Intra-individual Crossover Comparison of Gadobenate Dimeglumine and Gadopentetate Dimeglumine for Contrast-Enhanced Magnetic Resonance Angiography of the Supraaortic Vessels at 3 Tesla

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Objective: To compare gadobenate dimeglumine (Gd-BOPTA) and gadopentetate dimeglumine (Gd-DTPA) for contrast-enhanced magnetic resonance (MR) angiography of the supraaortic vessels at 3 Tesla.

Materials and Methods: Twelve healthy volunteers each underwent two contrast-enhanced magnetic resonance angiography examinations, one with Gd-BOPTA and one with Gd-DTPA each at a dose of 0.1 mmol/kg bodyweight. The 2 examinations were performed in randomized order and were separated by at least 72 hours. Imaging was performed in the coronal plane at 3T (Magnetom TIM Trio Siemens) using a 12-channel neurovascular array coil. The MR sequence parameters were identical for all examinations. Maximum intensity projection reconstructions were evaluated separately and in matched-pairs by a single independent blinded reviewer in terms of qualitative (5-point scales for technical quality and vessel delineation) and quantitative (relative contrast-to-noise ratio) contrast enhancement across 19 arteries/arterial segments comprising the internal carotid arteries; anterior, middle, and posterior cerebral arteries; vertebral arteries; and basilar artery. Findings were compared using the Wilcoxon signed rank test.

Results: The mean technical quality across all examinations was significantly ($P = 0.031$) greater after Gd-BOPTA. The overall median score for vessel delineation was also significantly higher for Gd-BOPTA than for Gd-DTPA (4.3 vs. 3.7; $P = 0.005$). Matched-pairs assessment revealed significant ($P \leq 0.026$) preference for Gd-BOPTA both globally and for assessments of the extracranial arteries, Circle of Willis and vessels distal to the Circle of Willis. The relative contrast-to-noise ratio was significantly ($P \leq 0.021$) greater after Gd-BOPTA, with overall increases of 23.3%, 26.7%, and 28.5% noted for the internal carotid, middle cerebral, and basilar arteries, respectively.

Conclusion: Significantly improved image quality and contrast enhancement is achieved at 3T with 0.1 mmol/kg Gd-BOPTA compared with 0.1 mmol/kg Gd-DTPA.

Key Words: magnetic resonance angiography, contrast agent, 3 Tesla

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Three-dimensional contrast-enhanced magnetic resonance angiography (ceMRA) is widely considered the minimally invasive technique of choice for diagnostic imaging of the supraaortic arterial vasculature.[1–7] Compared with noncontrast time-of-flight (TOF) MRA techniques, ceMRA provides superior image quality and is far less prone to flow, saturation, and motion artifacts.[8–11] Moreover, the advent of parallel imaging and time-resolved MRA sequences have improved both the spatial and temporal resolution achievable to the point at which most examinations now look to include vessels from the aortic arch to the Circle of Willis with typical examination times of no more than 20 to 25 seconds.[4,12,13] In comparison, several minutes would be required for a field-of-view of this size using noncontrast TOF MRA sequences. The availability of "high field" MR imaging systems operating at 3 Tesla (3T) provides an additional means to improve spatial and/or temporal resolution and hence diagnostic image quality compared with imaging on traditional 1.5T systems. This has been demonstrated not only for the vessels of the head and neck,[14,15] but also for other vascular districts.[16,17]

Specific advantages of MR imaging at 3T compared with 1.5T are an increased baseline signal-to-noise ratio (SNR) and hence improved vessel tissue contrast and improved background suppression.[18–20] For examinations in which parallel imaging is used, the increased baseline SNR at 3T has the potential to offset the loss of SNR associated with the technique.[18,19] Conversely, if parallel imaging techniques are not used the greater inherent SNR at 3T may obviate the

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need for gadolinium contrast agent entirely, or else reduce the dose required to achieve adequate diagnostic image quality.

At many centers ceMRA of the supraaortic arteries is performed with conventional gadolinium contrast agents such as gadopentetate dimeglumine (Gd-DTPA, Magnevist; Bayer-Schering, Berlin, Germany). These agents do not interact with serum proteins and have similar r1 relaxivity values in vivo of between 4.3 and 5.0 $L \cdot mmol^{-1} \cdot s^{-1}$.[21–23] Gadobenate dimeglumine (Gd-BOPTA, MultiHance; Bracco Imaging SpA, Milan, Italy) resembles Gd-DTPA in terms of its physicochemical properties[24,25] and safety profile,[25–28] but differs in demonstrating partial hepatobiliary elimination[29] and markedly greater r1 relaxivity in vivo due to weak and transient interaction of the Gd-BOPTA contrast-effective chelate with serum albumin.[21,22,30,31] The greater r1 relaxivity of Gd-BOPTA compared with Gd-DTPA is apparent at all commercially available MR field strengths, ranging from 10.9 versus 4.7 $L \cdot mmol^{-1} \cdot s^{-1}$ at 0.2T to 5.9 versus 3.9 $L \cdot mmol^{-1} \cdot s^{-1}$ at 3T.[22]

Several studies have been performed at 1.5T to compare Gd-BOPTA and Gd-DTPA for ceMRA applications.[32–37] These studies have unequivocally demonstrated superior image quality and diagnostic performance with Gd-BOPTA when these agents are administered at identical dose[32–35] and equivalent diagnostic performance when a standard 0.1 mmol/kg dose of Gd-BOPTA is compared intra-individually with a double 0.2 mmol/kg dose of Gd-DTPA.[36] To date, the only study performed in the supraaortic vasculature has revealed superiority for 0.1 mmol/kg Gd-BOPTA compared with 0.2 mmol/kg Gd-DTPA.[37]

To our knowledge, no studies have yet been performed to compare Gd-BOPTA with Gd-DTPA for ceMRA at 3T. The present prospective study was therefore performed to determine whether the higher r1 relaxivity of Gd-BOPTA confers similarly greater vascular contrast enhancement at 3T to that seen at 1.5T.

SUBJECTS AND METHODS

This prospective study was a double-blind, randomized, single-center, intra-individual crossover comparison of 0.1 mmol/kg bodyweight doses of Gd-BOPTA and Gd-DTPA for ceMRA of the supraaortic arterial vessels at 3T. The study was approved by the ethics committee of our institution, and written informed consent was obtained from each volunteer before participation.

MR Imaging

Twelve healthy male volunteers [mean age (±standard deviation): 27.9 ± 7.6 years; range, 18–38 years] underwent 2 ceMRA examinations of the supraaortic vessels between June and July 2005. All examinations were performed on a 3T MR system (Magnetom TIM Trio; Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel neurovascular array coil (Siemens Medical Solutions). Both examinations in all subjects were performed in the coronal plane using a standard protocol with repetition time: 3.03 milliseconds, echo time: 1.26 milliseconds, flip angle: 20 degrees, matrix: 312 × 512, field-of-view: 260 × 320, number of excitations: 1, slice thickness: 1 mm, and no interslice gap. Parallel imaging (generalized autocalibrating partially parallel acquisitions) was used with an acceleration factor of 2. A total of 72 slices were acquired and the overall image acquisition time was 18 seconds.

The two examinations in each subject differed only in terms of the contrast agent used. The contrast agent for each examination was ascribed according to a randomization list (computed using the ProcPlan procedure of the statistical software package SAS, version 8.0; SAS Institute, Inc., Cary, NC) and was administered by an independent drug dispensing person to ensure complete blinding of the investigating radiologist. All contrast agent administrations were performed intravenously by power injector at a rate of 2 mL/s and were followed by 20 mL of saline solution administered at the same rate. The total dose of contrast agent for each examination was 0.1 mmol/kg bodyweight, corresponding to 0.2 mL/kg of commercially available 0.5 M formulations of each agent. Image acquisition was initiated manually as soon as the contrast agent bolus became visible in the ascending aorta. The 2 examinations in each subject were separated by approximately 10 days (minimum 7 days, maximum 14 days) to ensure complete elimination of the first contrast agent before administration of the second.

Image Analysis

Image evaluation was performed of maximum intensity projection reconstructions prepared from the original subtracted source images. All images were evaluated at a central reading facility by an experienced independent reviewer who was fully blinded to the contrast agent used in each examination. Initial assessment was performed to determine the technical quality of the images. For this assessment, the technical quality was rated as inadequate (insufficient), poor (but usable), moderate, good, or excellent. Images that were deemed of insufficient quality were excluded from further evaluation.

Subsequent evaluations were performed of individual image sets from each examination separately (assessments of qualitative and quantitative parameters) and of images from the two examinations in each subject in matched-pairs (qualitative parameters only).

Qualitative Assessments

Blinded qualitative evaluation of separate image sets was performed with the images presented in fully randomized order. A total of 19 extracranial and cerebral arteries/arterial segments were evaluated for both hemispheres, as follows:

- Internal carotid artery (ICA),
- anterior cerebral artery,
- middle cerebral artery, M1 segment (MCA-M1),
- middle cerebral artery, M2 segment (MCA-M2),
- middle cerebral artery, M3 segment (MCA-M3),
- posterior cerebral artery, P1 segment,
- posterior cerebral artery, P2 segment,
- posterior cerebral artery, P3 segment,
- vertebral artery,
- basilar artery (BA).

TABLE 1. Separate Qualitative Assessments of Vessel Delineation

	ICA		ACA		MCA-M1		MCA-M2		MCA-M3		PCA-P1		PCA-P2		PCA-P3		VA		BA	
Score	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**	**MH**	**MG**
None	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Poor	0	0	0	0	0	0	0	0	2	3	0	1	0	0	3	5	0	0	0	0
Moderate	0	2	1	3	0	4	8	15	8	13	2	5	3	7	18	17	0	1	0	0
Good	4	14	13	19	15	17	12	7	14	6	11	12	16	16	3	2	6	13	1	5
Excellent	20	8	9	1	9	3	4	2	0	0	7	2	5	1	0	0	18	10	11	7
Missing	0	0	1	1	0	0	0	0	0	2	4	4	0	0	0	0	0	0	0	0

Numbers represent scores from left and right hemispheres combined.

MH indicates Gd-BOPTA (MultiHance); MG, Gd-DTPA (Magnevist). None, no artery/segment depicted; poor, artery/segment poorly delineated; moderate, artery/segment adequately delineated; Good, artery/segment sharply delineated; excellent, artery/segment very sharply delineated.

The delineation of each artery or arterial segment was assessed using a 5-point scale in which 1 = none (no artery/segment depicted), 2 = poor (artery/segment poorly delineated), 3 = moderate (artery/segment adequately delineated), 4 = good (artery/segment sharply delineated), and 5 = excellent (artery/segment very sharply delineated).

Qualitative assessment of individual subject images in matched-pairs was performed after completion of the evaluations of separate image sets. Matched-pairs evaluations comprised a pairwise comparison of global vessel delineation across all arteries/arterial segments combined and individual assessments of the extracranial vessels, the vessels of the Circle of Willis, and the vessels distal to the Circle of Willis. Each assessment was performed using a continuous scale from 0 (images from first examination much better than images from second examination) through 9 (image sets are equal) to 18 (images from second examination much better than images from first examination).

Quantitative Assessments

Quantitative measurements of signal intensity (SI) were made at regions of interest (ROIs) placed in the ICA, the M1 segment of the MCA of both hemispheres, the BA and in the identical surrounding tissues of corresponding images from both examinations. Background noise was measured in a ROI placed at a standardized distance of 1 cm from the head. ROIs were as large as possible (typically approximately 8 mm^2 in the ICA and 4 mm^2 in the MCA and basilar artery) and were positioned to cover only the lumen of the vessels of interest. ROIs were positioned by the same experienced independent reviewer who was fully blinded to the contrast agent used in each examination.

Statistical Evaluation

Qualitative data deriving from all separate and matched-pairs evaluations were displayed for each contrast agent using frequency distribution tables and compared using the Wilcoxon signed rank test. The data for vessel delineation were summed across all arteries/segments and presented as mean and median values. All comparisons were considered significant for $P < 0.05$.

The quantitative SI measurements determined at each ROI were used to calculate values for relative contrast-to-noise ratio (rCNR) in the ICA, MCA, and BA. Each rCNR value was determined using the following equation:

$$\mathrm{CNR} = \frac{\mathrm{SI}_{\mathrm{vessel}} - \mathrm{SI}_{\mathrm{surrounding\ tissue}}}{\mathrm{SI}_{\mathrm{noise}}}$$

RESULTS

All studies were performed successfully without complications. None of the volunteers experienced any adverse events with either contrast agent.

Qualitative Assessments

The technical quality of the ceMRA examinations performed with Gd-BOPTA was considered excellent for nine volunteers and good for the remaining three volunteers. Conversely, only four examinations were considered excellent with Gd-DTPA, whereas six were considered good and two merely moderate. None of the examinations was considered poor after either contrast agent. The overall greater technical quality achieved with Gd-BOPTA across all examinations was statistically significant ($P = 0.031$).

Individual assessment of each of the 19 arteries/arterial segments evaluated separately for quality of vessel delineation resulted in more scores in higher quality delineation categories for Gd-BOPTA than for Gd-DTPA (Table 1). The overall median score across all 19 arteries/arterial segments evaluated was significantly higher for Gd-BOPTA than for Gd-DTPA (4.3 vs. 3.7; $P = 0.005$) (Table 2).

Comparison among arteries/arterial segments revealed a clear tendency towards declining vessel delineation with increasing distance from the basilar artery. Nevertheless, the superior delineation achieved with Gd-BOPTA compared

TABLE 2. Comparison of Vessel Delineation After Gd-BOPTA and Gd-DTPA ($P = 0.005$)

Delineation Score	Gd-BOPTA	Gd-DTPA
Mean ± standard deviation	4.2 ± 0.3	3.8 ± 0.4
Median	4.3	3.7
Range (min, max)	(3.5, 4.4)	(3.5, 4.6)

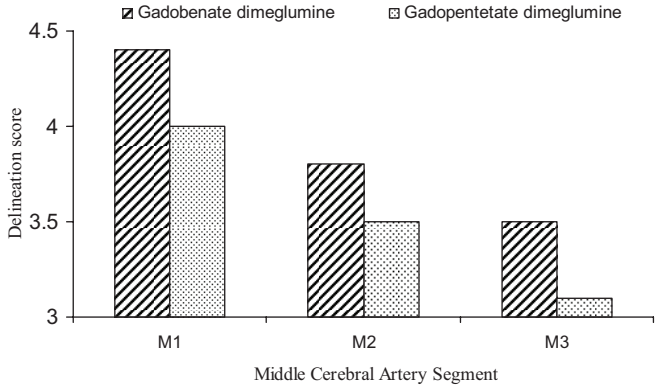


FIGURE 1. Average vessel delineation scores for Gd-BOPTA and Gd-DTPA ascribed to the MCA segments.

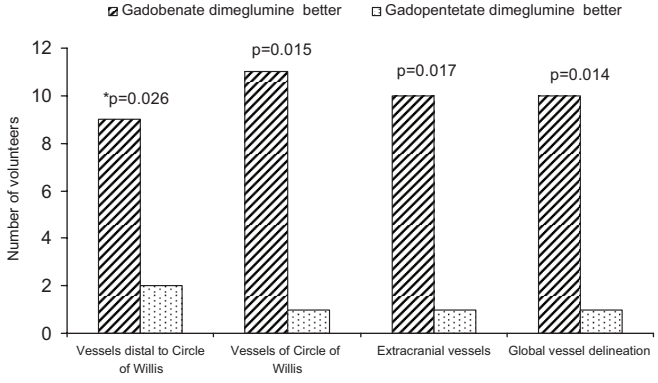


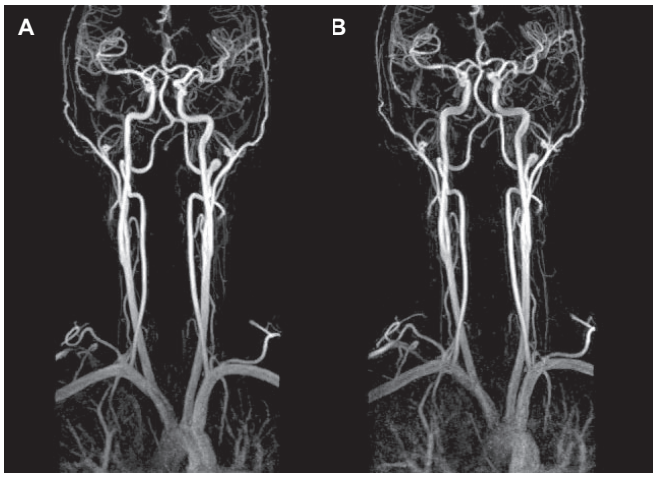
FIGURE 2. Matched-pairs comparison of image sets demonstrating significant preference for Gd-BOPTA globally and at individual vessel territories. Note: only patients for whom a preference was expressed are presented. *Data for one patient were missing.

with Gd-DTPA was maintained, as demonstrated for the MCA (Fig. 1).

The matched-pairs assessment of images from each examination in each subject revealed significant ($P \leq 0.026$) preference for Gd-BOPTA both at a global level and for separate assessments of the extracranial arteries, vessels of the Circle of Willis and vessels distal to the Circle of Willis (Fig. 2). Examples of the improved image quality are shown in Figures 3 and 4.

Quantitative Assessments

Gd-BOPTA produced significantly ($P \leq 0.021$) higher SI enhancement than Gd-DTPA in the arteries examined (Table 3). The mean SI values determined in the ICA, M1 segment of the MCA, and BA were 890.4, 643.1, and 700.6, respectively, after Gd-BOPTA compared with 782.6, 546.1, and 588.4, respectively, after Gd-DTPA. Similarly, the rCNR values in the ICA, MCA (segment M1), and BA were consistently significantly ($P \leq 0.021$) greater after administration of Gd-BOPTA compared with after administration of Gd-DTPA (Fig. 5). Overall, the mean rCNR was 23.3% higher after Gd-BOPTA in the ICA, 26.7% higher in the MCA-M1, and 28.5% higher in the BA.



A Gadobenate dimeglumine B Gadopentetate dimenglumine

FIGURE 3. Intra-individual blinded comparison of (A) Gd-BOPTA and (B) Gd-DTPA for ceMRA of the supraaortic vessels. Higher image quality with more homogeneous signal of the intracavernous ICA is apparent with Gd-BOPTA.

DISCUSSION

MR imaging of the supraaortic vasculature is inherently challenging because of the rapid arterial-venous circulation time in the brain and the complexity of the intracranial circulation.[38] Although noncontrast TOF imaging approaches are frequently used for MR imaging of the supraaortic vasculature[39,40] and would benefit from the 2-fold higher baseline SNR at 3T compared with 1.5T,[41] these approaches are limited by relatively long acquisition times leading to venous imposition and motion artifacts, and by progressive saturation of distal arterial branches during image acquisition leading to an overall reduction of diagnostic accuracy.[42] As a consequence, imaging approaches involving the use of exogenous contrast agent are today in widespread use both at 1.5T[12,14,43–45] and at 3T.[14,18,20,46,47]

As regards imaging of the supraaortic vessels at 3T, studies have shown this to be superior to both noncontrast TOF MRA[20] and ceMRA at 1.5T.[46] However, to date, most published studies on the role of ceMRA at 3T have used conventional gadolinium contrast agents,[18–20,46] often at a double dose of 0.2 mmol/kg bodyweight.[18,19] Just one comparatively small-scale study in 7 patients with suspected giant cell arteritis used Gd-BOPTA at a dose of 0.1 mmol/kg bodyweight; that study demonstrated excellent image quality from the cranial and temporal arteries of the head to the aortic arch and subclavian arteries.[47]

The results of our study not only support the findings of Markl et al[47] in demonstrating excellent image quality with Gd-BOPTA at a dose of 0.1 mmol/kg bodyweight, but show also that the image quality, vessel delineation, and contrast enhancement (rCNR) achieved is significantly superior to that obtained with an identical dose of the conventional gadolinium contrast agent, Gd-DTPA. The overall improved image quality obtained from blinded randomized assessment of separate image sets was confirmed in the matched-pairs

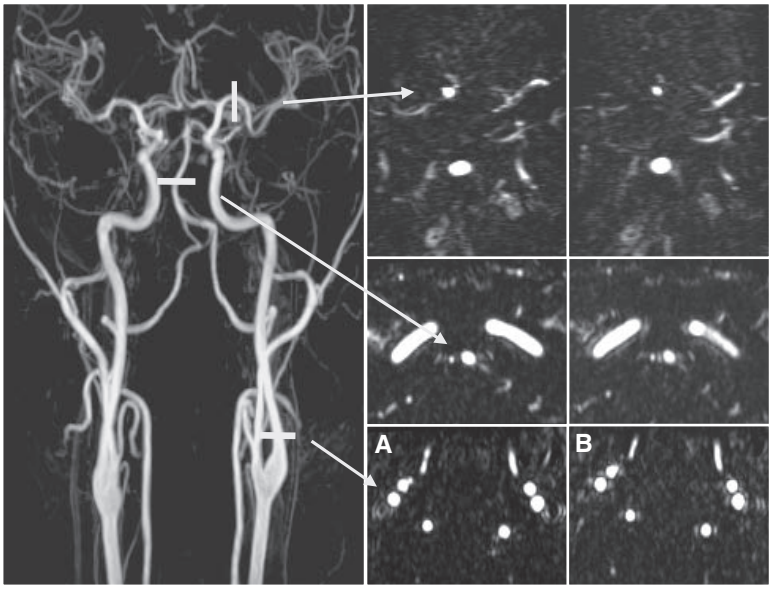


FIGURE 4. Placement of the ROIs in the ICA, M1 segment of the MCA, and BA. Quantitative measurements of the SI at these ROIs revealed higher and more homogeneous signal with (A) Gd-BOPTA compared with (B) Gd-DTPA.

TABLE 3. Quantitative Signal Intensity Measurements in the ICA, MCA-M1, and BA

	ICA		MCA-M1		BA	
	Gd-BOPTA	**Gd-DTPA**	**Gd-BOPTA**	**Gd-DTPA**	**Gd-BOPTA**	**Gd-DTPA**
Mean ± standard deviation	890.4 ± 92.5	782.6 ± 108.6	643.1 ± 107.8	546.1 ± 120.1	700.6 ± 77.1	588.4 ± 86.8
Range (min, max)	660.8; 1023.0	536.7; 896.8	422.0; 828.1	372.4; 744.9	550.4; 807.0	433.6; 748.8
P	0.002		0.021		0.003	

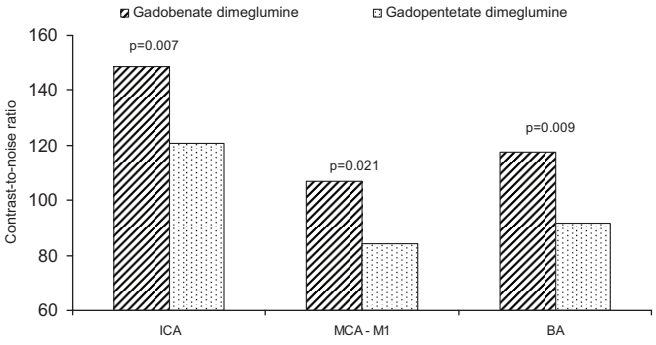


FIGURE 5. Mean relative contrast-to-noise ratios in the ICA, MCA, and BA after administration of Gd-BOPTA and Gd-DTPA.

analysis in which Gd-BOPTA was preferred globally for 10 of 12 volunteers and for at least 9 of 12 volunteers for specific comparisons of the extracranial vessels, vessels of the Circle of Willis and vessels distal to the Circle of Willis. As with other direct intra-individual crossover comparisons of Gd-BOPTA with Gd-DTPA and other conventional agents for both ceMRA[32,33,36,37] and other MR applications[48–53] at 1.5T, the improved image quality and potentially better diagnostic performance can be ascribed to the greater r1 relaxivity of Gd-BOPTA deriving from weak, transient interaction of the Gd-BOPTA chelate with serum albumin.[21–24,30,31] A recent study in a rat brain tumor model has shown that the increased r1 relaxivity of 0.1 mmol/kg Gd-BOPTA leads to significantly higher CNR at 3T compared with 1.5T and that the CNR achieved at 3T with 0.1 mmol/kg Gd-BOPTA is significantly greater than that achieved with Gd-DTPA at equivalent dose.[54] Other recent studies have shown that the increased r1 relaxivity of Gd-BOPTA is particularly beneficial for maintaining sufficient SNR when used in combination with highly accelerated parallel acquisitions at 3T.[55]

Concerning the significantly greater rCNR obtained with Gd-BOPTA, this ranged from 23.3% in the ICA to 28.5% in the BA. Increases of similar magnitude have been reported elsewhere for intra-individual comparisons of Gd-BOPTA and Gd-DTPA in patients with tumors of the central nervous system,[50,51] and were considered analogous to the increase in contrast enhancement seen with a double dose of conventional gadolinium agent compared with a single dose.[56] Given the roughly 2-fold greater r1 relaxivity of Gd-BOPTA compared with Gd-DTPA,[21–23] a significant increase of rCNR of this magnitude might be expected. From a clinical perspective, the benefits of this increased rCNR might be particularly evident in the more distal cerebral arteries and arterial segments where contrast enhancement is typically reduced relative to that in the major arteries and more proximal segments. This was shown in our study by the

vessel delineation scores for the MCA, which, despite dropping off between segments M1 and M3, were nevertheless consistently higher with Gd-BOPTA. The possibility to obtain excellent image quality at 3T with just a single 0.1 mmol/kg bodyweight dose of Gd-BOPTA might obviate the need for higher doses of conventional agent,[18,19] which would clearly be beneficial in terms of patient safety and cost-effectiveness. Moreover, the need for just a single dose of contrast agent might be particularly attractive given the current widespread concern over the use of higher doses, particularly in patients with renal insufficiency.[57]

Although the results of this study consistently show significant benefits for Gd-BOPTA relative to Gd-DTPA for ceMRA of the supraaortic vessels at 3T, the study is limited in that only 12 healthy volunteers were evaluated and that the average age of the volunteers (27.9 years) was considerably lower than that of patients likely to develop occlusive disease of this vascular territory. Further studies in larger volunteer and patient populations are clearly warranted to confirm these preliminary findings, although it is to be expected that the benefits noted in our population in terms of improved contrast enhancement with Gd-BOPTA will be maintained in older patient populations irrespective of the severity of disease.

A second limitation, and a potential bias against Gd-BOPTA, is that the ceMRA sequence parameters were optimized for use with Gd-DTPA and other conventional gadolinium agents rather than Gd-BOPTA. Recent in vitro work at 1.5T and 3T has shown that increased SI enhancement can be achieved by modifying the sequence parameters to take into account the unique physicochemical properties of Gd-BOPTA. Specifically, the optimal repetition time and echo time lengths are shorter for Gd-BOPTA than for Gd-DTPA and other conventional agents at all magnetic field strengths including 3T.[58,59] The benefit of adapting standard imaging and assessment approaches to take into account the increased relaxivity and increased SI enhancement achievable with Gd-BOPTA has recently been demonstrated for breast MRI.[60] A controlled in vivo study should certainly be performed to determine whether modification of the ceMRA acquisition parameters would further benefit the image quality achievable with Gd-BOPTA at 3T. Similarly, further work should also be performed to compare a lower dose of Gd-BOPTA with standard dose Gd-DTPA for ceMRA of the supraaortic vessels. Given that a standard 0.1 mmol/kg dose of Gd-BOPTA has previously been shown to be superior to a double 0.2 mmol/kg dose of Gd-DTPA in this vascular territory[37] and that a single dose of Gd-BOPTA is at least equivalent to a double dose of Gd-DTPA for ceMRA of the renal arteries,[36] it is conceivable that a lower (half) dose of Gd-BOPTA may be sufficient to obtain equivalent vessel enhancement to that obtained with 0.1 mmol/kg Gd-DTPA, particularly if the acquisition parameters are optimized appropriately for use with Gd-BOPTA.

A final possible limitation of the study is that comparison with noncontrast TOF imaging was not performed. Although a comparison of this type would be of considerable interest in a large patient population given the greater available SNR at 3T, it was not considered appropriate in this case given that the study aim was to compare 2 MR contrast agents for contrast enhancement and supraaortic vessel visualization. Nevertheless, additional work should certainly focus on comparing optimized noncontrast and contrast-enhanced approaches, not only in terms of diagnostic performance but also in terms of protocol feasibility and clinical applicability given the longer acquisition times of the noncontrast sequences.

In conclusion, our study reveals significantly better qualitative and quantitative contrast enhancement of the supraaortic vessels with Gd-BOPTA compared with Gd-DTPA when these 2 agents are compared intra-individually at 0.1 mmol/kg bodyweight using identical ceMRA sequence parameters at 3T.

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