The Diagnosis of Acute, Recurrent, Deep-vein Thrombosis:
A Diagnostic Challenge

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SUMMARY Recurrent venous thrombosis presents a diagnostic challenge. Venography, impedance plethysmography and fibrinogen leg scanning all have potential limitations, and their role in this context has not been evaluated. We performed a prospective cohort study evaluating impedance plethysmography and leg scanning, plus venography, using outcome on long-term follow-up as the end point in 270 patients with clinically suspected recurrent deep-vein thrombosis. Anticoagulant treatment was withheld in the 181 patients negative by noninvasive testing and was given in patients positive by impedance plethysmography if leg scanning was positive or if intraluminal filling defects were detected by venography. The validity of this approach was tested by long-term follow-up. Three of 181 patients (1.7%) negative by noninvasive testing had a recurrence, compared with 18 of 89 (20%) with positive findings ($p < 0.001$). Our objective diagnostic approach has high clinical utility; an objective rationale for withholding or giving treatment was established in 95% of patients.

THE PATIENT with clinically suspected recurrent deep-vein thrombosis presents a diagnostic challenge for the clinician because the accuracy of currently accepted tests for deep-vein thrombosis has not been formally evaluated in this context. Furthermore, although the clinical diagnosis of recurrent deep-vein thrombosis is thought by many to be nonspecific, this has not been formally documented. Based on the findings of extensive prospective clinical trials of objective testing, combined impedance plethysmography and leg scanning plus venography are now recognized as accurate, clinically useful tests in patients with their first episode of clinically suspected venous thrombosis. The role of these tests, however, has not been firmly established in patients with clinically suspected recurrent deep-vein thrombosis. Careful evaluation of these diagnostic tests is necessary because each objective test has potential limitations in diagnosing acute recurrence in the presence of previous venous disease.
Venography alone has the limitation that the diagnostic hallmark, a constant intraluminal filling defect, may be masked because of obliteration and recanalization leading to impaired visualization. Consequently, the venographic findings may be inconclusive in patients with previous disease. Impedance plethysmography may be falsely positive because of persistent venous outflow obstruction because of a previous episode of venous thrombosis or falsely negative because of large collateral channels that have developed consequent to the first episode. Leg scanning with $^{125}$I fibrinogen is useful for detecting active calf and distal thigh vein thrombi but is relatively insensitive in the upper thigh and cannot detect external and common iliac vein thrombi.

Conventional methods cannot be used to assess the accuracy of diagnostic tests in this condition because of the lack of an acceptable standard for the diagnosis of acute recurrent venous thrombosis. In our study, this problem was overcome by establishing a prior diagnostic criteria for the presence or absence of acute recurrence and then testing their validity by recording outcome after long-term follow-up.

**Methods**

Between July 1977 and August 1981, 270 patients considered by their physicians to have symptoms and signs of acute, recurrent, deep-vein thrombosis were referred to four hospitals in the Hamilton District Thromboembolism Programme (which serves a population of over 750,000 people). Each patient was examined on the day of referral by either a nurse-practitioner or a consulting physician from the program, and a clinical history and physical findings (including leg pain, tenderness and swelling) were assessed in a standard fashion and recorded.

The patients were then investigated as follows (fig. 1). Impedance plethysmography was done immediately; if the results were negative, the patient was injected with $^{125}$I-fibrinogen. Leg scanning was done 1 and 3 days later, and impedance plethysmography was repeated. If the initial impedance plethysmography was positive, venography was performed to determine if a constant intraluminal filling defect was present. If a constant intraluminal filling defect was not detected by venography, the patient was injected with $^{125}$I-fibrinogen and leg scanning was performed 1 and 3 days later.

At the onset of the study, we decided to withhold anticoagulant therapy in patients with negative results by impedance plethysmography and leg scanning irrespective of the severity or extent of the clinical findings. Anticoagulant therapy was commenced in all patients positive by impedance plethysmography in whom venography detected a constant intraluminal filling defect. Anticoagulant therapy was also commenced if the $^{125}$I-fibrinogen leg scan result was positive. Patients with a positive impedance plethysmographic result, “indeterminate” venogram result (abnormal findings by venography characterized by recanalization, obliteration, loss of filling of segments) and a negative leg scan result presented a dilemma; in these patients, anticoagulant therapy was withheld.

Anticoagulant therapy was given according to the following regimen: Full-dose i.v. heparin therapy was given for 7–10 days to maintain the partial thromboplastin time at 1.5–2 times control value. Warfarin sodium therapy was commenced at a dose of 10 mg/day for the first 2 days and then adjusted according to the prothrombin time (Simplastin; General Diagnostics), which was maintained at 1.5–2 times control value; warfarin sodium therapy and i.v. heparin therapy were overlapped for 4 days and warfarin sodium therapy was continued for 3 months.

The methods for performing and interpreting occlusive cuffed impedance plethysmography (using optimal venous filling) have been described and are summarized in the Appendix. The methods for performing and interpreting $^{125}$I-fibrinogen leg scanning and venography have also been described.

Two experienced observers independently interpreted the findings by impedance plethysmography, $^{125}$I-fibrinogen leg scanning and venography; disputes were resolved through adjudication by a third. The results of leg scanning, impedance plethysmography and venography were interpreted independently of each other and without knowledge of the patient’s condition. The radiographic criterion used for acute venous thrombosis was the presence of an intraluminal filling defect that was constant in two or more films. If the deep venous system was poorly visualized with either recanalization or nonfilling (with or without collaterals) despite repeated examination, the venogram was coded as “indeterminate.”

All patients were then followed long term. Each

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**Figure 1.** Diagnostic process and outcome on entry. IPG = impedance plethysmography using occlusive cuff technique; Leg Scan = $^{125}$I-fibrinogen leg scanning.
patient was followed at 3 months by telephone or in the clinic. No patient was lost to follow-up and all patients were then kept under surveillance for an additional time averaging 20 months. All patients were asked to return immediately if signs or symptoms of venous thrombosis or pulmonary embolism occurred. Patients with symptoms suggestive of venous thromboembolism on routine follow-up or who returned in an emergency were seen in the emergency room or a special clinic. At the time of follow-up, an interval history was obtained addressing general health; specific symptoms, including leg pain, tenderness and swelling, chest pain, dyspnea, hemoptysis and syncope; hospital admission; and the use of anticoagulants. The cause of death was documented by autopsy, coroner’s report or clinical review.

In patients with clinically suspected recurrent deep-vein thrombosis, the diagnosis was confirmed by objective testing with impedance plethysmography, leg scanning and venography using the diagnostic criteria applied on entry. In patients with clinically suspected, nonfatal pulmonary embolism, the diagnosis was confirmed by pulmonary angiography. The diagnostic end point for pulmonary embolism was the presence of constant intraluminal filling defects by pulmonary angiography or pulmonary embolism found at autopsy.

Confidence limits for the complication rates during long-term follow-up were calculated from the binomial distribution. The difference in the outcome during long-term follow-up between patients negative by impedance plethysmography and leg scanning and positive by impedance plethysmography or leg scan was analyzed by Fisher’s exact test (for death due to pulmonary embolism) and by the chi-square method (for all venous thromboembolic events).

Results

The 270 patients with clinically suspected recurrent deep-vein thrombosis who were referred to the Hamilton District Thromboembolism Programme during the study period were 18–88 years old (mean 52 years). One hundred twenty-seven of 270 patients were males and 143 were females. Forty-nine of 270 were inpatients (18%) and 221 were outpatients (82%) at the time of referral. Two hundred fifty-seven of 270 patients (95%) presented 3 months or more after their initial episode of deep-vein thrombosis and were no longer receiving anticoagulant therapy at the time of referral. Two hundred of the 270 patients (74%) were negative by the initial impedance plethysmography and 70 patients (26%) were positive (fig. 1).

Initially Negative Impedance Plethysmography

Leg scanning was negative in 181 of the 200 patients (91%) with initially negative results by impedance plethysmography and was positive in the remaining 19 patients. Anticoagulant treatment was withheld in the 181 patients negative by impedance plethysmography and leg scanning, but was commenced in the 19 patients positive by leg scanning. Venography, performed in the 19 patients positive by leg scanning, demonstrated constant intraluminal filling defects in 14 patients.

Initially Positive Impedance Plethysmography

Venography was performed in the 70 patients with positive impedance plethysmography results. In 45, intraluminal filling defects that were constant in more than two films were detected; venography showed indeterminate findings in 23 patients and was normal in two. Leg scanning was performed in the 23 patients with indeterminate findings by venography; the leg scan result was positive in 10 and negative in 13. Anticoagulant therapy was given to patients who had either a constant intraluminal filling defect by venography or a positive leg scan result.

All patients were followed and none were lost to follow-up. New findings on long-term follow-up are shown in figure 2.

Patients with Negative Results by Impedance Plethysmography and Leg Scanning

Three of the 181 patients negative by both impedance plethysmography and leg scanning (1.7%) returned with new symptoms and signs of venous thromboembolism; objective tests showed new episodes of venous thromboembolism. One patient returned 48 hours after the initial assessment complaining of a

\[\text{Figure 2. Outcome during long-term follow-up. IPG = impedance plethysmography; VTE = venous thromboembolism. Asterisk indicates patients with positive IPG results and constant intraluminal filling defects on venography; patients with positive leg scan result.}\]
marked exacerbation of leg pain, tenderness and swelling; the results of both impedance plethysmography and leg scanning were positive, and venography confirmed the presence of calf vein thrombosis. One patient returned 2 weeks after the initial assessment complaining of pleuritic chest pain; pulmonary angiography confirmed the presence of pulmonary embolism. The remaining patient returned 16 months later with new symptoms of pain, tenderness and swelling; repeat testing with impedance plethysmography was positive and constant intraluminal filling defects were shown by venography.

No patient died from pulmonary embolism; two patients died from disseminated carcinoma and one patient from myocardial infarction.

Patients Positive by Impedance Plethysmography or Leg Scanning

Eighteen of the 89 patients (20%) with positive results by impedance plethysmography or leg scanning returned with documented recurrent venous thromboembolism during follow-up. At entry, each of the 18 patients had intraluminal filling defects detected by initial venography. All 18 patients were seen as emergent cases with florid symptoms and signs. Four of these 18 patients died from massive pulmonary embolism; three died while not receiving anticoagulant therapy and one patient died while receiving heparin therapy (partial thromboplastin time < 50 seconds for 3 days). One patient had concomitant subdural hematoma and could not be treated with anticoagulants; this patient died with massive pulmonary embolism, documented by autopsy, 2 days after intake. One patient died 2 weeks after entry and one patient at 9 weeks; both had discontinued anticoagulation therapy prematurely and both had massive pulmonary embolism at autopsy. The final patient presented 33 months after entry with a massive proximal vein thrombosis that was not present in the initial venogram. Thrombosis was complicated by major pulmonary embolism manifest as acute respiratory failure, and death was due to respiratory arrest.

Fourteen patients returned during long-term follow-up with nonfatal recurrent venous thromboembolism; 13 patients had recurrent venous thrombosis and one patient had pulmonary embolism. Two of the 14 patients returned 2 weeks after entry, 10 between the 3 and 12 months and two after 12 months. Eight months after entry, one patient developed pleuritic chest pain after major knee surgery, and pulmonary angiography confirmed the presence of pulmonary embolism. Two patients returned 2 weeks after entry with objectively documented, acute, recurrent, deep-vein thrombosis confirmed by both noninvasive testing and venography; neither patient was receiving warfarin at the time of recurrence. Both patients had new intraluminal filling defects in the proximal venous system that were not present in the initial venograms. Nine patients returned between 3 and 12 months after entry with objectively documented, acute, recurrent, deep-vein thrombosis by both noninvasive testing and venography; in seven, venography demonstrated constant intraluminal filling defects in the proximal venous system that were not present in the initial venogram and, in two, new constant intraluminal filling defects were detected in the calf. Two patients returned after the 12-month follow-up with objectively documented, recurrent, deep-vein thrombosis by noninvasive testing and venography; venography demonstrated new constant intraluminal filling defects in the proximal venous system. Interestingly, the impedance plethysmography result was normal before the acute episode of recurrent venous thrombosis during long-term follow-up in 12 of the 13 patients with recurrent venous thrombosis; at the time of the subsequent acute recurrent event, the impedance plethysmography result had changed from normal to abnormal in all 12 patients.

An additional six patients in this group died during follow-up, five from disseminated carcinoma and one from a cerebrovascular accident.

Comparison of Long-Term Outcome in Positive and Negative Cohorts

Four of 89 patients (4.5%) in whom the results of impedance plethysmography and leg scanning were positive died from massive pulmonary embolism, compared with none of 181 patients in whom impedance plethysmography and leg scans were negative (p = 0.01). Three of 181 patients with objectively documented recurrent venous thromboembolism died, a frequency of 1.7% (95% confidence interval 0.4–4.8%). In contrast, 18 of 89 patients positive by impedance plethysmography or leg scanning died, a frequency of 20.2% (95% confidence interval 12.5–30.1%). The difference between these two groups was statistically significant (p < 0.001).

Discussion

The results of this prospective clinical trial indicate that the objective diagnostic process evaluated here can be used to separate patients with clinically suspect ed recurrence into two groups: a negative cohort in whom it is safe to withhold anticoagulant therapy and a positive cohort that requires anticoagulant therapy. The observations made by prospective comparative study with long-term follow-up have important clinical implications. One hundred eighty-one of 270 patients (67%) had negative impedance plethysmography and leg scan results; only three of these 181 patients (1.7%) returned with recurrent venous thromboembolism during long-term follow-up, and no patient died from pulmonary embolism. In contrast, patients with positive impedance plethysmography or leg scan results had a high frequency of acute, recurrent, deep-vein thrombosis during long-term follow-up; 18 of 89 (20.2%) had new episodes of objectively documented venous thromboembolism, including four deaths from pulmonary embolism (p < 0.001). In the majority of positive patients, recurrent venous thromboembolism occurred after anticoagulant therapy had been terminated either inadvertently or after 3 months.

The diagnostic approach we used has a high clinical
value. We established definitive management in 257 of 270 patients (95%). In the remaining 13 patients (5%) who had a positive impedance plethysmography result, an indeterminate venogram result and a negative leg scan result, acute, recurrent venous thromboembolism could not be confidently ruled out. These patients were not treated, but it can be argued that they should have been because the leg scan may have failed to detect proximal vein thrombosis in the upper thigh or in the axial veins of the pelvis. Given the infrequency of this combination of test results, it would be prudent to err on the side of treating these patients rather than to risk death from massive embolism.

Our findings indicate that patients in the positive cohort had a surprisingly poor prognosis; 18 of these 89 patients (20%) had a recurrence of thromboembolism. This high frequency suggests that patients positive by impedance plethysmography or leg scanning may not have been treated long enough. We are performing a randomized trial to determine whether a longer course of oral anticoagulant therapy is preferable to 3 months of therapy.

Our findings suggest that a baseline impedance plethysmography evaluation performed as a part of routine follow-up has clinical value. The majority of patients returning on long-term follow-up with a further episode of recurrent deep-vein thrombosis had impedance plethysmography results that had become normal but reverted to abnormal at the time of the recurrence.

Our results are of considerable clinical relevance because, for the first time, the clinician is provided with a practical approach to the patient with clinically suspected, recurrent, deep-vein thrombosis. The use of noninvasive tests and venography in such patients is highly cost effective, for 181 of 270 patients (67%) were spared the need for in-hospital care and long-term anticoagulant therapy.

Acknowledgment
We are indebted to C. England, P. Dodd, C. Hiscoe, D. Kinch and K. Kinnon for assistance; to the Hamilton Red Cross for providing fibrinogen; and to D. L. Sackett, M.D., for support and encouragement.

References

Appendix
Impedance plethysmography was performed with the IPG 200 machine (Codman) as described in detail elsewhere. Each patient was tested while supine with the lower limb elevated 25–30°, the knees flexed 10–20° and the ankle 8–15 cm higher than the knee. A pneumatic cuff 15 cm wide was applied to the mid-thigh and inflated to 45 cm H2O, thereby occluding venous return. After a predetermined time (see below), the cuff was rapidly deflated and the changes in electrical resistance (impedance) resulting from alterations in blood volume distal to the cuff were detected by circumferential calf electrodes and recorded on an ECG strip. The changes in impedance during cuff inflation and deflation were measured and both the total rise during cuff inflation and the fall during the first 3 seconds of deflation were plotted on a two-way impedance plethysmography graph reported elsewhere. The changes in impedance were plotted as impedance units. One impedance unit was defined as a 1-mm deflection on the ECG paper obtained when the sensitivity was set so that 0.4% impedance units produced a 10-mm deflection. The graph included a ‘‘discriminant line’’ developed by discriminant function analysis, which provided optimal separation of impedance plethysmography results into normal and abnormal for proximal vein thrombosis.

The accuracy of impedance plethysmography is critically dependent on obtaining optimal venous filling during the temporary occlusion of venous outflow. Optimal venous filling was obtained by using repetitive testing and prolonged cuff occlusion. Five tests were performed at each examination. The duration of occlusion during these tests was 45, 45, 120, 45 and 120 seconds, and the time interval between them was 20–30 seconds. We used this protocol because optimal venous filling rarely occurred until the leg was subjected to three to five cycles of inflation and deflation as well as prolonged venous occlusion.

Scoring and Interpretation of the Impedance Plethysmograph Results
The rise and fall of each test were both plotted on the two-way graph containing the discriminant line (fig. 3); the point used as the patient’s plethysmograph result was that which showed the highest rise

![Figure 3](http://circ.ahajournals.org/Downloaded from http://circ.ahajournals.org/) To score the impedance plethysmography result, the rise (venous capacitance) and fall (venous outflow in three seconds) of each test were plotted on the two-way graph containing the discriminant line. The point used as the patient’s plethysmography result was that which showed the highest rise and greatest fall. This result was coded as ‘‘normal’’ if it fell above the discriminant line, and ‘‘abnormal’’ if it landed on or below the discriminant line.
Figure 4. The four characteristic response patterns observed using occlusive cuff impedance plethysmography and the sequential technique to obtain optimal venous filling. In patients without proximal venous thrombosis (patterns a and b), a progressive increase in venous filling is accompanied by an increase in venous emptying. In the presence of proximal venous thrombosis, increased venous filling is not associated with a proportionate increase in venous emptying (patterns c and d). Thus, the accuracy of the test is enhanced with increased venous filling.

In the rare instance when the greatest rise and fall did not occur in the same test of a sequence, the examination was regarded as inadequate and was repeated. Four patterns of impedance plethysmography response are observed using occlusive cuff impedance plethysmography and the sequential technique to obtain optimal venous filling (fig. 4): (1) All points in the five-test sequence may fall below the discriminant line. (2) Initial tests of the sequence may be above the discriminant line, but later tests including the test with the highest rise and greatest fall, are below the discriminant line. (3) All five points in the five-test sequence may be above the discriminant line. (4) The initial tests of a sequence may be below the discriminant line, but the later tests, including the test with the highest rise and greatest fall, are above the discriminant line.

We have shown that the use of optimal venous filling by sequential testing enhances sensitivity and specificity. In patients without proximal vein thrombosis, a progressive increase in venous filling is accompanied by an increase in venous emptying (fig. 4, patterns a and b). When proximal vein thrombosis is present, increased venous filling is not associated with a proportionate increase in venous emptying (fig. 4, patterns c and d). The progressive separation between normal and abnormal test results that occurs with increased venous filling enhances the accuracy of the test.

This technique cannot distinguish between obstruction due to acute proximal vein thrombosis and persistent chronic venous outflow obstruction due to previous proximal vein thrombosis. In over 80% of patients with acute proximal vein thrombosis, the impedance plethysmography result returns to normal 3–6 months after the acute event. In the remaining patients, persistent venous outflow obstruction yields an abnormal impedance plethysmography result that is indistinguishable from that associated with acute proximal vein thrombosis.
The diagnosis of acute, recurrent, deep-vein thrombosis: a diagnostic challenge.

Circulation. 1983;67:901-906
doi: 10.1161/01.CIR.67.4.901

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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