
Optimizing Images of Acute Deep-Vein Thrombosis Using Technetium-99m-Apcitide

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Objective: The purpose of this paper is to introduce the nuclear medicine technologist to a new radiopharmaceutical, ^{99m}Tc -apcitide, for imaging acute venous thrombosis. After reading this paper, the technologist should be able to: (a) describe patient preparation for imaging with ^{99m}Tc -apcitide; (b) state the amount of ^{99m}Tc -apcitide that is administered to patients for imaging acute venous thrombosis; (c) explain patient positioning for optimal image acquisition; and (d) discuss gamma camera acquisition parameters and their importance in obtaining high-quality images. Clinical cases illustrate both the whole-body distribution and diagnostic value of ^{99m}Tc -apcitide in detecting acute deep-vein thrombosis.

Key Words: thrombosis imaging; technetium-99m-labeled peptide; deep-vein thrombosis; technetium-99m-apcitide; AcuTectTM; contrast venography

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The potential sequelae of acute deep-vein thrombosis (DVT), such as postphlebitic syndrome, pulmonary embolism and even death, point to the urgent need for objective methods for the definitive diagnosis of DVT. Physicians cannot rely on the clinical signs and symptoms of acute DVT—pain, swelling and discomfort—as a means of diagnosis (1) because they are mimicked by those of congestive heart failure, Baker's cysts, cellulitis and postphlebitic syndrome (2), which eventually develop in as many as 50% of patients with acute DVT (3).

One or more episodes of DVT occur in an estimated 5 million individuals in the US annually (4). DVT of a lower extremity is the most common source of pulmonary embolism (PE) (1). Twenty percent of the annual 500,000 cases of PE result in death (4).

Without accurate diagnosis of acute DVT, anticoagulant therapy cannot be properly prescribed, subjecting patients to additional medical risks. Although anticoagulant therapy is effective in preventing the extension, embolization and recurrence of acute DVT, it is associated with an approximately 5%

increased risk of major bleeding (5) and other potentially serious side effects. Definitive diagnosis of acute DVT can serve to both confirm the need for anticoagulant therapy in patients with acute DVT and prevent unnecessary exposure of patients to anticoagulant therapy in the absence of acute DVT.

CURRENT INVASIVE AND NONINVASIVE METHODS

Current diagnostic methods used for detecting venous thrombosis include contrast venography and duplex ultrasonography. Of these, contrast venography is considered the gold standard, but it is invasive, often painful and highly dependent on skill and experience for adequate administration and interpretation. Contrast venography is no longer used routinely as the primary diagnostic method in the US.

Duplex ultrasonography is a noninvasive procedure combining real-time or continuous wave-compression sonography with Doppler evaluation to allow direct visualization of proximal DVT, but its sensitivity below the knee is decreased and its successful use is highly dependent on operator skill and patient cooperation. Obesity, postoperative trauma and casts also may compromise the results of this diagnostic method.

A NEW SCINTIGRAPHIC IMAGING RADIOPHARMACEUTICAL

A new radiopharmaceutical, AcuTectTM (kit for preparing ^{99m}Tc -apcitide injection; Diatide, Londonderry, NH), was recently approved by the FDA for use in the scintigraphic imaging of acute venous thrombosis in the lower extremities. Technetium-99m-apcitide, a complex of the small synthetic peptide, apcitide, and the ^{99m}Tc radionuclide, has a mechanism of action dependent on the thromboembolic process. During thrombus formation, platelets are activated at the site of the thrombus and express GP IIb/IIIa adhesion-molecule receptors (of the integrin family), leading to platelet aggregation (6). In vitro and in vivo animal data indicate that ^{99m}Tc -apcitide binds preferentially to GP IIb/IIIa receptors on activated platelets (7,8). Technetium-99m-apcitide is the first imaging modality to target acute DVT and to differentiate acute venous thrombosis from chronic venous thrombosis. Technetium-99m-apcitide is a functional rather than anatomical imaging modality, thus

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eliminating the common drawbacks of contrast venography and ultrasonography.

CLINICAL EXPERIENCE WITH TECHNETIUM-99M-APCITIDE

Sensitivity, Specificity, Agreement Rates

In Phase III clinical trials, involving 243 evaluable patients, the sensitivity, specificity and agreement rates of blind-read ^{99m}Tc -apcptide compared with blind-read contrast venography ("agreement" rate rather than accuracy is used because objective standards for assessing the accuracy of venography have not been established), were 73%, 68% and 69%, respectively (7). The agreement rate between blind-read contrast venography and blind-read ^{99m}Tc -apcptide for 6 individual ^{99m}Tc -apcptide readers ranged from 56%–73% (9). The sensitivity, specificity and agreement rates of investigator-read ^{99m}Tc -apcptide compared with those of blind-read venography were 81%, 65% and 70%, respectively (7).

Contrast venography can be positive due to chronic (non-acute) DVT, whereas ^{99m}Tc -apcptide would be expected to be positive only in the presence of acute DVT. Therefore, contrast venography is not a good gold standard for detecting specifically acute DVT in a population that also could have chronic DVT. In a subset of the Phase III patients ($n = 60$) who presented within 3 d of onset of signs and symptoms and with no history of DVT, in other words patients who were not expected to have nonacute DVT which could confound the venography result, the respective sensitivity, specificity and agreement rates of blind-read ^{99m}Tc -apcptide compared with blind-read venography were 83%, 74% and 77%, respectively, and for investigator-read ^{99m}Tc -apcptide, 100%, 69% and 78%, respectively (7). These results highlight the high sensitivity of ^{99m}Tc -apcptide for imaging acute DVT. Clinical outcomes studies to confirm that negative ^{99m}Tc -apcptide scans indicate the absence of acute venous thrombosis have not been completed. In view of this planned research, therefore, the decision to withhold anticoagulant treatment for a patient with clinical signs and symptoms of acute venous thrombosis should not be based on a negative ^{99m}Tc -apcptide scan alone.

Safety

Technetium-99m-apcptide was generally well tolerated in clinical trials involving 642 patients. Technetium-99m-apcptide is not a murine-based antibody and will not cause a human antimouse antibody (HAMA) response.

OPTIMIZING SCAN PERFORMANCE

To determine the presence of acute venous thrombosis, at least 2 sets of anterior and posterior planar images of the pelvis/thighs, knees and calves should be obtained after injecting ^{99m}Tc -apcptide, one set at 10 min (early) and one set starting at 60–90 min (late) postinjection.

Preparing the Patient

Tight clothing should be removed, including stockings or any lower extremity vascular compression devices. Although ^{99m}Tc -

apcptide scanning may be conducted with a cast in place, it should be recognized that the vasculature may be constricted.

Patients should be well hydrated by oral or intravenous fluids, unless contraindicated, to facilitate voiding. Patients should be directed to empty their bladders immediately before the study and should be encouraged to void frequently during the first few hours after the injection of ^{99m}Tc -apcptide.

Patient Positioning

Accurate image interpretation depends upon correct patient positioning, among other factors. Proper patient alignment must be maintained for all images acquired at all time points.

The patient should be positioned supine on the imaging table and table guides should be used to confirm straight limb position. The lower extremities should be symmetrically positioned to allow comparison of early and late images. It is advantageous to bind the feet together to stabilize the anterior-posterior (A-P) position. Flexion of the knees should be avoided.

Bedclothes, bedding, absorbent pads or pillows should be checked so that they do not compress the limbs, especially behind the knees. Urinary drainage catheters should be positioned so that they drain freely and are out of the field of view. Marking the right side of the patient in all images using a ^{57}Co or ^{99m}Tc marker is helpful in patient positioning and image interpretation. Patient comfort should be confirmed to avoid motion during imaging. The urinary bladder should be shielded for optimal imaging of the veins of the pelvis.

Gamma Camera Parameters

A large field-of-view single- or dual-head gamma camera will provide optimal images. Either a low-energy all-purpose (LEAP) or low-energy high-resolution (LEHR) parallel-hole collimator is preferred, with a 15%–20% energy window centered at 140 keV. A 128×128 image matrix is preferred because a smaller matrix provides insufficient resolution.

Radiopharmaceutical Administration

Technetium-99m-apcptide should be administered as a peripheral intravenous injection in an upper extremity at a dose of approximately 100 μg of peptide radiolabeled with 20 mCi of ^{99m}Tc . Technetium-99m-apcptide may be administered using an indwelling venous catheter or butterfly administration set.

Image Acquisition

Spot or regional images should be acquired using fields of view that provide uninterrupted views of the thighs, knees and calves. Preferred fields of view for optimum image interpretation are: from the lower edge of the bladder to just above the knees for the pelvis and thighs; from the midthigh to the midcalf for the knees; and from just above the knees to just above the ankles for the calves. The full width of both limbs should be in each view, and the detector should be positioned as close to the patient as possible.

Two sets of images should be acquired: one set starting at 10 min and the second starting at 60–90 min after injection. Planar images should be acquired for a minimum of 750,000 counts for images over the pelvis, and a minimum of 500,000 counts for

images over the legs. For most equipment this may be conveniently accomplished using an image acquisition time of 5 min. Images should be acquired digitally. The images should be acquired in the same sequence for each time point, preferably anterior pelvis/thighs, then knees, then calves, followed by a posterior series in the same order. An image should be repeated if the patient moves during acquisition. Points to be considered to ensure that the images are of high technical quality are listed in Table 1.

IMAGE INTERPRETATION

Preferably the images should be presented digitally to allow image adjustment (brightness, contrast, and/or threshold and color) during interpretation. When formatting, images should be aligned by view for both time points to facilitate comparisons.

Review the Clinical Status of the Patient

Before beginning image interpretation, the clinician should review the patient's clinical status for conditions associated with acute DVT or for conditions that may be confused with acute DVT. Several important points to be considered are listed in Table 2.

Interpreting the Images

It is preferable that image interpretation be conducted using digital images to allow the adjustment of image brightness, contrast and threshold, and to use color. If images must be read from film, it is important for the images to be appropriately enhanced (by adjustment of brightness, contrast and/or threshold) and faithfully reproduced to show asymmetric, deep-venous ^{99m}Tc-apcitide uptake, if present. A diagram of the venous anatomy of the lower extremities may be helpful, especially to distinguish the deep veins from the superficial veins.

In a normal scan, ^{99m}Tc-apcitide distribution in the lower extremities shows symmetrical (right-left) uptake in the deep and superficial veins, symmetric and low soft-tissue uptake, and bilaterally symmetrical limb sizes.

Acute DVT is indicated by asymmetric linear uptake of

TABLE 1
Considerations to Ensure High Technical Image Quality

- Both early (10-min) and late (60- to 90-min) images should be available.
- Images should be aligned by view for both time points.
- Images must be in correct left/right presentation (look for right side marker).
- Images must have sufficient count density to be evaluable.
- Fields of view should provide images of both legs in their entirety.
- Legs should be positioned correctly (parallel and not rotated) at all time points.
- Bladder activity should not interfere with evaluation of the pelvis.
- Confounding artifacts, such as motion, misplaced urinary drainage catheter or urinary contamination, should be eliminated.

TABLE 2
Considerations When Reviewing the Clinical Status of the Patient

- Location and duration of signs and symptoms, such as edema/swelling, warmth, redness and pain.
- Prior history of DVT—studies in patient with recurrent clinical signs and symptoms have shown that only 1/3 actually had acute DVT (10,11).
- Recent pelvic operation or hip or knee replacement—these procedures are associated with an increased risk of acute DVT.
- History of cancer or estrogen therapy also is associated with an increased risk of acute DVT.
- Other risk factors such as recent travel, stasis, congestive heart failure, obesity and family history of thrombosis.
- Recent trauma—although a high percentage of trauma patients have DVT, trauma or fractures also may cause hyperemia.
- Cellulitis or arthritis, which may cause soft-tissue tracer uptake.
- Varicosities, which may result in superficial tracer uptake.
- Results of other diagnostic tests, for example, ultrasound and D-dimer test.

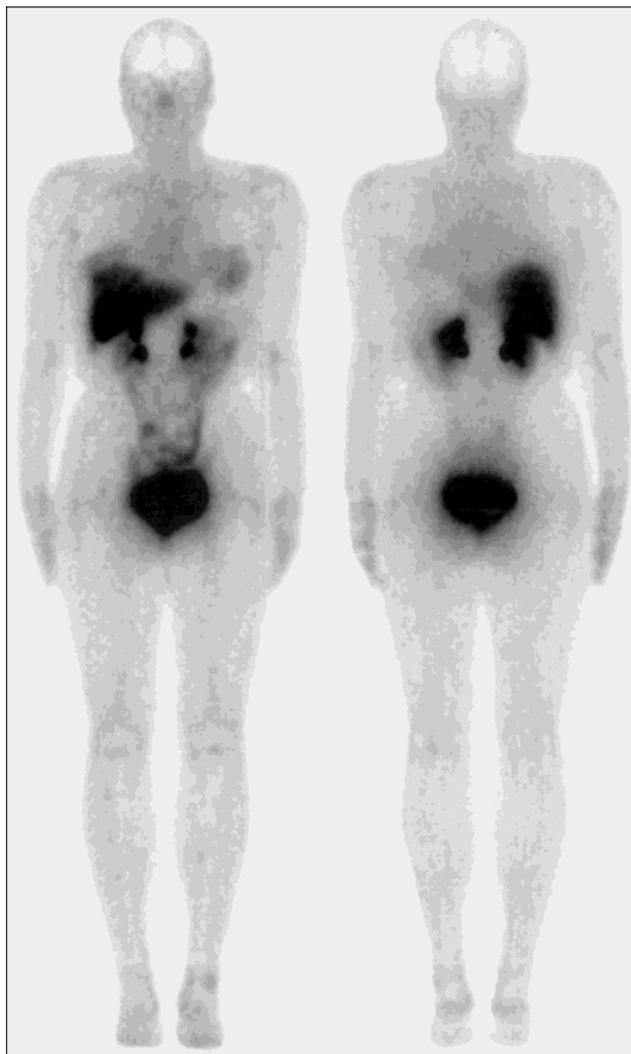


FIGURE 1. Normal biodistribution in a 41-y-old woman volunteer with no DVT, at 60 min postinjection of ^{99m}Tc-apcitide, shows uptake in the liver, kidneys, ureters and urinary bladder.

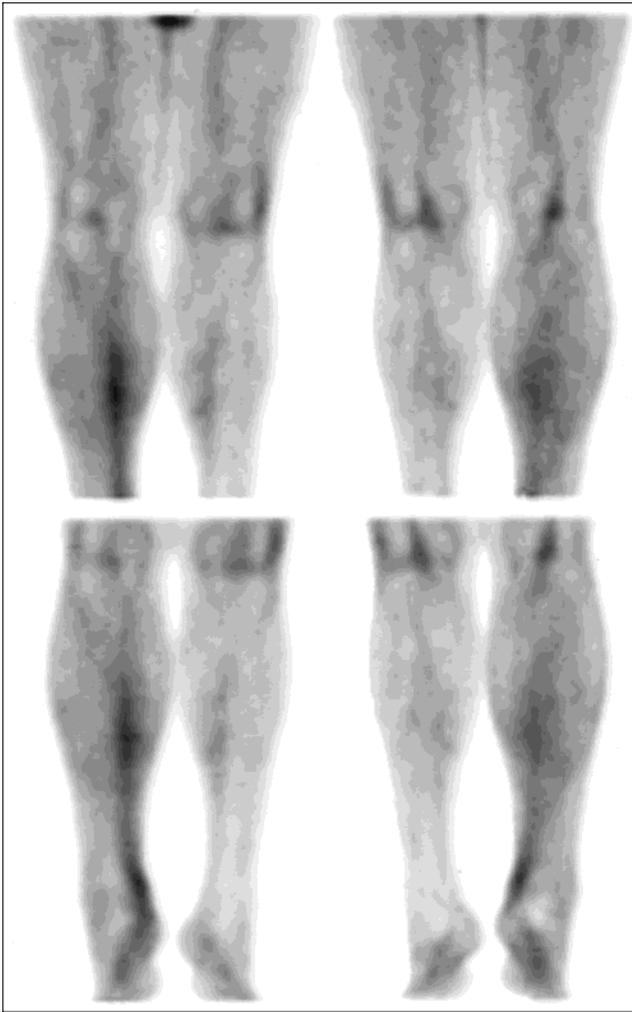


FIGURE 2. A 72-y-old man with no history of DVT presented with pain, tenderness, swelling and increased warmth in the right calf of 5 d duration. Top: Contrast venography findings at 60 min; thrombus visualized in the right calf and knee. Bottom: ^{99m}Tc -apcitide findings at 60 min; increased asymmetric linear uptake is seen in the right calf that was visible at all time points (only 60 min shown here). This abnormal uptake is indicative of acute DVT.

^{99m}Tc -apcitide in a deep-vein segment (greater uptake than is observed in the corresponding contralateral deep-vein segment) that persists, or becomes apparent on late images. (Asymmetry in anterior and posterior views should be consistent with the anatomic location of the vein.)

If delayed clearance of the radiopharmaceutical agent from the lower extremities (secondary to edema, congestive heart failure, etc.) is noted, then obtaining images at approximately 3 h postinjection should be considered.

Abnormal ^{99m}Tc -apcitide localization may occur that is not diagnostic of acute DVT but may accompany acute DVT. Examples include: (a) abnormal ^{99m}Tc -apcitide uptake in collateral veins and in superficial veins, and should not be confused with deep-venous uptake usually indicative of superficial thrombus which may be secondary to venous insufficiency or occlusion; (b) abnormal ^{99m}Tc -apcitide uptake in postsurgical sites; (c) abnormal ^{99m}Tc -apcitide uptake in nonvascular locations, including joints, surrounding prostheses, muscle, skin

and soft tissue; and (d) increased limb size, noting that limb size often does not increase in cases of acute DVT alone but an increase can accompany acute DVT in cases with concomitant venous insufficiency and/or occlusion. It should be kept in mind that deep-venous ^{99m}Tc -apcitide uptake that does not persist, or is not apparent on late (≥ 90 min) images, is not indicative of acute DVT.

CLINICAL EXAMPLES

Scintigraphic images of 3 patients are included to illustrate both the normal biodistribution and the diagnostic value of ^{99m}Tc -apcitide in DVT (Figs. 1, 2, 3).

CONCLUSION

A new physiological marker for imaging acute venous thrombosis has recently been approved by the FDA. It is a ^{99m}Tc -based imaging agent, ^{99m}Tc -apcitide, which is a complex of the small synthetic peptide, apcitide, and the radionuclide ^{99m}Tc . Technetium-99m-apcitide binds preferentially to activated platelet receptors and, thus, targets acute DVT and differentiates acute DVT from chronic venous thrombosis.

Clinically, this agent is most useful in patients who have had equivocal or technically inadequate ultrasonography and a high index of suspicion of acute DVT, or in patients with recurrent DVT, in an attempt to differentiate an acute episode from chronic venous disease. It is extremely important to have



FIGURE 3. A 66-y-old man with a history of DVT in the left leg 4 y before. He presented with pain, tenderness, swelling and erythema in the right calf and knee of 5 d duration. Top: Contrast venography findings at 60 min; thrombus visualized in the right popliteal vein. Bottom: ^{99m}Tc -apcitide findings at 60 min; increased asymmetric linear uptake is seen in the right calf and knee that was visible at all time points (although only 60-min images are shown here) and is indicative of acute DVT.

adequate patient preparation, imaging technique, imaging acquisition, processing and display, as described in this article, to give the patient's health care provider the best possible clinical picture.

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