Diagnostic Performance of Gadobenate Dimeglumine–Enhanced MR Angiography of the Iliofemoral and Calf Arteries: A Large-Scale Multicenter Trial

Siegfried Thurnher[1]
Stephan Miller[2]
Günther Schneider[3]
Claudio Ballarati[4]
Georg Bongartz[5]
Christoph U. Herborn[6]
Stefan Schoenberg[7]
Maria Assunta Cova[8]
Giovanni Morana[9]
Khusrow Niazi[10]
Roberto Iezzi[11]
Matthias Taupitz[12]
David A. Bluemke[13]
Karl-Friedrich Kreitner[14]
Miles A. Kirchin[15]
Gianpaolo Pirovano[16]

OBJECTIVE. The purpose of this study was to compare gadobenate dimeglumine–enhanced MR angiography and unenhanced time-of-flight MR angiography for the detection of significant peripheral arterial occlusive disease using digital subtraction angiography as our reference standard.

SUBJECTS AND METHODS. Two hundred seventy-two patients underwent MR angiography and digital subtraction angiography of the iliofemoral arteries. MR angiography was performed before (2D time-of-flight acquisitions) and after (spoiled gradient-echo acquisitions) the administration of 0.1 mmol/kg of gadobenate dimeglumine at 1–2 mL/s. Contrast-enhanced MR angiography and digital subtraction angiography of the calf arteries were performed in 241 of 272 participants. Images were evaluated on-site and by four blinded reviewers (three for MR angiography, one for digital subtraction angiography). Comparative diagnostic performance for the detection of significant (≥ 51% vessel lumen narrowing) disease was evaluated using the McNemar test and generalized estimating equations. Interobserver agreement was assessed with generalized kappa statistics. The chi-square test was used to compare technical failure rates.

RESULTS. Digital subtraction angiography confirmed significant disease (597 stenoses, 386 occlusions) in 983 iliofemoral segments. The sensitivity (54–80.9%), specificity (89.7–95.3%), and accuracy (85–87.5%) of contrast-enhanced MR angiography for the detection of significant iliofemoral disease were significantly ($p < 0.001$, all reviewers) better than those of time-of-flight MR angiography (33.2–62.8%, 74.3–88.9%, and 68–77.3%, respectively). Similar diagnostic performance was obtained for the calf arteries. The technical failure rate with contrast-enhanced MR angiography (2.5–3.4%) was similar to that of digital subtraction angiography (1.4%) and significantly ($p < 0.001$) lower than that of time-of-flight MR angiography (6.2–18.0%). Significantly better reproducibility ($p < 0.001$) was obtained with contrast-enhanced MR angiography (82% vs 65.2% agreement; $\kappa = 0.66$ vs 0.45).

CONCLUSION. Improved diagnostic performance and reproducibility are achievable with gadobenate dimeglumine–enhanced MR angiography in patients with peripheral arterial occlusive disease.

Keywords: contrast agents, diagnostic performance, gadobenate dimeglumine, MR angiography, peripheral arterial occlusive disease

DOI:10.2214/AJR.07.2218

Received March 5, 2007; accepted after revision May 19, 2007.

G. Schneider is a speaker for Bracco Imaging, D. A. Bluemke is a consultant for Bracco, and M. A. Kirchin and G. Pirovano are salaried employees of Bracco.

Presented at the 2006 annual meeting of the American Roentgen Ray Society, Vancouver, BC, Canada.

AJR 2007; 189:1223–1237

0361–803X/07/1895–1223

[1]Department of Radiology and Nuclear Medicine, Hospital Brothers of St. John of God, Grosse Mohrengasse 9, Vienna, Austria A-1020. Address correspondence to S. Thurnher (siegfried.thurnher@bbwien.at).

[2]Department of Diagnostic Radiology, Eberhardt Karls University, Tuebingen, Germany.

[3]Department of Diagnostic Radiology, Homburg University Hospital, Homburg/Saar, Germany.

[4]Department of Radiology, Hospital Valduce, Como, Italy.

[5]Institute for Diagnostic Radiology, University Hospital, Basel, Switzerland.

[6]Medical Prevention Center, University Mxedical Center, Hamburg-Eppendorf, Germany.

[7]Institute of Clinical Radiology, Ludwig Maximilians University, Munich, Germany.

[8]U.C.O. di Radiologia, Ospedale di Cattinara, Trieste, Italy.

[9]Department of Radiology, Ospedale Cà Foncello, Treviso, Italy.

[10]Crawford Long Hospital, Atlanta, GA.

[11]Department of Radiology, Università G. D'Annunzio, Chieti, Italy.

[12]Institut für Radiologie, Charité-Universitäts medizin, Berlin, Germany.

[13]Department of Radiology, Johns Hopkins Medical Center, Baltimore, MD.

[14]Klinikum der Johannes, Gutenberg Universität, Mainz, Germany.

[15]Worldwide Medical and Regulatory Affairs, Bracco Imaging SpA, Milan, Italy.

[16]Worldwide Medical and Regulatory Affairs, Bracco Diagnostics Inc., Princeton, NJ.

Peripheral arterial occlusive disease of the lower extremities is a prevalent disorder, causing a wide spectrum of disturbances and symptoms with substantial morbidity. Typical manifestations include intermittent claudication, pain at rest, tissue loss, and gangrene [1].

In patients with symptoms suggestive of peripheral arterial occlusive disease, information about the number and severity of vascular lesions is essential for planning appropriate revascularization therapy. Traditionally, assessment of peripheral arterial occlusive disease before treatment has been performed with conventional catheter angiography. However, conventional angiography is a highly invasive procedure that carries substantial risk to the patient [2]. The advent of alternative minimally invasive procedures such as MDCT angiography (MDCTA) [3–6] and contrast-enhanced MR angiography (CE-MRA) [7–16] has markedly reduced the need for preoperative diagnostic catheter angiography, effectively limiting its use to patients undergoing interventional treatment.

Of the minimally invasive techniques available, CE-MRA has the advantage of not requiring ionizing radiation or large volumes of iodinated contrast material. Moreover, with improvements in MRI hardware and sequence design [17–20] that permit greater spatial resolution and faster image acquisition, CE-MRA is increasingly considered the method of choice for imaging large vascular territories such as the peripheral runoff vessels. The advent of MR contrast agents with beneficial properties for vascular imaging may further improve the diagnostic impact of CE-MRA.

Gadobenate dimeglumine (MultiHance, Bracco Imaging) is a gadolinium contrast agent whose r1 relaxivity in blood is roughly two times higher than the r1 values of conventional gadolinium contrast agents at available magnetic field strengths up to 3 T [21, 22]. The increased r1 relaxivity derives from weak and transient interaction of the Gd-BOPTA contrast-effective chelate of gadobenate dimeglumine with serum albumin [23] and results in significantly better vascular contrast enhancement and better vessel delineation than that achieved with conventional gadolinium agents at equivalent or higher doses [24–28]. In the peripheral vasculature, a 0.1 mmol/kg dose of gadobenate dimeglumine has been shown to be superior to an equivalent dose of gadopentetate dimeglumine in terms of diagnostic image quality [27] and to permit better visualization of the arterial vasculature, particularly in the lower runoff territory [27, 28].

Previously, sensitivity and specificity values of 94% and 89–93% have been reported for the diagnostic accuracy of gadobenate dimeglumine–enhanced MR angiography in patients with peripheral arterial occlusive disease [28]. However, these values were obtained in a relatively small single-center population of just 28 patients using a standard contrast agent volume of 34 mL per patient. Our study was performed in a much larger multinational, multicenter patient population using a standard gadobenate dimeglumine dose per patient of 0.1 mmol/kg. Values for sensitivity, specificity, and overall diagnostic accuracy for the detection of significant (≥ 51%) stenoocclusive disease were determined using digital subtraction angiography as the reference standard and were compared with values obtained using unenhanced 2D time-of-flight MR angiography (TOF MRA).

Subjects and Methods

This was a phase III, multicenter, open-label trial conducted at 26 investigational centers in Europe and North and South America. The study was reviewed and approved by the local institutional review board or ethics committee of each of the participating centers in accordance with good clinical practice [29] and was performed in adherence to the Declaration of Helsinki [30] and subsequent amendments and clarifications. Written informed consent was obtained from each patient before inclusion in the study.

Study Population

All patients were enrolled between May 2003 and November 2004. Men and women were eligible for enrollment if they were 18 years old or older and had known or suspected peripheral arterial occlusive disease in the iliofemoral arteries based on clinical examination or sonographic findings. All patients were required to undergo a conventional digital subtraction angiography examination within 1–30 days before or after the CE-MRA examination and to exhibit no change in clinical symptoms related to peripheral arterial occlusive disease between the two procedures. Patients were not permitted to undergo any therapeutic intervention for vascular disease between the MR angiography and the digital subtraction angiography procedures or any other surgical procedure within 24 hours after the administration of gadobenate dimeglumine.

Patients with known allergies to one or more of the study agent ingredients or a known history of hypersensitivity to metals, including gadolinium or iodinated contrast media, were ineligible for inclusion, as were patients who received any other investigational agent within 30 days before the study or any other contrast agent within 24 hours before or after gadobenate dimeglumine administration. Similarly, patients who suffered severe claustrophobia, had class III or IV congestive heart failure according to the American Heart Association classification [31], or had a pacemaker, metallic cardiac valve, or metallic vascular stent in one or more of the vessels of interest were also ineligible for inclusion. Finally, pregnant or lactating women were ineligible for inclusion, as were patients with any medical condition or other circumstances that would significantly decrease the chances of obtaining reliable data or of achieving study objectives. A total of 294 patients with known or suspected peripheral arterial occlusive disease based on clinical or sonographic findings were enrolled. Of these 294 patients, 287 (207 men, 80 women; mean age, 65.7 ± 9.95 years; range, 40–93 years) underwent TOF MRA and CE-MRA.

MR Angiography

The 287 participants underwent MR angiography at 1.5 T on commercially available MR scanners equipped with a gradient of ≥ 20 mT/m. The MR scanners used for the study were from Siemens Medical Solutions (Symphony, $n = 69$ [24.0%]; Sonata, $n = 75$ [26.1%]; Avanto, $n = 12$ [4.2%]), Philips Medical Systems (Gyroscan Intera, $n = 69$ [24.0%]), or GE Healthcare (Genesis Signa, $n = 40$ [13.9%]; Excite, $n = 22$ [7.7%]).

MR angiography was performed using a 2D TOF MRA sequence before contrast agent administration and a 3D spoiled gradient-echo MR angiography sequence immediately after administration of gadobenate dimeglumine. The large number of investigating centers involved in the study and the wide variety of imaging systems used resulted in necessarily slightly different parameters among centers for the TOF MRA and CE-MRA sequences. Nevertheless, each sequence at each center was selected to meet minimal requirements for image acquisition and interpretability.

The parameters for the TOF MRA sequence varied among centers as follows: axial orientation; TR/TE range, ≤ 60/4.2–7.2; flip angle, 30–70°; excitations, 1–2; slice thickness, < 4 mm; matrix, ≥ 256 × 160; overall acquisition time, 5–12 minutes. ECG gating was performed for 75% of the patients. CE-MRA of the peripheral arteries was performed with a dedicated phased-array peripheral coil (225 patients) or with a body coil (62 patients) and a bolus chase technique using the following sequence parameters: coronal orientation; TR range/TE range, 2.3–6/0.78–2.15; flip angle, 25–45°; excitations, 0.5–1; slice thickness, 1–3.5 mm; matrix, ≥ 256 × 224; true in-plane spatial resolution, 0.68 × 0.68–1.3 × 1.3 mm; overall acquisition time, ≤ 50 seconds. The iliofemoral field of view for both the TOF MRA and CE-MRA sequences was tailored for each patient to include arterial vasculature from 2 cm above the aortic bifurcation to a point on the popliteal artery at the level of the knee joint line. MR

angiography of the calf arteries was optional at all investigational centers as a secondary acquisition after full CE-MRA of the iliofemoral arteries.

The CE-MRA sequence was acquired after the administration of gadobenate dimeglumine at a dose of 0.1 mmol/kg of body weight. Contrast agent administration was performed using a power injector at a rate of 1–2 mL/s, followed by a 20-mL saline flush at the same rate. Timing for the CE-MRA sequence was achieved by means of a bolus timing acquisition (n = 173 participants) or through the use of an automatic or MR fluoroscopic bolus detection technique (SmartPrep [GE Healthcare], BolusTrak [Philips Medical Systems], or CARE Bolus [Siemens Medical Solutions], depending on the scanner manufacturer; n = 114 subjects). The test bolus timing approach involved acquisition of 45–60 dynamic single-slice T1-weighted fast gradient-echo images of the common femoral artery at a frequency of one image per second after the administration of a 1- to 2-mL bolus of gadobenate dimeglumine.

Digital Subtraction Angiography

Conventional digital subtraction angiography was performed by injecting an iodinated contrast medium through a pigtail or straight 4- to 5-French catheter inserted via a femoral artery puncture using the Seldinger technique. The catheter tip was positioned in the abdominal aorta 5–10 cm above the aortic bifurcation. Anteroposterior, right anterior oblique, and left anterior oblique projections at angulations of 15–30° were obtained of the aortoiliac station as appropriate according to each center's standard operating procedure. Anteroposterior projections were obtained for the upper and lower leg stations. Most digital subtraction angiography examinations were performed using iodinated contrast media having iodine concentrations of > 200 mg I/mL (200–300 mg I/mL in 58% of the subjects; > 300 mg I/mL in 42% of the subjects). The total volume of contrast medium administered was 50–200 mL. Individual injections of 15–40 mL were administered at rates of 4–12 mL/s depending on the vessel of interest.

Image Evaluation

Images were evaluated by on-site investigators and by four off-site independent, experienced (at least 10 years of experience in vascular imaging) board-certified radiologists (three for MR angiography, one for digital subtraction angiography) who were not affiliated with any of the study sites and who were fully blinded to all patient information and to the results of other diagnostic procedures.

Off-site evaluation of digital MR angiography and digital subtraction angiography images was performed at an independent core imaging laboratory equipped with two separate Windows (Microsoft)-based workstations (AquariusNet Viewer, TeraRecon) for evaluation of images (two monitors) and for recording of assessment findings using an electronic Case Report Form (e-CRF) system. All TOF MRA and CE-MRA images were combined into a single randomization pool, and each image set for each patient was reviewed separately, one at a time and in random order. In each case, axial source images and volumetric maximum-intensity-projection (MIP) reconstructions were always displayed on the two monitors set up for image evaluation. All routine image review tools (window and level, zoom, pan, and so forth) were available to the reviewers.

The three off-site reviewers of MR angiography images performed their evaluations independently in a fully blinded fashion. Evaluation of the iliofemoral arterial anatomy from 2 cm above the aortic bifurcation to the popliteal arteries at the level of the knee joint was performed on a segmental basis in which standard segments comprised the left and right common, internal, and external iliac arteries; the left and right common, superficial, and deep femoral arteries; and the left and right popliteal arteries.

Initial off-site evaluation was performed to determine the technical adequacy (quality of visualization) of the TOF MRA and CE-MRA image sets. If any segment was not entirely in the field of view or was considered technically inadequate for any reason, no further assessment was performed for that segment. Assessment of all segments considered technically adequate was then performed using a 3-point scale in which 1 = stenosis of ≤ 50% (vessel with no clinically significant disease), 2 = stenosis of 51–99% (vessel with clinically significant disease), and 3 = occlusion (vessel with 100% blockage of the vessel lumen). Evaluation of calf vessels was performed using similar assessment methodology with the calf vasculature divided into segments comprising the left and right tibiofibular trunk, the left and right anterior and posterior tibial arteries, and the left and right peroneal arteries.

The presence and location of collateral circulation was assessed in a yes-or-no manner. Collateral circulation was assigned to one of the following locations per side (right and left): station 1 (from the abdominal aorta to the external iliac artery), between stations 1 and 2 (from the abdominal aorta to the popliteal artery), station 2 (from the common femoral artery to the popliteal artery), between stations 2 and 3 (from the common femoral artery to the tibial arteries), and station 3 and below (from the tibiofibular trunk to downstream). Finally, the presence and type of associated disease in each iliofemoral segment was recorded as none, aneurysm, dissection, or other.

Off-site evaluation of digital subtraction angiography images was performed by a fourth independent radiologist who had 12 years of experience in angiographic procedures, was not affiliated with the study centers, and was blinded to all clinical and radiologic information. Digital subtraction angiography images were combined into a second pool, different from the MR angiography pool, for blinded reviewing purposes, but were evaluated using similar assessment methodology and criteria.

On-site evaluation of MR angiography images was performed using similar criteria to those of the off-site evaluation. Evaluation of MR angiography and digital subtraction angiography images was performed independently by two experienced radiologists (one for each technique) at each investigational site. Each reviewer was fully blinded to the results of the other imaging technique.

Safety Evaluations

Physical examination was performed within 24 hours before gadobenate dimeglumine administration and at 24 hours after administration. Measurement of vital signs (blood pressure, heart rate) was performed within 24 hours before dosing and before the participant entered the magnet, and at 30 minutes, 1 hour, and 24 hours after gadobenate dimeglumine administration. Recording of ECGs was similarly performed before the patient entered the bore of the magnet and at 1 hour and 24 hours after administration of gadobenate dimeglumine.

In addition, blood and urine samples were collected within 24 hours before gadobenate dimeglumine administration and at 24 hours after administration. Laboratory evaluation of collected samples was performed for hematology (hematocrit, hemoglobin, and counts of RBCs, WBCs, and platelets), blood chemistry (glucose, creatinine, total bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, sodium, potassium, and chloride), and urinalysis (protein, glucose, ketones, blood, and pH).

Finally, the safety of gadobenate dimeglumine was assessed in terms of the incidence of adverse clinical events from the time of signed informed consent until 24 hours after gadobenate dimeglumine administration. Adverse events were classified as serious (i.e., death, life-threatening, or requiring or prolonging hospitalization) or not serious (rated as mild, moderate, or severe). The relationship of each adverse event to the study agent was classified as probable, possible, not related, unknown, or missing.

Statistical Analysis

The primary objectives were to determine the diagnostic accuracy of CE-MRA with gadobenate dimeglumine for detection of significant stenoocclusive disease (defined as stenosis of ≥ 51% or occlusion) of the iliofemoral arteries using digital subtraction angiography as a reference standard, and to compare the diagnostic performance of CE-MRA with that of unenhanced TOF MRA. Data from each of the three off-site MR angiography reviewers and from the on-site investigators were analyzed and presented separately.

TABLE 1: Technical Adequacy of TOF MRA and CE-MRA for Evaluation of Iliofemoral Arteries in 287 Patients

Adequacy	No. (%) of Segments							
	Reviewer 1		Reviewer 2		Reviewer 3		On-Site Reviewer	
	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA
Total no. of segments[a]	4,138	4,261	4,086	4,220	4,058	4,240	4,276	4,276
Adequate	3,393 (82.0)	4,142 (97.2)	3,624 (88.7)	4,113 (97.5)	3,807 (93.8)	4,094 (96.6)	2,899 (67.8)	3,994 (93.4)
Inadequate	745 (18.0)	119 (2.8)	462 (11.3)	107 (2.5)	251 (6.2)	146 (3.4)	1,377 (32.2)	282 (6.6)
p[b]	< 0.001		< 0.001		< 0.001		< 0.001	

Note—TOF MRA = time-of-flight MR angiography, CE-MRA = contrast-enhanced MR angiography.
[a]In field of view.
[b]Chi-square test comparing TOF MRA and CE-MRA.

Sensitivity for detection of significant stenoocclusive disease was defined as the number of correctly identified significantly (≥ 51%) diseased segments on TOF MRA or CE-MRA divided by the total number of significantly (≥ 51%) diseased segments on digital subtraction angiography. Specificity was defined as the number of correctly identified segments in TOF MRA or CE-MRA that were not diseased or not significantly (< 51%) diseased divided by the total number of segments on digital subtraction angiography that were not diseased or not significantly (< 51%) diseased. Accuracy was defined as the number of correctly identified segments (either diseased or nondiseased) on MR angiography divided by the total number of segments evaluated on digital subtraction angiography. All uninterpretable MR angiography images were considered inaccurate for all determinations of diagnostic performance. If a segment was technically inadequate on MR angiography, this segment was considered false-positive if the corresponding digital subtraction angiography revealed a stenosis of ≤ 50%; however, this segment was considered false-negative if the corresponding digital subtraction angiography revealed a stenosis of ≥ 51% or occlusion.

The sensitivity, specificity, and accuracy of TOF MRA and CE-MRA were compared using the McNemar test. In addition, supplemental supporting analyses of sensitivity and specificity were performed using generalized estimating equations (GEEs) [32] to eliminate potential correlation-related bias caused by evaluation of multiple segments for each patient. "Reviewer" was considered a fixed effect in the GEE model.

Determinations of positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio were performed and compared descriptively for the two MR angiography sequences. Determination of interobserver agreement was evaluated by means of the generalized kappa (κ) coefficient and by the percentage of concordance among the three MR angiography reviewers.

The technical failure rate for each MR angiography sequence was defined as the total number of technically inadequate segments divided by the total number of segments included in the field of view. Comparison of the technical failure rate for TOF MRA with that for CE-MRA for the iliofemoral arteries was performed using the chi-square test.

A power calculation was performed on the basis of the assumption that the expected difference in sensitivity for detecting significant (≥ 51%) stenoocclusive disease between TOF MRA and CE-MRA was 10%. Assuming that the proportion of discordant pairs was 0.26 and that the sensitivity of TOF MRA was 0.70, then for a two-sided 0.05 alpha level McNemar test of equality of paired proportion, 225 participants with at least one significant stenosis were required for statistical power of 85%. Assuming a 10% dropout rate, at least 265 subjects were required to enter the study. The total number of subjects assessed for sensitivity was also sufficient for specificity because each subject could have many negative segments contributing to specificity.

All statistical analyses were performed using the statistical software package SAS version 8.2 (SAS Institute).

Results

Of the 294 patients enrolled, 287 received gadobenate dimeglumine at a dose of 0.1 mmol/kg of body weight and underwent TOF MRA and CE-MRA. Each of these 287 patients was evaluated for safety and technical adequacy of the MR angiography examinations. The remaining seven patients discontinued their study participation before contrast agent administration.

Most patients (171/287, 59.6%) were 65 years old or older; the remainder were 40–64 years old. Most patients who received gadobenate dimeglumine (165/287, 57.5%) presented with moderate to severe claudication (stage IIb according to the classification of Fontaine et al. [33]). The remaining patients had mild claudication (stage IIa; 53/287, 18.5%), ischemic pain at rest (stage III; 38/287, 13.2%), ulceration or gangrene (stage IV; 29/287, 10.1%), or were asymptomatic (2/287, 0.7%) at presentation. Most participants underwent MR angiography to confirm or evaluate a previously detected stenosis (131/287, 45.6%) or because of clinical symptoms suggestive of stenosis (117/287, 40.8%). A smaller proportion of participants (39/287, 13.6%) underwent MR angiography to guide revascularization or as follow-up to a previous treatment.

Of the 287 participants to undergo MR angiography, only 272 (94.8%) also underwent the required digital subtraction angiography examination. Consequently, assessment of diagnostic performance was performed for 272 participants overall.

Technical Adequacy and Quality of Segment Visualization

The technical adequacy of TOF MRA and CE-MRA for evaluation of the iliofemoral arteries in all 287 participants who received gadobenate dimeglumine is shown in Table 1. The technical failure rate of CE-MRA for reviewers 1, 2, and 3 (2.8%, 2.5%, 3.4%, respectively) was in all cases significantly ($p < 0.001$) lower than the failure rate of TOF MRA (18.0%, 11.3%, 6.2%, respectively). Similar findings were noted by the on-site investigators (6.6% of iliofemoral segments were considered inadequate on CE-MRA compared with 32.2% on TOF MRA; $p < 0.001$). Overall, the technical failure rate of CE-MRA for the iliofemoral arteries was low in absolute terms for each reviewer and comparable to the failure rate of digital subtraction angiography (1.4%).

Off-site assessment of the calf arteries revealed slightly greater numbers of technically inadequate segments for both TOF MRA and CE-MRA when compared with the iliofemoral arteries (technical failure rate, 45.0%, 26.6%, and 25.3% for TOF MRA compared with 12.0%, 8.2%, and 14.2% for CE-MRA rated by reviewers 1, 2, and 3, respectively). However, a similar trend for significantly ($p < 0.001$, all

TABLE 2: Sensitivity, Specificity, and Accuracy of TOF MRA and CE-MRA for Detection of Significant Stenoocclusive Disease of the Iliofemoral Arteries Using Digital Subtraction Angiography as the Reference Standard

Performance Measure	Reviewer 1		Reviewer 2		Reviewer 3		On-Site Reviewer	
	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA
Sensitivity (%)	33.2 (314/945)	54.0[a] (527/976)	62.8 (590/940)	80.9[a] (786/971)	42.0 (389/926)	67.4[a] (657/975)	39.9 (359/900)	61.6[a] (552/896)
Specificity (%)	79.4 (2,273/2,862)	95.3[a] (2,809/2,947)	74.3 (2,096/2,820)	89.7[a] (2,619/2,920)	88.9 (2,504/2,817)	94.0[a] (2,763/2,940)	59.4 (1,853/3,119)	86.9[a] (2,719/3,128)
Accuracy (%)	68.0 (2,587/3,807)	85.0[a] (3,336/3,923)	71.4 (2,686/3,760)	87.5[a] (3,405/3,891)	77.3 (2,893/3,743)	87.4[a] (3,420/3,915)	55.0 (2,212/4,019)	81.3[a] (3,271/4,024)

Note—TOF MRA = time-of-flight MR angiography, CE-MRA = contrast-enhanced MR angiography.

[a]Statistically significant increase from TOF MRA ($p < 0.001$ based on McNemar test).

reviewers) lower numbers of technically inadequate images on CE-MRA was apparent. Moreover, the number of technically inadequate calf segments on CE-MRA was comparable to the failure rate of digital subtraction angiography (10.2%).

Diagnostic Performance

Iliofemoral arteries—Of the 272 participants to undergo both MR angiography and digital subtraction angiography, only eight (2.9%) did not have any iliofemoral segment with significant (≥ 51%) stenoocclusive disease; the remaining 264 (97.1%) participants had at least one iliofemoral segment with significant disease. These 264 participants comprised 14 (5.1%) who had one segment with clinically significant disease, 29 (10.7%) who had two segments with clinically significant disease, 43 (15.8%) who had three segments with clinically significant disease, 41 (15.1%) who had four segments with clinically significant disease, and 137 (50.4%) who had five or more segments with clinically significant disease.

Overall, 4,003 iliofemoral segments were considered in the field of view on digital subtraction angiography. Of these, 2,962 (74.0%) segments were considered to be without significant disease, whereas 983 (24.6% segments were considered to have significant disease (597 [14.9%] segments with significant (≥ 51%) stenosis, 386 [9.6%] segments with occlusions). The remaining 58 (1.4%) segments were considered to be technically inadequate.

The diagnostic performance of MR angiography for the detection of significant stenoocclusive disease of the iliofemoral arteries using digital subtraction angiography as the reference standard is summarized in Table 2. All off-site reviewers and on-site investigators obtained significantly ($p < 0.001$) higher sensitivity, specificity, and overall accuracy for the detection of significant stenoocclusive disease for CE-MRA compared with TOF MRA. After eliminating the possibility of within-cluster correlation effect, the results of the GEE model analysis confirmed the significantly better sensitivity (odds ratio [OR], 4.3 [95% CI, 3.4–5.5]) and specificity (OR, 3.6 [2.7–4.8]) of CE-MRA compared with TOF MRA. Overall increases in accuracy of 17.0% (15.5–18.5%), 15.9% (14.2–17.5%), and 9.9% (8.5–11.3%) were determined for off-site reviewers 1, 2, and 3, respectively, whereas a greater increase in accuracy of 26.1% (24.4–27.8%) was determined for the on-site investigators. Examples of the improved image quality achievable on CE-MRA with 0.1 mmol/kg of gadobenate dimeglumine compared with TOF MRA and of the excellent correlation of gadobenate dimeglumine–enhanced MR angiography and digital subtraction angiography are shown in Figures 1–4.

A significant ($p < 0.00001$) increase in agreement among the three MR angiography reviewers was noted for the CE-MRA image sets (82% agreement; κ, 0.66) compared with the TOF MRA image sets (65.2% agreement; κ, 0.45) (Table 3).

Determinations of PPV, NPV, positive likelihood ratio, and negative likelihood ratio confirmed the better performance for CE-MRA compared with TOF MRA for both off-site reviewers and on-site investigators (Table 4).

Calf arteries—CE-MRA of the calf arteries was performed for 263 (91.6%) of the 287 participants who underwent CE-MRA of the iliofemoral arteries. Conversely, only 141 (49.1%) participants underwent TOF MRA of the calf arteries. Digital subtraction angiography correlation was available for 241 (91.6%) of the 263 participants who underwent CE-MRA of the calf arteries.

A total of 1,507 calf artery segments were considered to be in the field of view on digital subtraction angiography. Significant stenoocclusive disease was noted in 465 (30.9%) of these 1,507 segments (150 [10.0%] segments with significant (≥ 51%) stenosis, 315 [20.9%] segments with occlusions), whereas 889 (59.0%) of 1,507 segments were considered to be without significant disease. The remaining 153 (10.2%) segments were considered technically inadequate.

The diagnostic performance of MR angiography for the detection of significant stenoocclusive disease of the calf arteries relative to digital subtraction angiography is summarized in Table 5. Although slightly lower values for sensitivity, specificity, and accuracy were obtained compared with values obtained for the iliofemoral arteries, significantly better performance was noted in all cases by each MR angiography reviewer for CE-MRA compared with TOF MRA. Similar trends to those observed in the iliofemoral arteries were also noted for PPV, NPV, positive likelihood ratio, and negative likelihood ratio.

Collateral Circulation and Associated Disease

Collateral circulation was detected in a greater percentage of stations on CE-MRA (8.5–10.3% of the stations examined at MR angiography and digital subtraction angiography) compared with TOF MRA (3.7–4.0% of the stations) across the three blinded MR angiography reviewers. A similar trend was noted by on-site investigators (26.8% on CE-MRA compared with 10.1% on TOF MRA). Accuracy for the detection of collateral circulation ranged from 82.0% to 89.0% for CE-MRA and from 71.5% to 88.3% for TOF MRA when compared with the collateral circulation detected on digital subtraction angiography. The difference in accuracy between TOF MRA and CE-MRA for the detection of collateral circulation was significant for MR angiography reviewer 3 ($p = 0.027$) and for the on-site investigators ($p < 0.001$) but not for MR angiography reviewers 1 and 2.

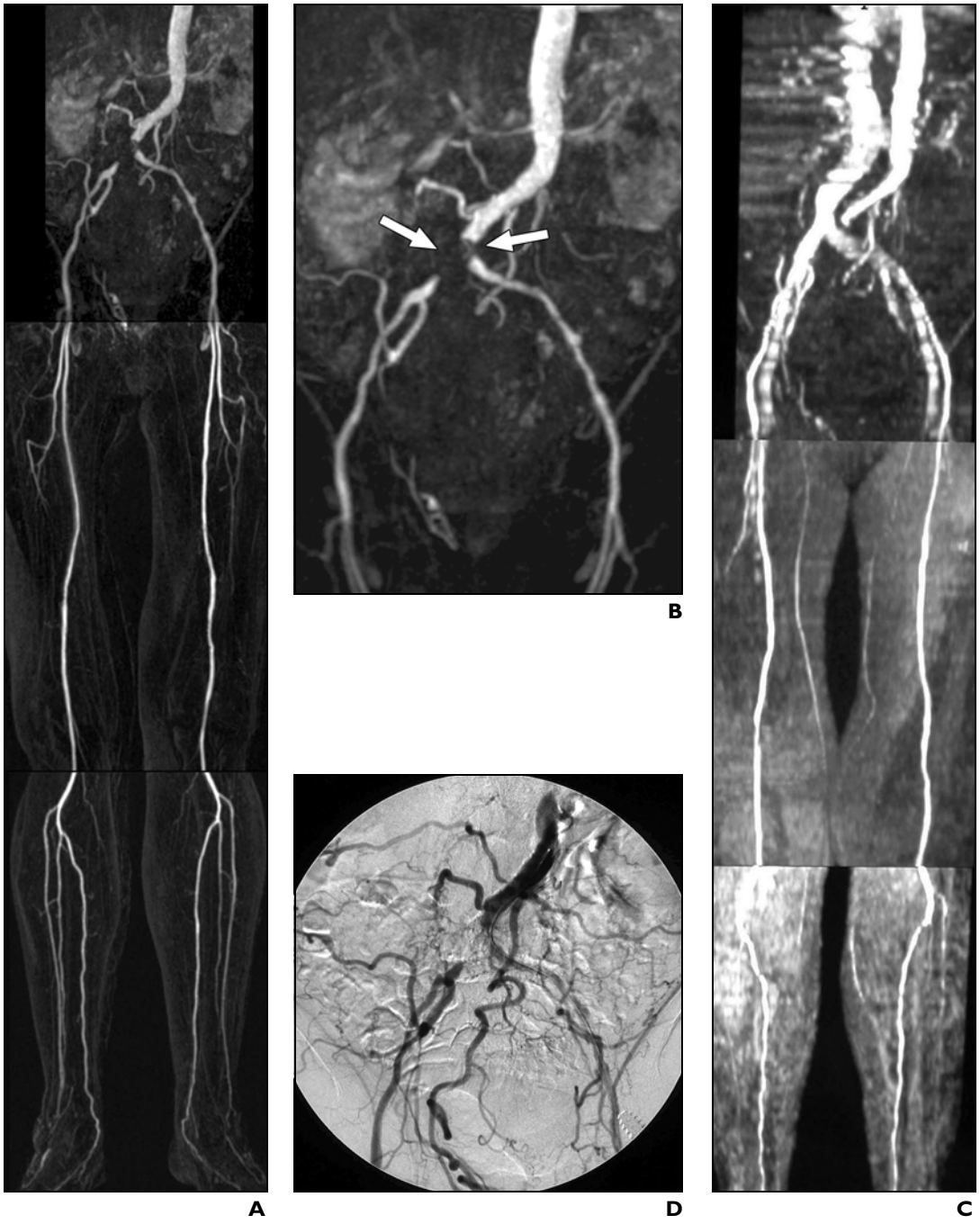


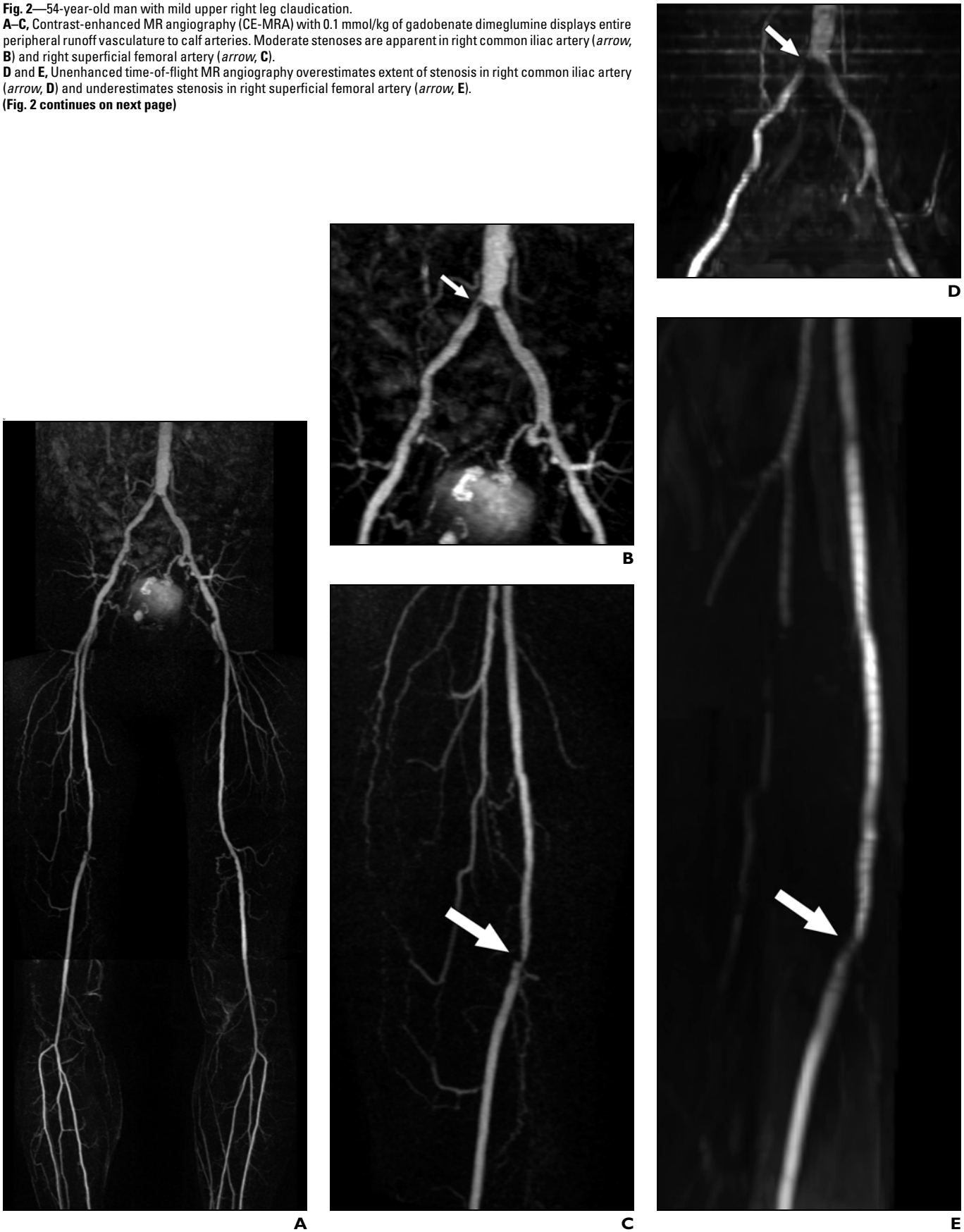
Fig. 1—52-year-old man with Leriche syndrome.
A and **B,** Contrast-enhanced MR angiography (CE-MRA) with 0.1 mmol/kg of gadobenate dimeglumine displays entire peripheral runoff vasculature to calf arteries. Short segment occlusion of right common iliac artery and high-grade stenosis of left common iliac artery are evident (*arrows,* **B**).
C, Unenhanced time-of-flight MR angiography shows occlusion of both common iliac arteries and suggests segmental occlusion of calf arteries. However, image quality is compromised by venous overlay.
D, Digital subtraction angiography confirms findings of CE-MRA examination.

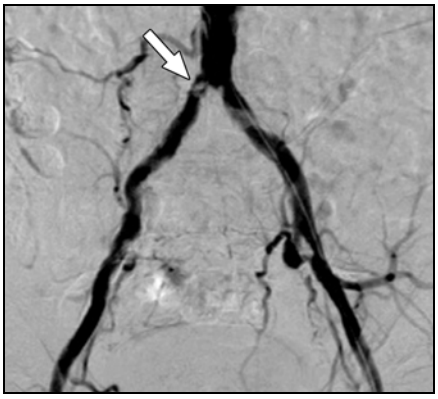
Blinded evaluation of digital subtraction angiography images revealed associated disease in 172 (4.4%) of 3,945 iliofemoral segments (aneurysm in 45 [1.1%] segments and associated disease classified as "other" in 127 [3.2%] segments). In 3,773 (95.6%) segments, no associated disease was present. The three blinded MR angiography reviewers detected associated aneurysms in 43 (1.1%), 22 (0.6%), and 34 (0.9%) segments, respectively, on CE-MRA and in three (0.1%), 18 (0.5%), and eight (0.2%) segments, respectively, on TOF MRA. No associated disease was recorded for 98.3–98.8% of segments on CE-MRA and 99.2–99.7% of segments on TOF MRA.

Safety

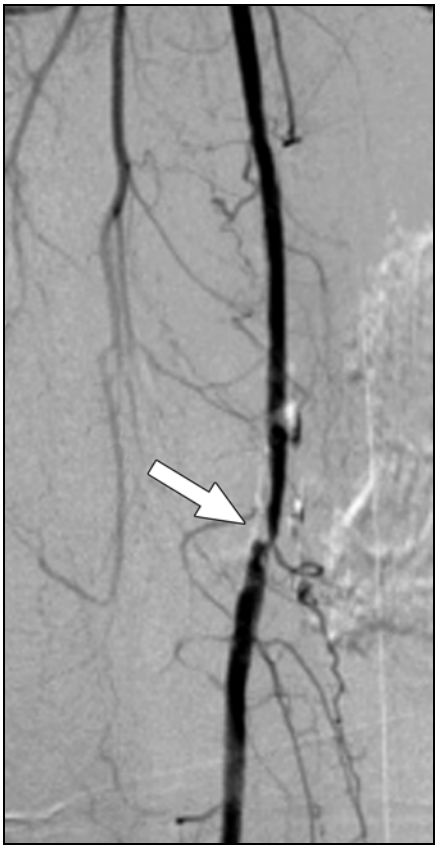
A total of 43 nonserious adverse events were reported by 30 (10.5%) of 287 participants overall, of which 32 events in 22 (7.7%) participants were considered of probable, possible, unknown, or missing relationship to the administration of gadobenate dimeglumine. The remaining events were considered unrelated. All events were either mild (87%) or moderate (13%) in intensity, and no serious adverse events were reported. The most commonly reported events that were considered of potential relationship to the administration of gadobenate dimeglumine were injection site warmth

Fig. 2—54-year-old man with mild upper right leg claudication.
A–C, Contrast-enhanced MR angiography (CE-MRA) with 0.1 mmol/kg of gadobenate dimeglumine displays entire peripheral runoff vasculature to calf arteries. Moderate stenoses are apparent in right common iliac artery (*arrow*, **B**) and right superficial femoral artery (*arrow*, **C**).
D and **E,** Unenhanced time-of-flight MR angiography overestimates extent of stenosis in right common iliac artery (*arrow*, **D**) and underestimates stenosis in right superficial femoral artery (*arrow*, **E**).
(Fig. 2 continues on next page)





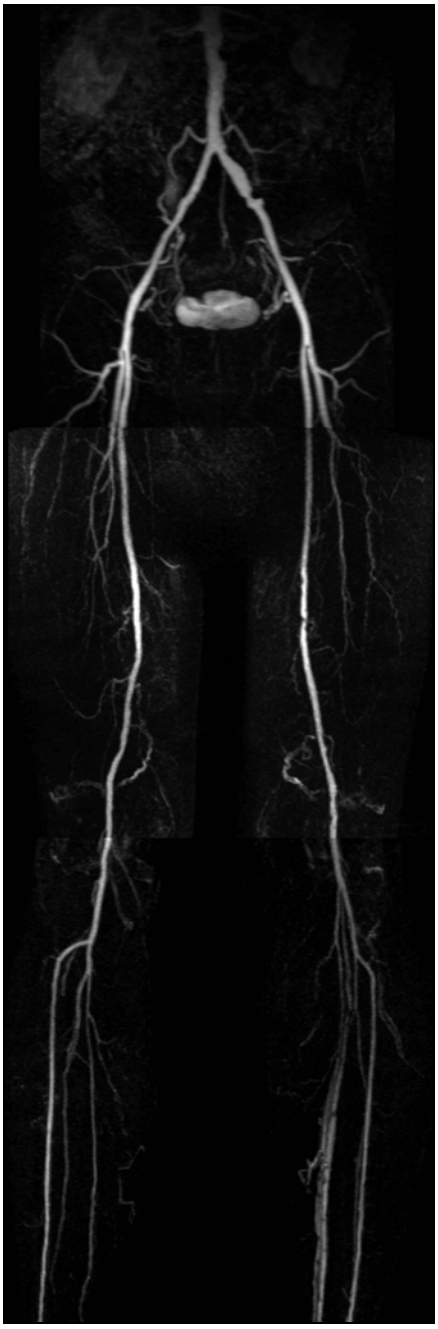
F



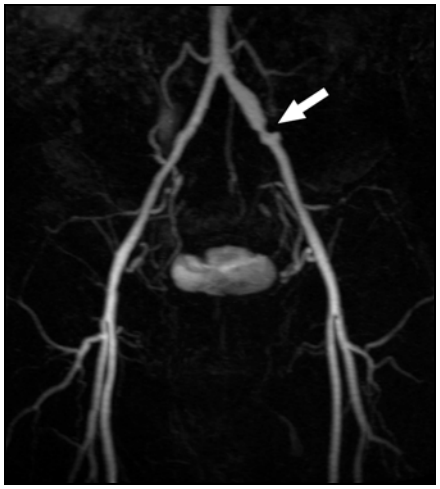
G

Fig. 2 (continued)—54-year-old man with mild upper right leg claudication.
F and **G,** Digital subtraction angiography confirms findings of CE-MRA examination: Moderate stenoses are apparent in right common iliac artery (*arrow,* **F**) and right superficial femoral artery (*arrow,* **G**).

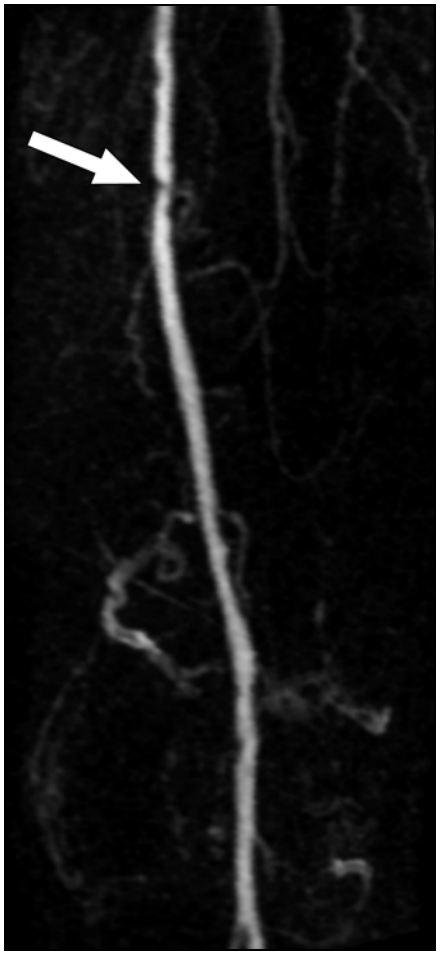
(1.7%, 5/287), increased systolic blood pressure (1.4%, 4/287), increased diastolic blood pressure (1.0%, 3/287), and nausea (0.7%, 2/287). All increases in blood pressure reported as adverse events were recorded in one participant at one site. No other event was reported by



A

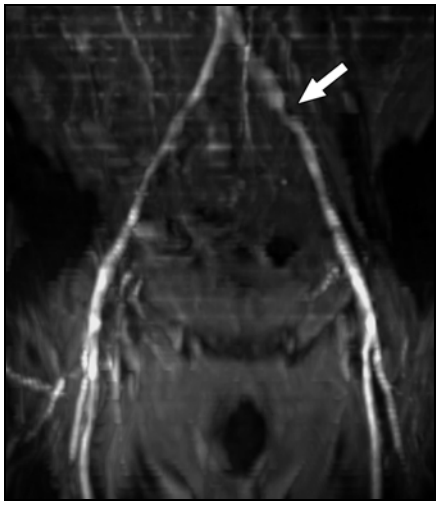


B

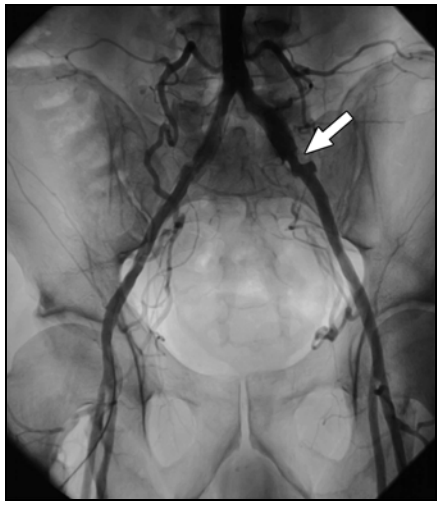


C

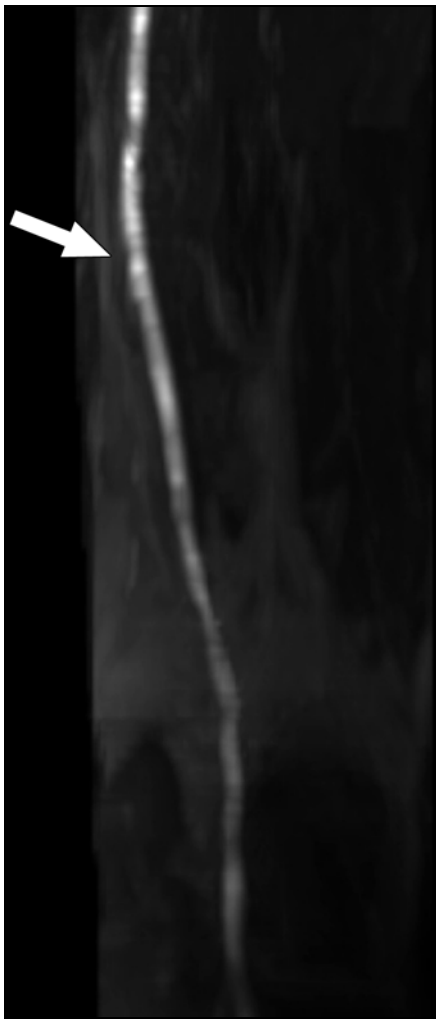
Fig. 3—59-year-old man with moderate to severe upper left leg claudication.
A–C, Contrast-enhanced MR angiography (CE-MRA) with 0.1 mmol/kg of gadobenate dimeglumine reveals aneurysm, high-grade stenosis of left common iliac artery (*arrow,* **B**), and high-grade stenosis of left superficial femoral artery (*arrow,* **C**).
(Fig. 3 continues on next page)



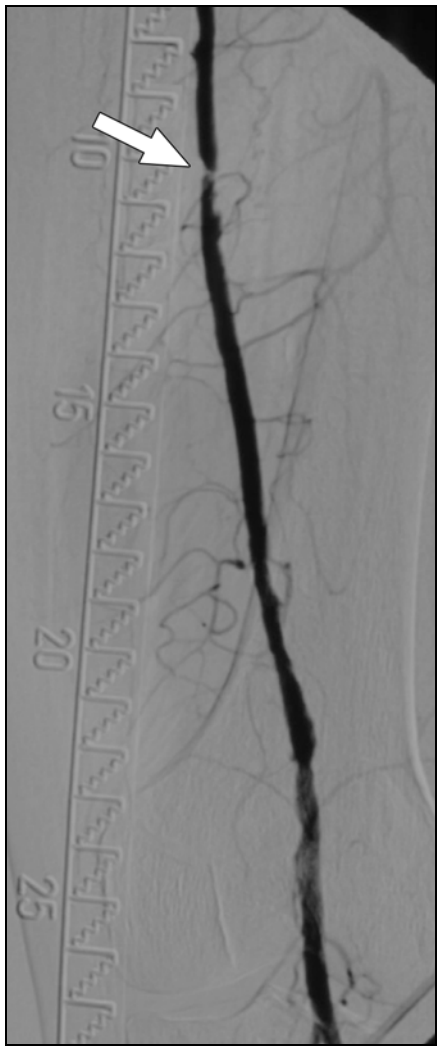
D



F



E



G

Fig. 3 (continued)—59-year-old man with moderate to severe upper left leg claudication.
D and **E,** Unenhanced time-of-flight MR angiography (TOF MRA) fails to adequately show vascular disease in left common iliac artery because of artifacts caused by turbulent flow (*arrow*, **D**). High-grade stenosis in left superficial femoral artery is underestimated on TOF MRA (*arrow*, **E**).
F and **G,** Digital subtraction angiography confirms findings of CE-MRA examination: Note aneurysm, high-grade stenosis of left common iliac artery (*arrow*, **F**), and high-grade stenosis of left superficial femoral artery (*arrow*, **G**).

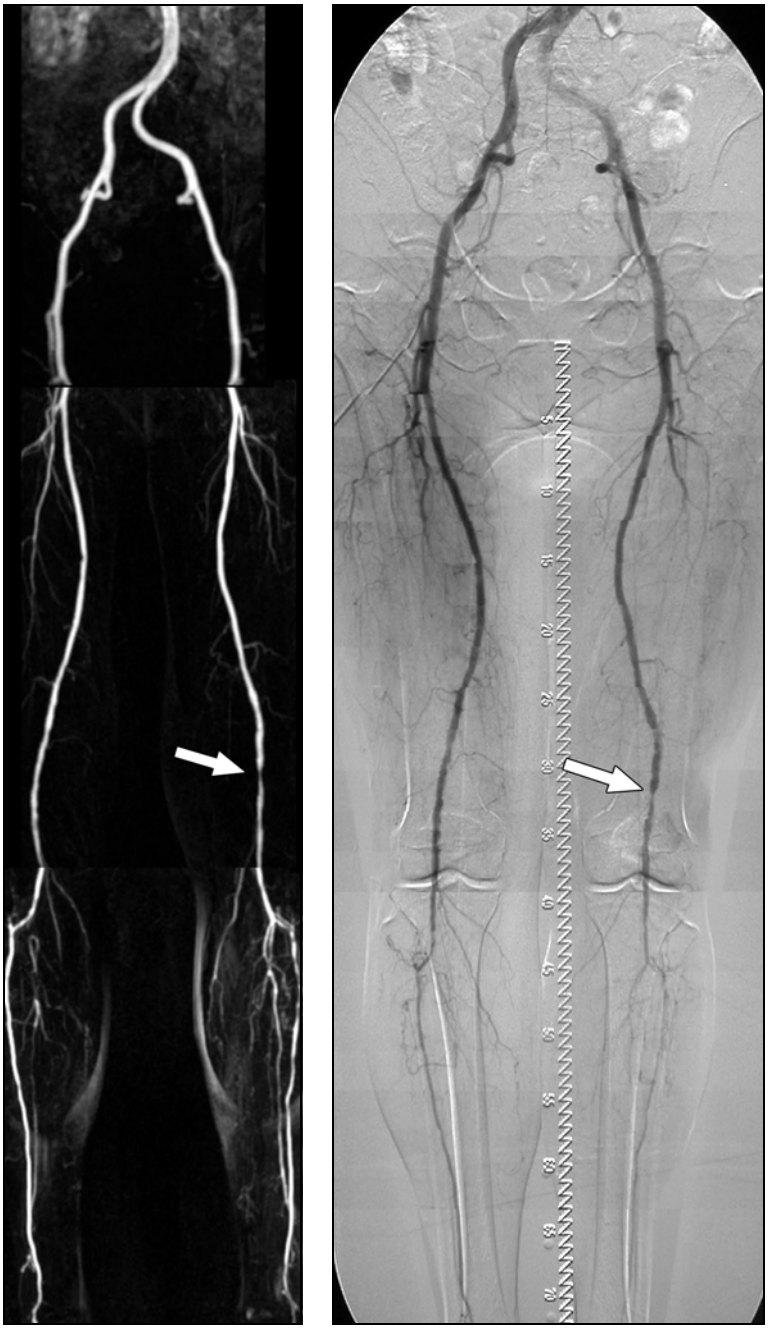


Fig. 4—66-year-old man with diabetes.
A, Contrast-enhanced MR angiography (CE-MRA) with 0.1 mmol/kg of gadobenate dimeglumine reveals severe stenosis (*arrow*) of left popliteal artery. In addition, bilateral occlusion of posterior tibial artery and segmental stenoses of anterior tibial artery and tibiofibular trunk are apparent.
B, Digital subtraction angiography confirms high-grade stenosis (*arrow*) of left popliteal artery and arterial disease of calf arteries.

more than one participant. No clinically meaningful time-related changes were noted for vital signs or clinical laboratory investigations, and no significant effects were noted for any cardiac electrophysiology parameter.

Discussion

Appropriate management of patients with suspected peripheral arterial occlusive disease depends on accurately differentiating patients with clinically relevant stenoocclusive disease who typically require some form of therapeutic intervention from participants without clinically relevant disease for whom a more conservative approach to treatment is generally preferred. Usually stenoocclusive disease resulting in vessel lumen narrowing of ≥ 51% is considered the threshold for defining patients for whom therapeutic intervention should be considered. Accordingly, our study was performed predominantly in patients with moderate to severe peripheral arterial occlusive disease (232/287 [80.8%] patients with stage IIb–IV disease according to the staging of disease by Fontaine et al. [33]) because these patients are the population most likely to undergo routine CE-MRA of the peripheral vasculature.

Although our primary objective was to assess the diagnostic performance of CE-MRA with 0.1 mmol/kg of gadobenate dimeglumine relative to conventional digital subtraction angiography, additional comparison with unenhanced TOF MRA was performed to meet guidelines issued by the U.S. Food and Drug Administration (FDA) [34] and the Committee for Proprietary Medicinal Products (CPMP) [35] concerning the development of diagnostic imaging agents. However, because the unacceptably long acquisition times of TOF MRA sequences precluded successful unenhanced TOF imaging of the entire runoff vasculature including the calf station in a large number of patients (only approximately half the patients underwent TOF MRA of the calf arteries, and many could not lie still in the bore of the magnet for the entire acquisition time of the sequence), the primary focus of our study was the iliofemoral vasculature, comprising the aortoiliac and femoropopliteal stations.

As was to be expected on the basis of findings from previous comparisons of CE-MRA

TABLE 3: Interobserver Agreement for Determinations of Accuracy for TOF MRA and CE-MRA Using Digital Subtraction Angiography as the Reference Standard

Agreement	No. (%) of Segments	
	TOF MRA	CE-MRA
No. of segments[a]	3,968	4,202
All 3 reviewers agree	2,588 (65.2)	3,445 (82.0)
At least 2 of 3 reviewers agree	3,848 (97.0)	4,180 (99.5)
κ	0.45	0.66

Note—TOF MRA = time-of-flight MR angiography, CE-MRA = contrast-enhanced MR angiography.
[a]Includes all segments in field of view for all reviewers.

TABLE 4: Positive and Negative Predictive Values and Likelihood Ratios for TOF MRA and CE-MRA Using Digital Subtraction Angiography as the Reference Standard

Performance Measure	Reviewer 1		Reviewer 2		Reviewer 3		On-Site Reviewer	
	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA
PPV[a] (%)	34.8 (314/903)	79.2 (527/665)	44.9 (590/1,314)	72.3 (786/1,087)	55.4 (389/702)	78.8 (657/834)	22.1 (359/1,625)	57.4 (552/961)
NPV[b] (%)	78.3 (2,273/2,904)	86.2 (2,809/3,258)	85.7 (2,096/2,446)	93.4 (2,619/2,804)	82.3 (2,504/3,041)	89.7 (2,763/3,081)	77.4 (1,853/2,394)	88.8 (2,719/3,063)
PLR[c]	1.6	11.5	2.4	7.9	3.8	11.2	1.0	4.7
NLR[d]	0.8	0.5	0.5	0.2	0.7	0.3	1.0	0.4

Note—TOF MRA = time-of-flight MR angiography, CE-MRA = contrast-enhanced MR angiography, PPV = positive predictive value, NPV = negative predictive value, PLR = positive likelihood ratio, NLR = negative likelihood ratio.

[a]Number of correctly identified diseased (≥ 51%) segments / total number of segments considered positive.

[b]Number of correctly identified nondiseased (≤ 50%) segments / total number of segments considered negative.

[c]Sensitivity / (1 – specificity).

[d](1 – sensitivity) / specificity.

TABLE 5: Diagnostic Performance of TOF MRA and CE-MRA in the Calf Arteries Using Digital Subtraction Angiography as the Reference Standard

Performance Measure	Reviewer 1		Reviewer 2		Reviewer 3	
	TOF MRA	CE-MRA	TOF MRA	CE-MRA	TOF MRA	CE-MRA
Sensitivity (%)	3.7 (4/107)	45.0[a] (157/349)	47.9 (45/94)	79.0[a] (282/357)	33.3 (32/96)	67.8[a] (248/366)
Specificity (%)	63.8 (187/293)	89.3[a] (625/700)	64.7 (163/252)	74.4[a,b] (539/724)	75.3 (198/263)	82.5[a,c] (586/710)
Accuracy (%)	47.8 (191/400)	74.5[a] (782/1,049)	60.1 (208/346)	75.9[a] (821/1,081)	64.1 (230/359)	77.5[a] (834/1,076)
PPV[d] (%)	3.6 (4/110)	67.7 (157/232)	33.6 (45/134)	60.4 (282/467)	33.0 (32/97)	66.7 (248/372)
NPV[e] (%)	64.5 (187/290)	76.5 (625/817)	76.9 (163/212)	87.8 (539/614)	75.6 (198/262)	83.2 (586/704)
PLR[f]	0.1	4.2	1.4	3.1	1.3	3.9
NLR[g]	1.5	0.6	0.8	0.3	0.9	0.4

Note—TOF MRA = time-of-flight MR angiography, CE-MRA = contrast-enhanced MR angiography, PPV = positive predictive value, NPV = negative predictive value, PLR = positive likelihood ratio, NLR = negative likelihood ratio.

[a]Statistically significant increase from TOF MRA ($p < 0.001$ based on McNemar test).

[b]Statistically significant increase from TOF MRA ($p = 0.01$).

[c]Statistically significant increase from TOF MRA ($p = 0.024$).

[d]Number of correctly identified diseased (≥ 51%) segments / total number of segments considered positive.

[e]Number of correctly identified nondiseased (≤ 50%) segments / total number of segments considered negative.

[f] Sensitivity / (1 – specificity).

[g](1 – sensitivity) / specificity.

with unenhanced MR angiography [36–38], CE-MRA of the iliofemoral arteries with gadobenate dimeglumine was significantly ($p < 0.001$) better than TOF MRA for all main measures of diagnostic performance (i.e., sensitivity, specificity, and accuracy for detection of significant stenoocclusive disease). Each of the three off-site blinded reviewers reported values of ≥ 85% for the diagnostic accuracy of CE-MRA for the detection of significant stenoocclusive disease of the iliofemoral arteries compared with digital subtraction angiography. These values compare favorably with values reported elsewhere for CE-MRA with other gadolinium-based MR contrast agents [8, 9, 39] and imply that correct classification of patients in terms of the need for interventional treatment or conservative follow-up is achievable in at least 85% of cases. Although the on-site investigators reported a slightly lower combined value for overall accuracy (81.3%), these investigators, like the off-site reviewers, were fully blinded to the results of the digital subtraction angiography procedure.

Because of the artificial full-blinding conditions of the off-site reviewers to all patient clinical and radiologic information in this study, a reduction of the diagnostic accuracy by 10–15% might not be unexpected [40]. Notably, a recent study comparing the conventional extracellular gadolinium contrast agents gadodiamide and gadopentetate dimeglumine for the detection of hemodynamically relevant stenosis reported accuracy values of 71–100% for the common iliac arteries, 57–71% for the external iliac arteries, and 12–50% for the internal iliac arteries [41]. Moreover, two recent phase III clinical trials performed to obtain regulatory approval for gadofosveset for peripheral CE-MRA determined diagnostic accuracy values of 83.8–90.3% [42] and 80.3–87.6% [43] for the detection of significant aortoiliac occlusive disease. Each of these studies was performed using an MR angiography protocol design similar to that used in our study, using similar CE-MRA sequences and similar assessment methodology involving fully blinded evaluation of all MR angiography images by three highly experienced independent reviewers.

Regarding other parameters of diagnostic performance, whereas the values for specificity (≥ 89.7% for all three off-site reviewers) were in line with values reported elsewhere

[8–12, 37, 39, 41–45], slightly lower values for sensitivity (33.2–62.8% for TOF MRA, 54.0–80.9% for CE-MRA) were obtained. In particular, the sensitivity for off-site reviewer 1 was lower than the values determined for the other two reviewers. On the other hand, strong interreviewer agreement for the diagnosis of clinically significant stenoocclusive disease was shown both for agreement between two reviewers and for agreement among all three reviewers. Specifically, all three blinded reviewers agreed in 82% ($\kappa = 0.66$) of segment evaluations on CE-MRA compared with just 65.2% ($\kappa = 0.45$) on TOF MRA. On the basis of the guidelines provided by Landis and Koch [46] for describing the clinical value of degree of concordance, the kappa value obtained in this study leads to the conclusion that gadobenate dimeglumine–enhanced MR angiography is a diagnostic test with substantial reproducibility. Similar consensus among reviewers was noted regarding the technical adequacy of CE-MRA for visualization of the iliofemoral arteries. For each off-site blinded reviewer, the technical failure rate reported for CE-MRA (2.5–3.4%) was significantly ($p < 0.001$) lower than that reported for TOF MRA (6.2–18.0%) and comparable to that reported for digital subtraction angiography (1.4%).

Because sensitivity and specificity may provide an incomplete picture of the clinical usefulness of MR angiography, additional assessment was made of the PPV and NPV values. Although the PPV indicates the actual likelihood of disease in instances of a positive examination, the NPV indicates the likelihood of no disease in instances of a negative examination. The PPV determinations for the blinded reviewers in this study indicate that a positive iliofemoral segment on CE-MRA with gadobenate dimeglumine is likely to be significant stenoocclusive disease in approximately 80% of cases. These results can be judged positively, especially considering the artificial environment in which they were obtained. The NPV results (86.2–93.4%) indicate that the risk of overlooking stenoocclusive disease on CE-MRA with gadobenate dimeglumine is low. Therefore, a normal study at CE-MRA with gadobenate dimeglumine should obviate further potentially hazardous conventional angiographic or surgical procedures.

Differently from predictive values and values for sensitivity and specificity, the values for positive likelihood ratio and negative likelihood ratio are not affected by the prevalence of disease [47]. Thus, determination of these values offers an approach to assessing diagnostic performance that is unaffected by the condition being evaluated in the population. The positive likelihood ratio indicates the effect of a positive examination finding on the probability that the condition in question exists, and the negative likelihood ratio addresses the effect of a negative examination on the probability that the condition in question is present. Likelihood ratio values therefore provide quantification of the effect of MR angiography on diagnostic thinking—that is, the impact of the MR angiography test result on the a priori probability of clinically significant stenoocclusive disease versus the a posteriori probability of such disease [48]. A positive likelihood ratio of ≥ 7.9 for each blinded reviewer in this study suggests that a positive finding on CE-MRA of the iliofemoral arteries would in each case lead to a moderate to large and often conclusive shift in the probability of ≥ 51% stenoocclusive disease being present. The PPV, NPV, and likelihood ratios determined for CE-MRA were consistently superior to those determined for TOF MRA, thereby providing supplemental confirmation of the superiority of CE-MRA for diagnostic imaging of the iliofemoral arteries.

Concerning the calf arteries, excellent visualization has previously been shown with both unenhanced MR angiography [49–51] and CE-MRA [7, 11, 44, 52], although venous contamination and reduced signal-to-noise ratio (SNR) have sometimes been reported for the latter approach [53, 54]. In this study, markedly better diagnostic performance (sensitivity, specificity, and accuracy) and favorable predictive values and likelihood ratios were noted by all three off-site blinded reviewers for CE-MRA of the calf arteries compared with TOF MRA. As in the iliofemoral arteries, the technical failure rate determined by the off-site reviewers for CE-MRA of the calf arteries (8.2–14.2%) was comparable to that of digital subtraction angiography (10.2%). Although the technical failure rate and overall accuracy values (74.5–77.5%) for detection of significant stenoocclusive disease of the calf arteries were slightly inferior to those of the iliofemoral arteries, the caliber of the calf vessels is much smaller than that of the iliofemoral arteries and the acquisition of good-quality images is more technically challenging.

Although comparison of the diagnostic performance of gadobenate dimeglumine with that of other gadolinium agents was not performed in this study, the calf arteries are one vascular territory in which the greater relaxivity of gadobenate dimeglumine compared with that of other agents [21–23] is likely to prove beneficial in terms of vessel visualization and diagnostic performance. In this regard, previous studies [27, 28] have shown that the contrast enhancement (SNR and contrast-to-noise ratio) and visualization of below-the-knee segments is significantly better after the administration of 0.1 mmol/kg of gadobenate dimeglumine compared with an equivalent dose of gadopentetate dimeglumine [27], and that gadobenate dimeglumine may have a significant beneficial effect on the ability to assess below-the-knee segments [28].

Specifically, a study by Wyttenbach et al. [28] not only showed better diagnostic performance for gadobenate dimeglumine compared with gadoterate meglumine at an equivalent dose but also noted significantly fewer nonassessable below-the-knee segments after gadobenate dimeglumine. Wyttenbach et al. administered a standard volume of 34 mL of either gadobenate dimeglumine or gadoterate meglumine to all patients. Given that both agents are formulated at concentrations of 0.5 mol/L [22], this volume equates to an administered dose of almost 0.25 mmol/kg of body weight for an average 70-kg person. Although this dose may be appropriate in the case of gadoterate meglumine and other conventional gadolinium agents [12, 45, 55] with standard r1 relaxivity [21, 22], previous studies have shown that doses of gadobenate dimeglumine of 0.2 mmol/kg of body weight have at best minimal and at worst slightly deleterious effects on overall CE-MRA image quality [56, 57]. Studies performed in vitro have supported these clinical observations in showing that the r1 relaxivity of gadobenate dimeglumine is concentration-dependent, with higher relaxivity values, and hence greater signal intensity enhancement, at lower concentrations [58]. Possibly Wyttenbach et al. might have obtained even better results for peripheral CE-MRA with gadobenate dimeglumine had just a single 0.1 mmol/kg dose been used.

A single 0.1 mmol/kg dose of gadobenate dimeglumine has previously been shown to be equivalent to a double dose of a conventional gadolinium agent (gadopentetate dimeglumine) for CE-MRA of the renal arteries [26] and superior to a double dose of this agent for CE-MRA of the carotid arteries [25], with particular benefits noted for the visualization of small or narrow vessels. Given the current widespread concern among the radiology community about the use of double and triple doses of gadolinium contrast agents, particularly in patients with

renal insufficiency who may be at risk of nephrogenic systemic fibrosis [59, 60], our results with just a single 0.1 mmol/kg dose of gadobenate dimeglumine might be of considerable additional interest, especially given the relatively favorable physicochemical properties of this agent compared with other agents [58, 61]. Furthermore, part (4–5%) of the injected dose of gadobenate dimeglumine is eliminated by the hepatobiliary system [62], and a reduced 0.1 mmol/kg dose may result in potential cost savings.

A principal limitation of our study inherent to its multicenter design is the range of MRI systems and sequence parameters used. Moreover, because innovative technology such as parallel imaging [63] and time-resolved MR angiography [38] were in their infancy and not widely available at the time the study was planned and conducted, and because most of the 26 investigational centers did not have access to state-of-the-art MRI systems, the study was performed using conventional MR angiography technology appropriate to the respective imaging capabilities of the individual centers. Both image quality and diagnostic performance might have improved had this more advanced technology been available. Because gadobenate dimeglumine has a higher r1 relaxivity and boosts intravascular signal more than other available extracellular gadolinium agents [24–28], it may prove useful in conjunction with parallel imaging, which penalizes SNR, especially in vascular territories such as the peripheral arteries, for which increased spatial resolution or speed is beneficial. Further investigation of this effect may be of interest in the future.

In conclusion, our study shows that CE-MRA of the lower extremities with gadobenate dimeglumine is significantly more efficacious than TOF MRA, and that CE-MRA is an appropriate alternative to invasive digital subtraction angiography for the diagnostic evaluation of the pelvic and lower leg vasculature in patients with known or suspected peripheral arterial occlusive disease. Moreover, the administration of gadobenate dimeglumine was safe, and no clinically meaningful effects on vital signs, clinical laboratory investigations, or cardiac electrophysiology parameters were observed.

Acknowledgments

The authors would like to thank Ningyan Shen and Usha Halemane (Bracco Diagnostics Inc., Princeton, NJ) for the statistical analysis performed for the study and the following investigators for enrolling patients: Ingolf Arlart, Institut fur Radiologie, Katharinenhospital, Stuttgart, Germany; James Meaney, MRI Department, St. James's Hospital, Dublin, Ireland; Gerardo Cardenas, Hospital y Clinica OCA, Monterrey, N.L., Mexico; Dan Reimer, Sunbelt Research Group, LLC, Mobile, AL; Lorenzo Bonomo, Department of Radiology, Policlinico Agostino Gemelli Roma, Italy; Michael Lee, Department of Radiology, Beaumont Hospital & Royal College of Surgeons, Dublin, Ireland; Matthijs Oudkerk, Department of Radiology, Academisch Ziekenhuis Groningen, Groningen, The Netherlands; Kevin DeMarco, Laurie Imaging Center, UMDNJ, New Brunswick, NJ; Val Runge, Radiology Department, Scott and White Clinic and Hospital, Texas A&M University Health Science Center, Temple, TX; Orjan Smedby, Department of Radiology, Universititetssjukhuset, Linkoeping, Sweden; Pablo Niedmann, Department of Radiology, Hospital Clinico de la Universidad de Chile, Santiago, Chile; Luigi Grazioli, Department of Radiology, University of Brescia, Italy; Jelle Barentsz, Department of Radiology, Universitair Medisch Centrum St. Radboud, Nijmegen, The Netherlands; Robert Lookstein, Department of Radiology, Mount Sinai Hospital, New York, NY; W. Ross Stevens, Department of Radiology MRI, St. John's Hospital, Southern Illinois University School of Medicine, Springfield, IL; and William Romano, Department of Radiology, William Beaumont Hospital, Royal Oak, MI.

References

1. Rofsky NM, Adelman MA. MR angiography in the evaluation of atherosclerotic peripheral vascular disease. *Radiology* 2000; 214:325–338
2. Hessel SJ, Adams DF, Abrams HL. Complications of angiography. *Radiology* 1981; 138:273–281
3. Catalano C, Fraioli F, Laghi A, et al. Infrarenal aortic and lower-extremity arterial disease: diagnostic performance of multi-detector row CT angiography. *Radiology* 2004; 231:555–563
4. Ota H, Takase K, Igarashi K, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: importance of reviewing cross-sectional images. *AJR* 2004; 182:201–209
5. Willmann JK, Baumert B, Schertler T, et al. Aortoiliac and lower extremity arteries assessed with 16-detector row CT angiography: prospective comparison with digital subtraction angiography. *Radiology* 2005; 236:1083–1093
6. Schertler T, Wildermuth S, Alkadhi H, Kruppa M, Marincek B, Boehm T. Sixteen-detector row CT angiography for lower-leg arterial occlusive disease: analysis of section width. *Radiology* 2005; 237:649–656
7. Winterer JT, Laubenberger J, Scheffler K, et al. Contrast-enhanced subtraction MR angiography in occlusive disease of the pelvic and lower limb arteries: results of a prospective intraindividual comparative study with digital subtraction angiography in 76 patients. *J Comput Assist Tomogr* 1999; 23:583–589
8. Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US—a meta-analysis. *Radiology* 2000; 216:67–77
9. Nelemans PJ, Leiner T, de Vet HC, van Engelshoven JM. Peripheral arterial disease: meta-analysis of the diagnostic performance of MR angiography. *Radiology* 2000; 217:105–114
10. Kreitner KF, Kalden P, Neufang A, et al. Diabetes and peripheral arterial occlusive disease: prospective comparison of contrast-enhanced three-dimensional MR angiography with conventional digital subtraction angiography. *AJR* 2000; 174:171–179
11. Wang Y, Winchester PA, Khilnani NM, et al. Contrast-enhanced peripheral MR angiography from the abdominal aorta to the pedal arteries: combined dynamic two-dimensional and bolus-chase three-dimensional acquisitions. *Invest Radiol* 2001; 36:170–177
12. Bezooijen R, van den Bosch HC, Tielbeek AV, et al. Peripheral arterial disease: sensitivity-encoded multiposition MR angiography compared with intraarterial angiography and conventional multiposition MR angiography. *Radiology* 2004; 231:263–271
13. Vavrik J, Rohrmoser GM, Madani B, Ersek M, Tscholakoff D, Bucek RA. Comparison of MR angiography versus digital subtraction angiography as a basis for planning treatment of lower limb occlusive disease. *J Endovasc Ther* 2004; 11:294–301
14. Lapeyre M, Kobeiter H, Desgranges P, Rahmouni A, Becquemin JP, Luciani A. Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. *AJR* 2005; 185:1641–1650
15. Leiner T. Magnetic resonance angiography of abdominal and lower extremity vasculature. *Top Magn Reson Imaging* 2005; 16:21–66
16. Pavlovic C, Futamatsu H, Angiolillo DJ, et al. Quantitative contrast-enhanced magnetic resonance imaging for the evaluation of peripheral arterial disease: a comparative study versus standard digital angiography. *Int J Cardiovasc Imaging* 2007; 23:225–232 [Epub ahead of print 2006 Jul 27]
17. Leiner T, de Vries M, Hoogeveen R, Vasbinder GB, Lemaire E, van Engelshoven JM. Contrast-

enhanced peripheral MR angiography at 3.0 Tesla: initial experience with a whole-body scanner in healthy volunteers. *J Magn Reson Imaging* 2003; 17:609–614

18. Li W, Vu AT, Tutton S, et al. Scoutless stepping-table peripheral contrast-enhanced MR angiography. *J Magn Reson Imaging* 2006; 23:235–241
19. Madhuranthakam AJ, Hu HH, Kruger DG, Glockner JF, Riederer SJ. Contrast-enhanced MR angiography of the peripheral vasculature with a continuously moving table and modified elliptical centric acquisition. *Radiology* 2006; 240:222–229
20. Huegli RW, Aschwanden M, Scheffler K, Bilecen D. Fluoroscopic contrast-enhanced MR angiography with a magnetization-prepared steady-state free precession technique in peripheral arterial occlusive disease. *AJR* 2006; 187:242–247
21. Pintaske J, Martirosian P, Graf H, et al. Relaxivity of gadopentetate dimeglumine (Magnevist), gadobutrol (Gadovist), and gadobenate dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. *Invest Radiol* 2006; 41:213–221. [Erratum in *Invest Radiol* 2006; 41:859]
22. de Haën C, Cabrini M, Akhnana L, Ratti D, Calabi L, Gozzini L. Gadobenate dimeglumine 0.5 M solution for injection (MultiHance) pharmaceutical formulation and physicochemical properties of a new magnetic resonance imaging contrast medium. *J Comput Assist Tomogr* 1999; 23[suppl 1]:S161–S168
23. Cavagna FM, Maggioni F, Castelli PM, et al. Gadolinium chelates with weak binding to serum proteins. *Invest Radiol* 1997; 32:780–796
24. Knopp MV, Schoenberg SO, Rehm C, et al. Assessment of gadobenate dimeglumine for magnetic resonance angiography: phase I studies. *Invest Radiol* 2002; 37:706–715
25. Pediconi F, Fraioli F, Catalano C, et al. Gadobenate dimeglumine (Gd-BOPTA) vs gadopentetate dimeglumine (Gd-DTPA) for contrast-enhanced magnetic resonance angiography (MRA): improvement in intravascular signal intensity and contrast to noise ratio. *Radiol Med (Torino)* 2003; 106:87–93
26. Prokop M, Schneider G, Vanzulli A, et al. Contrast-enhanced MR angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. *Radiology* 2005; 234:399–408
27. Knopp MV, Giesel FL, von Tengg-Kobligk H, et al. Contrast-enhanced MR angiography of the run-off vasculature: intraindividual comparison of gadobenate dimeglumine with gadopentetate dimeglumine. *J Magn Reson Imaging* 2003; 17:694–702
28. Wyttenbach R, Gianella S, Alerci M, Braghetti A, Cozzi L, Gallino A. Prospective blinded evaluation of Gd-DOTA- versus Gd-BOPTA-enhanced peripheral MR angiography, as compared with digital subtraction angiography. *Radiology* 2003; 227:261–269
29. European Medicines Agency. Guideline for Good Clinical Practice. CMPH/ICH/135/95, July 2002. Available at: www.emea.europa.eu/pdfs/human/ich/013595en.pdf. Accessed July 11, 2007
30. World Medical Association. *Declaration of Helsinki: ethical principles for medical research involving human subjects*, revised. Edinburgh, Scotland: World Medical Assocation, 2000
31. Criteria Committee of the American Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels,* 9th ed. New York, NY: Little, Brown, 1994
32. Lipsitz SH, Kim K, Zhao L. Analysis of repeated categorical data using generalized estimating equations. *Stat Med* 1994; 13:1149–1163
33. Fontaine R, Kim M, Kieny R. Die chirurgische Behandlung der peripheren Durch-blutungsstörungen. *Helv Chir Acta* 1954; 21:499–533
34. Guidance for Industry. Developing medical imaging drug and biological products. Part 2, Clinical indications. June 2004. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) Website. Available at: www.fda.gov/cber/gdlns/medimageind.htm. Accessed July 13, 2007
35. The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP): Points to consider on the evaluation of diagnostic agents. London, 16 November 2000, CPMP/EWP/1119/98. Available at: www.eudra.org/emea.html. Accessed February 12, 2007
36. Poon E, Yucel EK, Pagan-Marin H, Kayne H. Iliac artery stenosis measurements: comparison of two-dimensional time-of-flight and three-dimensional dynamic gadolinium-enhanced MR angiography. *AJR* 1997; 169:1139–1144
37. Ho KY, de Haan MW, Kessels AG, Kitslaar PJ, van Engelshoven JM. Peripheral vascular tree stenoses: detection with subtracted and nonsubtracted MR angiography. *Radiology* 1998; 206:673–681
38. Thornton FJ, Du J, Suleiman SA, et al. High-resolution, time-resolved MRA provides superior definition of lower-extremity arterial segments compared to 2D time-of-flight imaging. *J Magn Reson Imaging* 2006; 24:362–370
39. Koelemay MJW, Lijmer JG, Stoker J, Legemate DA, Bossuyt PMM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. *JAMA* 2001; 285:1338–1345
40. Hamm B, Thoeni RF, Gould RG, et al. Focal liver lesions: characterization with nonenhanced and dynamic contrast material-enhanced MR imaging. *Radiology* 1994; 190:417–423
41. Schaefer PJ, Boudghene FP, Brambs HJ, et al. Abdominal and iliac arterial stenoses: comparative double-blinded randomized study of diagnostic accuracy of 3D MR angiography with gadodiamide or gadopentetate dimeglumine. *Radiology* 2006; 238:827–840
42. Rapp JH, Wolff SD, Quinn SF, et al. Aortoiliac occlusive disease in patients with known or suspected peripheral vascular disease: safety and efficacy of gadofosveset-enhanced MR angiography—multicenter comparative phase III study. *Radiology* 2005; 236:71–78
43. Goyen M, Edelman M, Perreault P, et al. MR angiography of aortoiliac occlusive disease: a phase III study of the safety and effectiveness of the blood-pool contrast agent MS-325. *Radiology* 2005; 236:825–833
44. Janka R, Fellner C, Wenkel E, Lang W, Bautz W, Fellner FA. Contrast-enhanced MR angiography of peripheral arteries including pedal vessels at 1.0 T: feasibility study with dedicated peripheral angiography coil. *Radiology* 2005; 235:319–326
45. Swan JS, Carroll TJ, Kennell TW, et al. Time-resolved three-dimensional contrast-enhanced MR angiography of the peripheral vessels. *Radiology* 2002; 225:43–52
46. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33:159–174
47. Dujardin B, Van den Ende J, Van Gompel A, et al. Likelihood ratios: a real improvement for clinical decision making? *Eur J Epidemiol* 1994; 81:1546–1564
48. Jaeschke R, Guyatt JH, Sacket DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test B: what are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994; 271:703–707
49. Cortell ED, Kaufman JA, Geller SC, Cambria RP, Rivitz SM, Waltman AC. MR angiography of tibial runoff vessels: imaging with the head coil compared with conventional arteriography. *AJR* 1996; 167:147–151
50. Yucel KE, Kaufman JA, Geller SC, Waltman AC. Atherosclerotic occlusive disease of the lower extremity: prospective evaluation with two-dimensional time-of-flight MR angiography. *Radiology* 1993; 187:637–641
51. Snidow JJ, Harris VJ, Trerotola SO, et al. Interpretations and treatment decisions based on MR angiography versus conventional arteriography in symptomatic lower extremity ischemia. *J Vasc Interv Radiol* 1995; 6:595–603
52. Sueyoshi E, Sakamoto I, Matsuoka Y, et al. Aortoiliac and lower extremity arteries: comparison of three-dimensional dynamic contrast-enhanced subtraction MR angiography and conventional angiography. *Radiology* 1999; 210:683–688
53. Meaney JF, Ridgway JP, Chakraverty S, et al. Stepping-table gadolinium-enhanced digital subtraction

MR angiography of the aorta and lower extremities arteries: preliminary experience. *Radiology* 1999; 211:59–67

54. Wang Y, Chen CZ, Chabra SG, et al. Bolus-arterial-venous transit in the lower extremity and venous contamination in bolus chase three-dimensional magnetic resonance angiography. *Invest Radiol* 2003; 37:458–463
55. Krause U, Kroencke T, Spielhaupter E, et al. Contrast-enhanced magnetic resonance angiography of the lower extremities: standard-dose vs. high-dose gadodiamide injection. *J Magn Reson Imaging* 2005; 21:449–454
56. Kroencke TJ, Wasser MN, Pattynama PMT, et al. Gadobenate dimeglumine–enhanced magnetic resonance angiography of the abdominal aorta and renal arteries. *AJR* 2002; 179:1573–1582
57. Wikström J, Wasser MN, Pattynama PMT, et al. Gadobenate dimeglumine–enhanced magnetic resonance angiography of the pelvic arteries. *Invest Radiol* 2003; 38:504–515
58. Laurent S, Elst LV, Muller RN. Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. *Contrast Media Mol Imaging* 2006; 1:128–137
59. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR* 2007; 188:586–592
60. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; 243:148–157
61. Kirchin MA, Runge VM. Contrast agents for magnetic resonance imaging: safety update. *Top Magn Reson Imaging* 2003; 14:426–435
62. Spinazzi A, Lorusso V, Pirovano G, Kirchin M. Safety, tolerance, biodistribution and MR imaging enhancement of the liver with gadobenate dimeglumine. *Acad Radiol* 1999; 6:282–291
63. Wilson GJ, Hoogeveen RM, Willinek WA, Muthupillai R, Maki JH. Parallel imaging in MR angiography. *Top Magn Reson Imaging* 2004; 15:169–185