Diagnostic and therapeutic management of venous and arterial disease

Bernardi, E.

Citation for published version (APA):
CHAPTER 4

THE DIAGNOSTIC VALUE OF COMPRESSION ULTRASONOGRAPHY IN PATIENTS WITH SUSPECTED RECURRENT DEEP VEIN THROMBOSIS


Thrombosis and Haemostasis 2002;88:402-406

Department of Medical and Surgical Sciences, 2nd Chair of Internal Medicine, University of Padua Medical School, Padua, Italy, *Center for Vascular Medicine, Academic Medical Center, University of Amsterdam, the Netherlands

† Other participants in the DERECUS Study are: Benedetti L, Frulla M, Marchiori A, Piccioli A, Scarano L, Tormene D

Summary

Diagnosis of recurrent deep-vein thrombosis (DVT) is difficult because of limitations in distinguishing acute from old thrombi. In the past, an ultrasound method for diagnosis of recurrent ipsilateral DVT was developed, which relies on repeated measurements of the diameters of the common femoral and popliteal veins. To assess the safety of withholding anticoagulation from patients with improved or stable compression vein diameters, 205 consecutive patients presenting with suspected recurrent ipsilateral DVT were evaluated. The vein diameter was measured under compression with the transducer and compared with earlier ultrasound results. Patients with stable or improved ultrasound findings had repeat ultrasound assessments after 2 (±1) and 7 (±1) days. Patients with repeatedly normal ultrasound results were followed-up for six months to determine the incidence of symptomatic recurrent venous thromboembolism. Of the 205 patients, 153 had stable or improved ultrasound findings. Repeat ultrasound assessment became abnormal in 3, and recurrence was confirmed
by venography in all. Six months of follow-up was done in the remaining 150 patients with repeatedly normal ultrasound tests and showed 2 (1.3%; 95% CI, 0.02 to 4.7%) confirmed non-fatal venous thromboembolic complications. The positive predictive value of a stable or improved ultrasound was 90% (95% CI, 77% to 97%).

In conclusion, it is safe to withhold anticoagulant treatment from patients with suspected recurrent ipsilateral DVT in whom compression ultrasonography showed improved or stable vein diameters.

Introduction

Long-term follow-up studies have now recognized that recurrent venous thromboembolic complications occur more frequently than previously thought. Thus, after a mean follow-up of approximately eight years in patients with a first episode of deep-vein thrombosis (DVT), one-third had developed a new confirmed venous thrombotic complication. Recurrent venous thromboembolism will be manifested by pulmonary embolism in approximately one-fifth of these patients, whereas the remaining patients will present with a new DVT of the leg. Recurrent DVT of the leg occurs with a similar frequency in the leg that had been initially involved and the previously asymptomatic contralateral leg.

The diagnostic management of patients presenting with clinical manifestations of recurrent ipsilateral DVT still represents a challenge for clinicians. Based on the unreliability of clinical diagnosis, several diagnostic strategies have been evaluated including contrast venography, the combination of $^{125}$I-fibrinogen leg scanning with impedance plethysmography, and serial impedance plethysmography alone. Contrast venography, the reference method for the diagnosis of acute venous thrombosis, often does not allow the visualization of a new constant intraluminal filling defect in vessels that have been obliterated by the previous thrombotic process. Despite proven accuracy, the other two strategies are applied to a limited extent in medical practice mainly because of their scarce availability.

The introduction of ultrasonography in the late 80’s has revolutionized the diagnostic approach to patients with clinically suspected DVT. Ultrasound facilities are available in virtually all hospitals, the test has high accuracy for the disease, and test procedures are simple and reproducible. Ultrasonography diagnosis of venous thrombosis relies on the impossibility to collapse the vein walls by transducer compression due to presence of thrombi. Although anticoagulant treatment blocks further thrombus growth and ultimately may lead to reduction of
clot, a substantial proportion of patients, who improve clinically, remain testing abnormal on compression maneuvers over time. Although suspected pulmonary embolism and suspected DVT of the leg previously not involved can be reliably diagnosed, the inability to distinguish acute venous thrombosis from old disease poses an important barrier for the diagnosis of ipsilateral recurrent DVT.

In 1993 we developed an ultrasound method for the diagnosis of recurrent DVT in patients earlier diagnosed with proximal DVT. The method relies on repeated measurements of the diameters of the common femoral and popliteal vein during compression with the transducer. We were able to demonstrate a constant reduction in vein diameter over time in the absence of recurrent DVT. In contrast, vein diameters increased by at least 2 mm, or returned abnormal after earlier normalization, in patients who showed to have a confirmed recurrent DVT. However, an unchanged or improved ultrasound test could not exclude with certainty limited (but potentially extending) recurrent DVT. The primary aim of this study was to assess the safety of withholding anticoagulant therapy from patients with suspected recurrent ipsilateral DVT who had improved or stable vein diameter assessments during serial (day 1, 2 and 7) testing.

Patients and Methods

Patients

Patients referred to our center because of suspected recurrent ipsilateral DVT were potentially eligible for the study if they had been evaluated for a first episode of proximal-vein thrombosis at our center and if they had agreed to participate in the ultrasound surveillance program which was scheduled after 3 and 12 months from the first thrombotic episode. Patients were excluded from the study if they were still receiving anticoagulant treatment, had contraindications to venography, or lived too far from the hospital to return for follow-up visits. In addition, patients were excluded if they presented with suspected recurrent thrombosis in combination with confirmed pulmonary embolism. Patients had been treated for their first episode with an initial course of high dose adjusted intravenous standard heparin or low-molecular-weight heparin for at least 5 days. Sodium warfarin was started during the first week of treatment and continued for a period of at least 3 months. The dose of oral anticoagulant therapy was adjusted regularly to maintain the international normalized ratio between 2.0 and 3.0. Heparin treatment was discontinued after two consecutive values higher than 2.0. Patients were asked to return immediately to
our center if they developed symptoms suggestive of recurrent venous thromboembolism. The study protocol was approved by the Institutional Review Board.

**Ultrasound protocol**

Ultrasound assessments of the vein distention of the compressed veins were done at 3 and 12 months and if recurrent DVT was suspected. Briefly, repeat ultrasound investigations were done with knowledge of the original ultrasound result. The common femoral and the popliteal vein were scanned in the transverse planes. With the patient in a supine position, the common femoral vein was located in the groin. The popliteal vein was located in the popliteal fossa with the patient in the prone position. Subsequently, in the abnormal venous segments, the thickness of thrombus mass was estimated above the saphenofemoral junction (for the common femoral vein) and/or in the mid-popliteal (for the popliteal vein). The maximum compressibility of the vein diameter was assessed by pressing on the vein with the transducer while observing changes in the caliber of the vein on the monitor. When the maximum compressibility was reached, then a freeze-frame image was obtained, and the residual vein diameter was measured in millimeters.

Ultrasonographic findings in patients with suspected recurrent DVT were classified as negative for recurrent disease if both the common femoral and the popliteal vein were fully compressible, or if the residual vein diameter was reduced or unchanged (<2mm) compared to the previous assessment. Ultrasound findings were positive for recurrent venous thrombosis if a previous normal(ized) vein had become non-compressible, or if the residual vein diameter in either venous segment had enlarged 2 mm or more compared to the previous assessment. These criteria have been shown to be reproducible and accurate in a previous study.

**Study design**

This was a prospective follow-up study in a cohort of consecutive patients with clinically suspected recurrent ipsilateral DVT. Patients with normal ultrasound findings were not treated with anticoagulants but were scheduled for repeat ultrasound assessment after 2 (±1) and 7 (±1) days. If these tests did not indicate the presence of recurrent venous thrombosis, six months follow-up was done to detect the incidence of subsequent venous thromboembolic complications. Patients were instructed to return immediately to the center if they
developed signs or symptoms of recurrent venous thromboembolism for confirmatory testing (i.e., contrast venography, perfusion-ventilation lung scanning, or pulmonary angiography). Pulmonary embolism was confirmed if the perfusion lung scan revealed at least one segmental defect and the ventilation scan was normal in that area. Pulmonary angiography was performed for all other ventilation-perfusion lung scan abnormalities. Autopsies were requested in all patients who died and in whom pulmonary embolism could not be excluded as the cause of death. Patients with abnormal ultrasound findings were scheduled for venography within 24 h, and were managed accordingly. The only venographic criterion for recurrent DVT was the presence of a constant intraluminal filling defect on at least two projections. Venograms were performed by expert radiologists in the presence of an investigator. To minimize inadequate venograms, the venography procedure included repeated contrast injections if indicated. An independent physician determined the cause of death if autopsy could not be obtained. All ultrasounds, venograms, lung scans and pulmonary angiograms were interpreted by independent experts who were blinded for clinical information and related tests.

Analysis

It was calculated that follow-up should include 150 patients with serial normal ultrasound tests to conclude with sufficient confidence that the observed venous thromboembolic complication rate during follow-up is comparable with those found with the earlier non-invasive diagnostic strategies. The total rate of venous thromboembolic complications was defined as either a pulmonary embolism during the interval of baseline to repeat ultrasound or a pulmonary embolism or deep-vein thrombosis during follow-up. Exact confidence intervals (CI) for the incidence of venous thromboembolism were calculated using the binomial distribution (CIA, version 2.0.0, 2000).

Results

Study Patients

From January 1992 to May 1999, 231 consecutive patients with clinically suspected recurrent ipsilateral DVT were referred to the study center for objective testing. Twenty-six patients (11%) were excluded from the study because they were receiving anticoagulants (n=23), or had concurrent confirmed sympto-
matic pulmonary embolism (n=3). Therefore, our analysis included 205 patients. The main demographic and clinical characteristics of the study patients are shown in Table 1.

Initial Ultrasound Results

Adequate compression ultrasound tests for recurrent DVT were obtained in all patients. Abnormal test results at the day of referral were found in 52 patients (25.4%). Of these, 14 patients (26.9%) had a non-compressibility of a previous normal(ised) vein, and the remaining 38 (73.1%) had an enlargement of thrombus mass compared to the previous evaluation (>4 mm in 29, ≤4 mm in 9). The interpretation of ultrasound findings at the time of suspected recurrent episode was performed in all patients by comparison with the test obtained at 3 or 12 months from the initial proximal DVT. The 153 patients with an initial normal ultrasound findings were not treated with anticoagulants and returned after two and seven days for repeat ultrasound assessments.

Repeat Compression Ultrasound

Repeat ultrasound assessments were adequate in all 153 patients in whom recurrent DVT could not be demonstrated by the initial ultrasound test. The test

Table 1 – Characteristics of patients included in the study.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>62 (22-88)</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>48.8</td>
</tr>
</tbody>
</table>

Ultrasound location of the first DVT episode

- popliteal vein    78
- common femoral vein 39
- both              88

Interval between the first DVT and the suspected recurrence

- 3 to 6 months          20 (9.8%)
- 6 to 12 months         26 (12.7%)
- 12 to 24 months        66 (32.2%)
- longer than 24 months  93 (45.4%)
became abnormal in 1 patient after two days, and in other 2 patients after seven days. Confirmatory venography showed recurrent proximal DVT in all 3 (2.0%) patients. Repeat testing remained normal in the remaining 150 patients, anticoagulant treatment was not instituted, and follow-up was done for six months.

**Incidence of Venous Thromboembolism**

Of the 150 patients, 1 died after four months because of acute myocardial infarction. All the remaining 149 patients with repeatedly normal ultrasound test completed the six-month follow-up period. Seven patients (4.7%) returned before the scheduled follow-up appointment because of suspected venous thromboembolism. Six of them presented with recurrent leg symptoms or deterioration of their leg complaints; compression ultrasound and venography confirmed a recurrent proximal DVT in 2, after three and four weeks, respectively. One patient presented with clinically suspected pulmonary embolism, which was subsequently excluded by a normal perfusion lung scan. In none of the five patients in whom the clinical suspicion of recurrent thromboembolism was ruled out by objective testing was anticoagulant treatment instituted, and long-term follow-up was uneventful. Therefore, the incidence of confirmed venous thromboembolism during the six-month follow-up period in patients with repeatedly normal ultrasound test was 1.3% (95% CI, 0.02 to 4.7%).

**Positive Predictive Value of Compression Ultrasound**

Venograms could not be obtained in 3 patients, and were inadequate for interpretation in 7 patients. Thus, adequate venograms were obtained in 42 patients with abnormal ultrasound findings. The clinical characteristics of patients in whom venography either was not performed or was inadequate did not differ from those of patients with adequate venograms. Venography confirmed the diagnosis of recurrent proximal-vein thrombosis in 38 (positive predictive value, 90%; 95; CI, 77% to 97%). Specifically, the diagnosis was confirmed in all 10 patients with non-compressibility of a previous normal(ised) vein, and in 28 of the 32 patients with an enlargement of the thrombus mass (in all 20 patients with an enlargement >4 mm, and in 4 of the 8 patients with an enlargement £4 mm). Patients in whom venography ruled out the diagnosis of recurrent thrombosis were not anticoagulated, and a six-month follow-up was uneventful in all. The 10 patients in whom venography could not be obtained or was inadequate were managed according to the results of ultrasound. The 9
patients with non-compressibility of a previously normal(ised) venous segment or an enlargement of thrombus mass >4 mm were regarded as having a recurrent thrombosis. The last patient with an increase of thrombus mass <4 mm underwent repeated (after 2 and 7 days) ultrasound assessments, that did not show variations. This patient was not anticoagulated and had an uneventful 6-month follow-up.

Discussion

There is a clear need for a simple and accurate diagnostic test for suspected recurrent DVT. First, as shown in this and previous studies, up to two-thirds of patients presenting with new leg symptoms do not have recurrent DVT but other non-thrombotic disorders which do not require anticoagulant therapy.\(^\text{3,5,8}\) Second, recurrent venous thromboembolic complications following a first episode of DVT occur more frequently than was believed earlier. Thus, recurrent venous thromboembolic complications are found with a cumulative incidence of approximately 30% after a mean follow-up of eight years.\(^1\) While detection of thrombosis in the previously unaffected contralateral leg does not raise diagnostic problems, diagnosis is difficult if patients present with clinical manifestations suggestive of recurrent ipsilateral DVT.\(^2,9,10\) Clinical diagnosis is indeed highly non-specific,\(^3,5,8\) and all available diagnostic strategies have serious limitations in this context. Contrast venography is often inadequate for interpretation.\(^3,5\) The combination of radiofibrinogen leg scanning with impedance plethysmography has been abandoned because of its complexity and the use of plasma-derived fibrinogen.\(^3,4\) Serial plethysmography alone has received a limited evaluation, and can only be applied in patients with an already normalized test result.\(^3\)

The results of our study performed in a large series of patients with suspected recurrent ipsilateral DVT indicate that it is safe to withhold anticoagulant treatment from patients with serial normal ultrasound findings by using changes in the vein diameter over time. During six months of follow-up, only 2 of the 150 patients with repeatedly normal ultrasound tests (1.3%; 95% CI, 0.02 to 4.7%) had subsequent confirmed non-fatal venous thromboembolic complications. This figure compares favorably with those obtained in earlier studies that used the combination of \(^{125}\text{I}\)-fibrinogen leg scanning with impedance plethysmography,\(^3,4\) or serial impedance plethysmography alone\(^5\) (Table 2).

As our diagnostic approach was entirely confined to the proximal-vein system, we likely missed some isolated calf vein thrombi. It has, however, be clearly
Table 2 - Earlier and current studies evaluating subsequent venous thromboembolic complications in patients presenting with suspected ipsilateral recurrent DVT in whom anticoagulant treatment was withheld based on a normal diagnostic work-up.

<table>
<thead>
<tr>
<th>Diagnostic work-up</th>
<th>patients with suspected ipsilateral DVT</th>
<th>patients with normal diagnostic work-up</th>
<th>follow-up (months)</th>
<th>subsequent VTE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial IPG on day 1,2,4 and $^{125}$I-fibrinogen leg scanning $^3$</td>
<td>270</td>
<td>181 (67%)</td>
<td>12</td>
<td>3 (1.7%; 0.3-4.8)</td>
</tr>
<tr>
<td>Serial IPG on day 1,2,5,10 $^4$</td>
<td>31</td>
<td>18 (58%)</td>
<td>6</td>
<td>0 (0%; 0-18.5)</td>
</tr>
<tr>
<td>This study</td>
<td>205</td>
<td>150 (73%)</td>
<td>6</td>
<td>2 (1.3%; 0.02-4.7%)</td>
</tr>
</tbody>
</table>

DVT = deep-vein thrombosis, VTE = venous thromboembolic complications, IPG = impedance plethysmography

Demonstrated that calf vein thrombi are only clinically important when they extend into the proximal veins, at which point detection with ultrasonography is possible. Therefore, we repeated the compression ultrasound test to identify and treat those patients with extending calf vein thrombosis. In our investigation, compression ultrasound detected proximal extended calf vein thrombosis in 3 of the 153 patients with clinically suspected recurrent DVT and a baseline negative ultrasound test. Although venography has limitations for the detection of recurrent DVT, we elected to calculate the positive predictive value of abnormal ultrasound tests using this technique as reference method because of the lack of accepted (non-ultrasound) diagnostic alternatives. Although the estimate of this parameter could be performed only in 80% of patients with an abnormal ultrasound test (because of the high rate of infeasible or inadequate venographies), the positive predictive value for recurrent DVT of an abnormal ultrasound result was high (90%; 95% CI, 77% to 97%). It should be noted that the positive predictive value was related to the size of the residual vein diameter. Thus, recurrent DVT was indeed confirmed in all patients who had an ultrasound test showing incompressibility of a previously normal(ised) vein or an increase of thrombus.
diameter of more than 4 mm. However, in the small subset of patients with an increase of the vein diameter ranging between 2 and 4 mm, recurrent DVT could not be confirmed in half of them. These findings are consistent with those obtained by others,\textsuperscript{13,14} who suggested that at the time of new complaints a vein diameter increase $<4$ mm should be considered with caution to avoid unnecessary anticoagulation. In such patients, venography seems to be indicated.

Although the ultrasound method described by us has the potential to greatly improve the diagnostic work-up of patients with suspected recurrent DVT, an important limitation is the dependence on previous examinations. At the time of the acute initial thrombosis, the vein diameter during compression is usually maximal and therefore can not be used as a reference value for later comparisons. After three and/or twelve months of anticoagulant therapy, substantial shrinking of the thrombus can be found in the majority of patients with further improvement after subsequent months.\textsuperscript{8} Therefore, follow-up ultrasound examinations are indicated to obtain baseline values to allow diagnosis for possible future recurrent DVT.

The need for repeating the test twice in a week in all patients with a negative baseline ultrasound is inconvenient and also expensive, since the great majority of patients who return for a repeat test do not have a recurrent disease. As for the initial diagnosis of DVT, the use of clinical decision rules or D-dimer assays (i.e., blood tests specific degradation products of fibrin) may be helpful in simplifying the diagnosis of recurrent DVT.\textsuperscript{15-18} It should be noted that our results were obtained by confining the examination to the mid-popliteal and inguinal regions, and by using a real-time B-mode imaging technique, without duplex or color facilities. The low rate of venous thromboembolism during follow-up in patients with repeatedly normal results indicates that the addition of duplex or color imaging is unlikely to produce a clinically important improvement in outcome for these patients. Whether use of flow characteristics might help differentiate recurrent from old thrombotic disease, thereby obviating the need of availability of an earlier performed ultrasound examination, is still debated.\textsuperscript{19}

We believe that the results of our study are valid and generalizable. Selection bias was prevented in our study by enrolling consecutive patients and the prevalence of confirmed recurrent thrombotic episodes was comparable to that reported in earlier studies.\textsuperscript{3,5,7,8} The ultrasound criteria we used had been previously validated against venography and proved to be reproducible.\textsuperscript{8} Furthermore, in all patients with serial normal ultrasound tests a six-month follow-up was done. Finally, in patients with abnormal ultrasound findings, obser-
vation bias was prevented by performing the ultrasound technique before venography and by having an independent and blind interpretation of both diagnostic techniques. We conclude that serial ultrasound using vein diameter assessments is accurate for the diagnosis of suspected recurrent DVT and that anticoagulant therapy can be safely withheld from patients with normal test results.

References


