Introduction

Venous thromboembolic disease is a major cause of morbidity and mortality worldwide and is comprised of two main conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). Its exact incidence is uncertain, but the incidence of first time venous thromboembolism (VTE) in the United States is estimated at approximately 100 persons per 100,000 each year.\(^1\) Multiple factors result in increased incidence of VTE, including advanced age, race (higher prevalence in Caucasians and African Americans), and presence of risk factors, such as cancer, surgery, trauma, inherited thrombophilic states, and immobilization. Approximately 25-50% of cases are considered idiopathic, 15-25% are associated with cancer, and approximately 20% occur after surgery. The 30-day incidence of death after treated VTE is approximately 6% for DVT and 12% for PE.\(^1\) Pulmonary embolism can occur in 50% to 60% of patients with untreated DVT with an associated mortality rate of 25% to 30%.\(^2\) Clinical diagnosis of VTE can be difficult and unreliable as presenting symptoms can be caused by a multitude of other etiologies. Once diagnosed, treatment decisions are based on the location and extent of disease, severity of symptoms, physiologic sequelae, and underlying risk factors. Diagnostic and interventional radiologists play crucial roles in the diagnosis and management of VTE.

Diagnosis

Appropriate clinical and laboratory evaluations, including physical examination with pretest probability scoring systems such as Wells/Modified Wells Criteria (Table 1) and D-dimer assay, before imaging evaluation can help reduce the number of negative imaging studies.\(^2,3\)

The historic gold standard for imaging diagnosis of both lower and upper extremity deep vein thrombosis is contrast venography. However, this modality has been replaced with other modalities and is now primarily reserved for instances where non-invasive studies are inconclusive, for patients with more complex presentations (e.g., patients with suspected acute on chronic DVT), and for patients undergoing endovascular intervention. Ultrasound is the modality of choice for the imaging diagnosis of both proximal upper and lower extremity deep vein thrombosis.\(^2,4\) (Fig. 1). Advantages of ultrasound include a high sensitivity and specificity for diagnosing proximal DVT, reliability for serial evaluation, ability to be performed bedside, cost effectiveness, and lack of exposure to ionizing radiation. Ultrasound has been found to have lower sensitivity for diagnosing calf vein/distal DVT in the extremities, however.\(^2\)

<table>
<thead>
<tr>
<th>Modified Wells criteria</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Signs or symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternate diagnosis less likely</td>
<td>3</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (&gt;3days) or surgery in the last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>History of PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer within last 6 months</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk for PE</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Moderate risk for PE</td>
<td>2 to 6</td>
</tr>
<tr>
<td>High risk for PE</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

Diagnostic criteria for direct evidence of thrombus are loss of compression and visualization of intraluminal filling defect on gray scale imaging, which is usually expansile and may be hypoechoic or echogenic (Fig. 1). These primary findings are combined with color Doppler imaging and augmentation with duplex (if no thrombus is visualized), which provide indirect evidence of thrombus. In the upper extremity, compression can be used for the jugular, axillary, basilic, cephalic, and brachial veins. Although Doppler interrogation of the subclavian vein can be performed, the examination is limited due to osseous structures obscuring the vasculature and preventing use of compression.

Computed tomography venography (CTV) is another noninvasive alternative to diagnose DVT. A main advantage of CTV is the ability to perform a comprehensive evaluation of proximal lower extremity DVT, as well as PE when combined with CT pulmonary angiography (CTPA). Both CTPA and CTV can be accomplished with the same bolus of contrast agent, first by imaging the opacified pulmonary arteries 20-25 seconds after contrast injection, followed by venous imaging from the knees to the diaphragm 2-4 minutes later (Fig. 2). Additional advantages include the ability to identify sources of extrinsic venous compression as an underlying cause of DVT (Fig. 3) and to evaluate for extravascular causes of the patient’s symptoms which may mimic VTE. CTV disadvantages include patient exposure to ionizing radiation and iodinated contrast media. Recent literature indicates that CTV has a sensitivity and specificity similar to Doppler ultrasound; however, there is little evidence to support the routine use of CTV outside of a work-up for PE and proximal DVT.

Magnetic resonance venography can also be used for evaluation of the central veins of the chest, the pelvic veins, and veins of the thigh when ultrasound is non-diagnostic. Approaches included black-blood and flow-based or contrast-enhanced bright blood techniques.

Although catheter angiography is considered the gold standard for diagnosis of pulmonary embolism, it has been replaced by CTPA as the test of choice and standard of care for the diagnosis of PE. Detection of pulmonary emboli to the level of the subsegmental arteries using thin-slice multidetector CTPA has been found in recent studies to have a sensitivity of 96%-100% and a specificity of 89%-98%. Emboli present as filling defects within the pulmonary arterial system when an adequate contrast bolus is achieved (Fig. 4). Radionuclide ventilation/perfusion scans are an alternative if CTPA is contraindicated or results are inconclusive. Posterior-anterior (PA) and lateral chest
radiographs are an important component of the study to exclude other causes of chest pain or shortness of breath and is required for accurate interpretation of abnormal radionuclide ventilation/perfusion scans.

Special attention should be given to assess for VTE on routine oncologic staging CT examinations, since there is a higher incidence and prevalence of VTE in this patient population. Prevalence of unsuspected VTE in oncology patients has been found to be 6.3% and is more common in inpatients and those with advanced disease. Many cases of VTE are unfortunately not diagnosed in oncology patients, despite the known increase risk, which can prove fatal. Staging CT can provide an important diagnostic opportunity to evaluate the pulmonary arteries and/or deep venous structures for VTE (Fig. 5).

Management

The medical treatment of choice for non-life-threatening PE and proximal lower and upper extremity DVT is anticoagulation. Treatment of DVT reduces the risk of extension, PE and recurrent DVT. Anticoagulation is administered for a minimum of 3 months. The role of anticoagulation in DVT isolated to the deep calf veins (below the knees) remains controversial, as distal DVT rarely results in PE. Approximately one-sixth of patients with distal DVT will experience extension of thrombus above the knee; therefore, serial imaging assessment at 1 week is recommended to exclude proximal DVT extension if anticoagulation is not initiated.

Inferior vena cava (IVC) filters also play a role in the management of VTE in certain settings. In patients with VTE and contraindications to anticoagulation,
those who experienced a complication of anticoagulation, cases where adequate anticoagulation could not be achieved, or patients with recurrent embolus despite anticoagulation, IVC filters are considered an absolute indication. Proposed relative indications for IVC filters include prophylactic use in patients with major trauma; those undergoing hip or knee replacement with compromised cardiopulmonary reserve; pregnant women with DVT; burn patients; patients undergoing thrombectomy, embolectomy, or thrombolysis; and in patients with free-floating iliofemoral thrombus. Other prophylactic use is considered controversial.

Suprarenal IVC filter placement may be considered in the setting of an absolute indication for filter placement and thrombus extending above a previously placed infrarenal filter (Fig. 6), when thrombus in the infrarenal IVC precludes normal filter placement, during pregnancy, in cases of gonadal vein thrombus, and in the presence of certain anatomic variants. Filters can be placed in the superior vena cava (SVC), but there are no filters specifically designed or approved for this location; therefore, use of current filters in the SVC is considered off-label. Retrievable filters should be removed when initial indications no longer exist or contraindications to anticoagulation have resolved.

Anticoagulation is effective in decreasing the risk of PE and propagation of DVT but has no direct effect on lysis of thrombus. Venous valves can become damaged by the presence of thrombus in as little as a few weeks, thereby rendering them dysfunctional. This can lead to recurrent VTE and post-thrombotic syndrome (PTS). PTS is characterized by edema, heaviness, stasis dermatitis, hyperpigmentation, chronic leg pain, and ulceration, which can result in decreased quality of life, disability, and even limb loss. Severe PTS is reported in 50% of cases of proximal DVT, and leg ulceration can occur in up to 10%. An uncommon but serious complication of DVT is phlegmasia cerulea dolens. This entity is characterized by extensive DVT that results in massive swelling and cyanosis of the limb. Limb loss is a common consequence of phlegmasia cerulea dolens and associated mortality is high.

Primary treatment of acute proximal DVT for threatened limbs or to prevent the development of PTS include endovascular interventions performed by interventional radiologists and surgical thrombectomy. Surgical thrombectomy is not widely performed due to the availability and success of nonsurgical options. Current endovascular options are catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT), and pharmacomechanical thrombolysis (a combination pharmacologic thrombolysis and PMT). For CDT, an infusion catheter and/or wire are placed through the thrombosed vein and a pharmacologic thrombolytic
agent is delivered into the thrombus for a period of 8-24 hours. The patient then returns for follow-up venography, which can be followed by additional CDT (sometimes up to 72 hours), PMT, angioplasty, and/or stent placement depending on angiographic findings and underlying cause for thrombosis. PMT refers to the use of percutaneous catheter-based devices, which mechanically remove thrombus by microscopic fragmentation, maceration, and/or aspiration. The American Heart Association recommends CDT as first-line therapy to reduce PTS in patients with low bleeding risk (level IIA/B). The Society of Interventional Radiology considers the following as indications for CDT in appropriately selected patients: phlegmasia cerulea dolens with low to moderate bleeding risk and any life expectancy, acute/subacute IVC thrombosis in patients with low to moderate bleeding risk and any life expectancy, and acute/subacute/chronic proximal DVT in patients with low bleeding risk and long life expectancy. General contraindications to CDT include any patient with a hemorrhagic disorder, an anatomic lesion that is prone to bleeding, or an absolute contraindication to anticoagulation therapy. Risk of major bleeding with CDT is approximately 8%.

With regards to PTS, conclusive evidence for the use of catheter based techniques has not been established despite multiple studies that support the benefit of adding CDT to anticoagulation for treatment of proximal DVT. However, data from the ATTRACT study, an ongoing multicenter, randomized, controlled clinical trial designed to determine if the use of pharmacomechanical catheter-directed thrombolysis reduces the occurrence of PTS over the 2-year follow-up period, will help clarify its role. For now, use of CDT has been shown to significantly reduce pain and swelling and promotes a higher rate of restored venous function. Addition of graduated compression stockings for 2 years has been shown to significantly reduce the incidence of PTS.

Treatment of PE is based on risk stratification. Patients with acute PE with sustained systemic hypotension (systolic blood pressure < 90 mmHg), cardiogenic shock, or need for cardiopulmonary resuscitation are defined as high risk of having massive PE. Intermediate risk or submassive PE is defined as evidence of right ventricular dysfunction on echocardiography or elevated cardiac biomarkers, but with preserved systolic pressure. Patients with acute PE whose systolic pressure is preserved and echocardiography and cardiac biomarkers are negative are considered to have low risk PE; these patients are treated with anticoagulation. Current recommendations by the American Heart Association (AHA) suggest systemic fibrinolysis in massive PE and in submassive PE if bleeding risk is low. The AHA recommendations suggest surgical embolectomy or catheter-based intervention if systemic fibrinolysis is contraindicated or if urgent recanalization is indicated at an experienced center. The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines state similar recommendations. Catheter-based treatment includes CDT and/or mechanical techniques, such as mechanical thrombus fragmentation and rheolytic, suction, or rotational thrombectomy. Ultrasound accelerated thrombolysis can be used in conjunction with CDT and aids in fibrinolysis and increased penetration of the thrombolytic agent in the thrombus.

**Conclusion**

Interventional and diagnostic radiologists play key roles in the diagnosis and management of VTE. Multiple imaging modalities are available for the diagnosis of VTE, but ultrasound and CT pulmonary angiography are the standards of care for imaging diagnosis of proximal DVT and PE, respectively. Accurate diagnosis of VTE is critical in treatment planning. The treatment of choice for non-life-threatening PE and proximal extremity DVT is anticoagulation. Catheter-directed therapy for DVT and PE is employed for mechanical and/or pharmacologic thrombolysis in specified clinical settings.
References


