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Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg

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ABSTRACT

Accurate diagnosis of acute recurrent deep vein thrombosis (DVT) is relevant to avoid improper diagnosis and unnecessary life-long anticoagulant treatment. Compression ultrasonography has high accuracy for a first episode of DVT, but is often unreliable in suspected recurrent disease. Magnetic resonance direct thrombus imaging (MRDTI) has been shown to accurately detect acute DVT. The purpose of this prospective study was to determine the MR signal change during 6 months follow-up in patients with acute DVT.

This study was a prospective study of 43 consecutive patients with a first episode of acute DVT demonstrated by compression ultrasonography All patients underwent MRDTI. Follow-up was performed with MRDTI and compression ultrasonography at 3 and 6 months respectively. All data were coded, stored and assessed by two blinded observers.

MR direct thrombus imaging identified acute DVT in 41 of 43 patients (sensitivity 95%). There was no abnormal MR-signal in controls, or in the contralateral extremity of patients with DVT (specificity 100%). In none of the 39 patients available at 6 months follow-up was the abnormal MR-signal at the initial acute DVT observed, whereas in 12 of these patients (30.8%) compression ultrasonography was still abnormal.

Magnetic resonance direct thrombus imaging normalizes over a period of 6 months in all patients with diagnosed DVT, while compression ultrasonography remains abnormal in a third of these patients. MRDTI may potentially allow for accurate detection in patients with acute suspected recurrent DVT, and this should be studied prospectively.

INTRODUCTION

In patients with clinically suspected acute deep vein thrombosis (DVT) of the leg objective diagnostic testing, including D-dimer test or ultrasonography, is mandatory because a diagnosis based upon clinical symptoms and signs is nonspecific.[1] Compression ultrasonography (CUS) has consistently shown high diagnostic accuracy (sensitivity and specificity>95%) in the diagnosis of a first episode of proximal DVT of the leg.[2] In patients with established DVT, incomplete compression of the vein on CUS is still present in up to 50% of patients after 12 months follow-up.[3-5] As 15–20% of patients with DVT may develop recurrent episodes of DVT after stopping anticoagulant treatment, CUS has limitations in the diagnostic work-up of patients with clinically suspected recurrent DVT.[6,7] This is especially true when the thrombosis recurs in the previously affected venous segment.

Accurate diagnosis in these patients is of great importance, because recurrent DVT usually is treated by life-long anticoagulant treatment.[8] Magnetic Resonance direct thrombus imaging (MRDTI) is a novel tool in DVT diagnosis. The technique is based on a high signal within the thrombus on MRDTI due to the T1 shortening of methemoglobin within red blood cells present in cloth in the acute phase of DVT.[9] In patients presenting with acute first episode of clinically suspected DVT, MRDTI was shown to have a high sensitivity (94–96%) and specificity (90–92%) vs. contrast venography.[9] Theoretically, a subsequent loss of paramagnetic characteristics could result in the absence of high signal intensity on MRDTI during follow-up after 3–6 months anticoagulant treatment. Reliable clinical data in the literature on this particular subject are virtually absent. In an animal study it was shown that in acute thrombosis detected by MRDTI, the thrombus signal decreased with age.[10] The purpose of this study was to assess the change in signal intensity on MRDTI in patients with acute DVT evolving over a follow-up period of 6 months and to correlate this to the concomitant CUS findings in these patients.

PATIENTS AND METHODS

Patients and setting

This prospective cohort-study was performed at the Departments of Radiology and General Internal Medicine of the Haga Teaching Hospital-Leyenburg in the Hague, the Netherlands, a secondary and tertiary referral hospital. The local institutional review board had approved the study. All participating patients gave written informed consent before entering the study. At the Department of General Internal Medicine it is routine practice that all patients with a clinically suspected DVT of the leg are referred to the Department of Radiology for compression ultrasonography testing. All patients with

DVT of the leg by CUS were considered for enrollment into the study. Both inpatients and outpatients were considered eligible for the study if they presented with a first episode of DVT, and if they were 18 years or older. Patients with a documented history of DVT of the leg or pulmonary embolism, pregnancy, a life expectancy of less than 6 months, or a contra-indication for undergoing MRDTI examination, and those in whom the MRDTI could not be performed within 48 h or who were expected not to be able to attend follow-up visits, were excluded from study participation. Contra-indications for MRI included the presence of electronically, magnetically and mechanically activated implants (such as defibrillators, pacemakers or nerve stimulators), ferromagnetic hemostatic clips in the central nervous system, metallic eye splinters, prosthetic heart valves and lead wires. All study patients underwent a full clinical examination, complete CUS of both legs and subsequent MR imaging of both legs within 48 h after the initial diagnosis of DVT. All patients with acute DVT were treated by therapeutic doses of nadroparin (9500 IU mL) adjusted to their body weight, followed by orally administered vitamin K antagonists (VKA) for a period of 3 (for patients with DVT with temporary risk factors) to 6 months (for patients with permanent risk factors or idiopathic DVT). The decision to continue or stop VKA treatment was not influenced by any imaging test performed during follow-up. To control for false positivity of the MRDTI method, in a randomly selected group of patients of the same cohort, in whom DVT had been excluded by compression ultrasonography, MRDTI was also performed.

Clinical examination

A full clinical history and an additional general physical examination were carried out by a staff member of the Department of General Internal Medicine. A personal history included the presence (or absence) of established riskfactors of venous thrombosis, a personal history of venous thrombosis, duration of symptoms, and co-morbid diseases. A general physical examination was performed and included a specific examination of the affected leg. The following signs and symptoms were recorded: pain or tenderness, discoloration, local swelling or leg-edema and visible collateral circulation. D-dimer or additional hematological tests were not routinely performed.

Ultrasonography

Compression ultrasonography was performed as described earlier, using a Siemens Sonoline Elegra, Erlangen, Germany, 5.0 MHz curved array and 7.5 MHz linear array transducer.[2,11] The criterion for thrombosis was non-compressibility of the popliteal and/or femoral vein and this criterion was used to take treatment decisions. In patients in whom ultrasonography demonstrated acute DVT, complete CUS was performed within 48 h after the diagnosis of DVT of the leg. Both the affected and contralateral legs were imaged. During follow-up, CUS was defined as still abnormal if compression ultrasonog-

raphyshowed a diameter of 4 mm or greater of the previously affected venous segment and defined as normalized when compression showed a diameter of less than 4 mm at that venous segment.[5,12] Recurrent DVT of the leg was defined as an increased diameter of the affected venous segment or an abnormal CUS in the contralateral leg or in a previously normal venous segment of the leg.

Magnetic resonance direct thrombus imaging

MRDTI was performed with a 1.5 T unit (Philips, Best, The Netherlands) and a quadrature receive-transmit body coil. The technique used was a T1-weighted magnetization-prepared 3D gradient-TFE sequence that includes a selective water-excitation radio frequency pulse as part of the manufacturer's pulse sequence package (repetition time ms/echo time ms = 11.0/5.5, 15o flip angle, 1200 ms inversion prepulse time, 400 • 360 field of view, 256 • 256 matrix, 60 overlapping partitions with zero filled interpolation, one signal acquired, 299 Hz/pixel bandwidth). Images were acquired in the coronal plane, in the range from the ligament of Poupart to just distal to the trifurcation of the calf veins. The number of partitions and inversion time were chosen so that the middle lines of k space occurred at such a time as to nullify signal from flowing blood. This arrangement took into consideration the incomplete relaxation afforded by the delay time of 1200 ms. A water selective pro-set prepulse was given to suppress the signal of fat. A transverse 80 mm thick saturation slab was placed cranial to the field of view, equal for all patients. The resultant image acquisition time took 2 min. Depending on patient (leg) length, one or two coronal scans were obtained. Both legs were imaged simultaneously. The MRDTI study was considered positive (abnormal) for acute thrombosis on the T1 sequence if there was a high signal in the course of a deep vein, against a background in which the signal of fat and blood was suppressed.[9]

Follow-up

All patients received two prescheduled follow-up visits at 3 and 6 months. At these follow-up visits, patients received a full clinical examination, complete CUS examination of both legs and a subsequent MRDTI examination.

Data-handling and statistical analysis

All data obtained from imaging studies were coded and stored anonymously in a computerized data base. All imaging-data were independently read by two blinded observers. Interpretation was performed on Easy vision® (Philips MedicalSystems, Best, the Netherlands) or Vitrea® (Vital Images Inc.,Minnetonka, MN, USA) Workstation (coronal coupes and MIP reconstructions). MRI studies were classified according to diagnosis (acute thrombosis or not), and in case of an abnormal study according to venous segment (calf, popliteal and femoral vein). In the case of disagreement between both

observers, a third opinion was sought. Sensitivity and specificity were calculated for the initial diagnosis of DVT with MRDTI. Interobserver agreement on data was analyzed using Cohen's kappa coefficient (k) and reported as a point estimate 95% confidence interval. Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

From January 2005 until May 2006, 746 patients were referred with clinically suspected of the leg. In 105 of these patients (incidence of 14%) DVT was demonstrated by CUS and these patients were considered for enrollment into the study. Thirty-two patients (31%) met one of the exclusion criteria: documented history of DVT of the leg or pulmonary embolism (n = 10); pregnancy (n = 1); life expectancy of less than 6 months (n = 7); contra-indication for undergoing MRDTI examination (n = 5); and nine patients could not be included within 48 h for variable logistic reasons or were expected to be unable to attend follow-up visits. Thirty patients refused to participate or were not competent to give informed consent. Thus, 43 of 105 patients (41%) gave informed consent and entered the study. The baseline patient characteristics are listed in Table 1. All patients had idiopathic DVT or had a continuing risk factor and were treated with VKA for a period of 6 months. There were no patients with simultaneously occurring, symptomatic

Tabel 1. Baseline characteristics of included patients (n=43).

Number of patients (n)	43 (100%)
Male	20 (46.5%)
Female	23 (53.5%)
Right side DVT	20 (46.5%)
Left side DVT	23 (53.5%)
Number of days before presentation (mean, range)	11.6 (0-75)
Vitamin K antagonists	2 (4.7%)
Malignancy	9 (20.9%)
Air travel	8 (18.6%)
Family history of DVT	14 (32.6%)
Postsurgery	5 (11.6%)
Oral contraceptive therapy	4 (9.3%)
Length (cm) (median, range)	174 (143-193)
Weight (kg) (median, range)	80 (44-113)
Age (years) (median, range)	59 (25-85)

N: number; DVT; deep vein thrombosis

contralateral DVT. From 115 MRDTI studies, 108 studies were identically diagnosed by the two observers (93.9%). Seven studies were interpreted differently, six on extension of thrombosis in the proximal venous segment, and one in the diagnosis of acute DVT (proximal DVT vs. isolated calf vein thrombosis) (κ-statistics = 0.87).

Imaging results at baseline

At presentation, 41 of the 43 patients (95%) with proximal DVT by complete CUS showed a hyperintense T1-signal by MRDTI of the symptomatic leg. An example of a patient with abnormal CUS and abnormal MRDTI at the acute event is shown in Figures 1 and 2. One patient with (ileo)femoral DVT by CUS at presentation had initially a normal T1 signal by MRDTI, performed the same day. The MRDTI became abnormal 7 days later. This patient had presented within 12 h after the start of symptoms of DVT, which occurred immediately after accidental venous puncture during a coronary catheterization procedure. Another patient who presented with 7 days of complaints had an abnormal CUS and normal MRDTI at the day of presentation and at day seven. In the control group of patients without DVT on CUS (n = 43) there were no patients with a high-intensity signal on MRDTI.

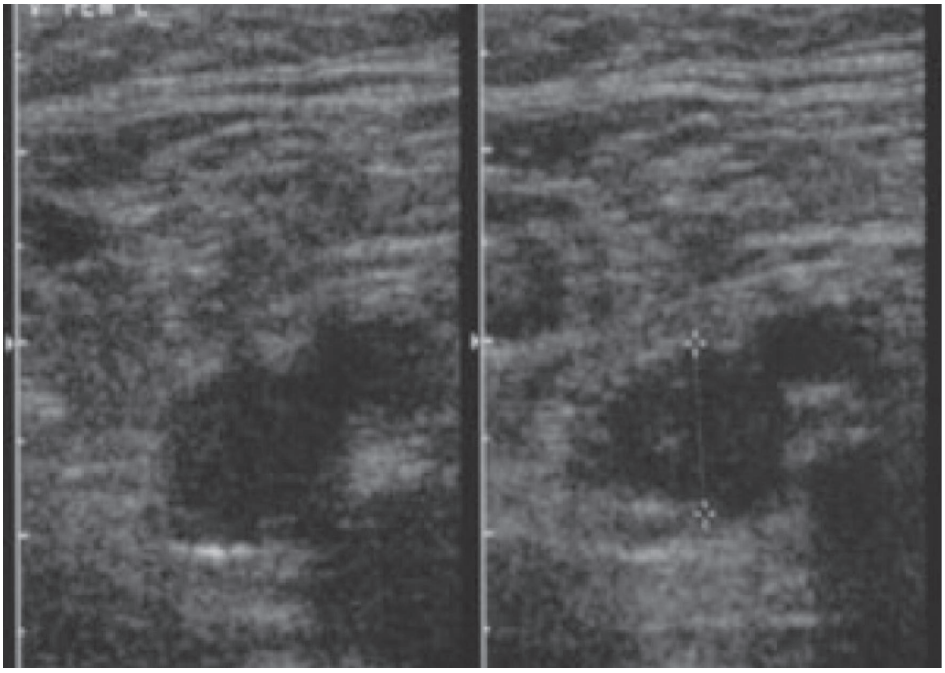

Figure 1. Compression ultrasonography showing deep vein thrombosis in the left femoral vein. Left image without compression, right image with incomplete compression of the femoral vein. Male, 58 years, presented with swelling, discoloration and pain of the left leg. Complaints were present for 1 week

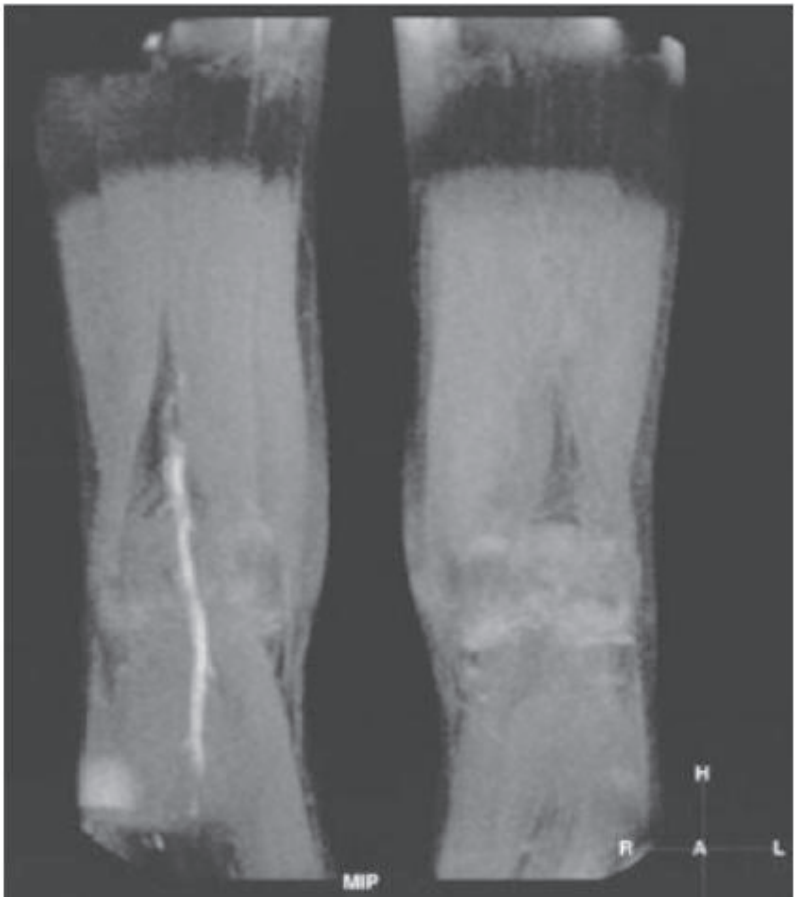

Figure 2. Magnetic resonance direct thrombus imaging displays hyperintense signal of the thrombus (as diagnosed by compression ultrasonography in the right popliteal vein. Left leg shows normal findings. This male patient presented with swelling of the right leg. Complaints were present for 2 weeks

Imaging results during follow-up

During follow-up, two patients died of disseminated cancer at 2 and 3 months, while one patient withdrew informed consent. In a fourth patient, recurrent symptoms of DVT occurred 5 months after the initial diagnosis and recurrent DVT was diagnosed. Post-hoc analysis of the complete CUS at 3 months showed only an asymptomatic, small residual thrombus in a calf vein. Recurrent DVT was demonstrated by non-compressibility of CUS in a different segment (proximal femoral) than at the initial presentation of the first episode of thrombosis (popliteal vein). Subsequent MRDTI showed a new hyperintense T1-signal in the corresponding venous segment. At 3 months follow-up, 33 patients attended the outpatient clinics of the hospital. Ten patients were not able to attend at their prescheduled follow-up appointment. In 12 patients (36%) CUS was still abnormal.

In none of the patients was an increased diameter of incomplete compression observed at follow-up, as compared with CUS performed at the acute episode. In nine of these 12 patients, MRDTI did not show a hyperintensive T1 signal anymore within this venous segment. In the other three patients the abnormal hyperintensive T1- signal was still present. In 21 of 33 patients (64%) both the CUS and MRI imaging test had become normal at 3 months (Table 2). At 6 months, 39 of 43 patients attended follow-up. In none of the 39 patients was a hyperintensive MR signal noted, while in 12 patients (31%) CUS

Table 2. Follow- up at 3 months.

	CUS abnormal	CUS normal	Total
MRDTIpositive	3	0	3
MRDTI negative	9	21	30
Total	12	21	33

CUS: compression ultrasonography; MRDTI: magnetic resonance direct thrombus imaging

still showed non-compressibility of the previously affected venous segment of 4 mm in diameter or greater. In none of the patients was an increased diameter of incomplete compression observed at 6 months follow-up as compared with CUS performed at the acute episode or at 3 months follow-up (Tables 3 and 4; figure. 3). In Figure 4 an example of recurrent acute DVT is shown.

Table 3. Follow-up at 6 months.

	CUS abnormal	CUS normal	Total
MR-DTI positive	0	0	0
MR-DTI negative	12	27	39
Total	12	27	39

CUS: compression ultrasonography; MRDTI: magnetic resonance direct thrombus imaging

DISCUSSION

In this study, we have shown that a hyperintensive T1-signal by MRDTI in the acute stage of proximal DVT of the leg in symptomatic patients normalizes within a period of 6 months. Importantly, simultaneously performed compression ultrasonography still showed incomplete compressibility in a third of our patients at 6 months. In line with an earlier observation, we showed an accurate detection of acute DVT by MRDTI in patients with clinically suspected DVT.[9] Our results may have important clinical implications for

Table 4. Results of compression ultrasound in patients with abnormal findings at follow-up. In millimeters (mm) the maximum distance of incomplete compression of the vein in the transverse plane.

Patient	Initial presentation	3-month follow-up	6-month follow-up
1	FV & PV (14mm)*	FV & PV (12mm)	FV & PV (12mm)
2	FV & PV (12mm)*	FV & PV (9mm)*	FV & PV (5mm)
3	FV & PV (12mm)*	FV & PV (6mm)	FV & PV (6mm)
4	PV (10mm)*	Not attended	PV (5mm)
5	FV & PV (unknown)*	PV (5mm)*	PV (5mm)
6	FV & PV (10mm)*	FV & PV (6mm)*	FV & PV (5mm)
7	PV (12mm)*	PV (5mm)	PV (6mm)
8	PV (14mm)*	PV (6mm)	Normalized
9	FV & PV (8mm)*	PV (5mm)	PV (6mm)
10	FV & PV (12mm)*	PV (9mm)	PV (7mm)
11	FV & PV (11mm)*	PV (8mm)	PV (9mm)
12	FV & PV (10mm)*	FV (6mm)	FV (5mm)
13	FV & PV (14mm)*	PV (5mm)	PV (4mm)

FV: femoral vein; PV: popliteal vein; * MRDTI at the acute episode and 3 months follow-up with positive results. At 6 months all MRDTI results were negative

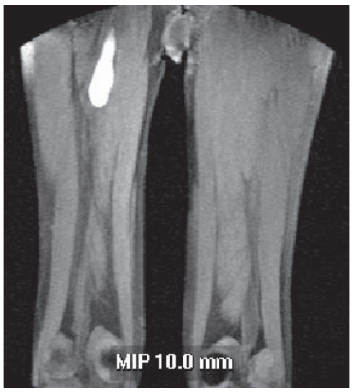

Figure 3. Magnetic resonance direct thrombus imaging at 6 months of the left femoral-popliteal venous segment does not show hyperintense signal, although residual thrombus was still objectified at compression ultrasonography (popliteal vein). Initial compression ultrasonography and magnetic resonance direct thrombus imaging (MRDTI) showed femoral-popliteal deep vein thrombosis of the left leg. The hyperintense collection at the right groin was due to arterial hemorrhage after catheterization 1 week before MR. No complaints were present at 6-month follow-up

the diagnostic and therapeutic management of patients in whom acute recurrent DVT is suspected, given the fact that the abnormal signal by MRDTI normalized in all patients over a period of 6 months and in 90% within 3 months, a period that coincides with the consensus-based duration of anticoagulant treatment.[8] On the basis of these changes

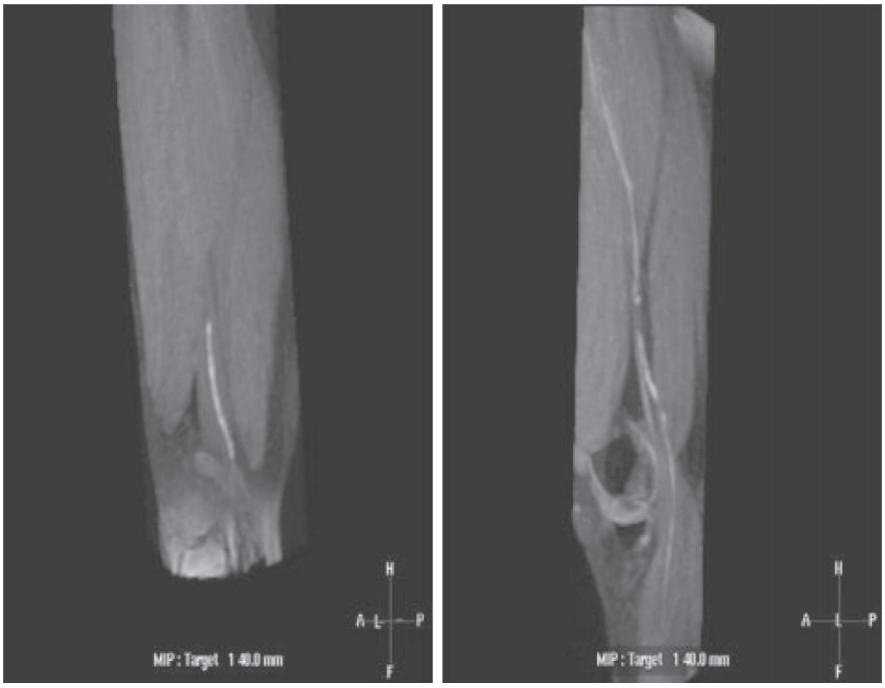

Figure 4. Left picture represents a sagital reconstruction of MRDTI from a DVT of the left distal femoral and popliteal vein in a male patient with a retroperitoneal mass (not shown). At 5 months after the initial diagnosis oral anticoagulant medication was discontinued because of CT guided biopsy of the mass. This patient developed recurrent complaints of the left leg and compression ultrasonography and MRDTI showed an extension of the thrombus into the proximal femoral vein.

towards normal, occurring over 6 months in all patients, the MRDTI technique has the potential to accurately diagnose acute recurrent DVT in these patients, should they return with recurrent symptoms.

The hypothesis is that in those patients who have recurrent DVT, a hyperintensive T1 signal will re-occur. Although new non-compressible vein segment by CUS is considered diagnostic of recurrent DVT,[12] this method has limitations regarding the persistent abnormal CUS occurring in 50% of patients 1 year after initial deep venous thrombosis.[3-5] Prandoni and colleagues used the criterion of stable or improved vein diameter by repeated CUS in the diagnosis of clinically suspected recurrent DVT.[5,12-14] Important caveats using this technique for management of suspected recurrent DVT are that a low interobserver agreement in patients with previous venous thrombosis has been reported, and in daily clinical practice previous detailed CUS test results are frequently not at hand.[15] Alternatively, D-dimer testing has shown a low venous thromboembolism failure rate in a large management study and a small study.[16,17] However, D-dimer is nonspecific and as a sole test not able to demonstrate recurrent DVT. Scintigraphy has been

evaluated for its potential utility in patients with suspected recurrent DVT but it also proved to be operator dependent, although a high accuracy was reported by skilled and experienced readers.[18]

Magnetic resonance DTI has important practical advantages over other diagnostic tests. Thrombosis is detected by an endogenous contrast agent, and there is no need for intravenous contrast agents, such as iodine contrast or gadolinium, nor does MR involve radiation. The MR technique had a high inter-observer agreement and is operator independent. Furthermore, high field MRI (1.5 Tesla) is widely available nowadays, and a full examination of both legs is obtained within 5 min of acquisition-time. In a selected group of patients (such as in the differentiation between acute or rest clot) this would allow MR to be performed in an outpatient setting. We could perform MR DTI within 48 h after the initial presentation. Our study had some limitations. First, a certain time is needed for the transformation of hemoglobin into a sufficient amount of methemoglobin to cause T1 shortening mandatory for detecting acute DVT. In fact, in one of our patients, seen within 12 h after a traumatic venous puncture at a coronary catheterization procedure, CUS was incompletely compressible at the proximal femoral vein, whereas the initial MRDTI study, performed within 12 h, did not yet show a hyperintense T1-signal within the thrombus. A later follow-up scan after 1 week was compatible with acute DVT. In an outpatient setting, the median number of days with symptoms for DVT prior to presentation as outpatients is 7–10 days, and therefore this problem is of less importance.[18] However, inpatients with suspected DVT often display a much shorter duration of complaints and may be potentially more at risk of a false negative MRDTI test. In a second patient MRDTI remained negative in the acute stage. The reason for this observation is unclear and remains speculative. Second, we studied a relatively small number of patients and as a result the confidence limits around our result estimates are relatively wide. However, our main goal was to establish how the hyperintensive MR-signal would extinguish over time. The normalization was present in all patients within 6 months, which coincides with the advised period of anticoagulation with VKA for acute DVT by international consensus.[7]

In conclusion, this study shows that in patients with acute proximal DVT of the leg, MRDTI normalizes over a period of 6 months in all patients, despite CUS still being abnormal in about a third of patients. Therefore MRDTI may allow for accurate diagnosis of acute recurrent DVT in patients in whom acute recurrent DVT is clinically suspected. Additional studies should therefore be performed to demonstrate whether this technique can indeed accurately detect recurrent DVT in the setting of patients presenting with clinically suspected recurrent DVT and to demonstrate the validity of a negative MRI to safely exclude recurrent DVT.

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