Acute Pulmonary Embolism
Part II: Treatment and Prophylaxis
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Case presentation: A 66-year-old man with a history of deep venous thrombosis (DVT) presented with acute dyspnea. He was normotensive, with a resting tachycardia of 110 beats per minute and an oxygen saturation of 76% on room air. The only electrocardiographic abnormality was sinus tachycardia. His brain-type natriuretic peptide (BNP) and cardiac troponin levels were elevated. Chest computed tomography (CT) with contrast demonstrated a large saddle pulmonary embolus and increased diameter of the right ventricle (RV) compared with the left ventricle (LV). The patient received intravenous bolus followed by continuous infusion unfractionated heparin. Within several hours, the patient became progressively more hypotensive and hypoxic. Bedside transthoracic echocardiography (TTE) showed RV dilatation and hypokinesis. He then received intravenous fibrinolysis, with rapid improvement in hemodynamics and oxygenation. What were the clues that he was likely to suffer from progressive hypotension and hypoxemia?

Risk Stratification
Pulmonary embolism (PE) represents a spectrum of syndromes ranging from small peripheral emboli causing pleuritic pain to massive PE resulting in cardiogenic shock or cardiac arrest. Most patients with PE present with normal blood pressure. However, some may rapidly deteriorate and manifest systemic hypotension, cardiogenic shock, and sudden death despite therapeutic levels of anticoagulation. Risk stratification to identify such patients has emerged as a critical component of care.

The history and physical examination provide the starting point for risk stratification. The International Cooperative Pulmonary Embolism Registry (ICOPER) identified age 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, and systolic blood pressure less than 90 mm Hg as significant predictors of increased mortality. Elevated cardiac biomarkers correlate with the presence of RV dysfunction, a powerful independent predictor of early mortality. Whereas cardiac troponins are released as a result of microinfarction due to RV pressure overload, BNP is secreted from cardiac myocytes in response to RV shear stress. Patients with PE and elevated cardiac biomarkers should undergo TTE to test for the presence of RV dysfunction.

Echocardiography is the imaging test of choice for risk stratification of patients with PE. Although normotensive patients with PE and no evidence of RV dysfunction generally have a benign hospital course, patients with RV dysfunction on echocardiography have an increased risk of hypotension, cardiogenic shock, and early death.

RV enlargement as detected by chest CT has also been evaluated in the risk stratification of patients with acute-onset PE. Using measurements from a reconstructed CT 4-chamber view, RV enlargement, defined as a ratio of RV to LV dimension of greater than 0.9, was a significant independent predictor of 30-day mortality. An algorithm that synthesizes clinical indicators, cardiac biomarkers, and echocardiography or RV size on CT helps detect those patients with an increased risk of adverse events (Figure 1).

Management
Spectrum of Disease
Patients with acute PE presenting with a normal blood pressure and no evidence of RV dysfunction generally...
have a stable hospital course when treated with anticoagulation alone. Normotensive patients with PE and evidence of RV dysfunction are classified as having submassive PE and represent a population at elevated risk for adverse events and early mortality. Finally, massive PE describes patients presenting in cardiogenic shock.

**Primary Therapy**

Primary therapy with fibrinolysis or embolectomy is generally considered for patients presenting with either massive or submassive PE. However, because of a relative paucity of randomized controlled trials, the use of primary therapy in the treatment of massive and submassive PE remains controversial.

The Food and Drug Administration (FDA) has approved t-PA (alteplase) 100 mg administered as a continuous infusion over 2 hours for the fibrinolysis of massive PE. Every patient being considered for fibrinolysis requires meticulous screening for contraindications because the bleeding risk may be as high as 3.0% for intracranial hemorrhage.1,6 Although fibrinolysis is generally considered to be a lifesaving intervention in patients with massive PE, the extent of the clinical benefit remains unclear.7 In a recent analysis of the ICOPER data, fibrinolytics did not reduce the rate of mortality or recurrent PE at 90 days.7 In submassive PE, the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial (MAPPET-3) demonstrated a reduction in the need for escalation of therapy among patients receiving alteplase.8

In patients with massive or submassive PE in whom fibrinolysis is contraindicated or has failed, surgical embolectomy may be considered. Additional indications include paradoxical embolism, persistent right heart thrombi, and hemodynamic or respiratory compromise requiring cardiopulmonary resuscitation. In specialized centers caring for patients with massive PE, surgical embolectomy has been demonstrated to be a safe and effective treatment technique.9,10 Catheter-based pulmonary embolectomy is an emerging modality for the primary therapy of acute PE.11 Catheter-based strategies are considered when fibrinolysis and open surgical embolectomy are contraindicated. In general, catheter-based embolectomy is most successful when applied to fresh thrombus within the first 5 days of symptoms of PE.

**Anticoagulation**

Whether or not patients undergo primary therapy, anticoagulation is a critical component of the management of PE. The majority will receive intravenous unfractionated heparin administered as a bolus followed by continuous infusion titrated to a target activated partial thromboplastin time of 2 to 3 times the upper limit of normal (approximately 60 to 80 seconds). Weight-based nomograms may achieve therapeutic levels of anticoagulation more quickly. Unfractionated heparin, which can be rapidly reversed, is preferred in patients undergoing fibrinolysis or embolectomy. In contrast to fibrinolysis in myocardial infarction, heparin is withheld during the administration of t-PA for PE and is not restarted until the activated partial thromboplastin time has fallen to less than twice the upper limit of normal.

Low-molecular-weight heparins (LMWHs) such as enoxaparin have been shown to be as safe and effective as intravenous unfractionated heparin.12,13 LMWH monotherapy without oral anticoagulation appears promising and may be preferable in patients with malignancy.14–16 LMWHs offer several advantages over unfractionated heparin including a longer half-life, increased bioavailability, and a more predictable dose response. In addition, LMWHs are dosed by weight, administered subcutaneously, and usually do not require dose adjustments or laboratory monitoring. Whereas unfractionated heparin is largely hepatically cleared, LMWHs are renally cleared. Patients with chronic kidney disease, massive obesity, pregnancy, or unanticipated bleeding or thromboembolism despite correct weight-based dosing of LMWH may benefit from laboratory monitoring. However, the utility of anti-Xa testing continues to be the subject of debate because the correlation of anti-Xa levels to antithrombotic effect and risk of bleeding has been questioned.17,18

Although the risk is lower with LMWH, use of both unfractionated heparin and LMWH is associated with the development of heparin-induced thrombocytopenia (HIT). HIT results from heparin-dependent immunoglobulin G antibodies directed against...
heparin-platelet factor 4 complex and may lead to devastating arterial and venous thromboembolism. Whereas a benign transient decrease in platelets may be seen within the first few days of heparin administration, a decrease in platelet count of greater than 50% of baseline or a new thromboembolic event in the setting of any heparin product including heparin flushes should raise concern about possible HIT and lead to discontinuation of all heparin. Although it typically occurs within 4 to 14 days of heparin exposure, HIT may occur earlier if the patient has been previously exposed to heparin. Delayed-onset HIT should be considered in patients recently exposed to heparin who present with thrombocytopenia on re-exposure. If HIT is suspected or confirmed, clinicians should administer a direct thrombin inhibitor such as argatroban or lepirudin.

Fondaparinux is a synthetic pentasaccharide with anti-Xa activity approved by the FDA for the initial treatment of venous thromboembolism including PE. In hemodynamically stable patients with acute symptomatic PE, fondaparinux is as safe and effective as intravenous unfractionated heparin. Fondaparinux is administered subcutaneously on a once-daily basis in fixed doses of 5 mg for body weight <50 kg, 7.5 mg for body weight of 50 to 100 kg, and 10 mg for body weight >100 kg. Unlike intravenous unfractionated heparin, fondaparinux is administered in a fixed dose and does not require dose adjustment with laboratory coagulation tests. Fondaparinux, cleared through the renal route, is contraindicated in patients with severe renal disease. In contrast to heparin compounds, fondaparinux does not cause HIT.

Oral vitamin K antagonists such as warfarin have remained the mainstay of outpatient anticoagulation for venous thromboembolism (VTE). Oral anticoagulation is usually initiated simultaneously with heparin, LMWH, or fondaparinux and overlapped for at least 5 days until full therapeutic efficacy has been achieved. The target international normalized ratio (INR) is between 2.0 and 3.0 for the majority of patients with PE. Oral anticoagulation with warfarin must take into account the many drug–food, drug–alcohol, and drug–drug interactions. Genetic variation in warfarin metabolism leading to very slow metabolism of the drug and lower maintenance doses presents an additional challenge.

The effect of polymorphisms in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) on the response to warfarin was evaluated. Ten common noncoding VKORC1 single-nucleotide polymorphisms and 5 major haplotypes were identified. The 5 major haplotypes were categorized into either a low-dose haplotype group (A) or a high-dose haplotype group (B). The maintenance dose of warfarin differed significantly among the 3 combinations of these 2 haplotype groups, low-dose (A/A), intermediate-dose (A/B), and high-dose (B/B). Of note, Asian-Americans demonstrated a higher proportion of group A haplotypes, whereas blacks had a higher proportion of group B haplotypes. On the basis of these data, VKORC1 haplotypes may explain differences in maintenance dose requirements among various patient populations and may permit stratification of patients into low-, intermediate-, or high-dose warfarin groups.

The optimal duration of anticoagulation depends on the risk of recurrent VTE. In patients without reversible causes for DVT or PE, VTE represents a chronic illness with a high risk of recurrence after completion of standard anticoagulation. Several studies have evaluated the efficacy of indefinite anticoagulation for patients with idiopathic VTE. A therapeutic algorithm that considers indefinite anticoagulation for patients with idiopathic VTE is critical (Figure 2).

Inferior Vena Cava Filters
Inferior vena cava (IVC) filters are indicated for patients in whom anticoagulation is contraindicated, those who experience recurrent PE despite adequate anticoagulation, and those undergoing open surgical embolectomy. IVC filters are associated with an increased incidence of DVT. Although further studies are required, a recent analysis from ICOPER demonstrated a significant reduction in 90-day mortality associated with IVC filters. Con-
Consider using retrievable IVC filters for patients with transient contraindications to anticoagulation.29

Prevention

Although mechanical and pharmacological VTE prophylaxis should be nearly universal among hospitalized patients, implementation of prophylaxis continues to be inconsistent. A computer-alert program at Brigham and Women’s Hospital increased physician utilization of VTE prophylaxis and resulted in a 41% risk reduction in the frequency of symptomatic DVT or PE.30

The risk of VTE persists after hospital discharge especially among postoperative patients. Several studies have validated the use of extended VTE prophylaxis for 4 to 6 weeks in patients undergoing oncological or orthopedic surgery.31–33

Prophylactic regimens use mechanical and pharmacological modalities (Table).34 Mechanical prophylactic devices including graduated compression stockings and intermittent pneumatic compression increase venous blood flow and may enhance endogenous fibrinolysis, leading to reductions in VTE.35 Agents for pharmacological prophylaxis include subcutaneously administered unfractionated heparin, LMWH, warfarin, and fondaparinux. Certain high-risk populations such as neurosurgical patients may benefit from a combination of mechanical and pharmacological prophylaxis.

The DVT Free Registry demonstrated that VTE prophylaxis continues to be underutilized in hospitalized patients on Medical Services.36 Several studies have evaluated the safety and efficacy of various VTE prophylactic regimens in medical patients. Daily subcutaneously administered enoxaparin has been shown to safely reduce the risk of VTE among patients admitted with acute medical illnesses.37 In a large, randomized, placebo-controlled trial of acutely ill medical patients, the LMWH dalteparin (5000 IU subcutaneously once daily) halved the rate of VTE, with a low risk of bleeding.38 The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) found that fondaparinux (2.5 mg subcutaneously once daily) reduced the risk of VTE among medical patients by 47%.39

Orthopedic patients demonstrate a significantly elevated risk of VTE even after discharge from the hospital. Several studies have validated extended out-of-hospital prophylaxis with warfarin or LMWH in the prevention of VTE among orthopedic patients.32,33 Fondaparinux (2.5 mg subcutaneously once daily) reduced the risk of VTE in patients undergoing hip replacement, major knee surgery, and hip fracture repair.41–44

Abdominal or pelvic surgery for malignancy is associated with an elevated risk of postoperative VTE. The Enoxaparin and Cancer (ENOXACAN) II study demonstrated that extended-duration prophylaxis with enoxaparin reduced the risk of VTE in this patient population.31

Case Presentation

The case presented highlights the fact that a subset of initially normotensive PE patients will deteriorate and develop hemodynamic instability. The case also demonstrates that these high-risk patients may be identified by elevations in cardiac biomarkers including troponin as well as by echocardiographic and chest CT evidence of RV dysfunction. RV dysfunction is an important predictor of adverse events and should lead the clinician to consider the option of fibrinolysis or embolectomy in addition to anticoagulation.

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