Radionuclide venography (RNV) of the pelvis and lower extremity veins using $^{99m}$Tc-albumin microspheres was performed in 53 patients with pulmonary emboli or venous disease. In 25 patients who underwent both contrast and RNV studies, there were no false-positive studies and one false-negative. In this series the accuracy of RNV exceeded that of Doppler alone. When the results of these two methods were combined, false-negative studies were eliminated. Over half the patients with pulmonary emboli and clinically normal lower extremities had abnormal RNV studies. The exact method of thrombus localization is not known but both mechanical and electrostatic factors may be involved. RNV has been shown to be a safe, accurate, and easily performed examination which is particularly useful in evaluating patients with pulmonary emboli.

Improvements in diagnostic techniques have demonstrated pulmonary embolism to be more frequent than previously suspected. This disease accounts for many deaths in the postoperative period, is the single greatest factor in mortality in childbirth, and has a high incidence in protracted medical illnesses (1).

The source of pulmonary emboli is no mystery. Autopsy studies have shown 50–80% of hospitalized patients have lower extremity venous thrombi. Three-fourths of these thrombi were not evident clinically during life (2). Since so many thrombi are silent, other methods of diagnosis had to be developed. Those most commonly employed are contrast venography, Doppler ultrasound, and the radiodinated fibrinogen uptake. A combination of technical and diagnostic limitations make the routine performance of these tests uncommon in a general hospital.

Those thrombi which occur above the calf are most likely to embolize (1,3). There is indirect support for this conclusion in a recent study of 47 patients with laboratory evidence of calf vein thrombosis, none of whom had evidence of emboli (4).

These observations led us to evaluate radionuclide venography (RNV) as a diagnostic modality for detection of lower extremity venous disease.

Previous studies by Webber with $^{99m}$Tc-macroaggregated albumin (MAA) demonstrated the ability of this agent to localize thrombi when static images were made after injection into pedal veins (5). However, false-positives were reported.

Rosenthall investigated both static and dynamic imaging of lower extremity veins using $^{99m}$Tc-MAA. The results of the dynamic studies were encouraging but there were no consistent findings on static imaging (6,7).

We felt that $^{99m}$Tc-human albumin microspheres (HAM)* might prove useful in both static and dynamic venous imaging and evaluated this agent in the diagnosis of venous thrombosis and occlusion above the calf.

MATERIALS AND METHODS

Patients were referred for RNV from the medical and surgical services of Northwestern Memorial Hospital, most commonly for symptoms of lower extremity venous disease or pulmonary emboli. All patients were evaluated clinically prior to radionuclide venography by one of the investigators (JSY or JJB). The majority of patients (50 of 53) were studied by Doppler ultrasound using a Directional Doppler unit Model 806† as described by Yao (8).


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* 3M Co.
† Parks Electronics.
Patients were positioned under the camera so that the iliac veins and lower inferior vena cava were in the field of view. These veins were imaged by injection of 1–1.5 mCi of $^{99m}$Tc-HAM into each leg simultaneously followed by a 3–5-cc heparinized saline flush. If one iliac vein had abnormal transit (early or delayed filling) that leg was studied first as outlined below.

If both iliac veins filled normally, the left femoral vein in the upper and mid-thigh was imaged next by unilateral injection of 0.5–0.75 mCi of $^{99m}$Tc-HAM followed by heparinized saline flush. The left popliteal vein was similarly evaluated after placing a $^{57}$Co marker lateral to the patella. The calf veins

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**FIG. 1.** Contrast (A) and radionuclide studies (B) of pelvic veins in patient with left iliofemoral occlusion of 6-months duration. Arrows identify corresponding collateral veins on both studies.

Radionuclide venography was performed using a Nuclear-Chicago Pho/Gamma III or Pho/Gamma HP scintillation camera equipped with either a 4,000-hole or 16,000-hole (high-sensitivity) collimator.

Microspheres were prepared from kits, according to directions, so that the final radioactive concentration was approximately 4 mCi/ml.

Patients were placed supine on a cart with a floating top. Two tourniquets 1–2 in. apart were placed 2 in. above each ankle. Butterfly needles (19–25 gage) with attached three-way stopcocks were inserted into a dorsal vein of each foot.

**FIG. 2.** (A) Radionuclide venogram of right iliac vein in patient with acute right lower extremity edema. RNV was interpreted as extrinsic pressure (arrow) and incomplete obstruction. (B) Repeat RNV 6 days later demonstrates development of collateral circulation. Original area of extrinsic pressure is still present. (C) Contrast venogram immediately following B demonstrates soft-tissue mass compressing right iliac vein (arrows). Biopsy of mass yielded diagnosis of reticulum cell sarcoma.
FIG. 3. (A) Contrast venogram demonstrating incomplete obstruction and thrombus formation (arrow) in left femoral vein. (B) RNV dynamic study of same area delineates more clearly the collateral veins. (C) Delayed RNV image demonstrates hot spot (Arrow) at site of thrombus.

above the tourniquets were imaged in like manner. A similar set of images was then obtained for the right leg.

The elapsed time from injection to the first appearance of activity in the field of view was recorded. Images were recorded simultaneously on either Polaroid or 70-mm photographic film and digital videotape.

At the conclusion of the study, a four-view camera lung scan was performed. If contrast venography was to be performed immediately, the needles were left in place with a heparin lock and the patient sent to the x-ray department.

Contrast venography was performed by simultaneous and sequential injections of Renografin-60 via needles placed at RNV or needles placed in a similar manner. Injections were made with the patient tilted at a 30–45-deg angle, feet down. Tourniquets were not employed. This method is essentially the same as that described by Thomas (9).

RESULTS

All venograms were classified at the time of interpretation into one of the following categories: (A) normal; (B) suspicious (equivocal)—increased transit time, nonspecific flow abnormalities, or deep venous “hot spots” which faded by five min postinjection; (c) abnormal—deep venous occlusion with or without collaterals or “hot spots” seen at injection and persisting more than 5 min postinjection. Calf vein images were not evaluated diagnostically for this study.

Fifty-three patients were evaluated by RNV using the above classifications (Table 1). Twenty-five of these patients were further evaluated by contrast venography. There was complete agreement in 24 or 25 studies (96%) (Table 2).

When patient data were analyzed according to the major reasons for referral, those patients with clinical phlebothrombosis, as expected, had a majority of positive scans (25 of 31) (Table 3). However, 53% of patients (9 of 17) with pulmonary emboli of unknown origin (no clinical signs of venous disease) had positive RNVs (Table 4).

Positive agreement of Doppler ultrasound and RNV was seen in 39 of 50 cases (78%) (Table 5). There was one false-negative RNV and 6 false-negative Doppler studies. Four patients had insufficient followup data to confirm definitely venous disease.

A tabulation of the abnormalities noted on RNV by side and site was made (Table 6). There were 16 sites at which hot spots were identified in the group of patients who underwent both

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<th>TABLE 2. PATIENTS EVALUATED WITH RNV AND CONTRAST STUDIES</th>
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contrast and radionuclide venography. These results are tabulated for patients with documented, partial, and complete deep venous occlusion (Table 7).

**DISCUSSION**

The need for a simple, low-risk, easily interpretable test for lower extremity venous occlusive disease is evident. Of the currently available diagnostic tests, only contrast venography can be relied upon for accurate localization of proximal venous disease. The currently available techniques have shortcomings. Contrast venography can lead to venous damage if contrast media is not adequately flushed out after the study. The risk of hypersensitivity reaction inherent in the intravenous injection of any contrast medium accompanies this procedure as well. In our experience, patient acceptance of contrast venography compared with RNV is quite low. It may therefore be quite difficult to convince patients to undergo necessary, repeat contrast studies.

Doppler ultrasonography, a simple bedside test for venous occlusion, failed to identify a case of partial venous occlusion as well as several cases of chronic venous disease. The precise anatomical location of thrombi by this method was not as accurately determined as by RNV.

Because of its low energy, $^{125}$I-fibrinogen is incapable of imaging the deep venous structures of the leg and only point counting can be employed. A disadvantage of this technique is the 24-hr delay before definitive diagnostic results can be obtained. The greatest accuracy of the fibrinogen test appears to be in diagnosing calf vein thrombosis. As one moves more proximally in the leg, the accuracy decreases due to increased background (10).

Radionuclide venography fills the gap between the less specific noninvasive tests, radioiodinated fibrinogen uptake, Doppler ultrasound, and the more accurate but invasive technique of contrast venography. The data presented above demonstrate RNV to have an accuracy comparable to contrast studies (96% agreement) and to exceed the accuracy of Doppler studies alone.

The RNV examination requires 30 min or less to perform. A knowledge of the deep venous anatomy of the legs and pelvis is essential for accurate interpretation of the images. Since only major vessels are visualized and interpretation of calf pathology is not routinely made at present, skill in recognizing the diagnostic patterns is achieved quickly.

The radiopharmaceutical of choice for these studies should fulfill several requirements. First, it should not recirculate. Recirculation from the necessary multiple injections increases background, making interpretation of the study difficult. Secondly, the radiopharmaceutical should be readily available and easily prepared. Finally, it should be a suitable agent for lung imaging in view of the possibility of emboli in this group of patients.

Two radiopharmaceuticals satisfy these criteria: $^{99m}$Tc-MAA and $^{99m}$Tc-HAM. Earlier studies with MAA cited above suggest that HAM might be a more suitable agent for the following reason: if mechanical factors alone were responsible for thrombus localization with MAA, then it would be difficult to explain the incidence of false-positives previously noted (5).

An electrostatic attraction (or repulsion) may occur between clot, vein wall, and radiopharmaceutical as suggested by Webber (11). Radiopharmaceuticals with different shapes should have different surface charge distributions. Webber's experimental data further demonstrate decreased in vivo thrombus uptake of HAM as compared with MAA. We elected to investigate HAM in the hope of a decreased incidence
of false-positive studies. This indeed has been the case.

The accumulation of microspheres at the site of a thrombosis appears from our data to be somewhat variable. These data suggest that the stage in the evolution at which a thrombosis is studied may affect microsphere localization.

Those patients with incomplete obstruction were symptomatic and studied during the acute phase whereas those patients with total occlusion were often studied after thrombosis was established.

One of our criteria for diagnosis of venous disease has been the presence of collateral circulation. We have been particularly impressed with the visualization of collateral venous channels in the pelvis. As a rule visualization is better on the radionuclide than the contrast study.

The explanation of this observation appears to be twofold. The long imaging time of RNV results in an integrated image being obtained. This image is essentially a composite instead of representations of contrast distribution at one or several instants in time conventionally obtained at contrast venography.

Secondly, it is not necessary to penetrate the heavy bony pelvis during RNV. The presence of the bony pelvis decreases the image contrast and, therefore, image quality on x-ray studies.

RNV is of special value in those patients with pulmonary emboli of undetermined origin. Fifty-three percent of the patients studied in this group had abnormal RNVs. It is perhaps in this group of patients that RNV can have its greatest clinical utility by identifying those patients in need of more extensive evaluation and therapy.

A followup lung scan is often performed in a patient with known emboli. Injection of microspheres via the pedal veins at the time of followup scan provides additional important clinical information at extremely low risk.

Analysis of the transit time data is under way at present. These data are not easily obtained by any other means. Preliminary observations indicate that there is a group of patients whose sole abnormality is an increase in transit time. The exact clinical significance of this abnormality is not known at present.

RNVs place in the evaluation of patients with venous occlusive disease is still being defined. We currently advocate the use of this technique in patients with pulmonary emboli and in patients who are clinically suspected of having lower extremity venous disease.

In summary, while the precise mechanism of thrombus localization is not known, vascular occlusion, collateral circulation, and thrombi are accurately identified with minimal discomfort and risk to the patient by radionuclide venography.

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REFERENCES

Radionuclide Venography (RNV) in Lower Extremity Venous Disease

Robert E. Henkin, James S. T. Yao, James L. Quinn III and John J. Bergan