

# Systematic Approach to the Diagnosis and Management of Venous Thromboembolism

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## Epidemiology

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are significant causes of morbidity and mortality in the United States.<sup>1-4</sup> The incidence of venous thromboembolism is 117 per 100,000. The incidence of pulmonary embolism is 69 per 100,000. Nearly 10% of patients with DVT suffer from a pulmonary embolus and 10% of pulmonary embolism is fatal.

## Risk Factors

- Common risk factors for DVT/PE are:
- Morbid obesity
- Age greater than 40
- Congestive heart failure
- Prolonged immobilization
- Recent major surgery
- Malignancy
- Hypercoagulable states like protein C, S and antithrombin III deficiencies, lupus anticoagulant, anticardiolipin antibody and hyperhomocysteinemia. In addition activated protein C resistance (factor V Leiden) is one of the most common inherited disorder.

## Signs and Symptoms

With DVT, swelling (90%), pain, tenderness and warmth of the involved extremity are common manifestations. Homan's sign and palpable cord are non-specific findings. In PE, acute onset of dyspnea, tachypnea, tachycardia and chest pain are common manifestations. Hemoptysis, pleural rub, hypotension and shock are ominous signs. Chest X-ray may reveal localized infiltrates, pleural effusion and atelectasis. Arterial blood gases often reveal reduced PO<sub>2</sub> and PaCO<sub>2</sub> and increased A-a gradient. Common EKG findings are sinus tachycardia, new onset atrial fibrillation, S wave in lead I and inverted T wave and Q wave in lead V<sub>3</sub>.

## Differential Diagnosis of DVT/PE

Conditions that can mimic DVT include muscle rupture, popliteal cyst, lymphedema, nerve compression and arterial occlusive disorders. Pulmonary embolism is also known as the "great masquerader". Myocardial infarction, pneumonia, COPD exacerbation, congestive heart failure, asthma, pericarditis, primary pulmonary

hypertension, rib fracture, pneumothorax, costochondritis and anxiety disorders need to be ruled out while evaluating a patient for PE.

## Diagnosis of DVT

Impedance plethysmography measures changes in electrical impedance of venous system during sequential inflation and deflation of blood pressure cuff.<sup>5</sup> It is highly sensitive and specific and can be performed at patient's bedside. However false positive rates can be high (33%) in conditions such as obesity, heart failure, pregnancy and chronic DVT. It is not recommended for upper extremity thrombosis.

Compression ultrasonography provides direct visualization of vascular anatomy. It is non-invasive and is 99-100% sensitive and specific for proximal DVT. However it is not reliable for pelvic vein thrombus.

D-dimers are sensitive markers of thrombosis, they lack specificity but have high negative predictive value and therefore are useful as an exclusionary test. In case of negative ultrasound and negative D-dimer finding, the need for serial imaging can be obviated.<sup>13</sup> The assay is also useful in emergency situations when ultrasound and impedance plethysmography are not available. After a thrombotic event, D-dimer levels may normalize within fifteen to twenty days and are most useful for diagnosis within eleven days of symptom onset.<sup>13</sup> MRI is a highly sensitive test to detect DVT.<sup>6</sup> It is useful when ultrasound and plethysmography are non-conclusive. It is highly accurate in detecting iliac vein or upper extremity thrombi, thrombi below the knee and in pregnancy. Experience is increasing with the use of computed tomography for diagnosis of DVT though currently the use is mainly experimental.

Venography is the gold standard for diagnosing DVT. However, its invasiveness and risk of contrast induced nephrotoxicity limits its use.

In summary, compression ultrasonography is the non-invasive approach of choice. Impedance plethysmography is an acceptable alternative and preferred for possible recurrent DVT since it normalizes more quickly after a previous episode. If clinical suspicion is high for DVT and initial studies are negative a repeat study should be obtained day five to day seven. Venography is only used when non-invasive testing is not clinically feasible or results are equivocal.

### **Diagnosis of PE**

Ventilation-perfusion scans may be used to diagnose PE and are read as high probability, intermediate, low or normal.<sup>7</sup> The PIOPED study (Prospective Investigation Of Pulmonary Embolism Study) suggested that combining clinical suspicion with the lung scan result is very helpful in making or excluding the diagnosis of pulmonary embolism. Hence a high probability scan in a suggestive clinical setting is strongly associated with angiographically proven pulmonary embolism, a normal finding virtually excludes the diagnosis. However most V/Q scans fall into intermediate or low probability and those require further investigation via noninvasive lower extremity imaging or CT angiography and in some cases even pulmonary angiography.

CT angiography is an alternative for evaluation of suspected PE.<sup>7,9</sup> It is highly useful in patients with underlying lung disease like COPD and pneumonia. It offers the advantage of definitively identifying PE more frequently than V/Q scans, identifying alternate diagnosis in significant number of cases, and having the potential to visualize both the pulmonary vasculature and the pelvic and thigh veins in a single study. However, it can miss a central clot in middle right pulmonary artery or lingular branch of left pulmonary artery because of their horizontal take-off.

Echocardiogram is helpful in thermodynamically unstable patient. In a setting of PE, it may show right ventricular dilation, decreased left ventricular diameter, septal wall motion abnormality, increased pulmonary artery pressures and increased tricuspid regurgitation.

Pulmonary angiography is the gold standard for diagnosing PE, however it is highly invasive and therefore is only used when other non-invasive diagnostic tests are inconclusive.

Plasma D-dimers are also useful in diagnosis of pulmonary embolism. In patients with non-high clinical suspicion for PE and non-high probability V/Q scan and a negative D-dimer assay anticoagulation therapy can be safely withheld.<sup>13</sup>

### **Treatment of DVT/PE**

Heparin exerts its anticoagulant effect by acting as a catalyst to accelerate the action of antithrombin III on thrombin and activated factor X.<sup>10</sup> Its effectiveness is measured by the prolongation of activated partial thromboplastin time (APTT). It is administered intravenously to maintain PTT levels

1.5 to 2.5 times control. It is recommended for 5 to 10 days along with oral anticoagulant (Warfarin) for overlap. Side effects include bleeding, heparin induced thrombocytopenia and hyperkalemia.

There are three low molecular weight heparins available in USA: Enoxaparin, Ardaparin and Daltparin. They act by inhibiting factor Xa and augmenting tissue factor pathway inhibitor, therefore a PTT measurement is not useful.<sup>11</sup> Advantages include ease of administration (given subcutaneous), easy dosing and bioavailability greater than 90%. It is dosed by patients weight at 1mg per kilogram twice daily. There is no need to monitor levels except in patients weighing greater than 80 Kg, less than 50 Kg and those with creatinine clearance of less than 40ml, when it is recommended to check anti Xa levels in blood. Low molecular weight heparin is much less likely to cause heparin-induced thrombocytopenia. It is recommended for inpatient treatment of DVT and possibly PE and outpatient treatment of DVT.

Warfarin exerts its anticoagulant effect by inhibition of vitamin K dependent coagulation factors II, VII, IX and X. The laboratory test most commonly used to measure its effectiveness is the prothrombin time (PT) in blood and international normalized ratio (INR). It is dosed at 5 to 10mg/day for the first 2 days and then dose is adjusted based on therapeutic levels of INR<2.0 to 3.0>. Side effects include bleeding, wide fluctuations in levels with vitamin K rich diet, many potential drug interactions, frequent INR determinations and risk of warfarin induced skin necrosis in protein C deficiency

The use of thrombolytic agents like urokinase, streptokinase or tissue plasminogen activator in acute massive venous thrombosis or pulmonary embolism is controversial. Several randomized trials have not demonstrated a difference in mortality rate or in resolution of symptoms. Although there may be more rapid resolution of venous thromboemboli, the risk of serious bleeding including intracerebral hemorrhage remains a significant concern.

Insertion of an inferior vena caval filter is recommended in clinical setting of recurrent DVT on oral anticoagulation, when oral anticoagulation is contraindicated, when there is a large free floating thrombus in iliac vein or in case of recurrent PE causing pulmonary hypertension. It is also indicated as a prophylactic measure in some high-risk patients such as those with previous history of DVT or PE who have developed acetabular fracture or cancer.

Patients who have had pulmonary embolectomy should also have an IVC filter placed.

Patients with a first thromboembolic event in context of a reversible factor should be anticoagulated for 3 to 6 months. Patients with idiopathic first thromboembolic event should be anti coagulated for full 6 months. Patients with recurrent venous thrombosis or a continuing risk factor should be treated indefinitely.

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