Review: Clinical Cardiology: New Frontiers

Acute Pulmonary Embolism: Part II
Risk Stratification, Treatment, and Prevention

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Pulmonary embolism (PE) presents with a wide clinical spectrum, from asymptomatic small PE to life-threatening major PE that causes hypotension and cardiogenic shock (Table). Traditionally, our risk assessment is done by gestalt. However, a more precise risk assessment can be obtained by using a formal clinical scoring system, such as the Geneva Prognostic Index. The Geneva Prognostic Index uses an 8-point scoring system and identifies 6 predictors of adverse outcome: 2 points each for cancer and hypotension and 1 point each for heart failure, prior deep vein thrombosis (DVT), arterial hypoxemia, and ultrasound-proven DVT. As points accumulate, prognosis worsens. Remarkably, hypoxemia accounts for only 1 of 8 points.

Physical examination, ECG, chest radiograph, CT scan, and echocardiogram can provide evidence of right ventricular dysfunction, a key prognostic marker of high risk and increased major adverse clinical events. The most recent development in prognostication is the use of biomarkers, such as troponin elevation, which indicates right ventricular microinfarction, and elevations of pro-B-type natriuretic peptide and B-type natriuretic peptide, which indicate right ventricular overload.

On physical examination, general clinical appearance is useful, but young patients may appear deceptively well despite massive PE. Clues to right heart failure include distended jugular veins, an accentuated pulmonic heart sound, and a tricuspid regurgitation murmur.

The ECG may show a classic S1Q3T3 pattern but more often will demonstrate a less commonly recognized sign of right ventricular strain, T wave inversion in leads V1 through V3. New incomplete or complete right bundle-branch block is a very useful sign of right ventricular dysfunction. The chest radiograph may show enlarged pulmonary arteries, especially an enlarged right descending pulmonary artery, indicating pulmonary hypertension. Although the chest CT scan is performed primarily to detect or exclude PE, information about right ventricular dilatation can also be gleaned in the phase of the scan in which the right and left ventricles are imaged. If the right ventricle is as large as the left ventricle, then right ventricular dilatation attributable to right ventricular dysfunction can be confidently diagnosed.

The echocardiogram is a low-yield diagnostic tool in patients with PE, because it will usually be normal. However, in acutely ill patients, the echocardiogram is quite useful because it can often help differentiate right ventricular dysfunction typical for PE from other catastrophic illnesses, such as pericardial tamponade, dissection of the aorta, and acute myocardial infarction. Among patients in whom the diagnosis of PE is established, the echocardiogram provides rapid and accurate risk stratification. Moderate or severe right ventricular hypokinesis, pulmonary hypertension, a patent foramen ovale, and free-floating right-heart thrombus are markers for a high risk of death or recurrent PE.

Anticoagulation

When acute PE is considered likely, heparin anticoagulation should be begun while pursuing the diagnostic workup. Short-acting, intravenously administered unfractionated heparin is initiated with a bolus of 80 U/kg followed by a continuous infusion of 18 U/kg per hour. The target activated partial thromboplastin time is usually between 60 and 80 seconds. After discontinuing the infusion, the anticoagulant effect will quickly abate. This rapid reversibility is important for patients who may require thrombolyis or embolectomy.

For stable patients with PE, there is increasing interest in using weight-based dosing of low-molecular-weight heparin in lieu of unfractionated heparin. In the therapy of DVT, a meta-analysis indicated that low-molecular-weight heparin reduces mortality with no increase in bleeding compared with unfractionated heparin. A DVT trial using contrast venography showed that the low-molecular-weight heparin reviparin is more effective than unfractionated heparin in reducing the size of the thrombus. An alternative approach to anticoagulation is use of a long-term, low-molecular-weight heparin without oral anticoagulation. This strategy reduces the risk of recurrent venous thromboembolism in patients with cancer. Monotherapy with low-molecular-weight heparin is also suitable for patients either intolerant of warfarin or unable to maintain therapeutic levels of warfarin. When heparin-induced thrombocytopenia complicates management, the intravenous direct thrombin inhibitors argatroban and lepirudin can be used.

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Risk Stratification

Clinical assessment
Gestalt
Geneva Prognostic Index
Right ventricular dysfunction
Clinical evaluation
Jugular venous distension
Tricuspid regurgitation murmur
Accentuated pulmonic heart sound
Electrocardiogram
T-wave inversion in leads V₅–V₆
New right bundle-branch block
S1Q3T3
Chest CT
Right ventricular enlargement relative to left ventricular size
Echocardiogram
Right ventricular dilatation
Right ventricular free wall hypokinesia; decreased right ventricular systolic function with increased right ventricular afterload and decreased right ventricular stroke work
Pulmonary hypertension with Doppler estimate of pulmonary artery systolic pressure
Impaired left ventricular diastolic filling, with leftward displacement of the interventricular ventricular septum; A/E ratio is >1
Biomarkers
Troponin (increased right ventricular end diastolic pressure impairs subendocardial perfusion, limits the coronary oxygen supply, and leads to right ventricular microinfarction)
Pro–B-type natriuretic peptide
B-type natriuretic peptide

"Saddle" or large proximal PE on CT scan

Inferior Vena Caval Filters

Inferior vena caval filters can be inserted percutaneously to prevent PE, but they do not halt the thrombotic process. They also serve as a nidus for recurrent venous thromboembolism. In a large California database, use of a filter was associated with a 2.6-fold increase in the likelihood of rehospitalization for venous thrombosis within 1 year of filter placement. The 2 principal indications are an absolute contraindication to anticoagulation and recurrent PE despite extended and therapeutic-level anticoagulation. Retrieved filters provide the option of temporary use.

Thrombolysis

Thrombolysis in PE has been hampered by a paucity of clinical trials. Therefore, guidelines for its use and data on efficacy and safety are far less precise than for acute myocardial infarction. There is a consensus to use thrombolysis in massive PE, but controversy arises because most patients who are potential candidates have preserved systemic arterial pressure with moderate or severe right ventricular dysfunction. The only contemporary Food and Drug Administration–approved agent is recombinant tissue plasminogen activator (rt-PA), administered as a 100-mg continuous infusion over 2 hours without concomitant heparin. We withhold heparin because reocclusion does not seem to be a clinical problem during administration of thrombolysis.

In 1993, a multicentered United States trial randomized 101 hemodynamically stable patients to tissue plasminogen activator followed by heparin versus heparin alone. No clinical episodes of recurrent PE were observed among rt-PA patients, but there were 5 recurrences, including 2 fatalities, among heparin-alone patients within the ensuing 14 days (P=0.06). Right ventricular wall motion improved in more than twice as many rt-PA compared with heparin-alone patients. This improvement was accompanied by a decrease in right ventricular end diastolic area. The rapid reversal of right ventricular dysfunction provides a mechanism to explain potential reduction in mortality from PE.

In 2003, the MANagement strategies and Prognosis of Pulmonary Embolism-3 Trial (MAPPET-3) group compared rt-PA plus heparin and heparin alone in a double-blind trial of 256 PE patients with right ventricular dysfunction but without hypotension or shock. The primary end point was death or escalation of therapy, defined as the need for catecholamine infusion, open-label thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency embolectomy. The primary end point occurred in 25% of patients treated with heparin alone compared with 10% of patients treated with rt-PA plus heparin (P=0.006). No intracranial hemorrhage occurred. However, in the registry of 2454 patients with PE, 304 received thrombolysis, of whom 3.0% had intracranial bleeding. This contrast in bleeding rates points out how safety can vary markedly in the context of a controlled clinical trial compared with real-life clinical practice.

Hardly any data provide long-term follow-up of patients in clinical thrombolysis trials for PE. One small study demonstrated preservation of the normal hemodynamic response to exercise in patients who received lysis on average 7 years earlier, whereas those who had received heparin alone developed a pulmonary arterial hypertensive response.

Embolectomy

For patients with contraindications to thrombolysis, catheter-based or surgical embolectomy should be considered if risk stratification indicates a high likelihood of an adverse outcome. Catheter-based approaches include clot fragmentation, rheolytic thrombectomy using a high-velocity saline solution jet to create a strong Venturi effect, and clot aspiration with a large syringe using a coronary guiding or Greenfield embolectomy catheter.

Open surgical embolectomy has recently undergone a renaissance. The operation had been disparaged because of historically poor survival. However, use of contemporary risk stratification provides early identification of patients who will deteriorate hemodynamically. They often have preserved systemic arterial pressure but profound right ventricular dysfunction. Successful outcome hinges on an interdisciplinary team dedicated to identify, screen, and operate on these patients. Round-the-clock availability is essential, because
these patients rarely present during the daytime on weekdays. Technical innovations include avoiding aortic cross-clamping, operating on a warm beating heart to prevent cold injury, and avoiding blind instrumentation of the pulmonary arteries. This approach to embolectomy resulted in an 89% survival rate in 29 operations performed in a 2-year time period at Brigham and Women’s Hospital.21

**Initiation and Monitoring Oral Anticoagulation**
In the United States, warfarin is the only anti–vitamin K agent used for oral anticoagulation. It is administered after the initiation of unfractionated heparin or low-molecular-weight heparin, which are continued for 5 or more days until a stable dose of warfarin is achieved. For patients with PE, the dose of warfarin is titrated to a therapeutic international normalized ratio (INR), usually a target range of 2.0 to 3.0. Coordination of laboratory monitoring and dosing of warfarin for large numbers of patients is best accomplished with a multidisciplinary nurse-pharmacist-physician anticoagulation service.22 Some patients will be extremely sensitive to small doses of warfarin because of a genetic mutation that causes slow metabolism of the S-enantiomer of warfarin.23 Excessively high INRs are classically managed by withholding warfarin and administering oral vitamin K.24 For critically prolonged INRs, human recombinant factor VIIa concentrate can avert or reverse bleeding safely and rapidly.25 Unfortunately, the INR is not ideal for monitoring anticoagulation intensity, because patients with similar INRs show wide individual variability in their tissue factor coagulation response.26

**Novel Anticoagulants**
The next generation of anticoagulants to treat acute PE will provide simplified dosing with minimal laboratory monitoring. The anti-Xa agent fondaparinux is a synthetic pentasaccharide that, at a dose of 7.5 mg SC once daily, is at least as effective and safe as intravenous heparin.26a Fondaparinux is already approved by the Food and Drug Administration at a dose of 2.5 mg daily for prophylaxis in patients undergoing total hip or knee replacement or hip fracture surgery.27 Ximelagatran, an oral direct thrombin inhibitor administered in a fixed dose twice daily, is a promising alternative to warfarin in the treatment of venous thromboembolism28 and in prophylaxis of patients undergoing total knee replacement.29 Another approach that warrants investigation is combining optimal anticoagulant therapy with an antiplatelet regimen to provide additional antithrombotic protection. There is experimental and clinical evidence to suggest that antiplatelet agents can attenuate the pulmonary vasoconstriction, bronchospasm, and hypoxia associated with PE.30

**Optimal Duration and Intensity of Oral Anticoagulation**
The rate of recurrent PE after discontinuing anticoagulation is twice as high in patients with idiopathic PE compared with PE ascribed to temporary risk factors such as surgery.31 Six months of anticoagulation for both idiopathic and nonidiopathic venous thromboembolism has been the standard duration of anticoagulation to minimize recurrences after discontinuation of therapy. This approach halved the rate of recurrences, from 18% to 9.5%, during the 2 years after cessation of anticoagulation.32 However, when standard-intensity anticoagulation is continued indefinitely for patients at high risk of recurrent PE, such as those who have suffered a second episode of venous thromboembolism, major hemorrhaging may become problematic. In a Swedish trial, indefinite anticoagulation averted 0.43 episodes of recurrent thromboembolism per month per 100 patients at a cost of 0.20 major hemorrhages per month.33

Because of the high risk of recurrent venous thromboembolism after cessation of oral anticoagulation, a series of trials examined prolonged anticoagulation regimens in patients with idiopathic PE and DVT. A Canadian study demonstrated that a strategy of prescribing 2 years of warfarin anticoagulation is more effective than 3 months of therapy.34 An Italian trial showed that the clinical benefit associated with extending the duration of anticoagulation to 1 year is not maintained after the warfarin is discontinued.35

A subsequent Canadian trial found that prolonged-duration conventional-intensity warfarin, with a target INR of 2.0 to 3.0, is more effective and no less safe than low-intensity warfarin, with a target INR of 1.5 to 1.9.36 An international trial, Thrombin Inhibitor in Venous Thromboembolism (THRIVE) III, randomized 1233 patients with idiopathic venous thromboembolism who had received 6 months of standard warfarin therapy to an oral direct thrombin inhibitor (ximelagatran 24 mg twice daily) versus placebo for 18 months.36a The ximelagatran group exhibited an 84% decrease in recurrent events compared with placebo, from 12% to 2%, with no increase in major bleeding.

The PREVENT Trial tested low-intensity warfarin, target INR of 1.5 to 2.0, against placebo in 508 patients with idiopathic PE or DVT who had previously completed an average of 6 months of standard anticoagulation.37 Patients assigned to low-intensity warfarin required routine blood testing only once every 2 months. Warfarin reduced by two thirds the frequency of recurrent events. All subgroups benefited, including patients with factor V Leiden or the prothrombin gene mutation.

Based on presently available evidence, we recommend a fixed course of 6 months of anticoagulation for patients with PE attributable to surgery or trauma. Most other patients should receive indefinite-duration therapy (Figure).

**Prevention**
Prevention is critical in reducing the death rate, morbidity, and cost of PE. Mechanical measures include graduated compression stockings, intermittent pneumatic compression devices, and placement of a temporary or permanent inferior vena cava filter. Intermittent pneumatic compression stimulates endogenous fibrinolytic activity in addition to direct physical stimulation of increased venous blood flow.38 Pharmacological options include unfractionated heparin, low-molecular-weight heparin, warfarin, and fondaparinux.37 For patients at high risk, a combination of mechanical and pharmacological measures can be used, such as graduated compression stockings plus intermittent pneumatic compression boots plus low-molecular-weight heparin.
Therapeutic strategy for pulmonary embolism.

Perioperative prophylaxis is widely accepted by general, subspecialty, and orthopedic surgeons. However, because of abbreviated hospitalizations, most postoperative PEs occur after hospital discharge. After surgery for abdominal and pelvic cancer, 4 weeks of enoxaparin prophylaxis was safe and reduced by more than half the frequency of venous thromboembolism compared with enoxaparin prophylaxis for 1 week. A meta-analysis of randomized trials indicated that among patients undergoing total hip or knee replacement, extended-duration prophylaxis for 30 to 42 days reduced the frequency of symptomatic venous thromboembolism by approximately two thirds without an increase in major bleeding complications. There was a greater reduction in venous thromboembolism among those undergoing hip replacement compared with knee replacement.

In contrast to surgical patients, hospitalized medical patients often do not receive effective, evidence-based prophylaxis. Two large placebo-controlled trials have demonstrated the efficacy of fixed, low-dose, low-molecular-weight heparin for reducing the DVT rate among hospitalized patients with medical illness. A double-blind study of 1102 patients showed that enoxaparin 40 mg once daily reduced the frequency of DVT by two thirds without an increase in major bleeding complications. Another trial with similar design studied more than 3000 patients with medical illness and found that a fixed dose of dalteparin 5000 units daily halved the DVT rate compared with placebo.

All hospitals should develop and enforce protocols that ensure routine prophylaxis of patients at moderate and high risk of venous thromboembolism. Implementation of clinical guidelines can be facilitated with computer-based order entry systems. This approach has been proven to motivate physicians to order prophylaxis on an orthopedic surgical unit.

Enforcing the use of evidence-based prophylactic regimens during hospitalization and extending these protocols at the time of discharge to skilled nursing facilities, rehabilitation hospitals, and home will enhance patient safety.

Summary

Acute PE is increasingly appreciated as a major cardiopulmonary illness and public health issue. As the public becomes familiar with signs and symptoms of PE and DVT, more patients will be transported to emergency departments for urgent evaluation and treatment. Great progress has been made in the rapid detection and exclusion of PE, especially with the advent of d-dimer testing and chest CT scans. Rapid risk stratification facilitates selection of patients who warrant aggressive intervention with thrombolysis or embolectomy. For patients with idiopathic venous thromboembolism, there seems to be a lifelong tendency for recurrent thrombosis unless anticoagulation is continued.

New frontiers in molecular genetics will provide a better appreciation of the interaction between inherited and environmental risk factors for PE. Novel mutations for thrombophilia will emerge in patients who presently have normal laboratory evaluations. Point of care blood testing will provide accurate screening of patients with suspected PE to triage those most appropriate for noninvasive imaging. When PE is confirmed, cardiac biomarkers will assist in rapid risk stratification so that the intensity of treatment matches the predicted risk profile of the patient. The definition of idiopathic PE will undergo refinement, and indefinite duration anticoagulation will become commonplace. Novel anticoagulant regimens will be safer and more convenient. Efforts to prevent PE will be pervasive, and computerized order entry and surveillance will ensure that hospitalized patients received appropriate prophylaxis.

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