EDITORIAL

Imaging of the "Active" Thrombus: Can It Be a New Gold Standard for Acute Deep Vein Thrombosis?

Detection of deep vein thrombosis (DVT) is one of the most important issues in clinical diagnosis because this condition frequently precedes a life-threatening disease, namely pulmonary thromboembolism. Several imaging techniques are available to diagnose DVT, with contrast-enhanced venography being widely accepted as the gold standard. However, this technique has well-recognized limitations, such as cannulation of dorsal foot veins, patient discomfort, allergic reactions to contrast material and potential nephrotoxicity. Venous sonography overcomes many of these problems but suffers from diagnostic blind spots within the deep veins of the calf and pelvis (*1*). MRI is also capable of showing DVT noninvasively and directly (*2*). However, DVT detection with MRI requires that the thrombus be sufficiently mature to generate a high-intensity signal and may result in false-negative diagnoses. In addition, all these techniques are based on only morphologic information about the vascular obstruction and cannot distinguish fresh, unstable thrombi from chronic, organized thrombi.

In deciding whether to start anticoagulant therapy in either symptomatic or asymptomatic patients, one must determine whether the thrombus is active. Only nuclear medicine can provide an image that includes biochemical information on thrombus formation, in contrast to the techniques that diagnose DVT on the basis of morphologic information. Numerous tracers have been reported useful for detecting DVT (*3–15*). These studies targeted several components of the thrombus, i.e., fibrinogen, white blood cells and platelets, to detect thrombi. However, direct labeling of these components was not ideal for thrombus imaging. For instance, although radiolabeled platelets were incorporated into acute thrombi and successfully revealed DVT in vivo, the long blood-pool clearance time of platelets not bound to thrombi resulted in poor target-to-background ratios until long after administration of the radiolabeled platelets. In addition, the separation and radiolabeling procedure for autologous platelets is difficult and requires handling the patient's blood. Monoclonal antibodies targeted to platelets or fibrin have enabled in vivo labeling (*12*). However, these agents also have the disadvantages of slow pharmacokinetics and a potential for inducing an immune response.

Under normal conditions, platelets are quiescent and circulate freely in the blood, because they do not attach to normally functioning endothelium. Vessel injury, however, exposes subendothelial connective tissue to various elements to which platelets can adhere. Platelets adhere to the vascular wall under the existence of the Willebrand factor. Adhered platelets lose their discoid shape, spread over the injured surface and then release several mediators, such as phospholipase C, which releases calcium. The release of calcium results in platelet contraction and the release of adenosine diphosphate, serotonin and thromboxane A_2, which induce platelet aggregation with recruiting circulating platelets. On the platelet membrane, platelet glycoprotein (GP) IIb/IIIa undergoes conformational changes in the activation process. These changes allow interaction with plasma fibrinogen and other adhesive proteins that serve to link platelets into a tighter aggregate. Activation of GP IIb/IIIa is an essential process in platelet aggregation and the initial step after thrombus formation. However, GP IIb/IIIa is not activated on normal platelets. Therefore, an imaging agent that binds specifically to the GP IIb/IIIa receptor on activated platelets would represent a true biochemical marker of active thrombosis (*16*).

In this issue of *The Journal of Nuclear Medicine*, Taillefer et al. (*17*) report the usefulness of ^{99m}Tc-apcitide (^{99m}Tc-P280) in the detection of acute DVT (ADVT). This agent is a small synthetic peptide (fewer than 20 amino acids) containing the peptide sequence arginine-glycine-asparatate, which binds to the GP IIb/IIIa receptor with a high enough affinity to effectively compete with endogenous fibrinogen. In preliminary studies, ^{99m}Tc-apcitide had good target-to-background contrast, i.e., a thrombus-to-blood ratio of 4.4 and a thrombus-to-muscle ratio of 11 at 4 h after injection (*16*). Rapid clearance from the blood and rapid renal excretion were also reported. Taillefer et al. chose contrast-enhanced venography as the gold standard and found ^{99m}Tc-apcitide to be highly sensitive and specific for detecting ADVT. The sensitivity and specificity were 86.4% and 88.2%, respectively, when the three sets of images, i.e., those obtained 10, 60 and 120 min after tracer injection, were analyzed together. These values are comparable with those obtained through other imaging modalities, such as sonography (*1*) and ^{99m}Tc-labeled

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modified recombinant tissue plasminogen activator scintigraphy (*15*).

Contrast-enhanced venography is considered the most accurate way to detect thrombotic disease in the extremities and is usually chosen as the gold standard for assessing new procedures. To interpret the sensitivity or specificity of a new procedure, however, one must take into account the errors of the standard reference test. For instance, when the standard test is incorrectly assumed to have no false-negative findings, the false-positive rate of the new test (1 − specificity) is overestimated. As Line et al. (*18*) showed, use of contrast-enhanced venography as a gold standard possibly causes significant underestimation of the sensitivity and specificity of a new test. Therefore, the accuracy of ^{99m}Tc-apcitide scintigraphy for detecting ADVT might be much higher than the percentages given above.

Thrombus imaging with ^{99m}Tc-apcitide has several advantages in the diagnosis of ADVT. First, the procedure is noninvasive, and immediate diagnosis is possible within 2 h after injection because of rapid clearance of tracer from blood. Second, the accuracy of the technique in detecting ADVT is almost satisfactory. Third, the technique provides good accuracy in diagnosing isolated calf vein thrombi, for which compression sonography has been shown to be less sensitive. Fourth, the accumulation of ^{99m}Tc-apcitide is, in theory, not influenced by the thrombolytic or heparin therapy that frequently precedes diagnostic tests in clinical settings. Fifth, because this agent is a synthetic peptide, human antimurine antibody responses and contamination with foreign proteins or virus are not an issue. Sixth, and above all, ^{99m}Tc-apcitide allows biochemical detection of the localized active thrombus, because this peptide binds only to activated platelets, not to normal platelets, in the bloodstream.

Clarification is needed on how long this agent is able to attach to thrombi, because the duration of platelet activation and consequent exposure of GP IIb/IIIa receptor should be relatively short. Accuracy and usefulness should be validated by comparisons with other modalities, such as sonography. Determining the feasibility of this agent for detecting DVT in nonsymptomatic patients is also important. Moreover, the influence of the antiplatelet therapy must be clarified.

Although many aspects, from several points of view, require clarification, scintigraphic detection of active thrombi with ^{99m}Tc-apcitide has the potential to become a new gold standard for biochemical detection of DVT.

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