Venous Thromboembolic Disease: Diagnosis and Treatment

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Venous Thromboembolic Disease: Diagnosis and Treatment

Elliott S. Cohen, MD

I. INTRODUCTION

Venous thromboembolic disease remains one of the most important preventable causes of morbidity and mortality among hospitalized patients. Although deep venous thrombosis (DVT) and pulmonary embolism (PE) are often considered in the differential diagnosis of sudden or worsening dyspnea, the unequivocal diagnosis of these conditions is difficult to make. The true incidence of venous thromboembolism (VTE) is unclear because there are many cases of DVT and PE that are never diagnosed, either because of sudden death or failure to consider the possibility of these conditions. Failure to consider the diagnosis among patients with widely varying presenting symptoms leads to delays in therapy and ultimately increased morbidity and mortality from the disease. This manual reviews the predisposing conditions, diagnostic modalities, and treatment options for venous thromboembolic disease and uses case presentations to illustrate key points.

II. ACQUIRED AND HEREDITARY RISK FACTORS

Virchow’s original nineteenth century description of the risk factors for VTE encompassing the triad of hypercoagulability, stasis, and injury to the vessel wall remains clinically relevant, as nearly all of the known risk factors fall into one or more of these categories (Table 1). Although the role of stasis and injury in increasing risk for VTE may be intuitively obvious, there have been important recent developments in our understanding of inherited hypercoagulable states (Table 2). Prior to 1994, an inherited cause of hypercoagulability was detectable in a relatively small percentage of patients presenting with VTE, and the known hereditary causes were restricted to deficiencies in antithrombin III, protein C, and protein S. In 1994, resistance to activated protein C was reported as a new risk factor for VTE and was later found to be caused by a single point mutation in the factor V gene at the major cleavage site for activated protein C (Arg506Gln). In 1996, the prothrombin G20210A mutation was discovered to be a significant cause of inherited hypercoagulability, leading to an approximately 30% increase in prothrombin activity in heterozygotes compared to normal persons. In addition, hyperhomocystinemia, which occurs in several inborn errors of metabolism, has been shown to be a significant risk factor for VTE and to increase the risk of arterial thrombosis. For some time, the antiphospholipid antibody syndrome has been recognized as a predictor of acquired or inherited risk for VTE, but only recently has it become clear that patients with a single episode of VTE and this syndrome are at significant risk of recurrent VTE and death if anticoagulation is stopped.

Deficiencies of antithrombin III, protein C, and protein S are rare and if present are associated with recurrent episodes of VTE. Therefore, it may not be cost-effective to test for these conditions in patients who are “weakly thrombophilic” (first episode of VTE after 50 years of age, no history of recurrent thrombosis, and no family history of VTE). Testing may be appropriate in patients having one or more of the following: first episode before 50 years of age, history of recurrent thrombosis, or positive family history (Table 3). If one is going to test for these conditions, however, it should be remembered that anticoagulation by whatever means might complicate the interpretation of the tests. Testing 2 weeks after discontinuation of anticoagulation therapy is recommended. Since there is no evidence of a higher risk of hereditary causes in patients with an episode of VTE in the setting of a clearly identifiable acquired cause of hypercoagulability, testing for hereditary causes of thrombophilia in this clinical scenario may not be warranted. However, patients who have a VTE episode associated with pregnancy, the puerperium, or oral contraceptive use should be tested.

CASE PATIENT 1: PRESENTATION

A 35-year-old woman presents to the emergency department with the complaint of sudden onset of dyspnea and chest tightness. The symptoms began 1 hour after the patient arrived at her office, where she works...
as a tax lawyer. Her past medical history is significant for cleft lip and palate repair as a child and a miscarriage 2 years ago. She has not attempted pregnancy since that time. She denies previous thromboembolic events. Her medications include oral contraceptive pills. There have been no recent surgeries. The family history is negative for recurrent thrombosis. Her oxygen saturation on room air is 91%. A portable anteroposterior chest radiograph is normal. A ventilation-perfusion scan is read as high probability for PE, and subsequent lower extremity duplex ultrasonography shows a proximal thrombus in the superficial femoral vein.

- Should this patient be screened for hereditary causes of thrombophilia?

Laboratory screening for hereditary causes of thrombophilia should be performed in this patient. Her oral contraceptive pills likely played a role in the development of the DVT and PE; however, if she is found to have another inherited abnormality of coagulation, her risk of recurrent VTE while remaining on birth control pills will be extremely high. Her previous history of miscarriage combined with the current thromboembolic event should raise suspicion for the antiphospholipid antibody syndrome.

**CASE PATIENT 1: MANAGEMENT**

Testing shows that the patient is heterozygous for the factor V Leiden mutation. She is anticoagulated with coumadin for 6 months and advised to stop her oral contraceptive pills.

### III. DIAGNOSIS OF ACUTE DVT

Symptoms and signs of DVT include swelling, warmth, erythema, pain, or tenderness in the lower extremities. However, the diagnosis of lower extremity DVT requires objective testing, as numerous studies...
have demonstrated the poor sensitivity and specificity of the history and physical examination, even in the most experienced clinician’s hands and the highest risk patients. Even obvious swelling of the calf or leg has inconsistent utility, with a sensitivity between 35% and 97% and specificity between 8% and 88%.8

**DUPLEX ULTRASONOGRAPHY**

**Lower Extremity DVT**

Methods available for the diagnosis of lower extremity DVT include contrast venography (the gold standard), duplex ultrasonography, impedance plethysmography, computed tomography (CT), and magnetic resonance imaging. Venous ultrasonography is the most commonly used method to diagnose lower extremity DVT, and this review will focus on the strengths and weaknesses of this method.

Duplex ultrasonography combines B-mode imaging (ie, brightness modulation producing a real-time, 2-dimensional image) and Doppler techniques (measurement of direction and speed of blood flow), with the color Doppler signal superimposed on the B-mode image. The primary diagnostic criterion for the presence of thrombus is noncompressibility of a vein. Although there are differences between ultrasonography techniques, a clear advantage of one over another has not been demonstrated in prospective clinical trials as long as compression is used.8

Venous ultrasonography is more accurate in diagnosing DVT when proximal thrombi versus distal thrombi are being assessed, as the distal veins are smaller, have slower flow, and are more anatomically variable than the proximal veins.8 Isolated distal thrombi are much less common than proximal thrombi and are rarely associated with PE. Sensitivity and specificity of venous ultrasonography for symptomatic proximal DVT are approximately 95% and 96%, respectively, and the positive and negative predictive values are 97% and 98%.9 The true accuracy of ultrasonography for isolated distal DVT is uncertain but is much less than that for proximal DVT, with a sensitivity of about 73%.9 Current recommendations for patients with negative ultrasonography findings and high suspicion of isolated DVT include repeating the examination in 7 days as any missed distal calf thrombi would have migrated proximally by that time.

**Case Patient 2**

A 47-year-old woman who underwent laparoscopic cholecystectomy 2 days ago for chronic cholecystitis complains of increased dyspnea over the past 6 hours. She denies chest pain or diaphoresis. Additional past medical history includes well-controlled asthma, chronic stable renal insufficiency secondary to staghorn calculi (baseline creatinine, 2.1 mg/dL), and generalized anxiety disorder. Postoperatively, she remained in bed for the first night and most of the next day. Her first oral intake after surgery was this morning. She did not receive DVT prophylaxis. Her current medications include intravenous cefazolin, morphine as needed for pain, and lorazepam as needed for anxiety. Physical examination reveals an extremely anxious woman in moderate respiratory distress. Blood pressure is 110/70 mm Hg, pulse is 100 bpm, respiratory rate is 24 resp/min, and temperature is 38°C. Her oxygen saturation on oxygen 2 L/min via nasal cannula is 95%. Her lungs are clear to auscultation, and her abdomen is benign. Lower extremities reveal no tenderness or swelling. A chest radiograph shows atelectasis at the right base. There is a high clinical suspicion of PE. Ventilation-perfusion scan is ordered, which is subsequently interpreted by the radiologist as low probability for PE. The patient refuses to undergo contrast-enhanced spiral CT or pulmonary angiogram for fear of contrast-induced acute renal failure. Venous ultrasonography of the lower extremities reveals a left proximal thrombus.

- **How can venous ultrasonography findings be applied in the evaluation of suspected PE?**

This case illustrates the utility of venous ultrasonography in the workup not only of DVT but PE as well. The observation that PE rarely occurs in the absence of preceding proximal DVT may be used to simplify the diagnostic process in patients with suspected PE. A positive finding of proximal DVT in the case patient, who has a low probability of PE on lung scan, would provide indirect evidence of PE requiring anticoagulation. Positive venous ultrasonography is found in 5% to 10% of patients with nondiagnostic ventilation-perfusion scans.9 In addition, a meta-analysis found that 35% to 45% of patients with documented PE will have a positive noninvasive lower extremity study.10 Negative ultrasonography findings in the case patient make PE less likely but do not exclude the possibility. Approximately 80% of cases with an indeterminate ventilation-perfusion scan and normal ultrasonography of proximal lower extremity do not have pulmonary emboli.11,12 The remaining 20% of patients may have small residual distal calf thrombi or no residual thrombus. Note that these patients are at high risk for recurrent PE if these distal calf thrombi extend proximally or a new thrombus forms. Prior to recurrent PE, however, these patients may develop proximal DVT, which should be detectable if serial lower extremity venous ultrasonography is performed. Note that a calf thrombus can pass through the thigh without a thigh
clot and can cause PE in 25% of cases.13 These patients with distal calf thrombosis are at highest risk for VTE during the first 2 weeks after the initial embolic episode.9 As such, patients in this situation who do not undergo pulmonary angiogram for definitive diagnosis should have serial ultrasonography studies performed. With this approach, approximately 2% of patients will have an abnormal proximal ultrasonography study during serial testing.5,14 Patients with continued negative ultrasonography during serial testing are expected to have a low risk for recurrent DVT or PE.

**Upper Extremity DVT**

Upper extremity DVT may occur along the axillary–subclavian venous system and is of clinical importance since PE occurs in a significant portion of these patients. In a prospective study that used duplex ultrasonography with results confirmed by contrast venography, a thrombus was found in 27 of 58 patients with suspected upper extremity DVT.15 The sensitivity and specificity of ultrasonography in this study was 96% and 93.5%, confirming the diagnostic accuracy of ultrasonography for upper extremity DVT. PE occurred in 36% of the patients with confirmed upper extremity thrombus. Central venous catheters, thrombophilic states, and previous lower extremity DVT were found to be significant risk factors for the development of upper extremity DVT. Because the majority of the subclavian vein runs underneath the clavicle, compression ultrasonography may be limited and greater reliance on Doppler evaluation is required.8

### IV. DIAGNOSIS OF ACUTE PE

**CLINICAL EVALUATION**

The history and physical examination are notoriously inaccurate for the diagnosis of PE and, therefore, objective testing is required. A significant proportion of VTE research is aimed at developing accurate, noninvasive strategies for rapid diagnosis. The confusion related to clinical ability to diagnosis PE is underscored by postmortem studies documenting embolism in cases where either there was no attempt to make the diagnosis or false-negative results led to ineffective or no treatment.1 The development of pulmonary angiography as the gold standard test confirmed the inaccuracy of signs and symptoms in the diagnosis of PE.

Key symptoms should be used as important clues to further pursue the diagnosis of PE. Of course, PE should always be considered in the differential diagnosis of unexplained dyspnea, especially when associated with pleuritic chest pain. Hemoptysis also may occur with PE, but this finding is highly nonspecific. One or more of these symptoms, however, may result from pneumonia, asthma, exacerbations of chronic obstructive pulmonary disease, pneumothorax, congestive heart failure, pleural effusion, or thoracic cancer. Physical examination will classically show tachycardia, tachypnea, and clear lung fields, all nonspecific findings. Syncope and sudden hypotension should always be associated with PE and may indicate significant clot burden and more severe clinical course.8

Electrocardiographic abnormalities frequently occur with PE, but these changes also are quite nonspecific. These include ST-segment abnormalities and T-wave changes. Findings that may occur with larger clot burden and manifestations of acute cor pulmonale include the S1Q3T3 pattern, right bundle branch block, right axis deviation, and P pulmonale.

Although hypoxemia is common in acute PE, many patients may have normal oxygenation and alveolar-arterial oxygen tension difference. In short, the diagnosis of acute PE cannot be excluded on the basis of normal oxygen tension or a normal alveolar-arteriole oxygen tension difference.8

Chest radiography abnormalities may frequently be seen with PE but are generally nonspecific. A normal chest radiograph may be most helpful because acute PE should be strongly considered in the setting of acute dyspnea without evidence of bronchospasm. The classic chest radiograph findings of pulmonary infarction, such as Hampton’s hump and Westermark’s sign, are significant but rarely seen.

**ROLE OF D-DIMER TESTS**

Plasma D-dimers are produced when fibrin is degraded by the endogenous fibrinolytic system and are composed of 2 identical subunits derived from 2 fibrin molecules. Unlike fibrin degradation products, which are derived from fibrinogen and fibrin, D-dimers are a specific cross-linked fibrin derivative, making them sensitive indicators of thrombosis.16 Any condition in which fibrin is formed and degraded can lead to elevated D-dimer level. In addition to VTE, these conditions may include infections, cancer, surgery, stroke, acute coronary syndromes, cardiac and renal failure, pregnancy, and sickle cell crisis.16 Following acute VTE, D-dimer levels are elevated approximately eightfold compared to controls; they return to baseline levels after about 2 weeks.

There are a number of techniques and commercially available kits used to measure D-dimer levels either qualitatively or quantitatively. The accuracy of the test is...
highly dependent on the method used for measurement. The gold standard test with the best sensitivity remains the standard microplate enzyme-linked immunosorbent assay (ELISA) utilizing monoclonal antibodies directed at epitopes on D-dimer fragments.\(^6\) This technique is not useful in the emergency setting, however, as it is labor intensive, time consuming, and impractical for running a single sample. Newer ELISA techniques can be performed rapidly with similar accuracy to the standard microplate ELISA technique. Qualitative or semiquantitative techniques involve agglutination of latex beads or red blood cells, with results available within several minutes.\(^6\) When ordering D-dimer measurement, physicians should be aware of what method is used in their institution as results from studies using different methods cannot be compared to each other.

In patients with suspected VTE, a low plasma D-dimer level measured by ELISA has a 95% negative predictive value. Even with this level of sensitivity, the test cannot be used solely to rule out VTE since 5% of VTE cases will be missed. D-Dimer measurement combined with venous ultrasonography has nearly 100% sensitivity for DVT, and this strategy has been shown to obviate the need for serial ultrasonography in patients with initial normal results from both tests.\(^6\) A recent study suggests that the accuracy of D-dimer for PE may depend on location of the embolus. Interobserver agreement was not perfect and depended on the location of the embolus.\(^8\) The mortality rate associated with pulmonary angiography is considered the gold standard test for the diagnosis of PE. The diagnosis is definitively established angiographically by demonstrating the presence of an intraluminal filling defect in 2 views and demonstrating an occluded pulmonary artery with or without a trailing edge.\(^8\) It should be noted that interobserver agreement in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study for interpretation of PE was not perfect and depended on the location of the embolus. Interobserver agreement was 98% for lobar and 90% for segmental emboli but only 66% for subsegmental emboli, bringing into question the overall clinical relevance of subsegmental emboli.\(^8\)

The mortality rate associated with pulmonary angiography in the PIOPED study was 0.5%.\(^2\) In another large study, the mortality rate was 0.2%, with death occurring in 3 patients with pulmonary hypertension and cor pulmonale, all having a right ventricular (RV)

**Case Patient 3**

A 46-year-old woman with metastatic breast cancer presents to the emergency room with complaints of left lower extremity tenderness and swelling increasing over the past 3 days. There is no other significant past medical history. She denies dyspnea or chest pain. Physical examination reveals 1+ pitting edema of both lower extremities, with tenderness over the left calf and a positive Homan’s sign. There are decreased breath sounds and dullness to percussion at the right lung base. Chest radiograph shows a moderate-size right pleural effusion. D-Dimer testing is performed using a rapid whole blood agglutination kit and is found to be nonreactive. Duplex ultrasonography studies of both lower extremities reveal no thrombus. The patient is sent home with a prescription for venous compression stockings.

### Has the accuracy of D-dimer testing in cancer patients been assessed?

This case illustrates the utility of D-dimer testing and venous ultrasonography and highlights the question of whether D-dimer testing remains highly sensitive in the setting of cancer. As discussed, cancer is among the complicating clinical conditions that can result in elevated D-dimer levels, making the test less accurate in excluding VTE. This question has recently been addressed in a large study of 1739 consecutive patients, 12% of whom had cancer.\(^2\) D-dimer evaluation was found to have an equally good positive predictive value of 97% in patients with cancer and without cancer.

Isolated pleural effusion can be seen with PE, and although this patient did not complain of dyspnea, PE should still be considered in the setting of possible DVT. Pleural effusions with PE may be either transudates or exudates, although they more commonly are exudative. This patient’s effusion turned out to be malignant from her breast cancer. The nonspecific nature of the history and physical examination in the evaluation of VTE also is illustrated in this case.

### LUNG IMAGING MODALITIES

#### Pulmonary Angiography

Pulmonary angiography is considered the gold standard test for the diagnosis of PE. The diagnosis is definitively established angiographically by demonstrating the presence of an intraluminal filling defect in 2 views and demonstrating an occluded pulmonary artery with or without a trailing edge.\(^8\) It should be noted that interobserver agreement in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study for interpretation of PE was not perfect and depended on the location of the embolus. Interobserver agreement was 98% for lobar and 90% for segmental emboli but only 66% for subsegmental emboli, bringing into question the overall clinical relevance of subsegmental emboli.\(^8\)

The mortality rate associated with pulmonary angiography in the PIOPED study was 0.5%.\(^2\) In another large study, the mortality rate was 0.2%, with death occurring in 3 patients with pulmonary hypertension and cor pulmonale, all having a right ventricular (RV)
end diastolic pressure of at least 20 mm Hg. Pulmonary hypertension itself should not be considered an absolute contraindication to use of this test, however, as more recent large-scale experience with angiography (performed in tertiary referral centers) in patients with chronic thromboembolic pulmonary hypertension has been found to be extremely safe.23–25

**Ventilation-Perfusion Lung Scanning**

Ventilation-perfusion scanning remains a viable diagnostic tool in the workup of PE with certain limitations, especially regarding the specificity of the test. The most comprehensive assessment of the sensitivity and specificity of ventilation-perfusion scans was reported in the PIOPED study.26 This report stressed the importance of combining the clinical pretest probability with the results of the ventilation-perfusion scan. Scans were classified as normal or low, intermediate, or high probability of PE. Revised criteria for interpretation of ventilation-perfusion scans were published in 1993, based on reanalysis of the original data.27 In the PIOPED study, 755 patients underwent ventilation-perfusion scan and pulmonary angiography within 24 hours of onset of symptoms. A total of 251 (33%) patients had angiographically confirmed PE. Essentially all (98%) of these patients had abnormal ventilation-perfusion scans, confirming the high sensitivity of the test. A high-probability lung scan was associated with proven PE in 96% of cases, but a low probability scan also was associated with PE in 40% of patients. The majority of patients with PE (57%) had intermediate or low-probability scans. The important points to remember from this study are that (1) a normal ventilation-perfusion scan essentially rules out PE, (2) a high-probability lung scan combined with a strong clinical suspicion for PE is sufficient to make a diagnosis of PE and obviates the need for further workup in most situations, and (3) the majority of ventilation-perfusion scans will be read as intermediate or indeterminate probability, making further evaluation necessary to determine whether PE is present.

**Helical Contrast-Enhanced CT**

Helical contrast-enhanced CT scanning has rapidly become a useful and important modality in the noninvasive diagnosis of PE. Studies reporting on the accuracy of this modality have used pulmonary angiography as the comparison test. CT scanning directly identifies the PE as an intraluminal filling defect within a pulmonary artery. In addition to being noninvasive, CT scanning can identify other conditions that may have signs and symptoms similar to PE, giving it an advantage over pulmonary angiography.

Multiple studies have shown high sensitivity and specificity for CT scanning when emboli are located in the main, lobar, or segmental arteries. Subsegmental emboli, however, may be missed, leading to false-negative scans and lower sensitivity for emboli at this location. The clinical significance of subsegmental emboli can be questioned since emboli limited to this location are uncommon (PIOPED study, 6%). Sensitivity and specificity as high as 96% and 92%, respectively, have been reported with proximal emboli, but these test characteristics decrease to 86% and 92% when subsegmental emboli are included.28 More recent systematic reviews of published studies found a sensitivity range of 53% to 100% and specificity range of 81% to 100%. In a retrospective review of 118 patients, Perrier et al found a sensitivity of only 70% and specificity of 91% and concluded that a negative helical CT scan by itself was not adequate to justify withholding therapy.29 The negative predictive value of helical CT for PE was recently addressed in a retrospective study of 1512 patients with clinically suspected acute PE.30 CT results were interpreted as being negative for acute PE in 67% of patients. During 3 months’ follow-up, DVT or PE occurred in 8 of the patients with negative CT findings. The cumulative 3-month incidence of DVT or PE was 0.5%, with an incidence of fatal PE of 0.3%. The authors thus concluded that it was safe to withhold anticoagulation in patients with negative CT findings, assuming there is no other evidence of VTE. Results from this study should be interpreted with caution, however, since more than 10% of the patients died from all causes during the 3-month period, making full evaluation of PE difficult.

In summary, the role of helical CT scanning in diagnosing PE is not yet conclusively defined. Hopefully, results from PIOPED II, a large prospective study currently in progress, will answer this question.

**CT Pulmonary Angiography/Venography**

Combining CT pulmonary angiography with CT venography (CTV) of the iliac, femoral, and popliteal veins is increasingly being utilized as a way to diagnose both possible PE and DVT simultaneously utilizing the same contrast bolus. A recent study of 136 patients who underwent both scans showed a sensitivity and specificity of 71% and 93% respectively for the diagnosis of DVT. In addition to being less sensitive than ultrasonography for the diagnosis of DVT, CTV is also more costly. The advantage of the technique is that it assesses the iliac and intra-abdominal vessels on a limited basis.

**Magnetic Resonance Angiography**

Magnetic resonance angiography (MRA) also has been used for the diagnosis of PE. In a recent prospective
study of 118 patients, the sensitivity of MRA for diagnosis of PE was 77% while the specificity was 98%.34 Earlier smaller retrospective studies found significantly better sensitivities than this study, however.35,36 Overall, the accuracy of MRA is probably similar to that of helical CT; its main benefit over CT may be the avoidance of nephrotoxic iodinated contrast.

Echocardiography

Echocardiography can be useful in the workup of PE, although its main utility is in identifying patients more prone to hemodynamic compromise and in the decision to administer thrombolytics. Among patients with documented PE who underwent echocardiography, a finding of RV hypokinesis was associated with a doubling of the mortality rate at 14 days; at 3 months this finding was associated with a mortality rate 1.5 times that in patients without hypokinesis.37 Studies of patients with documented PE have revealed that more than 80% of patients have abnormalities of RV size or function that may suggest acute PE.8 However, these findings are nonspecific and may be associated with many other cardiopulmonary disorders. Free-floating thrombi within the right heart and main pulmonary arteries have been diagnosed with both transthoracic and transesophageal echocardiography, respectively (Figure 1), and would obviously confirm the diagnosis of PE.38–41 Echocardiography may be especially useful in critically ill patients with suspected PE. A recent review on this topic contains examples of typical echocardiographic images.42

V. TREATMENT OF VTE

ANTICOAGULATION
Prophylaxis

For many years, prevention of VTE focused on postoperative surgical patients, especially orthopedic patients. More attention has recently been given to prophylaxis of high-risk medical patients (Table 4). The MEDENOX trial showed that treatment with enoxaparin 40 mg subcutaneously daily in acutely ill medical patients was safe and associated with a significant reduction of VTE compared to placebo.43 There are no convincing data, however, showing that low-molecular-weight heparin (LMWH) is superior to unfractionated heparin in these patients, although there are probably fewer complications (eg, bleeding and thrombocytopenia) with LMWH. Critically ill patients are at especially high risk for VTE, and every effort should be made to use some form of prophylaxis in these patients. In this population, the rate of VTE may be more than twice (29% versus 13%) the rate in patients on the general hospital ward.44 A recent review of the literature found that 10% to 30% of medical and surgical intensive care unit (ICU) patients develop DVT within the first week of ICU admission, with an overall rate between 22% and 80%.45 Complete current recommendations for prophylaxis in surgical and medical patients can be found in the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.46

Figure 1. (A) Transthoracic echocardiogram demonstrating a mobile right atrial thrombus 4 cm in length prolapsing through the tricuspid valve (arrows). (B) Transesophageal echocardiogram demonstrating a large, mobile right atrial thrombus of approximately 10 cm in length (arrow). (Reprinted with permission from Rose PS, Punjabi NM, Pearse DB. Treatment of right heart thromboemboli. Chest 2002;121:807.)
Therapeutic Regimens

Treatment regimens for DVT and PE will be discussed together under the single heading of VTE since these 2 conditions are manifestations of the same disease process. Unfractionated heparin has long been the mainstay of initial treatment, with eventual conversion to warfarin. LMWH is being increasingly recognized as an acceptable if not superior alternative.

Unfractionated heparin acts by catalyzing the effect of antithrombin III so that it more efficiently inactivates thrombin, factor Xa, and factor IXa. The activated partial thromboplastin time (aPTT) is used for monitoring unfractionated heparin treatment. It is important to exceed the lower limit of the therapeutic range when heparin is initially administered. Clinical trials have convincingly shown high rates of recurrent VTE with initial failure to exceed this lower limit. The therapeutic range consists of a plasma heparin level of 0.2 to 0.4 U/mL, which corresponds to an aPTT of 46 to 70 seconds (1.5–2.3 × normal). Body-weight–based dosing of intravenous heparin is recommended, with an initial bolus of 80 U/kg and an initial maintenance infusion of 18 U/kg. The aPTT should be rechecked 6 hours later, with adjustments made according to Sixth ACCP Consensus Conference on Antithrombotic Therapy guidelines. Warfarin should be administered on day 1 at 5 mg, and combined therapy should be continued until the international normalized ratio is greater than 2.0 (usually 4 or 5 days).

LMWH offers many distinct advantages over unfractionated heparin and should be considered as initial therapy in most situations. The advantages of LMWH include no need for monitoring in most situations (exceptions discussed below), decreased incidence of heparin-induced thrombocytopenia (HIT), decreased incidence of bleeding complications, and ability to administer to outpatients. Patients in whom outpatient administration of LMWH is considered must meet the following minimal requirements: (1) stable proximal DVT or PE, (2) normal vital signs, (3) low risk of bleeding, (4) absence of severe renal insufficiency, (5) availability of a practical system for administering LMWH and warfarin (with appropriate monitoring), and (6) availability of a practical system for surveillance and treatment of recurrent VTE and bleeding complications. In addition, we recommend that patients with documented PE undergo echocardiography prior to considering outpatient therapy since patients with RV dysfunction seem to have a more complicated course.

The dosage of LMWH is adapted to body weight and is based on the level of inhibition of factor Xa. Regardless of the specific LMWH administered, the dosage for treatment should correspond to 150 to 200 anti-factor Xa U/kg per day, delivered in 1 or 2 subcutaneous injections. For the most commonly used LMWH enoxaparin, this corresponds to a dosage of 1 mg/kg every 12 hours or 1.5 mg/kg once daily.

In contrast to unfractionated heparin, the kidneys essentially eliminate LMWH. As such, consideration should be given to monitoring patients with moderate to severe renal insufficiency who receive LMWH. Other patients to consider for monitoring are those with significant bleeding risk or obesity and the elderly. Monitoring is accomplished through measurement of anti-factor Xa activity. The patient should be maintained near the mean anti-factor Xa activity that was found efficient and safe in the clinical trials for a specific LMWH. Samples for monitoring should be drawn after the third dose and approximately 3 or 4 hours after the previous dosage of LMWH was given. Recommended duration of therapy based on patient characteristics is shown in Table 5.

**CASE PATIENT 4**

A 44-year-old man hospitalized with an exacerbation of his multiple sclerosis complains of light-headedness and acute dyspnea on the morning of his third hospital day immediately after using the commode at his bedside. He is being treated with high-dose steroids and is not receiving DVT prophylaxis. His only other medications include ranitidine and baclofen. Vital signs include a blood pressure of 88/60 mm Hg, respirations of 34 resp/min, pulse of 118 bpm, and temperature of 38°C. Pulse oximetry is 75% on room air. On physical examination, the patient is in severe respiratory distress. His skin is cold and clammy. Lungs are clear to auscultation. Heart sounds are distant. There is no lower extremity swelling or tenderness.

He is immediately placed on a 100% non-rebreather
mask, after which pulse oximetry increases to 91%. Arterial blood gases while on this oxygen delivery device are as follows: pH of 7.50, PCO₂ of 28 mm Hg, and PO₂ of 62 mm Hg. Portable chest x-ray is ordered and is read as clear. He is transferred to the ICU and given a 5600 U bolus of heparin and a maintenance infusion due to high clinical suspicion of PE. A contrast-enhanced helical CT scan confirms the diagnosis of PE (Figure 2).

An echocardiogram reveals RV hypokinesis and right atrial/RV dilatation with septal dyskinesia. His blood pressure remains low normal, but he is making adequate urine. Four days later he remains stable, but his platelets abruptly drop to 40,000 from 145,000/mm³, prompting a change in his anticoagulation regimen.

- What are the treatment considerations in this patient?

**THROMBOLYTIC THERAPY**

This case raises the question of when thrombolytic therapy should be considered in PE. Historically, the only clear indication for thrombolytic therapy in PE has been overt shock because of the complication of intracranial hemorrhage, which occurs in 1% to 2% of treated patients. Proponents have argued for the administration of thrombolytics to patients with hemodynamic instability or RV dysfunction on echocardiography, even with stable hemodynamics. Small, nonrandomized case series have shown more rapid improvement in hemodynamics and oxygenation but no mortality benefit. The results of the first randomized controlled trial to assess the utility of thrombolytics in patients with documented PE and RV dysfunction on echocardiogram but normal hemodynamics were recently published. This study randomized a total of 256 patients to receive heparin plus alteplase or heparin alone. Alteplase administration was associated with a significant reduction in the risk of clinical deterioration and escalation of treatment but had no significant effect on mortality. No fatal bleeding or cerebral bleeding occurred in the patients who received alteplase. Although this study provides important clinical information, there still are no good data to show that thrombolytics improve mortality, and the decision to administer thrombolytics must be carefully weighed.

**ALTERNATIVE ANTICOAGULANTS**

This case also addresses the issue of HIT. The frequency of this complication is thought to be less than 1% when either unfractionated heparin or LMWH are administered for less than 5 to 7 days. When the platelet count falls precipitously or drops below 100,000/mm³, heparin should be stopped. Recombinant hirudin and danaparoid are now available for anticoagulation in patients with HIT.

**FILTERS**

Placement of a vena caval filter may be another option in this patient. Patients with known DVT may be

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**Table 5. Recommended Duration of Treatment in Venous Thromboembolism**

<table>
<thead>
<tr>
<th>Duration of Therapy</th>
<th>Patient’s Level of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 6 months</td>
<td>First event with reversible or time-limited risk factor(s) (patient may have underlying heterozygous Factor V Leiden or prothrombin 20210)</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>Idiopathic venous thromboembolism, first event</td>
</tr>
<tr>
<td>12 months to lifetime</td>
<td>First event with: Cancer, until resolved Anticardiolipin antibody Antithrombin deficiency Protein C or S deficiency Homozygous factor V Leiden Homocystinemia Multiple thrombophilias Recurrent event, idiopathic or with thrombophilia</td>
</tr>
</tbody>
</table>


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**Figure 2.** A contrast-enhanced helical computed tomography scan of the chest showing thrombus in the main pulmonary arteries, confirming the diagnosis of pulmonary embolism in case patient 4.
candidates for placement of vena caval filters when they are considered high risk for the subsequent development of PE or when subsequent PE occurs in the face of therapeutic anticoagulation. While placement of vena caval filters offers an initial beneficial effect in the prevention of PE, this is counterbalanced by an excess of recurrent DVT without any difference in mortality. Placement of vena caval filters may necessitate lifelong anticoagulation due to this thrombogenic potential, and one should consider this prior to placing a filter.

REFERENCES


26. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED).


