Management of Pulmonary Embolism in 2005

Bruce L. Davidson, MD, MPH, and Witold Z. Tomkowski, MD

Pulmonary embolism is a common, life-threatening, yet still misdiagnosed and mistreated disease. Many aspects of the management of pulmonary embolism have changed significantly in recent years, while others have not. This review will summarize key aspects of diagnosis and treatment. Readers are referred to key texts and longer reviews for specific areas of interest.

Diagnosis

It is critical to understand that the vast majority of diagnostic studies have included symptomatic outpatients rather than inpatients. Inpatients have increased disease burden and more complicated illnesses. Since predictive values of diagnostic tests depend to a great degree on the preexisting probability of having a pulmonary embolism and this can be more difficult to estimate in complicated inpatients, it is understandable that the predictive values of the tests may be lower for inpatients. In outpatients, the incidence of a proven pulmonary embolism with a “negative” D-dimer accompanied by a “low clinical probability” is ≤1% h.¹ Two warnings pertain to using this information: This does not apply to borderline D-dimer values, and inexperienced physicians should use a clinical scoring system to arrive at their estimate of clinical probability. In outpatients, a management study of suspected pulmonary embolism has shown that no treatment is needed if the following three conditions pertain: (a) clinical suspicion is low or moderate; (b) duplex ultrasound of both proximal lower extremities (including the popliteal vein) is normal; and (c) the contrast helical CT pulmonary angiogram is truly negative (a CT that shows isolated subsegmental clot is considered indeterminate, not negative, and not positive).² If clinical suspicion is high, further testing is required.
The usefulness of D-dimer testing remains controversial in inpatients, in part due to a high percentage of “positive” D-dimer values among them consequent to a broad spectrum of diseases (other than pulmonary embolism) and procedures related to the hospitalization. Moreover, for inpatients, a negative D-dimer reduces suspicion but its sensitivity is only 89%, unsatisfactory to exclude pulmonary embolism. If the helical contrast CT angiogram is negative and ultrasound is negative, there is still a 5% false-negative rate for inpatients. There are no convincing data regarding a negative CT alone for inpatients. Accordingly, CT and D-dimer evidence may add information but conventional pulmonary arteriography may still be required to make a secure diagnosis. In its absence, a “clinical” decision to treat (and suspend treatment, if contraindications supervene) may be required.

Multislice CT for confirmation and exclusion of pulmonary embolism appears to be more promising than prior CT technology but remains under investigation. The identification by CT of other pathology in the chest that might explain symptoms, while considered by some authors to help exclude pulmonary embolism, is not persuasive to us, since occult pulmonary embolism can accompany many of these diseases (pneumonia, cancer, etc.)

**Oxygenation**

A pulse oximeter should be employed on every encounter with the patient and supplementary oxygen should be supplied as needed to keep the O$_2$ saturation $>92\%$. Patients should be checked with activity (eg, stair-climbing), since most will do such minimal activity as outpatients. When supplemental oxygen is no longer required by these criteria, it may be discontinued. Supplemental oxygen, especially in patients with overload of the right ventricle and coexisting hypoxemia, is itself a vasodilator which can decrease pulmonary artery pressure and pulmonary vascular resistance, which has been pathologically elevated by pulmonary embolism.

**Hemoptysis**

Hemoptysis may be safely ignored most of the time—it is usually attributable to pulmonary infarction. Under these circumstances, it is not a contraindication to anticoagulation and patients may be reassured that it will stop soon. In rare instances, when persistent or of large volume, it may be a signal of an undiscovered bronchogenic tumor that warrants bronchoscopy or CT of the chest. Primary lung cancer or pulmonary metastases of various tumors can coexist with pulmonary embolism.
Pleuritic Pain

Pleuritic-type pain is common with pulmonary embolism. It is easily relieved by indomethacin,4 which we dose at 50 mg every 6 to 8 h, or perhaps with another nonsteroidal antiinflammatory drug prescribed at appropriate dosage and intervals. Some physicians administer 30 ml antacid with each dose to prevent dyspeptic distress. Pleuritic-type pain is reduced within 24 h after this regimen and usually eliminated within 48 h. There is no need for concern regarding the possibility of worsening bleeding risk due to possible platelet inhibition by such drugs. Moreover, there is usually no need for narcotics with attendant constipation and sleepiness preventing ambulation.

Pleural Effusion

Pleural effusion is common, usually unilateral, and exudate, and is bloody a little less than half the time if it is sampled, and occupies <50% of the hemithorax.5 Draining a pleural effusion secondary to pulmonary embolism is not necessary, but thoracentesis is sometimes done before the diagnosis is made or before anticoagulation is begun. If the patient is already anticoagulated, bleeding sites to which pressure cannot be directly applied should be minimized, precluding elective thoracentesis.

Low Cardiac Output

Clinical signs of low cardiac output after pulmonary embolism include tachycardia, weakness, and dyspnea with limited exertion. The reason is obstructed pulmonary arteries and an enlarged right ventricle encroaching on left ventricular filling. It is critical first to recognize that these signs point to serious cardiopulmonary compromise, whatever the oxygen saturation. Urine output should be monitored closely; oxygen and minimal exertion should be enforced, and the patient should be transferred to the intensive care unit and given pressor if required.6

Shock

Thrombolytic therapy should be considered if shock is due to pulmonary embolism and there is no contraindication. Drug choices include rt-PA (100 mg iv over 2 h), streptokinase (1.5 million units infused over 1 hour [an unapproved regimen]7; or 250,000 units as a bolus, then 100,000 units/h for 24 h), and other drugs approved in various nations.8 Other techniques, including pulmonary embolectomy, catheter clot fragmentation, pulmonary artery angioplasty, clot retrieval, and surgery on cardiopulmonary bypass have also been employed in selected patients.9
“Submassive Pulmonary Embolism”

Submassive pulmonary embolism is pulmonary embolism without shock but with echocardiographic evidence of right ventricular dysfunction. The argument for echocardiography in this setting is that echocardiography reveals many patients with right ventricular dysfunction (inconsistently defined) without overt shock, and that thrombolysis may save the lives of some such patients who would have a poor outcome. Thirty-one percent of acute pulmonary embolism patients have such findings without shock; this is 40% of the normotensive patients with pulmonary embolism.\(^{10}\) Thrombolysis generally reduces pulmonary vascular obstruction when baseline and 24-h perfusion lung scans or pulmonary arteriography has been employed for evaluation. Moreover, a recently published controlled, partially blinded clinical trial\(^{11}\) showed that if “escalation of therapy” were the outcome, rt-PA was superior to unfractionated heparin in such patients. The increased incidence of treatment escalation (25% in heparin versus 11% in t-PA recipients, \(P = 0.006\)) was due to a statistically significantly increased “requirement” for thrombolysis (determined after unblinding) in the heparin recipients (23% versus 8% in the t-PA recipients). Moreover, the heparin recipients had a higher incidence of major bleeding (3.6 versus 0.8%) and fatal bleeding, and no patients suffered hemorrhagic stroke. These safety results are quite contrary to prior reports. This study report prompted several rebuttal letters subsequently published.

The arguments against thrombolysis for submassive pulmonary embolism are that, although it improves pulmonary perfusion at the end of day 1, day 7 perfusion is not changed and mortality is not improved. Also, prior studies have shown it increases the intracranial hemorrhage rate from 0.2% with heparin alone to around 2.2%, and increases the major bleeding rate from around 2% with heparin alone to 6 to 15%, depending on the study.\(^{12}\) Modeling of thrombolysis use employing the incidence figures cited above (not those from the recently published Konstantinides study) would lead to approximately 1800 excess hemorrhagic strokes per 300,000 incident patients with pulmonary embolism. This is a large safety cost, in addition to the economic cost. For these reasons, many experts recommend reserving thrombolysis for patients with shock.

**Duration of Pulmonary Embolism Treatment**

Most commonly, patients receive a minimum of 6 months of treatment. Occasionally, some physicians will use 3 months of treatment after relief of a temporary risk factor. The British Thoracic Society\(^{13}\) recently
recommended 4 to 6 weeks of treatment in this latter circumstance, a recommendation with which the authors cannot agree. There is renewed interest in reimaging the pulmonary vasculature (eg, with a radionuclide perfusion scan or CT scan) when treatment cessation is considered, to confirm resolution or help decide, in conjunction with the patient, to continue therapy (see below, “Chronic Thromboembolic Pulmonary Hypertension”).

Initial Anticoagulant Therapy

Initial anticoagulant therapy must be injected and continued for at least 5 days together with oral anticoagulant optimally started at the first day, and the patient must have an international normalized ratio (INR) >2.0 (target 2.5) for two consecutive days to assure it is safe to discontinue initial anticoagulant therapy.8,14 Although sometimes this can be accomplished in 4 to 5 days, more often it takes 6 to 9 days in the setting of pulmonary embolism.15 Since injected anticoagulants are more effective than oral anticoagulants, patients who are not recovering well from pulmonary embolism should remain on injected anticoagulant until they do substantially improve, even if the INR criterion is met earlier with an oral vitamin K antagonist. The latter patients can receive both drugs together.

There are several acceptable choices for initial anticoagulant therapy. They are unfractionated heparin, 80 U/kg iv bolus, and then 18 U/kg/h by continuous infusion in water with 5% dextrose. This should be regulated with frequent aPTT monitoring (eg, q 6 h) until it is 1.5 to 2.5 times the laboratory control value. Problems with this choice are (a) the requirement for frequent monitoring and dose adjustment; (b) the fact that evidence (Matisse investigators, unpublished data) suggests that if aPTT values fall below the target range, the risk of recurrence is increased; and (c) the requirement for laboratories to determine the therapeutic range with each new batch of aPTT reagents and equipment changes, a requirement not commonly met. Advantages of this choice are the short half-life of infused heparin (60 min) and reversibility with protamine sulfate (1 mg per 100 U unfractionated heparin) if bleeding ensues.

Fondaparinux given subcutaneous once daily (5 mg for <50 kg, 7.5 mg for 50 to 100 kg, 10 mg for >100 kg)15 is approved in the USA for pulmonary embolism treatment. Its half-life is 16 h, allowing once-daily dosing. It does not require monitoring and was found comparable to iv heparin with respect to recurrence and bleeding in a large international clinical trial.15 Advantages include minimal adjustment for weight, once daily dosing (self-administered or with a health provider daily check-up),
and the possibility of early discharge for selected patients at low risk for complications.

Several low molecular weight heparins have been studied for treatment in patients who have pulmonary embolism and concurrent deep vein thrombosis or deep vein thrombosis alone.\textsuperscript{16-20} Although some are approved for once-daily dosing, twice-daily dosing is preferred by some experts to increase the chance of maintaining antithrombotic activity throughout a 24-h period (these drugs have considerably shorter half-lives than fondaparinux, eg, 6 h). Like fondaparinux, these do not require monitoring and selected patients may be discharged early after observation.\textsuperscript{15,20}

Patients with significant renal insufficiency have impaired hemostasis and may require downward adjustment of low molecular weight heparin or fondaparinux dosage. Regardless of the anticoagulant received, if these patients bleed, hemostasis may require more attention than other patients.

**Vena Cava Interruption**

Recently developed retrievable inferior vena cava filters (and permanent ones) may be used when a contraindication to injected anticoagulant is sufficiently grave so as to prevent its use. When the contraindication remits, anticoagulant therapy should start. Implanted permanent vena cave filters significantly increase the rate of recurrent deep venous thrombosis at 2 years.\textsuperscript{21}

**Chronic Anticoagulation Therapy**

Vitamin K antagonists (eg, warfarin, acenocoumarol, etc.) are begun orally, usually once daily, when patients are considered stable enough not to require immediate reversal of anticoagulation, because reversal with vitamin K and fresh frozen plasma requires many hours. These drugs are given in daily maintenance dosages rather than loading dosages (eg, 4 or 5 mg once daily of warfarin) and continued until the INR is $>2.0$ for two consecutive days. After the criterion of five consecutive days of injected anticoagulant therapy has been met, the injected anticoagulant can be discontinued if other criteria are met. In community practice, the INR target of 2.5 is rarely consistently achieved.\textsuperscript{22} The range of 2.0 to 3.0 is met approximately 50% of the time. In specialty clinics and studies, it is met approximately two-thirds of the time, but clinicians should keep trying (see below).
Patients with Cancer

Patients with cancer have higher risks of recurrence and bleeding than other patients when given the above acute and chronic treatments. Several studies suggest that prolonged injected anticoagulant (low molecular weight heparin) provides a better result. In some centers, unless there is no way to pay for prolonged injected anticoagulant, cancer patients with pulmonary embolism receive prolonged low molecular weight heparin (eg, dalteparin 200 U/kg once daily for 1 month, then 150 to 160 U/kg once daily\textsuperscript{23}; or enoxaparin\textsuperscript{24}) for 5 months or longer. Some centers use different low molecular weight heparins with supportive but less compelling data.

Chronic Thromboembolic Pulmonary Hypertension

Recent data from the first published study\textsuperscript{25} to follow the incidence of this disease in patients suffering a first pulmonary embolism demonstrated it occurred in 4% of patients and was established by 2 years after the first event. How to prevent this is uncertain at this time. Close attention to proper anticoagulation and sufficient oxygenation are reasonable suggestions while studies are developed. Patients with established thromboembolic pulmonary hypertension require therapeutic anticoagulation indefinitely, and possibly, thromboendarterectomy.

REFERENCES