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NONINVASIVE DIAGNOSIS OF PULMONARY EMBOLISM

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ABSTRACT

Background and Objective. Pulmonary embolism (PE), with an incidence of 23 per 100,000 patients per year, is a frequent clinical problem, responsible for 200,000 deaths each year in the United States. Pulmonary angiography, the gold standard for diagnosing PE, is invasive, costly and not universally available. Moreover, PE is confirmed in only approximately 30% of patients in whom it is suspected, rendering noninvasive screening tests necessary. Several strategies have been recently proposed to reduce the need for pulmonary angiography in the diagnostic workup of pulmonary embolism. The objective of this article is to analyze the individual performance of the new diagnostic instruments and their combination in rational diagnostic strategies.

Methods. The author has been working in this field and has contributed original papers on diagnosis of pulmonary embolism and cost-effectiveness of noninvasive diagnostic tests. In addition, the material examined in this article includes articles published in the journals covered by the Science Citation Index® and Medline®.

Results. Several strategies have been recently proposed to reduce the need for pulmonary angiography in the diagnostic workup of pulmonary embolism. The PIOPED study has established the value of ventilation-perfusion lung scan, a normal perfusion lung scan virtually ruling out PE, whereas a high probability lung scan is considered diagnostic in face of reasonable clinical suspicion. All other lung scan results are nondiagnostic. However, clinical evaluation, although insufficiently accurate to yield a definitive diagnosis, is probably reliable enough to be used for estimating pretest probability of PE. The combination of a low clinical probability of PE and a so-called low probability lung scan yields a very low posttest probability of PE, thus foregoing the need for pulmonary angiography. Other useful instrument in patients with nondiagnostic scans is plasma D-dimer (DD) measurement (ELISA assay), which when under a cutoff value of 500 µg/L potentially exclude PE, due to high sensitivity (97%). Conversely, venous compression ultrasonography of the lower limbs (US) is highly specific (98%) for deep vein thrombosis (DVT), and disclosing a DVT warrants anticoagulant treatment without resorting to angiography. The potential role of echocardiography is also discussed. The rational sequence of noninvasive tests is currently under discussion. Performing D-dimer and US before lung scan may be the most cost-effective strategy, pulmonary angiography being performed only in case of an inconclusive noninvasive workup.

Interpretation and Conclusions. Even though PE remains a difficult diagnostic challenge, the availability of novel noninvasive tests (plasma D-dimer and ultrasonography of the lower limbs) and the rehabilitation of clinical assessment allow a more rational and sparse prescription of pulmonary angiography. More work needs to be done to assess test performances and refine diagnostic strategies in distinct patient subgroups, particularly those hospitalized. Screening patients with plasma D-dimer and ultrasonography of the lower limbs may be the most cost-effective strategy, at least in outpatients.

Key words: pulmonary embolism, diagnosis

Pulmonary embolism (PE), with an incidence of 23 per 100,000 patients per year, is a frequent clinical problem, responsible for 200,000 deaths each year in the United States.[1,2] Pulmonary angiography, the gold standard for diagnosing PE,[3] is invasive, costly and not universally available.[4] Moreover, PE is confirmed in only approximately 30% of patients in whom it is suspected, rendering noninvasive screening tests necessary. Significant progress has been made in recent years in this respect. The value of lung scan has been firmly established.[3,5] Investigation of the lower limb deep venous system by plethysmography or compression ultrasonography has been

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incorporated in most diagnostic strategies for PE,[6] and the usefulness of plasma D-Dimer measurement for excluding PE is being increasingly recognized.[7] Clinical evaluation for establishing pretest probability of PE may allow further reduction in the number of angiograms necessary.[3,8] Lastly, several decision analyses have evaluated the cost-effectiveness of noninvasive strategies.[9,10] The individual performance of these diagnostic instruments and their combination in rational diagnostic strategies will be discussed.

Lung scan

The contribution of ventilation-perfusion lung scan has been extensively studied. A normal or near-normal lung scan reasonably rules out PE, whereas a high probability pattern has a high positive predictive value for PE (96%), and is usually considered diagnostic of PE, in face of reasonable clinical suspicion.[3] In patients with a low or intermediate probability pattern, the prevalence of PE varies between 4-30%, and such scintigrams should be considered nondiagnostic. Using such criteria, lung scan is diagnostic in approximately 30-50% of patients,[3,5] the remainder having inconclusive results. More recently, one study has found a high positive predictive value of single or multiple wedge-shaped perfusion defects,[11] challenging contribution of ventilation scans; this finding has yet to be confirmed.[11]

Clinical evaluation

Clinical assessment of patients with suspected PE is notorious for its inaccuracy, due to lack of sensitivity and specificity of symptoms, signs, and findings on routinely available tests such as EKG, blood gases and chest roentgenogram. Although this holds true for individual clinical and paraclinical findings in suspected PE, several studies have shown that these variables, when combined either empirically[3,8,12] or by prediction scores,[12,13] may allow an accurate estimate of the pretest likelihood, or clinical probability, of PE.

Indeed, in a recent management study,[8] PE was present in only 14% of the patients with a low clinical probability (0-19%), against 84% of patients with a high clinical probability (> 80%). It has been proposed that angiography be withheld in patients with both a low clinical probability of PE and a low probability lung scan,[3] since this combination results in a very low posttest probability of PE (0-7%). In the aforementioned management trial,[8] 48 patients had this combination and were discharged without anticoagulant treatment. None had a thromboembolic event during the 6-month follow-up period. In summary, clinical estimate of the probability of PE from history, physical examination and a few simple paraclinical tests may identify the patients with a low likelihood of the disease; for them, no further tests are necessary, in case of a low probability lung scan.

Examination of the lower limbs

In 90% of cases, PE originates from a deep venous thrombosis (DVT) of the lower limbs. Moreover, finding a DVT in a patient with suspected PE warrants anticoagulant treatment without resorting to pulmonary angiography. Consequently, systematic examination of the lower limbs in patients with suspected PE is rational, and has been rendered possible by the development of effective noninvasive diagnostic tests for proximal DVT. A number of studies resorted to impedance plethysmography.[6] However, recent trials in DVT diagnosis have demonstrated that the sensitivity of this test was considerably lower for proximal DVT (65%) than previously shown,[13,14] and direct comparison between plethysmography compression ultrasonography (US) established the latter higher sensitivity (approximately 95%).[14]

Recently, our group assessed the proportion of patients with PE in whom US could diagnose a DVT in a cohort of 308 consecutive patients presenting with suspected PE in the emergency ward.[8] A DVT was found in 66 of 109 patients with PE, yielding an overall sensitivity of 61%, with a specificity of 97%. Interestingly, the diagnostic yield was slightly lower (48%) in patients with a nondiagnostic lung scan, due to the higher proportion of patients with a positive US in cases of a high probability lung scan (70%). It should be noted that the performance of US in hospitalized patients with suspected PE has not yet been assessed. US is cost-effective,[9,10] and could be performed before lung scan, especially in unstable or difficult-to-transport patients, a frequent situation in the ICU. Due to low sensitivity (61%), a negative US would not rule out PE, and another test should be performed, but finding a DVT would allow treatment without further testing.[6,8]

Plasma D-dimer measurement

D-Dimer (DD) is a crosslinked fibrin degradation product, resulting from activation of the coagulation and fibrinolysis processes. When assayed by an ELISA method, DD has proven highly sensitive (97%) for diagnosing acute venous thromboembolism, above a cutoff value of 500 µg/L.[7] Thus, a negative DD (i.e. below the cutoff value) has a high negative predictive value for DVT and PE. In contrast, DD has poor specificity (45%) due to the number of conditions activating coagulation (inflammatory processes, neoplasms, etc.), so that a positive DD is virtually useless for positive diagnosis. In the management trial already referred to above,[8] none of the 100 patients with a negative

DD, who were discharged and not anticoagulated, had a thromboembolic event during a 6-month follow-up.

Noteworthy limitations of DD are the necessity of an ELISA assay, ill-suited for emergency situations, and a lower specificity in hospitalized patients, hence a lower utility because of the lower number of patients without PE in whom DD is negative. Novel whole blood latex assays or automated ELISA-derived methods seem promising in order to increase availability of DD measurement in emergency situations.

Other noninvasive tests

Several other imaging procedures such as spiral CTscan and MRI are currently being investigated, but their contribution to PE diagnosis is not yet well established. Transthoracic echocardiography deserves to be mentioned, showing indirect repercussions of PE, such as pulmonary hypertension (estimated from velocity tricuspid regurgitation velocity), and its hemodynamic consequences (right ventricular dilatation, abnormal septal motion, etc.). It also serves the purpose of differentiating between PE and other diseases such as pericardial tamponade, cardiogenic shock, or aortic dissection.

A recent small matched case-control study reported a sensitivity of 67% and a specificity of 97% for a right ventricle/left ventricle ratio > 0.6.[15] Specificity is of course highly dependent on the existence of previous causes of pulmonary hypertension, a common occurrence in emergency ward or ICU patients. However the combination of an abnormal, although nondiagnostic lung scan, and findings suggestive of pulmonary hypertension in a patient without preexisting cardiopulmonary disease may be sufficient evidence of PE to warrant treatment without angiographic confirmation, especially in high risk patients. Reports of direct visualization of clots in the right heart chambers or pulmonary arteries are anecdotal, except with transoesophageal echocardiography, a technique the use of which is limited by its relatively invasive character.

Diagnostic strategies

All proposed strategies have in common the resort to serial noninvasive tests, pulmonary angiography being performed only in patients with an inconclusive noninvasive workup. The choice and sequence of noninvasive tests is usually determined by their availability in a particular clinical setting. A diagnostic strategy is proposed in Figure 1. This strategy is based on a decision analysis suggesting that performing DD and US before lung scan is the most cost-effective strategy.[10] Moreover, such a strategy would allow screening patients in centers devoid of nuclear medicine and/or angiographic facilities. In this strategy, patients with a normal DD (below 500 mg/L by an ELISA assay), would not be treated without further testing, and the diagnosis of PE would be abandoned. This would be found in approximately 30% of outpatients. Patients with an abnormal DD level would proceed to US, which, when disclosing a deep vein thrombosis (20% of patients), would warrant anticoagulant treatment. Due to its low negative predictive value, a negative US should be followed by another test, preferably lung scan if available. A normal lung scan would rule out PE; a high probability lung scan would establish the diagnosis, yielding a definitive diagnosis in another 16% of patients. The remaining 31% of patients would undergo angiography and be treated accordingly.

This strategy remains valid if one or another noninvasive test are not available. For instance, in a center devoid of the DD ELISA assay, the strategy

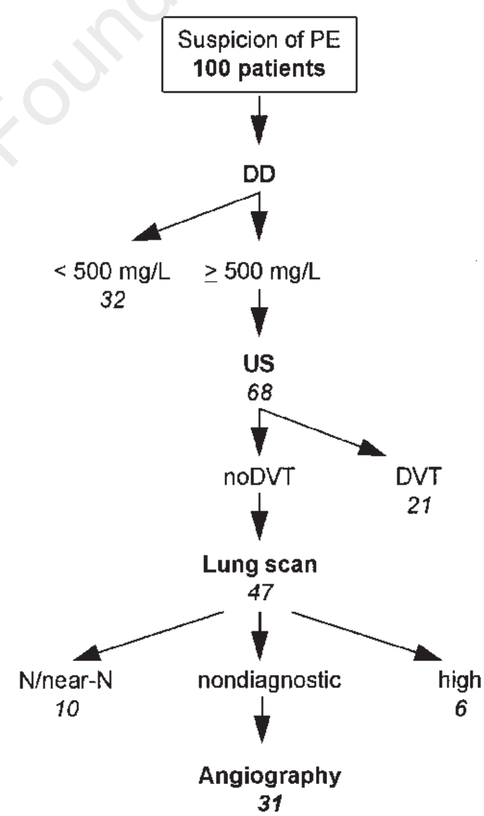

Figure 1. Noninvasive diagnosis of pulmonary embolism. In this hypothetical cohort of 100 outpatients with a 35% prevalence of pulmonary embolism (PE), only 47 patients would undergo lung scan and angiography would be performed in 31.
DD: D-Dimer. US: lower limb venous compression ultrasonography. DVT: deep vein thrombosis. N/near-N: normal/near-normal.

would start with US. If an institution were equipped with DD, US and angiography, but not with lung scan, all patients with an abnormal DD and an US not showing DVT would proceed to angiography. Finally, if a decision must be taken in the absence of any of the afore mentioned tests, most patients with a clinical suspicion of PE should be anticoagulated. Indeed, due to the high mortality of untreated PE (30%) and the low mortality of a 3-month anticoagulant treatment (0.25 to 0.8%), it can be shown by decision analysis that all patients with a clinical probability of PE above 15% should be anticoagulated.[2]

Conclusions

Event though PE remains a difficult diagnostic challenge, the availability of novel noninvasive tests (DD and US) and the rehabilitation of clinical assessment allow a more rational and sparse prescription of pulmonary angiography.

More work needs to be done to assess test performances and refine diagnostic strategies in distinct patient subgroups, particularly hospitalized and patients. Screening patients with DD and US may be the most cost-effective strategy, at least in outpatients.

References

1. Ascari E, Siragusa S, Piovella F. The epidemiology of deep vein thrombosis and pulmonary embolism. Haematologica 1995; 80(suppl):36-41.
2. Perrier A, Junod A. Has the diagnosis of pulmonary embolism become easier to establish? Resp Med 1995; 89:241-51.
3. The PIOPED Investigators. Value of the ventilation-perfusion scan in acute pulmonary embolism. JAMA 1990; 263:2753-9.
4. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation 1992; 85:462-8.
5. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985; 88:819-28.
6. Hull RD, Raskob GE, Ginsberg JS, et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. Arch Intern Med 1994; 154:289-97.
7. Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism : an overview. Thromb Haemost 1994; 71:1-6.
8. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis based strategy including clinical probability, D-dimer and ultrasonography: a management study. Arch Intern Med 1996; 156:531-5.
9. Oudkerk M, van Beek JR, van Putten WLJ, Büller HR. Cost-effectiveness analysis of various strategies in the diagnostic management of pulmonary embolism. Arch Intern Med 1993;153:947-54.
10. Perrier A, Buswell L, Bounameaux H, et al. Noninvasive diagnostic aids are cost-effective in the diagnosis of suspected pulmonary embolism. Arch Intern Med 1997; in press.
11. The PISA-PED Investigators. Invasive and noninvasive diagnosis of pulmonary embolism. Preliminary results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PEDR) [abstract]. Chest 1995; 107:33S-38S.
12. Celi A, Palla A, Petruzzelli S, et al. Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. Chest 1989; 95:332-7.
13. Ginsberg JS, Wells PS, Hirsh J, et al. Reevaluation of the sensitivity of impedance plethysmography for the detection of proximal deep vein thrombosis. Arch Intern Med 1994; 154:1930-3.
14. Heijboer H, Büller HR, Lensing AWA, Turpie AGG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 1993; 329:1365-9.
15. Nazeyrollas P, Metz D, Chapoutot L, et al. Diagnostic accuracy of echocardiography-Doppler in acute pulmonary embolism. Int J Cardiol 1995;47:273-80.
16. Sie P. The value of laboratory tests in the diagnosis of venous thromboembolism. Haematologica 1995; 80(suppl):57-60.
17. Hull RD, Feldstein W, Stein PD, Pineo GF. Cost-effectiveness of pulmonary embolism diagnosis. Arch Intern Med 1996; 156:68-72.