Clinical Validity of a Negative Venogram in Patients with Clinically Suspected Venous Thrombosis

RUSSELL HULL, M.B., B.S., JACK HIRSH, M.D., DAVID L. SACKETT, M.D.,
D. WAYNE TAYLOR, M.Sc., CEDRIC CARTER, M.B., B.S., ALEXANDER G.G. TURPIE, M.B., CH.B.,
PETER POWERS, M.D., AND MICHAEL GENT, M.Sc.

SUMMARY Although it is generally accepted that negative venography excludes deep vein thrombosis (DVT) in patients in whom it is clinically suspected, there is no evidence to support this conclusion. To test the correctness of withholding anticoagulant therapy in these patients, we followed 160 consecutive patients who had clinically suspected DVT and negative venograms to determine the frequency of postvenographic DVT. Anticoagulant therapy was withheld in all patients. No patient died or developed pulmonary embolism during 3 months of follow-up. Two of the 160 patients (1.3%) attended the clinic on an emergency basis during follow-up with new symptoms of DVT and in both patients, DVT was confirmed by objective testing. These events developed within 5 days of venography, which suggests that they were induced by venography. Nevertheless, the findings indicate it is safe to withhold treatment in patients with clinically suspected DVT and negative venograms.

ASCENDING bilateral venography is the accepted reference method for the diagnosis of deep vein thrombosis (DVT). More than 50% of patients with clinical manifestations compatible with venous thrombosis have negative venograms, even though the clinical findings may be strongly suggestive of venous thrombosis and are present in both the calf and thigh. Although it is generally accepted that a negative venogram excludes a diagnosis of DVT, there is no information in the literature that documents this.

We have taken the clinical view that a negative result with adequate venography excludes a diagnosis of venous thrombosis as a cause of symptoms in patients with clinically suspected DVT. Accordingly, these patients have not been treated irrespective of the clinical manifestations.

To test the safety of our clinical approach we performed a follow-up study in 160 consecutive patients with clinically suspected DVT who had negative venograms and determined the frequency of postvenographic thromboembolism in these patients.

Methods

One hundred sixty consecutive patients with negative venograms who were referred to the Hamilton Regional Thrombosis Programme with their first episode of clinically suspected DVT were entered into the study.

Ascending venography was performed by the method of Rabinov and Paulin in two hospitals and by a previously described method in the other two. After the procedures were completed, the veins of each leg were flushed with 100 ml of saline. Venography was interpreted as previously described. The venographic findings were interpreted independently without knowledge of the clinical findings.

In 158 patients, ascending venography showed a well-opacified deep vein system in both legs, and the posterior tibial veins, peroneal veins, the soleal pluxis, the popliteal, superficial femoral, common femoral, external and common iliac veins were visualized. Careful attention was given to technique and injection of contrast medium was repeated if inadequate visualization occurred on the first attempt. In two patients, the external and common iliac veins were not adequately visualized by repeat injection and a direct femoral vein puncture was required for successful visualization.

The patients were 17-84 years old, mean age 51 years. Sixty-five were males and 95 were females. In all cases, a consulting physician agreed, after examining the patient, that the clinical findings suggested DVT and that this diagnosis could not be confidently ruled out in favor of an alternate diagnosis.

The history and physical findings were assessed in a standard fashion and recorded prospectively on the study data forms. The findings recorded included the presence or absence of pain, tenderness, swelling, edema, cord, Homans' sign, and localization of these symptoms and signs to the calf region only, the thigh only, or calf and thigh.

In each patient, baseline impedance plethysmography and leg scanning were performed in both legs at the time of venography and repeated at 72 hours. The methods for performing and interpreting impedance plethysmography and leg scanning have been described.

No patient received anticoagulant therapy before venography. Because the venographic findings were

622
negative, the patients did not receive anticoagulant therapy after venography.

At one center (Chedoke Division, Chedoke-McMaster Hospital, to which the majority of the patients were referred), consecutive patients were reviewed by the consulting physician within 72 hours after venography (with the knowledge that venography was negative) to establish an identifiable cause for the clinical findings, and the alternate diagnosis (if arrived at) was recorded at that time.

Follow-Up

All patients were asked to return if they developed new clinical events suggestive of venous thromboembolism, and all were contacted routinely at 3 months. In all patients who returned on an emergency basis with clinically suspected DVT, the diagnosis was confirmed by impedance plethysmography and venography. At routine 3-month follow-up, information on the state of health, hospital admissions and use of anticoagulant therapy was obtained. The patients who were geographically accessible were seen in a special clinic and impedance plethysmography was performed in both legs. This objective, noninvasive test was used to determine the presence or absence of obstructive proximal DVT.

Results

The clinical manifestations that led to the diagnosis of clinically suspected DVT in the consecutive 160 patients with negative venograms are shown in Table 1. Ninety-four patients (59%) had pain, tenderness and swelling, 35 had pain and tenderness only, 18 had swelling only and 13 had tenderness and swelling. In addition, edema was noted in 38 patients, Homan's sign was present in 35 patients and a cord was noted in eight patients. The clinical manifestations were confined to the calf in 90 patients (56%), but involved the calf and thigh in 56 patients (35%) or thigh only in 14 patients (9%).

The 87 consecutive patients referred to Chedoke Division were reviewed after venography by the consulting physician to determine the cause of the clinical manifestations. In 64 of the 87 patients (74%), the clinical manifestations were consistent with an alternate diagnosis, and in 23 patients an alternate diagnosis could not be made. The alternate diagnoses are shown in Table 2.

In 21 patients, the clinical diagnosis of muscle strain was made and the common feature in these patients was the observation that the clinical manifestations (pain, tenderness and swelling) followed unaccustomed activity. In nine patients, the clinical manifestations were associated with and attributed to a twisting muscle injury of the leg. The clinical manifestations (edema and swelling) in the eight patients with leg paralysis after stroke were attributed to vasomotor changes due to the stroke. The common features in the six patients with venous reflux were the presence of severe varicose veins, deep venous reflux on Doppler ultrasonography and an association with recently prolonged ambulation. These patients had no history of DVT and the deep venous system by venography was normal. In five patients, several of whom had a cord, the onset of the clinical manifestations during exercise suggested a torn muscle. Lymphatic obstruction or insufficiency was confirmed by lymphangiography in four patients and in two others presumed lymphatic disruption was attributed to recent total knee replacement. Cellulitis was clinically apparent in three patients. In four patients, Baker's cysts were suspected on the basis of a history of arthritis or of previous injury to the knee; this diagnosis was confirmed by arthrography. An internal abnormality of the knee was confirmed in two patients by arthroscopy.

In 23 patients, the clinical manifestations did not

Table 1. Symptoms and Signs Suggestive of Deep Vein Thrombosis in 160 Consecutive Patients with Negative Venograms

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>No. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, tenderness and swelling</td>
<td>94</td>
<td>59</td>
</tr>
<tr>
<td>Pain and tenderness only</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Swelling only</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Tenderness and swelling</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Other clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Homan's sign</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf only</td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td>Calf and thigh</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>Thigh only</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2. The Alternate Diagnosis in 87 Consecutive Patients with Negative Venograms

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strain associated with unaccustomed exercise</td>
<td>21</td>
</tr>
<tr>
<td>Direct twisting injury to leg</td>
<td>9</td>
</tr>
<tr>
<td>Leg swelling in paralyzed leg</td>
<td>8</td>
</tr>
<tr>
<td>Venous reflux</td>
<td>6</td>
</tr>
<tr>
<td>Lymphangitis, lymphatic obstruction</td>
<td>6</td>
</tr>
<tr>
<td>Muscle tear</td>
<td>5</td>
</tr>
<tr>
<td>Baker's tear</td>
<td>4</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3</td>
</tr>
<tr>
<td>Internal abnormality of knee</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
</tr>
</tbody>
</table>

*Diagnosis made after venography with knowledge of the negative venogram.
suggest another diagnosis. In these patients the distribution of symptoms or signs did not differ from that in patients in whom an alternate diagnosis was made.

Before venography, the clinical suspicion of venous thrombosis was strong enough to require its exclusion by objective testing. The above alternate diagnosis could only be made after venography with knowledge of the negative findings.

No patient died during the 3-month follow-up. Two patients attended the clinic on an emergency basis early in the course of follow-up with new clinical manifestations suggestive of DVT. None of the other 158 patients developed new clinical features suggestive of DVT.

One hundred twenty-one patients were seen in the clinic at 3 months; 28 were contacted directly by telephone and nine through their family doctor or relatives. The results of impedance plethysmography remained negative in all patients who attended the clinic on routine follow-up.

In both patients who attended the clinic on an emergency basis with a new episode of clinically suspected DVT in the previously involved leg, the diagnosis was confirmed by objective testing. One patient presented 2 days after the initial venogram complaining of severe pain, tenderness and swelling in the calf and thigh and the impedance plethysmogram, which was previously normal, was markedly abnormal. Repeat venography was unsuccessful for technical reasons in this patient. The other patient returned 8 days after the initial venogram with a 4-day history of pain, tenderness and swelling in the calf. Repeated impedance plethysmography was again negative, but repeat leg scanning was positive in the calf and a second venogram showed acute venous thrombosis (constant intraluminal defect) involving the posterior tibial and peroneal veins, which on the previous venogram were well visualized and normal.

Six patients were admitted to hospital for other reasons during the follow-up period. One patient was admitted with ischemic heart disease, two had heart surgery, one had a fractured hip, one had elective hip surgery and one patient had a cholecystectomy. The patient with ischemic heart disease was admitted late in the course of the follow-up to a remote community hospital and his recovery was subsequently complicated by the development of a clinically diagnosed pulmonary embolism. Neither lung scanning nor pulmonary angiography was available, so this diagnosis could not be confirmed.

Discussion

Although venography is generally accepted as the standard against which therapeutic decisions can be made, the validity of withholding treatment in patients with a negative venogram has not been previously formally evaluated. In this study we validated the correctness of not treating patients who have a negative venogram by performing a prospective follow-up incorporating objective tests for DVT. Using this approach, we detected DVT after venography in two of 160 patients (1.3%).

The two episodes of DVT after venography could represent thrombi that were undetected in the initial venogram or thrombi that occurred as a complication of venography. The patients who developed new clinical manifestations of DVT did so within 5 days after venography, suggesting that these events may have been induced by venography.

Review of the initial venogram supports this concept in the patient who underwent successful repeat venography, as the venous segments subsequently involved in the second venogram were well visualized by the initial venogram. Further, in both patients the results of the noninvasive tests were negative at initial presentation and became positive when the new clinical manifestations occurred.

Thrombosis after venography is becoming increasingly recognized as a clinical entity. Positive results with I-fibrinogen leg scanning have been reported after venography in up to 30% of patients with negative venograms.10 Many of these could represent local inflammation rather than thrombosis. The frequency of clinically evident DVT developing after venography has been estimated to be 2–4% in ambulatory patients;10 this finding is similar to ours.

Our results indicate, therefore, that it is safe to withhold anticoagulant therapy in patients with clinically suspected DVT who have negative venograms.

The negative findings by objective testing in this patient group emphasize the nonspecificity of the clinical diagnosis of venous thrombosis. The symptoms and signs exhibited by these patients are similar to the clinical findings in symptomatic patients with venous thrombosis confirmed by objective testing. Although many patients had negative venograms, they had symptoms and signs in the thigh as well as the calf, and in many the symptoms and signs were florid. It was possible to arrive at an alternate diagnosis in a large subgroup of patients after a negative venogram was obtained based on clinical associations (e.g., muscle tear) and the clinical evolution of the disease (e.g., cellulitis). The alternative diagnosis was arrived at with knowledge of the negative venogram and this would not have been possible without the knowledge that DVT had been ruled out.

Although venography is considered to be the diagnostic standard, it has limitations. Incorrect therapeutic decisions may be made if visualization is not adequate. Venography is invasive and produces considerable discomfort in many patients. Further, its use is complicated by DVT in a small percentage of patients. Despite these limitations, it is clearly preferable to investigate all patients rather than to treat on clinical grounds, as objective testing avoids unnecessary treatment of the 50% or more of patients who are negative. Accurate noninvasive approaches for the diagnosis of DVT are now available and can be used as an alternative to venography. It is also likely that the morbidity of venography can be reduced by
the use of isotonic radiographic dye,\textsuperscript{14} which has recently become available, although it is considerably more expensive than the standard contrast medium.

\textbf{Acknowledgment}

We are indebted to Drs. D. McLaughlin, R. J. Tuttle, H. Stolberg, and P. Cockshott for their assistance and the Hamilton Red Cross for providing the fibrinogen.

\textbf{References}

Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis.
R Hull, J Hirsh, D L Sackett, D W Taylor, C Carter, A G Turpie, P Powers and M Gent

Circulation. 1981;64:622-625
doi: 10.1161/01.CIR.64.3.622

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/64/3/622

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/