THROMBOSIS AND HEMOSTASIS

Magnetic resonance direct thrombus imaging differentiates acute recurrent ipsilateral deep vein thrombosis from residual thrombosis

Melanie Tan,[1] Gerben C. Mol,[2] Cornelis J. van Rooden,[3] Frederikus A. Klok,[1] Robin E. Westerbeek,[4] Antonio Iglesias del Sol,[5] Marcel A. van de Ree,[2] Albert de Roos,[6] and Menno V. Huisman[1]

[1]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]Department of Internal Medicine, Diakonessenhuis, Utrecht, The Netherlands; [3]Department of Radiology, Haga Teaching Hospital, The Hague, The Netherlands; [4]Department of Radiology, Deventer Hospital, Deventer, The Netherlands; [5]Department of Internal Medicine, Rijnland Hospital, Leiderdorp, The Netherlands; and [6]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Key Points

- Diagnostic management of ipsilateral recurrent DVT of the leg is complicated because residual DVT is common and mimics acute DVT on CUS.
- MRDTI is able to reproducibly distinguish acute ipsilateral recurrent DVT from 6-month-old chronic residual thrombi in the leg veins.

Accurate diagnostic assessment of suspected ipsilateral recurrent deep vein thrombosis (DVT) is a major clinical challenge because differentiating between acute recurrent thrombosis and residual thrombosis is difficult with compression ultrasonography (CUS). We evaluated noninvasive magnetic resonance direct thrombus imaging (MRDTI) in a prospective study of 39 patients with symptomatic recurrent ipsilateral DVT (incompressibility of a different proximal venous segment than at the prior DVT) and 42 asymptomatic patients with at least 6-month-old chronic residual thrombi and normal D-dimer levels. All patients were subjected to MRDTI. MRDTI images were judged by 2 independent radiologists blinded for the presence of acute DVT and a third in case of disagreement. The sensitivity, specificity, and interobserver reliability of MRDTI were determined. MRDTI demonstrated acute recurrent ipsilateral DVT in 37 of 39 patients and was normal in all 42 patients without symptomatic recurrent disease for a sensitivity of 95% (95% CI, 83% to 99%) and a specificity of 100% (95% CI, 92% to 100%). Interobserver agreement was excellent ($\kappa = 0.98$). MRDTI images were adequate for interpretation in 95% of the cases. MRDTI is a sensitive and reproducible method for distinguishing acute ipsilateral recurrent DVT from 6-month-old chronic residual thrombi in the leg veins. (*Blood*. 2014;124(4):623-627)

Introduction

The diagnostic standard for a first episode of clinically suspected deep vein thrombosis (DVT) of the leg is compression ultrasonography (CUS).[1-3] This is a simple, noninvasive, highly accurate technique with sensitivity and specificity figures ranging from 89% to 100% and 87% to 100%, respectively: noncompressibility of the common femoral and/or popliteal vein is diagnostic for an acute symptomatic first DVT.[1-3] Within 5 years after a first episode of DVT, 20% to 40% of patients will present with suspected recurrent DVT.[3-5] For these patients, accurate diagnosis of recurrent DVT is of particular importance, because patients with proven recurrent DVT are, depending on their risk profile, often subjected to indefinite anticoagulant treatment with its associated bleeding risks.[6] Conversely, if they are left untreated, they are at risk for potentially fatal pulmonary embolism (PE) and the development of the postthrombotic syndrome.[3,4]

Ultrasonography abnormalities persist in approximately 80% of patients after 3 months and in 50% of patients after 1 year from initial DVT diagnosis, limiting the usefulness of CUS for the detection of recurrent DVT, since the ultrasonographer cannot determine whether incompressibility of the specific vein segment is caused by a new thrombus or residual thrombosis.[1-3,7] Measurement of thrombus diameter by CUS has been shown to be of some support in the diagnosis of ipsilateral recurrent DVT, although its interobserver agreement is poor.[8] The only reliable criterion is a new incompressible venous segment, but this requires knowledge of the prior ultrasound situation.

The most promising alternative to CUS to solve this diagnostic dilemma is using a technique called magnetic resonance direct thrombus imaging (MRDTI). MRDTI has been shown to be a highly accurate diagnostic test for first DVT.[9,10] The method is based on assessment of a shortening T1 signal. This signal is induced by the paramagnetic methemoglobin, which is being formed in a fresh thrombus. MRDTI does not require the injection of potentially nephrotoxic contrast medium and, hence, is not subject to interference by chronic residual thrombi.[9-11] For proximal DVT (ie, femoropopliteal and ileofemoral DVT), the diagnostic accuracy of MRDTI was shown to be very high (sensitivity 97% to 100%; specificity 100%), with excellent reproducibility (interobserver variability $\kappa = 0.89$ to 0.98). In a cohort follow-up study in 43 patients with a CUS-proven first symptomatic episode of DVT, it was shown that the high signal intensity compatible with thrombus, present in 41 patients at presentation, normalized completely over a period of 6 months in all

Submitted April 4, 2014; accepted June 3, 2014. Prepublished online as *Blood* First Edition paper, June 13, 2014; DOI 10.1182/blood-2014-04-566380.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

patients available for follow-up.[12] The presence of high signal intensity could thus potentially be used as a conclusive sign of a new DVT when a patient presents again with clinically suspected acute recurrent DVT.

We aimed to determine the sensitivity of MRDTI for the diagnosis of acute recurrent ipsilateral DVT, by comparing MRDTI scans of patients with established acute recurrent symptomatic ipsilateral DVT with MRDTI scans of patients with CUS-proven residual thrombosis without suspected acute recurrent disease.

Materials and methods

Study design

We performed a prospective multicenter study in 5 Dutch hospitals. Study participants were enrolled between November 2008 and May 2011 in The Netherlands. The study was approved by the institutional review board at each center, and all patients provided written consent. The study was conducted in accordance with the Declaration of Helsinki.

Patients

Two groups of patients were studied: those with acute recurrent symptomatic ipsilateral DVT (group 1) and those with previous DVT without symptoms of an acute DVT but with persistent intravascular abnormalities after a 6-month treatment period (group 2). In both groups, patients were potentially eligible if they were at least 18 years of age, did not use anticoagulant treatment at the time of enrollment, and were able and willing to provide informed consent.

The study patients in group 1 were identified in a consecutive order in the inpatient, outpatient, and emergency departments of the participating hospitals. Patients were enrolled at the moment they were diagnosed with acute recurrent symptomatic ipsilateral DVT according to predefined criteria (incompressibility of a new proximal venous segment, different from those reported incompressible in the original CUS report of the first DVT diagnosis), in combination with an abnormal D-dimer test result defined as $\geq$500 ng/mL. Patients were considered to have symptoms consistent with acute recurrent DVT if they had ongoing pain, swelling, tenderness, warmth, and/or erythema of the leg of recent onset (within the past 10 days).

Those in group 2 were a convenience sample of patients from the thrombosis outpatient clinic of the Leiden University Medical Center. In these control patients, an objectively proven proximal DVT had been diagnosed in the past, and a reference CUS examination, performed in a standard manner after completion of a minimum 3-month treatment period, indicated remaining complete or partial noncompressibility of one or more proximal deep veins. In addition, the control patients had a normal D-dimer test result but could not have any reports of symptoms of acute DVT at the time of enrollment.

In both groups, patients were excluded from the study if they had (1) contraindications to magnetic resonance imaging (MRI) such as claustrophobia, any trauma or surgery that may have left ferromagnetic material in the body, or ferromagnetic implants or pacemakers; (2) received any antithrombotic drug within 30 days of enrollment; or (3) had a CUS-proven acute symptomatic DVT within 6 months before presentation. Patients with lower-limb amputation and those with a medical condition, associated illness, or comorbid circumstances that made it unlikely that the study procedure would be completed were also excluded.

CUS

Lower-limb venous CUS was performed and interpreted as previously described.[13] The CUS was considered diagnostic of acute recurrent ipsilateral DVT in group 1 patients if there was a new noncompressibility of the common femoral and/or popliteal vein in the transverse plane in a previously compressible segment. Partial or complete noncompressibility of one or more of the deep veins was required to demonstrate chronic intravascular change in group 2 patients. Hard copies of freeze-frame images of the CUS procedure were stored and obtained.

D-dimer testing

D-dimer levels for all patients were measured on the day of enrollment by using a highly sensitive quantitative D-dimer test (cutoff level, 500 ng/mL). Among the study centers, the following high-sensitivity D-dimer assays were used: VIDAS D-Dimer Assay (bioMérieux, Marcy-l'Étoile, France), Tina-Quant Assay (Roche Diagnostica, Mannheim, Germany), STA Liatest D-Di (Diagnostica Stago, Asnieres-sur-Seine, France), or Innovance D-Dimer (Siemens, Marburg, Germany). These assays are sensitive for acute DVT and are expected to yield a normal result in individuals without acute ipsilateral recurrent DVT.[14] Thus, D-dimer tests were performed to confirm the chronic nature of the vascular changes in group 2 patients and the acute nature of the DVT in group 1 patients.

MRDTI

MRDTI was performed as previously described with a 1.5-Tesla unit using a T1-weighted magnetization prepared three-dimensional gradient-echo sequence within 48 hours of the CUS on which the diagnosis of acute recurrent DVT was based in group 1, and at a convenient time for the patients in group 2.[9,12] The sequence includes a water-only excitation radiofrequency pulse to abolish the fat signal, and the effective inversion time is chosen to nullify the blood signal. Imaging was performed on both legs simultaneously from the ankle to the inferior vena cava in two imaging blocks with a total acquisition time of 12 minutes by using a 55-cm body coil. Image assessment involves reading of coronal source data and standard image reconstruction techniques.

Image interpretation was conducted by means of digital images, allowing the readers the opportunity to adjust image brightness, contrast, and threshold. White contrast in the location of a deep vein segment against the suppressed background that was greater than that observed in the corresponding segment or in contiguous segments of the ipsilateral vein and that persisted or intensified with time was considered diagnostic for acute recurrent DVT. Abnormal localization in collateral vessels, superficial veins, postsurgical sites, and nonvascular locations were not considered indicative of acute DVT.

Image assessment and interpretation

All ultrasonograms and MRDTI images were presented to 2 independent readers with experience in MRDTI readings in sets of at least 10 examinations with patients from both groups. The readers were not involved with the diagnostic and/or therapeutic management of the study patients, and they interpreted the MRI examinations in a blinded fashion (ie, without knowledge of group 1 or 2 status or clinical condition of the study patients). A third reader was involved to resolve any disputes. The readers noted the presence or absence of acute ipsilateral recurrent DVT for each individual patient, based on the MRDTI.

Statistics

The primary requirement for this study was a sample size sufficiently large to provide reasonable estimates of the sensitivity and specificity of MRDTI. A sample size of 40 patients in each of groups 1 and 2 was chosen because with this sample size and an expected sensitivity of more than 85%, the 95% confidence intervals (CIs) on the point estimates would have a bandwidth of approximately $\pm$10%, ensuring that the point estimate was sufficiently accurate to make decisions about the appropriateness and safety of a future management study.

A diagnosis (positive for acute recurrent DVT, negative for acute recurrent DVT, or nondiagnostic) for each leg of interest based on an aggregate reading of the images was made by the readers described above. For each read, the sensitivity of MRDTI was determined by calculating the proportion of MRI scans that were read as positive for acute recurrent DVT in group 1 patients, and the specificity was determined by calculating the proportion of scans that were read as negative for acute DVT in group 2 patients. The corresponding exact 95% CI for each of the point estimates was calculated. In addition to

these estimates, the interobserver agreement was calculated and expressed by the κ statistic. All analyses were performed with SPSS 20.0 software.

Results

Study patients

Eighty-five patients (43 in group 1 and 42 in group 2) met the eligibility criteria and were subjected to an MRDTI examination. The MRI images of two patients with an ipsilateral recurrent DVT (group 1) were not interpretable: the first was a result of the presence of a knee prosthesis leading to artifacts on the images, and the second was because the popliteal and the femoral part of the venous system were not entirely imaged. Furthermore, two additional patients from group 1, who at their presentation had been diagnosed with new proximal recurrent DVT, were post hoc but before MRDTI reading adjudicated to have calf vein thrombosis restricted to the infrapopliteal deep veins of the lower limbs and were therefore also excluded from further analysis. Hence, 39 study patients were available for analysis in group 1 and 42 patients in group 2.

Baseline characteristics

The mean age of the patients in the study was 52 years (range, 18 to 77 years), and 52 (64%) were male. The patients enrolled in group 1 had a mean age of 54 years (range, 18 to 77 years) and 23 (59%) were male. Thirty-eight (97%) of the 39 patients in group 1 were outpatients. The median time between the previous DVT and the acute recurrent DVT was 83 months (interquartile range, 14 to 220 months). The thrombosis was in the left leg in 31 patients (80%). All patients were diagnosed by noncompressibility of a new venous segment compared with the first DVT. Regarding the patients in group 2, the mean age was 50 years (range, 18 to 71 years), and 28 (67%) were male. The mean time between the first acute DVT and the assessment of the residual thrombosis was 21 months (interquartile range, 12 to 34 months). The residual thrombosis was in the left leg in 43% of these patients.

Accuracy of MRDTI

MRDTI was abnormal in 37 of 39 patients of group 1 with symptomatic recurrent ipsilateral DVT. For two patients in this group, the MRDTI images were judged as normal. In the first 57-year-old male patient, recurrent DVT was demonstrated by CUS in a new proximal segment (popliteal vein) when compared with the original ultrasonography of his first DVT in the femoral vein only 10 months earlier (Table 1). The D-dimer level at the moment of suspected recurrence was 1195 ng/mL. The ultrasonography result of the second 18-year-old male patient was judged to be a more propagated thrombotic obstruction of the popliteal vein with new extension into the popliteal segment below the knee when compared with the ultrasonography of the first DVT diagnosed 17 months earlier. His D-dimer level at the most recent presentation of suspected recurrent DVT was 584 ng/mL (Table 1). The onset of symptoms of DVT was less than 48 hours in both patients, and neither reported respiratory or chest symptoms indicative of the presence of acute PE. MRDTI images and corresponding ultrasonography images are displayed in Figure 1 for a patient from study group 1 with acute recurrent ipsilateral DVT.

MRDTI was normal in all 42 patients of group 2, who had chronic thrombosis on CUS and no symptoms of acute recurrent DVT.

Table 1. Characteristics of the two patients with false-normal MRDTI result

Characteristic	Patient 1	Patient 2
Age, y	57	18
Sex	Male	Male
Symptom duration, d	2	2
D-dimer result at moment of recurrence, ng/mL	1195	584
Location of previous DVT on CUS	Femoral	Popliteal above knee level
New venous segment on CUS (diagnostic for recurrent DVT)	Popliteal	Popliteal below knee level
Duration between recurrence and previous DVT, mo	10	17

Figure 2 depicts the normal MRDTI signal in a patient from study group 2 with asymptomatic residual thrombosis.

The sensitivity of MRDTI was 95% (95% CI, 83% to 99%), and specificity was 100% (95% CI, 92% to 100%; Table 2). By using a selected group of study participants with an overall 48% frequency of acute recurrent DVT, the negative predictive value of MRDTI was 95% (95% CI, 83% to 98%), and the positive predictive value was 100% (95% CI, 88% to 100%).

From 162 readings (right and left leg), the two primary reviewers disagreed on 1 reading, resulting in a κ statistic of 0.98 (95% CI, 0.93 to 1.0). This specific patient had been enrolled in the acute recurrent thrombosis group because he presented with acute symptoms in the same leg. He was shown to have a high D-dimer level (1302 ng/mL) and had a new noncompressible proximal venous segment when compared with the echo results of the first DVT episode. The third reviewer judged the MRDTI as indicative of acute recurrent DVT.

Discussion

This study extends the reliable findings for MRDTI in acute DVT diagnosis. We showed that MRDTI has good sensitivity (95%) in patients with CUS-proven acute recurrent ipsilateral DVT and excellent specificity (100%) in patients with chronic thrombotic lesions, with excellent reproducibility ($\kappa = 0.98$). If MRDTI had been used to determine whether to initiate anticoagulant treatment, few unjustified decisions for putting patients on lifelong anticoagulant therapy with associated high bleeding risk would have been made. On the basis of the 95% sensitivity, we hypothesize that in a daily practice population with a DVT prevalence of 20%, the negative predictive value of MRDTI for suspected recurrent ipsilateral DVT could increase to 99%. Importantly, MRDTI was not used to diagnose suspected recurrent deep vein thrombosis in this study.

In current guidelines, a reference CUS that accurately determines the location and extent of residual thrombosis after cessation of anticoagulant treatment is considered necessary for an accurate diagnosis of acute recurrent ipsilateral DVT.[3] However, such a reference CUS is not routinely performed, and detailed previous ultrasonography reports are seldom available. In fact, a recent cohort study aimed at daily practice patterns in the diagnostic management of suspected ipsilateral recurrent DVT by CUS showed that recurrent disease could be ruled out in 58% and established in only 10% of patients. In the remaining 32% (95% CI, 23% to 43%), recurrent DVT could neither be ruled out nor confirmed.[15] The fact that these latter patients were all treated with anticoagulants is a strong argument for the presence of overtreatment and underlines the importance of

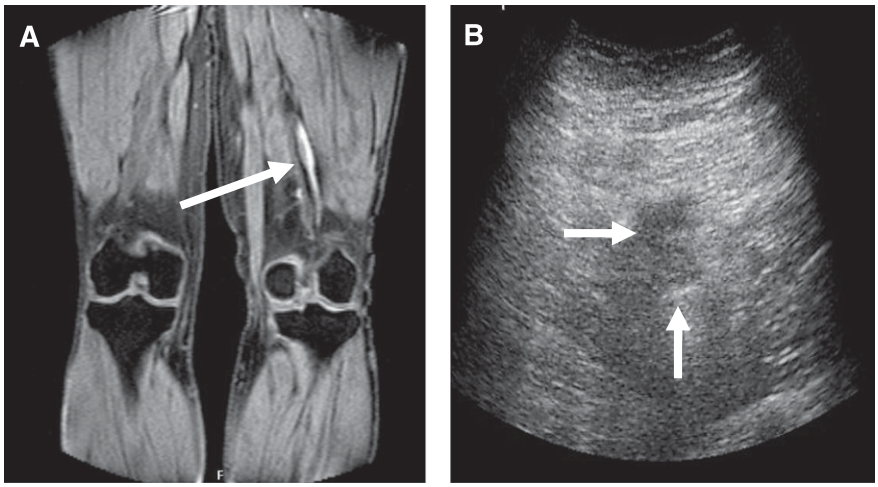

Figure 1. Abnormal signal on MRDTI in the popliteal vein of the left leg. (A) Arrow indicates positive MRDTI signal in a patient with symptomatic and CUS-proven ipsilateral recurrent DVT in the popliteal vein; (B) arrows indicate incompressibility of corresponding vein on ultrasonography.

development and validation of more accurate and reproducible diagnostic tests for clinically suspected recurrent ipsilateral DVT, such as MRDTI.

In our study, MRDTI images did not detect the acute recurrent thrombosis in two of the 39 patients. In both patients, the onset of symptoms started 36 to 48 hours before the MRDTI was performed. It is known that the first positive DTI signal can be demonstrated within a few hours after the formation of a thrombus,[11] which is underlined by the study by Fraser et al[9] who described a sensitivity of MRDTI of >97% in a population of patients in whom more than 25% underwent MRDTI within 8 hours of symptom onset. Hence, we hypothesize that the relatively early presentation in these 2 specific patients is a possible explanation for the (still) normal MRDTI signal. More patients presented within this short time frame of 2 days, but this was not accurately assessed for all patients from group 1. Hence, we cannot speculate accurately on the impact of a very short diagnostic delay on the diagnostic accuracy of MRDTI in the particular clinical setting under study.

Despite these 2 false-negative rulings, the observed sensitivity and specificity figures of MRDTI in our study compare well with the 97% (95% CI, 96% to 98%) sensitivity and 94% (95% CI, 90% to 98%) specificity for proximal DVT of CUS in patients with a first episode of clinically suspected DVT reported in an extensive meta-analysis.[2] Accuracy numbers for a single CUS without a reference examination—which in our experience is a common condition in daily clinical routine—for the presence of acute recurrent ipsilateral DVT are not readily available, although it is very likely that especially its specificity will be substantially lower than that of a first DVT or MRDTI.[15]

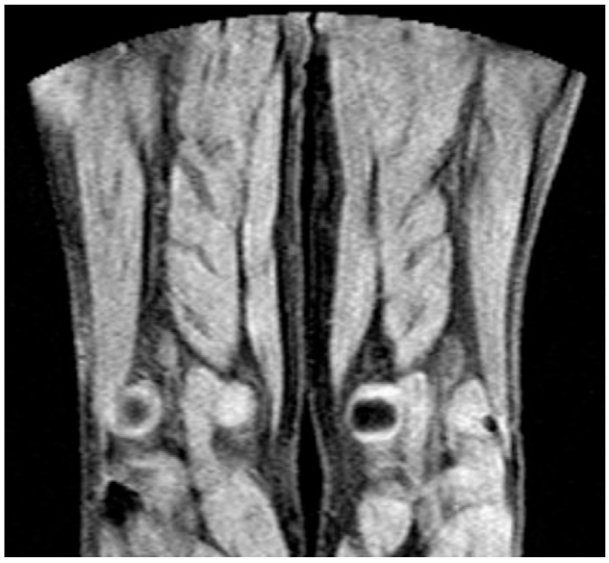

Figure 2. MDRTI image of a patient with ultrasonography-proven residual DVT but no acute recurrent thrombosis in the popliteal vein of the right leg. The scan did not indicate an abnormal MRDTI signal.

Our study did not establish the definite role of MRDTI in the most optimal diagnostic algorithm for suspected acute recurrent ipsilateral DVT. The group 1 patients do not represent the full spectrum of patients with an acute recurrent DVT; those being given anticoagulant treatment with longer symptom duration or those with inconclusive CUS results were not included. Second, the strength of a D-dimer test in combination with a clinical decision score to identify patients with a very low pretest risk in this specific patient category who can be managed without imaging is yet to be established. Although in 1 study, normal D-dimer levels were shown to rule out the presence of acute symptomatic recurrent DVT, the broad confidence interval and high point estimate of 6.0% (95% CI, 2.6% to 11%) for recurrent disease despite a normal D-dimer level in that study argue against a role for D-dimer as a stand-alone test to rule out recurrent DVT.[14] MRDTI has the potential to be used as a first-line imaging test, or as a second-line test for those patients in whom ultrasonography does not provide a conclusive test result. In addition to the high diagnostic accuracy, the fast, noninvasive, patient-friendly nature of MRDTI is a strong argument for the former scenario. Conversely, acute accessibility in the emergency department setting may be limited in some hospitals. Importantly, in the latter scenario of MRDTI being the second test after inconclusive CUS, standardized reference ultrasonography recordings should still be performed in all patients after treatment cessation. Strengths of the study include the application of an efficient design. One group of patients with symptomatic ipsilateral recurrent DVT, based on strict CUS criteria as well as a positive D-dimer test, formed the basis for an accurate sensitivity estimation, whereas patients with a residual thrombosis and negative D-dimer test provided a precise specificity estimation. By this design, this is the first study that was able to address the accuracy of MRDTI in a specific series of patients with acute ipsilateral recurrent DVT. This design had also been successfully applied previously for the evaluation of a new scintigraphy in the diagnostic work-up of suspected recurrent ipsilateral DVT.[16] Furthermore, exclusion criteria were designed to exclude only those patients who could not undergo MRDTI and those in whom the group 1 or 2 status

Table 2. Comparison of MRDTI and CUS

	CUS	
	Recurrent ipsilateral DVT, n	Chronic residual thrombosis, n
MRDTI		
Abnormal	37	0
Normal	2	42

could not be established with 100% certainty. In addition to evaluating the diagnostic accuracy of MRDTI, we studied its feasibility in daily clinical practice. Not only did we demonstrate a high reproducibility of the MRDTI results, MRDTI images in all participating hospitals were of good quality, suggesting that MRDTI could be broadly applicable on different MRI machines. The most important limitation of the study is that, by design, the subgroup of patients for which it is hoped MRDTI would be most helpful (ie, those with suspected recurrent DVT and inconclusive CUS) was not part of this study. A further limitation was that only patients with normal D-dimer levels were selected in the control group without recurrent DVT. Although this indeed is a strong argument for the absence of acute DVT, higher D-dimer levels are common in asymptomatic patients after completion of a 6-month treatment period for acute venous thromboembolism (VTE) and are associated with more extensive residual thrombosis as well as a higher recurrence risk.[17,18] Hence, although it is unlikely, we cannot rule out the possibility that the excellent specificity observed in our study might be an overestimation resulting from the selection of relatively nonsevere cases of residual thrombosis. Finally, the MRDTI images were read by readers who were already experienced MRDTI readers, possibly resulting in an overestimation of the reproducibility of the readings and generalizability to other settings. Even so, the images are relatively easy to read (Figures 1 and 2), and specific training of radiologists, in our experience, does not prove to be a major effort.

In conclusion, MRDTI is an accurate and reproducible method for distinguishing acute ipsilateral recurrent DVT from at least 6-month-old chronic residual thrombi in the leg veins when recurrence is not suspected, suggesting a high diagnostic accuracy of MRDTI for the diagnosis of acute proximal ipsilateral recurrent thrombosis when applied as a first- or second-line imaging test in the diagnostic work-up in that setting. Future management studies should confirm the safety of withholding anticoagulants in patients with a single normal MRDTI before this promising technique can be used in daily practice.

Acknowledgments

The authors thank the radiology departments, with special consideration of the magnetic resonance imaging technicians, from all participating hospitals for facilitating this study and performing the magnetic resonance imaging scans.

This study was funded by the Netherlands Heart Foundation (Grant No. 2007B146). All analyses were done independently of the funding source.

Authorship

Contribution: M.T. and M.V.H. designed the research, wrote the manuscript, and analyzed the data; G.C.M., C.J.v.R., R.E.W., A.I.d.S., M.A.v.d.R., and A.d.R. included patients and analyzed the data; and F.A.K. analyzed the data and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Melanie Tan, Leiden University Medical Center, Department of Thrombosis and Hemostasis, Room C4-70, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands; e-mail: m.tan@lumc.nl.

References

1. Tan M, van Rooden CJ, Westerbeek RE, Huisman MV. Diagnostic management of clinically suspected acute deep vein thrombosis. *Br J Haematol.* 2009;146(4):347-360.
2. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. *Ann Intern Med.* 1998;128(8):663-677.
3. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 (2 Suppl):e351S-e418S.
4. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet.* 2012;379(9828):1835-1846.
5. Baglin T, Douketis J, Tosetto A, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost.* 2010;8(11):2436-2442.
6. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl): e419S-e494S.
7. Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. *Haematologica.* 2002;87(5):515-522.
8. Linkins LA, Stretton R, Probyn L, Kearon C. Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity and Doppler venous flow in patients with previous venous thrombosis. *Thromb Res.* 2006;117(3):241-247.
9. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. *Ann Intern Med.* 2002;136(2):89-98.
10. Saha P, Andia ME, Modarai B, et al. Magnetic resonance T1 relaxation time of venous thrombus is determined by iron processing and predicts susceptibility to lysis. *Circulation.* 2013;128(7): 729-736.
11. Moody AR, Pollock JG, O'Connor AR, Bagnall M. Lower-limb deep venous thrombosis: direct MR imaging of the thrombus. *Radiology.* 1998;209(2): 349-355.
12. Westerbeek RE, Van Rooden CJ, Tan M, et al. Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg. *J Thromb Haemost.* 2008;6(7):1087-1092.
13. Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation.* 1993; 88(4 Pt 1):1730-1735.
14. Rathbun SW, Whitsett TL, Raskob GE. Negative D-dimer result to exclude recurrent deep venous thrombosis: a management trial. *Ann Intern Med.* 2004;141(11):839-845.
15. Tan M, Velthuis SI, Westerbeek RE, VAN Rooden CJ, VAN DER Meer FJ, Huisman MV. High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis. *J Thromb Haemost.* 2010;8(4): 848-850.
16. Bates SM, Lister-James J, Julian JA, Taillefer R, Moyer BR, Ginsberg JS. Imaging characteristics of a novel technetium Tc 99m-labeled platelet glycoprotein IIb/IIIa receptor antagonist in patients With acute deep vein thrombosis or a history of deep vein thrombosis. *Arch Intern Med.* 2003; 163(4):452-456.
17. Palareti G, Cosmi B, Legnani C, et al; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355(17):1780-1789.
18. Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA.* 2003;290(8): 1071-1074.