Deep venous thrombosis, or DVT, develops in approximately 2 million people annually in the United States. The third most common cardiovascular disease after acute coronary syndromes and cerebrovascular accidents, DVT has 2 distinct clinical presentations: venous thrombosis and pulmonary embolism (PE). The treatment of patients with suspected DVT is difficult. If DVT is undiagnosed, and hence untreated, fatal PE can develop. Treating every patient who presents with lower extremity symptoms is impractical and risky. Most patients who present with symptoms of DVT have nonthrombotic causes of lower extremity pain and swelling. Although highly effective in preventing extension, embolization, and recurrence of DVT, anticoagulant therapy is associated with an increased risk of major bleeding in approximately 5% of patients as well as other complications such as heparin-induced thrombocytopenia. For these reasons, accurate diagnosis is critical to the successful treatment of patients with suspected DVT.

Leg swelling, pain, and edema, although frequently present in DVT, are also associated with other entities such as trauma, cellulitis, and obstructive lymphadenopathy and therefore are not specific. Physical findings such as increase of leg circumference and elicitation of Homans’ sign (pain in the calf or popliteal region on forceful dorsiflexion of the ankle with the knee flexed) are also unreliable. In a study of 102 patients with suspected DVT, the sensitivity and specificity of the clinical diagnosis were 66% and 53%, respectively (2). Clinical appraisal alone is not sufficient, and over the past 20 y, reliance on objective diagnostic tests has increased.

Contrast-enhanced venography is the gold standard for diagnosing DVT. Although highly accurate for proximal and calf thrombi, the procedure is expensive, invasive, painful, and technically inadequate in approximately 10% of patients (1). The use of contrast material may induce allergic reactions and, in some patients, acute renal failure.

Impedance plethysmography does not directly show thrombi, but obstruction of venous outflow implies their presence. Although this technique reliably detects occlusive thrombi of the proximal veins, it is less useful for detecting nonocclusive thrombi and is insensitive for detecting calf thrombi (1).

Sonographic assessment of venous thrombosis depends chiefly on the compression technique. In response to Valsalva’s maneuver, the diameter of the normal femoral vein increases from 50% to 200%. In the absence of venous thrombosis, the vessel has a limited response and does not increase in diameter. This technique has limitations, however. Satisfactory performance of Valsalva’s maneuver requires excellent patient cooperation. Although the maneuver is effective in the proximal lower extremity, venous response decreases significantly with progression down the leg. A normal response excludes DVT, but a lack of venous dilatation is not specific for a clot and is associated with external venous compression and congestive heart failure. Finally, although the femoral veins are best evaluated with the patient supine, the popliteal veins are best evaluated with the patient prone or in the decubitus position, maneuvers not easily performed by all patients (3).

Color Doppler sonography uses computer processing to assess the Doppler shift produced by moving blood. This shift is assigned a color based on direction and a shade based on Doppler frequency shift. Normal veins fill with color, whereas thrombi appear as filling defects. Generally used in conjunction with the compression technique, color Doppler sonography is particularly useful in assessing the iliac veins, for which compression is not reliable (3).

A wide array of radionuclide methods for diagnosing DVT has been evaluated. Blood-flow and blood-pool studies, the radionuclide equivalents of contrast-enhanced venography, have been used to detect venous thrombosis. For both techniques, nonvisualization of any deep vein is considered evidence of vascular occlusion. Neither of these techniques, however, can distinguish acute from chronic DVT, and anatomic variations can confound interpretation (4,5). Direct thrombus detection using radionuclide methods was described nearly 40 y ago. After injection of radiiodinated fibrinogen, probe measurements in the legs were performed for up to 6 d, with a significant rise in counts in a leg segment indicating a forming thrombus. A few years later, thrombus imaging with 111In-labeled fibrinogen was reported. Although accurate for detecting actively forming thrombi, these procedures did not reveal established thrombi that were not propagating or thrombi in the deep veins of the upper thigh or the iliac veins. The need to wait for up to several days to establish a diagnosis is impractical, and as a consequence, these procedures are no longer used (6). Other, more recent, attempts at direct thrombus imaging include 111In-labeled
platelets and monoclonal antibodies directed against platelets and fibrin. Very sensitive for detecting forming thrombi, labeled platelet imaging is considerably less sensitive for detecting formed thrombi and in patients receiving anticoagulants (7,8). The procedure, which is labor intensive, requires in vitro handling of blood products. Multiple imaging sessions over several days may be required. Antipla
et and antifibrinogen monoclonal antibodies have also been used. Because of high background activity, delayed images are often required. As with labeled platelets, the sensitivity of these agents is greatest for detecting forming thrombi and may be adversely affected by heparin (6,9,10). No monoclonal antibody tracers for thrombus imaging have been approved for routine use in the United States.

Because of the success of sonography, the use of radionuclide methods for detecting venous thrombosis has declined precipitously. Even in those situations in which sonography is less useful, the lack of availability and cumbersome nature of radionuclide methods, as well as the length of time required for their completion, have dissuaded our clinical colleagues from taking advantage of what nuclear medicine has to offer. The data presented by Taillefer et al. (11) in this issue of The Journal of Nuclear Medicine offer hope that perhaps this attitude will change. The agent studied in this multicenter trial is a 99mTc-labeled peptide, aptic
tide, that competes with fibrinogen for binding to the glycoprotein IIb/IIIa receptors expressed on activated plate
ets (12). The advantages of this type of tracer are numerous. From a practical standpoint, the tracer is rapidly prepared and does not require in vitro handling of blood products. Once the tracer is injected, the study can be completed in a reasonable time, generally 2 h. The benefits of 99mTc as the radiolabel are obvious. The peptide is a direct thrombus imaging agent and thus allows a lesion to actually be “seen,” in contrast to anatomic procedures (including radionuclide bloodflow and blood-pool studies), in which the presence of a thrombus can be only inferred by the presence of anatomic alterations. Unlike other radionuclide thrombus imaging tracers, this agent is apparently not affected by anticoagulants. Finally, it is available for routine use.

The advantages of a test are meaningful, however, only if the test can accurately answer the questions posed and provide information not available from more easily performed tests. With respect to accuracy, the results of both animal and initial human studies indicated that aptic tide was sensitive for detecting acute venous thrombosis (13). Those results have now been confirmed in the larger multicenter trial. Although one could have hoped for an agreement rate of more than 75% between the peptide and venography, the authors quite correctly point out the flaws in the gold standard: venography is an anatomic study, whereas the peptide is a functional study; interpretation of venography is subject to considerable interobserver variability; and contrast-enhanced venography cannot always differentiate acute from chronic thrombosis. This last point is borne out in the data presented: the agreement rate between the peptide study and venography was higher in patients with no history of DVT than in the population as a whole.

Granted that aptic tide imaging is reasonably accurate for detecting DVT, in which patients will this technique be most useful? Ubiquitous availability, rapid completion, and accuracy make sonography the procedure of choice for diagnosing DVT, and to expect that aptic tide scintigraphy will assume this role in the future is unlikely and unrea
sonable. Despite the value of sonography, it is less successful in certain situations, and these are the circumstances in which the radionuclide study can potentially most contribute to patient care. For example, although highly accurate in the thigh, sonography is less useful in the calf, in which studies may be technically inadequate in up to 40% of patients (14). For many years, calf vein thrombosis was deemed clini
cally insignificant. With the increasing awareness of the association between deep vein thrombosis and PE, and because 30% of calf thrombi extend proximally, their diagnosis will likely become increasingly important. Because chronic clots can impede venous compression, one cannot always distinguish acute from chronic DVT sonographically (15). The peptide, however, binds to receptors on activated platelets that are present in acute, but not chronic, DVT, and will, perhaps, be useful in individuals with a history of DVT or PE. The results of sonography have also been disappointing in asymptomatic, high-risk patients, typified by indi
dividuals who have recently undergone orthopedic surgery. The sensitivity of compression sonography in this popula
tion has been reported to be as low as 60%, whereas the sensitivity of color Doppler sonography is even lower (16,17). The sensitivity of sonography might be improved by serial studies, but a more practical approach might be a single radionuclide receptor–based study.

In summary, the nuclear medicine community now has a readily available, reasonably accurate agent to image thrombi directly. We need to deter
mine only how best to use it.

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REFERENCES