Deep vein thrombosis : diagnostic and prognostic challenges

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Diagnosing upper extremity deep vein thrombosis with non-contrast-enhanced magnetic resonance direct thrombus imaging: a pilot study

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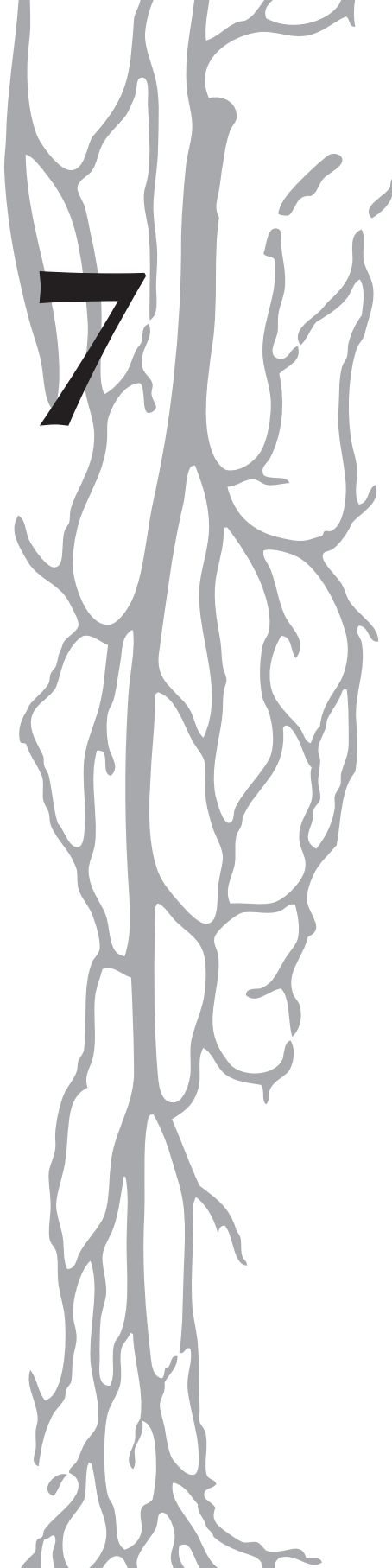

ABSTRACT

Diagnosing upper extremity deep vein thrombosis (UEDVT) can be challenging. Compression ultrasonography is often inconclusive because of overlying anatomic structures that hamper compressing veins. Contrast venography is invasive and has a risk of contrast allergy. Magnetic Resonance Direct Thrombus Imaging (MRDTI) and Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) are both non-contrast-enhanced Magnetic Resonance Imaging (MRI) sequences that can visualize a thrombus directly by the visualization of methemoglobin, which is formed in a fresh blood clot. MRDTI has been proven to be accurate in diagnosing deep venous thrombosis (DVT) of the leg. The primary aim of this pilot study was to test the feasibility of diagnosing UEDVT with these MRI techniques. MRDTI and 3D TSE-SPAIR were performed in 3 pilot patients who were already diagnosed with UEDVT by ultrasonography or contrast venography. In all patients, UEDVT diagnosis could be confirmed by MRDTI and 3D TSE-SPAIR in all vein segments. In conclusion, this study showed that non-contrast MRDTI and 3D TSE-SPAIR sequences may be feasible tests to diagnose UEDVT. However, diagnostic accuracy and management studies have to be performed before these techniques can be routinely used in clinical practice.

INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) accounts for 4-11% of all thromboses in the deep veins.[1,2] UEDVT is defined as a thrombus localized in the internal jugular, subclavian, axillary, brachial or brachiocephalic vein. Prompt and accurate diagnosis of UEDVT is important to prevent pulmonary embolism (PE) and long-term complications including the post-thrombotic syndrome.[3]

Compression ultrasonography has as major limitation when the thromboses are located more centrally in the subclavian region, compression is impeded due to overlying anatomical structures. Therefore, contrast venography is the reference standard in these cases, but this poses risks to the patient due to its invasive nature, radiation exposure and the potential for allergic reactions to contrast media.[4] CT-Venography (CT-V) can also be used to detect thrombi, but large studies with CT-V in patients with suspected UEDVT are lacking.[5] Moreover, CT-V is associated with exposure to contrast media and ionizing radiation as well. Magnetic Resonance Venography (MRV) has also been evaluated for diagnosing UEDVT. This MRI technique uses a gadolinium-based contrast agent, and has shown low accuracy in a feasibility study of 44 patients with a sensitivity of 50% and a specificity of 80%.[6] Time of Flight (TOF) MR venography is a non-contrast based technique, however has a long imaging time and showed low accuracy also.[6] Magnetic Resonance Direct Thrombus Imaging (MRDTI) and Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) are both MRI sequences that can visualize a thrombus directly without need of venous contrast by the visualization of methemoglobin, which is formed in a fresh blood clot. MRDTI has already been shown highly accurate in diagnosing a first DVT of the leg.[7] In a pilot study a three-dimensional black blood T1-weighted turbo spin-echo technique (VISTA), another direct thrombus imaging technique, has been compared to contrast-enhanced MRI for the diagnosis of DVT.[8] This technique is comparable with the T1 weighted 3D TSE-SPAIR sequence. To date, there are no published reports on the use of MRDTI or 3D TSE-SPAIR in patients with a suspected UEDVT. Since formation of methemoglobin in a thrombus is common in DVT within both the lower and the upper extremities, we hypothesize that MRDTI and 3D TSE-SPAIR may also be accurate diagnostic tests for UEDVT. In this pilot study we assess the feasibility of MRDTI and 3D TSE-SPAIR sequences to visualize UEDVT in 3 patients who were already diagnosed with UEDVT by ultrasonography and/or venography.

METHODS

This pilot study was performed in the context of the MAGNITUDE/Selene study (NTR5738), a prospective proof of concept study to explore the diagnostic accuracy of MRDTI and

3D TSE-SPAIR in the diagnostic management of UEDVT. It was pre-defined to first include 3 pilot patients with confirmed UEDVT, as to optimize the MRI scan techniques before including 60 additional patients. The study was approved by the institutional review board and all patients provided written consent.

Patients

We included three adult patients who were referred to the Radiology department of our hospital between December 2016 and March 2017 with a clinically suspected acute UEDVT, after symptom onset <10 days before presentation, who were diagnosed with UEDVT by ultrasonography and/or by venography and had no contra-indications for MRI.

MRI

MRI was performed using a 1.5-Tesla unit (Philips Ingenia 1.5T, release 5, Philips Medical Systems, Best, the Netherlands) to image the subclavian, axillary, brachial and brachio-cephalic vein. Image assessment involved acquiring images in the coronal plane with standard image reconstruction techniques. First, a MRDTI sequence was performed; directly followed by a 3D TSE-SPAIR sequence. Scan parameters of both sequences were optimized from imaging DVT of the legs to imaging UEDVT. MRDTI is based on visualization of methemoglobin which is formed in a fresh thrombus by the oxidation of haemoglobin. Methemoglobin has other paramagnetic properties which causes shortening of the T1- relaxation time and consequently appears as a high signal on a T1 weighted MRI scan.[9,10] This signal disappears completely after 6 months.[11] Therefore, this technique can also differentiate between acute recurrent thrombosis and asymptomatic residual thrombosis.[12,13] 3D TSE-SPAIR is based on the visualization of methemoglobin as well, but results in a higher spatial resolution of the vessel wall than MRDTI.[8] The time course of the methemoglobin signal is not known for this sequence.

Image analysis

Results of the MRDTI and 3D TSE-SPAIR images were evaluated by an expert panel (L.K. , C.D. and G. v. H.). Acute UEDVT was confirmed by high MRI signal against suppressed background.

RESULTS

Optimization of MRI sequences

MRDTI and 3D TSE-SPAIR sequences were used with an integrated 16-channel posterior coil and a 16-channel anterior body coil (scan parameters, **table 1**). MRDTI includes a

Table 1. MRDTI and 3D TSE-SPAIR scan parameters

	MRDTI	3D TSE-SPAIR
Technique	T1TFE	TSE
Orientation	Coronal	Coronal
FOV	400x405	350x400
Slices	60	180
Thickness	4.0	1.1
Voxelsize	1.6 x 2.24 acq. 1.6 x 1.6 recon	1.09 x 1.1acq. 0,5 x 0,5 recon
Scantime	5:53	5:33
Echo time	5.4	23
Repetition Time	11	400
Flip Angle	15	90
TFE prepulse Inversion Time	1200	-
SPAIR Inversion delay	-	110

Note: all times in ms

water-only excitation radiofrequency pulse to abolish the fat signal; the effective inversion time is chosen to nullify the blood signal. 3D TSE SPAIR is a T1 weighted 3D sequence using a spectral, adiabatic presaturation (inversion) pulse to achieve fat suppression. To optimise the MRDTI sequence for visualization of UEDVT, a saturation slab was placed obliquely over the heart for suppression of possible and potentially confusing high signal in the arteries due to inflow effects.

The anatomy of interest was placed as close as possible to the isocenter of the magnet for optimal image quality and fat suppression.

Patients and MRI results

The first patient was a 48-year-old woman, known with diabetes mellitus type II and hypertension. She presented with pain and swelling of her left arm three days after exercising with repetitive arm movements above her head. On examination, her left arm was swollen, red and painful and showed collateral superficial veins. Compression ultrasonography (CUS) revealed a thrombus in the brachial, axillary and subclavian vein up to the jugular vein. MRDTI and 3D TSE-SPAIR MRI was performed 11 days after initial CUS diagnosis. For both sequences a high signal, corresponding with DVT in the left subclavian and axillary vein was reported (**Figure 1A, 1B**).

The second patient was a 38-year-old male, without relevant medical history, who had progressive swelling of the left arm and hand for two days. Besides a brother who had experienced idiopathic pulmonary embolism at the age of 35, he had no other risk factors for thrombosis. On physical examination the left arm was edematous, warm, with red/purple colouring of the hand but without any pain. The left upper arm circumference

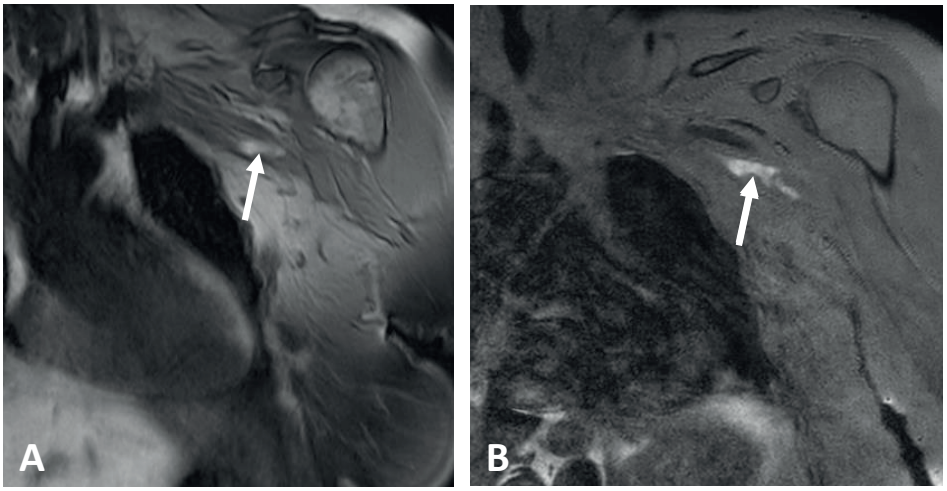

Figure 1A, 1B – Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.

48-year-old woman diagnosed with thrombosis in the left brachial-, axillary- and subclavian veins by compression ultrasonography. MRI: high signal intensity in the left subclavian vein, diagnostic for recent DVT (arrow).

was 5 cm larger than the right arm. CUS was performed, which showed no thrombosis but a slow venous return from the superficial and deep veins of the arms. Subsequently, a CT scan with venous contrast was performed, showing a lack of contrast in the left subclavian vein, but without an abrupt stop of contrast. This finding was highly suspected for UEDVT although not conclusive. Therefore, a contrast venography was performed, which finally confirmed a thrombosis in the left subclavian vein. MRI was performed 1 day after the venogram. MRDTI and 3D TSE-SPAIR MRI corresponded with the results of venography and were reported as DVT of the left subclavian vein (**Figure 2A,2B**).

The third patient was a 53-year old female known with Ehlers-Danlos type III in history, who was admitted to the hospital with fever and pain in her left arm. One week before admission, a long intravenous line, which was used for intravenous feeding, was replaced from her left subclavian vein to her right subclavian vein because of infection. On physical examination she had swelling and pain in her left arm. CUS revealed a thrombus in the left subclavian vein. MRDTI was performed 3 days after UEDVT diagnosis. MRDTI and 3D-TSE SPAIR were evaluated as diagnostic for a small thrombus in the subclavian vein based on a small high signal intensity focus that was only identified by following the precise course of the subclavian vein (**Figure 3A, 3B**).

The delay in performing the MRI scans in the first and third patient was due to logistic reasons. In all 3 patients 3D TSE-SPAIR was judged as visualizing the vessel walls with a higher spatial resolution, with improved anatomical distinction between the arteries and veins. The thrombus signal intensity was judged to be higher with 3D TSE-SPAIR

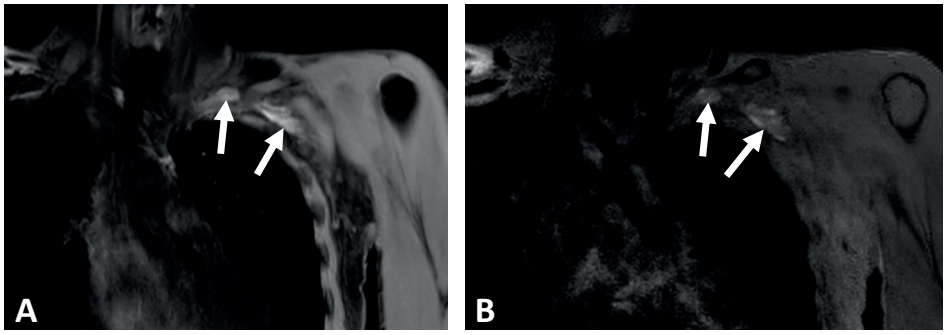

Figure 2A, 2B – Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.
38-year-old man, diagnosed with thrombosis in the left subclavian vein by contrast venography. MRI: striking high signal intensity in the left subclavian vein, diagnostic for recent DVT.

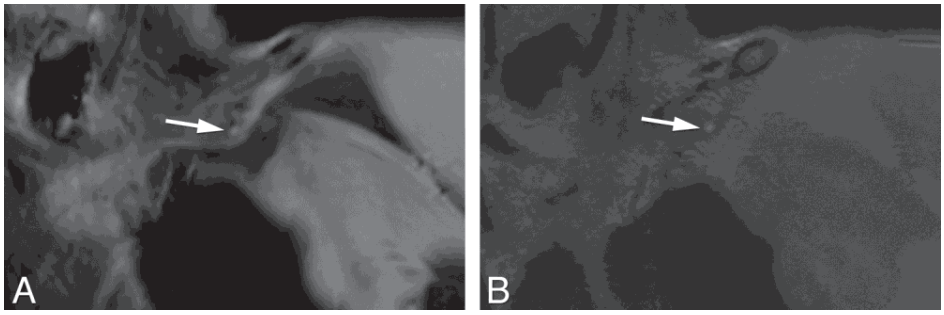

Figure 3A, 3B– Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.
53-year-old woman, diagnosed with a thrombus in the left subclavian vein by ultrasonography. MRI: Small high signal intensity focus that was only identified by following the precise course of the subclavian vein, diagnostic for recent DVT (arrow).

than MRDTI in patient 1, MRDTI was judged as showing higher signal intensity than 3D TSE-SPAIR in patient 2, and in patient 3 the signal intensity was evaluated as equal between the two sequences.

DISCUSSION

This feasibility study showed that both MRDTI and 3D TSE-SPAIR sequences were able to visualize UEDVT in 3 patients with confirmed UEDVT. The non-invasive diagnostic management of UEDVT is challenging, as illustrated by the case of patient 2. Ultrasonography, CT-venography and contrast venography had to be performed before the diagnosis could be established. MRI is both non-invasive and safe, and has particular

advantages over compression ultrasound for imaging the subclavian vein behind the clavicle. MRI is available in most hospitals, and radiology residents can be trained to independently review MRI investigations within a short training program.[14] Also, MRDTI and 3D TSE-SPAIR sequences together have a short imaging time of only 11 minutes. However, MRI is associated with higher costs than ultrasonography. Moreover, MRI scan time may not be readily available in the acute setting. Therefore MRI, after further validation, could potentially be used as a second test when CUS is not conclusive especially for the subclavian vein, i.e. in patients with a high clinical suspicion but normal CUS, instead of venography and/or in patients with known contrast allergy.

In this study we tested two different non-contrast enhanced MRI sequences, i.e. MRDTI and 3D TSE-SPAIR, which showed similar results in diagnosis, although with varying signal intensity of the thrombus. For the MRDTI sequence it is well established that a fresh thrombus results in a high signal by the visualisation of methemoglobin within 3 hours after thrombus formation and this high signal disappears completely after 6 months.[9,11] This last characteristic allows MRDTI to distinguish acute thrombosis from chronic residual thrombus.[12] However, the time frame for visualizing methemoglobin in thrombus is not known yet for the 3D TSE-SPAIR sequence. An advantage of 3D TSE-SPAIR over MRDTI is the higher spatial resolution of the vessel wall. Also, the signal of normal veins and arteries is low in this sequence whereas in the DTI sequence the signal in arteries may appear high due to inflow effect, even when using saturation slabs. Both sequences have to be tested in more patients to investigate the similarities and differences in thrombus-intensity on both sequences.

To our knowledge these are the first UEDVT cases confirmed by MRI by using MRDTI and 3D TSE-SPAIR sequences without using contrast-agents in patients with UEDVT. Two other MRI techniques have been tested in the past: time of flight vessel imaging and gadolinium contrast-agent enhanced MR-venography, but the first technique had long scan times and both techniques showed low accuracy for DVT.[6] In 2 of the 3 patients presented, MRI could not be performed within 24 hours after diagnosis of UEDVT because of logistical reasons. This could have led to a less high signal of the thrombus on both sequences due to resolution of thrombus after medical therapy over time.

We conclude that this pilot study suggests that both MRDTI and 3D TSE-SPAIR sequences may be feasible non-invasive non-contrast-enhanced tests to diagnose UEDVT. However, the sensitivity and specificity of these sequences have to be further explored and the safety of using these MR sequences to diagnose or rule-out UEDVT confirmed in an outcome study. Based on the presented 3 cases, the Magnitude/Selene study (NTR5738) will be performed to more accurately determine the diagnostic accuracy of MRDTI and 3D TSE-SPAIR in the diagnostic management of UEDVT.

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