Renal Artery Stenosis Evaluation: Diagnostic Performance of Gadobenate Dimeglumine–enhanced MR Angiography—Comparison with DSA[1]

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Purpose: To prospectively determine diagnostic performance and safety of contrast material–enhanced (CE) magnetic resonance (MR) angiography with 0.1 mmol per kilogram of body weight gadobenate dimeglumine for depiction of significant steno-occlusive disease (≥51% stenosis) of renal arteries, with digital subtraction angiography (DSA) as reference standard.

Materials and Methods: This multicenter study was approved by local institutional review boards; all patients provided written informed consent. Patient enrollment and examination at centers in the United States complied with HIPAA. Two hundred ninety-three patients (154 men, 139 women; mean age, 61.0 years) with severe hypertension (82.2%), progressive renal failure (11.3%), and suspected renal artery stenosis (6.5%) underwent CE MR angiography with three-dimensional spoiled gradient-echo sequences after administration of 0.1 mmol/kg gadobenate dimeglumine at 2 mL/sec. Anteroposterior and oblique DSA was performed in 268 (91.5%) patients. Three independent blinded reviewers evaluated CE MR angiographic images. Sensitivity, specificity, and accuracy of CE MR angiography for detection of significant steno-occlusive disease (≥51% vessel lumen narrowing) were determined at segment (main renal artery) and patient levels. Positive and negative predictive values and positive and negative likelihood ratios were determined. Interobserver agreement was analyzed with generalized κ statistics. A safety evaluation (clinical examination, electrocardiogram, blood and urine analysis, monitoring for adverse events) was performed.

Results: Of 268 patients, 178 who were evaluated with MR angiography and DSA had significant steno-occlusive disease of renal arteries at DSA. Sensitivity, specificity, and accuracy of CE MR angiography for detection of 51% or greater stenosis or occlusion were 60.1%–84.1%, 89.4%–94.7%, and 80.4%–86.9%, respectively, at segment level. Similar values were obtained for predictive values and for patient-level analyses. Few CE MR angiographic examinations (1.9%–2.8%) were technically inadequate. Interobserver agreement for detection of significant steno-occlusive disease was good (79.9% agreement; $\kappa = 0.69$). No safety concerns were noted.

Conclusion: CE MR angiography performed with 0.1 mmol/kg gadobenate dimeglumine, compared with DSA, is safe and provides good sensitivity, specificity, and accuracy for detection of significant renal artery steno-occlusive disease.

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Recognition of individuals with possible renal artery stenosis (RAS) is widely considered an important clinical application of contrast material–enhanced (CE) magnetic resonance (MR) angiography (1–21); the technique has been shown to offer superior accuracy compared with minimally invasive ultrasonographic (US) (22,23), scintigraphic (13,22), and unenhanced MR angiographic (2,8) techniques and accuracy comparable to that of the more invasive and riskier (24,25) conventional x-ray angiography (2–9,11, 12,14–16,23,26–28). Although comparable sensitivity and specificity for the detection of hemodynamically significant stenosis has been demonstrated for multi–detector row computed tomography (CT) (29), disadvantages of this approach are the requirements for ionizing radiation and large volumes of iodinated contrast material (21,30,31).

Previous studies have shown that gadobenate dimeglumine (MultiHance; Bracco Imaging, Milan, Italy) is an effective contrast agent for use in CE MR angiography of the renal arteries (32–34). Although a dose of 0.1 mmol per kilogram of body weight gadobenate dimeglumine is equivalent to a dose of 0.2 mmol/kg gadopentetate dimeglumine in terms of renal artery contrast enhancement and diagnostic image quality (32,34), no data have yet been reported concerning overall diagnostic accuracy of CE MR angiography with 0.1 mmol/kg gadobenate dimeglumine for the detection of hemodynamically significant steno-occlusive disease of the renal arteries. Thus, the purpose of our study was to prospectively determine the diagnostic performance and safety of CE MR angiography with 0.1 mmol/kg gadobenate dimeglumine for depiction of significant steno-occlusive disease (≥51% stenosis) of the renal arteries, with digital subtraction angiography (DSA) as the reference standard.

Advances in Knowledge

- MR angiography enhanced with gadobenate dimeglumine at a single dose of 0.1 mmol per kilogram of body weight provides good sensitivity (60%–84%), specificity (89%–95%), and diagnostic accuracy (80%–87%) for the detection of clinically significant renal artery stenosis (RAS).
- The use of gadobenate dimeglumine at a single dose of 0.1 mmol/kg in patients who are suspected of having renovascular disease is safe on the basis of clinical examination findings, 24-hour monitoring for adverse events, and results of blood tests and urinalysis.

Materials and Methods

This was a phase 3, multicenter, open-label trial conducted at 35 investigational centers in North and South America, as well as Europe. The study was reviewed and approved by the local institutional review board or ethics committee of each of the participating centers in accordance with the Good Clinical Practice guideline (Committee for Proprietary Medical Products, International Conference of Harmonization, direction 135/95, London, July 2002), which is available at *www.emea.europa.eu/pdfs/human/ich/013595en.pdf,* and was performed in adherence to the Declaration of Helsinki (Helsinki, Finland, 1964) and subsequent amendments. Centers in the United States of America were fully compliant with the Health Insurance Portability and Accountability Act. All evaluated patients provided written informed consent before enrollment in the study. Each investigator was supported by an operating grant from Bracco Diagnostics (Princeton, NJ) and was supplied with the investigational contrast agent solely for the purpose of the study. One author (D.A.B.) is a consultant to Bracco Diagnostics; another (J.H.M.) is on the speaker bureau and has received research funding from Bracco Diagnostics. The authors who are employees of Bracco Imaging (M.A.K.) and Bracco Diagnostics (G.P.) had no control over patient enrollment or data acquisition. All authors who were not Bracco employees had full control of all data and information included in the present article.

Implication for Patient Care

- MR angiography with gadobenate dimeglumine at a single dose of 0.1 mmol/kg can be used for the depiction of RAS in patients who are clinically suspected of having renovascular hypertension.

Study Group

All patients were enrolled between April 2002 and January 2005. For inclusion, patients had to be at least 18 years old with a diagnostic determination positive for RAS that was based on Doppler US, CT angiographic, or renal scintigraphic findings or a moderate (5%–15%) clinical index of suspicion for any renovascular form of hypertension (35). The clinical index of suspicion included at least one of the following criteria: severe hypertension (diastolic blood pressure, ≥100 mm Hg), hypertension unresponsive to standard therapy (hypertension resistant to treatment with at least three medications of different classes, including diuretics), abrupt onset of sustained moderate to severe hypertension at younger than 35 years of age, and progressive renal insufficiency (serum creatinine level, >2 mg/dL [>176 μmol/L]).

Patients were ineligible for inclusion if they had received a kidney transplant or had surgically implanted apparatuses, such as metallic vascular stents or

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Abbreviations:
CE = contrast enhanced
CI = confidence interval
DSA = digital subtraction angiography
MIP = maximum intensity projection
NLR = negative likelihood ratio
NPV = negative predictive value
PLR = positive likelihood ratio
PPV = positive predictive value
RAS = renal artery stenosis

Author contributions:
The complete list of author contributions is at the end of this article.

See Materials and Methods for pertinent disclosures.

pacemakers. Patients with a known history of hypersensitivity to metals or to gadolinium-based and/or iodinated contrast media also were ineligible. Patients who received any other investigational contrast agent within 60 days prior to the study or any other contrast agent within 24 hours prior to or after gadobenate dimeglumine administration also were ineligible. Pregnant or lactating women or patients with class III or IV congestive heart failure according to the New York Heart Association classification also were ineligible for inclusion (36). Patients were eligible for inclusion regardless of their serum creatinine level. Similarly, patients who were receiving ongoing dialysis were not considered ineligible for inclusion.

All patients were required to provide written informed consent before enrollment in the study and to undergo a DSA examination before or within 1 month after gadobenate dimeglumine administration. No patient was permitted any other surgical procedure within 24 hours after gadobenate dimeglumine administration.

A total of 304 patients met the inclusion criteria and were enrolled in the study. Of these 304 patients, 293 (154 men, 139 women; mean age, 61.0 years ± 14.5 [standard deviation]; range, 18–93 years) received gadobenate dimeglumine at a dose of 0.1 mmol/kg and were evaluated for safety (Fig 1). The remaining 11 discontinued participation prior to contrast agent administration for the following reasons: claustrophobia ($n = 3$), study cancellation by the interventionalist on the day of the study ($n = 1$), panic ($n = 1$), severe coughing ($n = 1$), withdrawal of consent before the trial ($n = 1$), technical problems with MR imager ($n = 1$), difficulty in placement of the intravenous catheter ($n = 1$), failure to meet inclusion criteria after signing the patient consent form ($n = 1$), and absence of medical history in regard to prior cardiac intervention ($n = 1$).

Of 293 enrolled patients, approximately one-half ($n = 136$, 46.4%) were 65 years or older, whereas 125 (42.7%) were 41–64 years old and 32 (10.9%) were 18–40 years old. The 293 evaluated patients included 241 (82.2%) with a moderate clinical index of suspicion for renovascular hypertension and 33 (11.3%) who had progressive renal insufficiency. The remaining 19 (6.5%) patients had no current symptoms but were suspected of having RAS on the basis of findings from previous imaging studies. Of the 293 patients in whom safety was evaluated, 25 patients were excluded from evaluation of diagnostic performance because no DSA examination was performed. Thus, in 293 patients, safety was evaluated, and in 268 patients who underwent DSA, diagnostic performance was evaluated.

MR Angiography

All patients underwent MR angiography with 1.5-T commercially available MR imagers equipped with a gradient strength of 20 mT/m or greater. Several MR imagers were used for the study: Four were from one manufacturer (Symphony [$n = 70$, 23.9%], Sonata [$n = 48$, 16.4%], Vision [$n = 35$, 11.9%], Avanto [$n = 4$, 1.4%]; Siemens Medical Systems, Erlangen, Germany). Two were from another manufacturer (Intera [$n = 63$, 21.5%] and Marconi Infinion [$n = 11$, 3.8%]; Philips Medical Systems, Best, the Netherlands). Two others were from a third manufacturer (Genesis Signa [$n = 49$, 16.7%] and Excite [$n = 13$, 4.4%]; GE Medical Systems, Milwaukee, Wis).

MR angiography was performed by using a three-dimensional spoiled gradient-echo sequence before and immediately after administration of gadobenate dimeglumine. The large number of investigating centers involved in the study and the wide variety of imaging systems in use resulted in necessarily different sequence parameters between centers. Nevertheless, each sequence at each center was selected to meet minimal requirements for image acquisition and interpretability. The sequence parameters for the image acquisition (before interpolation, if any) varied as follows: For coronal orientation, parameters included repetition time msec/echo time msec, 2.84–6.5/0.97–2.5; flip angle, 20°–45°; number of signals acquired, 0.5–1; section thickness, 1–2 mm; matrix, 256–512 × 192–320; pixel size, 1.41–0.55 × 1.41–1.10 mm; and overall acquisition time, 25 seconds or less. The vascular field of view was tailored for each patient to include the kidneys, the abdominal aorta, the renal arteries, and an area from 2 cm above the origin of the celiac trunk to the common iliac artery bifurcations, including the bifurcation of the celiac axis and the first 2 cm of the superior mesenteric artery. The overall image acquisition time ranged between 12 and 25 seconds, depending on the MR imager, sequence parameters, and field of view used.

The CE MR angiographic sequence was performed after administration of

Figure 1

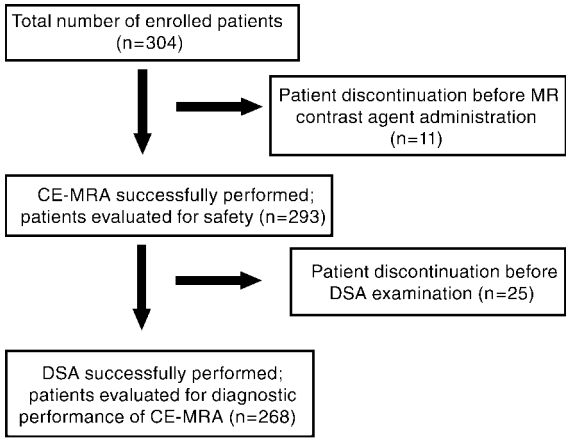


Figure 1: Flow diagram depicts patient enrollment, patient discontinuation, and diagnostic examinations performed. *MRA* = MR angiography.

gadobenate dimeglumine at a dose of 0.1 mmol/kg. Contrast agent administration was performed by means of a power injector at a rate of 2 mL/sec, followed by a 20-mL saline flush at the same rate. Timing for the CE MR angiographic sequence was achieved by means of a bolus-timing acquisition in 162 patients or through use of an automatic or MR fluoroscopic bolus detection technique (SmartPrep, GE Medical Systems; BolusTrak, Philips Medical Systems; CareBolus, Siemens Medical Systems) in 131 patients. The test bolus timing approach involved acquisition of 45–60 dynamic single-section T1-weighted fast gradient-echo images of the abdominal aorta at a frequency of one image per second after administration of a preliminary 2-mL bolus of gadobenate dimeglumine.

DSA: Reference Standard

DSA was performed by experienced (range, 6–22 years) investigators with injection of 20–40 mL of iodinated contrast medium at a rate of 10–20 mL/sec through a pigtail or straight 4–5-F aortic-flush catheter inserted via a femoral artery puncture by using the Seldinger technique. An anteroposterior projection, as well as right anterior oblique and left anterior oblique projections at angles of 15°–30°, of the renal arteries was obtained as appropriate according to each center's standard operating procedure. Selective cannulation and opacification of the renal arteries was performed if deemed necessary on the basis of the judgment of the local investigator. DSA examinations were performed with a matrix of 1024 × 1024 at a frame rate of at least 2 frames per second. Most (191 [71.5%] of 268) of the DSA examinations were performed within 30 days after the MR angiographic examination, whereas the remaining (77 [28.7%] of 268) examinations were performed within 60 days before MR angiography. Most (260 [97%] of 268) DSA examinations were performed by using iodinated contrast media with iodine concentrations of more than 200 mg of iodine per milliliter (200–300 mg of iodine per milliliter in 38% of the patients; >300 mg of iodine per milliliter in 62% of the patients).

Image Evaluation

Images were evaluated by on-site investigators at each of the 35 investigational centers (each investigator had 10–15 years of experience with MR angiography) and by four off-site independent experienced board-certified radiologists (R.C., M.N.W., and T.R.M. [with approximately 20, 15, and 15 years of experience in vascular imaging, respectively] for MR angiographic images and C.B. [with approximately 12 years of experience] for DSA images) who were not affiliated with any of the study sites and were fully blinded to all patient information and to the results of other diagnostic procedures. Each of the three off-site blinded readers of CE MR angiographic images evaluated all MR angiographic image sets from each of the 268 evaluable patients.

Off-site evaluation of digital MR angiographic and DSA images was performed at an independent core imaging laboratory equipped with two separate software-based (Windows; Microsoft, Redmond, Wash) workstations (Aquarius Net Viewer; TeraRecon, San Mateo, Calif) for evaluation of images (two monitors) and for recording of assessment findings by using an electronic case report form system. All CE MR angiographic images were combined into a single randomization pool, and each image set for each patient was reviewed separately, one at a time, and in a randomized order. For each reader, both source images and volumetric maximum intensity projection (MIP) reconstructions were displayed on the two monitors set up for image evaluation. All routine image review tools (window width and window level, zoom, pan, etc) were available to the readers.

The three off-site readers of MR angiographic images performed their evaluations independently in a fully blinded fashion. For evaluation, the renal arterial anatomy was divided into standard segments comprising the left and right main renal arteries (from the ostium to the subdivision in the dorsal and ventral segmental branches) and the left and right segmental branches of the renal arteries (second- and third-order segmental branches). Accessory arteries were assessed whenever present.

Initial off-site evaluation was performed to determine the technical adequacy (quality of visualization) of the CE MR angiographic 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 diagnostic performance was then performed for all technically adequate main renal artery segments by using a three-point scale in which a score of 1 indicated stenosis of 50% or less (blood vessel with no clinically significant disease); a score of 2, stenosis of 51%–99% (blood vessel with clinically significant disease); and a score of 3, occlusion (blood vessel with 100% blockage of the vessel lumen). All assessments were made visually on the basis of the experience of the blinded readers and as routinely performed in clinical practice. Electronic calipers were available, if necessary, for quantification of borderline stenoses (ie, stenoses of approximately 50% vessel lumen narrowing) but were not systematically used. In all cases, determination of the degree of stenosis was made by comparing the part of the blood vessel in question with areas of normal renal artery that were well away from areas below the stenotic dilatation.

Additional assessments were performed to determine possible involvement of the ostium (possible answers included yes, no, and ostium not visualized) for whichever main renal arteries were determined to harbor significant stenosis or occlusion, to determine the presence of accessory renal arteries originating either above or below the origin of the main renal arteries, and to ascertain whether detected disease was nodular in appearance (ie, fibromuscular dysplasia).

Off-site evaluation of DSA images was performed by using similar assessment methods and criteria. For this

evaluation, DSA images were combined in a second pool, different from the MR angiographic pool.

On-site evaluation of MR angiographic images was performed by using criteria similar to those of the off-site evaluation. Evaluation was performed by an experienced radiologist at each investigational site who was blinded to the results of the DSA examination. CE MR angiographic image sets were evaluated separately in terms of quality of visualization of arterial segments (technical adequacy), the presence and number of accessory renal arteries and the quality of their visualization, and the presence and grading of stenosis. With the same assessment criteria, on-site evaluation of DSA images was performed by a second experienced investigator who was fully blinded to the results of the on-site MR angiographic evaluations.

Safety Evaluations

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

In addition, blood and urine samples were collected within 24 hours prior to gadobenate dimeglumine administration and at 24 hours after administration. Laboratory evaluation of collected samples consisted of hematologic tests (hematocrit level, hemoglobin level, as well as red blood cell, white blood cell, and platelet counts), blood chemistry analysis (serum glucose, serum creatinine, total serum bilirubin, total serum protein, serum albumin, serum aspartate aminotransferase, serum alanine aminotransferase, serum alkaline phosphatase, serum γ-glutamyl transpeptidase, plasma sodium, plasma potassium, and plasma chloride levels), and urinalysis (amount of protein and glucose, presence of ketones and blood, and pH test).

Finally, the safety of gadobenate dimeglumine was assessed by on-site investigators in terms of the incidence of clinical adverse events from the time of signed informed consent until 24 hours after gadobenate dimeglumine administration. Adverse events were classified as either serious (ie, death, life threatening, requiring or prolonging hospitalization) or not serious (rated as mild [not resulting in disability or incapacity and resolved without treatment], moderate [not resulting in disability or incapacity but required treatment], or severe [resulting in temporary and/or mild disability or incapacity and required treatment]). The relationship of each adverse event to the study contrast agent was classified as probably related, possibly related, not related, or unknown. All decisions in regard to the severity of adverse events and their possible relationship to the study contrast agent were made by the investigating radiologist at each center.

Statistical Analysis

The primary objective was to determine the diagnostic performance of CE MR angiography with 0.1 mmol/kg gadobenate dimeglumine for detection of significant steno-occlusive disease (defined as stenosis of ≥51% or occlusion) of the main renal arteries, with DSA as the reference standard. Separate determinations were made of the sensitivity, specificity, and accuracy of CE MR angiography, including 95% confidence intervals (CIs) derived from generalized estimating equation analysis, as well as of the positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) for the detection of significant disease. Data from each of the three off-site readers of MR angiographic images and from the on-site investigators were analyzed and presented separately.

Sensitivity for detection of significant steno-occlusive disease at the segment level was defined as the number of correctly identified significantly diseased (≥51% stenosis) main renal artery segments evaluated on CE MR angiographic images divided by the total number of significantly diseased (≥51% stenosis) segments evaluated on DSA images. Specificity was defined as the number of correctly identified main renal artery segments that were not diseased or not significantly diseased (≤50% stenosis) evaluated on CE MR angiographic images divided by the total number of segments that were not diseased or not significantly diseased (≤50% stenosis) evaluated on DSA images. Accuracy was defined as the number of correctly identified main renal artery segments (either diseased or nondiseased) evaluated on CE MR angiographic images divided by the total number of segments evaluated on DSA images. All uninterpretable CE MR angiographic images were considered inaccurate for all determinations of diagnostic performance. If a segment was not adequately visualized or the image was technically inadequate, this segment was considered false-positive for steno-occlusive disease if the corresponding DSA image revealed a stenosis of 50% or less; however, this segment was considered false-negative for steno-occlusive disease if the corresponding DSA image revealed a stenosis of 51% or more or occlusion.

Determination of the diagnostic performance of CE MR angiography, including 95% CIs, also was performed at the patient level. For this evaluation, a patient with true-positive findings was one in whom at least one of the main renal arteries was true-positive for steno-occlusive disease at CE MR angiography, a patient with false-positive findings was one in whom one of the main renal arteries was false-positive for steno-occlusive disease at CE MR angiography, a patient with false-negative findings was one in whom one of the main renal arteries was false-negative for steno-occlusive disease at CE MR angiography, and a patient with true-negative findings was one in whom both main renal arteries were true-negative for steno-occlusive disease at CE MR angiography.

Interreader agreement at the segment level was assessed as the percent-

age of concordance among the three readers of MR angiographic images by means of the generalized κ coefficient. Interreader agreement was classified as very good for κ values great than 0.80, good for κ values of 0.61–0.80, moderate for κ values of 0.41–0.60, fair for κ values of 0.21–0.40, or poor for κ values of 0.20 or less.

The technical failure rate of the CE MR angiographic sequence was defined as the total number of technically inadequate segments divided by the total number of segments included in the field of view. A comparison with the technical failure rate of DSA was performed by using the Fisher exact test.

Statistical analysis of data was performed by using a statistical software package (SAS, version 8.2; SAS Institute, Cary, NC).

Results

Technical Adequacy and Quality of Segment Visualization

The technical adequacy rate of CE MR angiography for evaluation of the renal arteries in all 293 patients who received gadobenate dimeglumine ranged between 1.9% and 2.8% for the off-site blinded readers, whereas a slightly higher value of 4.5% was obtained for the on-site investigators (Table E1[*radiology.rsnajnls.org/cgi/content/full/2471070711/DC1*]). Overall, the technical failure rate of CE MR angiography for the renal arteries was low in absolute terms and was comparable to the technical failure rate of DSA (0.8%; four segments considered technically inadequate by the reader of DSA images).

Diagnostic Performance

A total of 268 patients underwent both MR angiography and DSA examinations and were included in evaluations of diagnostic performance. With DSA, 178 (66.4%) of 268 patients were determined to have significant steno-occlusive disease (≥51% stenosis) of one or more renal artery segments (including main and accessory renal arteries). These 178 patients comprised 113 (42.2%) with clinically significant disease in one segment and 65 (24.2%) with significant disease in more than one segment.

DSA images of eight of the 536 main renal artery segments theoretically available for evaluation (two per patient) were either technically inadequate or unavailable. Therefore, determination of the diagnostic performance of CE MR angiography was performed for a total of 528 main renal artery segments. A total of 200 (37.9%) of 528 main renal artery segments evaluated at DSA were determined to have either significant stenosis of 51% or greater (n = 187) or occlusion (n = 13). On CE MR angiographic images, off-site readers 1, 2, and 3 reported significant disease (≥51% stenosis or occlusion) for 26.2% (135 of 516), 30.8% (160 of 519), and 33.5% (174 of 519) of the main renal artery segments evaluated at DSA, respectively. Similar findings were reported by the on-site investigators (35.9% [188 of 523] of evaluated main renal arteries). Renal artery occlusion was noted for 1.6% (eight of 516), 2.5% (13 of 519), 1.9% (10 of 519), and 1.1% (six of 523) main renal artery segments by off-site readers 1, 2, and 3 and the on-site investigators, respectively.

With regard to the diagnostic performance of CE MR angiography for the detection of significant steno-occlusive disease of the main renal arteries (Table 1) for the segment-based analysis, sensitivity values of 60.1%, 74.5%, and 73.9% were determined by off-site readers 1, 2, and 3, respectively, whereas a slightly higher value of 84.1% was determined by the on-site investigators. Conversely, specificity values of 93.1%, 94.7%, and 89.4% were obtained by off-site readers 1, 2, and 3, respectively, whereas a slightly lower value of 87.7% was obtained by the on-site investigators. The values for diagnostic accuracy were similar for both off-site readers (80.4%–86.9%) and on-site investigators (86.4%). Comparable values for PPV, NPV, PLR, and NLR were obtained for both off-site readers and on-site investigators (Table 2).

The agreement among the three off-site readers for detection of clinically significant steno-occlusive disease was

Table 1

Sensitivity, Specificity, and Accuracy and 95% CIs of CE MR Angiography for Segment-Level Detection of Significant Steno-occlusive Disease of the Main Renal Arteries Relative to DSA

	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Investigators	
Parameter	Value (%)	95% CI	Value (%)	95% CI	Value (%)	95% CI	Value (%)	95% CI
Sensitivity*	60.1 (119/198)	52.8, 66.7	74.5 (149/200)	68.1, 80.1	73.9 (147/199)	67.6, 79.5	84.1 (153/182)	77.6, 88.8
Specificity†	93.1 (296/318)	89.1, 95.4	94.7 (302/319)	90.8, 96.5	89.4 (286/320)	85.0, 92.2	87.7 (299/341)	83.1, 90.7
Accuracy‡	80.4 (415/516)	76.6, 83.7	86.9 (451/519)	83.5, 89.6	83.4 (433/519)	79.8, 86.5	86.4 (452/523)	82.6, 89.1

Note.—Numbers in parentheses were used to calculate the percentages. Segments considered outside the field of view on CE MR angiographic images were excluded from assessment. The 95% CIs were derived from a generalized estimating equation, with patient cluster effect taken into account.

* Sensitivity is the number of correctly identified diseased (≥51% stenosis) main renal artery segments on CE MR angiographic images divided by the total number of significantly diseased segments on DSA images.

† Specificity is the number of correctly identified nondiseased or not significantly diseased (≤50% stenosis) main renal artery segments on CE MR angiographic images divided by the total number of nondiseased or not significantly diseased segments on DSA images.

‡ Accuracy is the number of correctly identified main renal artery segments (either diseased or nondiseased) on CE MR angiographic images divided by the total number of segments evaluated on DSA images.

good (79.9% agreement; κ = 0.69). Agreement of the CE MR angiographic findings with the DSA results was noted for 75%–77% of all cases (all readers) in which the location of a significant stenosis on DSA images was judged as ostial (Fig 2). Good correlation between CE MR angiography and DSA was also noted for cases of nonsignificant stenosis of 50% or less (Fig 3). Although only seven enrolled patients were diagnosed with fibromuscular dysplasia, a nodular appearance typical of this disease was well observed on CE MR angiographic images (Fig 4).

In regard to the diagnostic performance of CE MR angiography at the patient level (Table 3), overall values for sensitivity, specificity, accuracy, PPV, and NPV were similar to those determined in the segment-based analysis.

Detection and Evaluation of Accessory Renal Arteries

The blinded reader of DSA images reported a total of 113 accessory renal arteries. Blinded readers 1, 2, and 3 of CE MR angiographic images detected 66.4%, 67.3%, and 76.1%, respectively, of these accessory renal arteries (Table E2 [*radiology.rsnajnls.org/cgi/content/full/2471070711/DC1*]) (Fig 5). In 10 cases (three each for readers 1 and 2 and four for reader 3), accessory renal arteries were detected on CE MR angiographic images but not on DSA images.

Safety

A total of 39 nonserious adverse events reported by 27 (9.2%) of 293 patients were considered probably related or possibly related to the administration of gadobenate dimeglumine or the relationship was unknown. These events were mild in intensity in 26 (8.9%) patients and moderate in intensity in one (0.3%) patient. There was no trend in regard to the distribution of adverse events among the evaluated patients, and no consistent trends in vital signs, electrocardiogram, or laboratory parameters were observed. Overall, eight events in eight of these 27 patients (29.6%; 2.7% [eight of 293] overall) were considered local in nature (heat sensation or injection site pain, bruising, or swelling). A total of five gastrointestinal disorders (diarrhea [n = 1], nausea [n = 3], tongue edema [n = 1]) were reported as study contrast agent–related adverse events by four patients, whereas 11 minor and clinically unimportant alterations of laboratory parameters in eight patients were also reported as adverse events. The remaining nonserious adverse events were abnormal taste sensation (n = 4), fatigue (n = 3), headache (n = 3), hypotension (n = 2), chest pain (n = 1), burning sensation (n = 1), and hematoma (n = 1). No serious adverse events potentially related to the administration of gadobenate dimeglumine were reported. No additional potentially study contrast agent–related adverse events were reported following the specified 24-hour monitoring period.

Table 2

PPV, NPV, and Likelihood Ratios for CE MR Angiography Relative to DSA

Statistic	Off-site Reader 1	Off-site Reader 2	Off-site Reader 3	On-site Investigators
PPV (%)*	84.4 (119/141)	89.8 (149/166)	81.2 (147/181)	78.5 (153/195)
NPV (%)†	78.9 (296/375)	85.6 (302/353)	84.6 (286/338)	91.2 (299/328)
PLR‡	8.7	14.0	7.0	6.8
NLR§	0.4	0.3	0.3	0.2

* PPV is the number of correctly identified diseased (≥51% stenosis) segments divided by the total number of segments considered positive for steno-occlusive disease. Numbers in parentheses were used to calculate the percentages.

† NPV is the number of correctly identified nondiseased (≤50% stenosis) segments divided by the total number of segments considered negative for steno-occlusive disease. Numbers in parentheses were used to calculate the percentages.

‡ PLR is sensitivity divided by the remainder of specificity subtracted from one.

§ NLR is the remainder of sensitivity subtracted from one divided by specificity.

Discussion

Our study results confirm previous findings (32–34) in demonstrating that CE MR angiography with gadobenate dimeglumine is safe for diagnostic evaluation of the renal vasculature in patients with suspected renovascular disease. Moreover, our study results also confirm that CE MR angiography with gadobenate dimeglumine at a single dose of 0.1 mmol/kg provides good sensitivity and high specificity and diagnostic accuracy for the detection of clinically significant steno-occlusive disease (≥51% stenosis) of the renal arteries.

Researchers in previous studies with other gadolinium-based contrast agents have generally used doses of between 0.1 and 0.3 mmol/kg, with investigators in several studies advocating doses of 0.2 mmol/kg and higher (1,2,10,13–15, 20,21,26,29,31). The possibility to use a lower dose of gadobenate dimeglumine to achieve signal intensity enhancement similar to that achieved with a double dose of a conventional gadolinium-based contrast agent (32,34) is ascribable to its increased r1 relaxivity and the subsequent shorter blood T1 for any given dose. This effect derives from weak and transient interactions of the gadolinium benzyloxypropionictetraacetate complex of gadobenate dimeglumine with serum albumin (37–39), interactions that reduce the tumbling rate of the gadolinium benzyloxypropionictetraacetate complex in blood that results in increased r1 and r2 relaxivities of this contrast agent relative to those of other available contrast agents that do not interact with serum proteins (40).

Findings in studies in vitro (41), which have been supported by observations in the clinical setting (33,42), suggest that the r1 relaxivity of gadobenate dimeglumine is concentration dependent with higher relaxivity values and, hence, greater signal intensity enhancement at lower concentrations. Given the current widespread concern among the radiology community concerning the use of double and triple doses of gadolinium-based contrast agents, particularly in patients with renal insufficiency in regard to the risk of nephrogenic systemic fibrosis (43,44),

our results with just a single 0.1 mmol/kg dose of gadobenate dimeglumine are of interest.

Although the specificity of CE MR angiography was approximately 90% for all readers in the segment-based analysis, the sensitivity values were approximately 74% for two of the off-site blinded readers and slightly lower (60.1%) for off-site blinded reader 1. Conversely, the sensitivity determined by the on-site investigators was 84.1% in an image reading situation far more akin to that of the routine clinical environment than that with which the off-site blinded reading was conducted. To date, researchers in only one prospective multicenter study conducted in patients who were suspected of having RAS have combined independent blinded reading with a sample size larger than ours (45). In that study, Vasbinder et al (45) compared CE MR angiography with DSA in patients who were suspected of having RAS and found sensitivity and specificity values of just 62% and 84%, respectively. Although the precise dose of contrast agent was not reported in their study, the contrast agent volume administered to most of the patients was 30 mL, which corresponds to doses between 0.15 and 0.22 mmol/kg for patients who weigh 70–100 kg.

Figure 2

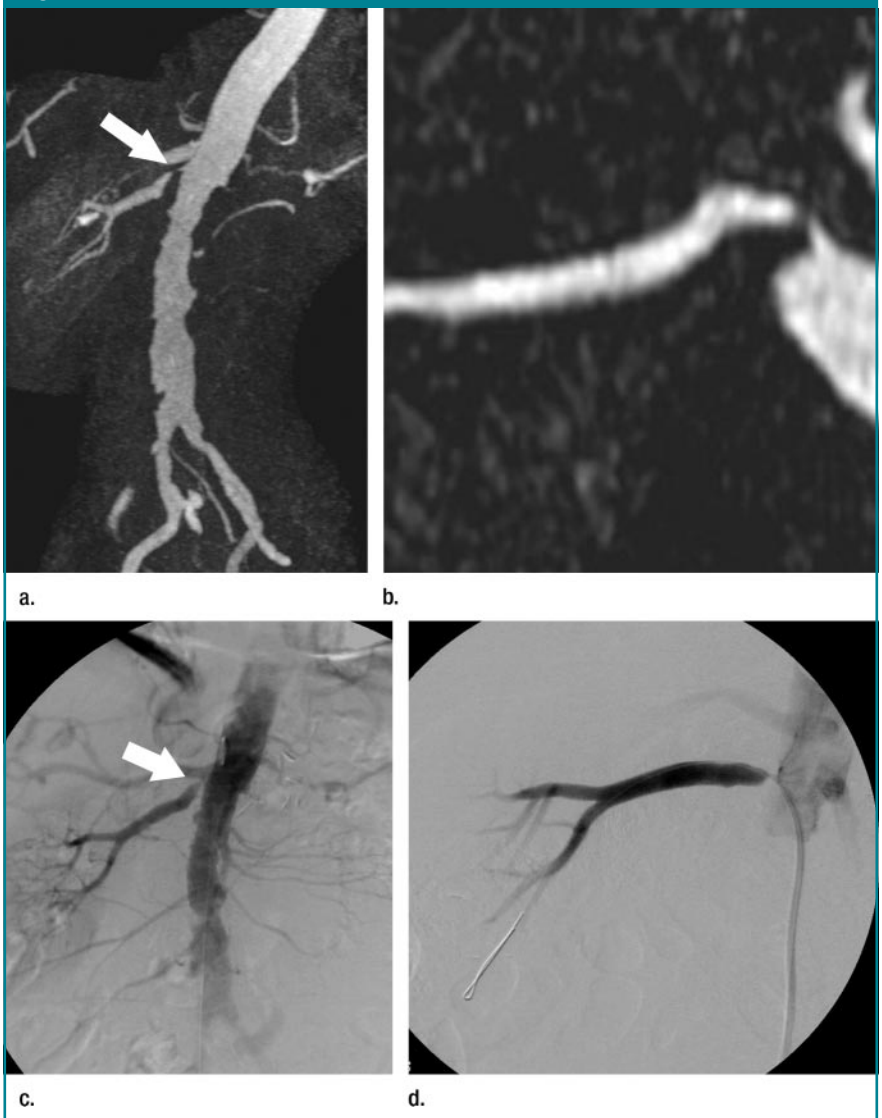


Figure 2: Images in 75-year-old man with history of left nephrectomy and high blood pressure with progressive renal failure. **(a)** Subvolume MIP coronal projection of CE MR angiographic acquisition (4.6/1.8) reveals severe ostial stenosis (arrow) of right renal artery. **(b)** Curved transverse multiplanar reconstruction confirms severity of stenosis in ostial portion of renal artery. **(c)** Aortographic image shows ostial stenosis (arrow) estimated at more than 90%. **(d)** Selective angiographic image of right renal artery acquired before balloon angioplasty confirms stenosis of more than 90%.

The overall accuracy for the detection of significant renal artery stenosis exceeded 80% for all readers in the segment-based analysis. This compares extremely favorably with values reported for gadodiamide (Omniscan; GE Healthcare, Oslo, Norway) and gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Berlin, Germany) in a study to evaluate 0.1 mmol/kg doses of these agents for detection of significant abdominal and iliac stenosis (46). Our values for sensitivity, specificity, and accuracy also compare favorably with corresponding values determined in phase 3 clinical trials to evaluate another gadolinium-based contrast agent (gadofosveset, Vasovist; Bayer Schering Pharma) for CE MR angiography of renal (47) and aortoiliac occlusive disease (48,49). Although the vascular territory under consideration was different for the studies with gadofosveset, the three readers in each case would have been subjected to similarly rigorous blinding and assessment conditions to those experienced in our study.

Overall, our results for diagnostic performance are slightly lower than the findings in a previous meta-analysis (50) in which sensitivity was reported to vary between 88% and 100% and specificity between 71% and 100%. Reasons for these lower results include methodological differences and the fact that all blinded readers in our study were not affiliated with the enrollment centers and were unaware of the patient eligibility criteria, as well as all clinical and radiologic information. Although blinded and independent reading eliminates much of the potential for bias, it imposes a condition that does not exist in clinical routine. This im-

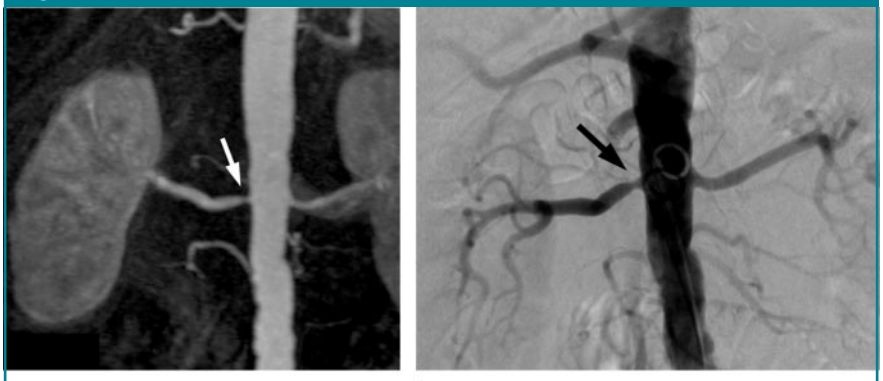
posed condition may hamper assessment of the clinical significance of a borderline stenosis, thereby leading to lower overall agreement with DSA findings. Nevertheless, the good reproducibility of the blinded reading results in this study, together with the acceptable magnitude of the results despite limitations imposed by the blinded reading method, indicates the high validity and reliability of this approach.

A further point that may contribute to the diagnostic performance results obtained is that determinations of diagnostic accuracy reported in the relevant literature typically do not include data from technically inadequate images (51). This omission potentially increases the sensitivity and specificity of CE MR angiography in those studies. In our study, all uninterpretable images of blood vessels were considered inaccurate and were included in the calculations for sensitivity, specificity, and overall accuracy. Although the elimination of evaluation bias in our study certainly affected the overall diagnostic performance values, the results should nevertheless be considered a more realistic reflection of clinical practice and should be borne in mind when considering apparent interstudy differences in diagnostic performance results.

When one assesses the diagnostic performance values obtained in this study, one must also consider that, whereas most studies reported in the literature have been performed in relatively small numbers of patients—thereby precluding the drawing of robust conclusions concerning study findings—our data derive from 35 different centers with widely varying equipment and, consequently, slightly different imaging protocols. Finally, it should also be borne in mind that DSA, as any reference standard, although very accurate, is not perfect; and discrepancies between MR angiographic and DSA findings can be caused by errors in interpretation of findings with either modality. Limitations of conventional DSA as a reference standard technique have recently been highlighted by Anzalone et al (52) for CE MR angiography of the carotid arteries. Notwithstanding the artificial environment with which offsite image evaluation was performed, the diagnostic performance determined by the three blinded readers can be considered very satisfactory for assessments performed at both the segment and the patient level.

Of particular interest in our study is the strong interreader agreement demonstrated for the diagnosis of clinically significant RAS. Specifically, all three blinded readers of MR angiographic images agreed in almost 80% of segment evaluations, yielding a κ value of 0.69.

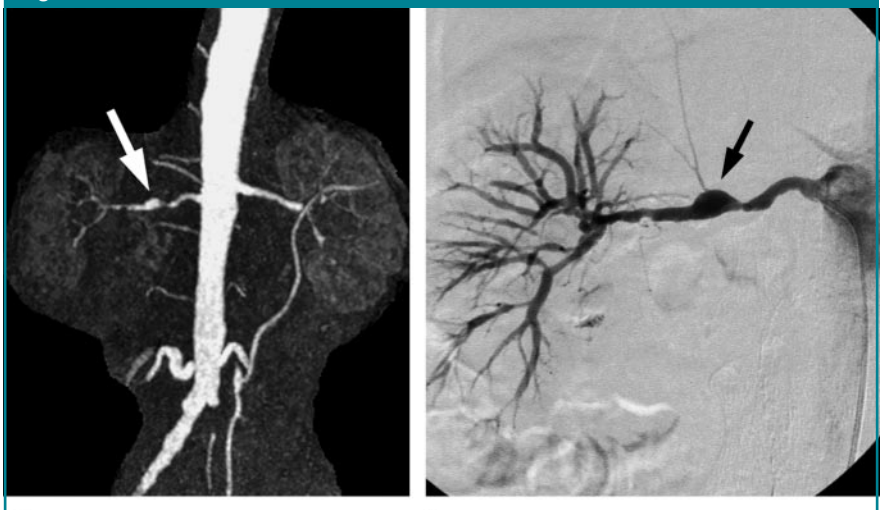
Figure 3



a. b.

Figure 3: Images in 65-year-old woman with coronary artery disease, diabetes, and hypertension. **(a)** MIP coronal projection of CE MR angiographic acquisition (3.29/1.17) reveals moderate nonsignificant stenosis (arrow) of right renal artery. **(b)** Angiographic image of abdominal aorta and selective opacification of right renal artery confirms moderate stenosis (arrow) of right renal artery and demonstrates good correlation with CE MR angiographic findings.

Figure 4



a. b.

Figure 4: Images in 56-year-old man with severe hypertension, cardiac transplantation, and renal insufficiency. **(a)** MIP coronal projection of CE MR angiographic acquisition (5.12/1.5) reveals dilatation (arrow) and stenosis of right renal artery indicative of fibromuscular dysplasia. **(b)** Corresponding DSA image similarly shows renal artery dilatation (arrow) and demonstrates good correlation with CE MR angiographic study. Atheromatous infiltration of right renal artery and intrarenal branches suggests a lesion combining fibromuscular dysplasia and atherosclerosis.

On the basis of the guidelines presented by Landis and Koch (53) to describe the clinical value of degree of concordance, this value indicates that gadobenate dimeglumine–enhanced MR angiography is a diagnostic test with "substantial" reproducibility. Notably, the agreement obtained in our study is considerably better than the moderate three-reader agreement ($\kappa = 0.40–0.51$) obtained by Vasbinder et al (45) and better also than the mean two-reader agreement ($\kappa = 0.49$) obtained by Völk et al (27) in a study to assess the value of time-resolved MR angiography for the detection of RAS.

Confirmation of the value of CE MR angiography for diagnostic evaluation of the renal arteries comes from the predictive values determined for the three blinded readers. The PPV determinations in this study indicate that a vascular segment with positive findings at CE MR angiography with gadobenate dimeglumine is up to 90% likely to have significant steno-occlusive disease. These results are highly encouraging, especially considering the artificial environment in which they were obtained. The NPV results (78.9%–85.6%) indicated that the risk of overlooking steno-occlusive disease at CE MR angiography with gadobenate dimeglumine is low. Therefore, normal findings at CE MR angiography with gadobenate dimeglumine should obviate further potentially hazardous conventional angiographic or surgical procedures and, thus, eliminate possible risks (contrast agent nephrotoxicity, exposure to ionizing radiation, and catheter-induced atheroembolism) associated with these procedures.

In contrast to the predictive values and values for sensitivity and specificity, the values for PLR and NLR are not affected by the prevalence of disease (54). Thus, determination of these values offers an approach to assessing diagnostic performance that is unaffected by the condition being evaluated in the population. Whereas the PLR indicates the effect of a positive examination finding on the probability that the condition in question exists, the NLR addresses the effect of a negative examination finding on the probability that the condition in question is present. The likelihood values therefore provide quantification of the effect of MR angiographic results on diagnostic thinking (ie, the effect of the MR angiographic test result on the a priori probability of the presence of clinically significant steno-occlusive disease versus the a posteriori probability of the presence of such disease) (55). In this study, a PLR value of seven or higher for each blinded reader suggests that a positive finding on CE MR angiographic images of the renal arteries would in each case lead to a moderate to large and often conclusive shift in the probability that greater than 50% steno-occlusive disease is present.

A final consideration concerns the detection of accessory renal arteries, which are present in up to 25% of patients, that originate above or below the main renal artery. Overall, the three blinded off-site readers of MR angiographic images detected approximately 70% of the total number of accessory arteries that were detected on DSA images. Previously, MR angiography has been associated with comparatively poor visualization of accessory renal arteries, as well as with lower accuracy for the detection of potential stenosis of accessory arteries compared with that of conventional angiography (56). However, there is some debate about the clinical relevance of accessory renal arteries and whether failure to detect them has any effect on the utility of noninvasive imaging for the detection of renovascular hypertension (57). In our

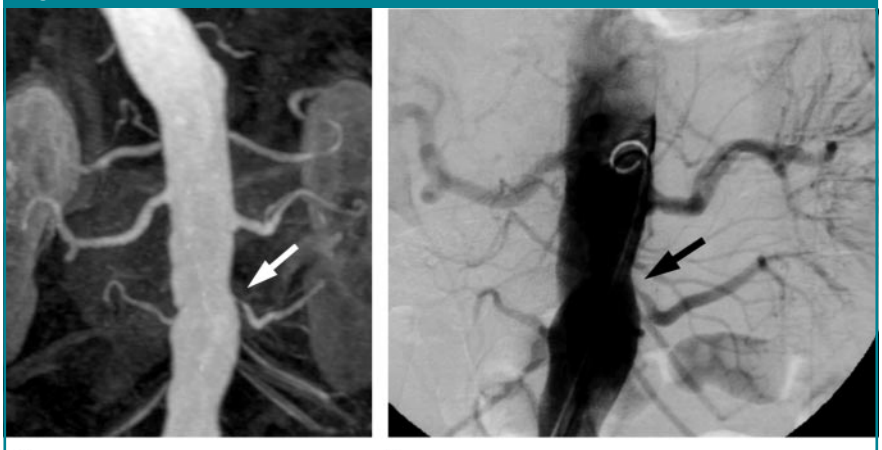
Table 3

Sensitivity, Specificity, Accuracy, PPV, NPV, and 95% CIs of CE MR Angiography for Patient-Level Detection of Significant Steno-occlusive Disease of the Main Renal Arteries Relative to DSA for Off-site Blinded Readers

Reader	Sensitivity	Specificity	Accuracy	PPV	NPV
1	65.2 (57.9, 72.6)	86.5 (80.0, 93.1)	73.6 (68.3, 78.9)	88.2 (82.4, 94.0)	61.6 (53.8, 69.5)
2	78.9 (72.6, 85.2)	91.4 (86.1, 96.8)	83.8 (79.4, 88.3)	93.4 (89.2, 97.6)	73.8 (66.3, 81.4)
3	79.9 (73.6, 86.1)	81.3 (73.9, 88.7)	80.5 (75.7, 85.2)	86.4 (80.9, 91.9)	73.1 (65.1, 81.1)

Note.—Data are percentages. Numbers in parentheses are 95% CIs.

Figure 5



a. b.

Figure 5: Images in 71-year-old man with severe hypertension, arteriosclerosis, and angina pectoris. **(a)** MIP coronal projection of CE MR angiographic acquisition (3.29/1.14) reveals inferior left and right accessory renal arteries with severe stenosis (arrow) of inferior left accessory artery. **(b)** Angiographic image confirms accessory renal arteries and severe stenosis (arrow) of left accessory artery.

study, some of the accessory renal arteries not seen on CE MR angiographic images may have been missed because of a larger section thickness in use at some of the 35 investigational centers.

A limitation of our study was that parallel imaging technology and time-resolved MR angiography were in their infancy and not widely available at the time the study was planned and conducted. Therefore, the unavailability of this more advanced MR technology might have negatively affected image quality, diagnostic performance, and the detection of accessory renal arteries compared with what is achievable with state-of-the-art MR imaging systems today (58). The increased imaging efficiency provided by parallel imaging allows increased temporal or spatial resolution and reduction of artifacts on CE MR angiographic images (59). Moreover, increased spatial resolution or volume coverage can be achieved in a single breath hold (eg, in renal CE MR angiography) or in otherwise clinically acceptable imaging durations (18,58, 59). Unfortunately, a drawback of parallel imaging techniques is an overall reduced signal-to-noise ratio. Because gadobenate dimeglumine has been shown to boost intravascular signal more than other available gadolinium-based contrast agents (32,34,60,61), further work should be performed to determine whether the reduced signal-to-noise ratio of more advanced sequences can be compensated with the use of this contrast agent, particularly in vascular territories for which increased speed and/or spatial resolution is beneficial.

In conclusion, our study results confirm that gadobenate dimeglumine at a dose of 0.1 mmol/kg is a safe gadolinium-based contrast agent for use in CE MR angiography of the renal arteries and provides an overall accuracy of 80%–87% for the detection of significant steno-occlusive disease.

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