
Magnetic resonance imaging of vein wall thickness in patients with Behçet's syndrome

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ABSTRACT

Objective. Vascular disease is a serious complication of Behçet's syndrome (BS), occurring in up to 20% of subjects. Superficial thrombophlebitis, deep vein thrombosis, and arterial aneurysm formation are the most common manifestations. Venous thrombosis is thought to result from vessel wall inflammation. This work investigated the potential usefulness of high resolution magnetic resonance imaging (MRI) to identify inflammation in the venous walls in BS subjects.

Methods. Seven healthy control (HC) subjects and five BS subjects were scanned with 3T MRI (Siemens Skyra). A standard MRI sequence was adapted for use in the venous system. Metronome guided breathing generated a regular respiratory variation of venous blood velocity. The vein wall imaging was triggered at an appropriate delay after the metronome. The popliteal vein was imaged. Vein wall images were ranked based on wall thickness and signal enhancement by two blinded, experienced observers.

Results. Popliteal vein rank scores were found to be significantly increased in BS versus HC subjects by the first observer ($p_{(\text{Observer } 1)}=0.025$, $p_{(\text{Observer } 2)}=0.07$) and also averaging both observers ($p=0.05$). The repeated images of each subject gave a degree of variability in results, potentially from drifting response to metronome guidance over the 10 minute scan.

Conclusion. MR imaging can detect increased vein wall thickness in BS subjects compared to healthy controls. Variable response to the metronome-guided breathing requires further development.

Introduction

Behçet's syndrome (BS) is a multisystem inflammatory disorder characterised by orogenital aphthous ulceration and uveitis (1). Vascular involvement is

a serious complication of BS, occurring in up to 20% of subjects (2). In contrast to other vasculitides, vascular involvement in BS predominantly affects the venous system (superficial thrombophlebitis and deep venous thrombosis). Where arterial involvement occurs, it may manifest as obstructions and aneurysms affecting arteries of any size (3). Young males from endemic regions have a higher likelihood of vascular involvement (4). No reliable clinical tool exists to accurately identify high risk patients or assess if inflammation is controlled adequately with immunosuppression. Therefore, development of a method to identify patients with vascular inflammation would be an important advancement in the clinical setting.

Previous studies assessing vessel wall thickness in BS have mainly been conducted on arteries (usually the carotid arteries) with the use of ultrasound. In a study of the cardiovascular prognostic value of ultrasound in BS patients, one group compared the carotid artery intima-media thickness (IMT) in BS (with/without vascular involvement) with healthy controls (5). Their results showed a small non-significant increase in the BS cohort. Another group showed a significant increase of ~50% in carotid intima-media thickness (IMT) in 21 patients with BS compared to age and sex matched HCs (6). This study also showed a correlation between carotid IMT and serum vascular endothelial growth factor.

MRI/MRA has been used in BS to screen for aneurysms and thrombosis, and cardiac MRI is also used with suspected cardiac involvement. Importantly, previous studies have not yet resulted in a clinically useful tool to anticipate vascular complications.

Blood vessel wall imaging and MRI

As venous thrombosis in BS is thought to result from inflammation in the vessel wall, there is a need for techniques

to show increased vessel wall thickness and inflammation-related signal enhancement. Whilst the use of MRI in the arterial system (*e.g.* carotid arterial wall thickness) is well established, MRI of the venous system is challenging. The walls of veins tend to be thinner and more deformable than those of arteries, and flow in veins distant from the heart contains little cardiac pulsatility, with flow and pressure variations induced by respiration and skeletal muscle activity moving the vein walls. Additional technical requirements include the need for the usually bright blood signal to be “nulled” to allow visualisation of the vessel wall, requiring a specified time between blood nulling and vessel wall imaging, which must be stable during the imaging period; and the requirement for multiple cycles to build up the required data for images. Because of these difficulties,

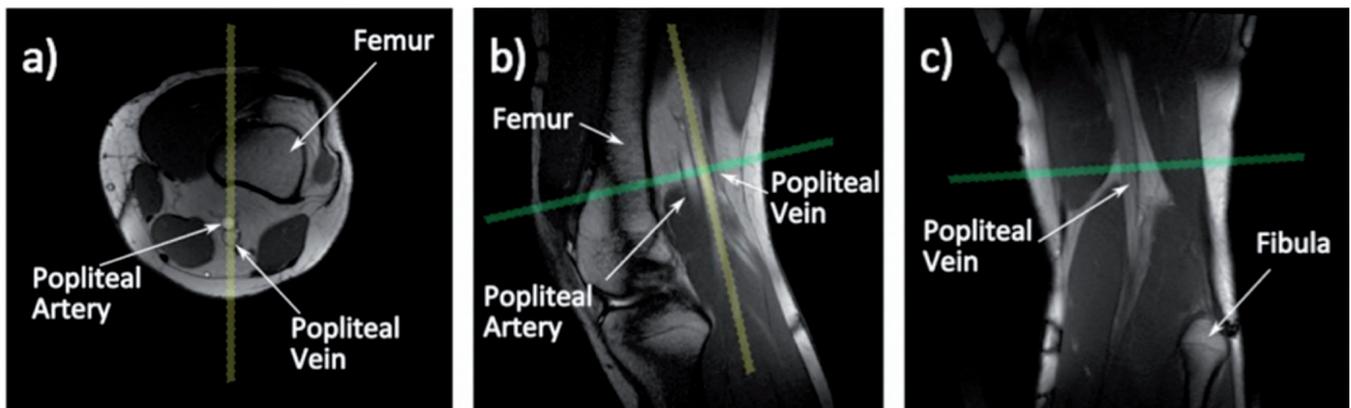
MRI of the venous system has been afforded relatively little attention.

This work investigated the potential usefulness of high resolution MRI in identifying inflammation in the venous walls in BS patients.

Methods

Ethical approval was obtained from the local ethics committee. Following written consent, 7 HCs (ages 21–46 years, median age 27 years) and 5 BS subjects (ages 23–47 years, median age 36 years) were scanned. All BS subjects fulfilled the International Study Group diagnostic criteria (7) and 3 had a history of vascular involvement. Subjects underwent an MRI examination using a 3T MR scanner (Skyra, Siemens, Erlangen, Germany) with the following protocol. The patients lay prone with a flexible surface coil (Siemens, 3T Tim Flex small, 36 x 17 cm) wrapped loose-

ly around the posterior of the left knee joint, centred slightly proximally to the bend of the knee. Metronome guided breathing generated a regular respiratory variation of venous blood velocity. The duration of the metronome breathing cycle was 5 seconds (inspiration 2 seconds, expiration 3 seconds) which was designed to be manageable for subjects to maintain a natural breathing rhythm. The metronome was signalled to subjects using an LED visible to them driven by an external pulse generator, which was also connected to the gating-input of the MRI scanner. A standard MRI sequence (fast-spin-echo (FSE), with double inversion-recovery (DIR) nulling of blood signal for improved visualisation of vein walls) was adapted for use in the venous system. The FSE vein wall imaging was triggered at an appropriate delay after the metronome, which was determined in-



d) Parameter	Value
FOV (Read x Phase) (mm)	100 x 81
Acquired resolution (Reconstructed) (mm)	0.384 x 0.384 x 3 (0.19 x 0.19 x 3)
TE / ES / Tacq (ms / ms/ mins)	12 / 12 / ~10
TI (s)	1
Echo train	7
Averages	2
Dark blood thickness (%)	110
Dark blood flip angle (°)	180
Bandwidth (Hz/Px)	303
PE direction	A-P

Fig. 1. bSSFP localiser images from a normal subject showing a: transverse slice through the leg proximal to the knee; b: a sagittal slice through the main popliteal vein; c: coronal slice along the vein. Green boxes indicate the final imaging slice; d: shows the blood-nulled fast spin-echo (FSE) sequence parameters used to obtain the images shown in Figure 2.

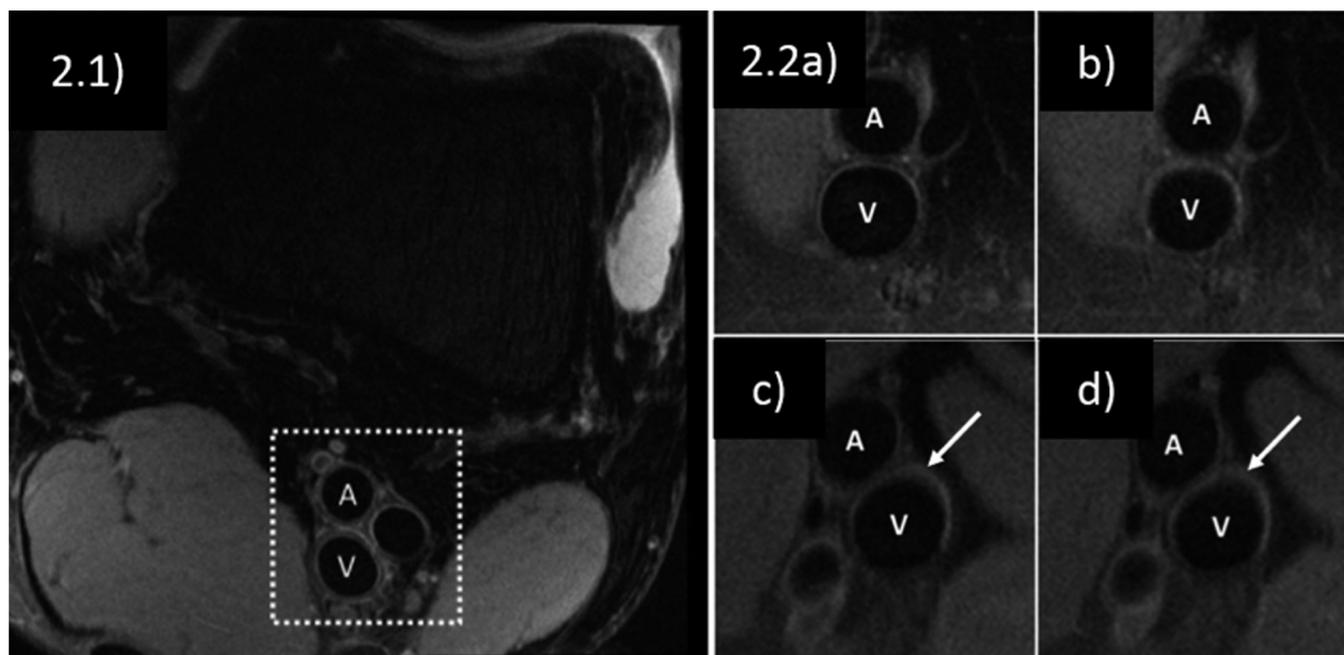


Fig. 2.1. A representative image of the final scan (A: artery; V: Vein). **Fig. 2.2.** Representative images acquired twice from a healthy control (a, b) and twice in a BS subject (c, d). Arrows show vessel wall thickening in BS images.

dividually for each subject using cine gradient-echo phase-contrast flow MRI acquired during the same metronome-guided breathing exercise, because the DIR nulling of blood signal in the FSE sequence depended on through-plane flow. An initial large field of view (FOV), 350 x 322 mm, balanced steady-state free-precession (bSSFP) localiser allowed selection of the left leg. Using this initial image for positioning, a series of typically 20 contiguous transverse bSSFP slices through the region was acquired at submillimetre inplane resolution to identify the path of the popliteal vein. The slice location was chosen such that the popliteal vein, in the region proximal to the knee, was surrounded by connective tissue and fat, as opposed to muscle, to increase contrast between the vessel wall and surrounding tissue.

Having chosen the approximate slice location, a sagittal image was taken positioned through the popliteal vein on the appropriate multi-slice localiser image. A further coronal image was adjusted to run along the vein in the sagittal image. The sagittal and coronal/‘along’-vein images allowed the angulation of further imaging slices to be exactly perpendicular to the axis of the vein (Fig. 1), which is crucial

for clear visibility of the thin wall by minimising the partial-volume effect. A 10 slice high resolution bSSFP scan was run, which allowed final selection of the imaging slice, also to check that no confluence of veins occurred within the immediate proximity of the image slice finally selected for the FSE image. This final multi-slice scan was acquired with metronome-guided breathing so that each slice was acquired at the same phase of the respiratory-induced venous blood flow cycle as used next for the FSE image acquired in the most suitable location of the 10 slices

The MRI imaging parameters are listed in Figure 1.d for the final scan using FSE with chemical-shift selective fat-saturation immediately prior to each FSE echo-train excitation. The repetition time between FSE echo-trains was driven by the metronome’s connection to the MRI scanner’s external trigger input, and was therefore 5 seconds. The delay from trigger to the FSE acquisition was determined for each subject using the flow information acquired above, aiming for the timing of maximum flow in order to ensure that the blood reinverted by the DIR preparation was washed out of the FSE image slice during the 1 second value given for TI.

The metronome-guided TSE was acquired in the same slice at least twice in all subjects aiming at some visual assessment of reproducibility, although this was not analysed formally.

Image analysis

Images from all subjects were randomised so that any single subject’s images were not adjacent; one main popliteal artery and vein were marked on each image. Marked vessels were ranked (1=normal to 5=diseased) based on wall thickness and presence of enhancement. Ranking was conducted by 2 blinded, experienced MR vessel wall observers. Wilcoxon Rank Sum tests were performed on the mean scores of the 2-3 TSE images from each subject (n=12) and were recorded for each subject from each observer. The mean of the combined results from both observers was also calculated.

Results

Example images (Fig. 2) show the nulling of blood signal and clear imaging of vessel walls aided further by the selective saturation of its surrounding fat, but with highly variable anatomy between different subjects. The repeated images of each subject gave a degree of variability in results (e.g. Fig. 2.2a-

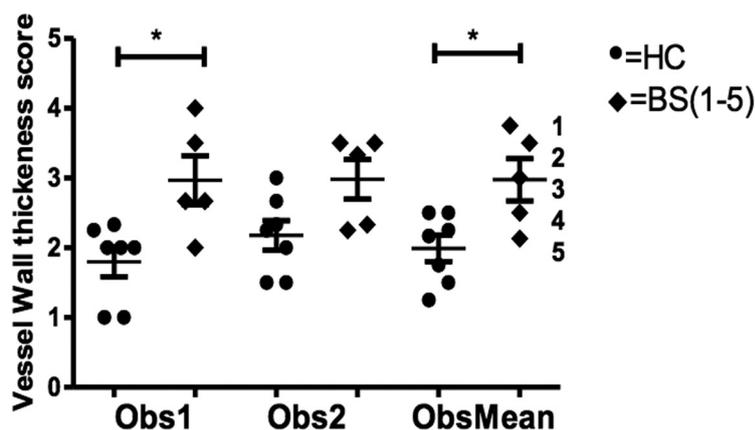


Fig. 3. The mean score of vessel thickening/ inflammation as scored by observer 1 (Obs1), observer 2 (Obs2), and the mean results. There is a significantly higher score with BS in Observer 1 results and in the combined results. HC: Healthy controls, BS: Behçet's syndrome subjects. * $p < 0.05$, $n = 12$.

Vessel wall thickness scored using an arbitrary scale from 1 (normal) to 5 (diseased), based on wall thickness and enhancement.

Brief clinical description of BS subjects: Subject 1: 43-year-old male, mucocutaneous disease and deep vein thrombosis (DVT); Subject 2: 47-year-old male, mucocutaneous disease and DVT; Subject 3: 23-year-old male, mucocutaneous and ocular disease; Subject 4: 35-year-old male with mucocutaneous disease and vascular aneurysm; Subject 5: 37-year-old male with mucocutaneous disease.

vs. Fig. 2.2b), potentially from drifting response to metronome guidance during each 10 minute scan. Popliteal vein rank scores were found to be significantly increased in BS vs. HC subjects by the first observer ($p_{(\text{Observer } 1)} = 0.025$, $p_{(\text{Observer } 2)} = 0.07$) and also averaging both observers ($p = 0.05$) (Fig. 3). This appeared to be even more pronounced in the two BS subjects with histories of DVTs but numbers too small for further analysis.

Conclusion

This feasibility study shows that MR imaging can detect vein wall abnormalities in patients with BS. Inflammation may result in wall thickening and/or increased vascular flow to the inflamed region, appearing as signal enhancement. Traditionally MRI has focused on arterial rather than venous imaging, as blood flow can be gated in the arteries much more simply by using the cardiac cycle. In this study, the respiratory cycle regulated with metronome guidance was employed requiring each subject's consistent co-operation during the main MRI acquisition to induce a regular venous flow waveform.

Limitations: This technique was relatively slow (scans required approximately 10 mins), during which time the subject's breathing could drift both in

synchronisation with the metronome and also in amplitude of the depth of breathing, leading to blurring of some images. Optimisation of breathing instructions for subjects and placement in a position allowing subjects to stay comfortable and still for 10 minutes require some further fine tuning. The venous wall acquisition was limited to only a single-slice in this work, but it is possible that it could be developed to acquire several slices in the same DIR-recovery (8) or developed further for volume imaging of the wall as used in carotid MRI imaging by dark-blood FSE (9), potentially including real-time flow gating by MRI and motion correction methods to improve consistency of the accepted imaging data, so that the concern of large variability between the repeated scans might be reduced.

There is also a possibility that a layer of slow-moving blood adjacent to the vein wall might not be washed out of the image slice during the 1 second TI. Such a boundary-layer failure of wash-out of reinverted blood would cause an apparent thickening of the walls. Variation in the timing and duration of the respiratory-induced flow pulse may have caused variability between subjects and between repeated scans. The application of external periodic foot compression might be another option

to drive this flow, if adapted for MRI safety (10) and provided that compression-induced motion at the imaged slice can be limited.

This was a feasibility study, and a further larger study is required to assess larger numbers of BS and HCs, and to look in more detail at subgroups of BS with or without vascular involvement.

This small study did demonstrate that MRI imaging may have potential to detect increased vein wall thickness in BS subjects compared to HCs, acting as a surrogate marker for vessel wall inflammation. The development of a reliable imaging modality to characterise inflammation in veins would be a useful step forward in the clinic with potential to predict those at risk of future vascular involvement by assessing vascular inflammation non-invasively. It may also prove to be a useful tool to assess if vascular inflammation has been adequately controlled with immunosuppression.

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