Thrombus Regression in Deep Venous Thrombosis

Quantification of Spontaneous Thrombolysis With Duplex Scanning

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Background. Thrombus regression in heparin-treated, acute deep venous thrombosis of the lower extremity is poorly documented in the literature; different rates of thrombus resolution and recanalization are reported.

Methods and Results. In a prospective follow-up study, duplex scanning was used to evaluate the thrombus regression in patients with documented acute femoropopliteal thrombosis. Eighty vein segments in 20 legs of 18 patients were subjected to repeat duplex scans at 1, 3, 6, 12, and 26 weeks after diagnosis; 49 segments showed thrombus at diagnosis. The popliteal vein showed the highest thrombus load at diagnosis, followed in descending order by the superficial femoral, profunda femoris, and common femoral vein segments (p<0.001). Thrombus regression was significant (p<0.001) in all segments and proceeded at an exponential rate that was equal in the different vein segments of the upper leg. Both thrombus resolution and recanalization appeared to be a function of the initial thrombus load and could not be related to individual vein segments. Recanalization was seen in 23 of 31 initially occluded segments and occurred within the first 6 weeks after diagnosis in 20 of 23 segments. Extension of thrombus despite anticoagulant therapy was observed in 15 vein segments and was not related to the initial thrombosis score (p=0.1) or individual vein segments (p=0.23). Thrombus extension in seven patients with prethrombotic conditions was not different (p=0.9) from the other patients.

Conclusions. Duplex scanning is an important noninvasive tool to quantify thrombus regression in acute deep venous thrombosis in detail without unnecessary discomfort to the patient. (Circulation 1992;86:414–419)

Key Words • thrombosis, acute femoropopliteal • duplex scanning • thrombus regression

The treatment of deep venous thrombosis (DVT) is primarily directed at the prevention of propagation of the thrombus and of the occurrence of life-threatening pulmonary emboli. Venous valvular incompetence caused by valve destruction or venous hypertension is thought to be responsible for late venous insufficiency associated with the disabling postthrombotic clinical manifestations of pain, leg edema, ulceration, and hyperpigmentation.1–6 The use of heparin alone has been of significant benefit in decreasing the mortality of DVT-induced pulmonary embolism but has been of limited value in lysis of thrombi. Thrombolytic therapy has been shown to be more successful in thrombus resolution when compared with standard heparin treatment8,9 and may preserve venous valvular function and prevent postthrombotic sequelae.10

Follow-up studies of DVT documented in the literature are primarily based on repeat phlebographic examinations carried out at various intervals ranging from months to years, and different rates of thrombus resolution and recanalization are reported.3,11–15

Duplex scanning, combining B-mode imaging and Doppler measurements, is presently gaining wide acceptance as the noninvasive test of choice in the diagnosis of DVT of the lower extremity.16 The experience with duplex scanning gained in our vascular laboratory has been reported recently.17

The aim of the present prospective follow-up study was to assess the spontaneous regression of thrombi in patients with acute femoropopliteal thrombosis treated with heparin. Two main questions were addressed: 1) What is the rate of change over time? 2) Do these changes differ between various vein segments?

Methods

Patient Selection

Twenty legs in 18 patients with a diagnosis of acute femoropopliteal thrombosis confirmed by conventional contrast phlebography and ultrasonic duplex scanning were submitted to repeat duplex scans at 1, 3, 6, 12, and 26 weeks after initial diagnosis. The patients were selected from a previously reported group of 64 patients with DVT of the lower extremity.17 The distribution of
thrombus at diagnosis in the study group (Figure 1) was comparable to the thrombus distribution in the whole group of 64 DVT patients. The study group included 12 female and six male patients with a mean age of 50 years. Thrombosis was seen postoperatively and after prolonged immobilization in nine patients, occurred spontaneously in seven patients, and was related to pregnancy in two patients. Two patients in the study had a history of calf vein thrombosis but showed clear signs of fresh rethrombosis on phleboraphic examination.

**Treatment**

All patients received treatment according to a standard protocol starting with an initial intravenous heparin bolus of 70 units/kg followed by continuous intravenous heparin infusion at a dose of 400 units/kg/24 hr and adjusted to maintain the activated partial thromboplastin time (APTT) at three to four times control. Heparin was continued for 7–10 days and followed by a maintenance dose of oral coumarin derivatives for a period of at least 3 months. One pregnant patient was treated with intravenous heparin according to this protocol followed by subcutaneous heparin in a dosage of 5,000 units twice daily.

**Duplex Examination**

The venous duplex scanning was performed with an ATL Ultramark 4 scanner with a 5-, 7.5-, or 10-MHz imaging probe, in conjunction with a 5-MHz pulsed Doppler. Venous segments studied included the common femoral, superficial femoral, profunda femoris, and popliteal veins. The popliteal vein was examined with the patient in the prone or lateral decubitus position with the knee slightly flexed to prevent compression of the vein. The other veins were scanned with the patient in supine position. The entire length of individual segments was scanned. Diagnostic criteria for thrombosis were visualization of thrombus with B-mode, incompressibility of the vein wall with probe pressure, and abnormal Doppler signals (i.e., no spontaneous, augmentable, or phasic flow).

**Thrombosis Scoring**

The distribution of thrombus throughout the four vein segments examined at each follow-up visit was expressed in a thrombosis score modified from Porter et al.,

using the following grades per vein segment: 0, patent vessel lumen; 1, (sub)segmental nonocclusive thrombus; and 2, (sub)segmental occlusive thrombosis.

Regression of thrombus was defined as a decrease of the thrombosis score; propagation of thrombus was defined as an increase in the thrombosis score. Recanalization was defined as a change from (sub)segmental occlusion, score 2, to partial occlusion or patent vessel lumen, scores 0 or 1.

**Laboratory Methods**

All patients had blood examinations to determine proteins C and S and lupus anticoagulant. Protein C was measured by electroimmunoassay of pooled plasma using rabbit anti–protein C serum, and protein S measurements were measured by immunoradiometric assay for protein S antigen. Lupus coagulant determination was done by APTT test with a commercially available reagent (PTTAs, Boehringer-Mannheim) with high and low phospholipid concentration and 1:1 dilution of normal plasma, with measurements direct and at 2 hours of incubation.

**Statistics**

The pattern of change in different vein segments over time was evaluated by a repeated-measures analysis with a Markov chain model. The thrombosis scores at the beginning and the end of each interval were depicted in a matrix. The comparison between matrices allows the accurate statistical analysis of the disease progression and regression. Logistic regression with a continuation ratio model was used to evaluate differences between various vein segments. Where appropriate, χ² analysis was performed. Statistical significance was defined as p<0.05.

**Results**

The study population consisted of 18 patients with an established diagnosis of lower limb DVT. In two patients, thrombosis was present in two legs. Four segments were studied in each affected leg. The distribution of thrombosis in the study population at diagnosis is shown in Figure 1. Thrombosis was present in 49 of 80 vein segments and was distributed as follows: common...
femoral vein (CFV), 10 of 20; profunda femoris vein (PFV), five of 20; superficial femoral vein (SFV), 16 of 20; and the popliteal vein (PV), 18 of 20 segments. Four-segment involvement was seen in 20% of the legs studied, and single-segment disease confined to the popliteal vein was found in three legs (15%). A breakdown of results by individual vein segments shows the following.

**Common Femoral Vein**

At diagnosis, thrombosis was present in 10 of 20 segments studied. Seven segments were rated as score 2 and three segments as score 1. Six of the seven occluded segments (score 2) recanalized. Residual lesions at 6 months were seen in seven of 10 segments. The frequency distribution of the thrombosis scores 0, 1, and 2 at various intervals is shown in Figure 2. Thrombus propagation was seen in five patients in the 6-month period (Table 1). In one case, this occurred in a previously affected segment. In the other four cases, fresh thrombus was observed in the previous patent vein segment, leading to occlusion in two patients. The Markov matrices depicting the frequency-shift of the thrombosis scores 0, 1, and 2 per interval are presented in Table 2. A comparison between the matrices showed no significant difference in the pattern of change between intervals ($\chi^2 = 18.99; p=0.75$). The increasing time interval between subsequent follow-up examinations suggested an exponential thrombus regression rate, which was confirmed by logistic regression. The decrease in thrombus was significant ($p<0.001$).

**Profunda Femoris Vein**

The PFV was the initially least affected segment. At diagnosis, three of the 20 segments had a thrombosis score of 2, two were rated as score 1, and the other 15 were not affected (score 0). All three occluded segments recanalized (Figure 2). Residual lesions at 6 months were seen in two of five affected segments. Thrombus propagation occurred in two patients during the first 2 weeks.

**Table 1. Propagation of Thrombus by Segment**

<table>
<thead>
<tr>
<th>Segment</th>
<th>0–1 Week</th>
<th>1–3 Weeks</th>
<th>3–6 Weeks</th>
<th>6–12 Weeks</th>
<th>12–26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common femoral vein</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Profunda femoris</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Superficial</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>2 (1)</td>
<td>1</td>
<td>1</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Totals</td>
<td>5 (4)</td>
<td>2 (1)</td>
<td>1</td>
<td>3 (3)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

Number of vein segments showing increase of thrombosis score per interval. Numbers in parentheses represent propagation into previously unaffected segments.

**Table 2. Matrices of Change in the Common Femoral Vein**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Score at start of interval</th>
<th>Score at end of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 Week</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1–3 Weeks</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3–6 Weeks</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6–12 Weeks</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>12–26 Weeks</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Row totals represent number of patients with score 0, 1, or 2 at the beginning of the interval. Individual numbers per row represent change in thrombosis scores 0, 1, and 2 during the interval; column totals represent number of patients with score 0, 1, or 2 at the end of the interval; row total of each matrix corresponds with the column total of the previous matrix. Matrices read as follows: At time 0 (interval 0–1 week), 10 segments have thrombosis score 0 (row total score 0). At 1 week, nine of these segments remain unchanged and one segment increases to score 1. At the end of the first interval, 10 segments still have thrombosis score 0 (column total score 0), nine of which had a score 0 at the beginning of the interval and one segment with score 2. The same applies for scores 1 and 2. Analysis of change in time between matrices is not significant ($\chi^2, p=0.75$).
TABLE 3. Matrices of Change in the Profunda Femoris Vein

<table>
<thead>
<tr>
<th>Interval</th>
<th>Score at start of interval</th>
<th>Score at end of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0–1 Week</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1–3 Weeks</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3–6 Weeks</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6–12 Weeks</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>12–26 Weeks</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Analysis of change in time between matrices is not significant ($\chi^2, p=0.99$).

three weeks (Table 1). The thrombus regression in the PFV over time is presented in Table 3. The decrease in thrombus load was significant ($p<0.001$) and showed an exponential rate of change similar to the CFV.

Superficial Femoral Vein

At diagnosis, thrombosis was seen in 16 of 20 segments studied. Eleven segments were rated as score 2, and five had a score of 1. Recanalization occurred in eight of 11 segments, whereas residual lesions were seen in 12 of 16 affected segments (Figure 2). Propagation of thrombus was seen in one patient; during the first week, a partially occluding thrombus occurred in a previously unaffected segment. Table 4 shows the Markov matrices of thrombus regression for the SFV. A significant regression ($p<0.001$) of thrombus was found, which proceeded at an exponential rate.

Popliteal Vein

The PV segment was the initially most affected segment. Thrombosis was diagnosed in 18 of 20 segments. Ten segments had a score of 2; eight were rated as score 1. Recanalization occurred in six of 10 occluded segments (Figure 2). Residual lesions were seen in 11 of 18 affected segments. Extension of thrombosis was seen in seven segments. A significant exponential decline ($p<0.001$) in thrombus load was observed (Table 5).

Statistical Analyses and Laboratory Studies

With logistic regression analyses, the thrombus load of the different vein segments at diagnosis and subsequent follow-up examinations were significantly different ($p<0.001$). Despite the differences in the extent of initial thrombus in various vein segments, the exponential rate of thrombus regression in all vein segments of the upper leg proved to be equal over time. No difference could be shown between the rate of thrombus regression in partially or totally occluded vein segments and an equal percentage (40% of the vein segments in both groups showed complete lysis).

Recanalization was seen in 23 of 31 (75%) initially occluded segments and is represented reciprocally in Figure 2C. Recanalization progressed at a similar rate in the four vein segments under study ($p<0.001$). In 20 of 23 segments (87%), recanalization occurred within 6 weeks after diagnosis.

Propagation of thrombus was observed in 15 vein segments and could neither be related to the individual vein segment ($p=0.23$) nor to the initial thrombosis score ($p=0.1$) of the affected segments. Thrombus propagation occurred in four previously affected segments (Table 1), whereas extension into proximal or distal segments was observed in 11 cases. Increase in thrombus, whether in previously affected or unaffected vein segments, was limited in all except one case to a
one-point increase of the thrombosis score. In none of the patients was extension of thrombus associated with clinical evidence of embolic sequelae. In only two cases, proximal extension of thrombosis resulted in subsegmental occlusion of a previous patent common femoral vein.

Laboratory studies identified two patients with protein C and protein S deficiency, respectively, and one patient with a circulating lupus anticoagulant. In two more patients, recurrent thrombosis was present. The frequency of thrombus propagation in this subgroup of patients was not different \( (p=0.9) \) from the other patients.

**Discussion**

The standard treatment of DVT is anticoagulation with intravenous heparin, which itself has no fibrinolytic activity but prevents further coagulation while allowing the body's natural thrombolytic system to act on the existing clot. In vivo studies in humans have described substantial resolution of pulmonary emboli within hours to days after embolization. The mechanism of canalization of thrombus in DVT of the lower extremity was excellently described by Cox and Sevitt, but no mention was made of the rate of thrombolysis in different vein segments. Lea-Thomas and McAllister found recanalization to be more frequent in calf vein thrombosis than femoral vein thrombosis, whereas Bergvall and Hjelmstedt reported the opposite with better recanalization in proximal vein thrombosis. Recanalization, according to the literature, is considered a late reaction occurring in up to 70% of affected limbs in periods ranging from 6 months to many years.

Our study showed an exponential thrombus regression rate equal for all vein segments of the thigh, despite a significant difference in initial thrombus load between the different vein segments. The amount of residual disease, although considerable in individual segments (SFV, PV) and the degree of recanalization, are therefore merely a function of the initial thrombus load and are not specifically segment related. The process of recanalization was shown to be confined mainly to the first 6 weeks after thrombosis and showed little progression afterward. Our observations confirm the report by Killichew et al., which showed recanalization of thrombus in lower-limb DVT not to be the slow process suggested in the past.

Few studies to date have used B-mode or duplex scanning in the assessment of the natural history of DVT. Our study is the first to describe thrombus regression in different vein segments in a quantitative manner using duplex scanning in combination with a thrombosis scoring system, which avoids subjective estimation of treatment results and allows the comparison of different patient groups over time. Our data provide a baseline regarding thrombus regression in heparin-treated DVT and may act as reference in the evaluation of other treatment regimens, i.e., thrombolysis.

Our study was limited to the femoropopliteal vein segment by the use of a conventional duplex scanner. The accuracy of conventional duplex scanning for diagnosing clinically suspected DVT of the femoropopliteal veins is well established, but the ability to detect thrombi in the calf and iliac vein area is more problematic. Color-flow imaging facilitates the identification of vascular structures, especially of the infrapopliteal veins, and its application will allow further study of proximal and distal vein segments.

The natural course of venous thrombosis is threefold; the initial loose thrombus becomes adherent to the vein wall by the end of the first week. The local inflammatory response of the vessel wall initiates the organization of thrombus with subsequent contraction, and spontaneous lysis of areas within the thrombus finally leads to recanalization. Thrombus regression as defined in our study reflects the overall outcome of these processes. Clearance of thrombus is a gradual process, which on B-mode imaging is depicted by an increase in vein wall compressibility. The Doppler flow measurements show a gradual change from no flow in the totally occluded segment, through augmentable flow on distal compression and continuous flow in the partially obstructed lumen, to a return of phasic flow in the segment with fully regained patency. Duplex scanning cannot differentiate whether the changes are due to lysis or organization. However, recanalization of an occluded vein segment, defined in our study by a change in thrombosis score from 2 to <2 at all times and by definition represents true lysis, either alone or in combination with retraction and organization.

In our opinion, B-mode imaging and Doppler measurements are equally important in the follow-up of DVT by duplex scanning. Vessel wall compressibility with B-mode will exclude thrombosis or indicate thrombus resolution in previously affected areas, whereas the Doppler examination is essential in differentiating between patency and partial or total obstruction of the vessel lumen.

If one considers the development of late venous insufficiency to be the result of direct damage to the valve cusps by thrombus, the more severe thrombotic insult in vein segments showing a higher percentage of residual lesions might be expected to induce more late valvular incompetence in these segments. The development of reflux after DVT will be the subject of a separate report.

Propagation of thrombus at different intervals during treatment found in a number of patients in our study has been reported by others. An increase in the thrombosis score in partially occluded vein segments (thrombosis score of 1) within the first weeks after diagnosis may in part reflect a progressive occlusion of the vein lumen caused by increased thrombus adherence and retraction; however, extension into previously unaffected segments represents true addition of thrombus to the existing load. An increase of thrombus might suggest the inadequacy of our current treatment protocol for continuous heparin infusions or insufficient monitoring of the plasma prothrombin time in coumarin-treated outpatients. In a recent study, Krupski et al. reported propagation of thrombus in one third of nine adequately anticoagulated patients, thus indicating that thrombus propagation is not necessarily synonymous with treatment failure. It seems likely, therefore, that although the level of anticoagulation in a patient can be satisfactory, the effectiveness of the anticoagulant on the thrombus may vary, depending on local factors such as the degree of occlusion of the vein and the presence of collaterals. Other possible explanations
of thrombus propagation include heparin-induced thrombocytopenia, which in our patients could be rejected on clinical grounds, and heparin-induced inhibition of endogenous fibrinolysis. If the latter were true, the occurrence could only be incidental; otherwise, its effect would have been shown as a generalized increase in the early thrombosis scores.

Thrombus propagation could not be related in our study to factors associated with recurrent thromboembolism such as a history of DVT or prethrombotic conditions.

The increase in thrombus remains a puzzling phenomenon of which the clinical significance remains as yet unclear. Thrombus propagation in our study was minor in 96% of the cases, with an increase of the thrombosis score of one point only in all except one case. Moreover, propagation did not influence the outcome in our patients, as no clinical evidence of embolic sequelae was found.

Conclusions

The results of our study do not justify a plea for a more aggressive treatment of DVT or a more intensive monitoring of patients during follow-up. Our study unequivocally shows, however, the potential of duplex scanning in the follow-up of individual patients and the possibility to define patients with aggressive extension of thrombus. As a research tool, duplex scanning may help to identify factors associated with rethrombosis and provide the opportunity to assess new therapeutic agents in the treatment of DVT in greater detail through sequential studies without unnecessary discomfort to the patient.

References

Thrombus regression in deep venous thrombosis. Quantification of spontaneous thrombolysis with duplex scanning.
B van Ramshorst, P S van Bemmelen, H Hoeneveld, J A Faber and B C Eikelboom

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