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CHAPTER 3

A SIMPLE ULTRASOUND APPROACH FOR DETECTION OF RECURRENT PROXIMAL-VEIN THROMBOSIS


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Abstract

Background – the objective of this study was to develop a simple ultrasound method for measuring thrombus regression in patients with proximal deep-vein thrombosis (DVT) and to test its utility for the detection of DVT recurrence.

Methods and Results - the study comprised a cross-sectional survey and a prospective investigation (149 and 145 patients, respectively). In both phases, the normalization rate of a previously abnormal ultrasound test, applying the criterion of full compressibility of the common femoral and the popliteal vein (CUS method), was assessed. In the prospective study, the vein diameter under maximum compression (thrombus thickness) was measured in the abnormal venous segments at scheduled times (1, 3, 6, and 12 months). In patients presenting with suspected DVT recurrence, the procedure was repeated and results compared to those available from the previous examination. Non-compressibility of a previously normal(ised) venous segment and enlargement of thrombus thickness (>2 mm) were considered as diagnostic of proximal DVT recurrence. The diagnostic accuracy of the CUS method alone, as well as of the combined ultrasound methods (CUS + thrombus thickness), were assessed against contrast phlebography. CUS test normalisation occurred in only 30% of patients within one year. A significant reduction of the thrombus mass (P<.0001) was recorded throughout the entire study period. However, a major decrease in thrombus mass (>50%) was recorded within the first three months.
Out of 29 patients who developed a suspected recurrent DVT, phlebography confirmed diagnosis in 11. The CUS method alone showed an excellent accuracy (100%) but was applicable in only 6 patients (21%). Both the sensitivity and the specificity for proximal DVT recurrence of the combined ultrasound methods were 100% (95% confidence interval, 69% to 100% and 81 to 100%, respectively) and were applicable in all patients. **Conclusions** - the serial ultrasound measurement of thrombus mass after an acute episode of DVT may allow the correct identification of patients who develop a recurrent proximal-vein thrombosis.

**Introduction**

Real-time B-mode ultrasonography has been shown to be a highly accurate, objective, and reproducible method for the detection of proximal deep-vein thrombosis (DVT) of lower extremities in patients with the clinical indication of the first episode of DVT. Whether or not this technique might be used in the approach of patients with suspected recurrence of DVT is still uncertain. A few studies enrolling limited series of patients have performed serial ultrasound examinations after an acute episode of DVT. Applying the single criterion of full compressibility of the common femoral and popliteal veins, compression ultrasound (CUS), a complete normalization of the test has been demonstrated in a small number of patients after 6 to 12 months; therefore, these studies suggest that real time CUS cannot be reused in a large proportion of patients with suspected DVT and has a limited value for the detection of recurrent DVT.

Recent reports suggest that the thrombus mass progressively decreases after the initial thrombotic episode. Furthermore, our experience in large series of patients with recurrent proximal DVT diagnosed with phlebography suggests that the apposition of fresh thrombotic material to the pre-existing clot follows the anatomic distribution pattern observed in the first episode, involving the common femoral vein, the popliteal vein, or both. Therefore, the ultrasound quantification of thrombus regression in these two venous segments could help in recognizing patients with recurrent proximal DVT by providing the baseline reference with which to compare the new ultrasound findings at the time of referral for suspected recurrence.

We performed a two-step study. First, in a cross-sectional survey, we rescanned 149 patients with proximal DVT with only the CUS method. Subsequently, we performed a prospective ultrasound investigation in 145 additional patients.
with proximal DVT. This second phase was designed to assess the reproducibility of a new technique for thrombus mass measurement and to test its utility for the diagnosis of recurrent DVT.

**Methods**

**Step 1**

To assess the frequency of normalized CUS test results in the follow-up of patients with acute proximal DVT, all consecutive outpatients were identified in whom a diagnosis of acute lower-extremity proximal DVT had been established with venography and CUS test between 1986 and 1988 at the Thrombosis Center of Padua University. All patients had been treated in the acute phase with full-dose heparin followed by at least 3 months of oral anticoagulants. Patients were asked to return to the Thrombosis Center and received a single CUS test with knowledge of the original clot location with an ATL Ultramark 4 scanner with a 7.5-MHz linear-array transducer. The method and criteria of diagnosis were defined previously. Briefly, only the common femoral vein and the popliteal vein were scanned. 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 while the patient was prone with his or her feet on a pillow to prevent spontaneous collapse of the vein wall. Both veins were scanned in the transverse planes only. The compressibility of the vein was assessed by simply pressing on the vein with the transducer probe. According to the results, the veins were judged to be either noncompressible or fully compressible. A vein was considered fully compressible, and thereby normalized, if no residual lumen was seen.

**Step 2**

**Acute thrombotic episode** - All consecutive outpatients referred by their general practitioners to the Thrombosis Center of Padua University with their first episode of clinically suspected DVT between 1989 and 1991 underwent CUS and, in the case of a positive test, confirmatory venography. Patients with confirmed proximal-vein thrombosis were treated in the acute phase with full-dose heparin, followed by at least 3 months of oral anticoagulants. Initially, the single ultrasound criterion of full compressibility of the common femoral and the popliteal veins was applied. Test results were defined as normal or abnormal, depending on the full compressibility of the vein. Subsequently,
in the abnormal venous segments, the thickness of thrombus mass was estimated above the sapheno-femoral junction (for the common femoral vein) and/or in the mid-popliteal fossa (for the popliteal vein), as follows. The maximum compressibility of the vein was assessed, in the transverse section only, by pressing on the vein with the transducer probe while observing changes in the calibre 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 on line, expressed in millimetres, and recorded on patient’s clinical chart. We interpreted this finding as an indicator of the thickness of thrombus mass.

**Serial follow-up and inter-observer variability** - The complete procedure was then scheduled after 1 month for patients with easy access to the hospital and for all patients after 3, 6, and 12 months. At each follow-up examination, the ultrasonographic assessment was performed by a trained physician who was unaware of the results obtained in the previous evaluations. Furthermore, to establish the reproducibility of the thrombus mass estimation, in a consecutive series of 100 noncompressible venous segments, an evaluation by a second independent observer was also obtained. Each observer stated whether or not a change in the residual vein diameter had occurred. Because of the resolution power of the ultrasound machine, it was agreed in advance that a true variation in residual vein diameter had occurred in the case of change of vein diameter ≥2 mm.

**Suspected DVT recurrences** - All patients who became symptomatic for recurrent vein thrombosis during the follow-up were asked to return immediately to the Thrombosis Center. They were rescanned by the above-mentioned procedure and underwent a repeated venography within 24 hours. Ultrasonographic findings were categorized as follows: negative for proximal DVT recurrence if both the common femoral and the popliteal veins were fully compressible or if in the noncompressible veins the residual vein diameter was reduced or unchanged (±1 mm), compared with the previous assessment; positive for proximal DVT recurrence if a previously normal(ised) vein had become noncompressible or if the residual vein diameter in either venous segment had enlarged (≥2 mm) compared with the previous assessment.

The decision to set up a cut-off level of 2 mm (±1, no change; ≥2 mm, DVT recurrence) was taken a priori on the basis on the following considerations. Because of the resolution power of the ultrasound machine, an inter-variability
of ±1 mm in the measurement of thrombus thickness does indeed exist. It was assumed that, when DVT recurs in a proximal venous segment that still has residual thrombotic material in its lumen, it results in an enlargement of thrombus mass detectable by ultrasonography. Accepting an interobserver variability of ±1 mm, the minimum cut-off level to prevent false-positive results is 3 mm; however, it would result in the possibility of missing thrombi as large as 4 mm. Consequently, the choice of 2 mm seemed the most adequate to identify clinically relevant thrombi, thus accepting the risk of false-positive results, but reducing the hazard of missing potentially dangerous thrombi.

The only phlebographic criterion for diagnosing a recurrence of DVT was an intraluminal filling defect absent in the previous venography. In the case of an indeterminate venographic picture, diagnosis was adjudicated by means of a radiofibrinogen uptake test, according to previously described criteria. Ultrasonographic, phlebographic and radioisotopic findings were interpreted by independent and blind observers. The study protocol was approved by the Institutional Review Board of Padua University.

Analysis

In the cross-sectional survey (step 1), percentages of normalization, and the relative 95% confidence intervals, were calculated for any time by standard methods.

In the prospective phase (step 2), the cumulative incidence of normalized venous segments was calculated separately for the common femoral and popliteal veins by use of life-table analysis (Kaplan-Meier product-limit method), and the difference in time of normalization between the two vein segments was tested for significance with the generalized savage (Mantel-Cox) test. For analysis of thrombus mass evolution, at any scheduled follow-up visit, all available patients were considered in whom the CUS test had not yet normalized. Differences observed in the residual vein diameter between each scheduled visit, separately in the common femoral and in the popliteal veins, were tested for statistical significance using the Wilcoxon rank sum test for paired data. Two-sided values of P<.05 were considered statistically significant. The interobserver agreement in the ultrasound estimation of thrombus regression was calculated in a subset of 100 tests by having an independent evaluation by a second observer. The agreement rate between the two observers was assessed by κ-function analysis.
The sensitivity and the specificity (and the 95% CI), of the CUS method as well as of the combined ultrasound methods (CUS and thrombus thickness) for detection of recurrent proximal-vein thrombosis were calculated by standard methods.

**Results**

**Phase 1**

Of the 178 patients identified, 12 had died, 11 had experienced recurrent DVT, and 6 did not agree to participate. Therefore, 149 patients were included in the study. The median age of the study patients was 61 years (range, 17 to 89 years); 79 were men and 70 women. At the time of the acute thrombotic episode, thrombi involved the popliteal vein in 13 patients, the popliteal and the superficial femoral veins in 62, the popliteal and both the superficial and the common femoral veins in 12, the femoral and the iliac veins in 12, and all the proximal venous system in the remaining 50 patients. Thus, the popliteal vein was rescanned in 137 patients and the common femoral vein in 74.

Twenty-four patients were investigated 3 to 6 months after the acute thrombotic episode, 40 after 6 to 12 months, 48 after 12 to 24 months, and 37 after 24 to 36 months. The CUS test had normalized in 5 patients of the first group (20.8%; 95% CI, 7.1% to 42.1%), in 12 of the second (30.0%; 95% CI, 16.6% to 46.5%), in 24 of the third (50.0%; 95% CI, 35.2% to 64.8%), and in 24 patients of the last group (64.9%; 95% CI, 47.5% to 79.8%).

**Phase 2**

**Patient characteristics**

Of 169 consecutive patients with a positive CUS test, venography was performed and was adequate for interpretation in 149. Among them, a proximal DVT was diagnosed in 148 patients. Three of them died before completing at least one month of follow-up and were therefore excluded from the analysis. Thus, the study population comprised 145 patients. Demographic characteristics of these patients are depicted in the Table. In 50 patients (34.5%), the clot was visualized by CUS only in the popliteal vein; in 14 (9.7%), only in the common femoral vein; and in the remaining 81 patients (55.9%), in both sites.
Table – Characteristics of patients included in phase 2 of the study.

<table>
<thead>
<tr>
<th>Patients (no)</th>
<th>145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>63 (18-87)</td>
</tr>
<tr>
<td>Sex (males:females)</td>
<td>65:80</td>
</tr>
</tbody>
</table>

**Location of thrombi**
- popliteal vein: 7
- popliteal and superf. femoral: 43
- popliteal, superf. and common femoral: 39
- femoral and iliac: 14
- all proximal system: 42

**Evolution of thrombus mass**

One-month follow-up was completed in 85 patients, 3-month in 138, 6-month in 122, and 12-month in 103.

The cumulative incidence of normalized CUS test results, separately for the common femoral and popliteal veins, is shown in **Figure 1**. No difference in the frequency and timing of normalization was recorded between the common femoral and the popliteal veins (P=.22). CUS test normalisation in both venous segments occurred in 30% of patients within 1 year. In no patients with normalized CUS results did the test revert to abnormal during follow-up in the absence of symptomatic DVT recurrence.

**Figure 2** shows the evolution of the residual vein diameter during vein compression, separately for the common femoral and the popliteal veins. A statistically significant reduction (P<.0001) was recorded both in the popliteal and in the common femoral veins throughout the entire study period. However, a major reduction of thrombus mass (62% in the common femoral and 50% in the popliteal veins) occurred within the first 3 months of follow-up.

**Interobserver agreement**

In the series of 100 consecutive ultrasound assessments in which the evaluation of a second independent observer was obtained, the test interpreta-
Figure 1 – Graph showing the cumulative incidence of normalised compression ultrasound test results separately for the common femoral and the popliteal veins.

Recurrence of DVT

During the study period, 29 patients developed symptoms suggestive of DVT recurrence. In 5, the clinical indications arose within 1 to 3 months of follow-up, in 11 within 3 to 6 months, in 6 within 6 to 12 months, and in the remaining 7 patients later.

In 11 patients (38%), phlebography showed a recurrent DVT: among them, 1 isolated distal and 10 proximal and distal thrombosis (involving the popliteal and the superficial femoral veins in 3, the iliofemoral tract in 2, and all the proximal venous system in the remaining 5) were recorded. In the remaining 18 patients, phlebography (alone or combined with radiofibrinogen uptake test) could exclude the development of recurrence of DVT.
Figure 2 – Bar graphs showing evolution of thrombus mass over time (ultrasound measurement of the residual vein diameter during compression) separately in the common femoral and the popliteal veins

Of the 29 patients with suspected DVT recurrence, CUS had already normalized in both the popliteal and the common femoral veins in 6 (20.7%; 95% CI, 8.0 to 39.7%) and reverted to abnormal in the 3 patients with proximal DVT recurrence (sensitivity and specificity, 100%). In all 10 patients with confirmed proximal recurrence of DVT, the ultrasound test demonstrated non-compressibility of a previously normal(ised) popliteal or common femoral vein and/or an increased vein diameter (≥2 mm) compared with the previous assessment (sensitivity of the combined CUS and thrombus thickness methods to proximal recurrence of DVT, 100%; 95% CI, 69% to 100%). In the patient with isolated calf recurrence of DVT, the test was unchanged compared with the previous assessment (sensitivity to all DVT recurrences, 91%; 95% CI, 59% to 100%). In all 18 patients without recurrence of DVT, the ultrasound test demonstrated an unchanged or improved residual vein diameter compared with the previous ultrasound assessment (specificity, 100%; 95% CI, 81% to 100%).
In the 7 patients in whom the thrombus thickness determination confirmed the diagnosis of recurrent proximal-vein thrombosis, the vein diameter was found to be enlarged by 2 mm in 1 patient, by 3 mm in 2 patients, and by ≥4 mm in the remaining 4 patients.

In all 24 patients who developed clinical indications of recurrence of DVT after at least 3 months of follow-up, the ultrasound assessment performed at the time of suspected recurrence could have been interpreted correctly by comparison with that recorded at the 3-month follow-up visit.

Discussion

The management of patients who develop clinical manifestations suggestive of recurrent venous thrombosis still need a practical and generally acceptable solution. Clinical diagnosis is indeed unreliable, and there is general agreement on the need to perform objective tests to make management decisions for patients with recurrent leg symptoms. Contrast venography, the gold standard for the diagnosis of acute venous thrombi, presents serious limitations in this context, because it is difficult to visualize a constant intraluminal filling defect (the diagnostic hallmark) in vessels that have been obliterated by the previous thrombotic process. Serial impedance plethysmography alone and the combination of radiofibrinogen leg scanning with impedance plethysmography are the only reliable alternative strategies. However, the latter approach is rather complicated and thus is applicable only in academic centres. Serial plethysmography is available only in a limited number of hospitals and can be applied only in patients with an already normalized test result. Moreover, its accuracy has recently been questioned even in patients with the first clinical indications of DVT. The implication of the lack of a practical diagnostic approach is that up to 70% of patients with non-thrombotic disorders are incorrectly labelled as affected by a recurrent episode of DVT and thus receive an unnecessary new course of long-term (often lifelong) anticoagulant therapy.

Real-time B-mode ultrasonography, applying the single criterion of full compressibility of the common femoral and the popliteal vein, has been shown to be a highly accurate, objective, and reproducible method for the detection of acute proximal-vein thrombosis in symptomatic patients. To be useful in patients with suspected DVT recurrence, however, the test should revert to normal in a substantial proportion of patients before symptoms recur. Available information in small samples of patients suggests that up to 50% of previously
abnormal CUS tests do not normalize during long-term follow-up.\textsuperscript{6,9} Both our cross-sectional survey and our prospective investigation in large series of patients, assessing frequency and timing of normalization of this test in patients with proximal DVT, confirm these data. The CUS test, indeed, normalized in only 30\% of patients with proximal-vein thrombosis within 1 year, when the expected incidence of DVT recurrence is notoriously higher.\textsuperscript{14,16} Moreover, in contrast to data recently reported,\textsuperscript{9} no difference in the normalization rate between the common femoral vein and the popliteal vein was recorded. As expected, only six (21\%) of the 29 patients presenting with new clinical symptoms had an already normalized CUS test and therefore could have been managed correctly with the CUS method alone. This rate is far lower than that reported for the serial IPG approach (about 80\%).\textsuperscript{14} Consequently, repeated CUS test using the single qualitative criterion of presence or absence of full compressibility is of small clinical utility for the diagnostic management of patients with recurrent DVT.\textsuperscript{9}

Two recent ultrasound studies indicated that in patients with an acute proximal-vein thrombosis the thrombus mass decreases progressively in the first months after the initial episode.\textsuperscript{7,10} Our study was designed to verify whether the precise quantification of thrombus regression could help in recognizing patients with new thrombotic episodes. Previous experiences in large series of patients with recurrent proximal DVT, diagnosed with repeated phlebography,\textsuperscript{11,12} suggested that the apposition of fresh thrombotic material to the preexisting clot follows the anatomical distribution pattern observed in the first episode,\textsuperscript{15} involving the common femoral vein, the popliteal vein or both. Therefore, we assumed that in the presence of a recurrent thrombotic episode, the residual thrombus mass enlarged and that the enlargement would be measurable by application of the ultrasound procedure to the common femoral and the popliteal veins only.

Our results support this hypothesis. By measuring the residual vein diameter at scheduled times, we were able to record in all patients a gradual decrease of thrombus mass in both the common femoral and the popliteal veins. Interestingly, in most patients we observed a substantial thrombus reduction (>50\%) in the first 3 months. Finally, in no patient was an enlargement of thrombus mass recorded during the follow-up in the absence of symptomatic recurrences.

In all patients with proximal DVT recurrence, as demonstrated by phlebography, ultrasound showed a non-compressibility of a previously normal(ised) popliteal or common femoral vein and/or an increased vein diameter (≥2 mm)
compared with the last assessment. In all patients in whom venography (alone or combined with leg scanning) could exclude a new proximal thrombotic process, the residual vein diameter was unchanged or improved. As a result, the addition of the thrombus thickness determination to the CUS method allowed a correct diagnosis in 100% of patients we investigated during the study period because of new symptoms.

A few limitations could compromise a widespread clinical use of the ultrasound technique described here in patients with suspected DVT recurrence. They deserve a careful analysis. First, the method is limited by the need to have an antecedent test for comparison at the time of new leg symptoms. This limitation is presented also by the serial ICG approach, which, in addition, has the disadvantage of being applicable only in patients in whom the test has already normalized," whereas the combination of CUS and thrombus thickness determination has the potential to allow a correct approach in all cases. Note, however, that in all 24 patients who developed clinical indications of DVT recurrence after at least 3 months of follow-up, the ultrasound assessment performed at the time of suspected recurrence could have been interpreted correctly by a simple comparison with that recorded at the 3-month follow-up examination. Therefore, it is possible that two assessments with ultrasound only (after 1 and 3 months) are sufficient to identify correctly all patients with an episode of recurrent proximal-vein thrombosis. This hypothesis should be tested in a properly designed prospective trial.

Second, the tiny echographic separation between patients with and without a new episode of proximal thrombosis raises the question of the consistency of the method and of its reliability in the hands of untrained operators. Because of the resolution power of the machine, we accepted an interobserver variability of ±1 mm. This resulted in a high reproducibility of the thrombus thickness method. In fact, in a consecutive series of 100 ultrasound assessments in asymptomatic patients in which evaluations by two independent observers were obtained, the $\kappa$-function was excellent (0.95). Note that in all asymptomatic patients in whom an echographic enlargement of 1 mm was observed, the subsequent follow-up did not disclose any thromboembolic event, even without anticoagulation. Moreover, in all 18 symptomatic patients in whom venography (alone or combined with leg scan) ruled out a new proximal thrombotic episode, the examiner did not detect ultrasound variation >1 mm (specificity, 100%; 95% CI, 81% to 100%). Because of the accepted limits of the interobserver variability, however, it should be noted that the application of this criterion raises the distinct possibility that enlargements up to 2 mm may
not represent a new thrombus. Conversely, an ultrasound enlargement of 1 mm (regarded as non-recurrence) incurs the theoretical risk of missing a deposition of fresh fibrin as large as 3 mm. In our limited experience, in all symptomatic patients but one in whom phlebography showed a new proximal thrombotic episode, the examiner detected an enlargement of the vein diameter of at least 3 mm (unequivocal variation), and in the remaining patient, an enlargement of 2 mm (sensitivity to proximal DVT recurrences, 100%; 95% CI, 69% to 100%). These findings are in agreement with those of our previous phlebographic experiences in large series of patients with recurrent proximal DVT.\textsuperscript{11,12}

They showed that very large new thrombi were usually detectable on the repeat phlebography at the time of the clinical recurrence. However, because of the limited number of patients with true DVT recurrence in the present series, the sensitivity of the ultrasound criteria suggested by us could be as low as 69%.

These considerations have three practical implications. First, our results require validation studies from other centres. Second, ultrasound measurement, both in asymptomatic patients during their follow-up and in cases of suspected DVT recurrence, requires a very careful determination. This makes the service of careful and motivate operators indispensable. Third, the clinical outcomes associated with negative test results require a properly designed investigation.

It should be noted that our results were obtained by simply confining vein examination to the midpopliteal and inguinal regions, in the transverse section only, and by using a real-time B-mode imaging technique, without the need for Duplex or color Doppler facilities. It is questionable whether the use of more expensive new methods, such as color Doppler, can improve the accuracy or the reliability of real-time B-mode ultrasonography in this setting. Proper investigations in symptomatic patients are lacking.\textsuperscript{4} To the best of our knowledge, only one adequate study is available in asymptomatic high-risk patients, showing an unacceptably low sensitivity and clinical utility of color Doppler for detection of proximal-vein thrombosis.\textsuperscript{19} As a result, there is no room to expect a substantial refinement of the ultrasound strategy with color Doppler in patients with suspected DVT recurrence.

Selection bias was prevented in our study by enrolling consecutively in our investigation all symptomatic patients referred by their practitioners and by performing both the ultrasound approach and phlebography in all patients with suspected recurrence of DVT. The incidence of suspected DVT recurrence (20%) and the prevalence of new thrombotic episodes (38%) are in agreement with those reported in the literature.\textsuperscript{14,15} Observation bias was prevented by per-
forming the ultrasound technique before phlebography in all patients with suspected recurrence and by having an independent and blind interpretation of both diagnostic techniques.

In summary, measuring the thrombus mass at scheduled times after an acute episode of venous thrombosis is most likely to allow a correct identification of patients who develop a proximal recurrence of DVT by comparing the residual vein diameter at the time of new leg symptoms with that recorded in the previous examination. An unchanged or improved ultrasound test essentially excludes such an eventuality. However, it does not exclude the isolated involvement of the calf vein system. Therefore, the safety of withholding anticoagulation in patients presenting with clinical indications of DVT recurrence and an unchanged or improved ultrasound finding should be tested in a management study, repeating this test serially and evaluating prospectively the clinical outcome of patients considered as not having a new thrombotic episode.

References


