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Deep vein thrombosis : diagnostic and prognostic challenges

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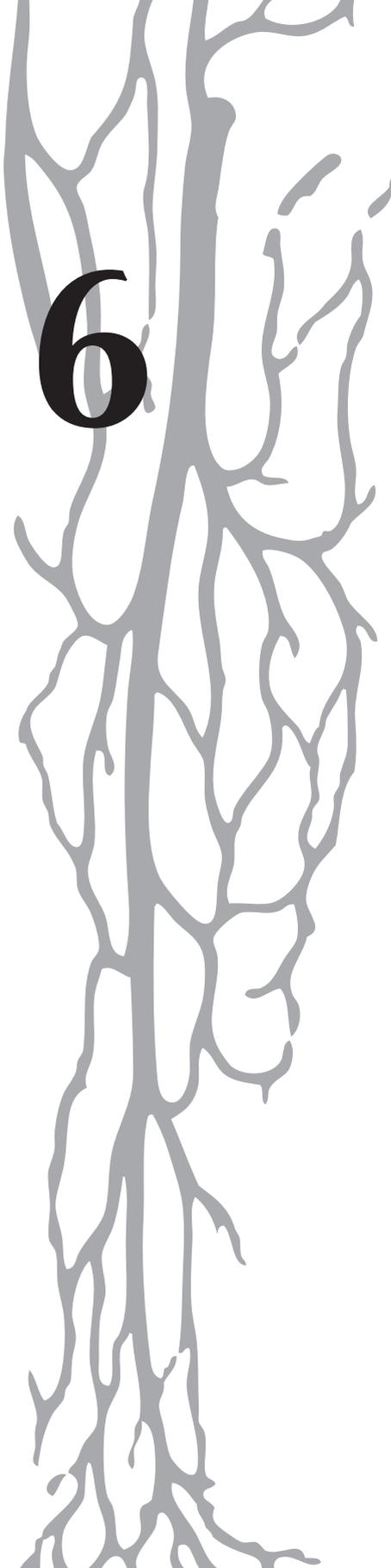
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Diagnosing recurrent DVT of
the leg by two different non-
contrast enhanced Magnetic
Resonance Direct Thrombus
Imaging techniques.

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Submitted

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ABSTRACT

Objectives

Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a promising technique to improve the diagnostic management of patients with a suspected ipsilateral recurrent DVT by direct visualisation of a thrombus. Another MRI technique, T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR), has the potential to image a thrombus directly with a high spatial resolution as well. The main aim of this study was to investigate if adding the TSE-SPAIR sequence to a MRDTI sequence performed in patients with suspected recurrent DVT may increase the diagnostic confidence of expert MRDTI readers.

Methods

Fifteen patients with suspected acute recurrent DVT were included in this study. The TSE-SPAIR sequence was scanned directly after the MRDTI scan but not used to guide clinical decision making, and both scans were adjudicated post-hoc two times separately by 3 independent expert MRDTI readers. Diagnostic confidence was scored on a 4 point Likert scale: 1) poor (definite diagnosis impossible), 2) fair (evaluation of major findings possible), 3) good (definite diagnosis possible), 4) excellent (exact diagnosis possible).

Results

The diagnostic confidence of expert readers increased when adding the TSE-SPAIR sequence on top of the MRDTI sequence from 'good' (median 3.0 [IQR 2.66-3.0]) to 'excellent' (median 3.67 [IQR 3.33-3.67]) $p=0.001$. Evaluation of the scans in the reversed order 5 months after initial reading showed similar results. Diagnostic accuracy for proximal DVT of both scan techniques was good.

Conclusion

The extra TSE-SPAIR sequence may help to increase diagnostic confidence of radiologists in case of uncertain diagnosis in patients with suspected ipsilateral recurrent DVT.

INTRODUCTION

The diagnostic management of suspected ipsilateral recurrent proximal deep vein thrombosis (DVT) is complicated, mainly because of persistent intravascular abnormalities after a first DVT.^{1,2}

With the current imaging technique of first choice, i.e. compression ultrasonography (CUS), it is not always possible to make a distinction between residual vein thrombosis and acute recurrent DVT. CUS can only diagnose recurrent DVT with certainty in case of a new non-compressible venous segment or an increase in vein diameter of a previously non-compressible vein when compared to a reference CUS assessed after a prior DVT.^{3,4} In clinical practice however, a reference CUS is often not available, making it impossible to diagnose an ipsilateral recurrent DVT with CUS.⁵

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique. Several sequences have been evaluated for diagnosing DVT. Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a T1 weighted gradient-echo sequence, that is based on a shortened T1 signal after formation of methaemoglobin in a fresh thrombus.⁶ MRDTI has been shown to accurately diagnose a first DVT and can make a distinction between chronic residual thrombotic scars and an acute recurrent DVT.⁷⁻⁹ MRDTI could therefore potentially be used in the diagnostic management of clinically suspected recurrent ipsilateral DVT.^{2,10}

In a pilot study, the T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence has been tested successfully in three patients with upper extremity DVT.¹¹ With this sequence, an acute thrombus can be directly visualised by the formation of methaemoglobin in a fresh blood clot as well. Moreover, this sequence results in high resolution images with a particular clear resolution of the vessel wall. This latter quality has the potential to increase the accuracy of the diagnosis of ipsilateral recurrent DVT.

We hypothesized that this TSE-SPAIR sequence may have additional diagnostic value on top of the MRDTI sequence in diagnosing acute recurrent ipsilateral DVT.

METHODS

Objectives

The objective of this study was to assess the additional value of a TSE-SPAIR sequence on top of the standard MRDTI sequence with regard to diagnostic confidence, image quality and diagnostic accuracy in the setting of suspected ipsilateral recurrent DVT. Diagnostic confidence was defined as the number of points on a 4 point Likert scale, specified as: 1) poor: definite diagnosis impossible, 2) fair: evaluation of major findings possible, 3)

good: definite diagnosis possible and 4) excellent: exact diagnosis possible. Image quality was scored on a 4 point Likert scale as well, specified as 1) insufficient: insufficient for diagnosis, 2) adequate: adequate for diagnosis, 3) good: minimal inhomogeneity, 4) excellent: no relevant artefacts. The reference standard against which diagnostic accuracy (number of false positive or false negative tests) was tested were the results of the standard MRDTI sequence in combination with a three month follow-up period. Our secondary objective was to explore the diagnostic accuracy of the TSE-SPAIR sequence as single diagnostic test.

Patients

Patients included in the Theia study at the Leiden University Medical Center (LUMC) between March and December 2016 were selected to participate in this study. The Theia study is a prospective, multicentre, single-arm management (cohort) study.¹⁰ The primary objective of this study is to assess the safety of a negative MRDTI scan to rule out acute, recurrent ipsilateral DVT. Inclusion criteria for this study are: 1) suspected acute recurrent ipsilateral DVT as defined by a documented prior objectivated episode of DVT in the same leg as where the current symptoms originate from, 2) Age \geq 18 years 3) ability of subject to understand the character and individual consequences of this study, 4) signed and dated informed consent. Exclusion criteria are: 1) General contraindications for MRI, 2) CUS- proven acute symptomatic DVT within 6 months before current presentation, 3) onset of symptoms suggestive of acute recurrent DVT more than 10 days prior to presentation, 4) suspected acute PE, 5) hemodynamic instability at presentation, 6) medical or psychological condition that would not permit completion of the study or signing of informed consent, 7) non-compliance or inability to adhere to treatment or follow-up visits. The study protocol was approved by the local Institutional Review Board (P4.295, NL50663.058.14) and all patients provided written informed consent.

MRDTI

In the context of the Theia study, patients underwent MRI within 24 hours after presentation with a suspected ipsilateral DVT with a 1.5-Tesla unit (Philips Ingenia 1.5T, release 5, Philips Medical Systems, Best, the Netherlands) with maximum gradient amplitude of 45 mT/m, slew rate of 200 T/m/s, using an integrated 16-channel posterior coil and an 16-channel anterior body coil for signal reception. For the MRDTI sequence a T1-weighted magnetization prepared three-dimensional gradient-echo sequence was used. The sequence includes a water-only excitation radiofrequency pulse (PROSET 121) to eliminate the fat signal, and the effective inversion time is chosen to nullify the blood signal. Scan parameters were: Echo time (TE) 5.2 ms, Repetition time (TR) 10 ms, TFE pre-pulse inversion time 1200 ms, flip angle 15 degrees, field of view 400 x 362, acquisition resolution 1.56 x 2.24 x 4 mm, 60 slices, slice thickness 4 mm (acq)/2mm (rec), slice gap 0

mm. Imaging was performed on both legs simultaneously, from the ankle to the inferior vena cava in two or three imaging blocks, dependent on the length of the patient, using a 55-cm body coil. Scan time was 1.59 minutes for the MRDTI sequence per imaging block. In case of a positive MRDTI signal, anticoagulant treatment was started.

Patients with a negative MRDTI were subjected to a standardized compression ultrasonography (CUS) within 48 hours after initial presentation. This CUS served as reference test in case the patient returned with symptoms of ipsilateral recurrent DVT during follow-up, however it was not used for management decisions at baseline. All patients were followed for three months for the occurrence of recurrent VTE.

TSE-SPAIR sequence

The TSE-SPAIR sequence was performed after the MRDTI sequence in the same session, without motion of the patient between the two scans. 3D TSE SPAIR is a T1 weighted 3D sequence using a spectral, adiabatic presaturation (inversion) pulse to achieve fat suppression. Scan parameters were: Echo time (TE) 24 ms, Repetition time (TR) 400 ms, SPAIR inversion delay 110 ms, flip angle 90 degrees, field of view 400 x 350, acquisition resolution 1 x 1 x 1 mm, 200 slices, slice thickness 1 mm, slice gap 0 mm. With this sequence the affected leg was scanned from the calve to the hip in two imaging blocks, with an extra imaging time of 4.15 minutes per block, leading to a total imaging time of 20 minutes. This extra TSE-SPAIR sequence was not shown to the radiologist who evaluated the MRI scan for the Theia study. This way, the TSE-SPAIR sequence did not influence the final diagnosis and treatment of the patients.

Image Analysis

After the follow-up period of the Theia study was completed for all patients included in the current analysis, the MRDTI and TSE-SPAIR sequences were evaluated separately by three independent readers with experience in MRDTI reading: KL (radiology resident with 5 years of experience) AR (radiologist with >20 years of experience) and AS (radiologist with 10 years of experience) who were blinded to the final clinical diagnosis and follow-up of the study subjects and had not seen the MRDTI images of the patients before the current reading. All scans were evaluated twice in two phases. First, the MRDTI scan was read and scored for diagnosis, diagnostic confidence and image quality (**Table 1**). Proximal DVT was defined as thrombus present in the external iliac, common femoral, deep femoral, superficial femoral or popliteal vein and distal DVT as thrombus located below the knee in the posterior or anterior tibial, peroneal or muscular veins. Secondly, the TSE-SPAIR sequence was shown to the readers, and the combination of the MRDTI and TSE-SPAIR scan was again scored for diagnosis, diagnostic confidence and image quality. To be able to explore the diagnostic accuracy of the TSE-SPAIR sequence alone, all scans were scored for the second time by all reviewers, in the reversed order

Table 1. Scoring Form Diagnostic Confidence and Image Quality: 4 point Likert scale [21]

Diagnostic confidence MRDTI		Image Quality MRDTI		Diagnostic confidence MRDTI + TSE-SPAIR/ TSE SPAIR + MRDTI		Image Quality TSE-SPAIR	
1) Poor	Definite diagnosis impossible	1) Insufficient	Insufficient for diagnosis	1) Poor	Definite diagnosis impossible	1) Insufficient	Insufficient for diagnosis
2) Fair	Evaluation of major findings possible	2) Adequate	Adequate for diagnosis	2) Fair	Evaluation of major findings possible	2) Adequate	Adequate for diagnosis
3) Good	Definite diagnosis possible	3) Good	Minimal inhomogeneity	3) Good	Definite diagnosis possible	3) Good	Minimal inhomogeneity
4) Excellent	Exact diagnosis possible	4) Excellent	No relevant artifacts	4) Excellent	Exact diagnosis possible	4) Excellent	No relevant artifacts

with a minimum period of 5 months in between the adjudications: first, the TSE-SPAIR sequence was scored for diagnosis, diagnostic confidence and image quality, and thereafter, the MRDTI sequence was shown, and the combination of the TSE-SPAIR and MRDTI sequence was scored for the same variables.

Statistics

It was predefined to include 15 patients in this study based on the number of patients included in comparable diagnostic studies.^{12,13} The Wilcoxon signed rank test was used to evaluate the difference in diagnostic confidence and image quality between the MRDTI and TSE-SPAIR sequence. To analyse overall differences, the Likert scale scores of the three independent readers were first combined and divided by 3. A p-value <0.05 was considered statistically significant. The number of false positive and false negative tests based on the MRDTI sequence alone and MRDTI plus TSE-SPAIR sequences together, as well as the TSE-SPAIR alone and combined with MRDTI, were calculated based on the results of the majority; i.e. two out of three reviewers, with the clinical diagnosis based on MRDTI and events occurring during 3-month FU as reference. Exact diagnostic accuracy numbers, i.e. sensitivity and specificity were not calculated since the sample size was too small. All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY).

RESULTS

Patients

Of the 15 included patients, 8 were female and 7 male, and their mean age was 49 years (range 24-71). The duration of complaints ranged from 1-10 days (median 3, IQR 2-8.5). With MRDTI 1 patient was diagnosed with proximal ipsilateral recurrent DVT (**Figure 1**) and anticoagulant therapy was started. Two patients were diagnosed with limited distal DVT, for which anticoagulant therapy was started as well. Twelve patients had a negative MRDTI scan, of which reference CUS was normal in seven. In the five remaining patients with a negative MRDTI scan CUS indicated thrombus material in the femoral vein (1 patient) or popliteal vein (4 patients). For none of these five patients it was possible to make a distinction between acute DVT and residual DVT with CUS. None of the 12 patients with a negative MRDTI were treated with anticoagulants and none developed clinical symptoms of a recurrent VTE during a 3-month follow-up period.

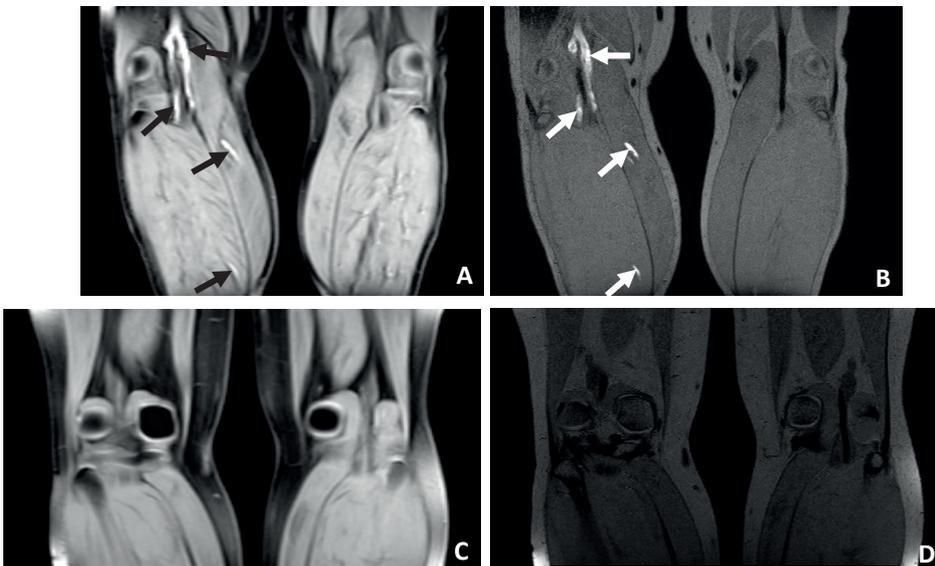


Figure 1. Panel A and B: 51 year old male patient (patient 1, table 2) with a recurrent DVT of the left leg, shown on the MRDTI sequence (panel A, black arrows) and TSE-SPAIR sequence (panel B, white arrows) Panel C and D: 42 year old female patient with a suspected recurrent DVT of the right leg (patient 11, table 2), ruled out based on the results of the MRDTI (panel C) and TSE-SPAIR (panel D) sequence

Diagnosis and accuracy of MRDTI and MRDTI + TSE-SPAIR

Table 2 shows the diagnosis of the individual scans of each reviewer and the number of false-positive and false negative tests of the 3 reviewers together based on the majority rule when comparing the MRDTI and MRDTI + TSE-SPAIR sequences against the results

of the MRDTI sequence at baseline. The evaluation of the MRDTI sequences by the three independent readers corresponded overall for 93% with the original MRDTI reading. After adding the TSE-SPAIR sequence on top of the MRDTI sequence for evaluation, the consensus diagnosis changed for one patient who 2 of 3 radiologists judged to have a normal MRDTI, to distal DVT based on the TSE-SPAIR. Notably, this patient was diagnosed with distal DVT and treated with anticoagulants based on the results of the MRDTI scan reading at baseline.

Table 2. Diagnosis and number of false positive or negative cases for the majority of the 3 reviewers

Patient	Clinical diagnosis: based on MRDTI and events occurring during 3-month FU		MRDTI			MRDTI+TSE-SPAIR			TSE-SPAIR			TSE-SPAIR +MRDTI					
			Proximal		Distal	Proximal		Distal	Proximal		Distal	Proximal		Distal			
			Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer	Reviewer			
	Proximal DVT	Distal DVT	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	+	-	-	+	-	-	-	-	+	-	+	-	+	+	+	+
4	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
5	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	+	-	-	+	+	+	-	-	+	+	+	-	-	+	-	+
8	-	-	-	-	-	-	-	-	-	+	-	-	-	+	+	-	-
9	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-
Number of false positive and false negative interpretations counted for the majority of the 3 reviewers.			1 false negative						2 false positive								

Note: += positive for DVT -=negative for DVT

MRDTI and TSE-SPAIR analysis: diagnostic confidence

The diagnostic confidence of MRDTI was scored overall, after pooling the results from the reviewers, as 'good' for a Likert scale score 3.0 (IQR 2.66-3.0). After adding the TSE-SPAIR sequence, the overall median diagnostic confidence increased significantly to 'excellent' for a Likert scale of 3.67 (IQR 3.33-3.67; $p=0.001$) (**table 3**).

Table 3. Overall diagnostic confidence MRDTI and MRDTI + TSE-SPAIR sequences and vice versa

	Overall
Diagnostic confidence MRDTI	Median: 3.0 (IQR 2.66-3.0)
Diagnostic confidence MRDTI+TSE-SPAIR	Median: 3.67 (IQR 3.33-3.67)
Wilcoxon signed rank test	$p=0.001$
Diagnostic confidence TSE-SPAIR	Median: 3.33 (IQR 3.0-3.67)
Diagnostic confidence TSE-SPAIR + MRDTI	Median: 3.67 (IQR 3.0-3.67)
Wilcoxon signed rank test	$p=0.176$

Note: IQR: interquartile range

MRDTI and TSE-SPAIR analysis: image quality

Overall, the image quality of the TSE-SPAIR sequence was judged to be slightly better than the MRDTI sequence with a median increase from 2.67 (IQR 2.67-3.00) to 3.00 (IQR 3.00-3.33; $p=0.018$) (**table 4**). There was no correlation between image quality and diagnostic confidence.

Table 4. Overall Image quality MRDTI and TSE-SPAIR

	Overall
Image quality MRDTI	Median: 2.67 (IQR 2.67-3.00)
Image quality TSE-SPAIR	Median: 3.00 (IQR 3.00-3.33)
Wilcoxon signed rank test	$p=0.018$
Image quality TSE-SPAIR	Median: 3.33 (IQR 3.0-3.33)
Image quality MRDTI	Median 3.0 (IQR 3.0-3.33)
Wilcoxon signed rank test	$p= 0.35$

IQR= interquartile range

Evaluation in reversed order: TSE-SPAIR alone and TSE-SPAIR + MRDTI

The evaluation of the TSE-SPAIR sequences alone corresponded overall for 82% with the original MRDTI reading (**table 2**). Based on the TSE-SPAIR sequence alone, 2 additional patients were diagnosed with distal DVT, on top of the 3 patients diagnosed with proximal or distal DVT on the aggregate reading of MRDTI. Indeed, after adding the MRDTI sequence, these two patients were adjudicated as not having DVT, which corresponded with the results of the MRDTI scan reading and management decision at baseline. Overall, the median diagnostic confidence increased after evaluation of the MRDTI sequence on top of the TSE-SPAIR sequence from a median of 3.33 (IQR 3.0-3.67) to 3.67 (IQR 3.0-3.67), although this change was not significant ($p=0.176$). Image quality of the TSE-SPAIR sequence was scored slightly better (table 4).

DISCUSSION

This study shows that after adding the TSE-SPAIR sequence on top of the MRDTI sequence for diagnosing proximal ipsilateral recurrent DVT, diagnostic confidence increased overall from 'good' (median 3.0, IQR 2.66-3.0) to 'excellent' (median 3.67, IQR 3.33-3.67). When the scans were evaluated in the reversed order, the diagnostic confidence did also increase but to a lesser extent. The image quality of the TSE-SPAIR sequence was scored higher than the MRDTI sequence for the first and second evaluation. The diagnostic accuracy of both imaging tests for proximal DVT was good, although the small sample size does not allow calculation and comparison of sensitivity.

With the MRDTI sequence, a thrombus can be visualized directly as a hyperintense signal based on the shorter T1 relaxation time in comparison with blood. The change in the T1 relaxation time is caused by change in paramagnetic properties by accumulation of methemoglobin in fresh thrombus, which is formed from haemoglobin by the oxidation of Fe²⁺ into Fe³⁺ during the acute phase of DVT.^{14,15} Previous studies have shown that this high signal appears within 3 hours after thrombus formation and resolves completely after 6 months.¹⁵ The same bright signal intensity can be visualized with the TSE-SPAIR sequence. Additionally, this sequence has a better spatial resolution, leading to improved visualization of the vessel-wall.¹³ The better visualisation of the vessel wall may help to (double) confirm that increased signal intensity is indeed present in one of the deep veins, and is not an artifact. In the MRDTI sequence the signal in arteries may appear high due to inflow effect, even when using a saturation slab. This may explain the overall increase in diagnostic confidence for the reviewers when the TSE-SPAIR sequence was evaluated on top of the MRDTI sequence in this study. This raises the question whether TSE-SPAIR may be standardly combined to MRDTI scanning, and/or has the potential to be used as a single test, instead of MRDTI. Importantly, for

the TSE-SPAIR sequence, the timing of development and disappearance of high signal intensity in thrombus is not validated yet. This was also noticed during evaluation of the TSE-SPAIR sequences alone: some venous segments were detected with an intermediate/ 'grey' signal and considered positive for DVT in two patients, although they were considered negative for DVT on the initial MRDTI evaluation. Of note and in contrast to MRDTI, TSE-SPAIR has to be tested against the gold standard in a larger patient group before it can be used as single test. An advantage of using the MRDTI and TSE-SPAIR sequences is that these are both non-contrast enhanced MRI sequences. Disadvantages of using Gadolinium-based contrast agents are costs of the contrast agent itself, application materials, and more importantly the extra time needed for contrast administration. Potential risks are adverse events (contrast allergy, and nephrogenic systemic sclerosis in patients with severe renal insufficiency).¹⁶ Also, recent research has suggested the potential risk of gadolinium retention in the human body.¹⁷

A disadvantage of using the TSE-SPAIR sequence on top of the MRDTI sequence is the significant increase in MRI scan time, approximately 8 minutes per investigation. With the high costs and low availability of MRI time, this may be an important issue.

Similar non-contrast enhanced direct thrombus imaging MRI techniques have been investigated for the visualization of the intracranial arteries, the carotid artery and the superficial femoral arteries.¹⁸⁻²⁰ To our knowledge there is only one other study that investigated a MRI technique that is comparable with TSE-SPAIR for diagnosing DVT.¹³ That was a small pilot study including thirteen patients with a CUS proven first DVT and using a 3.0 Tesla scanner with a volumetric isotropic turbo spin-echo acquisition technique (VISTA). Accuracy was calculated compared with contrast-enhanced MRI and ultrasonography as a reference standard. This resulted in a sensitivity of 77.8%, specificity of 94.8%, a negative predictive value of 91.6% and a positive predictive value of 85.4%. Image quality and diagnostic confidence level of VISTA were 3.54 and 3.80 respectively, both scored on a 4 point Likert scale. Compared with our study, that study included patients with a suspected first DVT, instead of recurrent DVT in our study, and they used a contrast-enhanced MRI and ultrasonography as reference to the VISTA technique instead of another T1 weighted MRI technique. Additionally, the diagnostic confidence was based on the VISTA technique alone instead of MRDTI +TSE-SPAIR together in our study so therefore direct comparison of the results of the two studies is not possible. However, the diagnostic confidence of VISTA and MRDTI+TSE-SPAIR was comparable with Likert scale scores of 3.80 and 3.67 respectively.

A limitation of our study was that we have no reference test to identify false-positive patients since it is not possible to differentiate residual thrombosis from acute recurrent thrombosis neither with ultrasound nor with venography. A second limitation was that the three independent readers were experienced in reading the MRDTI sequences, but had no experience in reading TSE-SPAIR sequences, which may have influenced our

findings. Thirdly, our sample size was small, most of them were negative cases and the study was not powered nor designed to compare the diagnostic accuracy of both scan sequences accurately.

In conclusion, this study shows that the diagnostic confidence improved when adding the TSE-SPAIR sequence to the MRDTI sequence for diagnosing acute recurrent proximal DVT. The extra (TSE-SPAIR) sequence may help to increase diagnostic confidence in case of uncertain diagnosis.

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