INVITED COMMENTARY

Use of Radiolabeled Peptides to Image Deep Venous Thrombosis and Pulmonary Embolism

The development of radiopharmaceuticals to image acute deep venous thrombosis (DVT) and pulmonary embolism (PE) has sparked the interest of many nuclear medicine researchers for years. At present, the development of radiolabeled peptides able to bind to fresh thrombi is an appealing subject of study. Knight et al. (*1*), who have made great efforts in this field, describe the potential use of ^{99m}Tc-labeled bitistatin in the imaging of both DVT and PE. This study, done in an animal model, poses potential for using ^{99m}Tc-labeled bitistatin in humans. However, these preliminary results still require confirmation in clinical studies.

Bitistatin, an amino acid polypeptide isolated from viper venom, has great avidity for the surface receptors of the integrin family, known as glycoprotein IIb/IIIa (GP IIb/IIIa) (*2*). These GP receptors are highly expressed by activated platelets, which gain the ability to bind fibrinogen and other platelets. Conversely, they are not expressed by resting platelets (*3*). Thus, these receptors may be considered as a molecular marker of acute thrombi.

The diagnosis of DVT and PE is not a trivial problem because of the significant prevalence of these 2 diseases. The prevalence of DVT is as high as 2–5 million cases per year in the United States, whereas the prevalence of PE has been estimated to be 500,000–600,000 cases per year (*4,5*). Such figures are comparable with those in Western Europe. The clinical diagnosis of DVT is extremely inaccurate; in fact, only one half of patients with signs and symptoms consistent with DVT are confirmed to have disease by imaging modalities. Basically, 2 objective methods are used: contrast venography (CV) and sonography, which are based on the detection of changes in the venous anatomy associated with the presence of an intraluminal thrombus that, if sufficiently formed, either reduces the vascular filling or resists to the compression. CV, although considered the gold standard, is associated with considerable patient discomfort and is time consuming, expensive, and inadequate in >30% of cases (*4,6*). CV also has extreme intraobserver variability (*4*) and is not reliable in differentiating recurrent, acute DVT from the sequelae of old DVT (*4,8*).

Sonography (real-time B-mode with compression and pulsed-wave Doppler flow) is used increasingly in combination with color Doppler flow imaging and has an increased sensitivity in the detection of DVT in the leg, although it is less accurate in the calves (*9,10*). Sonography, like CV, has some drawbacks: differential diagnosis of recurrent, acute DVT versus late sequelae; and low sensitivity in asymptomatic patients or in detecting thrombi located in the calves of obese patients or those having orthopedic casts, swollen limbs, or duplication of femoral veins (*9–13*). In addition, there are at least 5 main reasons why accurate diagnosis of both DVT and PE requires a prompt diagnosis. First, in approximately one third of the cases of PE, death occurs so quickly that there is little opportunity for diagnosis and treatment (*4*). Second, approximately 30% of the two thirds of patients who survive a first episode of PE will die untreated, whereas 8% will die in spite of treatment (*4*). Third, between 70% and 90% of PEs are derived from acute DVT of the lower extremities (*5,14*). Fourth, acute DVT causes postphlebitic syndrome (venous hypertension, which leads to edema, pigmentation, and ulceration of the leg) in 25%–65% of cases (*15–17*). Therefore, the prevention of such morbid conditions clearly ameliorates the quality of life. Fifth, anticoagulation, which is the usual treatment for acute DVT and PE, is associated with risks: major bleeding in 2%–7% of cases and thrombocytopenia in 1% of patients who received intravenous heparin (*18*).

Identification of an accurate and prompt diagnostic method that exploits biochemical and functional changes between acute thrombi and other conditions is extremely important and has undergone extensive investigation. Initially, ^{111}In-labeled monoclonal antibodies raised against these receptors were investigated (*19,20*). The lack of a significant clinical impact in the management of patients with both DVT and PE led to further studies. The evidence that GP IIb/IIIa also binds to peptides and proteins that contain the tripeptide sequence arginyl-glycyl-aspartate (RGD) enabled the development of synthetic peptides containing such specific sequences that, once labeled, could be used for the imaging of fresh thrombi. Some of these have been characterized in animal models and phase I studies in humans (*3,21,22*).

These peptides are labeled with ^{99m}Tc, which increases their favorable pharmacokinetic profile, enabling rapid localization of fresh thrombi as early as 30 min after intravenous administration. Different labeling procedures have been proposed and executed to ensure proper specific activities without lowering the affinity of peptides for target receptors. Generally, small peptides are modified by incubation with triaminemonothiol, propyleneamine oxime, tetramine, and hydrazinonicotinamide (*23*). This latter method has been used

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by Knight et al. (*1*) to label bitistatin using ^{99m}Tc-glucoheptonate as an intermediate. This labeling procedure, which ensures favorable biodistribution parameters in animals without loss of reactivity, enabled high lesion-to background ratios, which averaged 18:1 for DVT to blood, 34:1 for PE to lung, and 284:1 for DVT to muscle. These findings were significantly higher than those reported under similar conditions for other synthetic peptides raised against GP IIb/IIIa receptors and labeled with ^{99m}Tc (*1*).

The evidence that radiolabeled synthetic peptides have a role in the imaging of fresh thrombi has been well documented. Nevertheless, the clinical impact of peptide scintigraphy must be fully evaluated. Available data suggest that this approach is extremely accurate for prompt diagnosis of DVT or for differential diagnosis of recurrent, acute DVT from late sequalae of previous episodes. DVT imaging by radiolabeled peptide scintigraphy is easily performed in the nuclear medicine laboratory, without requiring specific devices or manipulating biologic fluids and cells. The test is well tolerated by patients and is risk free. The images are diagnostic 1 h after injection, and interpretation is uncomplicated. The test provides unique information on the biochemical and functional profile of the fresh thrombus. However, multicenter studies with larger series of patients are needed to offer solid statistical data to referring physicians with specific clinical questions.

The increasing number of radiolabeled peptides used to image DVT, PE, inflammation, atherosclerosis, and solid tumors can only augur well for the future of nuclear imaging.

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