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Early Thrombus Remodelling of Isolated Calf Deep Vein Thrombosis

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Objective: *this prospective study was designed to evaluate the evolution of thrombus propagation and lysis in relation to patterns and distribution of isolated calf DVT.*
Methods: *fifty-two limbs in 48 patients mean age 59 ± 15, range 24–78 years, with isolated calf DVT that had at least one exam within 10 days of DVT detection were included in the study. Patients with a documented episode of prior DVT or evidence of post-thrombotic changes during the initial ultrasound exam were excluded. The initial thrombus length, patterns and location of the thrombi were recorded. On follow-up the propagation and lysis patterns of the clot were studied.*
Results: *remodelling of the thrombus, excluding echotexture and vein diameter changes on ultrasound, occurred in 23 limbs, (44%). Ascending propagation only was seen in seven limbs (13%) descending propagation only in two (4%) and in both directions in five (10%). Propagation at least to popliteal vein was detected in seven limbs (13%). Thrombus developed or extended to initially uninvolved veins in six limbs (12%). Pulmonary embolism developed only in one patient (2%; 95% CI: 0–11%). The site and the size of thrombus or the number of veins involved in the baseline exam did not correlate with the remodeling of thrombus. Soleal and gastrocnemial veins were comparable with the posterior tibial and peroneal veins in terms of thrombus propagation and lysis.*
Conclusions: *early thrombus remodelling occurs in 44% of limbs with isolated calf DVT. This includes ascending and descending thrombus propagation and lysis. Thrombus development or propagation to initially uninvolved calf veins is found in 12%. Thrombus remodelling does not appear to be related to size, site and patterns of thrombosis.*

Key Words: Calf vein thrombosis; Thrombus remodelling; Duplex scanning.

Introduction

Several studies have demonstrated that many lower limb thrombi develop in the deep calf veins.[1,2] About half of symptomatic patients have calf deep vein thrombosis (DVT).[3–5] Although, significant pulmonary embolism (PE) is rare in patients with isolated calf DVT, propagation of thrombus into proximal veins and postthrombotic sequelae are more common.[6–11]

Because of this and in the absence of any definitive study on treatment of isolated calf DVT its management remains controversial.

With the advent of colour flow duplex scanning (CFDS) our knowledge on natural history of DVT has increased. Recanalisation, reflux development and rethrombosis have been studied in the proximal veins.[12–18] However, there is limited information on thrombus remodelling and patterns of propagation in patients with isolated calf DVT. This prospective study was designed to evaluate the evolution of propagation and thrombus remodelling in relation to patterns and distribution of isolated calf DVT.

Patients and Methods

Fifty-two limbs in 48 patients, 23 male and 25 female, mean age 59 ± 15, range 24–78 years, with isolated calf DVT that had at least one repeat exam within 10 days of DVT detection were analysed. Patients were recruited from two different centres. They would have been consecutive patients if nine were not excluded, as they did not come for their second scan. Patients' characteristics are shown in Table 1. Eighty-five percent of the second scans were performed 4–7 days after the baseline examination. The second scan was done as a part of their treatment protocol, worsening of their symptoms or simply ordered by the patients' physicians. All patients had symptoms of swelling, tenderness, burning sensation and pain alone or in

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Table 1. Patients' history and treatment.

48 patients		
22 inpatients		26 outpatients
Surgical 13	Medical 9	Cancer 4
Trauma 2	Cancer 3	Trauma 3
Orthopaedic 3	MI 2	Recent surgery 4
Abdominal surgery 6	COPD 1	Pregnancy 2
Cardiac bypass 1	Stroke 2	Long flight 1
Neurosurgery 1	Infection 1	Long drive 1
		CHF 1
		Nothing 10
19 Heparin and coumadin		29 other
UH 15		Aspirin 7
LMWH 4		Elastic stockings 4
		Both 15
		Nothing 3

Elastic stockings were used by 41 patients.
MI: myocardial infarction, COPD: chronic obstructive pulmonary disease.
CHF: chronic heart failure, UH: unfractionated heparin, LMWH: low molecular weight heparin.

combination. Patients with a thrombus in the popliteal vein or higher, an episode of DVT documented by CFDS or venography or evidence of post-thrombotic changes (old thrombus, partial recanalisation and luminal narrowing with wall thickening) during the initial ultrasound exam were excluded. Treatment with heparin and coumadin was given non-randomly at the physician's discretion for patients with isolated calf DVT. However, anticoagulation was always instigated on proximal propagation involving at least the popliteal vein. Data were entered prospectively in a customised database.

Duplex scanning

Duplex scanning was performed using the 4–7 MHz linear array transducer of an ATL, HDI 3000 scanner (Bothell, WA, U.S.A.). All scans were performed by registered vascular technologists with at least 18 months experience in the imaging of calf veins prior to the study. The examination technique for the proximal and the calf veins is similar to conventional duplex scanning and has been described previously.[19,20] The femoropopliteal segment and the proximal deep femoral vein were scanned by the compression technique using gray-scale transverse scanning and by the colour flow technique using both transverse and longitudinal imaging. The calf veins (tibioperoneal trunk, posterior tibial, peroneal, gastrocnemial and soleal veins) were imaged individually in both longitudinal and transverse planes from ankle to knee. When the imaging of the popliteal and calf veins was not optimal in the inclined position the examination was performed with the leg in the dependent position. Augmentation of blood flow by distal manual compression was frequently used to visualise the calf veins and the femoropopliteal segment. Using this technique the sensitivity, specificity, and overall diagnostic accuracy of duplex scanning for detecting calf DVT in our hands compared to venography were over 87%.[19]

The initial thrombus length, patterns and location of the thrombi were recorded. On follow-up, distal and proximal propagation, thrombus development in previously uninvolved vein segment, thrombus lysis and presence of reflux were studied. The echotexture of the thrombus in the different exams was not evaluated because imaging was not accurately standardised to allow such comparisons.

Ventilation/perfusion lung scanning or spiral CT was performed only in patients with symptoms and signs of pulmonary embolism subsequent to the calf thrombosis. Patients symptoms were evaluated one month after the episode of thrombosis. The patients were asked to come for a follow-up visit at one month. For patients that did not come to their appointment mail and phone conversation was used for contact and evaluation of their symptoms.

Data were analysed using descriptive statistics and Chi square test for the difference in proportions among the different groups. Fisher's exact test was used when the expected value in any of the cells was <5. Data are presented as mean, proportions and 95% confidence intervals. The level for statistical significant differences was set at 0.05.

Results

Baseline duplex scanning

Twelve hundred and thirty-five patients were studied for DVT in a period of 13 months. Sixty-five patients (5%), had isolated calf DVT. The total number of patients with DVT was 178 (14%). Proximal DVT only was found in 71 patients that is (40%) among patients with DVT. Proximal and calf DVT was found in 42 (24%), and isolated calf DVT was found in 65 (36%).

Of the 65 patients examined, 17 (26%) were excluded because of a documented episode of prior DVT or evidence of previous DVT at the time of the first duplex scanning exam ($n=8$) or did not come for a repeat scan ($n=9$). Nineteen patients were treated with heparin and coumadin, 22 were inpatients and 26 were outpatients.

Peroneal veins were most often involved, however

the prevalence of thrombosis was comparable among all veins ($p>0.22$ for all comparisons). Thrombus in a single vein segment was the most common pattern (30, 58%) followed by two (14, 27%), three (6, 11%) and four different veins (2, 4%). The length of thrombus varied from 1.2 cm to at least of 3/4 of a vein's extent. The mean thrombus length was 8 cm, 95% CI 4.4–12.8. All thrombi caused complete occlusion of the involved veins with the exception of three patients (6%).

The middle of the calf was involved in 44 limbs (85%) regardless of the vein type. Among muscular veins the middle of the calf was involved in 27/29 limbs (93%). Isolated DVT in the distal third ($n=5$) or proximal third of calf ($n=3$) was seen in 8 limbs (15%).

Follow-up duplex scanning exams

Thrombus propagation or lysis, excluding changes of echotexture on B-mode imaging, occurred in 23 limbs (44%). Thrombus remodelling had occurred in some of the remaining limbs since changes in the diameter of the veins was observed. However, the diameter of the thrombosed and normal vein segments were not measured systematically and therefore such changes were excluded from the analysis. Ascending propagation only was found in seven limbs (13%), descending propagation in two (4%), and in both directions in five (10%). Some degree of thrombus lysis or even complete lysis occurred in six limbs (11%), and both propagation and lysis in 3 (6%). Thrombus development at new site or extension from one vein to another i.e. from soleal to peroneal was seen in six limbs (12%). Extension to popliteal vein or higher was found in seven limbs (13%).

Of the seven patients with proximal extention to popliteal vein or higher two (11%) were already receiving anticoagulation and five (17%) did not ($p=0.28$). One of the two patients on anticoagulation one had an INR at the day of the exam of 1.8 and the other of 2.4. Because of the small sample size no attempt was made to relate other factors with propagation and lysis.

Only 32 patients came for a monthly follow up. Twelve patients replied by mail or on a phone conversation. Four did not reply at all, but were seen in the hospital from 5 to 11 months later for unrelated reasons. Symptoms were improved in 17 patients (35%) in the first week, remained the same in 27 (56%) and became worst in four (8%). At one month 42 patients (87%) were free of any symptoms, four (8%) did not respond and two (4%) were still symptomatic.

Pulmonary embolism

Six patients developed symptoms of pulmonary embolism. There was only one patient with a positive spiral CT (2%; 95% CI: 0–11%). This patient developed PE 7 days after the diagnosis of calf DVT. He was not on anticoagulation and came to the hospital for his repeat duplex scan. He had chest symptoms on that day but he was stable. His thrombus had propagated to the popliteal vein and a spiral CT showed emboli in the right lung. He was hospitalised and put on anticoagulation. He did fine and had no further problems at one month.

Discussion

Several studies have noted that isolated calf DVT leads to pulmonary embolisms on rare occasion.[11,21] Nonetheless, calf DVT is found in a significant amount of acute DVT, which is thought to lead to pulmonary embolism. Investigators have shown rates of PE in patients with calf DVT range from 0–33%.[5,11,22,23] The overall prevalence of isolated calf DVT among acute DVT cases has reportedly ranged from 12–49%.[4,5,24,25] The literature presents peroneal vein thrombosis as the most common isolated calf DVT, followed by the soleal, posterior tibial, and gastrocnemial veins.[8,20] These findings are supported by the current study. Anterior tibial veins were not examined routinely unless there was local trauma or symptoms. Thrombus in these veins has been shown to occur only in combination with other calf veins but almost never alone. In three recent reports, it was shown that the prevalence of isolated anterior tibial vein thrombosis varied from 0–0.3%.[8,11,26]

Proximal extension of thrombus from the deep calf veins to popliteal vein or higher has been shown by a number of authors to range from 4–38%.[3,11,21,27] On follow-up duplex scanning exams, as early as 10 days, we found ascending propagation in seven limbs (13%). Other studies using serial ultrasound scans had similar propagation rates of 13, 15 and 16%.[9,28,29] The clinical significance of calf DVT remains questionable as further study is needed to evaluate the long-term advancement of calf DVT and its relation to clinical syndromes. Undoubtedly, calf DVT shows evidence of progression to proximal veins early in its development. With the increased risk of pulmonary embolism from proximal DVT, questions arise on whether to treat isolated calf DVT before it progresses to a proximal level.

The value of treating patients with anticoagulants

to decrease the chance of progression has yet to be shown. A number of centers, including our own, continue to perform follow up duplex scanning with the purpose of administering anticoagulants if the thrombus progresses to more proximal veins. Because our study was not randomised and the treatment was at the referring physicians discretion, 19 patients received anticoagulation. No statistical significance was observed between patients who received anticoagulation and those who did not. In three different studies thrombus propagated despite treatment in 31%, 16% and 26%.[30–32] Caps *et al.*[32] showed that propagation was inversely related with the time during which the INR ≥ 2.0 and/or heparin concentration ≥ 0.2 IU/ml (Cox proportional hazard analysis, $p = 0.01$). This may indicate that many thrombi continue to extend when anticoagulation is below a therapeutic level. Solis *et al.*[28] have suggested that anticoagulation therapy does not impact propagation rates. Krupski *et al.*[21] showed that of their nine patients with thrombus propagation, six were adequately anticoagulated. Furthermore, there was no correlation between the level of the thrombus and propagation. In the nine patients who did propagate, six occurred on day 3, two on day 5, and one on day 7. Lohr *et al.*[33] found that no patient propagated to proximal veins when heparin was administered. However, only 12% received heparin with no significant differences being detected compared to the non-heparinised group. None of the above studies were randomised or had an adequate sample size. Therefore, further study is needed to determine whether anticoagulants should be administered.

It has been demonstrated that partial or complete thrombus lysis occurs in any proximal vein of most patients within the first 6 weeks after diagnosis.[30] Thrombus lysis has been shown to occur in 50–88% of limbs with calf DVT within 3 months.[11,13,29,34] Meissner *et al.*[9] reported that 50% of his subjects with calf DVT presented with a decrease in mean thrombus load by 1 month. Caprini *et al.*[34] showed that 8% of patients with calf DVT resolved at 1 week and overall 50% had a reduction in thrombus load. This included vein segments that decreased in size but had no evidence of lysis. In our study, partial or complete lysis at 10 days occurred in six limbs (12%) and both propagation and lysis in three (6%). The rate of lysis was lower as a result of the shorter follow-up and the excluded vein segments that had simply a change in their diameter. Thrombus load reduction as measured by diameter decrease was excluded in our study, because of the lack of systematic evaluation of the diameter of thrombosed vein segments. One other reason would be that diameter reduction might reflect thrombus contraction and/or lysis together. The site of thrombosis did not influence lysis or propagation rate. Muscular veins had a similar rate of propagation and lysis as compared to the peroneal and posterior tibial veins. Although many studies have been reported on calf DVT propagation, only one paper examined the role of location with rate of propagation. In that report the soleal veins had the highest incidence of propagation.[27] Given the current information, muscular veins should be examined routinely.

Propagation and lysis was uncommon but in the few cases that occurred indicates that local factors are responsible for these phenomena. The balance between coagulation and fibrinolysis may be tipped on either side at two different locations of a thrombosed venous segment. Lysis occurred at proximal and distal ends of thrombi and at vein confluences. This was probably due to the local flowing blood that could probably offer tPA released from adjacent endothelial cells. Killewich *et al.*[31] demonstrated that thrombus regression was associated with enhanced fibrinolysis as tPA activity was increased in these patients.

Conclusions

Early thrombus remodelling occurs in 44% of limbs with isolated calf DVT. Most often propagation occurs in an ascending direction but descending extension is also seen. Thrombus development or propagation to initially uninvolved calf veins is found in 12%. Lysis or simultaneous propagation and lysis are uncommon at this stage. Thrombus remodelling does not appear to be associated with the size, site and patterns of thrombosis.

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