jnm / CONCISE COMMUNICATION

# SCINTIGRAPHIC DETECTION OF DEEP-VEIN THROMBOSIS WITH $^{131}$I-FIBRINOGEN

N. D. Charkes, M. A. Dugan, W. P. Maier, R. Soulen, E. Escovitz, N. Learner, R. Dubin, and J. Kozar III

*Temple University Medical School and Hospital, Philadelphia, Pennsylvania*

***Twenty-nine postoperative patients and 8 with fractured hip were injected with $^{131}$I-fibrinogen and whole-body scintiscans made at frequent intervals for a week. Venography was performed in 20 of the patients and the concordance between the two studies was 93%. Deep-vein thrombi were found in eight postoperative patients (28%) and in three with fractured hip (38%). Scintiscanning with $^{131}$I-fibrinogen has certain advantages over the $^{125}$I-fibrinogen method including the possibility of detecting iliac-vein thrombi.***

Iodine-125-fibrinogen flat-field probe scanning studies have shown that deep-vein thrombosis (DVT) is a common complication of major surgical operations (*1–6*). The test, however, is unable to detect DVT in the iliac veins (*2*) which are regarded by some as a major site of origin of fatal (*7,8*) and nonfatal (*9–11*) pulmonary emboli. Inasmuch as the photons of $^{131}$I are considerably more energetic than those of $^{125}$I and permit localization of radioactivity (*12*) deep within the body, we have investigated the use of $^{131}$I-fibrinogen in detection of DVT by photoscanning in postoperative patients with particular regard to iliac-vein thrombosis. Preliminary studies in dogs showed the method to be feasible (*13*). We report here our initial results in 29 patients. Eight persons with fractured hip were also scanned.

## METHODS

Fibrinogen was obtained by cryoprecipitation from a man who had donated blood more than 100 times over a period of 10 years without evidence of jaundice or hepatitis in any of the recipients. His blood was tested for hepatitis-associated antigen on three occasions in the past 2 years by radial immunodiffusion and radioimmunoassay and was negative. The fibrinogen was iodinated for each patient by the Bocci modification of the chloramine T method (*13,14*) and was 90–95% clottable on numerous determinations. The TCA-precipitable labeled fibrinogen had a biologic half-life of 5.1 days in ten recipients. Up to 350 $\mu$Ci of sterile and pyrogen-free $^{131}$I-fibrinogen (about 23 $\mu$Ci/mg) were administered to each patient within 24 hr of operation, usually in the recovery room. Uptake by the thyroid of the metabolized $^{131}$I was minimized by oral doses of stable iodine daily for 1 week.

Thirty-seven patients undergoing abdominal or thoracic surgery, or hip pinning, were studied; eight of these patients had a recently fractured hip. Whole-body scintiscans were performed frequently (often daily) at the bedside, up to 7 days after injection, using a Baird-Atomic 5-in. crystal scanner with 4 : 1 image reduction. In some patients a second injection was made 1 week later.

Venography was performed in 20 of the patients, usually within 72 hr of an abnormal scan, and by the end of the first postoperative week if the scans were considered normal. Three patients with fractured hip had venograms after pinning.

## RESULTS

Normal and abnormal scintiscans are illustrated in Figs. 1–3. Thrombi appeared as discrete round or linear increases in counting rate against a background of random dots. To evaluate the scintigraphic patterns we first compared them with the findings at venography in the 20 patients who underwent both

Received Feb. 25, 1974; revision accepted June 26, 1974.

For reprints contact: N. David Charkes, Dept. of Nuclear Medicine, Temple University Hospital, 3401 N. Broad St., Philadelphia, Pa. 19140.

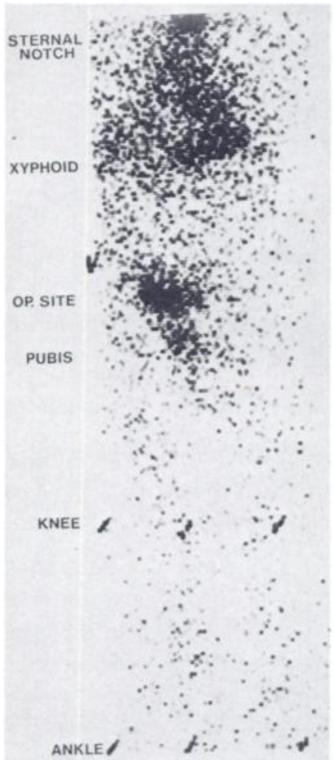


**FIG. 1.** Whole-body $^{131}$I-Fibrinogen scan (from neck to ankles) showing no evidence of thrombosis. Anatomic landmarks identified; also note $^{131}$I in thyroid, stomach, and bladder. Diffuse increase in counting rate in right calf is due to varicosities. Right lower-quadrant uptake in abdomen indicates herniorrhaphy site.

studies but it proved difficult to evaluate the whole patient or even a limb because different correlations were found in different areas in some patients. We therefore decided to compare regions instead—groin (iliofemoral), thigh (femoral–saphenous), and calf (popliteal–tibial–soleal; saphenous) (Table 1). There was concordance (both tests normal or both abnormal) in 93% of the regions studied. Both studies were abnormal (true-positive) in 7 of 101 regions. In three regions the scans were normal but the venograms showed thrombi (false-negative); these three patients had been at bed rest for 10 days or longer prior to the $^{131}$I-fibrinogen injection and thrombi may have formed but ceased to grow during this time.

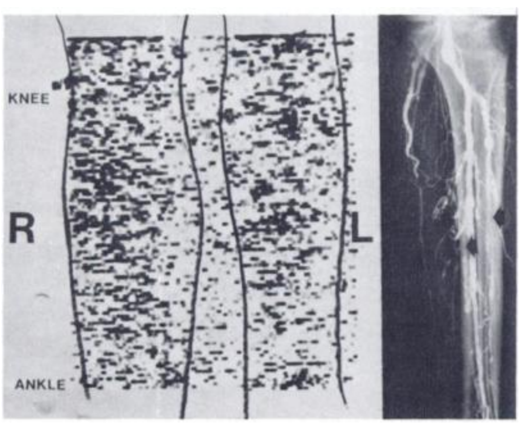


**FIG. 2.** Discrete foci of increased $^{131}$I-fibrinogen uptake in both legs resulting from multiple small venous thrombi, R, Right; L, Left. Venograms (left leg illustrated) confirmed scan findings.

In five regions the scan pattern was abnormal but the venogram showed no thrombi (false-positive). Two of these patients had varicosities. In another, the venogram was not performed until 10 days after the last abnormal scan but a subsequent normal scan obtained prior to the venogram was probably indicative of a lysed thrombus. In one patient (Fig. 3), a suspected thrombus in the profunda femoris vein was not visualized venographically because a competent valve prevented retrograde filling. Another patient was the first we studied prior to standardization of the scanning technique.

In applying these findings to the analysis of the scintiscans of the 17 patients who did not undergo venography, we accepted as abnormal only those scans in which the same pattern was seen on 2 or more days since the patients with varicosities had only transient abnormalities. In addition, with varicosities the uptake pattern was diffuse rather than focal or linear, the latter being typical of recent thrombosis. The results are given in Table 2.

DVT was found in 8 of the 29 postoperative patients (28%). In six of the eight patients the thrombi were confined to the calf veins; in no patient was the popliteal vein involved. A thrombus was suspected in the iliofemoral region in only one patient by scintiscanning but a subsequent scan and venogram showed no abnormalities. A pulmonary embolus was clinically suspected in this patient but not proved angiographically. Two other patients with calf-vein thrombi developed pulmonary emboli. In five of the eight patients who developed DVT, the thrombus was first seen on the second, third, or fourth hospital day.

DVT was detected in three of the eight patients with fractured hip (38%) and confirmed by venography in two of the three patients.

## DISCUSSION

We found DVT in 8 of 29 postoperative general surgical patients (28%), an incidence similar to that described by other investigators using $^{125}$I-fibrinogen scanning or venography (*1–6*). In only one of the eight (12% of patients with DVT) was iliofemoral thrombosis suspected. This figure is not significantly different from that of Nicolaides, et al, who found iliofemoral thrombosis in 11 of 68 patients (16%) with DVT by venography (*15*). These studies sug-

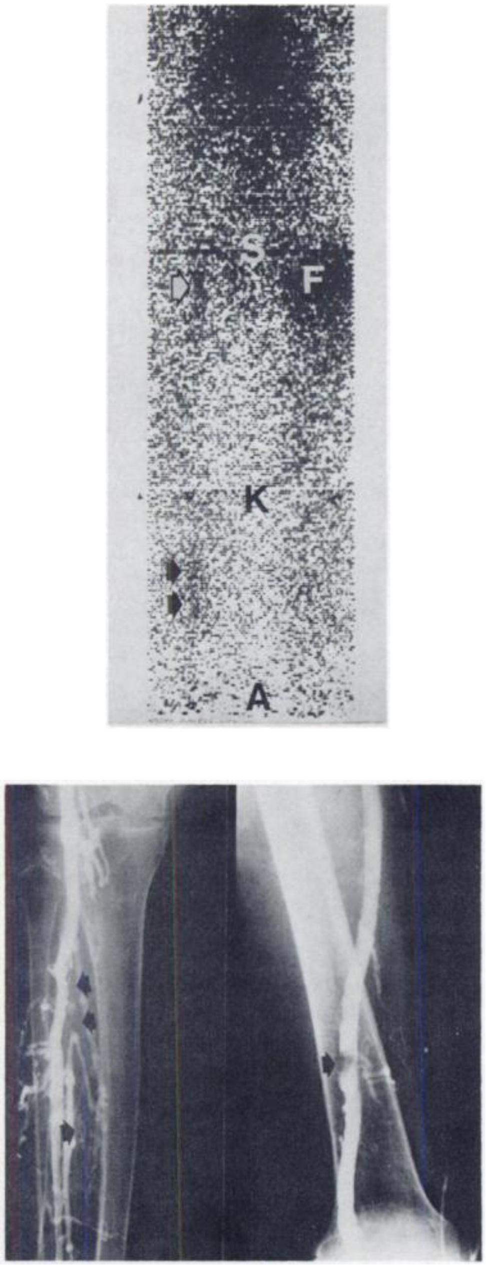


**FIG. 3.** (Top) Whole-body $^{131}$I-fibrinogen scan showing foci of activity (arrows) in right leg from venous thrombosis. Note fractured left femur, F. Scans made the next 2 days were similar. S, Symphysis pubis; K, knee; and A, ankle. Bottom, (left) Venogram of leg confirms scan findings. Bottom, (right) Venogram of thigh shows thrombus not seen on scan (false-negative). Iliofemoral venogram (not shown) did not reveal probable thrombus in profunda femoris vein because competent valve presented reflux of contrast medium into vein.

**TABLE 1. CORRELATION OF $^{131}$I-FIBRINOGEN SCINTISCANS AND VENOGRAMS IN 20 POSTOPERATIVE SURGICAL PATIENTS BY LIMB REGION**

| | Scan | | |
|---|---|---|---|
| Venogram | Abnormal | Normal | Total |
| Abnormal | 7 | 3 | 10 |
| Normal | 5 | 86 | 91 |
| Total | 12 | 89 | 101 |

Concordance 93%, sensitivity 70%, and specificity 95%.

**TABLE 2. SITES OF VENOUS THROMBOSIS IN 29 POSTOPERATIVE PAITENTS ($^{131}$I-FIBRINOGEN SCINTISCANNING)**

| | |
|---|---|
| Calf only | 6 (3)* |
| Calf-femoral only | 1 (1) |
| Iliofemoral only (suspected) | 1 (1) |
| None | 21 (12) |

* Numbers in parentheses indicate number of patients in whom venography was performed.

gest that although iliofemoral thrombosis may be an important cause of pulmonary emboli (*8–11*) (our patient was clinically suspected of embolization), it is numerically an infrequent sequel of surgical operation.

The $^{131}$I-fibrinogen scintiscan seems to be a useful method for detecting forming deep-vein thrombi. It does not appear to be diagnostically helpful in evaluating preformed thrombi, however, and our data (including unpublished findings) support the conclusion of Mavor, et al (*16*) and Walker (*11*) in this regard. Three of our patients with normal scans had thrombi by venography but they had all been at bed rest for more than 10 days prior to injection of the $^{131}$I-fibrinogen and may have developed DVT during this period.

An expanded blood pool in the calves resulting from varicose veins caused a false-positive scan in two patients. These were seen on one examination only but this is not a reliable criterion of varicosity as DVT occasionally may cause only a transient increase in fibrinogen uptake. However, a rise in the local counting rate in the calf on the day of injection but a normal scan thereafter is probably clinically inconsequential since these patients are said not to develop pulmonary emboli (*17*).

The $^{131}$I-fibrinogen scintiscanning technique has certain advantages over the $^{125}$I-fibrinogen scanning method, namely pictorial display and the ability to visualize deep-seated thrombi. Radioactive pulmonary emboli originating in thrombi that have incorporated fibrinogen have been identified in animals (*13*) but we failed to see such emboli in our patients.

The disadvantages of the scintiscanning method are the need for a cumbersome portable device, the long scanning time (1½ hr/study), and the inability to distinguish between blood pooling in varicosities and transient DVT. In addition, the half-life of $^{131}I$ is much shorter than that of $^{125}I$ and precludes examination after about 1 week, whereas $^{125}I$-fibrinogen is useful for 10–12 days (*18*).

A more suitable label for fibrinogen than $^{131}I$ would offset some of these disadvantages. Iodine-123-fibrinogen (*19*) might be advantageous for 24 or 48 hr postinjection, but its short half-life (13.3 hr) would probably preclude its use as a scanning agent thereafter unless repeated doses were given. Almost all of the deep-vein thrombi in our patients were first detected on the second postoperative day or later although 50% of patients studied with $^{125}I$-fibrinogen developed DVT during the operation (*1*). Preliminary studies have shown the feasibility of $^{111}In$ as a fibrinogen label (*20*), but human studies have not yet been carried out. Other radioisotopic methods for detecting DVT such as $^{99m}Tc$-albumin macroaggregates (*21*) and labeled streptokinase (*22,23*) or urokinase (*24*) require preformed thrombi in contrast to agents such as labeled fibrinogen which are incorporated into forming thrombi. We have recently reviewed some of the problems associated with the use of these agents (*25*).

### ACKNOWLEDGMENTS

This work was presented at the 20th Annual Meeting of the Society of Nuclear Medicine, Miami Beach, Florida, June 12–15, 1973.

We thank V. Marder and A. Budzynski for their help in preparation of the fibrinogen. Gerald Ganse provided technical assistance. This research was supported by Grant No. HE-14217 from the National Heart and Lung Institutes, National Institutes of Health, Bethesda, Maryland.

### REFERENCES

*1.* FLANC C, KAKKAR VV, CLARKE MB: The detection of venous thrombosis of the legs using $^{125}I$-labelled fibrinogen. *Br J Surg* 55: 742–747, 1968

*2.* KAKKAR VV: The diagnosis of deep vein thrombosis using the $^{125}I$ fibrinogen test. *Arch Surg* 104: 152–159, 1972

*3.* BROWSE NL, NEGUS D: Prevention of postoperative leg vein thrombosis by electrical muscle stimulation. An evaluation with $^{125}I$-labelled fibrinogen. *Br Med J* 3: 615–618, 1970

*4.* MILNE RM, GRIFFITHS JMT, GUNN AA, et al: Postoperative deep venous thrombosis. *Lancet* ii: 445–447, 1971

*5.* WILLIAMS HT: Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. *Lancet* ii: 950–952, 1971

*6.* NICOLAIDES AN, DUPONT PA, DESAI S, et al: Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. *Lancet* ii: 890–893, 1972

*7.* SEVITT S, GALLAGHER NG: Venous thrombosis and pulmonary embolism: A clinico-pathologic study in injured and burned patients. *Br J Surg* 48: 475–489, 1961

*8.* MCLACHLIN J, PATERSON JC: Some basic observations on venous thrombosis and pulmonary embolism. *Surg Gynecol Obstet* 93: 1, 1951

*9.* MAVOR GE, GALLOWAY JMD: The iliofemoral venous segment as a course of pulmonary emboli. *Lancet* i: 871–874, 1967

*10.* KISTNER RL, BALL JJ, NORDYKE RA, et al: Incidence of pulmonary embolism in the course of thrombophlebitis of the lower extremities. *Am J Surg* 124, 169–176, 1972

*11.* WALKER MG: The natural history of venous thrombo-embolism. *Br J Surg* 59: 753–754, 1972

*12.* NANSON EM, PALKO DD, DICK AA, et al: Early detection of deep venous thrombosis of the legs using $I^{131}$ tagged human fibrinogen: A clinical study. *Ann Surg* 162: 438–445, 1965

*13.* DUGAN MA, KOZAR JJ, CHARKES ND, et al: The use of iodinated fibrinogen for localization of deep venous thrombi by scintiscanning. *Radiology* 106: 445–446, 1973

*14.* BOCCI V: Efficient labelling of serum proteins with $I^{131}$ using chloramine T. *Int J Appl Radiat Isot* 15: 449–456, 1964

*15.* NICOLAIDES AN, KAKKAR VV, FIELDS ES, et al: The origin of deep vein thrombosis: A venographic study. *Br J Radiol* 44: 653–663, 1971

*16.* MAVOR GE, MAHAFFY RG, WALKER MG, et al: Peripheral venous scanning with $^{131}I$-tagged fibrinogen. *Lancet* 1: 661–663, 1972

*17.* KAKKAR VV, HOWE CT, FLANC C, et al: Natural history of postoperative deep-vein thrombosis. *Lancet* ii: 230–232, 1969

*18.* KAKKAR VV: Venous thrombosis after myocardial infarction (letter to the editor). *Lancet* 2: 258–259, 1972

*19.* DENARDO SJ, DENARDO GL, O'BRIEN T, et al: $^{123}I$ fibrinogen imaging of thrombi in dogs. *J Nucl Med* 15: 487, 1974

*20.* DUGAN MA, KOZAR JJ, GANSE G, et al: New radiopharmaceuticals for thrombosis localization. *J Nucl Med* 13: 782, 1972

*21.* WEBBER MM, BENNETT LR, CRAGIN M, et al: Thrombophlebitis—demonstration by scintiscanning. *Radiology* 92: 620–623, 1969

*22.* SIEGEL ME, MALMUD LS, RHODES BA, et al: Scanning of thromboemboli with $^{131}I$-streptokinase. *Radiology* 103: 695–696, 1972

*23.* DUGAN MA, KOZAR JJ, GANSE G, et al: Localization of deep vein thrombosis using radioactive streptokinase. *J Nucl Med* 14: 233–234, 1973

*24.* RHODES BA, TURAIHI KS, BELL WR, et al: Radioactive urokinase for blood clot scanning. *J Nucl Med* 13: 646–648, 1972

*25.* CHARKES ND, MALMUD LS, STERN HS: Comparative evaluation of current scanning agents for thrombus detection. In *International Symposium on Radiopharmaceuticals*, February 1974: in press