Patient Management of Pulmonary Embolism

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This is the first article in a four-part continuing education series addressing patient care and the clinical management of disease. This series is not directed at nuclear medicine procedures themselves, but focuses on topics related to patients referred for nuclear medicine studies. After reading this article, the reader should be able to: 1) discuss the diagnosis of pulmonary embolism; and 2) discuss conventional versus thrombolytic approaches to therapy.

Pulmonary embolism (PE) can cause respiratory distress, pulmonary hypertension, and right-sided heart failure. This article will review historical perspectives, diagnosis, conventional therapy, and thrombolytic therapy.

HISTORICAL PERSPECTIVES

In 1641, the first description of massive occlusion of the pulmonary artery was reported by Tulpius (*1*). Centuries later, Rudolph Virchow, a German pathologist, established the relationship between deep vein thrombosis and PE. Virchow cited three important etiologies for venous thromboembolism that are known as Virchow's Triad: stasis, hypercoagulability, and trauma to the veins (*2*).

Today PE is a common cardiovascular disorder that accounts for 300,000 hospitalizations annually in the United States, with an estimated 50,000 deaths per year (*3*). During the past decade, there has been no significant reduction in the death rate.

The most common source of PE is thrombus that embolizes from the pelvic or deep leg veins (Fig. 1). Pulmonary embolism can also originate from other sources, particularly from the right atrium or right ventricle. In at least one-third of instances, however, no source of thrombus is identified in PE patients (*4*).

It was once believed that thrombosis and embolism was primarily a postoperative complication. We now recognize that the predisposing factors include: obesity, COPD, cancer, immobility, trauma, and prior venous thromboembolism. Perhaps the most important risk factor is genetic. Unfortunately, a hereditary predisposition can often only be suspected by taking a careful family history. Only in rare instances are confirmatory blood tests available to prove that there is a genetic defect (*5*). Nonthrombotic emboli can be caused by tumor, amniotic fluid, fat, air or septic foci. It is important to consider these less common forms of PE because they require special therapy (*6*).

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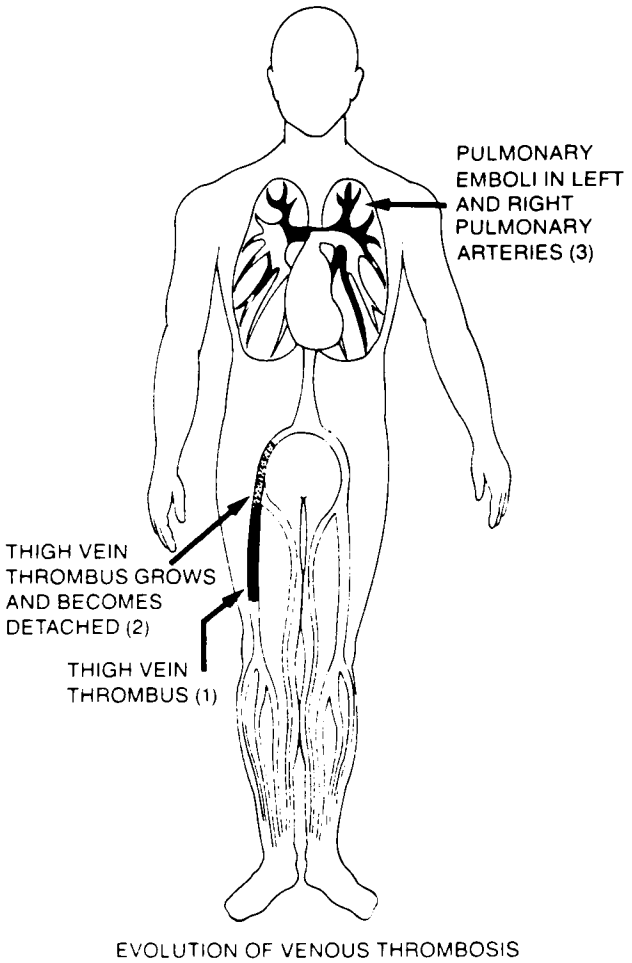

FIG. 1. Thrombi from deep leg veins embolize to the pulmonary arteries and occlude those arteries which are too narrow for passage (*24*).

DIAGNOSIS OF PULMONARY EMBOLISM

The signs and symptoms of PE range from shortness of breath, tachycardia, cough, pleuritic chest pain, and modest increase in pulmonary artery pressures, to syncope, acute respiratory distress, jugular venous distension, a large increase in pulmonary pressures, right-sided heart failure, and death. Interestingly, PE that are small and peripheral often cause pleural inflammation and intense pleuritic chest pain (*8*). On the other hand, more life-threatening central PE often causes no

chest pain but may present as syncope (*9*). In the setting of an acute massive PE, the pressure generated to the right ventricle may result in acute right heart failure, hypotension, and shock. An echocardiogram may document an enlarged right ventricle and moderate right ventricular hypokenesis. The EKG may show a right ventricular strain pattern and right ventricular hypertrophy. The body's inflammatory system is also activated and therefore an elevated temperature and white blood count may be noted. Pulmonary embolism is a difficult entity to diagnose because these signs and symptoms do occur in a variety of disease states and are not exclusive for PE (*3,8,9*) (Table 1).

Traditionally, the PO_2 from a room air arterial blood gas has been used as a screening test for PE. The rationale is that large emboli will block the blood flow to a significant number of alveoli and thereby reduce gas exchange. However, in the majority of patients, the body is able to shunt blood adequately around the thrombus. Therefore, serial blood gas determinations can be misleading. Many of our patients with PE have had room air arterial PO_2 levels > 90 mm Hg. Therefore, we do not believe that arterial blood gases should be obtained when one is trying to diagnose PE (*3*).

The lung scan was introduced in 1963, (*11*), and is the best screening test for PE. From April 1985 to April 1986, 595 lung scans were performed to screen for PE, and 88 patients were treated at the Brigham and Women's Hospital for PE.

TABLE 1. Percentage of Symptoms in 17 Patients with PE*

Variable	% Thrombotic PE (n=17)
Symptoms	
Dyspnea	64
Cough	14
Pleuritic chest pain	13
Nonpleuritic chest pain	11
Signs	
Temperature > 100 F	20
Heart rate > 100 per min	63
Respiratory rate > 20 min	43
Cyanosis	18
Hemoptysis	11
Laboratory Values	
WBC > 15,000 mm^3	30
Bilirubin > 2.0 mg/dl	20
SGOT > 100 IU/l	16
LDH > 400 IU/l	20
Associated Conditions	
Arrhythmia	64
Pneumonia	38
Deep venous thrombosis	21
Congestive heart failure	32
Chronic obstructive pulmonary disease	9
Pulmonary infarction	43

* See Ref. *20*.

The majority were treated on the basis of a high probability lung scan in the setting of high clinical suspicion. During that one-year period, the diagnosis of PE from a high probability lung scan was 93% accurate (*10*).

At our hospital, xenon-133 (15–20 mCi) gas is used for the ventilation portion of the exam. Technetium-99m MAA is prepared for the perfusion study and < 3 mCi is administered by the nuclear medicine technologist, to supine patients through a venous puncture. Six standard views are recorded and a chest film is performed prior to the lung scan interpretation (*11*).

An indeterminate lung scan or a moderate or low probability lung scan in the setting of a high clinical suspicion may warrant pulmonary angiography for definitive diagnosis. Conversely, high probability lung scans may also lead to pulmonary angiography for confirmation, particularly when thrombolytic therapy, inferior vena caval interruption, or embolectomy are being considered (*8*).

Pulmonary arteriography is accepted as the gold standard for the determination of pulmonary thromboembolic disease, because it affords direct radiographic visualization of constrast-filled arteries (*8*). An arteriogram should virtually always be performed when the question of PE remains a diagnostic dilemma after the lung scan. However, it is generally agreed that a normal radionuclide perfusion study excludes significant pulmonary emboli and the need for an arteriogram. In addition, a low probability lung scan in the absence of high clinical suspicion usually suffices for the diagnostic workup of PE (*8,11*).

CONVENTIONAL MANAGEMENT VERSUS THROMBOLYTIC THERAPY

Conventional management of PE has focused primarily on heparin anticoagulation followed by Coumadin. Heparin acts in conjunction with antithrombin III to prevent new thrombus from forming. These intravenous and oral anticoagulants protect the patient from additional clots while the patient's natural fibrinolytic mechanism gradually lyses the previously formed clot. Unfortunately, even after a year, 25% of the surviving patients may have residual thrombus. Some of these patients will develop disabling and potentially fatal chronic pulmonary hypertension (*3,8,12*).

Research with thrombolytic agents suggests that thrombolysis may be more effecacious than anticoagulation alone. The first generation thrombolytic agents, urokinase and streptokinase, were approved by the Food and Drug Administration in 1977 for thrombolytic therapy of acute PE (*13*). Furthermore, the 1980 Consensus Development Conference of the National Institutes of Health concluded that the ideal treatment for PE is thrombolytic therapy (*14,15*). Despite this strong endorsement, physicians have been reluctant to administer streptokinase and urokinase because of the associated increased morbidity from bleeding complications. Therefore, thrombolytic therapy has not been widely used in the treatment of PE.

The coagulation cascade (normal clotting sequence, Fig. 2) is activated when injury to a vessel wall results in the forma-

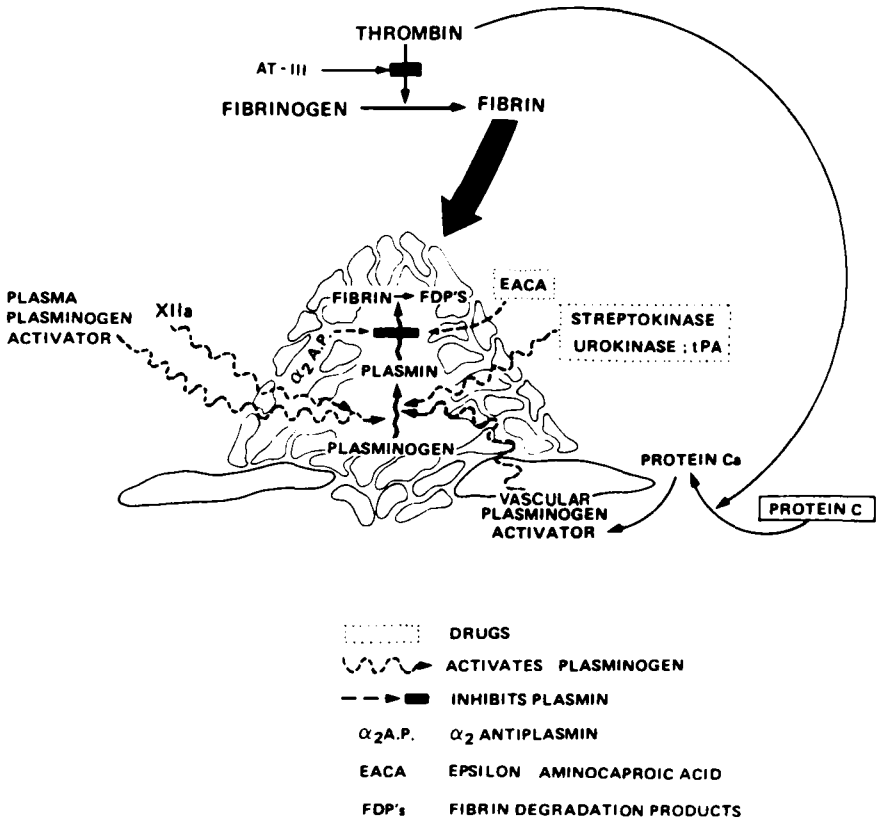

FIG. 2. Tissue plasminogen activator, urokinase, and streptokinase activate plasminogen. Plasminogen then forms plasmin which dissolves the fibrin clot (*18*).

tion of a clot which serves to protect the vessel wall from further injury (*16*). The injury to a vessel wall promotes the formation of prothrombin activator (*17*). This is the catalyst which converts prothrombin to thrombin. Thrombin then acts as an enzyme in the conversion of fibrinogen to fibrin threads. These fibrin threads form a complex meshwork which entraps platelets, plasma, and blood cells to form the blood clot (*17*).

The fibrinolytic system acts in direct opposition to the coagulation system by breaking down clots. A blood clot contains a large amount of plasminogen, an inactive protein synthesized in the liver (*16,17*). When plasminogen is activated, it becomes plasmin. Plasmin then acts to dissolve the fibrin threads, and plasmin also breaks down other clotting factors, thereby reducing the production of fibrin threads. When plasmin breaks fibrin down, the byproducts are fibrin degradation products which are also natural anticoagulants that prevent further fibrin threads from forming (*18*).

Several activator systems convert plasminogen to plasmin (*17*). Urokinase, produced by the renal tubules and found in urine, activates plasminogen directly. Streptococcal bacteria release yet another plasminogen directly. Furthermore, streptococcal bacteria release yet another plasminogen activator, streptokinase, which activates plasminogen indirectly. The endothelial lining produces tissue plasminogen activator which is released when injury to a vessel wall occurs. Tissue plasminogen activator has a high affinity for fibrin and preferentially converts the plasminogen which is bound to fibrin. However, excess tissue plasminogen activator administered therapeutically does convert some circulating plasminogen to plasmin (*16,19*).

The theoretical advantage of tissue plasminogen activator is related to the property of fibrin specificity. Both tissue plasminogen activator and urokinase are relatively fibrin specific compared with streptokinase. By activating only the plasminogen bound to fibrin clot, these agents may be more efficacious than streptokinase (*20,21*).

Tissue plasminogen activator (rt-PA) is called a second generation thrombolytic agent. The substrate was first identified in 1947 but was not isolated until 20 yr later (*13*). In 1982, a technique to successfully clone rt-PA was developed. Prior to this, rt-PA was only available in small quantities, abstracted from uterine cells or a melanoma cell line, at a very high cost. Recombinant DNA technology has made possible the industrial production of rt-PA. In several studies of patients with myocardial infarction, rt-PA has been demonstrated to be a more effective lytic agent than streptokinase. These developments have renewed the interest in the use of thrombolytic therapy for PE (*3,13,20*).

The single largest study to examine the use of thrombolytic therapy (urokinase) compared with heparin in PE was phase 1 of the Urokinase Pulmonary Embolism Trial (UPET). After 24 hr of therapy in these 160 patients, 45% of the urokinase-treated patients had angiographic improvement compared with 6% in the heparin group, and 24% of the urokinase group had lung scan improvement compared with 7% of heparin treated patients. The mortality rate and the rate of recurrent

PE were 25% lower in the urokinase group; however, these findings were not statistically significant because of the relatively small size of the study. However, major bleeding complications, defined as a hematocrit drop of more than 10 points or a transfusion requirement of more than two units of packed red blood cells, occurred twice as frequently among the urokinase group (*13,20*).

UPET demonstrated that urokinase therapy could achieve rapid angiographic and lung scan improvement in PE patients, whereas rt-PA appeared very effective in myocardial infarct patients. With these thoughts in mind, Goldhaber et al. administered rt-PA to 47 patients with angiographically documented acute PE (*20,21*). After 2–6 hr of therapy, 44 of 47 patients demonstrated significant clot lysis and 45 of 47 had no major bleeding complications. Goldhaber et al. are now in the process of conducting a PE trial in which patients are randomized to either rt-PA* or urokinase†. While these trials will examine the safety and efficacy of thrombolytic therapy among selected PE patients, future trials will be needed to determine whether thrombolytic therapy reduces the rate of mortality and recurrent PE (by dissolving the clot responsible for embolism to the lung) (*20,22*).

As the intense experience of initial hospitalization for PE is ending, patients require education about risk factors for recurrent PE, proper vein care, instructions for proper dosing of oral Coumadin anticoagulation, and guidelines for use of venous compression stockings. To optimize outpatient management, we have developed a Venous Thromboembolism Management Center as part of our new ambulatory care facility. A physician-nurse team obtains a history and performs a physical examination. If warranted, noninvasive evaluation for proximal deep venous thrombosis is carried out using impedance plethysmography‡. We then obtain a fingerstick blood specimen and determine the prothrombin time using a device§ that processes the blood sample within two minutes. If adjustments are needed in the Coumadin dose, they can be made immediately. If no dose adjustment is needed, the patient benefits by having immediate reassurance that the dose of Coumadin is appropriate. We usually treat our PE patients with Coumadin for one year unless irreversible risk factors are present (e.g., cancer or massive obesity) and warrant indefinite anticoagulation. When our patients are recumbent, we use venous compression stockings to help prevent recurrent PE. For ambulatory patients, a distributor of stockings is available within our institution to provide immediate customized fitting to help prevent chronic venous insufficiency of the legs.

Using all the resources, we seek careful patient follow-up and urge our patients to adopt a vigorous health-oriented lifestyle characterized by daily exercise and compliance with the prescribed Coumadin regimen. Thus, optimal management of PE requires prompt and accurate diagnosis, treatment with heparin anticoagulation (preceded by thrombolytic therapy in certain circumstances), and consolidated, frequent outpatient follow-up.

NOTES

* Genentech, Inc., South San Francisco, CA.

† Abbot Laboratories, Chicago, IL.

‡ IPG 200, Codman and Shurtleff, Inc., Randolf, MA.

§ Coumatrack,® DuPont, Wilmington, DE.

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