Ultrasonography and Diagnosis of Venous Thromboembolism

Brenda K. Zierler, PhD

Abstract—Venous thromboembolism (VTE) consists of two related conditions: pulmonary embolism (PE) and deep vein thrombosis (DVT). Objective testing for VTE is crucial because the clinical diagnosis is nonspecific and insensitive, and the consequences of a missed diagnosis are serious. The purpose of this review is to discuss the utility of venous ultrasonography as the foundation for diagnosis of acute lower extremity DVT. The effectiveness and practicality of venous ultrasonography as a stand-alone examination versus theoretically attractive, but perhaps less practical, combined approaches of ultrasonography with clinical probability assessment and D-dimer testing in the diagnosis of acute DVT is also addressed. Finally, the role of venous ultrasonography in a diagnostic algorithm for suspected PE is discussed. (Circulation. 2004;109[suppl I]:I-9-I-14.)

Key Words: thrombosis ■ pulmonary heart disease ■ diagnosis ■ ultrasonics ■ veins ■ prevention

Current Treatment Standards for DVT
Guidelines for antithrombotic therapy for the treatment of venous thromboembolism (VTE), developed in 2001 by the Sixth American College of Chest Physicians (ACCP), state that patients with acute VTE should be treated with low molecular weight heparin, unfractionated intravenous heparin, or adjusted-dose subcutaneous heparin.1 Treatment is recommended for both proximal and symptomatic distal (isolated calf) DVT. If anticoagulation cannot be administered or is contraindicated for calf DVT, then the recommendations are for serial noninvasive studies over the next 10 to 14 days to assess for proximal progression of the thrombus.1 These recommendations, in effect, require that an examination assessing the presence of DVT have both excellent sensitivity and specificity for diagnosis of both proximal (above knee) and distal (below knee) DVT.1

Unfortunately, most duplex ultrasound-based algorithms for the diagnosis of DVT, and some vascular laboratories, still do not include an initial ultrasound evaluation of the calf veins as part of their routine evaluation for DVT, even in symptomatic patients. This is largely the result of outdated perceptions of the inaccuracy of ultrasound evaluation of DVT isolated to the calf veins. Failure to perform a complete initial examination necessitates serial ultrasound examinations or alternative strategies to detect possible extension of venous thrombi initially isolated to the calf veins. Such strategies are inefficient, and unlikely to be cost effective, compared with the modern practice of a single stand-alone color flow duplex study of the proximal and distal lower extremity veins in patients with suspected DVT.

Limitations of Current Noninvasive Diagnostic Methods for DVT
Impedance Plethysmography
The objective diagnosis of DVT is not always straightforward. Venography was once accepted as the standard of accuracy for diagnosing DVT2 and still has some limited indications. However, because of its invasive nature, technical difficulty, and cost, venography is not suitable for routine clinical evaluation of possible DVT. Before the acceptance and widespread use of venous duplex scanning, impedance plethysmography (IPG) was employed as the initial noninvasive test for patients with suspected acute lower extremity DVT.3– 6 According to studies that compare IPG to venography and exclude clinical outcome, its sensitivity for proximal DVT ranges around 65%.7– 8 IPG may not detect nonocclusive proximal DVT or occlusive proximal DVT present in parallel venous systems, such as duplicated femoral or popliteal veins, and cannot detect DVT isolated to the calf veins.9

Venous Ultrasonography
Venous ultrasonography has become the most widely used diagnostic modality, invasive or noninvasive, for the diagnosis and exclusion of acute DVT. Duplex ultrasound is considered to be the primary noninvasive diagnostic method for DVT. It is required as primary instrumentation for peripheral venous testing according to the standards of the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL).10 Secondary instrumentation (IPG

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and continuous-wave Doppler) may still be used to supplement duplex ultrasonography in the diagnosis of DVT but are not considered primary diagnostic methods for ICAVL accreditation purposes.

There are several types of venous ultrasonography. They include compression ultrasound (B-mode imaging only), duplex ultrasound (B-mode imaging and Doppler waveform analysis), and color Doppler imaging alone. Although these types of venous ultrasonography are sometimes used interchangeably, their sensitivities and specificities for detecting acute DVT vary. Different lower extremity veins are best evaluated with different techniques. Compression ultrasonography is typically performed on the proximal deep veins, specifically the common femoral, femoral, and popliteal veins, whereas a combination of duplex ultrasound and color Doppler imaging is more often used to interrogate the calf and iliac veins.

Individual laboratories sometimes determine the type of venous ultrasonography to use and the segments of the venous system to be examined on the basis of local technologist experience and technical expertise. Unfortunately, venous ultrasonography examinations are not yet uniformly standardized and range from compression of as few as two deep veins to complete duplex and color Doppler evaluation of the entire lower extremity. Limited examinations as stand-alone studies are obviously incompatible with the recommendations of the American College of Chest Physicians. There are, however, factors that influence which venous segments can be evaluated in an individual examination. These include presence of morbid obesity, lower extremity edema or tenderness, and the presence of immobilization devices and bandages. Overall, however, a complete color flow venous duplex examination has become the standard of care for assessment of lower extremity DVT. It is recommended that, whenever possible, a venous duplex examination to exclude the presence of DVT consist of evaluation of both the proximal and calf veins.

**Accuracy of Venous Ultrasound**

Accuracy of venous ultrasonography in comparison to venography has been well established. The weighted mean sensitivity and specificity of venous ultrasonography (including all types) for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively. The high specificity of venous ultrasonography allows treatment of DVT to be initiated without further confirmatory tests, and the high sensitivity in diagnosing proximal DVT makes it possible to withhold treatment if the examination is negative. As noted above, some ultrasound examinations are constrained by practical matters involved in the clinical care of patients. Inability of the patient to fully cooperate with regard to positioning for the examination and/or intolerance of the pressure of the ultrasound scanhead on the skin, or inability of the examiner to obtain a complete examination secondary to the presence of bandages, casts, or extremity wounds may, in some cases, lead to a need for serial examinations or the performance of an alternative diagnostic procedure such as catheter-based contrast venography or CT (computed tomography) or MR (magnetic resonance) venography to exclude DVT. Currently, repeat or serial venous ultrasonography seems advisable for negative examinations in symptomatic patients who are highly suspicious for DVT and in whom an alternative form of imaging is contraindicated or not available.

**Venous Ultrasonography as a Stand-Alone Diagnostic Test**

Two types of studies are performed to evaluate diagnostic strategies for acute DVT: accuracy studies in which the new test (venous ultrasonography) is compared with the gold standard (venography), and management studies in which patients are monitored over time to determine the safety of managing patients according to the results of these tests. Kearon et al provided a comprehensive review of accuracy and management studies that evaluated objective tests for the diagnosis of first and recurrent DVT in symptomatic, asymptomatic, and pregnant patients. The authors of this review concluded that the majority of patients with suspected DVT could be managed with noninvasive testing; however, venography was recommended in patients whose noninvasive test results were nondiagnostic or discordant with the clinical assessment (eg, negative compression ultrasound and high clinical suspicion).

A widely recognized management trial using compression ultrasonography as a stand-alone examination in patients suspected of having a first episode of proximal DVT was performed by Birdwell et al on 405 consecutive symptomatic outpatients. The purpose of this study was to test the safety of withholding anticoagulation in patients who had a normal compression ultrasound examination of their proximal veins at presentation and a normal follow-up test completed within 5 to 7 days later. Patients with initially abnormal ultrasound studies were anticoagulated whereas those with normal studies underwent repeat ultrasonography. Anticoagulation was withheld from all patients whose compression ultrasound results remained normal regardless of their symptoms, and these patients were monitored for 3 months. Only two patients with initially normal studies developed DVT subsequently, and there were no deaths reported among patients managed according to this algorithm. These results demonstrate that it is safe to withhold anticoagulation in outpatients suspected of having a first episode of DVT if compression ultrasonography results are normal at presentation and on a single follow-up examination done 5 to 7 days later.

Current ultrasound technology is able to image calf veins in the large majority of patients. A well-trained technologist can interrogate these veins in 80% to 98% of cases using a combination of B-mode, Doppler waveform analysis, and color Doppler (Figures 1 and 2). Rose et al showed that in technically adequate studies, the sensitivity and specificity of color Doppler in isolated calf veins exceeded 90%. Others have also shown duplex ultrasound and color Doppler sensitivities for detecting isolated calf vein thrombosis to be greater than 90%. Extrapolating from this data, and the fact that in the Birdwell study only two patients developed DVT after the initial negative examination, it appears that an initial negative examination that includes both proximal and calf veins should be sufficient to withhold anticoagulation and preclude the need for routine follow-up studies in patients without clinical suspicion of pulmonary embolism.
Serial duplex scans are, however, indicated for patients who present with symptoms of possible DVT and have a negative venous ultrasound examination that has been limited to the proximal veins and in whom catheter-based contrast venography is not performed. The serial scans are performed to evaluate for propagation or extension of calf vein thrombi, the presence of which are not readily detected by CT or MR venography. Isolated calf vein thrombosis accounts for 20% of symptomatic DVT, and, in some studies, approximately one quarter of untreated symptomatic calf vein thrombi will extend proximally within 1 to 2 weeks. 19

The Problem of the Negative Study
It is currently estimated that 1 million patients per year undergo ultrasound examination for suspected DVT. Of these examinations, only 12% to 25% are positive. 9 Because of the cost associated with negative examinations and, in many locations, the burden that after-hours examinations place on retention of vascular technologists, a number of strategies have been developed to decrease the number of negative examinations. The most common alternatives that have been investigated as an alternative to immediate duplex evaluation of anyone suspected of DVT are clinical prediction models 20 and the measurement of D-dimer levels. 21

Combined Approaches in the Diagnosis of DVT
Recently, algorithmic approaches using a combination of clinical assessment, D-dimer measurements, and ultrasonography have been adopted into clinical practice with the goals of standardizing the diagnostic approach to DVT and reducing the number of negative ultrasound examinations. 22–27 The utility of algorithms in the diagnosis of DVT, however, depends on the availability of diagnostic testing, the expertise of the technologists performing the ultrasound examinations, the patient population, the cost and reimbursement of the different tests, and the interpretation of the results. What might be feasible for one institution may not be applicable to another, and each group should determine their own approach with some objective validation. For example, a strategy for diagnosing DVT that utilizes venography is useless for institutions where venography is no longer available. Therefore, potential approaches to limiting the use of ultrasound examinations in the evaluation of possible DVT will likely be organization-specific. Although algorithms offer multiple strategies for improving the diagnostic process for DVT, level 1 evidence on the validity and safety of these algorithms is lacking. There have been no large, randomized, multicenter studies comparing the outcomes of branching pathways that included adequate sample sizes, which are needed to test the safety of these algorithms. However, there have been some rigorously performed cohort studies that have incorporated algorithms utilizing clinical pretest probability in combination with ultrasonography and/or D-dimer testing. 22–27

Clinical Assessment in Combination With Venous Ultrasonography
Symptoms and signs are obviously inadequate alone for evaluation of possible DVT. However, some clinical presentations are more likely than others to be associated with DVT. Wells et al developed a model to assess the clinical likelihood of DVT in outpatients who present with suspected DVT. 20 Based on the presence of thrombotic risk factors, clinical signs, and symptoms, as well as the possibility of alternative diagnoses, patients are stratified into 3 risk categories—low, moderate, and high (Table 1). Patients who present with at least one DVT risk factor and the classical symptoms of unilateral pain and swelling have an 85% probability of
Clinical Model for Predicting Pretest Probability for Acute DVT

<table>
<thead>
<tr>
<th>Clinical Features/Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer within 6 months (ongoing treatment or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization by paralysis or plaster dressings</td>
<td>1</td>
</tr>
<tr>
<td>Recent surgery (within 4 weeks) or bed rest longer than 3 days</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling (&gt;3-cm increase in calf circumference compared to asymptomatic leg) measured 10 cm below tibial tuberosity</td>
<td>1</td>
</tr>
<tr>
<td>Thigh and calf swelling (entire swollen leg)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricosed)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or greater than that of DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

Pretest probability calculated as the total score: low = 0; moderate 1 or 2; high = ≥3. In the newer scoring system proposed by Wells et al the probability of having a DVT is likely if a score of two or higher is obtained; a score of less than two indicates that the probability of acute DVT is unlikely. The more symptomatic leg is used if patients have symptoms in both legs.

having DVT. Outpatients who present with no identifiable risk factors and with features not typically associated with DVT have about a 5% probability of actually having DVT.

Wells et al performed an evaluation of pretest probability assessment before compression ultrasound in 593 patients with possible DVT. Patients with low pretest probability underwent a single ultrasound test of the proximal veins. A negative ultrasound was considered to exclude acute DVT. A positive ultrasound was confirmed by venography. More than half the patients had 0 or fewer points and were classified as having a “low” pretest probability of DVT. One third had 1 or 2 points and were of “moderate” pretest probability, whereas 14% had at least 3 or more points and were assessed at “high” pretest probability. The incidence of positive venous ultrasound studies in these three groups (low, moderate, and high) was 3%, 17%, and 75%, respectively. The study did not address the issue of possible extension of calf vein thrombi over time.

D-Dimer Testing

The evaluation of a pretest probability model in conjunction with D-dimer testing has also been performed as a means to decrease the number of serial ultrasound examinations and to reduce the number of false-negative or false-positive ultrasound studies in patients suspected of acute DVT. The use of D-dimer is controversial and, more importantly, the precise role of D-dimer assays as an adjunct to ultrasound examination for DVT has not been definitively established. D-dimer measurements have a lower sensitivity for isolated calf vein thrombi, and the negative predictive value of D-dimer varies with the pretest probability of disease. Although the negative predictive value is exceptionally good in low-risk patients, it is unacceptable in high-risk patients. D-dimer assays are continuing to be explored as part of the diagnostic work-up of VTE, but at this time, these assays have not been standardized and the results are variable and depend on thrombus location, size, interpretation of the results, and other factors. Results from one study utilizing D-dimer assays cannot be extrapolated to results obtained by others because the various assays for D-dimer differ in their sensitivity and specificity.

Several studies have shown the utility of D-dimer in combination with clinical assessment in the initial investigation of outpatients with suspected DVT. In the most recent study by Wells et al, 1096 consecutive outpatients suspected of DVT were scored according to the clinical likelihood of having a DVT and were then randomized to undergo ultrasound imaging alone or to undergo D-dimer testing and then ultrasound imaging (unless the D-dimer test was negative and the patient was considered unlikely to have a DVT). Only 0.4% of patients in whom DVT was ruled out by D-dimer testing developed DVT. The authors concluded that DVT could be ruled out in a patient who was scored to be clinically unlikely to have a DVT and who had a negative D-dimer test (using two different D-dimer assays with high negative predictive value for DVT). They also concluded that ultrasound could be safely omitted in patients with a negative D-dimer and a low clinical likelihood of DVT. Although the results of this randomized trial are promising, it is important to note that the study population consisted of outpatients and further validation studies for high-risk inpatients with multiple comorbidities need to be performed.

The Problem of Acceptance of Limiting Venous Duplex Scans

Clinical models for standardizing the assessment of patients presenting with suspected DVT have been used in research settings and in some dedicated thrombosis centers in Canada and Europe. They are, however, not well accepted and infrequently used in routine clinical practice. Reasons for this include the complexity of the algorithms for routine clinical practice, medical-legal considerations, and the practical fact that a negative venous duplex ultrasound examination of the proximal and distal veins allows the evaluating physician to immediately consider alternative diagnoses.

Although the clinical diagnosis of VTE may be improved with the use of the Wells’ clinical probability model and D-dimer measurements, there is considerable disagreement about the order in which these strategies should be used to exclude the diagnosis of DVT and PE, and to reduce the number of serial ultrasound studies. There are several reviews that outline various approaches to the diagnosis of acute VTE. The reader is advised to consider one that most closely matches their practice and their patient population. It is likely that algorithms, particularly those incorporating D-dimer testing, will become more widely utilized in ongoing attempts to limit costs and improve the efficiency of diagnostic processes for patients. One such potential algorithm is outlined in Figure 3.

The Role of Venous Ultrasonography in the Diagnosis of PE

As for acute DVT, the diagnosis of PE cannot be established without objective testing. There have been several studies evaluating the utility of duplex ultrasonography of lower extremity veins in patients suspected of PE. These studies, often employing ultrasound of only the proximal
veins and nuclear-medicine-based ventilation perfusion (V/Q) scanning, unfortunately, have little relevance to modern practice in which complete proximal and distal vein ultrasound examinations are usually routine and in which CT (CTPA) or MR pulmonary angiography (MRPA) have largely supplanted V/Q scanning.

The rationale for employing lower extremity venous ultrasonography in patients who present with symptoms of PE is that a diagnosis of DVT may indirectly suggest the diagnosis of PE. Because anticoagulation is most often the initial therapy for DVT and PE, it is reasoned that further investigation to exclude PE may not be necessary in some clinical settings when there is also an ultrasound diagnosis of DVT. This approach, however, has several important limitations. First, it does not make a definitive diagnosis of PE. Patients can certainly have DVT and pulmonary symptoms and/or hemodynamic instability from causes other than PE. In addition, normal bilateral proximal venous ultrasound scans do not rule out PE. Even when PE is definitively present, DVT of the proximal lower extremity veins is detectable by compression ultrasound in only 50% of patients. When there is no evidence of lower extremity DVT and objective evidence of PE, the PE may have originated from pelvic veins or embolized completely from a lower extremity vein. Overall, the utility of venous ultrasonography to aid specifically in a diagnosis of PE is limited. An objective diagnostic test for PE is indicated in most cases. In most centers this would now be a CT pulmonary angiogram. A diagnostic algorithm for PE that does not include CT pulmonary angiography seems untenable in modern practice despite the lack of level 1 evidence to support CTPA in the diagnosis of PE. The use of MRPA is also increasing, but requires further validation in clinical trials.

Conclusions

Color flow venous duplex scanning of the proximal and distal veins is the current standard for routine clinical assessment of possible lower extremity DVT. Other invasive and noninvasive tests also are occasionally indicated in the assessment of possible DVT in clinical settings where venous duplex scanning is technically inadequate or cannot provide appropriate information. Diagnostic algorithms combining strategies employing adjunctive tests such as clinical risk stratification and D-dimer measurements to limit the number of negative duplex examinations have great potential but require that the safety of managing patients according to the algorithm be proven with local validation of safety by the local institution. Venous duplex scanning may in some cases be useful as an adjunct to the diagnosis of PE but, in most cases, other modern diagnostic techniques allow efficient, noninvasive, and direct objective diagnosis of PE in the clinical setting.

References


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