Update on Pulmonary Embolism

JORGE A. MUNDO-SAGARDÍA, MD; HÉCTOR DELGADO-OSORIO, MD

Pulmonary embolism is a medical condition frequently overlooked in patients who present clinical symptoms that may suggest other more common cardiovascular conditions. As a result, missing such a diagnosis may unfortunately cost many lives. In this article the pathogenesis, etiologies and clinical features of this illness is reviewed. The diagnostic tools as well as the medical treatment available at hand today in the management of this condition is also discussed.

Key words: Pulmonary embolism, Deep vein thrombosis, Venous thromboembolism, Lung perfusion-ventilation scan, Venous ultrasonography, Pulmonary angiography, Anticoagulation

Pulmonary embolism is the third most common cardiovascular cause of death. Results in death in 150,000 patients per year in the United States and contributes to death in another 150,000 patients (1). It is the most preventable cause of death in hospitalized patients and is the cause of death of 5 to 15% of patients dying in hospitals in the United States (2). Ninety percent of cases originate from thrombi in the deep venous system of the legs. Virtually all come from above the knee. Calf veins deep vein thrombosis (DVT) is associated with a low risk of clinically important pulmonary embolism (PE). Twenty percent of calf vein thrombi not treated extend into proximal venous system. Untreated proximal venous thrombosis has a 10% risk of fatal PE and a 50% risk of PE or recurrence of venous thrombosis. Other sites from which thrombi can originate are: upper extremities, internal jugular and subclavian veins (specially if catheters are in place), deep pelvic veins or renal veins, inferior vena cava, right heart and axillary veins. Pulmonary embolism is detected in 25 to 30% of routine autopsies and antemorten diagnosis is made in less than 30% of cases (2). Finally, it is important to indicate that pulmonary embolism and deep vein thrombosis are considered one single disorder: *venous thromboembolism.*

Pathogenesis

The major contributors to thrombus formation are: stasis of blood, abnormalities of the vessel wall and changes in the soluble and formed elements of the blood. Depending on the specific risk factor of the patient these alterations can contribute to venous thrombosis. Thrombocytes and clotting factors via both extrinsic and intrinsic pathways play an essential role in thrombus formation. Initially, platelets adhesion to vessel wall and its subsequent aggregation will lead to the white clot and afterwards with the presence of fibrin due to the clotting factors, the red thrombus is formed which will then be organized. The venous thrombus may detach from site of formation and if it is extremely large, may eventually lodge at the bifurcation of the pulmonary artery which is then known as a saddle embolus. This then becomes a massive PE. More commonly, a major pulmonary vessel is occluded. Once embolic obstruction of the pulmonary artery occurs, this may lead to increased alveolar dead space, vascular constriction due to multiple factors (hypoxemia, reflex pulmonary artery vasoconstriction, serotonin) and loss of alveolar surfactant with atelectasis. Eventually there will be increased resistance to blood flow and pulmonary artery pressure which will lead to increased right ventricular (RV) afterload which will cause increased RV wall tension, RV dilatation and dysfunction, interventricular septum shift to the left ventricle (LV), LV underfilling and decreased cardiac output (CO). Also due to RV dysfunction, RV CO is decreased leading to decreased LV preload, decreased CO compromising coronary perfusion and causing myocardial ischemia. When a massive PE occurs causing elevated RV wall tension, right coronary artery flow may be reduced, increasing RV myocardial oxygen demand, ischemia, cardiogenic shock, RV infarction, circulatory collapse and finally death. Although rare, in less than 10% of PE cases, lung tissue infarction may occur (2). Lung tissue is fed by multiple sources, mainly from the bronchial artery, pulmonary artery and from back diffusion through pulmonary venous system. These

From the Department of Medicine, Cardiology Section, Medical Sciences Campus, University of Puerto Rico.

Address correspondence to: Dr. Jorge A. Mundo-Sagardía, Department of Medicine, Cardiology Section, Medical Sciences Campus, University of Puerto Rico, PO Box 365067, San Juan, Puerto Rico 00936-5067.

sources are significantly compromised in order to cause lung infarction. A massive PE is considered when more than two thirds of a lung is involved, when there is obstruction of more than 50% of pulmonary vasculature or when embolism involves both lungs. A submassive PE is defined as embolism to one or more pulmonary segments without overt systemic arterial hypotension. The latter is more difficult to diagnose but usually carries a lower risk of death.

Etiology. The etiologies of PE were classically divided into either inherited (primary) or commonly acquired (secondary) risk factors. Now it appears that many patients who develop PE are genetically predisposed but often require a precipitating environmental stress to elicit thrombosis (3). In table 1 are examples of several conditions in which a patient is genetically predisposed to develop thrombosis and as a result PE. Table 2 shows multiple acquired conditions that may precipitate thrombosis.

Table 1. Inherited Risk Factors for Thrombus Formation*

Activated protein C resistance	tPA release deficiency
Antithrombin III deficiency	Increased tPA inhibitor
Protein C deficiency	Dysfibrinogenemia
Protein S deficiency	Homocystinuria
Fibrinolytic abnormalities	Heparin cofactor deficiency
Hypoplasminogenemia	Increased histidine-rich glycoprotein
Dysplasminogenemia	

* *Adapted from Prakash UBS. Pulmonary Diseases.* In: Prakash UBS, Habermann TM, eds. Mayo Internal Medicine Board Review 2000-01. 4th ed. Philadelphia: Lippincott Williams & Wilkins;2000. p.813-18.

Table 2. Acquired Risk Factors for Thrombus Formation

Cancer	Nephrotic syndrome
Postoperative states	Cigarette smoking
Lupus anticoagulant syndrome	Anticancer drugs
Increased factor VII and fibrinogen	Pregnancy/postpartum
Behçet disease and vasculitides	Oral contraceptives
Heparin-induced thrombocytopenia	Increasing age (> 40)
Paroxysmal nocturia hemoglobinuria	Obesity
Myeloproliferative disorders	Hyperlipidemia
Disseminated intravascular coagulation	Systemic arterial
Acute stroke/spinal cord injury	hypertension
Indwelling central venous catheter	Diabetes mellitus

* *Adapted from Prakash UBS.* Pulmonary Diseases. In: Prakash UBS, Habermann TM, eds. Mayo Internal Medicine Board Review 2000-01. 4th ed. Philadelphia: Lippincott Williams & Wilkins;2000. p.813-18.

Clinical features. Clinical suspicion of PE is of utmost importance in guiding diagnostic testing. According to the International Cooperative Pulmonary Embolism Registry the most common signs or symptoms in the order of more to less frequent are: dyspnea, increased respiratory rate, chest pain, increased heart rate, cough, syncope and hemoptysis (3). In some patients there may be transient dyspnea and tachypnea. If the patient develops syndrome of congestive atelectasis, pleuritic chest pain, cough, hemoptysis, pleural effusion and pulmonary infiltrates in chest x ray will be present (1). In acute massive PE the patient will show sudden onset of shortness of breath, hypoxemia, RV failure, central chest pain (angina-like), severe dyspnea, syncope, confusion or coma (1). In the physical exam of patients with PE, besides tachypnea and tachycardia, cyanosis, hypotension, large A wave on jugular vein, RV diastolic gallop and increased P2 sound may be found (1).

Diagnosis. Establishing the diagnosis of acute PE is crucial. The strategy involves integrating signs, symptoms, the clinical setting and the patient´s history with chest x rays, electrocardiograms (ECG) and emerging modalities like the plasma D-dimer blood test.

The D-dimer is a cross-linked fibrin degradation product that circulates in plasma after lysis of fibrin by endogenous fibrinolysis. A low concentration of plasma D-dimer as measured by ELISA method (levels below 500 ng/ml) has a strong negative predictive value in the evaluation for PE. It has a high sensitivity of about 98% but a rather poor specificity of about 45%. The D-dimer is a useful screening test for PE. The following are other important evaluation studies used in the diagnostic process for PE: ventilation/perfusion lung scan, venous ultrasonography, pulmonary angiography and echocardiography.

Ventilation and perfusion lung scans are very useful in the evaluation of patients with suspected PE. Usually they are reported as low, intermediate or high probability of PE. The hallmark of a high probability scan is normal ventilation and abnormal perfusion. This is also known as a ventilation-perfusion (V/Q) mismatch. A normal ventilation/perfusion scan excludes clinically important PE. The results of the lung scans are of greater value when the clinical picture is taken in consideration.

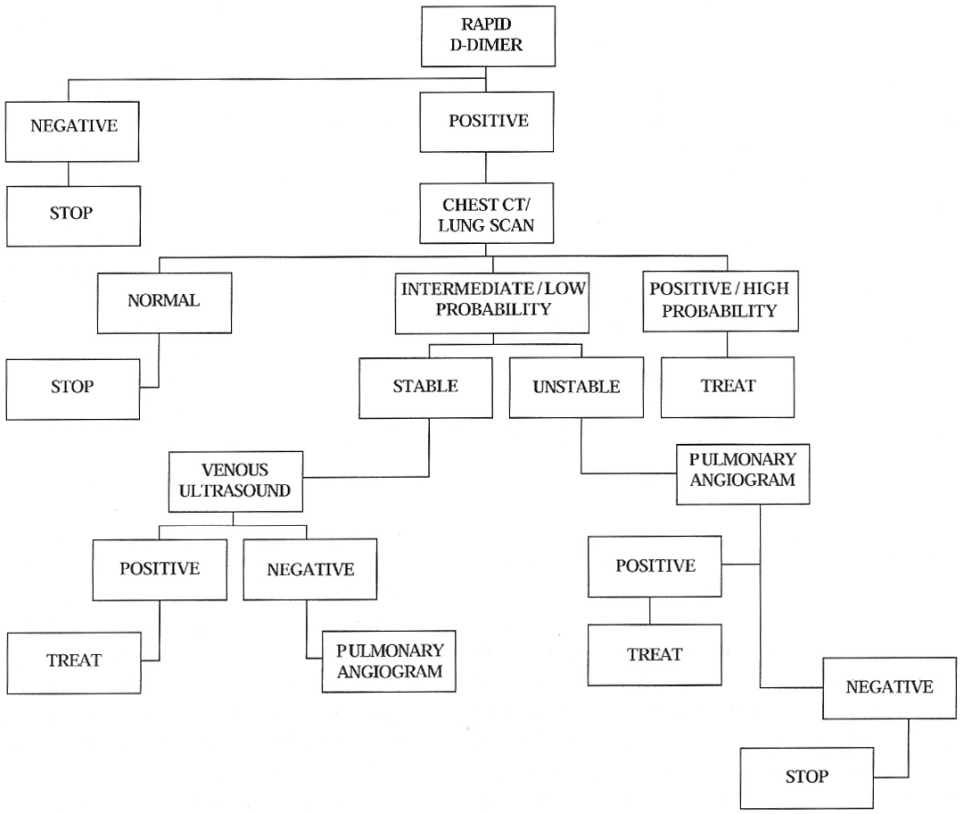
Close to 90% of PE are the result of thrombus from the deep venous system of the lower extremities, as a result, venous ultrasonography of the legs is very important in the early diagnostic work up of this condition. This test is excellent particularly for detecting proximal DVT. *Pulmonary angiography* is the cornerstone for definite diagnosis of PE. However it is invasive, can be difficult to interpret and increases both the risk and cost to the patient. Therefore pulmonary angiography is not without morbidity and mortality which although generally low, may be significant in the severely ill patient. Usually selective left and right pulmonary artery injections may be performed for a complete study. The value of this study is seen better in the patient with low probability V/Q scan with high clinical suspicion of PE.

The *echocardiogram* has emerged as a non invasive technique for assessing hemodynamically important PE and response to therapy. About half of PE patients have 2-D echo imaging or Doppler abnormalities of the right side of the heart. The following are possible signs of PE that can be observed in echocardiograms: direct visualization of thrombus (rare), RV dilatation , RV hypokinesis with sparing of the apex (McConnell's sign), abnormal interventricular septal motion, tricuspid regurgitation (Doppler of this regurgitation will estimate the systolic pulmonary artery pressure), pulmonary artery dilatation and lack of decreased inspiratory collapse of inferior vena cava (3).

Other emerging studies are *the spiral CT scan* or the *MRI of the pulmonary arteries* but they are expensive and difficult to perform in critically ill patients.

Diagnosis of PE is more difficult than treatment or prevention. In patients with PE the most dangerous period is that preceding the establishment of the correct diagnosis. Several ancillary tests are done upon evaluating these patients with the purpose of ruling out other conditions that may mimic PE, among them: arterial blood gases (ABG), chest x rays and ECG. ABG in PE usually has a normal Pa O2 and A-a gradient unless it is a very massive case. It is not useful in triaging for PE. On the other hand, the most common finding in a chest x ray of a patient with PE is a normal x ray. Findings suggestive of PE which may not be frequent are: pulmonary infiltrates with normal WBC, pulmonary consolidation associated with an elevated ipsilateral hemidiaphragm, Hamptom´s hump (pleural based wedge shape defect just above the diaphragm), Oligemia or Westermark´s sign (lack of vascular markings in area downstream of embolus) and a large right descending pulmonary artery. In the ECG it is common to find sinus tachycardia. In large PE, manifestations of right heart strain may be seen such as: incomplete or complete right bundle branch block, S in lead I and AVL of more than 1.5 mm, transition zone shift to V5, Q in leads III and AVF (not in II), low limb voltage and T wave inversion in leads III, AVF or V1 to V4 (3). In figure I it is shown the diagnostic strategy followed upon evaluation of a patient with suspected PE.

Figure 1. Diagnostic strategy for pulmonary embolism



Treatment

Rapid and accurate risk stratification is of vital importance. Patients with PE present with a wide spectrum of illness and appropriate care can range from prevention of recurrent PE to clot dissolution or removal with thrombolysis or embolectomy. Upon initial management of a patient with suspected PE, several measures may be taken such as: supplemental oxygen, if toxic and hypoxic prompt temporary mechanical ventilation must be instituted. Also pain relief must be taken into consideration, usually most effective with nonsteroidal antiinflammatory medications. Those with impending hypotension or poor organ perfusion require rapid institution of an inotrope. Dobutamine is the first-line agent to treat right heart failure and cardiogenic shock (3). Volume loading is another important element that must be provided in these patients. For patients with pulmonary hypertension and a patent foramen ovale, inhaled nitric oxide may reverse right to left shunting and improve oxygenation (3).

Heparin is the cornerstone of treatment for acute PE. Before heparin therapy is begun, risk factors for bleeding should be considered, such as prior history of bleeding with anticoagulation, thrombocytopenia, vitamin K deficiency, increasing age, underlying diseases and concomitant drug therapy. Unless a severe bleeding is detected, heparin can be started before lung scanning or pulmonary angiography. The conventional treatment strategy uses unfractionated heparin but the use of low molecular weight heparin (LMWH) for patients with acute symptomatic PE has become another therapeutic alternative. If anticoagulation treatment is started with unfractionated heparin in a patient with suspected embolism, baseline PTT,PT and CBC must be obtained. Also once ordered the respective diagnostic imaging study, it should be considered giving 5,000 IU intravenously (IV). Once embolism is confirmed, rebolus with heparin 80 IU/Kg IV and start maintenance infusion at 18 U/Kg. PTT must be checked every 6 hours to keep it in a range of 1.5 to 2.3 times mean normal. Also check a platelets (PLT) count between days three to five, as a measure for early detection of possible heparin-induced thrombocytopenia. Warfarin is also started on day one at 5 mg po daily and adjusted with INR. Heparin must be stopped at least after four to five days of combined treatment when INR is more than 2.0. Anticoagulate for at least three months with an INR between 2.0 to 3.0 (4). If anticoagulation treatment is started with LMWH in a patient with suspected embolism, baseline PTT, PT and CBC must be obtained. Once ordered the respective diagnostic imaging study, it should be considered giving 5,000 U IV of unfractionated heparin or LMWH. Once embolism is confirmed give LMWH. If the LMWH considered is enoxaparin , its dosis is 1 mg/Kg/day subcutaneously single dose (should not exceed 180 mg). Warfarin is also started on day one, 5 mg po daily and adjust subsequent daily dose according to INR. PLT count should also be checked between day three and five and LMWH may be stopped at least four to five days of combined therapy when INR is more than 2.0. Afterwards, anticoagulate with warfarin for at least three months at a INR between 2.0 to 3.0 (4).

Thrombolytic therapy is a useful adjunct to heparin in patients who have PE and who are hemodynamically unstable. Thrombolysis may prevent the downhill spiral of right heart failure by physical dissolution of anatomically obstructing pulmonary artery thrombus, also prevents continued release of serotonin and other neurohumoral factors that might lead to worsening pulmonary hypertension and also may dissolve the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent large PE (3). Infusion of these agents directly into venous thrombus has not shown to be superior to infusion of the agent through a peripheral vein. Thrombolytic therapy makes mostly a partial dissolution of the thrombus because venous thromboemboli are older, larger and more organized (4). Unlike patients with myocardial infarction thrombolysis, patients with PE have a wide window for effective use of thrombolysis. Patients who receive thrombolysis up to fourteen days after new signs or symptoms, maintain an effective response probably because of the bronchial collateral circulation. Patients with massive iliofemoral thrombosis are also candidates for this therapy. Among the most common thrombolytic agents used for this condition are: streptokinase, urokinase and tPA. Streptokinase is used first by giving a loading of 250,000 IU over 30 minutes followed by an infusion of 100,000 IU/hour for twenty four hours. Its contraindications are: active bleeding, recent surgery, stroke or severe trauma, any hemorrhagic disease, recent streptococcal infection and treatment with streptokinase documented hypersensitivity (4). On the other hand, urokinase is used first by giving a loading of 4,400 IU/Kg body weight over 10 minutes followed by an infusion of 2,200 IU/Kg/hour for twelve hours. Its contraindications are: active bleeding, recent surgery, severe trauma or any hemorrhagic disease (4). Finally tPA is administered by giving a 100 mg infusion over two hours (4). Its contraindications are: active bleeding, intracranial pathologic conditions, recent surgery, severe trauma or any hemorrhagic disease.

Mechanical interventions including procedures such as thrombectomy and embolectomy are other therapeutic

alternatives for patients with PE. They could be performed either by catheter-based interventional procedures or by surgery. These procedures are done when there is a massive PE (angiographically documented if possible), when there is failure of thrombolytic therapy or contraindications to use it and when there is hemodynamic instability (shock) despite heparin and resucitation efforts. The most common catheter-based thrombectomy procedures available are: fragmentation thrombectomy (based on the technique of rotablation), rheolytic thrombectomy (based on the strong Venturi effect caused by a high velocity saline jet) and aspiration thrombectomy (5). Surgical embolectomy, on the other hand, is undertaken when catheter-based strategies fail. Operative mortality is high, it was found to be from 10 to 75% in uncontrolled retrospective case series and 50 to 94% in patients who suffered cardiopulmonary arrest. Most common reported postoperative complications are: acute respiratory distress syndrome, mediastinitis, acute renal failure and severe neurologic sequelae.

Another therapeutic alternative in the management of PE is the inferior vena cava (IVC) filters. In a randomized study of filter placement, the device did not prolong early or late survival in patients after a first episode of venous thromboembolism. It did reduce the rate of pulmonary embolisms but a tendency of more recurrent DVT in patients who received a filter was found (3). In view of the latter, anticoagulation therapy, whenever possible, should be used once a filter is inserted. Indications for IVC filters include: patients with documented PE in which anticoagulation is contraindicated, anticoagulation failure despite documentation of adequate therapy (recurrent PE) and prophylaxis in high risk patients (extensive or progressive venous thrombosis, in conjunction with catheter-based or surgical pulmonary embolectomy and in severe pulmonary hypertension or cor pulmonale). The following are some of the most commonly used IVC filters: Greenfield filter, Bird´s Nest filter, L-G medical filter and Gunther filter. Most filters are placed below the renal veins. For suprarenal vein placement, the largest experience is with the Greenfield. Most satisfactory results are seen with the Bird´s Nest and Greenfield filters.

Once a patient with PE has been successfully treated in the hospital with any of the medical alternatives discussed previously and is in conditions to be discharged home, it is important to determine the amount of time anticoagulation treatment as outpatient will be required. It is recommended to continue therapy (specifically with warfarin) for three to six months in patients who had a first event with reversible or time-limited risk factor.

Six or more months in patients with idiopathic venous thromboembolism, first event. Twelve months to a lifetime in the case of a first event (with cancer until resolved, anticardiolipin antibody, antithrombin deficiency) or a recurrent event, idiopathic or thrombophilia (4).

Conclusion

Pulmonary embolism is one of the major cardiovascular causes of death in the United States. Hundreds of thousands of lives are lost each year because of this illness. Its clinical presentation may mimic other common medical conditions in view of which a very keen diagnostic eye must be present in order to prevent missing its identification. We have presented the pathogenesis, most common etiologies and clinical features of this disease as well as the diagnostic process that must be undertaken in order to effectively detect and treat this condition. The medical community must be more aware of this disease, since only by having it present in the clinical mind, will then result in the real possibility of saving many more lives.

Resumen

La embolia pulmonar es una condición frecuentemente ignorada en pacientes con síntomas que pueden sugerir otras condiciones cardiovasculares más comunes. El fallar el diagnóstico puede desafortunadamente precipitar la pérdida de muchas vidas. En este artículo se revisa la patogénesis, etiología y cuadro clínico de esta enfermedad. Se presentan además las herramientas diagnósticas y el tratamiento disponible hoy en día para el manejo de esta condición.

References

1. Hull RS, Pineo GF. Thromboembolic syndromes. In: Baum GL, Crapo JD, Celli BR, Karlinsky JB, eds. Textbook of pulmonary diseases. 6th ed. Philadelphia: Lippincott-Raven Publishers; 1998. p. 1297-1307.
2. Prakash UBS. Pulmonary Diseases. In: Prakash UBS, Habermann TM, eds. Mayo internal medicine board review 2000-01. 4th ed. Philadelphia: Lippincott Williams and Wilkins;2000. p. 813-18.
3. Goldhaber SZ. Pulmonary Embolism. In: Braunwald E, Zipes DP, Libby P, eds. Heart disease: a textbook of cardiovascular medicine. 6th ed. Philadelphia: W.B. Saunders Company; 2001. p. 1886-1903.
4. Hyers TM, Agnelli G, Hull RD, Morris TA, Samana M, Tapson V et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001; 119:176S-193S.
5. Goldhaber SZ. Profiles in Pulmonary Embolism. In: Grossman W, Baim DS, eds. Grossman´s cardiac catheterization, angiography and intervention. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 799-810.
6. Skibo LK, Wexler L. Pulmonary Angiography. In: Grossman W, Baim DS. Grossman´s cardiac catheterization, angiography and intervention. 6th ed. Philadelphia: Lippincott Williams and

Wilkins; 2000. p. 271-289.
7. Chronic Obstructive Pulmonary disease, pneumothorax, pulmonary embolism. In: Chou T, Knilans TK eds. Chou´s Electrocardiography in clinical practice. 4th ed. Philadelphia: W. B. Saunders Company; 1996. p. 289-291.
8. Wagner GS. Miscellaneous conditions. In: Wagner GS, ed. Marriott´s practical electrocardiography. 9th ed. Baltimore: Williams and Wilkins; 1994. p. 191-92.
9. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med 2002; 136:691-700.
10. Hyers TM. Venous thromboembolism:state of the art. Am J Respir Crit Care. 1999; 159: 1-14.
11. Despopoulos A, Silbernagl S, eds. Color atlas of physiology. 4th ed. New York: Thieme Medical Publishers; 1991. p.74-77.