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**Abbreviations:**
ROC = receiver operator characteristic
TOF = time of flight

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# 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[1]

**PURPOSE:** To prospectively determine the safety and efficacy of the gadolinium-based blood pool magnetic resonance (MR) imaging contrast agent gadofosveset in patients known to have or suspected of having peripheral vascular disease.

**MATERIALS AND METHODS:** Ethical committee approval and patient written informed consent were obtained. This study was compliant with the Health Insurance Portability and Accountability Act. Adults known or suspected to have peripheral vascular disease received gadofosveset (0.03 mmol per kilogram of body weight) for MR angiography of the aortoiliac region. Gadofosveset-enhanced MR angiography and unenhanced two-dimensional time-of-flight MR angiography were compared with the reference standard, conventional angiography, for the presence of vascular stenosis. All patients were monitored for adverse events with hematologic analysis, analysis of blood chemistry, urinalysis, and electrocardiographic parameters; these methods were analyzed to determine safety.

**RESULTS:** A total of 274 patients were enrolled at 37 centers. Gadofosveset-enhanced MR angiography showed significant improvement ($P < .001$) compared with unenhanced MR angiography for each of the readers for diagnosis of clinically significant (≥50%) stenosis. Specificity and accuracy were significantly greater for three readers, and sensitivity increased significantly for two readers. For all readers, the area under the receiver operator characteristic curve for both quantitative and qualitative measures of significant disease increased ($P < .001$) for gadofosveset-enhanced MR angiography versus two-dimensional time-of-flight MR angiography. All readers also expressed more confidence in diagnosis ($P < .001$) and found fewer images to be uninterpretable (0.5% vs 11.0%). The most common adverse events were as follows: feeling hot, 12 (4.4%) patients; nausea, 10 (3.6%) patients; headache, nine (3.3%) patients; and burning sensation, eight (2.9%) patients. Only four serious adverse events were reported, in three patients, and all events were rated as unlikely related to the drug. No patients were excluded because of adverse events or laboratory abnormalities. There were no clinically important trends in the findings of hematologic analysis, blood chemistry, urinalysis, electrocardiography, or physical examination.

**CONCLUSION:** On the basis of substantial improvements over noncontrast MR angiography in efficacy and a minimal and transient side-effect profile, gadofosveset was found to be safe and effective for MR angiography in patients known or suspected to have peripheral vascular disease.

There has been an evolution in magnetic resonance (MR) angiographic techniques used to image vascular disease over the past several years, which has resulted in substantial improvements of signal-to-noise ratios. This process has been driven by a combination of hardware development, better gradients and receiving coils, and the increased use of gadolinium as a contrast agent (1–4).

The first pass of bolus-injected gadolinium chelates shortens the T1 time of blood, thus increasing the intravascular signal intensity and reducing imaging times compared with previously developed time-of-flight (TOF) techniques (4,5). Commercially available gadolinium-based extracellular contrast agents have a short vascular half-life; therefore, they require rapid first pass imaging with rigorous bolus time mechanisms. Moreover, none of the extracellular contrast agents are currently approved for MR angiography in the United States.

Gadofosveset, a new contrast agent designed for vascular imaging, is a gadolinium-based compound that binds reversibly to albumin in the blood. This contrast agent gives both an increased signal intensity compared with that of other extracellular agents (6) and persistent intravascular image enhancement for at least 1 hour (7). Blood pool agents can provide dynamic images, such as those available with existing extracellular agents, and a longer steady-state phase in which to image the vasculature.

Following early phase I and II studies (8,9), a dose-ranging phase II study (10) demonstrated a dose response for gadofosveset and showed that a dose of 0.03 mmol per kilogram of body weight was the most clinically appropriate for MR angiography. As part of a prospectively designed clinical development program, the purpose of this study was to determine the safety and efficacy of the gadolinium-based blood pool MR contrast agent gadofosveset in patients known or suspected to have peripheral vascular disease.

## MATERIALS AND METHODS

### Study Design

The study was designed as an open-label, multicenter phase III trial. Gadofosveset is being codeveloped by EPIX Pharmaceuticals (Cambridge, Mass) and Schering (Berlin, Germany). All data were collected by the investigators and analyzed by third-party clinical research organizations that were subject to U.S. Food and Drug Administration controls and audits. The primary end points were sensitivity, specificity, and accuracy of two-dimensional TOF MR angiography and gadofosveset-enhanced MR angiography; an adjudicated conventional angiography–blinded interpretation served as the standard of reference. Secondary end points included the rate of uninterpretable MR angiograms, diagnostic confidence, and a receiver operator characteristic (ROC) evaluation of the likely presence of disease. Clinically significant stenosis was defined as narrowing of 50% or more of the diameter of the vessel (11–14). The ethical committees of the institutions participating in the study approved the protocol, and each enrolled patient provided written informed consent. This study was compliant with the Health Insurance Portability and Accountability Act.

### Patient Selection

At each center, all patients for whom conventional angiography of the aortoiliac arteries was completed or planned were considered; patients were enrolled in the study if they provided consent and met all inclusion criteria. MR and conventional angiography were performed within 3–30 days of each other, and no interventions were performed in the period between examinations. Patients were 18 or more years of age, and they were excluded if they had bilateral aortoiliac grafts, stents, or hip replacements.

Patients were also excluded from the study if they *(a)* had experienced a major cardiovascular event within 30 days prior to study enrollment; *(b)* had a history of abnormal renal function including, but not limited to, a serum creatinine level outside the normal range for the site laboratory; or *(c)* had a history of renal transplantation or hemodialysis. Other exclusion criteria included a history of hemoglobinopathy or specific MR exclusion criteria, such as the presence of a pacemaker, internal defibrillator, or ferromagnetic intracranial aneurysm clip. Warfarin was not administered at any time during the study and was withheld 3 days prior to drug administration. Also, patients could not have taken ibuprofen or naproxen within 4 hours prior to drug administration.

Patients were also excluded if they were hypersensitive to gadolinium-based contrast agents or had previously received gadofosveset. Patients could not have received iodine or other contrast agents within 3 days prior to or after gadofosveset administration. Finally, patients who underwent surgery within 30 days prior to drug administration were excluded from the study.

### Contrast Agent and Administration

Gadofosveset is a gadolinium-based small molecule (molecular weight, 975.77 Da) contrast agent designed specifically for MR angiography. Gadofosveset is 80%–96% noncovalently bound to albumin in human plasma, and it is primarily excreted renally (15). In plasma, gadofosveset exhibits a relaxivity of roughly 10 times that of gadopentetate dimeglumine at 0.5 T (16).

Intravenous injection of 0.03 mmol/kg gadofosveset was determined to be safe, well tolerated, and effective in phase I and II clinical trials (8–10). In our study, each patient received 0.03 mmol/kg gadofosveset diluted to 30 mL for hand injection or 15 mL for power injection. Per protocol, the dose was administered over a 30-second span via a catheter in the antecubital vein. The dose was followed by a 30-mL saline flush. Dynamic acquisitions were initiated with a fixed delay of 30 seconds from the start of the bolus, after a delay previously determined in the patient's medical history, or as determined by the timing of a bolus of no more than 10% of the specified dose of gadofosveset. Automated timing protocols were used if they were available.

### Imaging

Digital subtraction angiography was performed according to the standards at each institution. Imaging of the aortoiliac vessels in the left and right anterior oblique views was required, with an image intensifier matrix of at least $1024 \times 1024$ or cut films. Images were obtained in additional views if medically necessary.

MR imaging was performed with 1.0–1.5-T field strength MR systems with U.S. Food and Drug Administration-approved hardware and software. Prior to gadofosveset administration, unenhanced (baseline) MR angiograms were obtained according to the standard sequence of each institution or the sequence recommended by the vendor. Typical sequences were T1-weighted sequential section TOF protocols (repetition time msec/echo time msec, 15–25/2–5; flip angle, 30°–40°). In some cases, section-interleaved protocols with longer repetition times and flip angles near 70° were used. Prior to gadofosveset administration, a subtraction mask was obtained by

using the same imaging parameters specified for the dynamic images.

Aortoiliac MR angiography of dynamic and steady-state time points was performed after gadofosveset administration by using a three-dimensional spoiled gradient-echo technique. Dynamic images (1.7–3.0/6.6–10.0; flip angle, 25°–30°; acquisition time, 40–50 seconds) were acquired as a coronal slab with a 192 × 512 in-plane matrix. The field of view was 330 × 440 mm and included 22–32 partitions interpolated to 44–64 sections (acquired, <4 mm thick; reconstructed, <2 mm thick). Steady-state fat-suppressed images, obtained with one fat-saturated pulse per repetition time (2.0–3.0/18.9–28.0; flip angle, 25°–30°; acquisition time, 6–8 minutes), were acquired as a coronal slab with a 384 × 512 in-plane matrix. The field of view was 330 × 440 mm, with 50–64 partitions interpolated to 100–128 sections (acquired, 1.8 mm thick; reconstructed, 0.9 mm thick). One of the allowed timing methods was used to time the start of dynamic image acquisition. Acquisition of steady-state images began within 15 minutes of gadofosveset administration.

### Safety Monitoring

All patients were monitored for at least 72 hours, and some patients were monitored for as many as 96 hours after administration of gadofosveset. Safety was assessed by reviewing medical history and monitoring the following parameters: physical examination, vital signs, pulse oximetry, electrocardiograms, and results of clinical laboratory tests (including hematologic analysis, clinical chemistry, coagulation, anaphylaxis panel, and urinalysis). All reports of adverse events were recorded in accordance with International Conference on Harmonisation guidelines. Principal investigators[2] at each institution determined the likelihood of relationship between individual adverse events and gadofosveset administration.

### Standard of Reference

Diagnosis with conventional angiography was selected, as it is broadly accepted as a reference standard for the characterization of vascular morphology. The conventional angiograms were digitized and read at a NucLear MAC workstation (Scientific Imaging, Larkspur, Colo) at a central location by board-certified practicing radiologists. Three readers with 30, 6, and 17 years of experience, respectively, reviewed the conventional angiograms. All readers were blinded to all patient data, aside from the conventional angiograms. Two readers independently interpreted the conventional angiograms of each patient. The following seven vessels were evaluated: infrarenal aorta, left and right common iliac arteries, left and right external iliac arteries, and left and right common femoral arteries. The readers first determined if the images could be interpreted. Images of a patient's side were considered uninterpretable if more than one vessel, including the infrarenal abdominal aorta, was uninterpretable (ie, data were insufficient for diagnosis). If images obtained in the side were interpretable, the readers then measured the degree of maximum stenosis in each vessel to assess the presence or absence of disease in that vessel. Measurements were performed on source or reformatted images by using on-screen calipers. The minimum cross-sectional diameter at the level of stenosis was measured. To provide the denominator for the percentage of stenosis, readers measured the diameter of the most normal adjacent arterial segment. For the purposes of this study, clinically significant stenosis in each segment was defined as stenosis with a diameter of 50% or more. A third blinded reader (the adjudicator) evaluated all vessels for which the first two readers disagreed about either the interpretability or the presence or absence of clinically significant stenosis. Each vessel was assigned a diagnosis based on the agreement of at least two of the three blinded interpretations of conventional angiograms.

### MR Angiogram Readers

All MR angiograms were read at a ProVision (Algotec, Duluth, Ga) workstation at a central location. Images were evaluated by three board-certified practicing radiologists who had at least 2 years of experience in the evaluation of MR angiograms. All three radiologists evaluated MR angiograms for each patient, and they were blinded to all patient information aside from the MR angiograms. Gadofosveset and two-dimensional TOF examinations were presented separately and in random order. Gadofosveset examinations included both source images and maximum intensity projections of precontrast, dynamic postcontrast, and steady-state postcontrast images. Subtraction images (postcontrast images minus precontrast images for both precontrast and dynamic postcontrast MR angiograms) were also provided. Readers could perform further postprocessing themselves, including subvolume maximum intensity projections and transverse or oblique reformations. The images were assessed separately by the three independent MR angiogram–blinded readers who determined the disease state in the seven vessels from both the two-dimensional TOF and postcontrast MR angiograms. Interpretability was assessed, and quantitative stenosis measurement was performed as in the conventional angiographic interpretation.

In addition to this quantitative interpretation, the readers that were blinded to MR angiographic findings provided two qualitative assessments. As an adjunct to the determination of quantitative diagnostic efficacy, the readers who were blinded to MR angiographic findings were also asked to rate their first impression of the presence of significant stenosis in each vessel. The readers were required to record this qualitative impression before any measurements of stenosis were made, and they were not allowed to change this impression after measurement. The readers rated this interpretation by using a five-point scale (1, definitely no significant stenosis; 2, likely no significant stenosis; 3, indeterminate; 4, likely significant stenosis; and 5, definitely significant stenosis) (17). In a second qualitative analysis, the readers separately rated their overall diagnostic confidence in both TOF and gadofosveset diagnosis on a per-side basis by using a five-point scale (1, not confident; 2, somewhat not confident; 3, uncertain; 4, somewhat confident; and 5, very confident) (17).

### Analysis and Statistical Methods

The primary analysis was performed to determine the overall diagnostic efficacy for detection of clinically significant stenosis in the aortoiliac vessels of each patient for gadofosveset-enhanced MR angiography and unenhanced MR angiography. The efficacy parameters included sensitivity, specificity, and overall accuracy of MR angiography for detection of clinically significant stenosis versus the standard of reference. Sensitivity was defined as the number of correctly identi-

[2] Principal investigators were as follows: J.H. Rapp, S.D. Wolff, S.F. Quinn, J.A. Soto, S.G. Meranze, S. Muluk, J. Blebea, S.P. Johnson, N.M. Rofsky, A. Duerinckx, G.S. Foster, K.C. Kent, G. Moneta, M.R. Middlebrook, V.R. Narra, B.D. Toombs, and J. Pollak.

fied abnormal vessels divided by the total number of abnormal vessels. Specificity was defined as the number of correctly identified normal vessels divided by the total number of normal vessels. Accuracy was defined as the number of correctly identified vessels (either abnormal or normal) divided by the total number of vessels examined.

An intent-to-treat method was used, and all uninterpretable MR angiograms were considered inaccurate for the purposes of determining sensitivity, specificity, and accuracy. That is, if the MR angiogram was deemed uninterpretable by a reader blinded to MR angiographic findings and the vessel stenosis was diagnosed as clinically significant at MR angiography, it was counted as a false-negative image; however, if the vessel stenosis was diagnosed as not clinically significant at conventional angiography, it was counted as a false-positive image.

The primary statistical comparison between gadofosveset-enhanced MR angiography and unenhanced MR angiography was performed by using sensitivity, specificity, and overall accuracy. Statistical significance was assessed by using the cluster-corrected McNemar test, which serves to eliminate bias caused by potential correlation among the vessels of a given patient (18). In addition, each reader's quantitative diagnoses were used to construct an ROC curve to compare the overall diagnostic efficacy of postcontrast MR angiography and unenhanced MR angiography.

The ROC curves were constructed by plotting sensitivity versus 1 minus specificity, where each of 10 values on the ROC curve are defined parametrically on the basis of 10 different threshold degrees of stenosis considered to indicate a positive diagnosis of disease (ie, threshold stenosis extent of 0%–100%, in 10% increments). Difference between diagnostic value was inferred on the basis of a comparison of the areas under the ROC curves (19). ROC curves were also constructed by using qualitative diagnosis, where the five qualitative measures of disease state were separately considered to be the positive diagnostic threshold.

The average and standard deviation of the numerical confidence of diagnosis were computed. The statistical comparison of the post- and precontrast MR angiograms was performed by using a paired *t* test. All statistical tests were performed with a *P* value of less than .05 used to indicate statistical significance.

To evaluate the consistency of the diagnoses assigned by readers of conventional angiograms, each reader was judged against the other. The agreement between readers was assessed by computing the mean sensitivity (ie, agreement for the presence of ≥50% stenosis), specificity (ie, agreement for the absence of ≥50% stenosis), and accuracy (ie, overall agreement) of interpretation of each by using the other's diagnoses as the reference standard.

Counts and percentages of adverse events were tabulated. Also noted were changes in vital signs, laboratory results, physical examinations, or electrocardiographic measurements. For electrocardiographic recordings, changes from baseline for the PR interval, the QRS complex, QT interval, QTc interval, and the ST segment were summarized by using descriptive statistics, as well as being interpreted by an independent cardiologist. All changes were compared with zero by using the Student *t* test; *P* values of less than .05 were considered to indicate a statistically significant difference.

**TABLE 1**
**Baseline Characteristics**

| Characteristic | Finding |
|---|---|
| No. of patients | 274 (100) |
| Age (y) | |
| Mean ± SD | 65.8 ± 10.5 |
| Range | 33.0–87.9 |
| Sex | |
| Male | 190 (69.3) |
| Female | 84 (30.7) |
| Race | |
| White | 205 (74.8) |
| Black | 32 (11.7) |
| Hispanic | 36 (13.1) |
| Other | 1 (0.4) |
| Height (cm) | |
| Mean ± SD | 169.1 ± 11.1 |
| Range | 137.0–196.0 |
| Weight (kg) | |
| Mean ± SD | 74.5 ± 17.0 |
| Range | 35.0–120.0 |
| Diagnosis at enrollment | |
| Abdominal aortic aneurysm | 23 (8.4) |
| Peripheral vascular disease | 251 (91.6) |

Note.—Unless otherwise indicated, data are number of patients, and data in parentheses are percentages. SD = standard deviation.

## RESULTS

### Demographics

Patients were enrolled in the study between June 1999 and September 2001 in 37 centers. Of the 315 subjects who were initially enrolled (ie, signed consent forms), 41 were discharged before receiving gadofosveset. Reasons for discharge were as follows: withdrawn consent ($n$ = 12), noncompliance ($n$ = 19), adverse event related to conventional angiography ($n$ = 3), or other reasons ($n$ = 7). A total of 274 subjects received gadofosveset. Eight subjects were eliminated after they received gadofosveset because of withdrawn consent, noncompliance, or other reasons. Fifteen patients were eliminated from efficacy evaluation because of an absence of conventional angiographic data obtained according to the protocol. In the study group, there were 190 men and 84 women. The mean age was 65.8 years ± 10.5. Patient characteristics are summarized in Table 1.

### Efficacy

A total of 251 patients and 1646 vessels were evaluated for accuracy. Patients who were evaluated for sensitivity had one or more vessels that were judged to have disease at interpretation of conventional angiographic findings. This group numbered 140 patients, with 237 diseased vessels. There were 250 patients, with 1409 normal vessels, who were evaluated for specificity. Images from gadofosveset-enhanced MR angiographic examinations correlated more closely with images from conventional angiographic examinations than did images from unenhanced MR angiographic examinations for all three readers, as shown in Table 2. The three readers achieved, on average, a 14.5% increase in sensitivity, a 12.6% increase in specificity, and a 12.8% increase in accuracy when comparing diagnoses made with the gadofosveset-enhanced images with those made with the unenhanced images versus the adjudicated conventional angiograms. Sensitivity, specificity, and accuracy were significantly better for the gadofosveset-enhanced images than for the unenhanced MR angiograms for all readers, with the exception of the sensitivity of reader B; this reader showed improvement, but this improvement was not statistically significant ($P$ = .06). These results are summarized in Table 2, while similar analysis comparing the readers of conventional angiograms is summarized in Table 3. ROC curves for each of the three readers are shown in Figure 1.

For any given specificity, all readers showed increased sensitivity for detecting clinically significant stenosis when using gadofosveset-enhanced MR angiography as opposed to unenhanced MR angiography. The area under the ROC curve was significantly greater for gadofosveset MR angiography than for unenhanced

**TABLE 2**
**Diagnostic Specificity, Sensitivity, and Accuracy**

| Parameter | Gadofosveset-enhanced | Unenhanced | Difference | *P* Value |
|---|---|---|---|---|
| Accuracy ($n$ = 1646) | | | | |
| Reader A | 83.8 (1379)* | 73.2 (1205) | 10.6 | <.001 |
| Reader B | 90.3 (1486) | 82.2 (1353) | 8.1 | <.001 |
| Reader C | 90.3 (1486) | 70.6 (1162) | 19.7 | <.001 |
| Sensitivity ($n$ = 237) | | | | |
| Reader A | 80.2 (190) | 62.0 (147) | 18.1 | <.001 |
| Reader B | 73.0 (173) | 66.7 (158) | 6.3 | .06 |
| Reader C | 60.8 (144) | 41.8 (99) | 19.0 | <.001 |
| Specificity ($n$ = 1409) | | | | |
| Reader A | 84.5 (1191) | 75.1 (1058) | 9.4 | <.001 |
| Reader B | 93.2 (1313) | 84.8 (1195) | 8.4 | <.001 |
| Reader C | 95.3 (1343) | 75.4 (1062) | 19.9 | <.001 |

Note.—Data are percentages. Data in parentheses are counts of true diagnoses (ie, correctly evaluated vessel segments).

**TABLE 3**
**Mean Conventional Angiography Sensitivity, Specificity, and Accuracy**

| Parameter | Value |
|---|---|
| Accuracy ($n$ = 1594) | 90 (1447, 1410) |
| Sensitivity ($n$ = 206) | 70 (157, 334) |
| Specificity ($n$ = 1388) | 93 (1290, 1284) |

Note.—Data are percentages. Data in parentheses are number of true diagnoses for reader A and reader B, respectively.

MR angiography for all three readers ($P <$ .001). The results of each reader's confidence measure are shown in Table 4.

All three readers reported a significant ($P <$ .001) improvement in their confidence in the interpretation of images obtained with gadofosveset-enhanced MR angiography compared with the images obtained with unenhanced MR angiography. ROC curves constructed from these qualitative data (first impression of significant stenosis) for each reader for unenhanced and gadofosveset-enhanced MR angiography (not shown) follow the same trend as those generated from the quantitative stenosis measurements; again, they show a higher sensitivity for any given specificity for gadofosveset-enhanced MR angiography compared with unenhanced MR angiography.

The proportion of images that could not be interpreted is shown in Table 5. Significantly fewer images that could not be interpreted were generated with gadofosveset than with a two-dimensional TOF method ($P <$ .05 for all three readers). Before adjudication, the two individual readers who were blinded to conventional angiographic findings found that 5.1% and 9.8%, respectively, of the vessels depicted with conventional angiography could not be interpreted. By comparison with the values in Table 5, it can be seen that when rigorous blinded read methods were used, not only did gadofosveset provide significantly ($P \leq$ .001) fewer images that could not be interpreted than did two-dimensional TOF MR angiography, but also gadofosveset provided fewer images that could not be interpreted than did conventional angiography, which was the reference standard.

### Safety

A total of 101 patients reported 179 adverse events during the 72–96-hour MR angiography monitoring period. The majority of adverse events were judged to be mild: Of the 87 adverse events judged to be probably or possibly related to gadofosveset, 83 were termed mild, four were termed moderate, and none were termed severe. Three patients reported four serious adverse events during the MR angiography monitoring period, of which none were judged to be related to the study agent. These adverse events were aggravation of coronary artery disease, chest pain, aggravation of diabetes mellitus, and gangrene. A total of 87 adverse events in 59 (22.0%) of the 274 patients were judged to be possibly or probably related to gadofosveset. The related adverse events that occurred with the greatest frequency were feeling hot (12 incidents in 12 patients [4.4%]), nausea (10 incidents in 10 patients [3.6%]), headache (nine incidents in nine patients [3.3%]), and burning sensation (eight incidents in eight patients [2.9%]). The overall adverse event profile was similar to that previously reported for gadofosveset enhancement (10).

A total of 18 (6.6%) individual patients had blood chemistry, hematologic analysis, and urinalysis values during the MR angiography monitoring period that were considered indicative of adverse events. None of these events were judged to be serious, and there were no clinically concerning trends for any of these parameters over time. Similarly, there were isolated patients who had abnormal electrocardiographic readings, four of which were considered to be possibly related to gadofosveset injection, although no pattern was discernable over time, and these findings all occurred in subjects with a history of cardiovascular disease. No clinically important trends in electrocardiographic parameters were discerned. No individual changes in vital signs were considered to be serious or related to administration of gadofosveset.

During the 96-hour conventional angiography monitoring period, 90 patients reported 160 adverse events. The conventional angiography adverse event that occurred with the greatest frequency was "catheter-related complication," with 56 adverse events occurring in 48 patients (17.5%). The overwhelming majority of these catheter-related complications were pain or bruising at the puncture site. Five patients reported five serious adverse events during conventional angiographic monitoring, including atrial fibrillation, myocardial infarction, catheter-related complication, injury (not otherwise specified), and syncope. One of the serious adverse events (atrial fibrillation) was considered by the principal investigator to be possibly related to gadofosveset administration, but this event occurred 11 days after gadofosveset administration and during the conventional angiography monitoring period. There were no deaths.

## DISCUSSION

Gadofosveset-enhanced MR angiography performed well when compared with conventional angiography in the diagnosis of significant aortoiliac occlusive disease. The improvement in diagnostic efficacy compared with unenhanced MR angiography was clearly demonstrated. There was an improvement in overall accuracy, sensitivity, and specificity for each of the three blinded readers. Other measures of efficacy showed comparable results. ROC curve analysis showed that

gadofosveset-enhanced MR angiography gave greater sensitivity for any given specificity than did unenhanced MR angiography. In addition, the area under the ROC curve was significantly greater for all three readers ($P < .001$).

The improvement in gadofosveset-enhanced MR angiography compared with unenhanced imaging is consistent with the reported limitation of unenhanced aortoiliac MR imaging. Accurate diagnosis of stenosis in the aortoiliac region can be difficult with unenhanced MR angiography because of the tortuosity of the pelvic vessels, particularly the internal and external iliac arteries (3,20,21). Furthermore, poststenotic vessels on unenhanced MR angiograms can show decreased signal intensity due to intravoxel phase dispersion and nonuniform inflow enhancement, which can exaggerate the apparent degree of stenosis (22). These effects can cause flow artifacts at unenhanced MR angiography, resulting in a substantial number of false-positive findings. As a result, both sensitivity and specificity of unenhanced MR angiography can be affected. For these reasons, two-dimensional TOF is not commonly used for diagnosis in the aortoiliac region.

An important element of our evaluation of gadofosveset-enhanced MR angiography was the confidence that the readers had in the accuracy of the studies. While this is subjective, it is a measurement of the clarity of the studies, their ease of interpretation, and their likelihood of being accepted as an alternative to conventional angiography. Inability to interpret MR angiograms is not often addressed in the MR angiographic literature, as it is typical for only those images that can be interpreted to be included in the reported efficacy analysis. These data indicate that a dose of 0.03 mmol/kg gadofosveset effectively eliminated the problem of nondiagnostic images in the aortoiliac region.

The overall accuracy of gadofosveset-enhanced MR angiography for the three readers was 84%, 90%, and 90%, respectively. This amount of variation may be due to the inherent differences in the two imaging modalities or to the inherent variation between readers. When the results of conventional angiography were subjected to interreader comparisons, the variation in sensitivity, specificity, and accuracy between the readers for conventional angiography were very similar for gadofosveset-enhanced MR angiography versus conventional angiography. It is broadly accepted that conventional angiography has limitations, which makes complete concordance between MR angiography and conventional angiography unlikely. It is obvious that the two-dimensional projections formed with conventional angiography are not completely comparable with those formed with three-dimensional MR angiography, and previous studies of three-dimensional rotational angiography compared with two-dimensional projections have demonstrated discrepancies comparable with those seen here (23). Furthermore, catheter- and vasospasm-related artifacts, which are variably interpreted by clinicians, can result in over- or underestimation of disease.

Some of the difficulty of comparing MR angiography to a two-dimensional standard of reference was addressed in this study by comparing the individual readers who were blinded to conventional angiographic findings with each other. In this study, there was good, but not complete (approximately 90%), agreement between the two readers of conventional angiographic findings. Because it is impossible for a test modality to overcome the variability of the reference standard, the 84%–90% accuracy obtained with gadofosveset appears to approach the maximum achievable agreement when using this method to compare three-dimensional MR angiography with two-dimensional conventional angiography. Thus, we conclude that not only is imaging of the aortoiliac segment of the arterial tree with gadofosveset-enhanced MR angiography a sub-

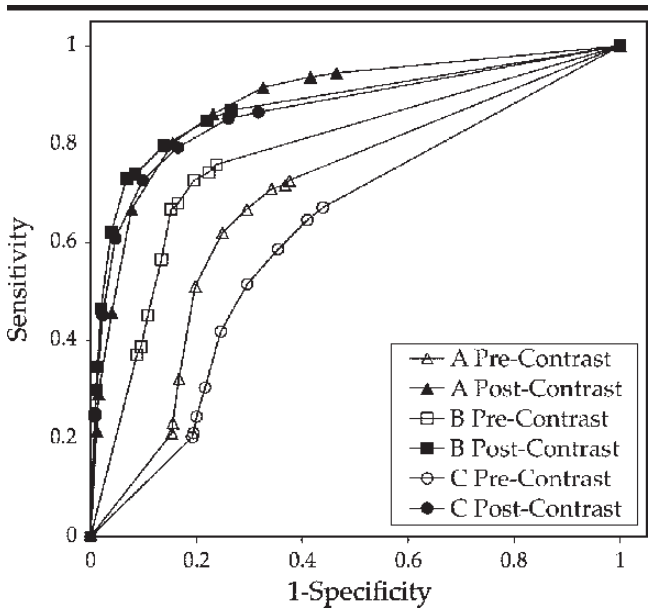


**Figure 1.** ROC curves generated for each reader show sensitivity and specificity throughout the range of quantitative stenosis measurements that may serve as a diagnostic criterion for disease. The area under the ROC curve implies total diagnostic value, and it is consistently greater for gadofosveset-enhanced diagnosis.

**TABLE 4**
**Diagnostic Readers' Confidence in MR Angiography**

| Body Side | Gadofosveset-enhanced | Unenhanced | *P* Value |
|---|---|---|---|
| Right | | | |
| Reader A | 5.0 ± 0.2 | 4.1 ± 0.8 | <.001 |
| Reader B | 4.8 ± 0.4 | 4.2 ± 0.7 | <.001 |
| Reader C | 4.7 ± 0.6 | 3.1 ± 1.1 | <.001 |
| Left | | | |
| Reader A | 4.9 ± 0.2 | 4.2 ± 0.8 | <.001 |
| Reader B | 4.8 ± 0.5 | 4.3 ± 0.7 | <.001 |
| Reader C | 4.7 ± 0.6 | 2.9 ± 1.2 | <.001 |

Note.—Data are mean ± standard deviation.

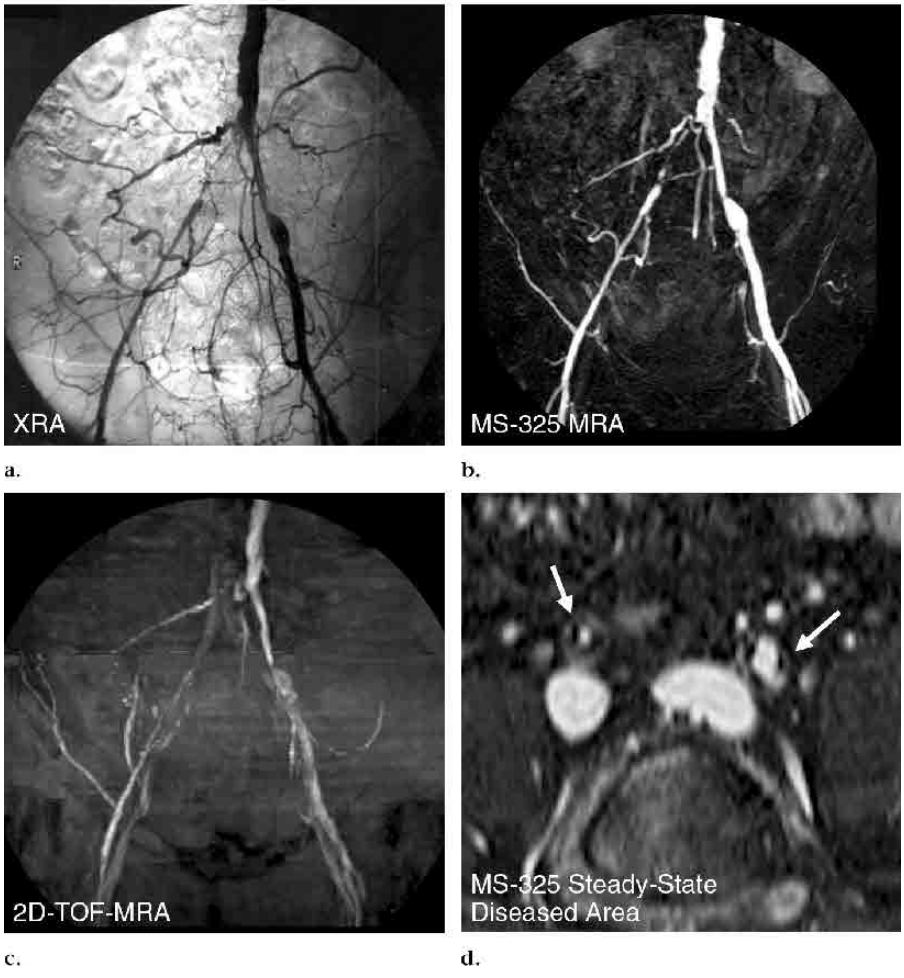


**Figure 2.** Comparable coronal projections of **(a)** conventional angiography, **(b)** gadofosveset-enhanced MR angiography, **(c)** two-dimensional TOF MR angiography, and **(d)** a transverse reconstruction of a steady-state gadofosveset dataset showing stenoses (arrows) in both right and left common iliac arteries.

**TABLE 5**
**Uninterpretable Images**

| Reader | Gadofosveset-enhanced *(n = 256)* | Unenhanced *(n = 256)* |
|---|---|---|
| Reader A | 3 (1.2) | 45 (17.6) |
| Reader B | 1 (0.4) | 12 (4.7) |
| Reader C | 1 (0.4) | 56 (21.9) |

Note.—Data are number of patients. Data in parentheses are percentages.

stantial improvement over imaging with unenhanced MR angiography but that it also appears to mimic conventional angiography in accuracy and study confidence.

There are potential limitations of this study, which are shared with previous studies of this contrast agent (10). The study was designed as a pure blinded-read comparison of the MR and conventional angiographic data; thus, the use of any other patient information was not allowed. The blinded setting, which is the preferred method for evaluation of the contribution of diagnostic information, does not mimic the typical clinical setting. In the clinical setting, patient history and measurements such as pressure gradients, exercise performance, and other functional measures are also used to determine the proper care of patients with peripheral vascular disease. Nevertheless, this method allows rigorous and statistically valid comparison with conventional angiography, which is considered the current standard in the evaluation of the anatomic characteristics of arterial disease. The quantitative measurement of the most significant stenosis in a vessel captures critical information in the assessment of occlusive disease, and excellent agreement with conventional angiography was achieved in this trial with gadofosveset-enhanced MR angiography.

Another limitation of the study is that it did not allow direct comparison of gadofosveset with existing extracellular contrast agents, nor did it quantify the added benefit of steady-state MR angiography. The use of extracellular contrast agents is the current standard for MR angiography, and dynamic acquisition performed in this study is comparable with the dynamic imaging performed with these existing agents. A direct comparison that quantifies any added benefit of steady-state images to the dynamic images was not possible in this study, however, since both dynamic and steady-state data were read together. In theory, steady-state MR angiograms could provide substantial benefits in terms of increased spatial resolution, ease of acquisition, and reduced artifact. In other studies, the more rapid imaging, which has reduced the artifacts caused by patient movement and flow artifacts in nonaxial arteries (24), has led to other artifacts, especially in quantitative evaluation of stenoses. For example, rapid imaging with extracellular agents may impair definition of the artery at the luminal surface because the bolus may not fully mix with the slower moving blood along the arterial wall (25). In addition, the parameters of dynamic gadofosveset-enhanced MR angiography align the frequency-encoding gradients (gradients less frequently switched during imaging) along the axis of the vessel. These two factors can result in an apparent reduction in vessel diameter both in areas with disease and in areas without disease when compared with TOF MR angiography (26). Both of these effects are reduced or eliminated on the steady-state images that can be obtained with a blood pool agent. Determining whether these benefits are achievable in clinical practice will have to be tested in further studies.

In conclusion, gadofosveset-enhanced MR angiography at a dose of 0.03 mmol/kg enabled improved diagnosis compared with TOF MR angiography and provided excellent accuracy compared with catheter conventional angiography, agreeing 88.5% of the time, averaged over three blinded readers. Side effects from the gadofosveset contrast agent were generally mild and transient in nature. Gadofosveset appears to be safe, well tolerated, and effective in the diagnosis of vascular disease in the aortoiliac region.

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