Diagnostic assessment of deep vein thrombosis and pulmonary embolism

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KEYWORDS:
Contrast venography; D-dimer assay; Magnetic resonance direct thrombus imaging; Pulmonary angiography; Venous thromboembolism

Venous thromboembolism (VTE) is a common disorder that can lead to substantial morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Although rapid diagnosis and treatment are critical in preventing PE, mortality and major morbidity due to conditions such as postthrombotic syndrome may complicate the differential diagnosis of VTE. The clinical symptoms associated with DVT are neither sensitive nor specific and can be indicative of a wide range of diagnoses. Because imaging studies can be expensive and are sometimes inconclusive, they should be used judiciously in patients with highly suspected VTE. This review offers a clinical perspective on the accurate, routine diagnosis of VTE, including an overview of common clinical signs and symptoms, as well as the advantages and drawbacks of available diagnostic strategies.

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Venous thromboembolism (VTE) is a common disorder that can lead to substantial morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Although rapid diagnosis and treatment are critical in preventing PE, mortality and major morbidity due to conditions such as postthrombotic syndrome may complicate the differential diagnosis of VTE. The clinical symptoms associated with DVT are neither sensitive nor specific and can be indicative of a wide range of diagnoses. Because imaging studies can be expensive and are sometimes inconclusive, they should be used judiciously in patients with highly suspected VTE. This review offers a clinical perspective on the accurate, routine diagnosis of VTE, including an overview of common clinical signs and symptoms, as well as the advantages and drawbacks of available diagnostic strategies.

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0002-9343/$ -see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2005.06.008
provides an overview of the clinical models and diagnostic strategies available to assess for thromboembolic disease.

Etiology of venous thromboembolism and relative risk

VTE can occur as an idiopathic syndrome or may be caused by an underlying condition that predisposes a patient to thrombosis. In a retrospective study of 366 validated cases of VTE, approximately 48% were idiopathic and 52% were secondary to an underlying condition. Rudolf Ludwig Karl Virchow was the first to identify 3 primary clinical factors associated with a substantial risk of thrombosis. Together, these factors are known as the Virchow triad and include (1) vessel wall damage due to inflammation or trauma; (2) changes in blood flow or volume due to immobility, ischemia, and other conditions; and (3) hypercoagulable factors present in the blood, including inherited and acquired coagulation disorders.

The consideration of risk factors in the assessment and diagnostic evaluation of patients with potential DVT is important; however, it is also important to consider the relative risk for each factor independently. Some reports suggest that hospitalized medical patients subjected to an extended period of immobility may be at risk for VTE, especially if presenting with additional risk factors, including acute infectious disease, previous history of VTE, or advanced age (>75 years). Although immobilization is commonly cited in the literature as a predisposing risk factor for VTE, results from some studies suggest that the associated risk may not be as significant. In a retrospective cohort analysis, Gatt and colleagues evaluated 18 mobile and 8 immobile patients with a mean age of 85 for a duration of 10 years. The immobile patients were bedridden for a prolonged period (>3 months). No difference in baseline characteristics, which included the assessment of risk factors, was observed between the 2 groups. The incidence of VTE was similar between the immobile and mobile patient groups (13.9 and 15.8, respectively; \( P = 0.77 \)). Although these results are not consistent with previous studies—an inconsistency that is due, in part, to a relatively small study population—they do highlight the importance of considering the added threat conferred by each risk factor both independently and in combination with other risk factors.

Similarly, an analysis that was conducted using data from the American College of Surgeons National Trauma Data Bank evaluated the frequency of VTE following trauma. The results demonstrated that incidence of VTE in these patients is also relatively low. Data was collected from 131 trauma centers. The following 6 risk factors were found to be associated with VTE: age ≥40 years, lower extremity fracture with Abbreviated Injury Score (AIS) ≥3, head injury with AIS ≥3, ventilator delays >3, venous injury, and history of a major operative procedure. Of the 450,375 patients who experienced trauma from 1994 to 2001, a total of 1,602 experienced DVT, resulting in an incidence of 0.36%.

In contrast to the lower relative risk conferred by immobilization and trauma, a much stronger association exists between VTE and cancer. In a recent study, 26% of patients presenting with bilateral DVT were diagnosed with cancer after the occurrence of DVT, and metastasis had occurred in 70% of these patients. Other reports cite as much as a 2-fold increase in DVT risk among patients with cancer and suggest that the risk of recurrent thromboembolism is as much as 3.5 times higher in patients with malignancy compared with cancer-free patients. Therefore, patients presenting with unprovoked VTE should be further assessed for potential malignancy by means of physical examination, laboratory tests, and appropriate imaging studies as indicated by physical findings.

Finally, hypercoagulability—especially hypercoagulability due to a genetic predisposition, acquired syndromes, and certain medications, such as oral contraceptives—can increase the risk of thrombosis. Hereditary risk factors include factor V Leiden mutation; prothrombin G20210A gene mutation; and deficiencies of protein C, protein S, and antithrombin III. Hyperhomocysteinemia and elevated levels of factors XIII and V, which may be hereditary and/or acquired, are also risk factors. Additionally, ABO blood type is another VTE risk factor that was recently noted in cancer patients and is believed to be associated with hypercoagulability resulting from influence on the levels of von Willebrand factor and factor VIII.

Diagnosis of venous thromboembolism

It is important to note that 50% of patients who have VTE do not present with any symptoms. Classic symptoms associated with DVT include leg swelling, pain upon palpation in the calf or thigh, and the Homans sign (calf pain with dorsiflexion of the foot). However, these signs have been proved to occur at the same frequency in those without DVT. The second diagnostic step in the identification of DVT is the stratification of patients through the assessment of risk factors. Such stratification increases the accuracy of diagnosis and reduces the unnecessary use of expensive imaging tests in patients with low risk.

Anderson and associates, Ruiz-Giménez and coworkers, and Wells and colleagues developed the first clinical model for the diagnosis of patients presenting with suspected DVT. This model includes a thorough clinical examination and identification of any risk factors that predispose patients to have increased risk of thrombosis. In accordance with this model, patients are first divided into 3 risk categories (low, moderate, or high) and are further assessed through ultrasonography (Table 1). Patients who are stratified to the high-risk category, or who have abnormal ultrasound results, are further assessed through venog-
mobilization for DVT, including heart rate of PE. Points are assigned based on clinical symptoms of for expensive imaging diagnostics. It uses a point system for Wells and colleagues also defined a clinical algorithm for number of specific criteria allow for a more accurate diagnosis of PE (with D-dimer testing, this algorithm safely reduces the need for venography in patients with normal compression ultrasound results. Additionally, the sensitivity of certain diagnostic tests is particular technology may influence the choice of approach. Additionally, the sensitivity of certain diagnostic tests is affected by the location of the thrombus. In addition to traditional tests, such as contrast venography for DVT and pulmonary angiography for PE, newer modalities such as D-dimer assays and magnetic resonance direct thrombus imaging (MRDTI) offer promise for better detection with less invasiveness and have the potential for use in detection of both DVT and PE.

### Objective testing for venous thromboembolism

Diagnostic evaluation of suspected VTE includes a clear correlation between clinical probability, test selection, and test interpretation. However, a variety of diagnostic approaches are feasible, and availability and familiarity with particular technology may influence the choice of approach. Additionally, the sensitivity of certain diagnostic tests is affected by the location of the thrombus. In addition to traditional tests, such as contrast venography for DVT and pulmonary angiography for PE, newer modalities such as D-dimer assays and magnetic resonance direct thrombus imaging (MRDTI) offer promise for better detection with less invasiveness and have the potential for use in detection of both DVT and PE.

### Imaging modalities for deep vein thrombosis

#### Contrast venography imaging

Contrast venography is no longer appropriate as the initial diagnostic test in patients exhibiting DVT symptoms, although it remains the “gold standard” for confirmatory diagnosis of DVT. Venography is nearly 100% specific and sensitive, and it provides the ability to investigate the distal and proximal venous system for thrombosis. Its use is no longer widespread owing to the need for administration of a contrast medium and the increased availability of noninvasive diagnostic strategies. However, venography is still warranted when noninvasive testing is inconclusive or impossible to perform. Additional drawbacks of venography include contraindication in patients with renal insufficiency and lack of accuracy in recurring cases of suspected DVT owing to the difficulty of visualizing an intraluminal defect in veins that have been thrombosed previously.

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**Table 1** Clinical model for predicting pretest probability for deep vein thrombosis

<table>
<thead>
<tr>
<th>Risk factor category</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>No alternative diagnosis plus</td>
<td>≥2 major risk factors</td>
<td>≥2 major and ≥2 minor risk factors</td>
</tr>
<tr>
<td></td>
<td>— ≥3 major risk factors or</td>
<td>— ≥2 major and ≥2 minor risk factors</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>No alternative diagnosis plus</td>
<td>— 1 major and ≥1 minor risk factor or</td>
<td>— ≥2 minor risk factors</td>
</tr>
<tr>
<td></td>
<td>— ≥3 minor risk factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis. Adapted with permission from Lancet.™

*Patient receiving ongoing treatment, treatment within previous 6 months, or palliative therapy.

†Elicited in the anatomic distribution of the deep venous system of either the thigh or calf.

‡Measured 10 cm below tibial tuberosity.

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For patients presenting with PE, shortness of breath, with or without leg pain, may be the first symptom; however, a number of specific criteria allow for a more accurate diagnosis. Similar to the clinical model for diagnosis of DVT, Wells and colleagues also defined a clinical algorithm for the diagnosis of PE (Figure 2). When used in conjunction with D-dimer testing, this algorithm safely reduces the need for expensive imaging diagnostics. It uses a point system for calculating the low, moderate, or high pretest probability of PE. Points are assigned based on clinical symptoms of DVT, including heart rate of >100 beats per minute, immobilization for ≥3 days or recent surgery in the past 4 weeks, a clinical history of VTE, hemoptysis, malignancy, or clinician determination that PE is as likely or more likely than another diagnosis (Table 2). The patient history and physical examination findings reported in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial illustrate the difficulty in quickly identifying or ruling out a diagnosis of PE. In PIOPED, the most common past and current physical findings included dyspnea, pleuritic chest pain, cough, tachycardia, and tachypnea (Table 3). These symptoms also can be indicative of heart failure, interstitial lung disease, or pneumonia. For this reason it is especially important to conduct thorough examinations and risk stratification when examining patients for potential VTE.
Compression ultrasound

Doppler compression ultrasound with real-time, B-mode imaging is used at most institutions due to its safety, availability, reliability, and noninvasive nature. Benefits include detection of acute symptomatic proximal DVT, as well as DVT of the upper extremities, and it is also capable of identifying other pathologies. Its 2-dimensional, cross-sectional representation of lower extremity veins is also useful in combination with venous flow detection (duplex ultrasonography). The demonstration of venous noncompressibility is the major diagnostic criterion for venous thrombosis. However, compression ultrasound is not specific or sensitive for the detection of DVT in patients with asymptomatic proximal DVT or in patients with symptomatic or asymptomatic DVT of the calf, and it demonstrates limited accuracy in cases of chronic DVT. Its use is also limited in patients who are obese or who have edema. Currently, a number of ongoing large trials are in progress for the assessment of magnetic resonance venography and computed tomographic (CT) venography in the diagnosis of DVT.

Diagnostic tests for pulmonary embolism

Blood gas analysis and electrocardiogram

Arterial blood gas analysis and electrocardiogram (ECG) are routinely used to diagnose PE with varying rates of success. Hypoxemia is a common feature of acute PE but is not present in all cases. Thus, although arterial blood gas levels reveal the blood oxygen saturation level, they are not specific or sensitive for the definitive diagnosis of PE. The use of transcutaneous oximetry will provide information regarding hypoxemia without the need for an arterial puncture, but it is not sensitive or specific for the diagnosis of PE. Hemodynamically significant PE induces transient ECG abnormalities reflecting right ventricular overload and/or strain; however, these abnormalities are neither sensitive nor specific for VTE, although a classic S1Q3T3 pattern (Figure 3) might warrant consideration of PE in the presence of other signs and symptoms. ECG can also be used to suggest an alternative cardiac diagnosis. Additionally, recent investigators have suggested that a simple scoring system based on ECG might be useful in predicting individuals with the greatest percentage of perfusion defect. Because neither of these methods is suggested as a proven diagnostic tool for the initial screening or exclusion of VTE, they should not be routinely used for definitive diagnosis. Instead, they should be used in conjunction with clinical examinations and other diagnostic studies to reinforce the clinical suspicion of PE.

Imaging techniques

Chest X-ray

Chest X-ray is often used in combination with ECG to reinforce suspicion of PE. Although chest X-ray is com-
Figure 2  Clinical algorithm for initial evaluation of patients with suspected pulmonary embolism (PE). DVT = deep vein thrombosis; PTP = pretest probability; spiral CT = spiral computerized tomographic pulmonary arteriography; V/Q = ventilation–perfusion. (Reprinted with permission from *Ann Intern Med.*

Table 2  Suspected pulmonary embolism (PE): a simple clinical model and d-dimer to assess pretest probability*

<table>
<thead>
<tr>
<th>Specific factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical DVT (objective leg swelling, tenderness)</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization ≥ 3 days or surgery in previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
<tr>
<td>PE as likely or more likely than alternative diagnosis</td>
<td>3.0</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.

*Interpretation of point total: < 2 points = low risk (mean probability, 3.6); 2–6 points = moderate risk (mean probability, 20.5); > 6 points = high risk (mean probability, 66.7).

Adapted with permission from *Ann Intern Med.*

Table 3  Common patient symptoms with a positive pulmonary embolism diagnosis in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study

<table>
<thead>
<tr>
<th>Patient history</th>
<th>Percentage of patients (N = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>73%</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>66%</td>
</tr>
<tr>
<td>Cough</td>
<td>37%</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>28%</td>
</tr>
<tr>
<td>Leg pain</td>
<td>26%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>13%</td>
</tr>
</tbody>
</table>

Adapted with permission from *Chest.*
monly ordered during the process of differential diagnosis of pulmonary conditions, PE patients most commonly have normal chest X-ray results. However, they sometimes present with nonspecific radiographic findings. A normal chest X-ray in the presence of severe dyspnea or hypoxemia without evidence of bronchospasm or cardiac shunt is strongly suggestive of but not diagnostic for PE.28

Figure 3 The S1Q3T3 pattern with concomitant symptoms and signs of pulmonary embolism warrants further investigation.

The Hampton hump, which is visible in some X-rays, is a classic finding caused by a pleural-based abnormality due to pulmonary infarction; its presence, however, is not common and cannot be used to confirm or exclude PE (Figure 4). Chest X-ray is most useful to rule out other conditions that may mimic PE, such as pneumothorax or pneumomediastinum.28,36

Figure 4 The Hampton hump (arrow), which is visible in some X-rays, is a classic finding caused by a pleural-based abnormality due to pulmonary infarction. Its presence is not common and should not be used to confirm or exclude pulmonary embolism.
Ventilation–perfusion scan

The ventilation–perfusion (V/Q) scan is used to detect areas of abnormal perfusion due to PE. It has long been considered a preferred diagnostic modality in suspected PE (Figure 5).28,30 The ventilation component of the test excludes a diagnosis of pneumonia and other respiratory conditions. However, the V/Q scan is only diagnostic of PE in a minority of cases. Moreover, PE frequently occurs in combination with other lung diseases, such as pneumonia or chronic obstructive pulmonary disease. Because most lung diseases affect pulmonary blood flow as well as ventilation, their presence may decrease the scan’s specificity.28 The PIOPED study investigators at the National Heart, Lung, and Blood Institute (NHLBI) reported that a high-probability V/Q scan was sensitive for the diagnosis of PE and that a low-probability scan was sensitive for the absence of PE. The V/Q scan was not useful in patients with previous VTE.37 Indeterminate scans require further diagnostic studies to assess disease accurately,38 and 33% of PIOPED participants with indeterminate scans were later found through angiography to have thromboemboli.37

Spiral CT pulmonary arteriography

Spiral (also known as helical) CT has demonstrated a higher degree of sensitivity and interobserver agreement than V/Q scan, making this strategy a less-invasive, alternative diagnostic tool in patients with suspected PE (Figure 6).39 Spiral CT has demonstrated a high rate of sensitivity and specificity in detecting PE to segmental levels, but it cannot accurately detect subsegmental emboli.40 Although the clinical significance of these subsegmental emboli has not been established, a negative spiral CT cannot safely rule out thrombosis and must be confirmed with pulmonary angiography.40 In addition, a low sensitivity rate of 70% has been reported in a previous study, providing additional evidence that confirmatory pulmonary angiography is required in patients with negative spiral CT findings.41 A 1-year follow-up study in patients with a normal spiral CT scan demonstrated a low 2% rate of clinical PE, suggesting that additional data will be required to characterize the safety of a negative spiral CT without other confirmatory diagnostics.42

Pulmonary angiography

Pulmonary angiography has been considered a gold standard test for PE.28 It is an invasive test that is used in some settings to detect PE in patients with indeterminate V/Q scans. However, it is not necessary for a diagnosis of PE in the acute setting when the perfusion scan is normal.28 One study of pulmonary angiography demonstrated sensitivity of 85% for the detection of lobar and segmental emboli, with less reliability in detecting peripheral subsegmental emboli (1 in 5).36 These results are consistent with those of the PIOPED study, in which interobserver agreement was 98% for lobar PE, 90% for segmental PE, and only 66% for subsegmental emboli.43 However, there has been some debate surrounding the true clinical importance of these peripheral emboli.36 Some investigators posit that they are caused by isolated calf vein thrombi and do not require treatment, whereas others believe that they are a precursor to larger emboli.44,45
Newer diagnostic techniques

Indirect CT venography

Indirect CT venography has been investigated as an adjunct to the pulmonary angiography conducted during the differential diagnosis of PE.46 This technique results in a high rate of detection of DVT—the underlying cause of many subsequent PE events—and requires no additional contrast material.47,48

MRDTI

MRDTI is a novel technique that has demonstrated accuracy and reproducibility for DVT diagnosis in limited studies.49 It detects the presence of methemoglobin in clots, allowing visualization of thrombi without using IV contrast material; the technique is thus useful for detecting subacute thrombosis.50

MRDTI has several major advantages over conventional modalities. Because data suggest that it is highly accurate in detecting both DVT and PE, MRDTI provides a single imaging modality for detecting VTE.50,51 This technique provides direct visualization of thrombi, avoiding the pitfalls of conventional techniques that have identified thrombi either as filling defects or in terms of surrogates. MRDTI also allows simultaneous imaging of the legs and chest, permitting a comprehensive assessment of thrombus load, minimizing the importance of overlooked subsegmental PE, and potentially facilitating more titrated treatment. The safety of withholding treatment in suspected DVT and PE on the basis of negative MRDTI alone is being evaluated in ongoing outcome studies.51 Additionally, because it has proved useful in identifying complicated plaque in the carotid arteries in the setting of transient and permanent cerebral ischemia, MRDTI offers promise as a technique that is capable of detecting high-risk vessel wall disease before significant or permanent end-organ damage.50 As costs for this type of imaging decrease and institutions gain wider access to the technology, it should offer an attractive alternative to the invasive use of contrast venography with application in a wide range of vascular disease settings.

Bedside d-dimer assays

A number of d-dimer assays have been evaluated as diagnostic markers for VTE and are considered to be inexpensive as well as timely.26 The predictive value of the assay depends on several attributes, including the prevalence of VTE in the population being tested. Ruiz-Giménez and colleagues23 found that the VIDAS (bioMérieux, Marcy L’Etoile, France) and enzyme-linked immunosorbent assay (ELISA) d-dimers are suitable approaches as a first diagnostic tool for the exclusion of DVT. However, some data suggest that d-dimer testing offers limited specificity and cannot be solely used to exclude a diagnosis of DVT; this has been demonstrated in patients who are elderly, in the emergency department, or hospitalized for >3 days.53 Another important issue is that some institutions do not have
access to immediate D-dimer results. Nevertheless, D-dimer testing, especially the most-specific ELISA, offers an attractive bedside assay that is sensitive for DVT diagnosis, if not specific under certain circumstances. D-dimer testing will still result in a reduction in the need for imaging diagnostics when DVT can be diagnosed and treated earlier. A positive D-dimer result is not necessarily useful for definitively diagnosing VTE, but a negative result, when it coincides with ultrasound results, can rule out the diagnosis. 

Although D-dimer testing is a recent addition to the strategy for diagnosing PE and has been shown to be a valuable tool with excellent sensitivity, there have been rare reports of patients with PE but negative D-dimer tests. One investigation at an academic health center indicated that D-dimer measurement was of limited utility in patients with suspected PE and nondiagnostic lung scans or negative spiral (helical) CT results. Another study of 150 patients admitted to the hospital for PE who underwent D-dimer measurement compared results in patients with negative D-dimers versus patients with raised D-dimers. The sensitivity of raised D-dimers for PE was high (96%), but the finding of chest pain was statistically greater in the group with negative D-dimers (P = 0.01). In these negative D-dimer cases, the emboli were all distal (P = 0.0003) and the diagnostic value of ultrasound investigations (echocardiography, ultrasonography of lower limb veins) was less than in patients with higher D-dimers (P <0.0001). The authors suggested that measurement of D-dimers by the ELISA method may be nondiagnostic in distal PE, perhaps because of the less-extensive thromboembolic process. They concluded that in cases with negative D-dimers, a strong clinical suspicion of PE should signal a need for further investigation.

**Summary**

Clinical evidence indicates that patients who are at moderate-to-high risk for developing VTE include those with a history of cancer, prior thrombosis, and acquired syndromes or genetic disorders that predispose them to a hypercoagulative state. Among these patients, VTE should be highly suspected with the presentation of classic symptoms. Such cases require rapid assessment and accurate diagnosis to prevent the progression of DVT, long-term morbidity due to postthrombotic syndrome, or the occurrence of potentially fatal PE.

Clinical presentation for 50% of patients with VTE is often nonspecific, and can be confused with a variety of other conditions, including heart failure, cellulitis, hema-toxa, or edema due to an unrelated condition. Although contrast venography remains the gold standard for diagnosis of DVT, the availability of less-invasive diagnostic techniques has limited the use of this test as a first-line diagnostic. Rather, it is used when the less-invasive tests, such as duplex ultrasonography, are inconclusive or impossible to perform.

When clinical symptoms warrant consideration of PE, objective testing should begin with less-invasive techniques such as D-dimer, V/Q scan, or spiral CT scan, followed by gold-standard pulmonary angiography when the scans are nondiagnostic. New additions to the diagnostic battery and increased awareness of risk stratification paradigms have the potential to allow more accurate identification of VTE in some patients, thereby greatly reducing the incidence of morbidity and mortality.

**References**


