Evaluation of Indium-111-Labeled Antifibrin Monoclonal Antibody for the Diagnosis of Venous Thrombotic Disease

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The potential advantage of using ^{111}In-antifibrin (^{111}In-AF) monoclonal antibody for the diagnosis of deep venous thrombosis (DVT) was studied in 44 patients with suspected DVT (27 underwent heparin therapy before ^{111}In-AF injection). All patients had contrast venography (considered as the gold standard) and ^{111}In-AF scintigraphy within 24 hr. Two to 3 mCi of ^{111}In-AF were injected intravenously, and planar scintigraphy of the limbs was recorded within 10 min (17 times), 3 hr (44 times), and 18 hr (39 times). Indium-111-AF images were then interpreted without knowledge of the results of the other examinations. The DVT diagnostic accuracy of ^{111}In-AF was greater when interpretation was based on images recorded at different time periods after injection. Indium-111-AF sensitivity for diagnosis of DVT was 85% (29/34) and was not apparently decreased by heparin therapy. None of the 10 patients with negative contrast venography had a positive ^{111}In-AF scan. The results demonstrate the importance of recording serial images and the excellent accuracy of ^{111}In-AF for diagnosing DVT.

J Nucl Med 1991; 32:785–791

Diagnosis of deep venous thrombosis (DVT) has long been based on contrast venography (*1*). However, noninvasive diagnostic methods are now being used, particularly Doppler examination in association with plethysmography (*2*) or ultrasonography (*3,4*). In general, these techniques have good diagnostic sensitivity for thrombosis situated between the inguinal ligament and the knee, but are less efficient for iliac and calf vein thrombosis (*5*). Nor do they always permit an old, inactive thrombus to be differentiated from a fresh, active one (*6*). Several scintigraphic methods have been proposed for diagnosis of DVT. Exploration with radiolabeled fibrinogen or ^{111}In-labeled platelets would seem to be the most efficient choices. Iodine-125-labeled fibrinogen can be used alone or in association with plethysmography (*7*), but the disadvantages of this method are delayed implementation and absence of imaging (*8*). Some authors have used other radionuclides (^{131}I, ^{123}I, ^{99m}Tc) for fibrinogen labeling, and clot images have thus been obtained within 6 to 24 hr after injection (*9,10*). However, problems related to fibrinogen of human origin and the influence of heparin on method sensitivity have limited the usefulness of exploration with radiolabeled fibrinogen, which currently plays only a minor role in diagnostic strategy for DVT (*8*). The use of ^{111}In-labeled platelets enables a fresh thrombus to be detected (*11–13*). Visualization of clots often requires 24 hr, and sometimes 72 hr, to ensure that basal radioactivity has disappeared (*14*). Administration of anticoagulants reduces method sensitivity (*15,16*), and platelet radiolabeling requires considerable time.

The potential advantage of using ^{111}In-labeled antifibrin monoclonal antibody for DVT exploration has been demonstrated in vitro and in the animal in several works (*17–19*). The aim of the present study was to define the modalities of interpreting this type of examination and to assess ^{111}In-antifibrin efficiency in the diagnosis of DVT. Our results confirm the benefit of using antifibrin antibody for diagnosis of DVT (*20–23*).

MATERIALS AND METHODS

The modalities of immunoscintigraphic interpretation after injection of ^{111}In-AF and its accuracy for diagnosis of DVT were defined in 44 patients (24 women, 20 men) hospitalized for clinically suspected phlebitis of the lower (42 cases) and upper (2 cases) limbs. The mean period since the initial appearance of clinical signs was 6 days (range: 24 hr to 21 days). The antibody used was an IgG1 in Fab fragment form reacting specifically with the fibrin monomer beta chain (C22A, Centocor).

All patients had contrast venography and scintigraphy within 24 hr. Contrast venography (one reader) and scintigraphy (another reader) were blindly interpreted. Contrast venography was performed in the classic manner, with the patient in dorsal decubitus, by catheterization of a dorsal pedal vein. A tourniquet was placed on the malleoli, and 30 cc of loxaglate were injected into each foot by electric syringe for 30 sec. Images were obtained at 25, 30, and 35 sec after injection on a 30 × 120-cm cassette.

Received Mar. 23, 1990: revision accepted Oct. 1, 1990.

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In 24 patients, DVT was strongly suspected (Doppler examination associated with ultrasound and/or plethysmography) before ^{111}In-AF was performed. However, the localization (side and level) of the suspected thrombosis was unknown to the physician interpreting the ^{111}In-AF scan. In the other 20 patients, ^{111}In-AF was performed first.

The thrombosis was located in the lower limbs in 42 patients, 25 of whom had received heparin treatment for 4–12 hr before injection of ^{111}In-AF. The other two patients, who underwent heparin treatment for 12 hr, had an axillohumeral thrombosis.

Following informed consent, patients received 2–3 mCi of ^{111}In-DTPA-antifibrin (0.5 mg of antibody) by slow i.v. injection followed by a 10-ml saline flush.

Mean radiolabeling efficiency as checked by chromatography was 90% (range: 80%–98%).

Images were obtained using a gamma camera (Sophy camera, Sopha Médical) equipped with a medium-energy collimator. Both ^{111}In photopeaks (173 and 247 keV) were used. With patients in the supine position, several series of images were recorded: at 10 min (17 times), 3 hr (44 times), and 18 hr (39 times) after injection of ^{111}In-AF. Each series included anterior views, with 200K counts for calves, knees, and thighs and 400 for the pelvis. For two patients with suspected phlebitis of the upper limbs, arm-forearm and then arm-shoulder images were recorded with the camera set respectively for 200 and 300K counts. Interpretation of ^{111}In-AF images of the limbs was done in all cases without knowledge of the results of contrast venography and the other noninvasive examinations (Doppler, ultrasonography, and plethysmography).

Images at 3 hr were considered positive if a region, compared to the contralateral side, showed greater activity than that of circulating blood and background. Interpretation based on comparison of 3-hr images and early (10-min) images was considered positive if the former showed a focus of high uptake not visualized on the latter. Interpretation of 3-hr and 18-hr images was judged to be positive if the activity of a region increased with time as compared to the contralateral region, vascular activity, and background.

The different modes of interpretation were evaluated with reference to contrast venography by determining the number of sites correctly and incorrectly rated and the doubtful results for diagnosis of thrombotic disease in each limb. For a given region, a result was considered correct when ^{111}In-AF and contrast venography were both positive (true-positive) or both negative (true-negative); incorrect when ^{111}In-AF was positive and contrast venography negative (false-positive) or ^{111}In-AF negative and contrast venography positive (false-negative); and doubtful when ^{111}In-AF was inconclusive regardless of the contrast venography result.

The diagnostic accuracy of ^{111}In-AF for detection of distal thrombosis was evaluated by using the entire series of recorded images. Accuracy was studied for diagnosis of thrombotic disease of the limbs, in which case ^{111}In-AF was considered true-positive if it visualized at least one of the clots revealed by contrast phlebography (i.e., ^{111}In-AF was considered true-positive if only one lesion out of many was visualized) and false-negative if it visualized none. Accuracy was also determined for clot localization as revealed by contrast venography, in which case ^{111}In-AF for a given region was considered true-positive if it visualized the clot or clots revealed by contrast phlebography and false-negative if it failed to visualize them.

When the number of cases was sufficient (i.e., no expected value lower than 5), the χ^2 test was used to compare the number of correct, doubtful, and incorrect results of the different modes of interpretation. The χ^2 test with continuity correction was used to compare results in patients with and without heparin therapy.

RESULTS

No side effects were observed during the 48-hr period of clinical monitoring following injection.

Method of Interpretation

For the 17 patients who had a recording at 3 hr as well as an early one at 10 min, it was possible to compare the results of 3-hr images (A) with the results of the early and 3-hr images combined (B) (Table 1) 34 times (right and left side). For calf images, there were approximately the same number of incorrect results for A and B. The number of doubtful cases was greater for A images (6/34 versus 3/34), but these cases proved to be correctly rated results for B images. This same tendency was even more apparent for thigh images, with more incorrectly rated (4/34 versus 2/34) and doubtful (7/34 versus 4/34) results for A than for B. Likewise, the accuracy of pelvic B images was greater than that of A (31/34 versus 28/34), particularly because of the smaller number of incorrectly rated results (1/34 versus 4/34). The number of cases was not sufficient to perform the χ^2 test.

For the 39 patients who had a recording at 3 hr and then a late one at 18 hr, it was possible to compare the results of 3-hr images (C) with the results of the 3-hr and 18-hr images combined (D) (Table 2) 78 times (right and left side). For the calves, the number of correctly rated D images (60/78) was clearly greater than that of C images (40/78), particularly because of the absence of doubtful interpretation ($p = 0.002$). For the thighs ($p = 0.002$) and pelvis ($p = 0.008$), the same tendency was apparent, with respectively 72/78 and 74/78 correctly rated D images as compared to 55/78 and 62/78 C images (Fig. 1).

TABLE 1
Comparison of 3-Hour Versus 3-Hour/Early (10-min) Images

Image		Image classification			
		CO	DO	IC	AC
Calves	A	21	6	7	0.62
	(nd)				
	B	25	3	6	0.73
Thighs	A	23	7	4	0.68
	(nd)				
	B	28	4	2	0.82
Pelvis	A	28	2	4	0.82
	(nd)				
	B	31	2	1	0.91

CO = correct results: true-positive + true-negative; IC = incorrect results: false positive + false negative; DO = doubtful results; AC = accuracy: CO/(CO + IC + DO); A = images recorded 3 hr after antifibrin injection; B = images recorded immediately after antifibrin injection; and (nd) = insufficient number of cases to perform the χ^2 test.

TABLE 2
Comparison of 3-Hour Versus 3-Hour/18-Hour Images

Image		Image classification			
		CO	DO	IC	AC
Calves	C *	40	13	25	0.51
	D	60	0	18	0.77
Thighs	C *	55	14	9	0.70
	D	72	2	4	0.92
Pelvis	C †	62	6	10	0.79
	D	74	0	4	0.95

CO = Correct results: true-positive + true-negative; IC = incorrect results: false-positive + false-negative; DO = doubtful results; AC = accuracy: CO/(CO + IC + DO); C = images recorded 3 hr after antifibrin injection; and D = images recorded 18 hr after antifibrin injection.

* $p = 0.002$.

† $p = 0.008$.

TABLE 3
Thrombotic Disease Detection Sensitivity

Localization of thrombus extension	Heparin +	Heparin −	Total
Calves	6/6	4/4	10/10
Thighs	1/1	0/0	1/1
Pelvis	1/1	0/0	1/1
Calf + thigh	5/5	0/0	5/5
Calf + pelvis	1/1	0/0	1/1
Thigh + pelvis	2/2	0/0	2/2
C + T + P	4/4	5/8	9/12
Axillohumeral	0/2	0/0	0/2
Total*	20/22	9/12	29/34

Number of positive AF-immunoscintigraphy/number of patients with positive contrast venography.

C + T + P = thrombus of the calf, thigh, and pelvis.

* χ^2 test not significant.

Accuracy of ^{111}In-AF for Diagnosing DVT

Table 3 shows ^{111}In-AF sensitivity (85%) for detection of thrombotic disease as a function of the extent of the thrombosis identified by contrast venography. Twenty-nine out of 34 patients with DVT had ^{111}In-AF uptake in at least one clot. Sensitivity was excellent when the thrombosis was limited to one area of the lower limbs, particularly in patients with a calf vein thrombosis (100%). However, only one patient had an isolated thrombosis of the thigh and pelvis. Indium-111-AF sensitivity was lower for extensive DVT. Three false-negatives were observed in patients with extensive thrombosis of the whole lower limb. Two axillohumeral thromboses were not detected, even though they were of clinically recent onset (48 hr). Heparin treatment prior to ^{111}In-AF injection had no apparent effect on sensitivity: ^{111}In-AF was positive in 20 out of 22 patients treated with heparin and in 9/12 who were not treated (ns).

Table 4 indicates the sensitivity for clot detection. A total of 49 out of 65 regions showing a clot in contrast venography were identified by ^{111}In-AF. Sensitivity was better for the calves than for the thighs and pelvis. Indium-111-AF was positive in 34 out of 41 clots in patients treated with heparin and in 15/24 clots in patients who were not treated (ns).

Specificity was excellent: in 10 patients with negative contrast venography, ^{111}In-AF was never positive. Five of these patients had been treated with heparin, and 4/5 of the other patients had sequelae of phlebitis diagnosed by contrast venography 6 mo to a year before (Fig. 2).

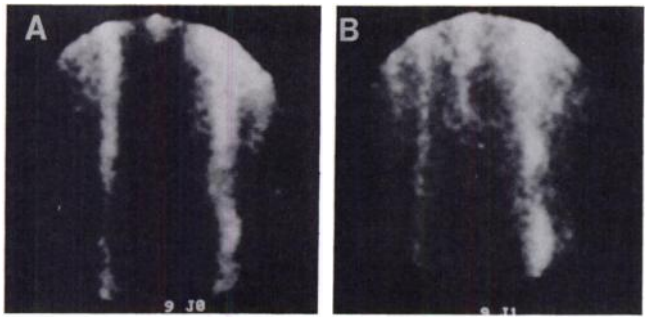

FIGURE 1. The 2.5-hr postinjection image (A) shows a hot spot in the left common femoral vein highly suggestive of thrombosis (short arrow) and slight uptake in the left superficial femoral vein (long arrow). The interpretation was positive for left common femoral vein and doubtful for left superficial femoral vein. On the 18-hr image (B), left common femoral vein activity still remains the same (short arrow) and left superficial femoral vein uptake clearly appears (long arrow). There is midline activity corresponding to the scrotum and penis. When the 2.5-hr image was compared with the 18-hr image, the result was positive for left common femoral and left superficial femoral veins.

DISCUSSION

The results of our study demonstrate the accuracy of ^{111}In-AF for diagnosis DVT when serial images are recorded.

TABLE 4
Clot Detection Sensitivity

Localization	Heparin +	Heparin −	Total
Calf	17/18*	7/10	24/28
Thigh	11/12	4/7	15/19
Pelvis	6/9	4/7	10/16
Axillohumeral	0/2	0/0	0/2
Total†	34/41	15/24	49/65

* Three bilateral thrombi (one false-negative).

† χ^2 test not significant.

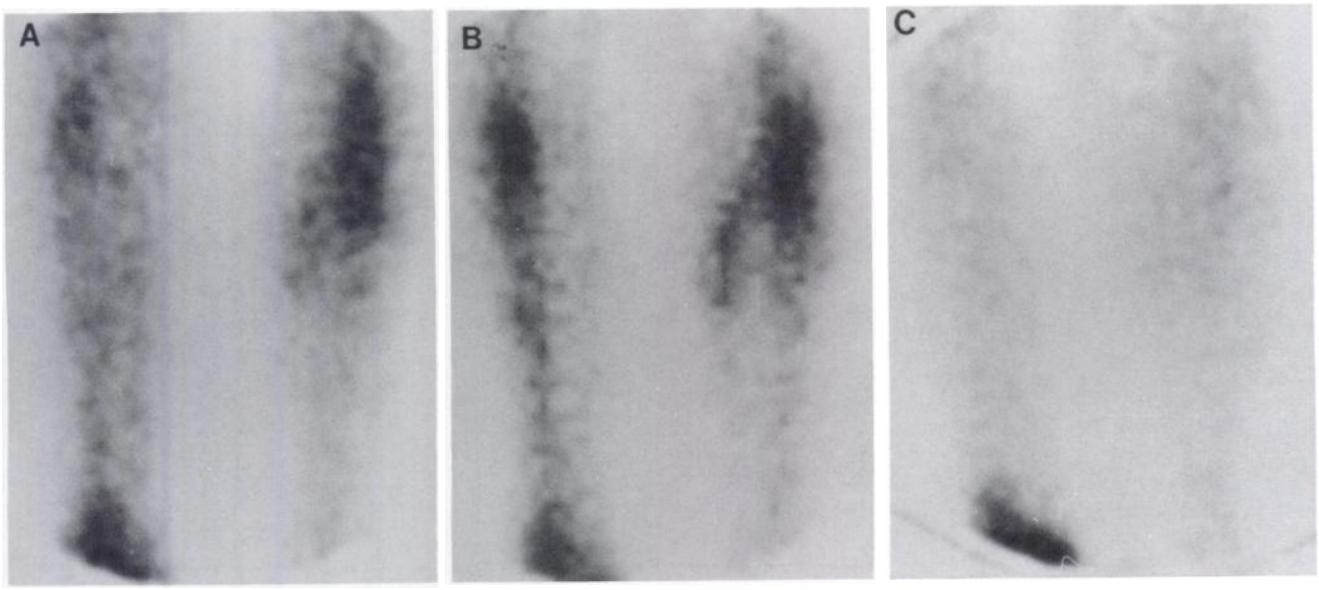

FIGURE 2. This calf image recorded 3.5 hr (A) after ^{111}In-AF injection shows a hot spot in the left calf suggestive of thrombosis. However, this patient had a past history of DVT, and the same hot spot is seen in the same area on the early postinjection image (B). Thus, if the 3.5-hr image is compared to the early image, the probability of thrombosis would seem low. Moreover, the activity has disappeared on the 18-hr image (C). Contrast venography showed no fresh clotting.

Early images showed, essentially, the blood pool. Blood stream activity decreased with time but was still noticeable in the 3-hr images. In these images, it was sometimes difficult to differentiate between an area of intense radioactivity due to the blood pool alone and one due to uptake by a clot (Fig. 2). Differentiation proved easier when 3-hr images were compared to early ones since the number of correctly rated interpretations was greater than for isolated interpretation of 3-hr images. Diagnostic accuracy was still greater when 3-hr images were compared to those recorded 18 hr after injection of antibody. This improvement can be attributed to two mechanisms: antibody clearance and antigen accessibility. Indium-111-AF is specific for the fibrin beta chain and is not reactive with fibrinogen. Thus ^{111}In-AF monoclonal antibody does not bind circulating fibrinogen (*17*) and blood-pool activity is due to free circulating ^{111}In-AF. Blood clearance of unabsorbed antibody is greater than that of antibody taken up by the clot. Thus, with time, blood-pool activity decreases (Fig. 2) and the contrast of clots-to-background activity increases (Fig. 1). To achieve antigen-antibody binding at the level of the target (the clot), the antigen must be accessible to the antibody. Some clots, particularly totally obstructive ones, are less accessible. Moreover, totally obstructive clots may have enlarged collateral vessels, so that ^{111}In-AF is shunted around the clots through extensive circulation. In this case, the time required to achieve adequate antibody uptake by the clot, and thus a significant contrast between the clot and circulating radioactivity, may be longer. These hypotheses could explain why images recorded 18 hr after injection are of essential importance in certain cases.

The sensitivity of ^{111}In-AF for diagnosis of thrombotic disease was 85% in our study. Three of the five false-negatives corresponded to extensive thromboses of the whole lower limb, with the presence of considerable collateral circulation. However, in nine other patients with extensive thrombosis of the lower limb, ^{111}In-AF was positive. These subjects had very limited collateral circulation and/or partially obstructive clots. Such false-negative results could be due to a lack of antibody accessibility to the thrombus and/or change in the antigenicity of the thrombus. During the development of a thrombus, the structure of the clot, particularly with respect to the type of fibrin involved, differs according to thrombus age (*24*,*25*). It is likely that a thrombus is composed progressively by a superposing of layers differing in structure (*24*) and in fibrin antigenic expression (*25*). Indium-111-AF, which recognizes only the epitopes carried by the fibrin monomer beta chain, cannot be taken up by that part of the clot which expresses the antigen inadequately (*25*).

Our two other false-negatives corresponded to axillo-humeral thromboses that had been detected clinically less than 48 hr before. There was extensive collateral circulation in both cases associated with total obstruction of the subclavian venous route. It is quite likely that the shunt phenomenon related to collateral circulation was a major cause of these two false-negative results.

Although ^{111}In-AF has good sensitivity for diagnosis of thrombotic disease, this antibody does not visualize all the clots present in different regions in the same patient. Only 75% (49/65) of the clots were visualized by ^{111}In-AF. Clot detection sensitivity was better for the calf (86%, 24/28) than the thigh (79%, 15/19) or the pelvis (62%, 10/16). The lower sensitivity for diagnosis of common femoral

and iliac thromboses may have been due to nonspecific intense activity of the urinary organs resulting from renal elimination of ^{111}In-AF Fab fragments. An intense nonspecific activity (scrotum, penis, bladder) can mask thrombosis, as is demonstrated in Figure 3. Moreover, in the case of thrombosis of both the calf and thigh, the existence of blood supply routes by the internal saphenous vein could explain why contrast between the clot and the bloodstream is less marked in the thigh.

Initiation of heparin treatment prior to injection of ^{111} In-AF had no adverse effects on ^{111}In-AF sensitivity for diagnosis of thrombotic disease or for clot detection. Heparin treatment was not involved in the three false-negative results for the lower limbs, whereas the two false-negatives at the axillohumeral level were treated by heparin. Thrombosis diagnostic sensitivity was thus 91% (20/22) for patients treated by heparin and 75% (9/12) for those not treated. Eighty-three percent (34/41) of clots were visualized in treated patients and 62% (15/24) in those not treated. These results, confirmed by other authors (*22,26*), are a priori contradictory with those reported concerning the influence of heparin on ^{111}In-AF uptake in clots in man and animal models (*20,27*). Alavi has shown in 16 patients treated by heparin at the time of examination that only 27/34 thrombosis sites visualized in contrast venography were detected by ^{111}In-AF (*20*). Data in animal studies suggest that heparin reduces ^{111}In-AF uptake in the thrombus, either by inhibition of clot propagation or by loss of antigenic sites due to fibrinolysis. However, Saito has shown that there is also an increase in plasma clearance of the antibody in dogs treated by heparin (*27*). The result for certain experimental thrombi could be an increase in the ratio between clot and bloodstream activity. In heparinized dogs with one-day-old thrombi injected with antifibrin monoclonal antibody (T2G1s), Rosenbrough found that thrombus-to-background ratios were 1.6 times greater. Both 4-hr and 24-hr images were positive in these dogs (*28*). These phenomena could account for the better results observed in patients treated with heparin.

Indium-111-AF specificity was good since ^{111}In-AF was negative in the 10 patients who did not have fresh, active venous thrombosis. Four of these patients presented thrombosis subsequent to phlebitis (confirmed by contrast venography), which had occurred 6 mo to a year before. Indium-111-AF was thus not taken up by old, no longer active clots. However, ^{111}In-AF specificity was closely dependent on the recording of sequential images. Since the complete and definitive occlusion of a venous trunk leads to the formation of an extensive collateral network in which blood flow is slowed down, this local blood-pool increase results in a greater emission of radioactivity by circulating ^{111}In-AF, which can create a focus as compared to the normal contralateral side. This abnormality can be a cause of false positive results if 3-hr images are not compared with those recorded early and/or 18 hr after injection of antibody (Fig. 2).

Several radioisotopic methods have been proposed for the diagnosis of DVT, notably radiolabeled fibrinogen and ^{111}In-labeled platelets. The disadvantages encountered with these techniques led to considering the use of two types of monoclonal antibodies: those directed against a fibrin epitope and those directed against platelet epitopes.

The various antiplatelet antibodies labeled with ^{111}In or ^{123}I have permitted limb clots to be visualized in animal

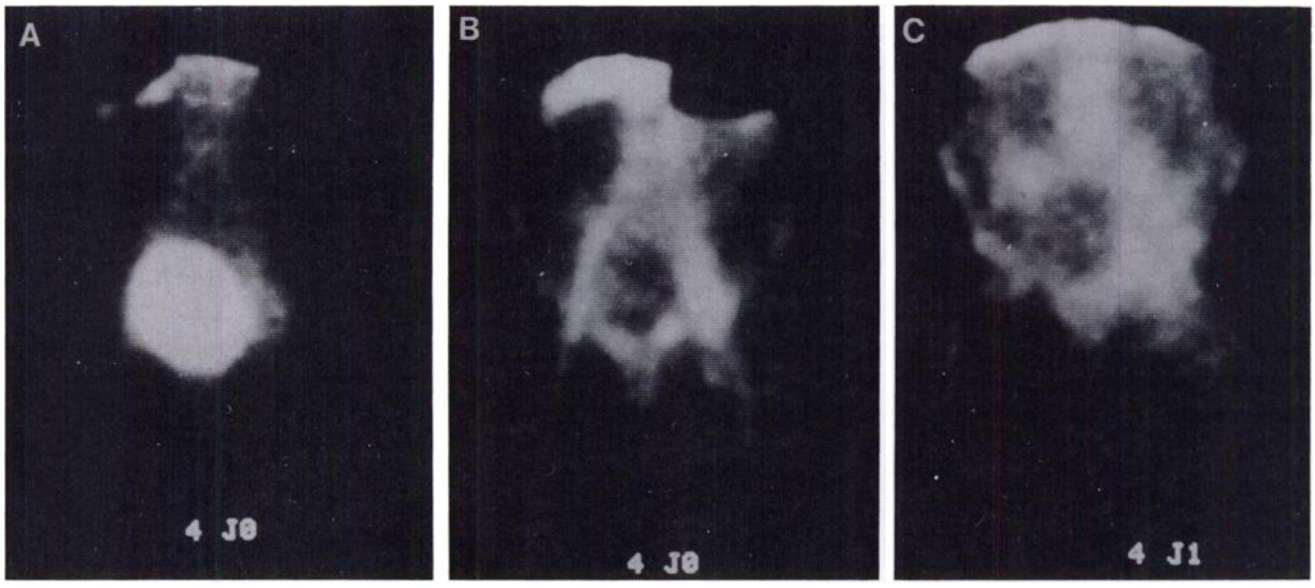

FIGURE 3. This image recorded 3 hr after ^{111}In-AF injection shows bladder activity (A) without any pathologic vascular uptake. Images recorded at the same time with an empty bladder (B) clearly show left common femoral and iliac vein hot spots corresponding to the clots visualized by contrast venography. Moreover, the image of the pelvis recorded 18 hr after ^{111}In-AF injection (C) shows the diseased veins more clearly.

models (*29–31*). However, platelet antibodies labeled in this way are not specific for those within the thrombus and also have the disadvantage of marking the presence of a blood pool. They have been incapable of detecting pulmonary embolism in the animal (*32*), and their clot affinity seems to be decreased by heparin therapy (*32*). Moreover, antiplatelet antibodies that alter platelet function can produce antithrombotic effects or hemorrhagic complications (*29,33*). However, these effects are dose-dependent, and the doses needed for imaging are far below those associated with any anti-platelet effects. The use of an antibody specific for a membrane protein of activated platelets would not have these undesirable side effects and would allow clot visualization within an hour after injection. The initial encouraging results in animal studies need to be confirmed in man (*31,34*).

The antifibrin antibody evaluated here is specific for the fibrin beta chain and does not react with fibrinogen (*17*). The modalities of preparation and injection are simpler than those for ^{111}In-labeled platelets or radiolabeled fibrinogen, and diagnostic sensitivity for distal thrombosis is comparable. Moreover, results are better for calf vein thrombosis than those obtained with radiolabeled fibrinogen. Contrary to results with methods using radiolabeled fibrinogen and ^{111}In-labeled platelets (*8,15,16*), diagnostic sensitivity for DVT was not decreased by heparin therapy. This is a very important factor for clinical practice since many patients with clinically suspected DVT receive heparin treatment before the end of the diagnostic examination. The ^{111}In-AF method would thus appear to be the scintigraphic technique of choice for the diagnosis of DVT, although the role of ^{111}In-AF still needs to be defined with respect to other diagnostic methods.

CONCLUSION

Further studies are required to assess the complementary role of antifibrin antibody, particularly for clinically suspected distal thrombosis in patients with a history and sequelae of phlebitis, for patients with pulmonary embolism when venous examinations of the lower limbs (Doppler ultrasound and/or contrast venography) are negative and for occurrence of pelvic phlebitis. However, the clinical value of this technique will depend strictly on the future availability of a ^{99m}Tc-labeled antifibrin antibody. The first studies with this type of labeling in the animal and man have been encouraging (*35–37*). If these results are confirmed, the clinical value of antifibrin antibody for the diagnosis of DVT would seem certain. This will ensure the availability of a diagnostic method providing essential data complementary to those of the other noninvasive techniques.

ACKNOWLEDGMENTS

The authors thank the technicians of the nuclear medicine department for their contribution to this study and J. Gray for his assistance in the writing of the manuscript.

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EDITORIAL

Do We Finally Have a Radiopharmaceutical for Rapid, Specific Imaging of Venous Thrombosis?

It has been known for some time that basing a diagnosis of deep venous thrombosis (DVT) on clinical signs and symptoms is highly unreliable. About half of patients with clinical symptoms suspicious for DVT do not have thrombi (*1*), and about half of patients who actually have thrombi are asymptomatic (*2*). Because anticoagulant therapies are associated with hemorrhagic side effects, it is highly desirable to obtain a reliable diagnosis of DVT before instituting therapy.

Although objective imaging tests for locating thrombi are currently available, they each have limitations. The most widely accepted objective tests for DVT today are contrast venography and B-mode ultrasound (compression ultrasound). Contrast venography is regarded as highly accurate for diagnosing venous thrombi, but it is invasive, painful, requires considerable expertise to perform and interpret properly, and has been associated with a significant incidence of postvenographic phlebitis. It is not suitable for mass screening or repeat studies. Although it has long been regarded as the gold standard, contrast venography is falling out of favor as vascular ultrasound imaging techniques gain in popularity.

In compression ultrasound, a transverse image of major veins is obtained, and pressure is applied with the transducer to attempt to collapse each vein. Incompressibility of a vein is indicative of the presence of thrombus at that location, whereas normal unoccluded veins should be completely collapsed by this procedure. This method and interpretation criteria have been shown to be highly sensitive and specific in the thighs in outpatients (*3*). The accuracy of the test in postsurgical patients has not yet been documented. Compression ultrasound has been shown to be less sensitive for isolated calf vein thrombi (*3,4*); however, a negative study is considered by many to be adequate criteria for withholding anticoagulant therapy (*3,5*). Isolated calf vein thrombi may resolve themselves without anticoagulants and are believed to have a low probability of embolization (*2*). Nevertheless, such thrombi can serve as a basis for propagation to hazardous thrombi in the proximal veins and should be followed until they resolve. A known limitation of compression ultrasound is the incidence of false-positives in patients who have had episodes of prior DVT, possibly because intimal thickening following resolution of a thrombus makes the vein resistent to compression (*6,7*). In addition, performing the test requires a skilled, experienced examiner in order to obtain the best accuracy. Because of the noninvasive nature of the ultrasound exam, it has become highly popular and may become the new standard. For a radionuclide test to be accepted, it will have to offer significant advantages over compression ultrasound. MRI has been proposed as a noninvasive method for locating thrombi with initial success (*8*). However, it is unlikely that this expensive modality, which is in demand for other examinations to the extent that it is booked far in advance, would ultimately be relied upon for mass screening of the lower extremities.

A major limitation of contrast venography and compression ultrasound is that they provide information only about venous morphology. These tests cannot reliably distinguish an acute thrombus from an aged, chronic thrombus. An acute thrombus may be considered as one in which the deposits of fibrin and platelets are exposed

Received Jan. 17, 1991; accepted Jan. 17, 1991.
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