Patient Perception of Lower Limb Non-Contrast Magnetic Resonance Angiography and Digital Subtraction Angiography in Diabetic Patients with Peripheral Arterial Disease

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Objective: Non-contrast magnetic resonance angiography (NC-MRA) is an attractive technique for imaging peripheral arterial disease (PAD) in diabetic patients where arterial calcification and renal impairment are common. Our purpose was to evaluate patient perception of lower limb NC-MRA and compare this perception to that of digital subtraction angiography (DSA).

Materials and Methods: Thirty-one diabetic patients (18 male, 13 female, mean age=69 years) with symptomatic PAD (critical ischemia, n=10) referred for DSA were prospectively recruited, and 1.5T quiescent-interval single-shot NC-MRA was performed before DSA (intervention performed during DSA, n=23). Patients rated anxiety, pain, discomfort, willingness to repeat (Likert scale: 1 most favorable to 7 least favorable), and difficulty compared to expectations (-3 better to +3 worse).

Results: Twenty-nine patients' results were analyzed (DSA under general anesthesia, n=1; incomplete NC-MRA due to morbid obesity, n=1). NC-MRA and DSA median scores were 1 vs. 3, 1 vs. 2, 2 vs. 2, and 1 vs. 1 for anxiety, pain, discomfort, and willingness to repeat, respectively. The median score for difficulty compared to expectations was 0 (as expected) for both examinations. The anxiety and pain scores for NC-MRA were significantly lower than those for DSA (p=0.006 and p=0.001, respectively). Reasons for the less favorable NC-MRA experience included machine noise (n=3), pain from coil pressure (n=3), and claustrophobia (n=1).

Conclusion: NC-MRA was well tolerated overall, and better than DSA for anxiety and pain. Although DSA is commonly required for intervention in PAD, NC-MRA may inform disease management and potentially obviate DSA where conservative management, or open surgery, are indicated. Reduced acoustic noise, lighter receiver coils, and wider scan bores may improve procedural tolerance.

Key words Magnetic resonance angiography · Digital subtraction angiography · Peripheral arterial disease · Diabetes mellitus, type 2 · Renal insufficiency.

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INTRODUCTION

Peripheral arterial disease (PAD) is common in diabetic patients, with an estimated prevalence of 20–29% in those over

50 years of age, and causes significant morbidity, with amputation or limb loss occurring in around 4% of patients [1]. The imaging diagnosis of PAD in diabetic patients is challenging because renal impairment is common and vessels tend to be

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more heavily calcified [1-3]. Additionally, elderly, frail patients or those with painful foot ulcers may find a long examination difficult to tolerate. An accurate diagnostic method for PAD that does not require potentially nephrotoxic contrast agents and is relatively tolerable for patients is desirable.

There are several imaging options in clinical practice for PAD [4]. Gadolinium-enhanced magnetic resonance angiography (MRA) is a non-invasive modality that can reliably assess PAD [5,6]. However, gadolinium-based contrast agents have been linked to nephrogenic systemic fibrosis in patients with renal impairment and are therefore undesirable in diabetic patients with nephropathy [7-11]. Gadolinium administration has also been correlated with a high T1 signal intensity in the dentate nucleus and globus pallidus [12]. Contrast-enhanced computed tomography angiography (CTA) is rapidly performed and non-invasive, but involves potentially nephrotoxic iodine-based contrast and radiation exposure, and assessment of below-the-knee vessels is challenging in the presence of heavy calcification and individual variability in the timing of peak arterial opacification [4,13,14]. Ultrasonography is safe and non-invasive, but also operator dependent and relies upon favorable acoustic windows [4]. Digital subtraction angiography (DSA) remains the gold standard for PAD imaging, and is often required for interventions such as angioplasty or stent insertion. Unless carbon dioxide is used as a contrast agent, which yields poorer quality images, the iodine-based contrast agents carry the risk of nephrotoxicity, which is possibly higher for intra-arterial than intra-venous administration [15-18]. DSA is also an invasive procedure, which potentially exposes patients who are best served by conservative management or open surgery to unnecessary risks, including local hemorrhage, embolization, or vessel damage [19].

Recently, several non-contrast MRA (NC-MRA) techniques have been developed to image peripheral arteries [20-26]. These include fresh-blood imaging, quiescent-interval single-shot (QISS) imaging, and flow-sensitizing dephasing gradient-prepared steady-state free precession imaging [20,25,27-30]. QISS MRA has good accuracy and robustness for PAD assessment, specifically in diabetic patients, with an estimated sensitivity of 87.0–89.7% and specificity of 94.6–96.5% using gadolinium-enhanced MRA for comparison [23,26]. QISS-arterial spin-labelled (QISS-ASL) MRA has been proposed for pedal arterial imaging [31].

Beyond accuracy, assessment of the acceptability of a new diagnostic test to patients is crucial before it can be applied in clinical practice. Patient acceptability has been initially assessed for several now widely-accepted imaging techniques, including magnetic resonance cholangiopancreatography (MRCP) [32,33], CT colonography [34-38], and coronary CTA [39]. Although the accuracy of NC-MRA has previously been described, to our

knowledge, no previous studies have specifically assessed the technique from the patients' perspective for PAD assessment. The purpose of this study was to evaluate patient perception of a comprehensive lower limb NC-MRA protocol comprising QISS and QISS-ASL MRA in a diabetic population with symptomatic PAD, with comparison to DSA.

MATERIALS AND METHODS

Institutional ethics approval was obtained for the study, and all participants provided informed consent for their participation.

Subjects

A total of 31 patients with diabetes (Type 2, n=30 and Type 1, n=1) and symptomatic PAD were prospectively recruited and underwent lower limb NC-MRA prior to clinically indicated DSA. Seven patients (23%) had severe renal impairment (estimated glomerular filtration rate <30), with three of these patients on dialysis and one post renal transplant. Twenty-one patients had symptomatic PAD with claudication (Rutherford stages 1–3), and 10 patients had critical ischemia (Rutherford stages 4–6) [40]. Patients were classified as having previously undergone MRI or angiography if they had previously undergone these procedures on any part of the body. Previous MRI status was included as a question on the survey, whereas previous angiography information was sourced from medical records. Patient characteristics are summarized in Table 1.

Imaging

All patients in this study underwent both NC-MRA and DSA, with two patients repeating both procedures after 5–6 months for symptomatic disease assessment in the contralateral leg. NC-MRA was conducted before DSA for all patients, with the two procedures occurring within 24 hours for 21 patients (68%), and up to a maximum of 9 days later, with no change in symptoms between examinations.

NC-MRA

NC-MRA was performed on a 1.5T system (Avanto, Siemens Healthcare, Erlangen, Germany), with patients imaged feet first in a supine position with electrocardiographic gating. Patients were offered music to listen to via headphones, and the total examination time was up to one hour. Imaging consisted of two parts:

- 1) 9-station QISS NC-MRA was performed from the level of the renal arteries to the feet. The imaging protocol followed that of a prior study by Edelman et al. [20]: a repetition time (TR)/echo time (TE)/quiescent-interval/flip angle (FA) of 3.0 ms/1.4 ms/228 ms/90°, trigger delay of 100 ms, 2.4-mm effective slice

thickness (3.0 mm, with 0.6 mm overlap), in-plane resolution of $1.0 \times 1.0 \text{ mm}^2$, parallel acceleration factor of 2, bandwidth of 658 Hz/pixel, and FA of 135° for the fat suppression pulse. Additional high resolution imaging of the below-the-knee arteries was also obtained with a 1.0-mm effective slice thickness (1.2 mm, with 0.24 mm overlap), with a $1.0 \times 1.0 \text{ mm}^2$ in-plane (axial) resolution. A 16-channel peripheral coil and 6-channel body phased array coil and spine coils were used for signal reception, with coils selected by the operator.

2) Imaging of the pedal vessels was also performed using a recently described QISS-ASL technique [31], given diabetic pa-

tients often have distal disease which may require assessment of the pedal arteries as bypass targets. Two datasets were acquired, the first employing venous and in-plane radiofrequency (RF) saturation pulses, and the second employing a non-selective RF saturation pulse. The second dataset was subtracted from the first to obtain bright blood imaging of the pedal arteries, with theoretically complete background suppression. Scan parameters were as follows: a TR/TE/quiescent-interval/FA of 3.7 ms/1.6 ms/350 ms/ 90° , trigger delay of 100 ms, 1.0-mm effective slice thickness (1.2 mm, with 0.24 mm overlap), in-plane resolution of $1.0 \times 1.0 \text{ mm}^2$, and bandwidth of 658 Hz/pixel. A 12-channel head coil was used for signal reception with a vacuum cushion to immobilize the feet. Fig. 1 shows the typical patient setup for both components of the NC-MRA examination.

Table 1. Patient characteristics

Patient characteristics	n (%)
Age (years)	
Mean (range)	69.2 (46–91 years)
Gender	
Male	18 (58)
Female	13 (42)
BMI (kg/m^2)	
<25	3 (10)
25–30	13 (42)
30.1–35	8 (26)
35.1–40	5 (16)
>40	2 (6)
HbA1c	
<5.7	2 (6)
5.7–6.5	7 (23)
6.6–8.0	13 (42)
8.1–9.5	7 (23)
>9.5	2 (6)
eGFR ($\text{ml}/\text{min}/1.73 \text{ m}^2$)	
>60	15 (48)
30–60	9 (29)
<30 or dialysis	7 (23)
Previous MRI	
Yes	22 (71)
No	9 (29)
Previous angiography	
Yes	17 (55)
No	14 (45)
PAD severity (rutherford classification)	
0	0 (0)
1	2 (6)
2	5 (16)
3	14 (45)
4	1 (3)
5	4 (13)
6	5 (16)

BMI: body mass index, HbA1c: glycosylated hemoglobin, eGFR: estimated glomerular filtration rate, PAD: peripheral arterial disease

DSA

DSA was performed using one of two systems (Philips Allura, Best, Netherlands or Siemens Artis Zee Biplane, Forchheim, Germany). The common femoral artery ($n=28$) or superficial femoral artery ($n=3$) over the femoral head was punctured us-

Fig. 1. Setup for NC-MRA examination. (A) Patient positioning for QISS NC-MRA of the lower extremities. (B) Patient positioning for pedal QISS-arterial spin-labelled NC-MRA. QISS: quiescent-interval single-shot, NC-MRA: non-contrast magnetic resonance angiography.

ing an antegrade (n=19) or retrograde approach (n=12), and a size 5 to 7 Fr sheath, as selected by the operator, was inserted. Either iodine-based contrast (n=25, Visipaque 320 mgI/mL or Omnipaque 350mgI/mL, GE Healthcare, Marlborough, MA, USA) or carbon dioxide (n=6, with one patient subsequently receiving iodine-based contrast due to poor tibial vessel imaging with CO₂), to minimize nephrotoxicity for patients with severe renal impairment not yet on dialysis, was given as required for the imaged segments. Imaging was unilateral (n=26) or bilateral (n=5) and included standard posterior-anterior projections, ipsilateral oblique projections of the common femoral artery, proximal superficial femoral artery and profunda femoral artery, and lateral foot views, as well as additional views as clinically required. Twenty-three of the 31 DSA procedures were both diagnostic and interventional, with angioplasty (n=23) and stent insertion (n=11/23, 47.8%) following diagnostic imaging. Eight patients underwent diagnostic DSA only. Procedures were performed with the patient supine, and fentanyl (n=26), midazolam (n=24), and/or morphine (n=1) were given as necessary. One patient underwent DSA under general anesthesia. Total DSA procedure time varied between approximately 35 min and 2 hrs 25 min, with diagnostic-only DSA time between 35 min and 1 hr 10 min.

Patient survey

After both NC-MRA and DSA examinations, all patients were asked to complete a survey (Fig. 2) about their experience during the procedure by a member of the research team. Patients were asked to rate anxiety, pain, discomfort, and willingness to repeat the test on a Likert scale from 1 (most favorable) to 7 (most unfavorable). Surveys included descriptors such as “not anxious” for 1, “extremely anxious” for 7, and similar descriptors for other items. Difficulty compared to expectations was rated on a slightly different scale from -3 (easier than expected) to +3 (more difficult than expected). Survey questions were based on those used in a previous study of MRCP and endoscopic retrograde cholangiopancreatography (ERCP) [32]. Patients sedated for DSA were surveyed after their mental status had returned to baseline.

Statistical analyses

Survey results were analyzed in the statistical platform R (version 3.22, R Foundation for Statistical Computing, Vienna, Austria). The medians and interquartile ranges (IQRs) were calculated for each of the five survey items for both imaging procedures. The Wilcoxon signed-rank test was applied to compare responses as paired data. Subgroup analyses were then performed for patients who had previously undergone MRI or DSA, and patients

Patient Label

Department of Radiology

Patient Satisfaction Survey

Study Date: _____

Study Type (✓) MRA OR Standard Imaging (✓)

CTA

Ultrasound

DSA

Dear Patient,

Have you had an MRI before? Yes No

For the following questions, please circle the number which best represents your experience.

Only circle ONE number in each line.

How anxious did you feel during today's test?	1	2	3	4	5	6	7
	Not anxious			Some anxiety			Extremely anxious
Did you have pain during the test?	1	2	3	4	5	6	7
	No pain			Some pain			Extreme pain
Did you feel any discomfort during the test?	1	2	3	4	5	6	7
	No discomfort			Some discomfort			Extreme discomfort
How difficult was the test compared to your expectations before the test?	-3	-2	-1	0	+1	+2	+3
	Easier			As expected			More difficult
Would you be willing to have the test again?	1	2	3	4	5	6	7
	Very willing			Undecided			Not willing

Thank you for completing this survey and participating in this study.

Fig. 2. Patient satisfaction survey conducted after non-contrast MRA and DSA. MRA: magnetic resonance angiography, CTA: computed tomography angiography, DSA: digital subtraction angiography.

Table 2. Survey responses after NC-MRA and DSA

Survey item	Scale	NC-MRA Median (IQR) [range]	DSA Median (IQR) [range]	p value
Anxiety	Nil 1 ... 7 extreme	1 (1–2) [1–7]	3 (1–4) [1–7]	<0.01
Pain	Nil 1 ... 7 extreme	1 (1–1) [1–5]	2 (1–4) [1–7]	<0.01
Discomfort	Nil 1 ... 7 extreme	2 (1–3) [1–6]	2 (1–3) [1–5]	0.29
Willingness to repeat test	High 1 ... 7 low	1 (1–4) [1–7]	1 (1–4) [1–7]	0.38
Difficulty compared to expectations	Easier -3 ... 3 harder	0 (-2–1) [-3–3]	0 (0–1) [-3–3]	0.22

NC-MRA: non-contrast magnetic resonance angiography, IQR: interquartile range, DSA: digital subtraction angiography

who had diagnostic DSA alone. Paired data within a subgroup was compared using the Wilcoxon signed-rank test, with unpaired comparisons evaluated using the Mann-Whitney U test.

RESULTS

Survey results of 29 of 31 participants were included in the final analyses (Table 2). Two patients were excluded: one patient who was unable to complete the entire NC-MRA examination due to large body habitus (BMI of 40) rendering them incompatible with the magnet bore diameter (60 cm), with imaging only possible from the knees to feet, and another patient who underwent DSA under general anesthesia.

NC-MRA patient experience

Responses after NC-MRA for anxiety, pain, discomfort, and willingness to repeat the study were overall favorable, with median scores of 1, 1, 2, and 1 respectively (corresponding to no anxiety, no pain, a low degree of discomfort, and a high willingness to repeat). The median response for difficulty compared to expectations after NC-MRA was 0, or “as expected.”

In patients who reported a less favorable experience, stated reasons included machine noise (n=3), pain related to coil pressure on the more affected limb (n=2), pain related to pressure on the shoulders (n=1), and claustrophobia (n=1), although these patients all completed the NC-MRA examination. One patient (Rutherford classification: 3) described pain in the affected leg during NC-MRA due to claudication induced by

walking to the MRI prior to examination.

DSA patient experience

Median responses after DSA for anxiety, pain, discomfort, and willingness to repeat the study were also relatively favorable, with scores of 3, 2, 2, and 1 respectively, corresponding to mild levels of anxiety, pain, and discomfort, and a strong willingness to repeat the test. Based on the median response of 0, the difficulty of DSA compared to expectations was also “as expected.”

In patients who reported a less favorable experience after DSA, stated reasons included pain at the puncture site (n=2), having to request additional anesthesia (n=1), and frustration due to previous failed interventional DSA (n=1).

NC-MRA and DSA comparison

Median responses for anxiety and pain were significantly more favorable for NC-MRA compared to DSA ($p=0.006$ and $p=0.001$, respectively). There were no differences in median scores between NC-MRA and DSA for discomfort, difficulty compared to expectations, and willingness to repeat the study. Results are summarized in Fig. 3.

Subgroup analyses

Subgroup analysis revealed that patients who had previously undergone MRI examination (n=22) reported slightly lower discomfort during NC-MRA, which was not statistically significant, with a median response of 1.5 (compared to 2 for the no previous MRI subgroup, $p=0.408$), and higher discomfort dur-

Fig. 3. Median and IQR of survey responses after NC-MRA and DSA. (A) Anxiety, pain, discomfort, and willingness to repeat the study. (B) Difficulty compared to expectations. NC-MRA: non-contrast magnetic resonance angiography, IQR: interquartile range, DSA: digital subtraction angiography.

ing DSA with a median response of 3 (compared to 2 for the no previous MRI subgroup, $p=0.044$). However, the difference between NC-MRA and DSA discomfort in the previous MRI subgroup was not statistically significant ($p=0.088$).

The subgroup of patients who had previously undergone DSA ($n=17$) reported a slightly higher willingness to repeat DSA compared to MRA (median response of 1.5 vs. 3, respectively) although this difference was not statistically significant ($p=0.344$). Patients who had previously undergone DSA reported lower levels of discomfort with DSA than those who hadn't, although this difference was not significant (median responses of 1.5 vs. 3, respectively; $p=0.084$). Patients who had not previously undergone DSA rated MRA discomfort lower than DSA discomfort, with median responses of 1 and 3, respectively ($p=0.007$).

Patients who underwent diagnostic DSA without intervention ($n=8$) reported less pain, with a median response of 1 (compared to 2 for the subgroup where DSA was also interventional, $p=0.009$). There was no difference in median scores for pain after NC-MRA and DSA for the diagnostic-only DSA subgroup (median response of 1 for both, $p=0.363$). Patients who underwent diagnostic-only DSA also reported slightly lower anxiety during DSA, with a median response of 2 (compared to 3 for the diagnostic and interventional DSA subgroup), although this difference was not significant ($p=0.164$). Anxiety during DSA was still significantly higher than during NC-MRA for this subgroup (median response of 2.5 vs. 1, respectively; $p=0.040$).

DISCUSSION

NC-MRA has emerged as a potential diagnostic technique for PAD [20-25], with QISS MRA specifically demonstrating good accuracy for hemodynamic stenosis in diabetic patients. Whilst DSA can be performed with carbon dioxide as a contrast agent to prevent nephrotoxicity, image quality is poorer [15,16] and DSA remains an invasive procedure with attendant risks. NC-MRA may thus enable stratification of patients to percutaneous intervention, open surgery, or conservative management, possibly obviating the need for DSA in the latter two, with potentially positive impacts on patient morbidity and costs.

Here, we evaluated the patient experience of NC-MRA compared to DSA, which to our knowledge has not been previously studied, in a symptomatic diabetic population with a relatively high proportion of patients with critical ischemia, and including patients with severe renal impairment. Median responses for NC-MRA and DSA for all five metrics assessed were relatively favorable, indicating that both procedures were generally well tolerated ($n=10$, 32%). Median responses for anxiety and pain significantly favored NC-MRA compared to DSA, which

may be due to the arterial puncture required for and invasive nature of DSA. Whilst there were no differences in median scores between NC-MRA and DSA for discomfort, difficulty compared to expectations, or willingness to repeat the study, the IQRs for difficulty compared to expectations favored NC-MRA. Previous studies comparing patient attitudes of contrast-enhanced MRA and DSA also demonstrated a preference for MRA regarding discomfort and willingness to repeat the test [6].

Subgroup analyses showed that patients who had previously undergone MRI ($n=22$) were possibly predisposed to having a more favorable experience during NC-MRA, as the median response for discomfort was lower than that for patients who had not previously undergone MRI, although this difference was not statistically significant. A similar trend was observed in patients who had previously undergone DSA ($n=17$), with these patients reporting slightly lower discomfort and higher willingness to repeat DSA than those who were naïve to the test. Personal experience with a diagnostic or screening procedure has been identified to improve patients' acceptability ratings in previous studies of colonoscopy and CT colonography [35]. The small group of patients ($n=8$) who underwent diagnostic-only DSA, without intervention, reported significantly less pain than those who underwent interventional DSA. This is a predictable finding, and similar to that in a previous study of ERCP and MRCP [32].

Patients in the study identified several factors during the NC-MRA examination that, if addressed, may improve overall acceptability. Firstly, machine noise, which has been previously documented as an annoyance during MRI [32,41,42], was noted by three patients. Acoustic noise reduction may be achieved with hardware-based techniques aimed at minimizing the mechanical gradient coil vibration to the rest of the system, and/or sequence-based techniques aimed at optimizing the gradient activity and avoiding acoustic resonance frequencies [43-45]. Future developments in silent MRI and quieter sequences specifically for MRA may help to minimize acoustic noise. Next, two patients experienced pain from coil pressure in their symptomatic extremities. Ongoing improvements in receiver coil design, such as weight reduction and improvements in the flexibility and shape, may reduce coil-related pressure [46,47]. Issues of claustrophobia ($n=1$) and large body habitus precluding positioning at the isocenter of the magnet bore ($n=1$) may be mitigated with wide-bore systems that are commercially available but were not available at our institution, and which have been demonstrated to decrease patient claustrophobia [48,49]. Open MRI systems are also available, although, to our knowledge, there are no such systems demonstrating sufficient extremity arterial image quality. Finally, minimizing the scan time would likely improve the patient experience of NC-MRA, given the relatively long scan time compared to contrast-enhanced CTA or contrast-enhanced MRA.

An important limitation of our study is that most DSA examinations (n=23) included intervention, impacting the procedure duration and associated pain level, and therefore likely contributing to a less favorable experience for these patients. Also, this confounded direct comparison between patient tolerance of NC-MRA and DSA, allowing only a small comparison using patients who had a diagnostic DSA without intervention (n=8). The duration of NC-MRA was approximately 15 min longer than in a previous study of QISS MRA accuracy in diabetic patients, most likely due to the inclusion of the pedal QISS-ASL MRA acquisition [23,26]. Further, patients were offered music to listen to during MRA, which was not offered during DSA. The overall sample size was low (n=31), which could lead to a type II error, particularly regarding the subgroup analyses, where the study was likely underpowered to detect true differences. Finally, the study order was not randomized, with NC-MRA performed prior to DSA in all cases to enable assessment of test accuracy in a separate study.

Future work with a larger patient population, further image acceleration techniques [50], and wider bore systems with updated coil designs could be of interest.

In conclusion, this study demonstrated that both NC-MRA and DSA are well tolerated by diabetic patients with symptomatic PAD, including patients with critical ischemia and severe renal impairment. NC-MRA was rated better by patients than DSA with regards to anxiety and pain, but there were no significant differences regarding discomfort, difficulty compared to expectations, or willingness to repeat the study. Although DSA is often required for disease intervention, NC-MRA provides a promising diagnostic alternative for PAD, particularly for patients with renal impairment or a contrast allergy, which may obviate CTA, contrast-enhanced MRA, or DSA in a select group of patients where open surgery or conservative management is indicated.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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