

Usefulness of Fast ELISA Determination of D-Dimer Levels for Diagnosing Pulmonary Embolism in an Emergency Room

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OBJECTIVE: To determine the sensitivity and negative predictive value of D-dimer levels measured by fast enzyme-linked immunoabsorbent assay (ELISA) in pulmonary embolism.

PATIENTS AND METHODS: Prospective study of consecutive patients with suspicion of pulmonary embolism attended in the Emergency Room of the Hospital de la Princesa in Madrid, Spain. Thromboembolism was diagnosed with an algorithm established in the hospital, and D-dimer levels were determined by fast ELISA (VIDAS D-dimer Assay) in each patient suspected of pulmonary embolism. Patients with negative findings from a test not considered a reference method for thromboembolism were followed for 3 months.

RESULTS: Of 132 patients with clinical suspicion, 28 (21.2%) were positive and 104 (78.7%) were negative for embolism. D-dimer levels were below 0.5 µg/mL in 31 patients, 30 of whom did not have pulmonary thromboembolism whereas 1 did. D-dimer levels were above 0.5 µg/mL in 101 patients; thromboembolism did not occur in 74 of these but was reported in the remaining 27. For a value of 1 µg/mL, 66 patients had values below the cut off, 3 of whom presented pulmonary embolism. The remaining 66 patients had D-dimer levels above or equal to 1 µg/mL; 25 of them had a positive diagnosis for embolism and 41 had a negative diagnosis. Sensitivity and negative predictive values were 96.4% (95% confidence interval [CI], 79.8%-99.9%) and 96.8% (95% CI, 81.5%-98.8%), respectively, at a cut off of 0.5 µg/mL; and 89.2% (95% CI, 70.6%-97.2%) and 95.45% (95% CI, 86.4%-98.8%), respectively, at a cut off of 1 µg/mL.

CONCLUSIONS: In an emergency room, thromboembolism can be excluded if plasma levels of D-dimer measured by fast ELISA are below 0.5 µg/mL because of the high negative predictive value at this cut off.

Key words: Pulmonary embolism. Thromboembolic disease. D-dimer.

Utilidad del dímero-D por ELISA rápido en el diagnóstico de la embolia pulmonar en un servicio de urgencias

OBJETIVO: Determinar la sensibilidad y el valor predictivo negativo del dímero-D, por enzimoanálisis (ELISA) rápido, en la embolia pulmonar.

PACIENTES Y MÉTODOS: Estudio prospectivo de pacientes atendidos consecutivamente por sospecha clínica de embolia en el Servicio de Urgencias del Hospital de la Princesa de Madrid. El diagnóstico de tromboembolia se basó en el algoritmo establecido en el hospital, y se determinó el dímero-D por ELISA (VIDAS) en cada paciente con sospecha de embolia pulmonar. A los pacientes con resultado negativo para tromboembolia, establecido por una prueba no considerada de referencia, se les realizó seguimiento clínico a los 3 meses.

RESULTADOS: De 132 pacientes con sospecha clínica, 28 (21,2%) fueron positivos y 104 (78,7%) negativos para embolia. El dímero-D fue < a 0,5 µg/ml en 31 pacientes, de los que 30 no tuvieron tromboembolia pulmonar y 1 sí la tuvo. De los 101 pacientes con dímero-D > 0,5 µg/ml, en 74 no se produjo tromboembolia y en 27 sí.

Si se considera como punto de corte 1 µg/ml, hubo 66 pacientes con valores inferiores, de los que 3 presentaron embolia pulmonar. Otros 66 pacientes mostraron un dímero-D ≥ 1 µg/ml; de ellos, 25 tuvieron un diagnóstico positivo para embolia y 41 negativo. La sensibilidad y el valor predictivo negativo para 0,5 µg/ml fue de 96,4 (intervalo de confianza [IC] del 95%, 79,8-99,9) y 96,8 (IC del 95%, 81,5-98,8), respectivamente; para 1 µg/ml fue de 89,2 (IC del 95%, 70,6-97,2) y 95,45 (IC del 95%, 86,4-98,8), respectivamente.

CONCLUSIONES: Los valores de dímero-D plasmático, determinados por la técnica de ELISA rápido (VIDAS), < 0,5 µg/ml permiten excluir con alto valor predictivo negativo una tromboembolia pulmonar en un servicio de urgencias.

Palabras clave: Embolia pulmonar. Enfermedad tromboembólica. Dímero-D.

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Introduction

Pulmonary embolism is a common condition whose diagnosis in emergency rooms remains problematical.¹ Clinical data and conventional chest x-rays are usually

not sufficiently specific for diagnosis. Lung scintigraphy has been one of the imaging techniques most widely used in patients with clinical suspicion of pulmonary embolism,² but although the technique is highly sensitive, it lacks specificity. In the last 10 years, spiral computed tomography (CT) has become an alternative in view of the problems of specificity of ventilation-perfusion scintigraphy.³ The sensitivity and specificity of spiral CT range from 53% to 100% and from 81% to 100%, respectively, when lung scintigraphy or pulmonary arteriography are used as reference methods.⁴⁻⁶ Spiral CT has been included in a number of diagnostic protocols that combine a series of tests in cases of clinical suspicion of thromboembolism. These protocols involve stratification of clinical risk, and also measurement of D-dimer plasma levels, Doppler ultrasound of lower limbs, and pulmonary arteriography.⁷⁻⁹

The negative predictive value of D-dimer levels has been reported to be high for ruling out a diagnosis of thromboembolic disease,^{3,7} but the positive predictive value is very low as D-dimer levels can also be elevated in venous thromboembolic disease and other disease processes such as heart failure, surgery, infections, connective tissue disorders, and cancer.^{10,11} The diagnostic value of D-dimer measurement is affected by many variables (particularly comorbidity, sedentary lifestyle, outpatient or hospital patient, thrombus size, anticoagulant therapy, and time between the event and D-dimer measurement) and the type of D-dimer assay used.⁷ The traditional latex agglutination assay has fallen into disuse because of its lower sensitivity compared to other methods; turbidimetric techniques and enzyme-linked immunoabsorbent assay (ELISA) techniques are the most sensitive, whereas the usefulness of the SimpliRED assay is still under debate.¹¹ Our study aims to establish the sensitivity and negative predictive value of D-dimer levels measured by a fast ELISA assay for diagnosis of pulmonary thromboembolism in the emergency room.

Patients and Methods

A prospective study of consecutive patients attended between September 2002 and July 2003 in the Emergency Room of the Hospital de la Princesa in Madrid with clinical suspicion of pulmonary embolism was conducted.

Study Design

The study included patients who presented with symptoms suggesting pulmonary embolism. Inclusion criteria were as follows: clinical suspicion of thromboembolism in patients attended in the emergency room, age over 18 years old, and measurement of D-dimer levels at the time of admission. Patients were excluded in the following instances: pregnancy, age under 18 years old, anticoagulant therapy, 3-month clinical follow-up not possible, and refusal to give informed consent for the tests or withdrawal of informed consent. The treating physician classified each patient according to pretest clinical probability (low, medium, high)⁸ and requested diagnostic tests for pulmonary thromboembolism according to

the workup established at the Hospital de la Princesa by the Venous Thromboembolic Disease Working Group (Figure 1). The diagnostic tests included in this workup were chest x-ray, perfusion scintigraphy, venous ultrasound of lower limbs, spiral CT, and pulmonary arteriography.

Patients diagnosed with pulmonary embolism by any of these tests were put on anticoagulant therapy. Those with negative findings in tests not considered a reference method (negative on venous ultrasound of the lower limbs combined with low clinical probability, low-probability lung perfusion scan, or a negative spiral CT) were observed for 3 months. The patient was considered as positive for pulmonary embolism if thromboembolic venous events occurred in this period. If the findings of the perfusion scan or pulmonary arteriography were normal, diagnosis of pulmonary embolism was ruled out, and patients neither received treatment nor were scheduled for further follow-up.

The protocol for this study was approved by the ethics committee of our hospital. Informed consent was not required, except for normal diagnostic procedures (spiral CT, lung scintigraphy, and arteriography).

D-Dimer Measurement

Plasma D-dimer levels were determined initially in all patients by the VIDAS[®] D-dimer technique (bioMérieux, Lyon, France), a double-sandwich enzyme-linked fluorescent assay. Concentrations were expressed in micrograms per milliliter of equivalent units of fibrinogen. The time between determination of D-dimer levels and imaging tests did not exceed 24 hours in any patient.

Clinical Follow-up

Patients who were considered negative for pulmonary embolism based on ultrasound images of the lower limbs, had a low-probability in lung perfusion scan or spiral CT, and those who were not put on anticoagulant therapy were assessed after 3 months. In this assessment, the medical history of the patient was recorded, and if this was not possible, the patient's family physician was contacted or the patient or family members were called by telephone. The appearance of possible signs and symptoms of venous thromboembolic disease or initiation of anticoagulant therapy was investigated. Other authors have described the same approach or a similar one for clinical follow-up in other studies.^{12,13}

A patient was considered to have thromboembolic disease when deep vein thrombosis was diagnosed in individuals with symptoms of pulmonary embolism, when the perfusion scan, spiral CT, or pulmonary arteriography was positive, or when events related to thromboembolic disease were reported during the 3 months of clinical follow-up (venous thrombosis or pulmonary embolism).

A patient was considered free of thromboembolic disease when the perfusion scan was normal or indicated low probability in patients with low clinical probability and with negative clinical follow-up, when 2 venous ultrasound examinations (initially and at 7 days) were negative in patients with low clinical probability and clinical follow-up at 3 months was negative, or when spiral CT was negative and clinical follow-up at 3 months was also negative, or when pulmonary arteriography was negative. When CT was inconclusive, the patient was reassessed and further diagnostic tests were requested. Clinical follow-up of 3 months was done in cases where the patient was considered

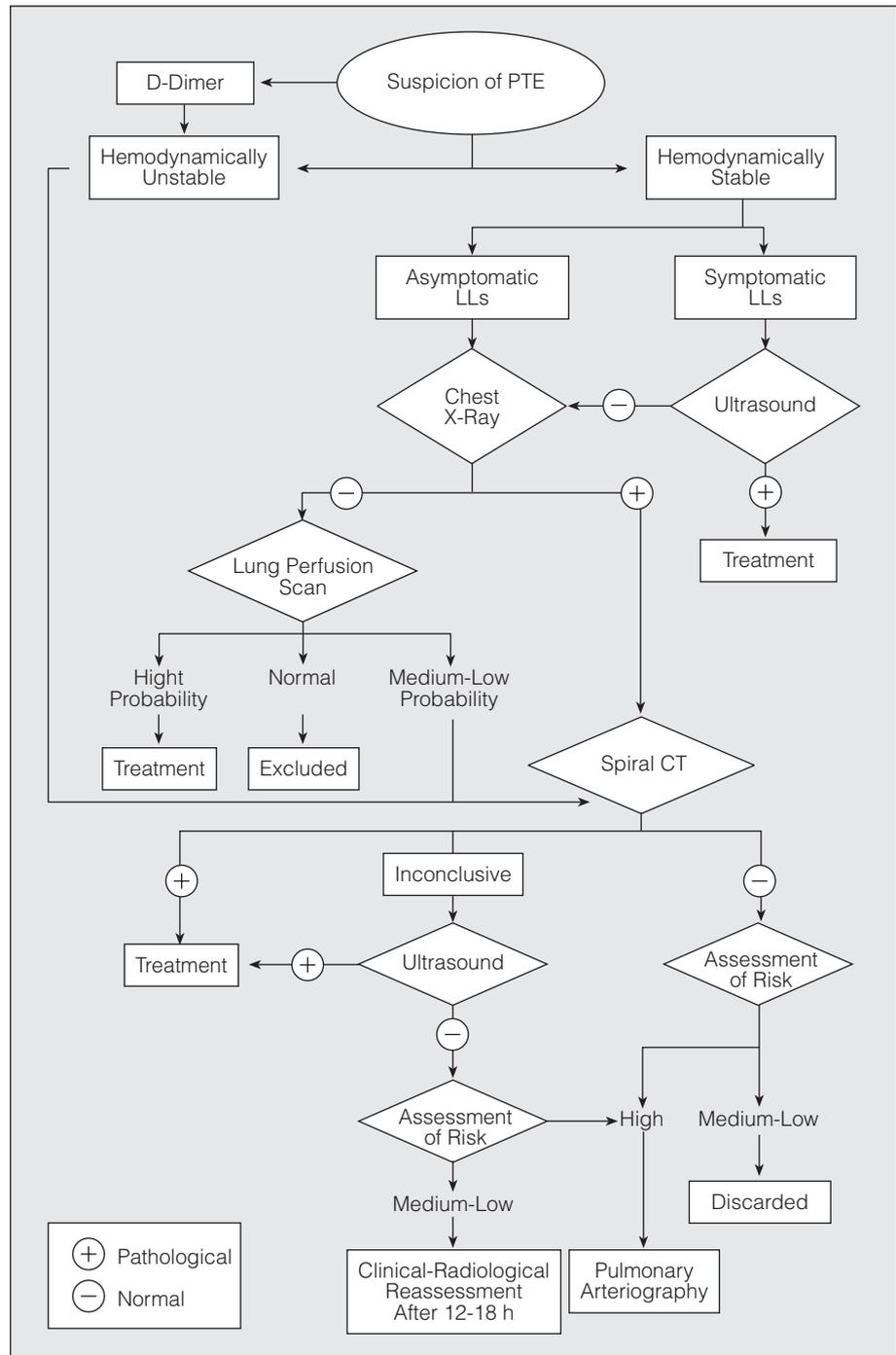


Figure 1. Flow diagram of the initial diagnostic workup for pulmonary thromboembolism (PTE) established by the Venous Thromboembolic Disease Working Group at the Hospital de la Princesa. D-dimer levels were analyzed for subsequent validation. LLs indicates lower limbs; CT, computed tomography.

negative. Patients who died were considered negative for thromboembolic disease provided emboli were not detected in the postmortem and provided the cause of death was not related to venous thromboembolic episodes.

Statistical Analysis

Means and SD were calculated with Excel (Microsoft, 2000). To calculate confidence intervals, we used the Confit program included in the Pepi software, version 3.0 (JH Abramson & PM Gahlinger, 1993-99, Salt Lake City, Utah,

USA). Sensitivity and specificity were determined for different D-dimer cutoff levels from a curve of diagnostic yield. The negative predictive values were obtained using the EPIDAT program, version 2.1 for Windows (April 1998, Xunta de Galicia, Spain).

Results

During the 10-month study period, 132 patients had suspected pulmonary thromboembolism. Of these, 77 were women (58.3%) and 55 were men (41.7%), and

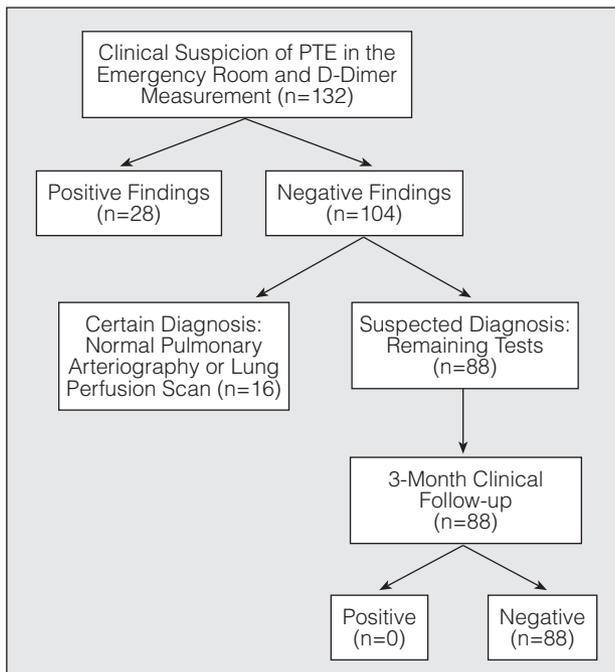


Figure 2. Flow diagram of actions taken in the 132 patients studied in the emergency room due to clinical suspicion of pulmonary thromboembolism (PTE).

their mean (SD) age was 66.7 (17.7) years. Diagnosis of pulmonary embolism was confirmed in 28 patients (21.2%) and negative in 104 patients (78.8%). Of the 28 positive patients, diagnosis was by CT in 23, by a high-probability perfusion scan in 3, by ultrasound detection of venous thrombosis in the lower limbs in 1 patient, and by positive pulmonary arteriography in 1 patient. Of the 104 negative patients, diagnosis was definitively ruled out by a normal perfusion scan or negative pulmonary arteriography in 16 patients.

Three of the remaining 88 patients negative for pulmonary embolism were classed as low clinical probability and also had low-risk lung perfusion scans. In 1 low-probability patient, initial venous ultrasound findings and clinical observations at the repeat examination 1 week later were negative. Of the 84 patients who underwent CT, negative findings were reported in 79. In 5 patients of low and medium clinical probability, CT was not conclusive for embolism due to poor vascular definition or respiratory movements. In 2 of these patients, the clinical signs and symptoms could be explained by an alternative diagnosis, namely, pleuropericarditis in 1 and hilar tumor in the other. In the remaining 3 patients, the study was completed by venous ultrasound of lower limbs, with negative findings. The negative diagnosis in these 88 patients was confirmed after 3 months of clinical follow-up. No patients were lost to follow-up, and no episodes of venous thromboembolism were reported. These findings are summarized in Figure 2.

Five patients died during clinical follow-up. Four of them had undergone spiral CT examinations, with

negative findings in 3 and inconclusive findings in the other patient. The following causes of death were reported for patients with negative findings: multiorgan failure in 1 patient, in whom thromboembolism or venous thrombosis was ruled out in the postmortem examination; stroke in 1 patient who presented with hypercapnic coma and pneumonia; and cardiorespiratory arrest in 1 patient with atrial fibrillation and heart failure. The patient with an inconclusive study died of advanced lung cancer with liver metastasis. The remaining patient, aged 68 years old, was asthmatic and had a low clinical probability of embolism, which was ruled out by a low-probability perfusion scan. She died the following day due to bronchospasm.

D-Dimer Results

D-dimer levels were less than 0.5 µg/mL in 31 patients, 30 of whom did not have pulmonary embolism whereas 1 did. D-dimer levels were greater than 0.5 µg/mL in 101 patients; thromboembolism did not occur in 74 of these but was reported in the remaining 27. Sixty-six patients had values below the cutoff of 1 µg/mL; 3 of them presented pulmonary embolism. The remaining 66 patients had D-dimer levels greater than or equal to 1 µg/mL; 25 of them had a positive diagnosis for embolism and 41 had a negative diagnosis. These findings are presented in the Table, along with the sensitivity and negative predictive value for these 2 cutoff points.

Discussion

Pulmonary embolism is an important and common condition that is hard to diagnose in an emergency room. Symptoms are often nonspecific, atypical, or masked by other associated diseases.^{1,14} Lung scintigraphy is very sensitive but has low specificity. When findings are normal, pulmonary embolism can be ruled out, but perfusion scans considered to indicate medium or low probability may fail to identify a large number of patients with pulmonary embolism, in fact, as many as 60% of the studies may not lead to diagnosis, in which case additional tests are required.^{2,3} Kutinsky et al¹⁵ showed that only 1 out of 98 perfusion scans in patients with suspected pulmonary embolism was normal. Of 6 patients with high-probability perfusion scans, pulmonary arteriography was normal in 5. In the remaining 91 patients, the findings did not lead to diagnosis. A number of authors have assessed a variety of diagnostic strategies for use when confronting clinical suspicion of pulmonary embolism. These include determining a pretest clinical probability, lung scintigraphy, venous ultrasound of lower limbs, spiral CT, pulmonary arteriography, and, recently, measurement of plasma D-dimer levels.^{8,14}

The Venous Thromboembolic Disease Working Group was set up in our hospital in 1999, and diagnostic workups were established for both venous thrombosis and pulmonary embolism. Figure 1 shows the protocol

TABLE
Relationship Between Plasma D-dimer Levels, the Group of Clinical Probability to Which the Patient Belongs, and Whether Pulmonary Thromboembolism is Present*

D-Dimer Level, µg/mL	Clinical Probability	Positive Patients	Negative Patients	All Patients	Sensitivity (95% CI)	NPV (95% CI)
<0.5	High	1	8	9	96.4% (79.8-99.8)	96.8% (81.5-98.8)
	Medium	0	13	13		
	Low	0	9	9		
	Total	1	30	31		
≥0.5	High	6	11	17	96.4% (79.8-99.8)	96.8% (81.5-98.8)
	Medium	16	39	55		
	Low	5	24	29		
	Total	27	74	101		
<1	High	1	13	14	89.3% (70.6-97.2)	95.4% (86.4-98.8)
	Medium	2	31	33		
	Low	0	19	19		
	Total	3	63	66		
≥1	High	6	6	12	89.3% (70.6-97.2)	95.4% (86.4-98.8)
	Medium	14	21	35		
	Low	5	14	19		
	Total	25	41	66		

*CI indicates confidence interval; NPV, negative predictive value.

for pulmonary thromboembolism. Initially, measurement of D-dimer levels was not considered part of the process for establishing or discarding a diagnosis and was only done to provide reference values for our center. Once validated, measurement of D-dimer levels was incorporated into the workup as an initial test for ruling out thromboembolic disease. Our diagnostic algorithm differs from the one proposed by Perrier et al,⁷ who systematically perform venous ultrasound of lower limbs even in patients with no symptoms of venous thrombosis. We, on the other hand, only use this diagnostic technique in symptomatic patients. In addition, these authors, unlike us, do not use lung scintigraphy.

The D-dimer is a fibrin degradation fragment and can be measured in peripheral blood. D-dimer levels are almost always elevated in thromboembolic disease. A variety of detection methods are available, and results are also variable. Latex agglutination assays, including the second generation ones, have proved to have low sensitivity for reliably ruling out pulmonary thromboembolism.¹⁰ Traditional ELISA techniques are highly sensitive but complex and time consuming, and so they are not very practical in an emergency room.^{7,16-19} Semiquantitative latex agglutination assays are rapid, simple, and cheaper, but sensitivity is limited (83%) and the negative predictive value for pulmonary embolism is 90%.¹⁰ Such techniques are therefore not recommended as a test for reliably excluding diagnosis of pulmonary embolism.^{3,10,19} Some authors have reported the fast ELISA technique (VIDAS) as a rapid, quantitative, automatic method that uses single-dose reagents prepared for immediate use.^{7,18,20-22} According to recent studies, D-dimer levels measured by fast ELISA techniques have a high negative predictive value for deep vein thrombosis.^{16,17} These studies also suggest that these techniques can be useful for reliably ruling out

deep vein thrombosis when used as an initial screening test. Measurement of D-dimer levels by fast ELISA techniques should therefore also be useful for assessing patients with clinical suspicion of pulmonary embolism, although such tests are less definitive because they may lead to underdiagnosis of thrombosis.⁸

Fast ELISA (VIDAS), a sandwich immunoenzymatic method, is used in our hospital. The advantage of this method is that it is easy to use and fast, interlaboratory variation is low, and sensitivity for detecting thromboembolic disease is high.^{7,8,17,18,21} Our working group has reported a sensitivity of 98% and a negative predictive value of 98.6% for deep vein thrombosis with measurement of D-dimer levels by the VIDAS technique. The high associated negative predictive value allows diagnosis of deep vein thrombosis to be reliably discarded. In the case of pulmonary embolism, the findings are less clear because the risk of diagnostic error is higher. For D-dimer levels less than 0.5 µg/mL measured with this same technique, Kruij et al²¹ did not detect thromboembolic complications during the clinical follow-up of patients with clinical suspicion of thromboembolism and with low clinical probability.

Other studies of pulmonary thromboembolism with the VIDAS fast ELISA technique have shown a sensitivity of 98% to 100% and a negative predictive value of 99% to 100% for a cutoff of 0.5 µg/mL. In our study, both the sensitivity and the negative predictive value were 96% for a cutoff of 0.5 µg/mL, whereas for a cutoff of 1 µg/mL, sensitivity was 89% and the negative predictive value was 98%.

Patients with pulmonary embolism have been observed to have higher levels of D-dimer than those with other pulmonary diseases, in particular pneumonia,^{3,18} such that levels of 9.5 µg/mL therefore have a specificity of 90% for embolism. D-dimer levels

drop gradually after the first week of anticoagulant therapy, and so they might be useful for assessing the course and recurrences of pulmonary embolism.²³

In conclusion, we believe that D-dimer levels less than 0.5 µg/mL, measured by the VIDAS fast ELISA technique, allow pulmonary embolism to be safely ruled out in an emergency room, although each center should validate the technique and establish its own diagnostic cutoffs.

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