Technetium-99m-RBC Venography in the Diagnosis of Deep Venous Thrombosis of the Lower Extremity: A Systematic Review of the Literature

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We systematically reviewed the six articles from the English-language medical literature, since 1979, which compared ^{99m}Tc-RBC venography with contrast venography for the diagnosis of deep venous thrombosis (DVT) of the lower extremity. The studies were generally small in size and poorly compliant with methodologic standards for diagnostic test research. There was considerable variation in both how the ^{99m}Tc-RBC venograms were performed and how they were interpreted. Sufficient clinical information on the patients was not provided. Although the overall sensitivities and specificities were high with a mean sensitivity of 0.89 and a mean specificity of 0.84, the small numbers of patients resulted in wide 95% confidence intervals. For distal disease, with only a total of 14 patients studied, the 95% confidence intervals were particularly broad. Although ^{99m}Tc-RBC venography is a promising technique, future studies with larger numbers of patients and closer adherence to methodologic standards are required.

J Nucl Med 1991; 32:2324–2328

The diagnosis of deep venous thrombosis (DVT) of the lower extremities cannot be made on the basis of history and physical examination alone. With hundreds of thousands of cases of DVT per year in the United States (*1*), there is a clear need for accurate diagnostic tests. The gold standard of diagnosis, contrast venography, is expensive, invasive, and potentially harmful. Consequently, many attempts have been made to develop noninvasive techniques for the evaluation of possible DVT. Such techniques have included real-time ultrasound and impedance plethysmography (IPG). Both methods correlate well with contrast venography for the evaluation of proximal DVT but have poor sensitivity and specificity when used in the calf area (*2*).

Received Apr. 9, 1991; revision accepted Jan. 26, 1991.
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Technetium-99m-RBC venography, a technique developed in the late 1970s, has been used for the detection of both proximal and distal DVT of the lower extremities (*3*). Although discussions of the use of ^{99m}Tc-RBC venography in the diagnosis of DVT have been published (*3,4*), there has been no systematic review of the literature comparing ^{99m}Tc-RBC venography with contrast venography. Therefore, using established methodologic standards regarding diagnostic test research, we reviewed the articles from the English-language medical literature which compared ^{99m}Tc-RBC venography with contrast venography in the diagnosis of DVT of the lower extremities.

METHODS

Selection of Clinical Studies

Using the Medline data base (1976 to 1990) and Current Contents (April through October 1990), we sought all articles published in English that evaluated the role of ^{99m}Tc-RBC venography in the diagnosis of DVT. Pertinent citations from this group of articles were reviewed. Studies selected for detailed review were those that established the diagnosis of lower extremity DVT by contrast venography and that reported the results of ^{99m}Tc-RBC venograms in those patients undergoing contrast venography. Nine articles were considered, and six met our criteria for inclusion in this review (*5–10*).

Critical Review of the Selected Studies

We performed a detailed review of each study to determine how well it satisfied seven basic methodologic standards addressing important issues in diagnostic test research. These standards, adapted from Becker et al. (*2*), are described below.

Standard 1: Description of the ^{99m}Tc-RBC Venogram Technique. To allow test interpretation, replication, and application, this standard required a clear description of the ^{99m}Tc-RBC venography technique, including the labeling of the RBCs and the acquisition of images. This standard also required a description of the criteria for a positive study.

Standard 2: Assessment of Test Reliability. Reliability is the extent to which repeated measurements of the same relatively stable phenomenon are reproducible. Technetium-99m-RBC venography involves the acquisition and interpretation of multiple images of the lower extremities and pelvis. To insure an assessment of the reliability of ^{99m}Tc-RBC venography for the diagnosis of DVT, this standard required that at least two nuclear medicine physicians read the ^{99m}Tc-RBC venograms without knowledge of other interpretations and that their interpretations be compared. Furthermore, it required that some patients have repeat ^{99m}Tc-RBC venograms and that the results be compared.

Standard 3: Identification of Groups Selected for Study. There is great variability in the clinical presentation of patients suspected of having DVT. These patients include young women on oral contraceptives, elderly patients with leg pain, severely ill cancer patients, and postoperative patients without symptoms. Different ways of identifying patients for inclusion in a study could result in the assembly of widely different clinical groups of patients and possibly different results. Consequently, in order to allow generalization of the results of a study, the method of patient selection and the types of patients included and excluded must be described. The first part of this standard required that the method of patient selection be described in sufficient detail to allow a similar group of patients to be selected if the study were to be repeated. The second part required that the age, sex, and a brief summary of the major clinical characteristics of the patients be provided. The third part of this standard required the study to provide the basic clinical data and the reason for exclusion of each of the eligible patients that were excluded from the study.

Standard 4: Analysis of the Anatomic Extent of Disease. DVT varies widely in extent, ranging from isolated calf (distal) DVT to extensive proximal disease. The natural history of proximal DVT differs from that of distal disease, and the accuracy of different diagnostic tests varies with the anatomic location of the DVT (*11*). To allow for evaluation of ^{99m}Tc-RBC venography over the full anatomic range of DVT, we required that separate results be provided for proximal and calf DVT, and that either the sensitivity and specificity for these sites or the data necessary to make the calculations be provided.

Standard 5: Analysis of Conditions That Mimic DVT. Many patients have symptoms and signs of DVT but prove to have other conditions that mimic DVT. The purpose of this standard is to insure that the performance of ^{99m}Tc-RBC venography is evaluated in the other conditions. For example, it is important to know the accuracy of the test in patients with such conditions as popliteal cysts or congestive heart failure. This standard required that a summary of non-DVT diagnoses be reported along with the results of the Tc-99m RBC venograms for each diagnosis.

Standard 6: Avoidance of Work-up Bias. Work-up bias occurs if the result of the ^{99m}Tc-RBC venogram influences the chance that a patient receives contrast venography (*12*). If a patient is more likely to be excluded from undergoing contrast venography when the ^{99m}Tc-RBC venogram is positive, then a disproportionate number of people with negative ^{99m}Tc-RBC venograms may be entered into the study. This increase in negative studies (both false-negative and true-negative) would result in a lower sensitivity and a higher specificity for ^{99m}Tc-RBC venograms. In contrast, excluding a patient from undergoing contrast venography when the ^{99m}Tc-RBC venogram is negative would result in a relative increase in positive studies, a higher sensitivity, and a lower specificity.

Standard 7: Avoidance of Diagnostic and Test Review Biases. This standard is concerned with the biases that can occur when the result of the ^{99m}Tc-RBC venogram is allowed to influence the interpretation of the contrast venogram (diagnostic review bias) or when the result of the contrast venogram is allowed to influence the interpretation of the ^{99m}Tc-RBC venogram (test review bias) (*12*). These two types of bias are likely to encourage concordance between the interpretations of the two types of studies. This increased concordance would spuriously increase both sensitivity and specificity.

RESULTS

Table 1 lists the six studies that were accepted for review, our ratings for compliance with the seven standards for diagnostic test research, the total number of patients involved in each study, the number of patients who had DVT diagnosed by contrast venography, and the overall sensitivity and specificity (with 95% confidence intervals) for ^{99m}Tc-RBC venography. When available, the sensitivity and specificity for proximal and distal DVT are also listed.

The six studies were small in size. Fogh et al. (*8*), who examined 85 extremities, had the largest study, but reported results in terms of limbs examined, while the other studies gave results in terms of patients. Otherwise, only three studies included more than thirty patients. For the six studies, the results of 232 ^{99m}Tc-RBC venograms were reported. DVT was established by venography for 123 (53%) of the ^{99m}Tc-RBC venograms. Results were reported separately for 55 proximal and 14 distal DVT.

The overall sensitivities ranged from 0.75 to 1.00 (mean 0.89), and the overall specificities ranged from 0.71 to 0.94 (mean 0.84). The sensitivities for proximal DVT ranged from 0.80 to 1.00 (mean 0.92), and the specificities ranged from 0.85 to 1.00 (mean 0.94). For distal disease, the sensitivities ranged from 0.67 to 1.00 (mean 0.86), and the specificities ranged from 0.80 to 0.92 (mean 0.88). Although the reported sensitivities and specificities were relatively high, the 95% confidence intervals were broad. For example, for the largest study (*8*), the 95% confidence intervals (CI) for the reported sensitivity was from 0.68 to 0.94 and for specificity was from 0.56 to 0.83.

The study with the highest sensitivity (*5*) had a 95% CI of 0.84 to 1.00, and the study with the highest specificity (*10*) had a 95% CI of 0.71 to 1.00. Furthermore, for the largest study to report distal disease (*6*), the 95% confidence intervals for the reported sensitivity and specificity were 0.22 to 0.96 and 0.59 to 1.00, respectively.

There was considerable variation among the reviewed studies in adherence to the seven methodologic standards. One study (*9*) met four of the standards, one study (*8*) satisfied three standards, three studies (*5,6,10*) met two standards, and one study (*7*) satisfied only one standard.

Only two of the six studies adequately described the ^{99m}Tc-RBC venogram technique. Furthermore, there was considerable variation in how the scans were performed. To outline these variations, Table 2 lists the method of RBC labeling, the amount of [^{99m}Tc]pertechnetate used, the type of gamma camera used, and the number of counts per image. Four studies used the in vivo labeling method, and two studies used the in vitro method. The amount of [^{99m}Tc]pertechnetate ranged from 5.4 mCi (*6*) to 20 mCi (*9,10*). Only Fogh et al. concluded that the type of camera

TABLE 1
Results of Methodologic Review*

Source	Year	Country	Standards satisfied†	Patients studied DVT/ Tot. (%)‡	DVT location: Prox	DVT location: Distal	Total: Sens. (95% CI)#	Total: Spec. (95% CI)	Proximal§: Sens. (95% CI)	Proximal§: Spec. (95% CI)	Distal¶: Sens. (95% CI)	Distal¶: Spec. (95% CI)
Beswick (*5*)	1979	Australia	4, 7	21/30 (70)	19	2	100 (84-100)	89 (52-100)	100 (82-100)	89 (52-100)	100 (16-100)	89 (52-100)
Kempi (*6*)	1981	Sweden	4, 6	16/27 (59)	10	6	75 (48-93)	91 (59-100)	80 (44-97)	100 (69-100)	67 (22-96)	91 (59-100)
Lisbona (*7*)	1982	Canada	4	21/35 (60)	17	4	95 (76-100)	79 (49-95)	100 (80-100)	85 (55-98)	75 (19-99)	92 (62-100)
Fogh (*8*)	1982	Denmark	1, 6, 7	37/85** (44)	—	—	84 (68-94)	71 (56-83)	—	—	—	—
Singer (*9*)	1984	Australia	1, 4, 6, 7	11/21 (52)	9	2	91 (59-100)	80 (44-97)	89 (52-100)	100 (63-100)	100 (16-100)	80 (44-97)
Littlejohn (*10*)	1985	Australia	6, 7	17/34 (50)	—	—	88 (64-99)	94 (71-100)	—	—	—	—

* DVT indicates deep venous thrombosis; sens = sensitivity; spec = specificity.
† See text for description of standards.
‡ Number of DVT proven by venography per total number of patients or extremities studied.
§ Proximal to and including popliteal vein.
¶ Distal to popliteal vein.
\# 95% confidence intervals calculated by using the binomial distribution.
** Number of legs studied.

played a significant role in the ^{99m}Tc-RBC venography results (*8*). In this study, an older camera (pho/gamma) had more false-negative results compared to a more modern camera (Searle, large field of view). The number of counts per image was listed in four of the studies and ranged from 400,000 to 1,200,000.

The criteria used for the diagnosis of DVT, presented in Table 2, varied considerably among the studies. Although

TABLE 2
Technetium-99m-RBC Venogram Techniques and Diagnostic Criteria

Study	Method of RBC labeling	Amount (mCi) of [^{99}Tc] pertechnetate	Type of gamma camera	Number of counts (in thousands) per image	Criteria for diagnosis of DVT*
Beswick (*5*) 1979	In vitro	10	Toshiba GCA 401	—	1, 2†, 4‡
Kempi (*6*) 1981	In vivo	5.4	—	—	—
Lisbona (*7*) 1982	In vivo	18	—	400	1, 3
Fogh (*8*) 1982	In vivo	15–20	Pho/gamma camera HIPV *and* LFOV§ (Searle)	600–800	Two or more of: 1, 2, 5
Singer (*9*) 1984	In vitro	20	LFOV pho/gamma 5 (Searle)	700—leg 900—thigh 1200—torso	1, 2
Littlejohn (*10*) 1985	In vivo	20	—	400	1, 2

* Criteria for the diagnosis of deep venous thrombosis includes:
1. Obliteration or poor visualization of a vein
2. Increased tracer in superficial veins and/or collaterals
3. Asymmetry compared to companion vessel in opposite limb
4. Increased blood pool below level of thrombus
5. Increased radioactivity in surrounding tissue.

† Generally noted.
‡ Occasionally noted.
§ Large field of view.

one study provided no indication of how the scans were interpreted (*6*), the others used at least two of five specific criteria. Five studies used "obliteration or poor visualization of a vein." Three used "increased tracer in superficial veins and/or collaterals." Only one study used "asymmetry compared to companion vessel in opposite limb."

While none of the studies satisfied both parts of the standard dealing with test reliability (Standard 2), one study had two nuclear medicine physicians interpret each ^{99m}Tc-RBC venogram blinded to the other's reading (*10*). In this study, there was no interobserver variation. Another study performed ^{99m}Tc-RBC venography on some patients before and after contrast venography and found that only 2 of 29 interpretations changed from the initial reading (*8*). In one of these instances, the change appeared to be due to propagation of thrombus.

The six studies provided very little clinical information about the patients evaluated with none satisfying Standard 3. Four studies included analyses of the anatomic extent of disease and thereby satisfied Standard 4. Although none of the studies provided complete information about conditions mimicking DVT (Standard 5), some studies provided limited information. Lisbona et al. described two false-positive studies resulting from Baker's cysts compressing the popliteal vein and a third false positive relating to the obliteration of distal veins from old thrombotic disease (*7*). Fogh et al. reported that seven of their false-positive studies had post-thrombotic venous changes (*8*).

Standards 6 and 7 were concerned with the effort to avoid bias, and five studies fulfilled at least one of these two standards. Four studies satisfied Standard 6 (avoidance of work-up bias). Beswick et al. did not meet this standard because "there was a general reluctance on the part of the individual doctors to perform" contrast venography on the patients with negative ^{99m}Tc-RBC venograms (*5*). Four studies satisfied Standard 7 (avoidance of diagnostic and test review bias).

In addition to the six studies reviewed above, three additional articles were identified but did not meet our criteria for inclusion in the systematic review. One of the earliest studies used patients with known DVT and normal controls who never underwent contrast venography (*13*). Another study failed to report the number of patients with and without DVT, so sensitivity and specificity could not be calculated (*14*). Finally, Leclerc et al. did not perform contrast venography on all patients (*15*).

DISCUSSION

The consensus of the authors of the reviewed studies was that ^{99m}Tc-RBC venography is an acceptable alternative to contrast venography in the diagnosis of lower extremity DVT. The relatively high sensitivities and specificities reported in these studies support this conclusion. However, our review has identified significant flaws in study methodology that lead us to question the accuracy and utility of this test.

If ^{99m}Tc-RBC venography were proven to be an accurate test, it would have some advantages when compared to contrast venography, ultrasound, and IPG studies. Technetium-99m-RBC venography is safer and easier to perform than contrast venography. With ^{99m}Tc-RBC venography, there is no concern for allergic reactions or nephrotoxicity from radiocontrast. In ^{99m}Tc-RBC venography, injections may be given in an upper extremity vein, while contrast venography frequently requires venous cannulation in a tender, swollen foot. Also, ^{99m}Tc-RBC venography may be useful in the evaluation of obese patients and patients with leg casts whose lower extremity veins are not accessible. Unlike ultrasound, ^{99m}Tc-RBC venography images the iliac veins, and unlike ultrasound and IPG, it images the calf veins. Furthermore, with ^{99m}Tc-RBC venography, bilateral images can be obtained more easily than with the other imaging techniques.

Although ^{99m}Tc-RBC venography has some advantages, it also has several disadvantages when compared to other imaging techniques. Compared to ultrasound and IPG studies, ^{99m}Tc-RBC venography takes longer to perform, costs more, and requires more personnel. While ultrasound and IPG studies can be performed at the bedside of severely ill patients, ^{99m}Tc-RBC venography usually requires that the patient be imaged in the nuclear medicine department.

Aside from commenting on the practical advantages and disadvantages of ^{99m}Tc-RBC venography, our review considered the methodologic basis for judging the potential clinical utility of the test, and we noted serious weaknesses. The small numbers of patients studied resulted in wide confidence intervals for the reported results. There was neither consensus on the technique of ^{99m}Tc-RBC venography nor uniformity in the diagnostic criteria for DVT. The lack of standardized criteria for interpreting the test makes it difficult to compare results across institutions. The available data are limited with regard to clinical spectrum of DVT and medical conditions that mimic DVT. In six studies, only 14 cases of calf DVT were described. The accuracy of ^{99m}Tc-RBC venography in such clinical settings as congestive heart failure, chronic venous insufficiency, recurrent DVT, and popliteal cysts is uncertain. The accuracy of the test also depends on how frequently it is used. Zorba et al. noted that results of ^{99m}Tc-RBC venography and contrast venography were discordant in 10 of their first 25 patients but in only 4 of the last 25 (*14*).

Future studies on ^{99m}Tc-RBC venography must combine the use of modern technology with careful research methodology. Since the studies in this review were relatively old, modern gamma cameras might provide more accurate results. However, the technical aspects of performing this test must be evaluated and standardized, and clear criteria for a positive study need to be adopted. Furthermore, the patients under study and those eligible but not included should be described in sufficient detail to allow their clinical characteristics, including risks for DVT and anatomic extent of disease, to be appreciated. Finally, future studies should include larger numbers of patients to provide narrower confidence intervals for the reported sensitivities and specificities.

Technetium-99m-RBC venography has potential but unproven clinical utility for the diagnosis of DVT. Other nuclear medicine techniques for the diagnosis of DVT are also promising. Tests based on anti-fibrin (*16*) or anti-platelet (*17*) monoclonal antibodies may provide accurate imaging for fresh thrombi in any location. However, there is insufficient data on the accuracy and utility of these new tests. While contrast venography remains the gold standard of diagnosis for DVT, and IPG and ultrasonography have clinical utility for proximal DVT, there may still be an important role for nuclear medicine imaging in the diagnosis of DVT in certain clinical settings.

ACKNOWLEDGMENTS

The authors thank C. David Teates, MD for reviewing the manuscript, and Ms. Mary Beth Meachum-Whitehill and Ms. Deanna Brown for typing the manuscript.

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EDITORIAL

Diagnostic Accuracy and Deep Venous Thrombosis: A Biostatistician's Perspective

In this issue of the *Journal of Nuclear Medicine*, Pinson, Becker, Philbrick and Parekh (*1*) make another contribution to the already extensive literature concerning noninvasive alternatives to the use of contrast venography (CV) in the diagnosis of deep venous thrombosis (DVT). The direction of the literature is clear—noninvasive diagnostic methods continue to chip away slowly at the position of CV as the gold standard in DVT detection and characterization. However, there seems to be some disagreement over the stability of CV's standing. In 1988, Redman (*2*) concluded an editorial in *Radiology* by commenting:

> Clearly, CU (compression ultrasound) for diagnosis of acute DVT, either alone or in conjunction with Doppler or impedance plethysmography, meets the criteria for a screening test. CV can retain the title of "gold standard" while each radiologist traverses the learning curve for CU, but then CV should be positioned as a backup procedure for the times when results of less invasive procedures raise more questions than answers.

A year later, an anonymous editorial in the *Lancet* (*3*) offered a different viewpoint, saying:

> Efficient treatment of venous thrombosis demands accurate knowledge of the extent and appearance of the thrombus and, in particular, the limit of its proximal extension; this information may not be satisfactorily obtained with non-invasive investigations alone.

From my perspective as a biostatistician, the most significant contribu-

Received Aug. 20, 1991; accepted Aug. 27, 1991.

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