Invited Review

Underdiagnosis of Pulmonary Embolism: A Recurrent Nightmare for Surgeons

Mustafa İdiz, Cüneyt Konuralp, Mehmet Ateş

Department of Cardiovascular Surgery, Siyami Ersek Thoracic and Cardiovascular Surgery Center, İstanbul, Turkey

Pulmonary embolism (PE) is a life-threatening condition or complication frequently seen after surgeries. Despite its all fatal potency, the clinical manifestation of PE is neither sensitive nor specific. Therefore it could be easily underdiagnosed or overdiagnosed, PE could be considered as one of the worst nightmares of cardiac surgeons.

Decreasing the mortality from PE depends on rapid and accurate diagnosis, which should be based on objective evidence.

Risk factors for venous thromboembolism, diagnostic values of symptoms and signs and the new diagnostic technologies are discussed, and a practical algorithm on PE diagnosis is presented in this review.

Key words: *Pulmonary embolism, deep vein thrombosis, heart disease, thromboembolism, open heart surgery, surgical complication*

Pulmonary embolism (PE) is a life-threatening condition or complication and could be considered as one of the worst nightmare for almost all surgeons. It is common and remains the most common preventable cause of death. The estimated annual incidence is 23 cases per 100.000 while about 50% of these cases remain undiagnosed. Undiagnosed and untreated PE is associated with a mortality rate of 30%; whereas, the mortality rate for patients treated with anticoagulants is about 8% (1). Incidence of PE after open heart surgery is found 2.7%, and in 62% of these patients, the diagnosis is established within the first week of surgery (2).

Clinical experiences have showed that PE could be underdiagnosed in morbidly ill patients, while overdiagnosed and overtreated in the healthy population. In fact, this statement reflects our imperfect understanding of venous thromboembolism (VTE). VTE includes both deep venous thrombosis (DVT) and PE. The overwhelming threat of embolism is almost exclusively from the deep veins above the knee; whereas calf-limited thrombosis poses a modest risk of clinically significant embolism. As many as 600.000 cases of VTE occur every year in the US, while only 260.000 of them are diagnosed (3).

Although many investigators have reliably established that DVT can not be diagnosed on basis of the history and physical examination, none has argued in favor of getting rid of bedside examination. In fact, the diagnosis of PE should be based on objective evidence. Clinical examination may not be relied upon to confirm or deny the presence of DVT, but it draws a line for a further logical evaluation.

The bedside diagnosis determines the clinical probability of PE on the basis of patient's history, physical examination, and routine studies (4).

Diagnostic algorhythm of PE: The diagnostic exercise begins with a suspicion of PE, since PE may occur without symptoms and signs **(**Figure 1) (1). It is mandatory to maintain a high index of suspicion particularly in patients at risk for DVT (Table I).

The history and physical findings suggesting PE depend on the extent and severity of vascular occlusion. Dyspnea is the most common symptom occurring in more than 75% of the patients. It is sudden in onset. The more massive the embolus, the more severe the dyspnea is. Often associated with dyspnea is a feeling of apprehension. Syncope (or near syncope) occurs in less than 10% and implies a major embolus. Pleuritic chest pain (66%), hemoptysis (15%), and anginal substernal pain (10%) are common; the first two indicate the presence of infarction, the third reflects the right ventricular ischemia due to massive embolism.

Table I. Risk factors for venous thromboembolism.

- Age > 40 years
- Obesity
- Cancer
- Prolonged immobilization
- Previous venous thromboembolism
- Severe cardiorespiratory disease
- Stroke or spinal cord injury
- Multiple trauma to legs
- Major abdominal surgery
- Hip or knee surgery
- Pregnancy or postpartum status
- Estrogens
- Biologic risk factors

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Table II. Diagnostic values of symptoms and signs in deep vein thrombosis.

	Sensitivity	Specificity
Calf pain	56-82%	66-91%
Calf tenderness	26-74%	3-87%
Homan's sign	35-97%	13-48%
Calf/leg swelling	8-88%	39-84%

Table III. A point score developed by Wells et al (5) to estimate probability of PE.

Sign/Symptom	Score*
Clinical sign/symptoms of DVT	3.0
An alternative diagnosis less likely	3.0
Heart rate >100/min	1.5
Immobilization/surgery past 4 weeks	1.5
History of DVT/PE	1.5
Hemoptysis	1.0
Malignancy (treatment/ treated in past 6 months)	1.0

*: *Probability of PE: Low, <2.0; Moderate, 2.0-6.0; High, > 6.0*

The frequent physical signs of PE are tachypnea, and tachyarrhythmia of sudden onset. In small emboli these findings may be transient or absent. Occasionally, focal rales or rhonchi may be heard. In major embolism a right ventricular S3 gallop, split second sound, and right ventricular tap along the left sternal border may be present. These are the signs of pulmonary hypertension (PHT) and acute right ventricular strain. One always should seek signs of deep venous thrombosis but they are present in only 15% of patients, and their specifities and sensitivities show great variance (4) (Table II).

Wells et al (5) have devised a simple model to classify probability of PE by using a point system for various clinical symptoms and signs (Table III).

The next step is to proceed with standard laboratory tests that include complete blood count, chest X-ray, ECG, and arterial blood gases. These tests do not establish the diagnosis of PE, but they serve two purposes: to exclude other diagnoses including pneumothorax, massive atelectasis, myocardial infarction, occult bleeding; and to provide some clue to the severity of a possible PE.

Based on our bedside evaluation and laboratory tests, we have a fairly good idea about the presence or absence of PE and whether the embolus is massive or nonmassive. Further, and more spesific tests are needed to confirm the diagnosis.

Ventilation-perfusion (V-Q) lung scanning: Traditionally in nonmassive cases the diagnostic work up has centered on V-Q radionuclide lung scanning. Until recently, diagnostic algoriythms for PE traditionally depended on radionuclear lung imaging. However, the use of V-Q lung scanning is fraught with problems. The major problem being that in as many as 80% of patients who have the test, the diagnosis of PE is neither established nor excluded. In Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (6), normal or near normal scans were observed in 14% of the patients and high probability scan in 13%, so the majority of the patients have had an inconclusive study (low or intermediate probability). Because V-Q lung scans are not always helpful, clinicians base their strategies on pretest clinical probability. For example, a high probability V-Q scan with a high pretest clinical probability has 96% positive predictive value for diagnosing PE. In PIOPED study (6), this combination occurred in only 3% of patients with suspected PE who had V-Q scanning. Similarly, a low probability reading on V-Q scanning with low pretest clinical probability occurred in only 10% of patients undergoing V-Q study for suspected PE. Thus the majority of patients required additional diagnostic techniques including pulmonary angiography or ultrasonography of the lower extremities or both.

Pulmonary angiography: Although pulmonary angiography is considered the "gold standard" in the diagnosis of PE and its mortality (<1%) and morbidity (2-5%) rates are low, many clinicians are reluctant to use the test because of its invasive nature (7). Furthermore, the technique is costly, not available in many hospitals, and difficult to interpret requiring special expertise.

Spiral computerized tomography (CT) pulmonary angiography: For the past ten years CT scans with bolus injections of contrast have been increasingly used to detect PE. Advances in CT technology have permitted more rapid acquisition of images in the chest with improved spatial resolution. Rapid sequence spiral scanning led to excellent resolution of the pulmonary arterial circulation on the lobar branches with a sensitivity of detecting PE of 90%; with lower segmental vessel sensitivity. Subsequent technical advances raised the sensitivity of segmental branch clot detection to 94% (8).

Spiral CT scanning can detect emboli from the pulmonary trunk to segmental arteries. For detecting emboli in main, lobar or segmental arteries spiral CT scanning is comparable to pulmonary angiography. Qanadli et al (9) found only one false negative in 157 patients having both spiral CT and contrast pulmonary arteriography. It has a mean sensitivity of 90% and mean specificity of 95%. Emboli in subsegmental pulmonary arteries are not readily visualized. Thus a normal spiral CT can not be used to exclude subsegmental and perhaps insignificant PE (10). When compared to V-Q scanning, CT angiography has better interobserver agreement and is comparable to standard pulmonary angiography (11).

The cost of V-Q scanning and CT angiography are identical. CT angiography is less invasive, widely available, and may uncover other intrathoracic diseases including cancer, pneumonia and effusion.

Multi-Detector CT pulmonary angiography (MD CTPA): It takes traditional CTPA to an even higher level of resolution. Sub-second rotation times and sequential slice viewing on-screen have permitted substantially improved accuracy in detecting or excluding PE. In a 16 seconds acquisition during a single inspiratory breath hold, these investigators were able to visualize each of the known segmental branches of the PA other than those judged to be altered by anatomic variants. Furthermore, 94% of all subsegmental branches and 74% of all fifth order branches were visualized; in these smaller vessels the major reason for non visualization was partial volume effects. In conclusion, MD-CTPA is presently the most useful clinical tool for detection of PE (12). It is as accurate as standard contrast arteriography, more widely and consistently available, and offers additional information leading to alternative diagnoses in patients in whom DVT is not present (12).

D-dimer: Recently, there has been an active interest in measuring the biologic markers of fibrinolysis. Among these, D-dimer, degradation product of cross-linked fibrin by plasmin, has been studied most extensively. Levels in plasma are increased for approximately ten days following VTE (13). A normal plasma D-dimer value, below a cut off value of 500ng/L by an ELISA method has a negative predictive value of 95% in excluding PE (14). The specificity of D-dimer is low around 50%, because many conditions including inflammation, necrosis, infection, and cancer can activate the coagulation and fibrinolytic system (15). Thus a positive value of plasma D-dimer level (>500ng/L) can not be used to confirm the diagnosis of PE. In hospital patients a normal plasma D-dimer level is rarely observed making its diagnostic value low. Thus in patients with low pretest clinical probability, a normal D-dimer level may exclude the diagnosis of PE (15)

Cardiac troponin I and T: Cardiac troponins I (cTnI) and T (cTnT) are reliable indicators of myocardial injury. It was reported that their level is elevated on acute PE cases (probably associated with right ventricular dysfunction caused by PE) (15). cTnI and cTnT may be a novel, particularly useful tool for optimizing the management strategy in patients with acute PE (15)

Detection of alternative diagnoses: Most clinical studies of CTPA indicate an incidence of PE 15-30% in patients suspected of DVT (16). Unlike typical contrast arteriography or radioisotope perfusion scans, CTPA revealed alternative diagnoses accounting for the clinical presentation in 65% of patients with CTPA results that were negative or inconclusive for PE (17, 18). The most common alternative diagnoses are lung infiltrates including pneumonia and atelectasis, cardiovascular disease, and pleural effusions (19). Many malignant masses are also discovered (11). Dissecting aortic aneurysm and pericardial effusions are less common but potentially important diagnoses (3).

Detection of lower extremity thromboses: Objective testing necessary to diagnose DVT includes contrast venography. It remains the gold standard for diagnosing DVT, but suffers from limited availability and complications including a morbidity of 4% and a mortality of 0.2% (20). The limitations of these various tests have contributed to the unacceptably high incidence of missed diagnoses. Many clinical trials have established the accuracy of ultrasound (US) in diagnosing suspected acute DVT (13).

Indirect CT Venography (iCTV) uses same contrast bolus given for CTPA evaluation of possible PE to detect lower extremity thrombi. CT acquisition in the legs (iliac crest to popliteal fossa) is initiated three minutes after contrast injection. A study of 541 consecutive patients undergoing CTPA and iCTV for suspected PE found PE in 17% and DVT in 8% (2). One third of the group with DVT by iCTV had no evidence of DVT, thus increasing the yield of VTE diagnoses by 18%. In 116 patients having both duplex ultrasonography and iCTV, 15 had DVT at US; in all 15 the iCTV was also positive. In addition, four patients had evidence of DVT at iCTV that was not detected by US. Another study of 650 patients at two centers found an 18% incidence of VTE; half with both PE and DVT and ¼ each with either PE or DVT (7). 308 of these patients also had simultaneous duplex US. Only two patients had DVT by use with a normal iCTV and four had a negative duplex with positive iCTV. Repeat duplex US confirmed the iCTV findings. The increase in yield of VTE using iCTV along with CTPA was 36% because of the isolated DVT detected. In summary, the routine combination of CTPA and iCTV requires three additional minutes of scan time no additional contrast injection but provides an improved diagnoses of VTE of nearly 20% with DVT detection as good as traditional US (21).

The last part of the algorithm: In patients with low clinical suspicion of VTE, a negative D-dimer combined with a negative duplex US probably is sufficient to exclude PE. In some centers, the normal D-dimer may be sufficient in this group. A positive D-dimer warrants either lung perfusion scan or CTPA/iCTV, while a positive US warrants therapy.

In patients without cardiopulmonary disease with a moderate or high clinical suspicion of VTE, a lung perfusion scan and indeterminate scan and lower extremity duplex are still the procedures of choice. A negative duplex and indeterminate scan warrant CTPA/iCTV.

In patient with underlying cardiopulmonary disease in whom the perfusion scan is more likely to be indeterminate, CTPA/iCTV is a useful initial test.

CTPA/iCTV using multidetector-row devices is rapidly becoming the test of choice and may replace both lung perfusion scans, lower extremity duplex and contrast

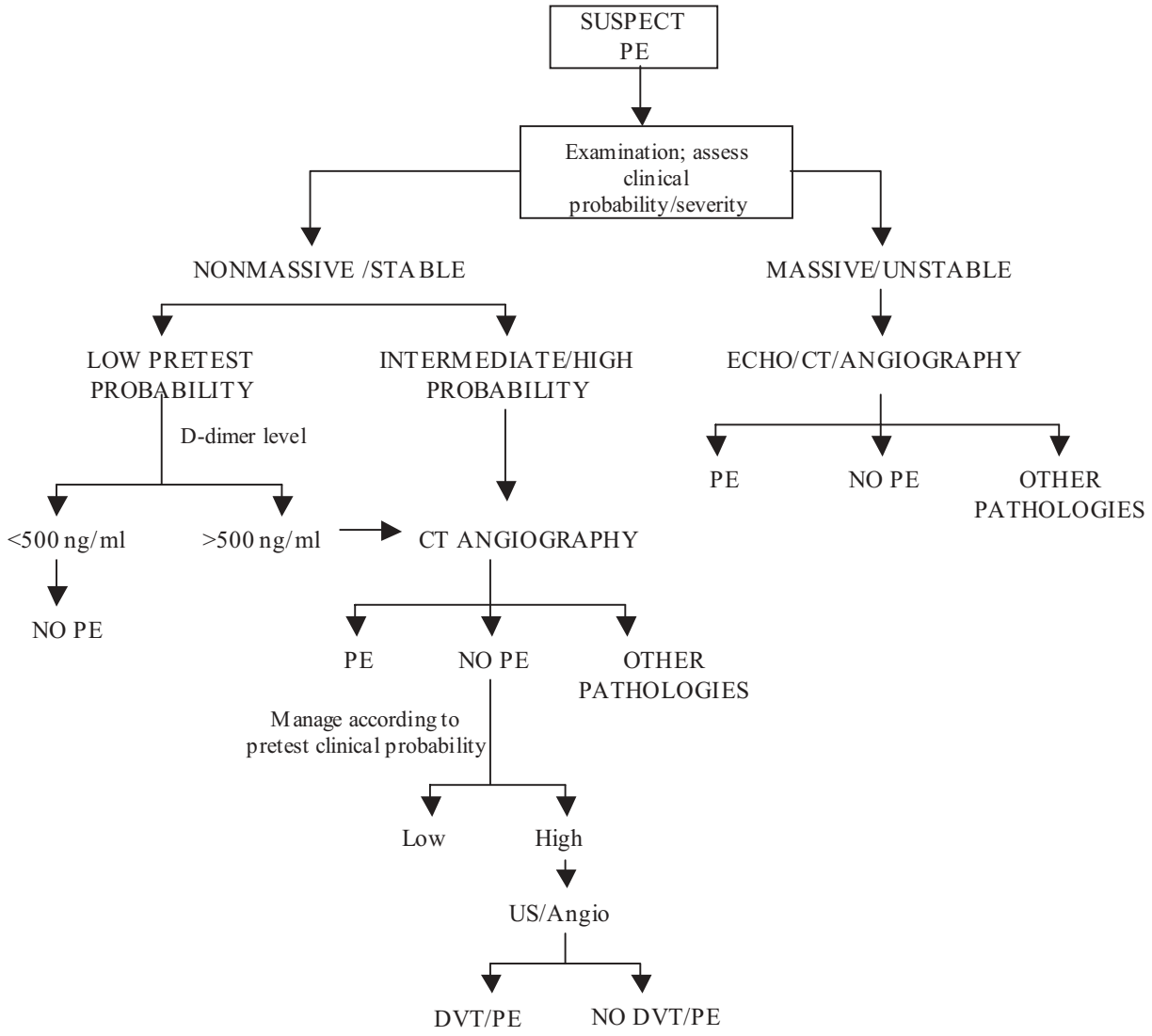

Figure 1. The algorithm for pulmonary embolism diagnosis (1).

arteriography in patients with suspected PE. A positive test warrants therapy. A negative test should be sufficient to withhold therapy unless the study is technically suboptimal.

In patients with renal failure or allergy to contrast, lung perfusion scanning followed by MR pulmonary angiography should be preferred if the result is indeterminate.

Special situations requiring surgeon's attention: Anticoagulant therapy can successfully prevent PE and re-thrombosis in most cases, but can not affect either early morbidity or the late post-thrombotic sequelae. In carefully selected cases, early clot removal by thrombolysis or thrombectomy may be justified by improved outcome. Because of the significant role, early and late outflow obstruction plays in determining the ultimate severity of post-thrombotic sequelae (22).

In chronic thromboembolic PHT, functions are impaired in the right as well as the left ventricles of the heart. Therefore, surgical treatment (urgent pulmonary thrombectomy) may be required as adjunct to nitric oxide inhalation (23). Improved lung perfusion and the reduction of right ventricular pressure overload are direct results of pulmonary thromboendarterectomy, which in turn, bring a profound reduction of right ventricular size and a recovery of systolic function. Normalization of interventricular septal motion as well as improved venous return to the left atrium lead to a normalization of left ventricular diastolic and systolic function, and the cardiac index improves (24).

The management of acute massive PE constitutes a major clinical problem because of the associated derangement of hemodynamic and respiratory functions from obstruction to pulmonary blood flow. Physiologic abnormalities caused by venous emboli are related to the cross-sectional area of occluded pulmonary arterial bed. Despite advances in management with thrombolytic therapy or open embolectomy, the mortality rate remains high. To improve the chance of survival, catheter

techniques that are capable of removing or fragmenting the clot have been developed. These include catheter pulmonary embolectomy and thrombofragmentation.

The success of the catheter technique in removing pulmonary emboli varies with different devices. The overall success rate is approximately 76%, with a mortality rate of 25%. Transvenous pulmonary embolectomy and thrombofragmentation are safe and effective techniques for treating patients with massive PE (25).

Some of the cases might be presented with sudden onset of shock signs. The presence of shock defines a three- to seven-fold increase in mortality, with a majority of deaths occurring within one hour of presentation. Thus, a rapid integration of historical information and physical findings with readily available laboratory data and a structured physiologic approach to diagnosis and resuscitation are necessary for optimal therapeutics in this very limited time frame (golden hour). Thrombolytic therapy is acknowledged as the treatment of choice, with embolectomy reserved for those in whom thrombolysis is contraindicated (26).

Patients with severe PHT are at risk for thrombotic events due to their sedentary lifestyle, venous insufficiency, dilated right-side heart chambers, and sluggish pulmonary blood flow (27). Even a small pulmonary vascular obstruction by thrombus can be life threatening in a patient with a compromised pulmonary vascular bed, which possesses little ability to dilate or recruit unused vessels. Indeed, patients with PHT frequently die suddenly, and a fresh intrapulmonary clot may be found at post-mortem examination. Thus, anticoagulation as a prophylaxis for thromboembolism may be justified in patients with PHT.

Uncommonly, PE might be resulted from the rupture of a hydatid in the cyst heart or the opening of a visceral hydatid cyst (often in the liver) into the venous circulation (hydatid PE) (28).

Another special situation is acute pulmonary thromboembolism with a right-heart thrombus which is a life-threatening problem (29). Therefore, every PE suspicion requires echocardiographic examination to rule out this catastrophic event. Immediate thromboembolectomy would be essential to decrease mortality.

Acute massive PE associated with right ventricular dysfunction is frequently lethal, despite high-dose thrombolytic therapy. Adjunctive catheter fragmentation may prevent a fatal outcome. Fragmentation by pigtail rotation catheter provided for a rapid and safe improvement of the hemodynamic situation and an average recanalization of about one-third of the pulmonary embolic occlusion (30).

These presented experiences allow us to conclude that the lives of patients with acute PE can be saved by early detection and prompt surgery, albeit that management of chronic PE involves difficulties in selecting surgical cases and in performing thromboendarterectomy (31).

It should be clearly known that PE is evasive and often deadly and therefore requires utmost attention and preparation by all members of the health care team. Decreasing the mortality from PE depends on correct and timely diagnosis. And the diagnosis depends on the alertness of the clinician. Because, PE often causes only vague and nonspesific symptoms and signs, the clinician should always intend to consider this possibility before it turns to a catastrophy. As explained in this review, the new diagnostic technologies allow us diagnose PE with almost 100% certainity. Therefore, the key element is still the physician, who will decide to initiate proper diagnostic tests.

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Correspondence:
Cüneyt Konuralp, MD
Ayşe Çavuş Sokak, No: 7/6, Huri Apt.,
Suadiye, 34740, İstanbul, TURKEY
E-mail: ckonuralp@usa.net