



A comparative analysis of noncontrast flow-spoiled versus contrast-enhanced magnetic resonance angiography for evaluation of peripheral arterial disease

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PURPOSE

This feasibility study aimed to obtain initial data to assess the performance of a novel noncontrast flow-spoiled magnetic resonance (MR) angiography technique (fresh-blood imaging [FBI]) compared to gadolinium-enhanced MR (Gd-MR) angiography for evaluation of the aorto-iliac and lower extremity arteries.

MATERIALS AND METHODS

Thirteen patients with suspected lower extremity arterial disease that had undergone Gd-MR angiography and FBI at the same session were randomly included in the study. FBI was performed using an ECG-gated flow-spoiled T2-weighted half-Fourier fast spin-echo sequence. For analysis, the aorto-iliac and lower limb arteries were divided into 18 anatomical segments. Two blinded readers individually graded image quality of FBI and also assessed the presence and severity of any stenotic lesions. A similar analysis was performed for the Gd-MR angiography images.

RESULTS

A total of 385 arterial segments were analyzed; 34 segments were excluded due to degraded image quality (1.3% of Gd-MR vs. 8% of FBI-MR angiography images). FBI-MR angiography had comparable accuracy to Gd-MR angiography for assessment of the above knee vessels with high kappa statistics (large arteries, 0.91; small arteries, 0.86) and high sensitivity (large arteries, 98.1%; small arteries, 88.6%) and specificity (large arteries, 97.2%; small arteries, 97.6%) using Gd-MR angiography as the gold standard.

CONCLUSION

Initial results show good agreement between FBI-MR angiography and Gd-MR angiography in the diagnosis of peripheral arterial disease, making FBI a potential alternative in patients with renal impairment. FBI showed highest accuracy in the above knee vessels. Technological refinements are required to improve accuracy for assessing the calf and pedal vessels.

Peripheral arterial disease continues to be a major cause of morbidity and mortality in the Western world, with an estimated prevalence of 20% in people over 75 years of age (1). It is important to depict peripheral arterial disease accurately in order to determine the need for medical and/or surgical therapy. Digital subtraction angiography (DSA) is currently the gold-standard radiological technique for evaluating the peripheral arterial system, but it is an invasive procedure with potential complications. These issues have driven the development of noncontrast imaging methods, such as magnetic resonance (MR) angiography. MR angiography using gadolinium-based contrast agents and multistation bolus chasing facilitates rapid and detailed assessment of the peripheral arteries. MR angiography does not require sedation, eliminates exposure to ionizing radiation and can accurately diagnose lower extremity vascular disease (2–7). Indeed in many centers, gadolinium-enhanced MR (Gd-MR) angiography now forms the mainstay of peripheral arterial assessment, with DSA largely reserved for therapeutic rather than diagnostic interventions (2).

In recent years, Gd-based contrast agents have been linked with nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment (8–13). NSF is a multisystem fibrosing disorder that predominately affects the skin but may also affect other organs (12). In view of this potential association, it is recommended that Gd-containing contrast agents be avoided in patients with a glomerular filtration rate (GFR) under 30 mL/min/1.73 m², in patients with hepatorenal syndrome, and in patients who have had or are awaiting liver transplantation if the GFR is less than 60 mL/min/1.73 m² (14). As many patients under investigation for suspected peripheral arterial disease have concomitant renal dysfunction, there is increasing interest in the development of robust MR angiography techniques that do not require administration of exogenous contrast media.

Fresh blood imaging (FBI) is an MR angiography technique that exploits the pulsatility of arterial blood flow to generate vascular contrast by utilizing an ECG-gated flow-spoiled T2-weighted half-Fourier fast spin-echo sequence (Fig. 1). FBI relies on loss of signal as a result of fast arterial flow during systole compared with maintained signal from slow arterial flow during diastole (15). Several early reports have shown promising results with FBI-MR angiography, and we have recently introduced this technique in our center, a large 1000-bed teaching hospital that serves as a national arterial referral center in the United Kingdom. The aim of the present study was to assess the accuracy of FBI-MR angiography compared to Gd-MR angiography in a group of patients with suspected peripheral arterial disease.

Materials and methods

This feasibility study was completed retrospectively. Institutional Review Board approval was obtained, and informed consent was waived.

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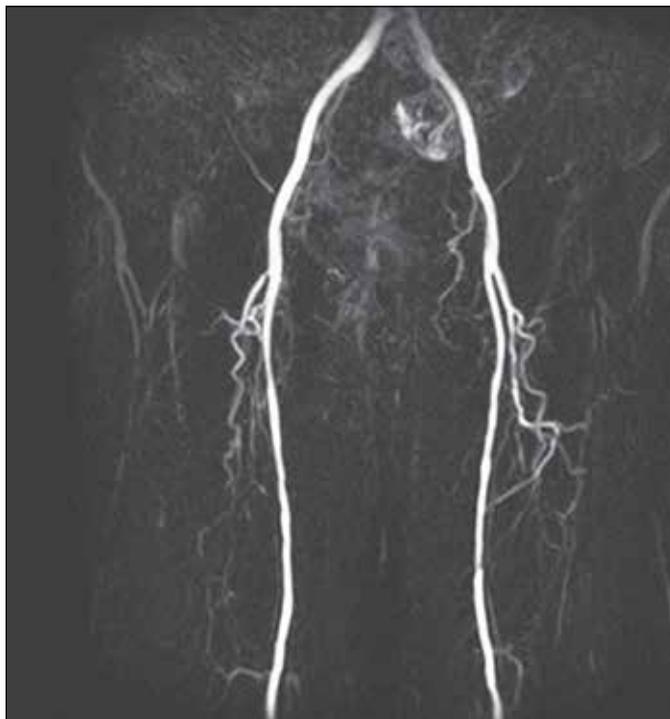


Figure 1. A 76-year-old man with insulin-dependent diabetes and renal impairment under investigation for buttock pain. FBI-MR angiography image shows normal proximal peripheral limb vasculature bilaterally. Gd-MR angiography images were also normal (not shown).

Research statisticians advised that a suitably powered sample for initial data would include 13 patients.

Our institution's clinical and radiological database was searched to identify all patients who had undergone lower extremity MR angiography with both FBI- and Gd-MR angiography techniques between June 2008 and June 2010. Of the identified patients that met these criteria, a random sample of 13 patients was selected for study.

Patients

Of the 13 patients included in the study, nine were male and four were female. The mean age was 72 years (range, 51–85 years). All patients were referred for investigation of suspected peripheral arterial disease and had routinely been screened with noninvasive imaging prior to invasive studies. None of the patients had undergone peripheral arterial bypass grafting. All patients had a GFR >30 mL/min/1.73 m², which was a prerequisite for the application of intravenous Gd-based contrast agent. All patients had been cooperative in completing both scans.

MR angiography technique

All imagings were performed with a clinical 1.5 Tesla MR system (Excelart Vantage, Toshiba Medical Systems, Zoetermeer, The Netherlands) equipped with high performance gradients (amplitude, 40 mT/m; rise time, 200 μ s). Phased-array coils were used for signal reception. Patients were positioned supine and feet first in the scanner. For both FBI- and Gd-MR angiography, scanning took 30–40 min and no intravenous sedation was used. In specific cases, extremity mobilization was required. In all cases, FBI-MR angiography was completed prior to Gd-MR angiography.

FBI-MR angiography

The FBI sequence was performed using a flow-spoiled T2-weighted three-dimensional (3D) half-Fourier fast spin-echo sequence with the following basic parameters: repetition time/echo time (TR/TE), 2700 ms/80 ms; flip angle, 90°; voxel size, 1.8×1.8×3.8 mm. Data was acquired using radiofrequency torso coils at three stations, each with a 45 cm field of view, and 5 cm overlap, from the juxta-renal abdominal aorta to the distal tibial shaft with a receiver

head coil for assessment of the pedal vessels. A magnetic resonance imaging (MRI) compatible three-lead ECG was used for synchronization with the cardiac cycle.

A series of two-dimensional (2D) single-shot fast spin echo acquisitions, each acquired with a progressively longer delay time following the R-wave on the ECG, were initially performed at each station to help select the optimal delay times for systolic and diastolic triggering ("ECG-prep", Toshiba Medical Systems). Semi-automated analysis software (Fresh Blood Imaging Navi, Toshiba Medical Systems) was then used to set the systolic trigger delay to the phase when intra-arterial flow void is maximal and set the diastolic trigger delay to the phase when the arteries appear brightest (1).

During the main FBI-MR angiography sequence acquisition, both systolic and diastolic phase images were acquired concurrently to minimize misregistration artifacts. The raw data was postprocessed into coronal maximum intensity projection (MIP) images and stitched together from each station to form a single image.

Gd-MR angiography

Contrast-enhanced data sets were acquired in the coronal plane using a fast spoiled 3D gradient-echo sequence with fat suppression. A standard three-step automated moving-table protocol covering pelvis, thigh, and calf station was used with the following basic parameters: TR/TE, 3.5 ms/1.3 ms; flip angle, 20°; voxel size, 1.7×1.7×3.5 mm. For all examinations, commercially available gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was used at a concentration of 500 mmol/L. This was administered through an intravenous catheter placed in the antecubital fossa using a power injector (Spectris, Medrad, Warrendale, Pennsylvania, USA). Patients under 75 kg in body weight received 20 mL of undiluted Gd, and patients over 75 kg received 30 mL Gd. A bolus timing technique was performed using real-time MRI of the pelvic station. Upon contrast agent reaching the distal abdominal aorta, manual triggering of the MR angiography acquisition was initiated. The injection protocol was biphasic, in which the first half was administered at a flow rate of 1 mL/s, and the second half at a flow rate of 0.5 mL/s, followed

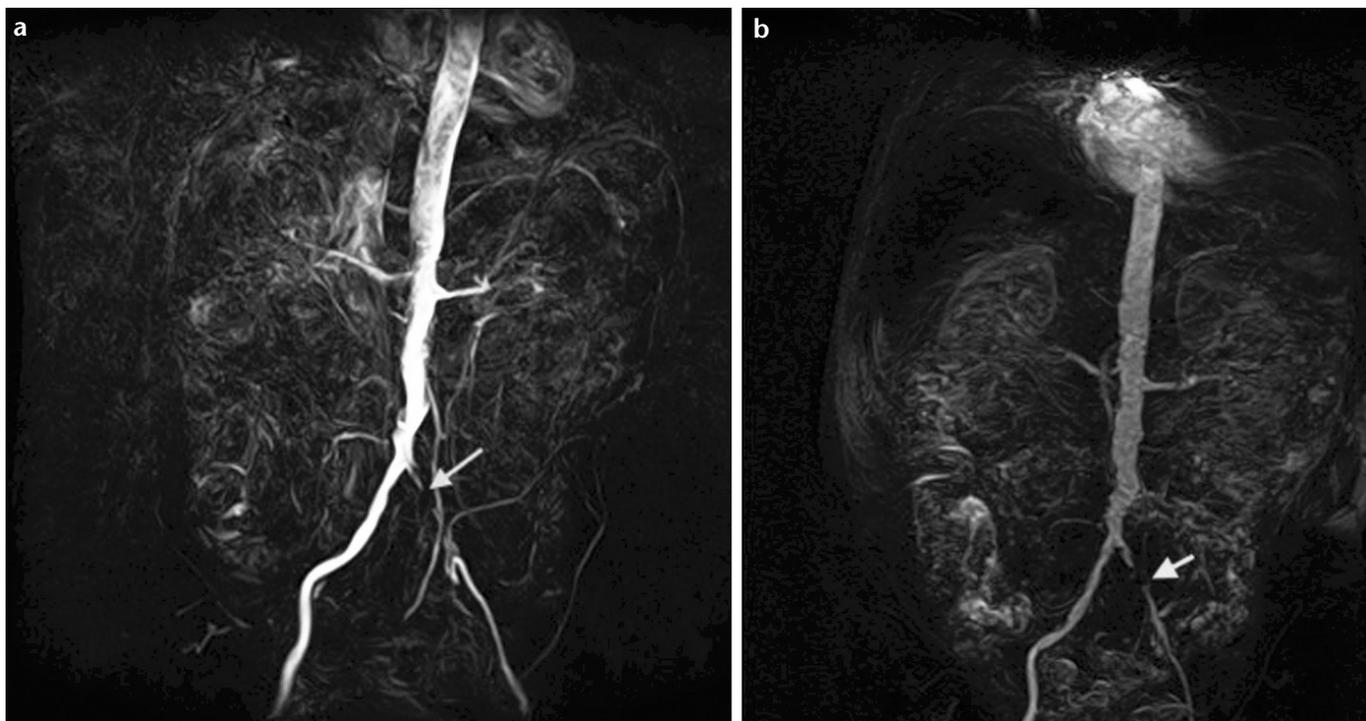


Figure 2. a, b. A 65-year-old man with a history of ischemic heart disease and left buttock claudication symptoms who underwent assessment with both FBI-MR angiography and Gd-MR angiography. FBI-MR angiography image (a) shows a left common iliac artery occlusion (arrow). Gd-MR angiography image (b) shows a left common iliac artery occlusion (arrow) which appears very similar to that depicted on the FBI image.

by a flush of 30 mL normal saline solution at a flow rate of 0.5 mL/s. The raw data was postprocessed into coronal MIP images and stitched together from each station to form a single image.

Data analysis

Two fellowship-trained board-certified radiologists (referred to as FBI-MR angiography reader 1 and FBI-MR angiography reader 2 in the results), each with over eight years of radiological experience, evaluated the Gd-MR angiography images. Each radiologist reported separately and was blinded to patient demographics and clinical data, and to each other's results. All images were reviewed on a Picture Archive Communication System (Impax, version 6.3, Agfa Healthcare, Septestraat, Belgium) with both the source images and reconstructed 3D MIP reconstructions (performed at the time of the clinical examination) available for review. Subsequently, both readers separately evaluated the FBI-MR angiography images blinded to the results of the Gd-MR angiography assessment (Fig. 2).

For analysis of both Gd-MR angiography and FBI-MR angiography, the arterial vascular system was divided into

the following 18 arterial segments: infrarenal aorta, common iliac artery, internal iliac artery, proximal external iliac artery, distal external iliac artery, common femoral artery, deep femoral artery, superficial proximal femoral artery, superficial distal femoral artery, proximal popliteal artery, distal popliteal artery, tibiofibular trunk, proximal anterior tibial artery, distal anterior tibial artery, proximal peroneal artery, distal peroneal artery, proximal posterior tibial artery and distal posterior tibial artery. The pedal arteries were not included in this assessment.

Each arterial segment was analyzed in regards to image quality and the presence of arterial stenoses in both the Gd-MR angiography and FBI-MR angiography groups. Image quality was subjectively judged and categorized as follows: good, acceptable, poor but still diagnostic, or nondiagnostic. Image quality of an arterial segment was considered nondiagnostic if diagnostic information could not be derived because of blurring of the arterial segment.

Stenosis severity was graded on a scale from 0% (no stenosis) to 100% (complete occlusion). In any case of

concurrent arterial stenosis in a single arterial segment, only the higher percentage stenosis was evaluated and recorded.

Statistical analysis

A direct comparison was made between FBI-MR angiography and Gd-MR angiography (as the gold-standard technique). As data was collected from multiple arterial segments, all data was initially considered together. Sensitivity, specificity, and positive and negative predictive values were calculated, along with the 95% confidence intervals (CI). For these calculations, images demonstrating insignificant stenosis (0%–49%) were treated as negative results, and those demonstrating significant stenosis were treated as positive.

The rate of agreement between FBI-MR angiography images and corresponding Gd-MR angiography images was expressed by calculating the kappa statistic. The kappa statistic is defined as the observed agreement not accounted for by chance. The index has a range of 1.0 (perfect agreement) to 0.0 (total disagreement). The kappa statistic was also used to establish the rate

of agreement between two radiologists looking at the same FBI-MR angiography images.

As it has been suggested that the diagnostic accuracy of FBI-MR angiography may be reduced in the calf and pedal vessels (16), a subgroup analysis was completed for the arteries down to the popliteal artery and arteries below the level of the popliteal artery. Sensitivity, specificity, and positive and negative predictive values and kappa statistics were calculated for these two subgroups to identify any significant differences.

All statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 19, SPSS Inc., Chicago, Illinois, USA).

Results

The selected cohort of 13 patients had their lower limbs imaged using both FBI-MR angiography and Gd-MR angiography, giving 385 sets of images.

Image quality and exclusions

Image quality with FBI-MR angiography was good or acceptable in 86% of images. In 34 segments (8%), images were not interpretable because of insufficient signal or technical failure. A further 23 images (6%) were of poor quality, but considered interpretable. In two segments, both FBI-MR angiography and Gd-MR angiography identified an aneurysm, and readers were therefore unable to give an accurate stenosis grade. In one segment, Gd-MR angiography images were severely distorted because of the presence of total knee replacement prosthesis. All together, FBI-MR angiography and Gd-MR angiography could be compared in 351 image segments (91% of total initial segments).

FBI-MR vs. Gd-MR angiography in all arterial segments

For the purpose of statistical calculations, each percentage stenosis was classified into one of three stenosis grades: grade 1, no stenosis (0%); grade 2, insignificant stenosis, not requiring intervention (1%–49%); or grade 3, significant stenosis (50%–100%)

Nondiagnostic segments were excluded from the analysis. When calculating specificity, sensitivity, and positive and negative predictive values, grades 1 and 2 were grouped together

and labeled as negative, and grade 3 was labeled positive.

Using the overall data set, the rate of agreement between FBI-MR angiography and Gd-MR angiography was expressed in the form of kappa statistics (Table 1). A high level of agreement was demonstrated when Gd-MR angiography readings were compared with FBI-MR angiography readings of first and second readers (0.89 and 0.87, respectively). These results represent a good standard for identifying FBI as a diagnostic test when classifying into these three grades of stenosis.

Gd-MR angiography identified significant stenosis in 87 segments, giving a prevalence of 25%. FBI-MR angiography reader 1 and FBI-MR angiography reader 2 identified 82 and 81 of the 87 significant stenosis segments, respectively (sensitivity, 94.3% [95%CI 86.5%–97.9%] and 93.1% [85.0%–97.2%]). Tables 2 and 3 show the direct

comparison between Gd-MR angiography and FBI-MR angiography for both readers and the resultant parameters of diagnostic accuracy, respectively.

FBI-MR vs. Gd-MR angiography in large and small arteries

Sub-classification into larger arteries (down to the popliteal artery) and smaller arteries (below the popliteal artery) revealed a significantly reduced accuracy of FBI-MR angiography compared to Gd-MR angiography in smaller vessels. Both kappa values (large arteries, 0.91 and 0.87 for first and second readers, respectively; small arteries, 0.86 for both readers) and sensitivities (large arteries, 98.1% [88.4%–99.9%]; small arteries, 88.6% [72.3%–96.3%]) demonstrated a significant reduction in accuracy (Tables 4 and 5).

Although FBI-MR angiography has shown favorable results compared with Gd-MR angiography, the image quality

Table 1. Kappa statistic values showing high levels of agreement between Gd-MR angiography and FBI-MR angiography, and between two readers

| | FBI-MR angiography | |
|------------------------------|--------------------|----------|
| | Reader 1 | Reader 2 |
| Gd-MR angiography | 0.893 | 0.866 |
| FBI-MR angiography, Reader 2 | 0.942 | - |

All *P* values < 0.001.

Table 2. Comparison of FBI-MR angiography findings recorded by readers 1 and 2 with Gd-MR angiography results

| FBI-MR angiography | | Gd-MR angiography | |
|---------------------------|----------|---------------------------|----------------------|
| | | No/insignificant stenosis | Significant stenosis |
| No/insignificant stenosis | Reader 1 | 256 | 5 |
| | Reader 2 | 256 | 6 |
| Significant stenosis | Reader 1 | 7 | 82 |
| | Reader 2 | 7 | 81 |

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of Gd-MR angiography when compared with FBI-MR angiography

| | Reader 1 | Reader 2 |
|-----------------|------------------|------------------|
| Sensitivity (%) | 94.3 (86.5–97.9) | 93.1 (85.0–97.2) |
| Specificity (%) | 97.3 (94.4–98.8) | 97.3 (94.4–98.8) |
| PPV (%) | 92.1 (83.9–96.5) | 92.0 (83.8–96.5) |
| NPV (%) | 98.1 (95.3–99.3) | 97.7 (94.8–99.1) |

PPV, positive predictive value; NPV, negative predictive value. Data are given as value (95% confidence interval).

is not always as high. In this study, 1.3% of Gd-MR angiography images were not interpretable compared with 8% of FBI-MR angiography images. A further 6% of FBI-MR angiography images were graded as “poor image quality but interpretable”.

Altogether, FBI-MR angiography was comparable to Gd-MR angiography for identifying different grades of stenosis severity, with highest accuracy observed for larger vessels. The probability of getting uninterpretable images was higher when imaging arteries by FBI-MR angiography.

Discussion

This study assessed the accuracy of FBI-MR angiography in comparison to Gd-MR angiography for identification of peripheral arterial disease. A robust and accurate noncontrast MR angiography technique is highly desirable, as it averts the risk of inducing NSF as well as provides significant savings with respect to costs of Gd-based contrast agents.

The results of this feasibility study showed a high level of agreement in identifying grades of stenosis between FBI-MR angiography and Gd-MR angiography as demonstrated by high kappa statistics (reader 1, 0.89; reader 2, 0.87). This study also identified a high level of accuracy of FBI-MR

angiography compared with Gd-MR angiography, as demonstrated by high values of sensitivity (reader 1, 94.3%; reader 2, 93.1%) and specificity (both readers, 97.3%).

The results also indicate a high level of accuracy between the two readers interpreting the FBI-MR angiography images, with a kappa statistic of 0.94, indicating that good quality images can be accurately interpreted. One shortfall with FBI-MR angiography relates to image quality, as 8% of FBI-MR angiography images were graded as “uninterpretable” compared to 1.3% of Gd-MR angiography images. High levels of image artifacts have been previously reported by Lim et al., (17) who compared FBI-MR angiography with both bolus chase Gd-MR angiography and time resolved MR angiography for imaging of the calf and pedal arteries in 36 patients. The investigators showed that FBI-MR angiography images were suboptimal in 47.5% of patients, resulting in poor diagnostic confidence. The reasons for FBI-MR angiography artifacts are multifactorial. FBI is extremely sensitive to even subtle movements, and patients with severe peripheral vascular disease frequently have rest pain and may develop an involuntary twitch. FBI images are also dependent on a good systolic flow void, hence acquisition

timing can be disrupted by poor cardiac function and/or arrhythmias (Fig. 3). Another major contributing factor is likely the relative lack of operator experience in performing FBI-MR angiography compared with traditional MRA techniques. There are continued efforts to further refine the technical aspects of performing FBI-MR angiography, which is anticipated to improve image quality as technology develops, especially if acquisition times can be further reduced (16).

A subgroup analysis of the two sets of images was completed for the above knee and below knee vessels. Results showed a significant reduction in accuracy in smaller vessels, as evidenced by reduced kappa values (large arteries, 0.91 and 0.87 for first and second readers, respectively; small arteries, 0.86 for both readers). There was also a significant reduction in sensitivity (large arteries, 98.1%, 96.2% for first and second readers, respectively; small arteries, 88.6% for both readers) indicating that small vessel stenosis is less accurately diagnosed with FBI-MR angiography. This is to be expected, as the lower velocity flow through the calf and pedal vessels makes it more difficult to separate out the arterial and venous waveforms, even when higher levels of flow spoiling are applied (13, 16).

To date, only a few clinical trials concerning FBI-MR angiography peripheral angiography have been reported. A feasibility study by Wong et al. (18) compared FBI-MRA of the lower limb arteries with time-of-flight MR angiography in five healthy volunteers and showed superior vessel-to-background image quality in the 40 segments that were analyzed. Nakamura et al. (19) assessed the accuracy of FBI-MR angiography in comparison to contrast medium enhanced multidetector computed tomography angiography in 13 patients with 56 diseased segments involving the iliac, femoral and calf arteries. They demonstrated a sensitivity of 94%, specificity of 94% and accuracy of 94% for detection of stenoses greater than 50% (19). Lim et al. (17) reported a sensitivity of 85.4%, specificity of 75.8%, and negative predictive value of 92.3% with comparison of FBI-MR angiography and both bolus chase Gd-MR angiography for imaging the calf and pedal arteries in 36 patients (17). They concluded that FBI

Table 4. Kappa values for subgroup analysis data

| Gd-MR angiography | FBI-MR angiography | |
|--|--------------------|----------|
| | Reader 1 | Reader 2 |
| Large arteries (down to the popliteal artery) | 0.910 | 0.868 |
| Small arteries (below the popliteal artery) | 0.864 | 0.862 |

All *P* values <0.001.

Table 5. Sensitivity, specificity, positive predictive value and negative predictive value for subgroup data identifying the variability in accuracy

| | Large arteries | | Small arteries | |
|-----------------|-------------------|------------------|------------------|------------------|
| | Reader 1 | Reader 2 | Reader 1 | Reader 2 |
| Sensitivity (%) | 98.1 (88.4–99.9) | 96.2 (85.7–99.3) | 88.6 (72.3–96.3) | 88.6 (72.3–96.3) |
| Specificity (%) | 97.2 (93.3–99.0) | 97.2 (93.3–99.0) | 97.6 (90.9–99.6) | 97.6 (90.9–99.6) |
| PPV (%) | 91.1 (79.6–96.7) | 90.9 (79.3–96.6) | 93.9 (78.4–98.9) | 93.9 (78.4–98.9) |
| NPV (%) | 99.4 (96.4–100.0) | 98.9 (95.5–99.8) | 95.3 (87.9–98.5) | 95.3 (87.9–98.5) |

NPV, negative predictive value; PPV, positive predictive value. Data are given as mean (95% confidence interval).

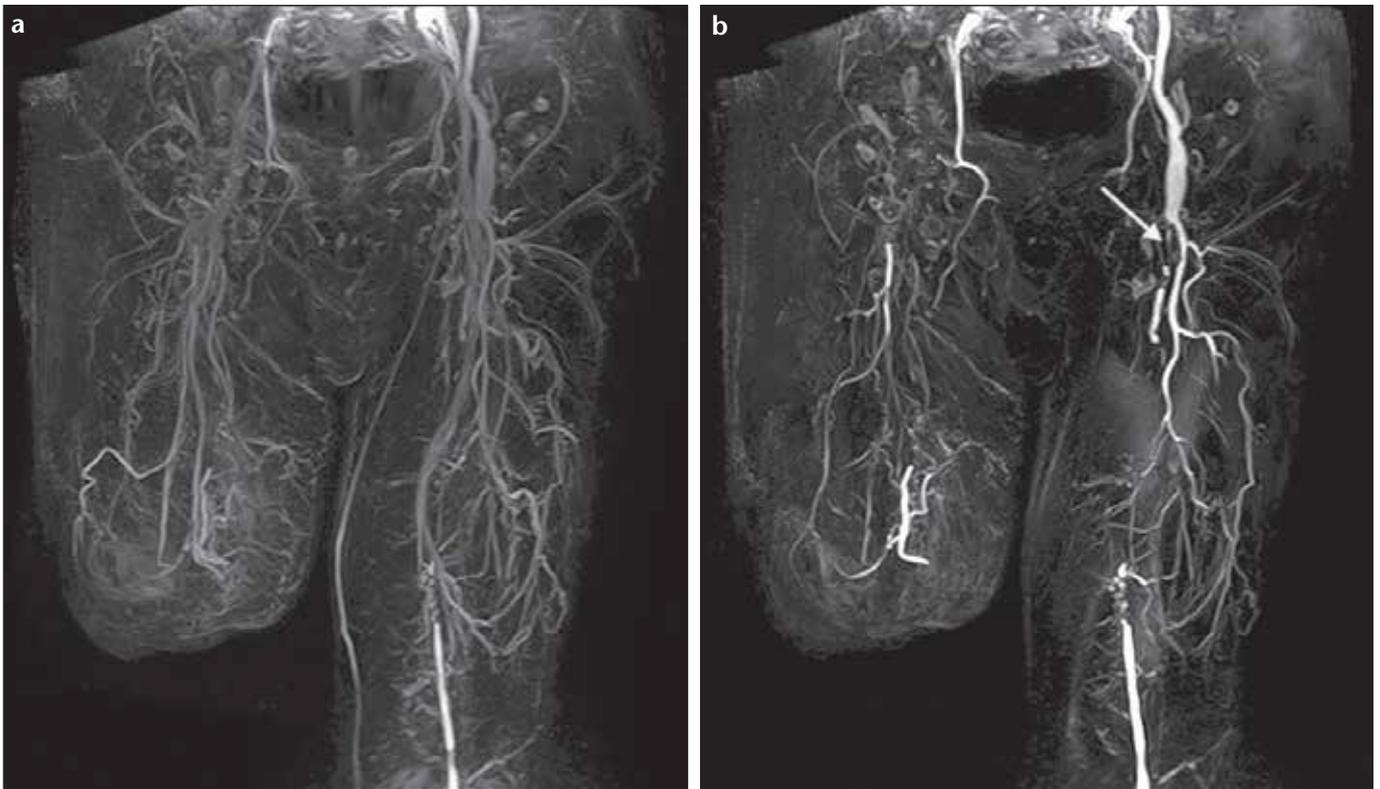


Figure 3. a, b. A 53-year-old woman with atrial fibrillation and a previous right above knee amputation under investigation for symptoms of left calf claudication. FBI-MR angiography image (**a**) shows generally poor signal of the arterial system with significant venous contamination which renders the study virtually uninterpretable. Gd-MR angiography image (**b**) shows a short segment stenosis in the left superficial femoral artery (*arrow*) with collateralization via the geniculate vessels; this finding is not apparent on the FBI-MR angiography image because of artifact.

has the potential to be a reliable diagnostic tool for lower extremity vascular imaging.

This study is limited by its retrospective nature. Data from all patients were retrieved; however, the image quality was extremely degraded in some arterial segments, especially the FBI-MR angiography sequences. This could have been improved if data had been prospectively reviewed at time of scanning, as the sequence could have been repeated. As this is a feasibility study, the sample size is relatively small and could have led to inaccurate conclusions regarding the performance of the respective techniques. These preliminary findings, however, gives enough evidence to warrant the continued collection of further data for future study. Finally, this study used Gd-MR angiography as the reference standard technique when DSA is the true gold standard. The final study with a larger sample of patients will include DSA along with the two modalities discussed in this study. Nevertheless, initial data demonstrates that Gd-MR angiography has high diagnostic accuracy for

assessment of the lower extremity arteries and does not carry the attendant risks of DSA. Data to compare DSA with FBI-MR angiography is currently being collated in our center.

As a conclusion, our results provide initial evidence that FBI-MR angiography is accurate, sensitive, and specific for grading stenoses secondary to peripheral vascular disease throughout the lower limb arterial tree. However, it carries highest sensitivities in the above knee vessels. As such, our initial data suggest that FBI-MR angiography is a reasonable first-line diagnostic tool in patients unable to undergo Gd-MR angiography. Suboptimal image quality is still an issue in some patients, and a multitude of factors, both technical and patient-related, are involved. For FBI studies with limited image quality or equivocal findings, we would advocate further investigation using low volume gadolinium MR angiography or catheter-directed carbon dioxide angiography in patients with renal impairment. This small feasibility study adds to the small but growing body of literature on FBI-MR angiography.

Data collection and patient recruitment in our center is continuing so that a larger data set comparing DSA, FBI-MR angiography and Gd-MR angiography can be completed.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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