Technetium-99m-Modified Recombinant Tissue Plasminogen Activator to Detect Deep Venous Thrombosis

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We report a method for deep venous thrombosis (DVT) detection which uses ^{99m}Tc-labeled modified recombinant tissue plasminogen activator (rt-PA) scintigraphy. A Phase III clinical trial was performed on 79 patients with suspected DVT. **Methods:** The plasminogen binding site of rt-PA was permanently inhibited without inactivating the fibrin binding site. The modified molecule was radiolabeled with ^{99m}Tc. Scintigraphy was performed and the results were compared to those of contrast venography. **Results:** Of 14 thrombosed proximal segments, 13 had positive scans; in the 53 nonthrombosed proximal segments, 49 had negative scans. In proximal vein thrombosis, rt-PA scintigraphy had a sensitivity of 93% and a specificity of 92%. Of the 36 thrombosed calf vein segments, 31 had positive scans; in the 30 nonthrombosed calf segments, 28 had negative scans. In calf vein thrombosis, scanning has a sensitivity of 86% and a specificity of 93%. **Conclusion:** Scintigraphic scanning with this ^{99m}Tc modified rt-PA permits accurate detection of thrombus in both proximal and calf veins in patients with clinically suspected DVT. The technique detects both fresh and aged thrombi and is unaffected by heparin administration. Further study in other patient groups is needed to define the overall clinical utility.

Key Words: technetium-99m-rt-PA; deep venous thrombosis; contrast venography

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Deep venous thrombosis (DVT) is a major disease in Australia. While DVT does not directly cause death itself, its major complication of pulmonary embolism (PE) is a lethal condition. In the United States, 5 million people will have an episode of DVT each year; approximately 10% of these patients will develop PE and about 10% of them will die as a direct consequence of PE (*1*). Despite clinical awareness of this problem, DVT and PE are underdiagnosed, with only 16%–38% of patients dying from PE correctly diagnosed before death (*2*). Furthermore, over the last 40 yr there has been a lack of improvement in the diagnostic capabilities to detect PE (*3*).

For the past two decades, standard diagnostic tools to detect DVT have been unreliable (*4,5*). Consequently, there has been considerable effort to devise an optimal technique for the accurate diagnosis of DVT. Presently, contrast venography is the reference technique to which all other thrombus detecting tests must be compared. It is, nevertheless, expensive, invasive, painful (*6*), thrombogenic (*7*) and potentially nephrotoxic (*8*). In addition, there are some patients in whom venous cannulation is not possible, and technically inadequate studies in up to 10% of patients have been reported (*9*). Interpretation of contrast venography requires considerable expertise, and even in experienced hands there is considerable variability in interpretation, with a reported interobserver variability of 10% (*10*).

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Venous ultrasonography (US) has recently been advocated as an alternative to contrast venography (*11*). Although this technique has reported sensitivities and specificities in excess of 90% in detecting proximal vein thrombosis, it is significantly less successful in identifying isolated calf vein thrombosis (*12*). Because up to 20% of isolated calf vein thromboses propagate proximally and may further embolize to the lungs (*13,14*), repeat US in negative cases has been proposed (*15*). In addition, venous US is technically demanding and time-consuming to perform. In asymptomatic patients, venous US is significantly less accurate than in symptomatic patients and cannot be used as an accurate screening test in high-risk patients (*16*).

Various radionuclide techniques have been proposed as possible alternatives to contrast venography (*17*). We investigated the clot-localizing properties of radiolabeled recombinant tissue plasminogen activator (rt-PA) after active site inhibition.

METHODS

Patients

Seventy-nine consecutive inpatients (47 women, 32 men; aged 28–93 yr; mean age 70 yr) with suspected DVT of a lower limb underwent contrast venography and scintigraphy with ^{99m}Tc-rt-PA. The mean time between contrast venography and scintigraphy was 20 hr (range; 1 hr to 4 days). Sixty-eight patients could accurately determine the time of onset of their symptoms. Symptoms (leg pain and/or leg swelling) occurred on an average of 5.4 days (range 0–42 days) prior to contrast venography. In those patients with positive contrast venography, 34 patients could accurately date their symptoms. The average delay was 5 days. All patients gave informed written consent and the study protocol was approved by the Legal, Ethics and Morals Committee of The Southern Sydney Area Health Service. Forty-six patients were receiving intravenous heparin at the time of scintigraphy. In all patients, contrast venography was performed before scintigraphy.

Preparation of rt-PA

Fifty milligrams of sterile lyophilized rt-PA was reconstituted with 10 ml sterile water (5 mg/ml) and dispensed into 500-μl aliquots and stored at −20°C. Plasminogen site inhibition was performed using modifications to a previously described method (*18*). A two-stage radiolabeling technique was performed using a modified transchelation technique (*19*). Briefly, 2.5 mg rt-PA are incubated for 4 hr with 69 μl d-phenylalanine-1-proline-1-arginine chloromethylketone (P-PACK) at 4°C (P.PACK:rt-PA; 15:1 mole ratio). Forty-eight microliters of a 1:6 dilution of 2-mercaptoethanol:water were mixed with the rt-PA solution for 30 min on a rotor (2-ME:rt-PA; 2600:1 mole ratio). The mixture was then purified on a 5 × 1-cm spinning column of P6-DG (Pharmacia, Stockholm, Sweden) and eluted with 0.05 *M* acetate buffer (pH 4.5) and dispensed into freeze-dry vials. Water for irrigation (500 ml) was purged with pure nitrogen for 30 min. Twenty milligrams of stannous fluoride (SnF_2) were added to the water. Fifty microliters calcium gluconate (1 g in 10 ml) 500 μl SnF_2 solution and 500 μl

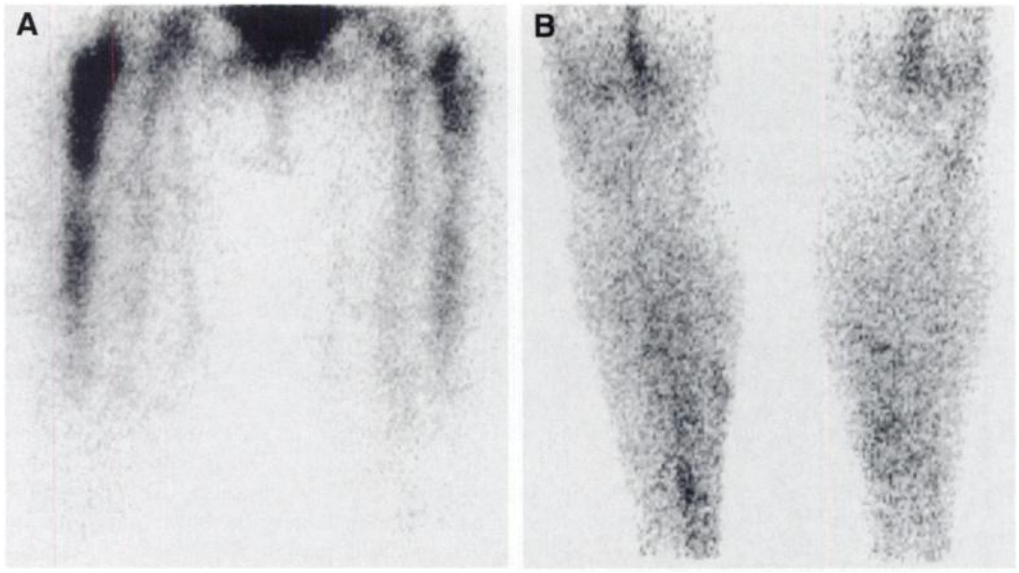

FIGURE 1. Normal scintigraphic study in a patient with normal contrast venography. (A) Anterior thigh image demonstrating normal uptake of tracer in bladder, pelvic bones and femora. Increased femoral uptake on the right is due to recent total hip replacement. There is minimal activity in the femoral veins and no asymmetry in the activity in these veins. (B) Posterior calf image demonstrates minimal activity in the calf veins. The activity in the popliteal veins is prominent due to their superficial location in the popliteal fossa.

20% mannitol were added to the reduced rt-PA. The mixture was mixed, then snap-frozen on dry ice and freeze-dried. To reconstitute the tracer, 2.5 ml ^{99m}Tc in normal saline were added to the lyophilized rt-PA kit and gently mixed and incubated for 5–10 min. The radiolabeled ^{99m}Tc-rt-PA was now ready for injection. In vitro assessment of fibrin binding, plasminogen activation and electrophoretic mobilty was assessed using previously described techniques (*20*). Each patient received 1.5 mg rt-PA with an average activity of 640 MBq (range 460–700 MBq). Instant thin-layer paper chromatography was performed prior to injection using ITLC-SG support (Gelman Sciences, Ann Arbor, MI) with normal saline and acetone as the eluants.

Contrast Venography

We used a standard methodology (*21*). Nonionic contrast (50–100 ml) was injected into the dorsal foot vein of the limb suspected of DVT after placement of tourniquets at the ankle and the calf. Anterior, lateral oblique and medial oblique radiographs of the calf were obtained along with anterior views of the thigh. Additional views were taken as needed. The criterion for thrombosis was the presence of a persistent intraluminal filling defect. Venograms were viewed by two radiologists who were blinded to all other test results. If there was disagreement between these two radiologists, the venogram was referred to a third radiologist. Venograms were analyzed on a patient-by-patient and segment-by-segment basis.

Segment-by-Segment. Venograms were divided into two segments: proximal (involving the popliteal and the femoral vein) or distal (involving only the calf veins). All segments were classified as being normal, positive for thrombosis or uninterpretable.

Patient-by-Patient. Patients were assigned to one of four categories: patients with no thrombosis, those with proximal vein thrombosis (thrombosis in the femoral or popliteal vein with or without concurrent calf vein thrombosis), those with isolated calf vein thrombosis and those whose results were inadequate for interpretation.

Scintigraphy

Images were obtained with a gamma camera interfaced to a computer. A high-resolution collimator was used and the data were acquired in a 256 × 256 format with a 15% asymmetric energy window centered on the ^{99m}Tc photopeak. The radiotracer was administered by bolus administration into an antecubital fossa vein. Imaging was performed at 4-hr postinjection. An anterior view of the thighs and a posterior view of the calves and knees were obtained. Imaging was performed for 10 min per image with 430K counts (s.e.m. ± 40K) obtained in the thigh image and 240K counts (s.e.m. ± 25K) in the calf. All scans were viewed by two nuclear medicine physicians and graded by consensus. The readers were blinded to the contrast venography results. Images were viewed on a video monitor using an interactive gray scale threshold. A representative image of a normal scan is shown in Figure 1. The positive criteria were as follows:

1. Femoral vein. Increased tracer accumulation in comparison with the contralateral side so that the increase was equal to or greater than adjacent bone marrow accumulation.
2. Calf veins. Increased tracer accumulation in the deep veins compared with the contralateral side.
3. Popliteal vein. Increased tracer accumulation in comparison with the contralateral side in a patient with co-existing calf or femoral thrombosis. Representative images of abnormal scans are shown in Figures 2–4.

Venography Versus Scintigraphy

After the initial analysis, all venograms and scans that did not correlate were reviewed in an attempt to understand the limitations of the scanning technique.

RESULTS

Technetium-99m-rt-PA Preparation

Fibrin binding was in excess of 50%. No plasminogen activation could be detected and ^{99m}Tc-rt-PA demonstrated identical electrophoretic mobility as unlabeled rt-PA. Autoradiography, however, demonstrated that greater than 90% of the ^{99m}Tc was associated with the rt-PA. Instant thin-layer chromatography with saline demonstrated that greater than 97% of the ^{99m}Tc was bound to rt-PA with less than 3% as ^{99m}Tc-gluconate or ^{99m}Tc-mannitol; in the acetone solvent system, less than 1% free TcO_4 was seen.

Contrast Venography

Segment-by-Segment Analysis. In the proximal vein segment, 67 segments were of diagnostic quality; 12 segments were excluded from the analysis. Thromboses were seen in 14 segments. In the calf veins, 66 segments were evaluable with 36 thromboses identified.

Patient-by-Patient Analysis. In this analysis, 66 patients had venograms of diagnostic quality, with 13 venograms considered to be inadequate for interpretation. Fourteen patients had proximal vein thrombosis (thrombosis in the femoral or popliteal vein with or without concurrent calf vein thrombosis), 25

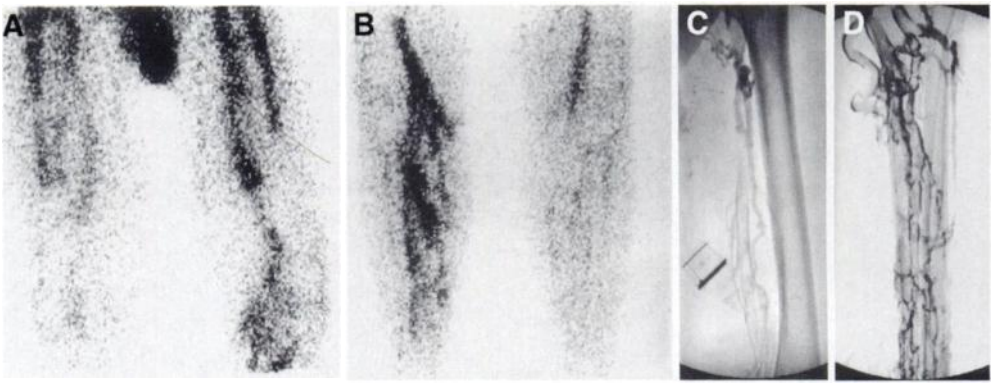

FIGURE 2. Abnormal scintigraphic study in a patient with positive CV in proximal and calf veins. (A) Anterior thigh image demonstrating marked asymmetry of activity in left femoral vein. (B) Posterior calf image demonstrates marked asymmetry of activity in left calf veins extending into popliteal vein. (C) Contrast venography demonstrates thrombosis involving the left femoral vein. (D) Contrast venography demonstrates thrombosis involving the left calf veins.

had isolated calf vein thrombosis and 27 patients had normal venograms.

Scintigraphy

All scans were of diagnostic quality.

Segment-by-Segment Analysis. Of the 14 thrombosed proximal segments, 13 had positive scans; in the 53 nonthrombosed proximal segments, there were 49 negative scans. One thrombosed proximal segment had a negative scan; four nonthrombosed proximal segments had positive scans. Thus, in proximal vein thrombosis, scintigraphy had a sensitivity of 93% and a specificity of 92%. Of the 36 thrombosed calf vein segments, 31 had positive scans; in the 30 nonthrombosed calf segments, 28 had negative scans. Five thrombosed calf vein segments had negative scans; two nonthrombosed calf vein segments had positive scans. For calf vein thrombosis, scintigraphy had a sensitivity of 86% and a specificity of 93%.

Patient-by-Patient Analysis. Of the 14 patients with proximal vein thrombosis, 13 had positive scans in the femoral vein, popliteal vein or both. Of the 52 patients without proximal vein thrombosis, 48 patients had negative scans. In the four patients without thrombosed proximal veins with positive scans, three had thrombosed calf veins with scans called positive in the calf and popliteal veins. Overall, scintigraphy had a sensitivity of 93% and a specificity of 92% in patients with proximal vein thrombosis. Of the 25 patients with isolated calf vein thrombosis, 20 had positive scans in the calf veins. Of the 27 patients with normal contrast venography, 25 had negative scans. The sensitivity and specificity were 80% and 93%, respectively, in these patients.

Venography versus Scintigraphy

One patient had a definite proximal vein thrombosis that was not identified scintigraphically 22 hr after contrast venography. The patient had undergone total hip replacement and 4 days after the operation complained of calf pain. Venography demonstrated a 5-cm nonocclusive thrombus in the midportion of the femoral vein with no proximal or distal extension. Four patients with positive scintigrams had no proximal vein thrombosis on the venograms. In three of these patients, scanning (performed at 25, 21 and 56 hr after contrast venography) and venography demonstrated calf vein thrombosis. The scintigrams, however, suggested extension of the thrombosis into the popliteal vein. In the remaining patient, the venogram demonstrated an extrinsic compression of the iliac vein with no thrombosis, but the scintigram (obtained 22 hr later) was positive for proximal thrombus. CT scanning demonstrated a pelvic mass subsequently diagnosed as non-Hodgkin's lymphoma. CT scanning also demonstrated that the femoral vein on the side of the lesion was significantly dilated in comparison with the other side. Five patients with calf vein thrombosis had a thrombus on the venogram, but the scintigrams were negative 24 hr later. Review of the venograms showed definite thrombus in three patients; in the two remaining patients, the reviewers could not unanimously agree as to the presence or absence of thrombosis. In the two patients with negative venograms and positive scintigrams, one patient was definitely negative for DVT and the other patient was retrospectively graded as equivocal.

DISCUSSION

One of the initial steps in the formation of a thrombus is the conversion of fibrinogen to fibrin. Fibrin rapidly polymerizes and then provides a network for platelet adhesion. The conversion of fibrinogen to fibrin has been well described. Moreover, there is little fibrin present in the circulation. It thus represents an ideal target for a radiotracer and several studies using radiolabeled monoclonal antibodies directed against fibrin have been published (*22*).

Tissue plasminogen activator is a naturally occurring serine protease enzyme that is intimately involved in vascular homeostasis (*23*). This enzyme is produced in the vascular endothelium and continuously released into the circulation. Recently, a recombinant DNA t-PA (rt-PA) was produced and is available commercially (*24*). The enzyme has at least two functional sites: a fibrin binding site(s) and a catalytic site that are responsible for the conversion of plasminogen to plasmin.

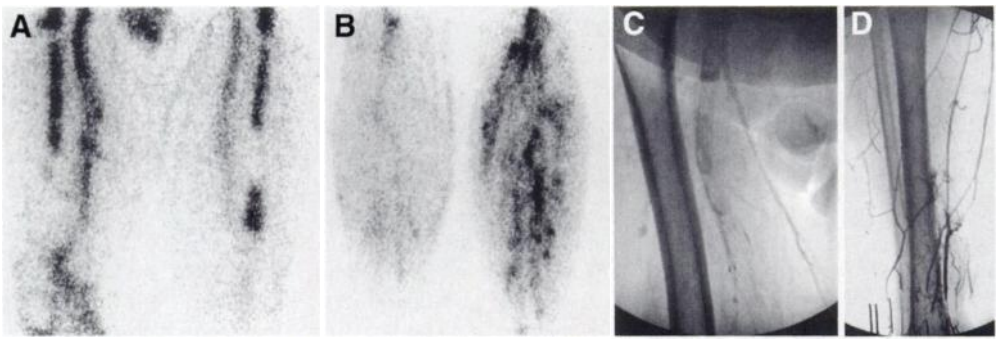

FIGURE 3. Abnormal scintigraphic study in a patient with positive contrast venography in proximal and calf veins. (A) Anterior thigh image demonstrates marked asymmetry of activity in right femoral vein. (B) Posterior calf image demonstrates marked asymmetry of activity in right calf veins extending into popliteal vein. (C) Contrast venography demonstrates thrombosis involving the right femoral vein. (D) Contrast venography demonstrates thrombosis involving the right calf veins.

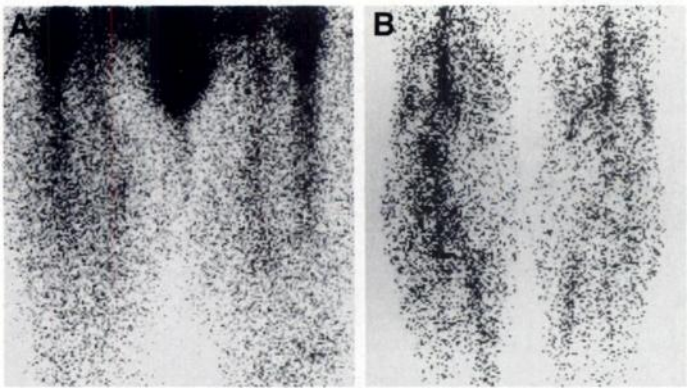

FIGURE 4. Abnormal scintigraphic study in patient with isolated calf vein thrombosis on contrast venography. (A) Posterior calf image demonstrates marked asymmetry of activity in right calf veins. (B) Contrast venography demonstrates thrombosis involving the right calf.

The rt-PA binds directly to fibrin and the resultant conformational change induces a large increase in its plasminogen catalytic activity. Thus, this thrombolytic agent is said to be fibrin-selective as compared to other agents such as streptokinase (*25*). As with other serine protease enzymes, the plasminogen catalytic site can be permanently inhibited (*18*). After such inhibition, the molecule predictably would bind to fibrin and not induce clot lysis.

Previous studies in animals have demonstrated that this approach to thrombus localization may be successful (*20,26*). The present study demonstrates that this approach is a highly specific and sensitive method of thrombus detection in humans. In addition, the technique is simple, utilizing a kit preparation of the radiopharmaceutical labeled with ^{99m}Tc. Performance of the scan itself is uncomplicated; only 20 min of imaging time are required. Because the rt-PA is a human-derived molecule, allergic reactions should be rare.

Importantly, this technique permits detection of thrombi of varying ages. Sixty-eight of the 79 patients with thrombosis were able to estimate the time between their first symptoms and venography. The mean age of the thrombi was 5.4 days. Furthermore, scanning accuracy does not appear to be affected by simultaneous heparin administration, since 36 of the 38 patients with thrombosis were on intravenous heparin administration at the time of scintigraphy.

The interpretation criteria used here were based on a Phase II clinical trial of 20 patients with DVT on contrast venography (unpublished data). These patients were scanned at various time points up to 6 hr postinjection, with 4 hr being the most suitable imaging time. Technetium-99m-rt-PA clears rapidly from the circulation biexponentially. The initial and terminal components have half-times 5–6 and 120–130 min, respectively (unpublished data). At 4 hr, approximately 10% of the initial blood activity still persists. Thus, even at 4 hr, there is some residual blood-pool activity, which explains how a dilated vein with its increased blood volume may be mistaken for thrombosis. Interpretation criteria were decided before the current trial commenced and were applied prospectively. These criteria do not permit detection of a thrombus confined only to the popliteal vein or bilateral thromboses. Isolated popliteal vein thrombosis with no involvement either proximally or distally, is a rare clinical entity. In our group of patients, no patient had isolated popliteal vein thrombosis. Bilateral thromboses are more common but are still rare. No patient in this group was suspected of bilateral DVT and contrast venography was only performed on the symptomatic side. No false-negative ^{99m}Tc-rt-PA scans occurred due to these limitations in interpretative criteria.

Scanning with ^{99m}Tc-rt-PA demonstrated marked bone marrow accumulation of tracer. This may be due to an intrinsic property of the tracer, to colloid formation or both. Gel electrophoresis with autoradiography did not show any colloid formation and there was no a priori reason to suggest tracer susceptibility to colloid formation. Previous work with ^{111}In-labeled rt-PA also demonstrated bone marrow accumulation, indicating that such uptake is probably characteristic of the tracer itself.

In all patients, contrast venography was performed before ^{99m}Tc-rt-PA scanning. This was due to the logistics of patient recruitment. From this study, we cannot ascertain whether tracer uptake was affected by previous contrast administration. In another study (*27*), the order of the tests was reversed and no change in the accuracy of ^{99m}Tc-rt-PA was seen.

The present study also demonstrates the problems of using venography as the reference test. As is well known, contrast venography is a difficult technique to perform and interpret. Thirteen patients had venograms that were inadequate for interpretation. This is somewhat higher than expected and is thought to be due to two factors. First, as we wished to use these venograms as a reference tool, very strict interpretative criteria were applied that may not reflect routine clinical practice. Second, all the patients were inpatients and probably represent a difficult group of patients to study.

The solitary patient who had proximal vein thrombosis and a negative scan, presented following hip replacement with calf symptoms and had isolated femoral vein thrombosis. Femoral vein thrombosis not extending to the calf veins is rare and constitutes 3%–5% of all thrombi arising in the deep veins of the leg. In the four patients with no proximal vein thrombosis on venography, three had calf vein thrombosis and the scans overestimated the extent of the thrombosis as extending into the popliteal vein. In each patient, scanning was performed after venography and it is possible that the thrombus had extended into the popliteal vein in the interval. In the remaining patient, the femoral vein was dilated in comparison with the contralateral side, thereby causing a false-positive scan interpretation. In the calf veins, scanning missed three patients with DVT. One patient had a thrombus in only one major vein of the calf, one patient had two veins involved and the third had three veins involved. All three patients had onset of symptoms less than 2 days before contrast venography. Thrombi of similar size were visualized in other patients and no simple explanation is available to explain these results.

CONCLUSION

The results of the present study are of comparable accuracy to compression ultrasound in thrombus detection in the proximal veins. Ultrasound evaluation of the calf, however, is less sensitive. Direct evaluation of the calf veins is not possible in 10%–40% of patients (*12*), and in the subset of patients in which a diagnostic examination is possible, the average sensitivity is 80% (*11*). Calf examination is highly operator-dependent and time-consuming. The well-recognized limitations of ultrasound evaluation of the calf veins has prompted several authors to advocate repeat studies to detect proximal extension of calf vein thrombus (*12,15*). While this approach may be suitable for outpatients, it is difficult to implement in a inpatient population as few clinicians can wait up to a week for a diagnosis.

We believe that scintigraphy with ^{99m}Tc-rt-PA is a promising technique for reliable detection of proximal and calf vein throm-

bosis in hospital inpatients suspected of deep venous thrombosis. The technique is simple to perform, is not operator-dependent, is sensitive to both fresh and aged thrombi and is unaffected by heparin administration. Further work in other patient groups needs to be performed to define the overall clinical utility.

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REFERENCES

1. Moser K. Venous thromboembolism. *Am Rev Respir Dis* 1990;141:235–249.
2. Palevsky HI. The problems of the clinical and laboratory diagnosis of pulmonary embolism. *Semin Nucl Med* 1991;21:276–280.
3. Anderson RE, Hill RB, Key CR. The sensitivity and specificity of clinical diagnostics during five decades. *JAMA* 1989;261:1610–1617.
4. Salzman EW. Venous thrombosis made easy. *N Engl J Med* 1987;314:847–848.
5. O'Donnell TF, Abbott WM, Athanasoulis CA, Millan VG, Callon AD. Diagnosis of deep venous thrombosis in the outpatient by venography. *Surg Gynecol Obstet* 1980;150:69–74.
6. Bettman MA, Paulin S. Leg phlebography: the incidence, nature and modification of undesirable side effects. *Radiology* 1977;122:101–104.
7. Albrechtsson U, Olson CG. Thrombotic side effects of lower limb phlebography. *Lancet* 1976;1:723–724.
8. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency or both. *N Engl J Med* 1989;320: 143–149.
9. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic efficacy of impedance plethysmography for clinically suspected deep venous thrombosis. *Ann Intern Med* 1985;102:21–28.
10. McLaughlin MSF, Thomson JG, Tayloe DW, Kelly ME, Sackett DL. Observer variation in the interpretation of lower limb venograms. *AJR* 1979;132:227–229.
11. Comerota AJ, Katz ML, Hashemi HA. Venous duplex imaging for the diagnosis of acute deep venous thrombosis. *Haemostasis* 1993;23(suppl 1):61–71.
12. Cronan JJ. Venous thromboembolic disease: the role of US. *Radiology* 1993;186:619–630.
13. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981;94:439–444.
14. Philbrick JT, Becker DM. Calf deep venous thrombosis: a wolf in sheep's clothing? *Arch Intern Med* 1988;148:2131–2138.
15. Heijober H, H.R. B, Lensing AWA, Turpie AGG, Colly LP, ten Cate JW. A comparison of real time compression ultrasonography with impedance plethysmography for the diagnosis of deep venous thrombosis in symptomatic outpatients. *N Engl J Med* 1993;329:1365–1369.
16. Jongbloets LMM, Lensing AWA, koopman MMW, Buller HR, ten Cate JW. Limitations of compression ultrasound for the detection of symptomless postoperative deep venous thrombosis. *Lancet* 1994;343:1142–1144.
17. Knight LC. Radiopharmaceuticals for thrombus detection. *Semin Nucl Med* 1990;20: 52–67.
18. Kettner C, E. S. Synthesis of peptides of arginine chloromethyl ketone: selective inactivation of human plasma kallikrein. *Biochem* 1978;17:4778–4784.
19. Mather SJ, Ellison D. Reduction-mediated technetium-99m labeling of monoclonal antibodies. *J Nucl Med* 1990;31:692–697.
20. Butler SP, Kader KL, Owen J, Wang TST, Fawwaz RA, Alderson PO. Rapid localization of indium-111-labeled inhibited recombinant tissue plasminogen activator in a rabbit thrombosis model. *J Nucl Med* 1991;32:461–467.
21. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972;104:134–144.
22. Knight LC. Scintigraphic methods for detecting vascular thrombus. *J Nucl Med* 1993;34:554–561.
23. Lascalo J, Braunwald E. Tissue plasminogen activator. *N Engl J Med* 1988;319:925–931.
24. Penica D, Holmes WE, Kohr WJ, et al. Cloning and expression of human tissue-type plasminogen activator cDNA in *E. coli*. *Nature* 1983;301:214–221.
25. Marder VJ, Sherry S. Thrombolytic therapy. *N Engl J Med* 1988;318:1512–1520.
26. Ord JM, Hasapes J, Daugherty A, Thorpe SR, Bergmann SR, Sobel BE. Imaging of thrombi with tissue-type plasminogen activator rendered enzymatically inactive and conjugated to a residualizing label. *Circulation* 1992;85:288–297.
27. Butler SP, Rahman T, Boyd SJ, Parkes SL, Quinn RJ. Detection of lower limb deep venous thrombosis in asymptomatic high risk patients using a new radiolabeled thrombus specific agent [Abstract]. *J Nucl Med* 1995;36(suppl):89P.

NUCLEAR CARDIOLOGY

Functional Assessment of Alcapa Syndrome by Dobutamine Stress Thallium-201 SPECT and Echocardiography

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Exercise ^{201}Tl SPECT has been used as a useful method for the assessment of patients with anomalous left coronary artery communicating to the pulmonary artery (ALCAPA syndrome). In this study, we described an adult patient with this anomaly who was evaluated by dobutamine stress testing in conjunction with simultaneous ^{201}Tl SPECT and echocardiography before and after surgery. A large perfusion defect in the anterior wall, septum and apex was detected on the preoperative stress scan with partial reversibility on reinjection scan. Worsening of wall motion abnormalities in the septum and anterior wall was detected by stress echocardiography. In the studies performed 3 mo and 1 yr after reimplantation of the left coronary artery in the aorta, a smaller fixed perfusion defect in the anterior wall and apex was detected without reversibility. No stress-induced wall motion abnormalities were detected. Despite the improvement of perfusion, there was no improvement of regional or global left ventricular function at rest. We report that both dobutamine ^{201}Tl SPECT and echocardiography were useful for the detection of reversible ischemia and for the assessment of the surgical outcome of an adult patient with ALCAPA syndrome.

Key Words: dobutamine stress echocardiography; thallium-201; SPECT; ALCAPA syndrome

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ALCAPA (anomalous left coronary artery communicating to the pulmonary artery) syndrome is a rare congenital anomaly characterized by an anomalous left coronary artery communicating to the pulmonary artery (*1*). Most of untreated patients with this anomaly die during childhood from myocardial infarction and heart failure. It is rare when patients survive to adulthood because of the extensive collateralization from the right coronary artery to the left coronary artery (*1,2*). The detection of myocardial ischemia in patients with ALCAPA is important to identify viable left ventricular (LV) myocardium at jeopardy of irreversible damage. Therefore, exercise thallium

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