 11 (10%) patients died during the 3-month period, six in the group with PE and five in the group without PE. Among the 41 patients with PE, no major haemorrhage was recorded. Among the 73 patients considered without PE after the initial diagnostic work-up, none was suspected of a thromboembolic event during follow-up (3-month

thromboembolic risk: 0% (95% CI 0–4.9%). None of the five deaths in the patients without PE was ascribed to VTE: metastatic breast cancer ($n = 1$), pneumonia ($n = 2$), cardiac insufficiency ($n = 1$), and coronary heart disease ($n = 1$). Moreover, two of these patients had a normal pulmonary angiogram at the time of the initial diagnosis.

Discussion

This series assessed the efficacy of a primarily non-invasive diagnostic strategy for clinically suspected PE in hospitalized patients, *i.e.* patients whose hospital stay was motivated by a medical or surgical problem unrelated to VTE. In this distinct patient population, noninvasive instruments yielded a definitive diagnosis in 61% of patients. The diagnosis was established by lung scan in 33% of patients, clinical probability in 18%, detection of DVT by US in 8%, and plasma DD in only 2% (table 2). Submitting all patients with a nondiagnostic lung scan in this series to an angiogram would have required invasive testing in 67%, compared to only 39% when using non-invasive diagnostic tools. Thus, adding clinical probability assessment, US and DD to lung scan allowed 28% of angiograms to be spared, as compared to lung scan alone. Overall, this strategy appears slightly less efficient than when applied to outpatients, in whom only 25% of patients require an angiogram [7]. In particular, plasma DD measurement was virtually useless in hospitalized patients, owing to its very low specificity in that population.

Most strategies designed to diagnose PE start with a ventilation/perfusion lung scan. In the present population, the lung scan was diagnostic in 33% of patients, which is similar to the figures reported in previous studies focusing on outpatient populations [4, 6, 8, 20], in spite of the higher prevalence of comorbid conditions in hospitalized patients that could have reduced the proportion of normal or near-normal lung scans [21].

In the present study, as in previous studies [4, 6, 7, 13], clinical probability was assessed empirically on the basis of history, physical examination and tests such as blood gases, chest radiographs, and electrocardiogram, whenever available. Clinical assessment (fig. 2) proved to be more accurate for detecting patients with a low probability of PE than to identify those having the disease, in keeping with the results of the PIOPED study [4]. Clinical

Table 2. – Diagnosis of pulmonary embolism in the study population

	All n (%)	Surgical patients n (%)	Nonsurgical patients n (%)
Patients n	114	55	59
Pulmonary embolism			
High-probability lung scan	22 (19)	12 (22)	10 (17)
DVT on ultrasound	9 (8)	4 (7)	5 (8)
High clinical probability of PE + nondiagnostic lung scan	1 (1)	1 (2)	–
Positive angiogram	9 (8)	7 (13)	2 (3)
Total	41 (36)	24 (44)	17 (29)
No pulmonary embolism			
Normal/near-normal lung scan	16 (14)	7 (13)	9 (15)
D-dimer $< 500 \mu\text{g}\cdot\text{L}^{-1}$	2 (2)	–	2 (3)
Low clinical probability + low probability lung scan	20 (18)	3 (5)	17 (29)
Normal angiogram	35 (31)	21 (38)	14 (24)
Total	73 (64)	31 (56)	42 (71)

DVT: deep vein thrombosis.

evaluation of PE is of course not sufficiently reliable to be used alone. However, when combined with a low probability lung scan result, it allows ruling out of PE in patients who were categorized in the low clinical probability group [4, 6]. In this series, none of the 20 patients in whom PE was deemed excluded by this combination had a thromboembolic event during follow-up (3-month thromboembolic risk 0% (95% CI 0–16.8%)). However, due to the small size of this subgroup, caution is warranted in using this diagnostic criterion.

As surgery is considered an important risk factor for VTE, a low clinical probability of PE was expected to be rare in surgical patients. Indeed, in these patients, PE could be ruled out by a low clinical probability of PE and a nondiagnostic lung scan in only 5% of patients, compared to 29% in the medical group. Overall, the association of clinical probability with lung scan proved useful, allowing the exclusion of PE in an additional 19% of patients. In only one patient was the clinical probability considered high enough to diagnose PE in the presence of a nondiagnostic scan. This low yield, combined with the poor accuracy of clinicians in detecting the subgroup of patients in whom the prevalence of PE is truly >80% (fig. 2), should probably lead to this combination being abandoned as a diagnostic criterion.

Ultrasound examination of the leg veins to detect DVT, a technique available in most hospitals, has been included in various diagnostic strategies of PE [11, 22–24]. An examination limited to the proximal veins (*i.e.* common femoral and popliteal) has been advocated as a quick, simple, and reproducible method. It is highly specific and a positive result warrants anticoagulant treatment without resorting to angiography. In the present study, the overall sensitivity of US was 38% (95% CI 22–55%). This is slightly lower than in a previous study in outpatients (51% (95% CI 44–58%)) [6], although the difference is not statistically significant. Interestingly, the sensitivity of US was significantly lower in the surgical than in the medical group (18 *versus* 67%), possibly reflecting a higher proportion of distal DVT in the surgical population that remain undetected with the US technique used.

Several studies have already highlighted the fact that most patients with comorbid conditions and/or inpatients have a DD higher than the cut-off value, thus questioning its usefulness in excluding PE [14, 19, 25]. This is due to the variety of conditions which cause an activation of the coagulation and fibrinolysis processes, such as inflammation, infection, tissue necrosis, and cancer. This limitation is confirmed by the present study, in which DD was <500 $\mu\text{g}\cdot\text{L}^{-1}$ in only 5/73 (7%) patients, of which three already had a definitive diagnosis reached by lung scan and clinical probability. Consequently, it is believed that DD measurement, at least by the ELISA technique, is of very limited utility, if any, in hospitalized patients with suspected PE. Whether newer latex or agglutination assays [14], which have a slightly higher baseline specificity than the ELISA assay, would be more useful in this patient population remains to be demonstrated.

None of the 73 patients in whom the strategy ruled out PE, experienced a thromboembolic event during the 3-month formal follow-up. Of the five patients who died in this group, no death was attributed to VTE. Hence, the thromboembolic risk was low (0%, 95% CI 0–4.9%) and comparable to that observed in other studies [6, 8]. The

confidence interval is, however, somewhat wide, owing to the small size of the study.

The main limitation of this series is the small number of patients. Moreover, 21% of the eligible patients were excluded from the study, and the conclusions do not apply to such patients. Two years were necessary to collect the present series of 114 consecutive inpatients with clinically suspected PE, whereas suspected PE in outpatients is encountered ~400-times each year in the authors' hospital, an urban 1,500-bed facility. It can only be speculated whether this lower incidence of clinically suspected PE in inpatients in this institution is due to the efficiency of DVT prophylaxis (given to 75% of the inpatients), to a too low index of suspicion by the physicians on the ward, or to the fact that clinical suspicion of VTE often occurs after patients have left the hospital, especially in the surgical group.

In summary, the present study demonstrates that non-invasive diagnosis of pulmonary embolism can be established by lung scan, clinical probability of pulmonary embolism and ultrasonography in 61% of hospitalized patients, thereby sparing 28% of pulmonary angiograms. This approach appears to be safe, although this should be confirmed by further studies. It also shows that diagnostic tests have different performances and clinical usefulness when applied to inpatients as opposed to outpatients. Thus, the very low specificity of the D-dimer in inpatients renders this test almost useless for evaluation of thromboembolic disease in that population. Moreover, pulmonary angiography, an invasive test that physicians are often reluctant to perform, is still needed in ~40% of inpatients. Further research is thus needed to develop and critically evaluate new, promising diagnostic instruments, such as spiral computed tomography scan, and to determine the best sequence of examination when pulmonary embolism is suspected in a hospitalized patient.

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