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ORIGINAL RESEARCH

MR Angiographic Follow-Up of Intracranial Aneurysms Treated with Detachable Coils: Evaluation of a Blood-Pool Contrast Media

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BACKGROUND AND PURPOSE: Blood-pool agents are promising in the imaging of small vessels with slow or complex flow. Our aim was to compare blood-pool contrast-enhanced MR angiography (BPCE-MRA) using gadofosveset trisodium (Vasovist) with 3D time-of-flight MRA (TOF-MRA) in the follow-up of intracranial aneurysms after endovascular therapy.

MATERIALS AND METHODS: We included 32 patients with a total of 37 coiled aneurysms. MRAs in the early steady-state phase were performed on a 1.5T scanner within 8 days of digital subtraction angiography (DSA). Two radiologists independently analyzed TOF-MRA and BPCE-MRA images. Consensus was reached by review involving a third neuroradiologist. DSA images were interpreted separately by an interventional radiologist. Findings were assigned to 1 of 3 categories: 1) complete occlusion, 2) residual neck, and 3) residual aneurysm.

RESULTS: Follow-up DSA demonstrated 13 complete obliterations (class 1), 13 residual necks (class 2), and 11 residual aneurysms (class 3). Weighted κ statistics showed substantial concordance of TOF-MRA and DSA (0.664) as well as BPCE-MRA and DSA (0.724) ratings. Comparison between TOF-MRA and BPCE-MRA found excellent agreement (0.818) with only 6 (16.2%) discrepancies. For detecting residual flow, the difference in accuracy of both MRA techniques (83.8% versus 91.9%) was not significant (McNemar, $P = 1.000$). BPCE-MRA showed a tendency towards higher sensitivity and specificity (91.7% and 92.3%, respectively) compared with TOF-MRA (87.5% and 76.9%).

CONCLUSIONS: In classifying the completeness of endovascular cerebral aneurysm therapy, we found that BPCE-MRA and 3D TOF-MRA showed very good agreement. The use of Vasovist did not lead to a significantly increased accuracy of MRA follow-up.

In the management of incidental intracranial aneurysms, selective endovascular treatment with detachable coils (DCs) is a well-established alternative to surgical clipping, whereas in ruptured aneurysms, coiling is the first choice.[1-3] The goal of coiling is to exclude the aneurysm from circulation by filling it with platinum microcoils and the use of microcatheters. Completeness of occlusion is commonly used as a measure of the success of therapy. However, even in cases of initial total occlusion, aneurysm recurrence is not uncommon.[3-7] According to outcome studies, patients after subtotal embolization treatment may be at increased risk for subarachnoid hemorrhage.[8] Follow-up imaging to detect eventual progression of aneurysm recanalization is recommended to assess the need for further treatment.[6,7,9] Mainly because of its inherent high spatial resolution, digital subtraction angiography (DSA) is considered the reference standard.[6]

MR angiography (MRA) provides a noninvasive alternative with generally less discomfort and morbidity for patients. A number of studies have evaluated the potential of 3D time-of-flight (TOF) MRA to partly replace DSA.[10-34] Relatively long scanning time and, moreover, spin dephasing and saturation constitute major limitations of 3D TOF-MRA.[10,13] Although some authors have not used contrast material,[10-14,16-20,23,29,33,35] some have used contrast-enhanced MRA (CE-MRA) to increase signal intensity in residual pouches.[7,15,17,21,22,24-28,31,32,34] The added value of arterial contrast enhancement in the follow-up of coiled aneurysms, however, remains controversial, and venous enhancement often degrades image quality.[15,17,25,31,32]

Blood-pool contrast media (BPCM) remain in the intravascular space for a longer time, therefore permitting both first-pass and delayed steady-state imaging.[36-38] Gadofosveset trisodium (Vasovist; Bayer Schering Pharma, Berlin, Germany) has been the first BPCM with an application filed with the US Food and Drug Administration and approval in the European Union, Switzerland, Canada, and Australia for CE-MRA.[39-41] This contrast medium is reversibly protein-bound in human plasma, resulting in a marked increase in relaxivity and, hence, a stronger T1 shortening effect compared with conventional gadolinium-based contrast agents. Its blood retention time is substantially prolonged.[38,42-45]

To our knowledge, this is the first report to address the role of BPCM for the follow-up of intracranial aneurysms after endovascular therapy. Our hypothesis was that they may be superior in contrasting vessels with slow or complex flow, like aneurysm remnants.[38,46] The aim of this study was to evaluate how accurately BPCM-enhanced MRA (BPCE-MRA) using Vasovist in the early steady-state phase could classify the completeness of DC treatment and to compare its diagnostic performance with 3D TOF-MRA. We did not focus on the therapeutic implications of follow-up results.

Materials and Methods

Patients

Thirty-two consecutive patients (13 men, 19 women) with a total of 37 aneurysms (16 in men, 21 in women) previously treated with DCs

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indicates article with supplemental on-line table.

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but without the use of stents were included in this retrospective study (On-line Table 1). The mean age was 52.2 years (age median, 51.5 years). Three men and 2 women had been treated for 2 aneurysms each. Twenty-five patients had experienced subarachnoid hemorrhage. In the remaining 7 patients, aneurysms were discovered incidentally or because of symptoms caused by their mass effect.

Twenty-eight aneurysms (75.7%) were located in the anterior circulation (internal carotid artery [ICA], 7; anterior cerebral artery, 1; anterior communicating artery, 9; pericallosal artery, 3; middle cerebral artery, 6; posterior communicating artery, 2), and 9 aneurysms (24.3%) were located in the posterior circulation (vertebrobasilar junction, 1; basilar artery, 7; posterior cerebral artery, 1). Taking the largest diameters for statistical calculations, we found a mean value of 7.5 mm (median, 7 mm) for initial aneurysm size. The mean size of aneurysm remnants at follow-up was 1.9 mm (median, 1 mm).

TOF- and CE-MRA examinations were performed at the same sitting in all cases and within 8 days of DSA. The interval between treatment and DSA follow-up examinations ranged from 3 to 19 months, with a median follow-up period of 12 months.

Image Acquisition

MRA was performed on an Intera 1.5T system (Philips Medical Systems, Best, the Netherlands) by using a standard 6-channel head coil, a sensitivity encoding factor of 2, and contrast-enhanced timing robust angiography (CENTRA) *k*-space acquisition. 3D TOF images were obtained with the following parameters: FOV, 230 mm; TR/TE, 25/6.9 ms; flip angle, 25°; axial plane; acquired voxel size, 0.44 × 0.81 × 1.0; reconstructed voxel size, 0.45 × 0.45 × 0.5; acquisition time, 4.36 minutes. The following protocol was used to acquire a CE-MRA sequence: FOV, 280 mm; TR/TE, 10/2.5 ms; flip angle, 25°; coronal plane; acquired voxel size, 0.5 × 0.5 × 0.5; reconstructed voxel size, 0.5 × 0.5 × 0.5; number of acquisitions, 1; acquisition time, 3.0 minutes. A bolus of 0.12 mL/kg of body weight of Vasovist was administered by hand at an injection rate of approximately 1 mL/s. Scanning was started 60 seconds after contrast application. Postprocessing on a ViewForum workstation (Philips Medical Systems) included the reconstruction of thin multiplanar maximum-intensity-projection (MIP) images (slab thickness, 10 mm). In addition, 3D images were reconstructed for the purpose of presentation.

All DSA examinations were performed on an Axiom Artis dBA biplane angiography system equipped with flat panel detectors (Siemens Medical Solutions, Erlangen, Germany) with a matrix of 2k. Selective catheterization of the internal carotid and vertebral arteries was performed via a transfemoral approach. DSA images were obtained in multiple views, including the working views determined during preoperative DSA and rotational angiography with 3D reconstructions. For the ICA, a bolus of 6 mL of nonionic contrast material was injected at 5 mL/s during each acquisition with a power injector. For the vertebral artery, 5 mL of contrast material was injected at a rate of 4 mL/s.

Image Interpretation

The reconstructions of MRA source images and targeted MIP images were interpreted in a blinded fashion by 2 radiologists (S.C. and E.R., 5 years of experience each) who were not aware of the DSA findings. The imaging studies were presented to both readers in a pseudorandom order for a second time 3 weeks later. Cases that led to a disagreement between observers were reviewed by both readers and an experienced neuroradiologist (J.G.) to reach a consensus.[47] DSA images were interpreted independently by a dedicated specialist in interventional radiology (K.A.H.), who was not aware of the MRA findings. DSA was the technique of reference. The results of DSA and MRA were graded according to the primarily descriptive classification of Raymond et al.[48] Each aneurysm was assigned to 1 of 3 categories as follows: class 1, complete occlusion; class 2, residual neck (including so-called "dog ear"); class 3, residual aneurysm.

Statistical Analysis

The first step of the analysis consisted of an evaluation of the level of inter- and intraobserver agreement for MRA image interpretation by the means of weighted κ statistics. In a second step, a comparison between MRA techniques and DSA for the detection of a residual neck or aneurysm was made with the use of the same statistical test. κ values >0.6 suggested substantial agreement, and values >0.8 indicated excellent agreement. Third, sensitivity, specificity, and positive and negative predictive values were calculated for the ability of BPCE-MRA and TOF-MRA to differentiate between complete occlusion of an aneurysm (class 1) and residual flow (classes 2 and 3). The accuracy of both MRA techniques was compared with the reference standard DSA and between the 2 techniques by using the McNemar test to assess the level of significance. P values $<.05$ were regarded as significant.

Results

Image Quality

Assessment of the quality of aneurysm occlusion on MR angiograms was judged possible by both readers for all 37 aneurysms in 32 patients. Venous overlaps were present on all CE MR angiograms (especially at the cavernous sinus) and on none of the nonenhanced images.

Comparison of MRA Techniques

Inter-rater agreement in classifying results of endovascular aneurysm therapy from BPCE-MRA studies was considered substantial (weighted $\kappa = 0.687$) in our series. Intrarater reliability for both readers was substantial (E.R., weighted $\kappa = 0.746$) and excellent (S.C., weighted $\kappa = 0.811$).

In DSA follow-up, residual aneurysms were revealed in 11 cases (29.7%), whereas a—partly minimal and, therefore, not necessarily relevant—neck remnant was found in 13 aneurysms (35.1%). In the remaining 13 aneurysms (35.2%), embolization was considered complete. Consensus reading of BPCE-MRA results found residual aneurysms in 11 cases (29.7%), neck remnants in 12 aneurysms (32.4%), and complete occlusion in 14 cases (37.8%). In TOF-MRA follow-up, residual aneurysms and neck remnants were revealed in 12 cases (32.4%) each, whereas embolization was considered complete in the remaining 13 aneurysms (35.2%).

For accurate classification according to the scale of the 3 classes of Raymond et al (On-line Table 1), weighted κ statistics found excellent agreement (weighted $\kappa = 0.818$) between TOF-MRA and BPCE-MRA (Figs 1 and 2). The level of agreement with the reference standard DSA was substantial for both BPCE-MRA (weighted $\kappa = 0.724$) and TOF-MRA (weighted $\kappa = 0.664$). When we differentiated complete occlusion (class 1) from residual lumen within an aneurysm (classes 2 and 3), BPCE-MRA using Vasovist showed a tendency toward higher accuracy (91.9%; sensitivity, 91.7%; specificity, 92.3%; positive predictive value, 95.7%; negative predictive value, 85.7%)

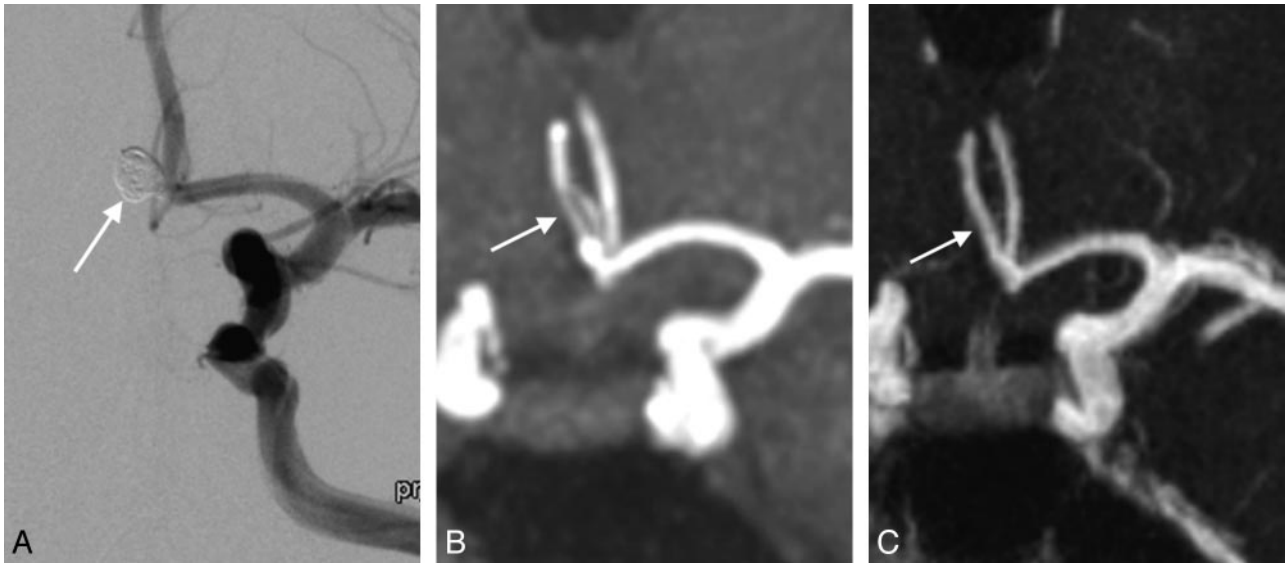

Fig 1. DSA. *A*, Half-axial anteroposterior (Towne's) projection confirms complete occlusion after coiling of an anterior communicating artery aneurysm (*arrow*). *B* and *C*, In 3D TOF-MRA with coronal MIP reconstruction (*B*), the right-sided A2 segment (*arrow*) shows narrowing, whereas in the BPCE-MRA using Vasovist (*arrow, C*), it does not.

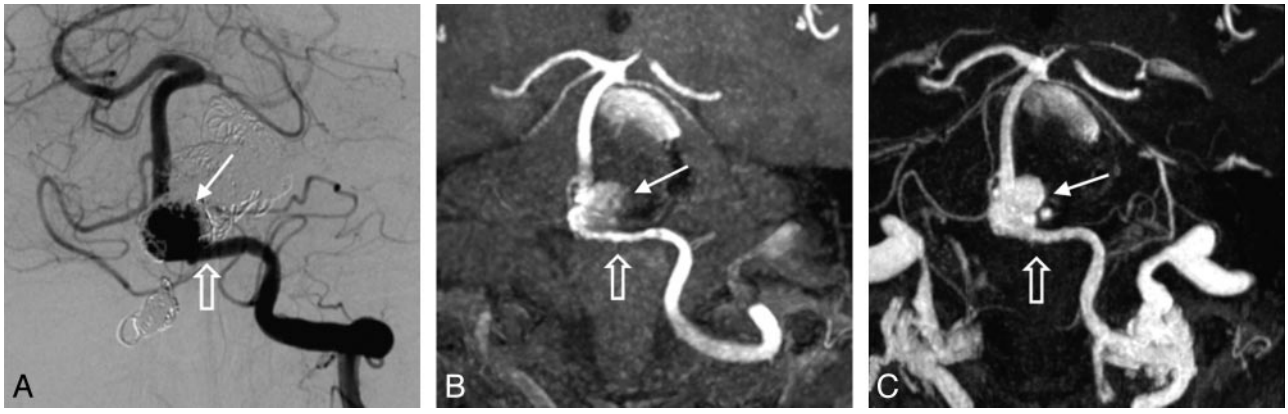

Fig 2. DSA. *A–C*, Frontal projection shows a large residual aneurysm at the vertebrobasilar junction (*arrow*), which might be primarily due to coil compaction. The parent vessel is patent, as confirmed by all 3 angiographic techniques (*broad arrows, A–C*). Coronal MIPs of both BPCE-MRA (*C*) and TOF-MRA (*B*) allow accurate classification according to Raymond et al; however, the signal intensity of residual flow was much higher and more defined after injection of Vasovist (*arrow, C*) than without a contrast agent (*arrow, B*).

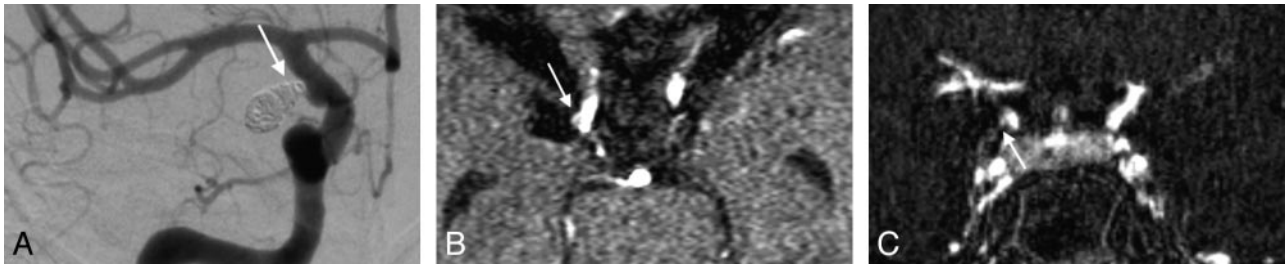

Fig 3. Complete embolization of a right ICA aneurysm (*arrow*) on DSA follow-up (oblique view, *A*). An axial source image of 3D TOF-MRA (*B*) and a coronal source image of BPCE-MRA (*C*) both show a small hyperintensity (*arrows*) falsely interpreted as a residual neck. The former may possibly be due to a partial volume effect; the latter was attributed to venous overlap.

compared with TOF-MRA (accuracy, 83.8%; sensitivity, 87.5%; specificity, 76.9%; positive predictive value, 87.5%; negative predictive value, 76.9%). This difference was, however, not significant ($P = 1.000$). Neither was DSA significantly better than 1 of the 2 MRA techniques in this regard (BPCE-MRA, $P = 1.000$; TOF-MRA, $P = .683$). Venous overlap was considered responsible for the single false-positive result of BPCE-MRA after coiling of an ICA aneurysm (Fig 3). False-negative results of BPCE-MRA were found in another 2 cases (anterior communicating artery and pericallosal artery aneurysms) in which DSA showed residual necks.

Discussion

Using completeness of coil therapy and angiographic recurrence as surrogate markers for risk of future hemorrhage from intracranial aneurysms is commonly accepted. Because the presence of a residual neck may be predictive of future recanalization, it is a worthwhile distinction to make.[48-50]

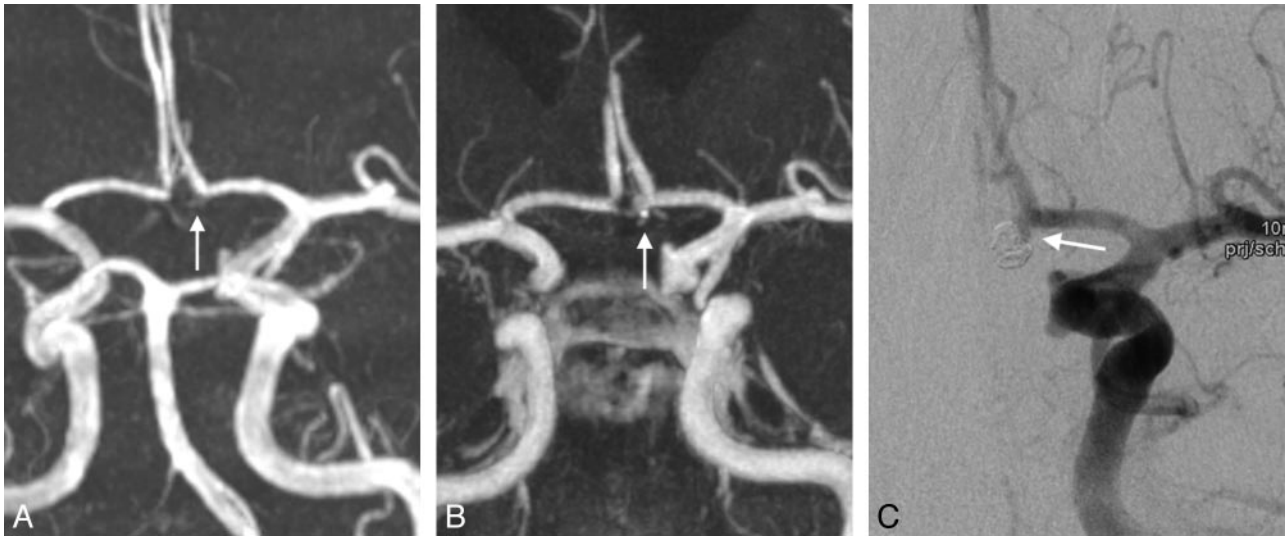

Fig 4. *A,* 3D TOF-MRA with coronal MIP reconstruction failed to detect residual flow in the basal part of a coiled anterior communicating artery aneurysm (*arrow*). *B,* Despite higher signal intensity, a suspicious structure (*arrow*) on the BPCE-MRA was misinterpreted as part of a patent vessel lumen. *C,* The residual neck (dog ear, *arrow*) is clearly depicted by DSA. Thus, both MRA techniques produced false-negative results in this case.

Raymond et al[4] described a simplified scale of 3 classes: complete, residual neck, and residual aneurysm. Even though therapeutic implications of this classification are limited, because it does not differentiate between stable and progressing remnants, the categories of Raymond et al are frequently used to compare the diagnostic accuracy of different imaging techniques. Not surprisingly, observer variability was previously shown to be substantially better in classification systems that offered fewer observer responses.[47] We, therefore, adopted the suggestion recently made by Cloft et al[47] to have >1 reader make the assessments and to have readers try to review difficult cases together to reach consensus.

MRA offers a safe and noninvasive alternative to DSA, requiring neither ionizing radiation nor iodinated contrast media. In general, MRA does not necessarily require contrast material, but CE-MRA has become a well-established technique because it is faster and flow-independent. Bolus-injectable BPCM not only allow first-pass CE-MRA with a higher relaxivity and, therefore, a lower dose than standard extracellular contrast media but also imaging in the steady-state phase with a broad time window.[46] They are particularly promising in contrasting smaller vessels, vessels with slow flow, and vessels with complex flow.[46]

In a systematic review of the literature published up to the year 2006, no statistically significant differences in pooled sensitivity and specificity were found between CE-MRA and TOF-MRA. This meta-analysis suggested that both TOF-MRA and CE-MRA achieved a moderate-to-high diagnostic performance in the follow-up of intracranial aneurysms treated with DCs. However, findings should be interpreted with caution. Not only were all pooled estimates subject to heterogeneity, but also, to that date, all studies used standard extracellular contrast media and not BPCM for CE-MRA.[30]

In their meta-analysis, Kwee and Kwee[30] calculated the pooled sensitivity and specificity of TOF-MRA for the detection of residual flow (within the aneurysmal neck and/or coil mesh) to be 83.3% and 90.6%, respectively. Pooled sensitivity and specificity of CE-MRA by using standard extracellular contrast media were found to be 86.8% and 91.9%, respectively. In our series of 37 aneurysms, sensitivity of TOF-MRA for the detection of residual flow (classes 2 and 3) was similar (87.5%) to the data presented in this meta-analysis, whereas we found a somewhat lower specificity (76.9%). Most interesting, the use of BPCM for early steady-state imaging did not lead to significantly higher sensitivity and specificity (91.7% and 92.3%, respectively) than those published for standard CE-MRA. The level of agreement with the reference standard DSA was substantial for both BPCE-MRA and TOF-MRA.

Preliminary studies have shown the potential of 3D TOF-MRA for depicting an aneurysm remnant with good spatial resolution in an acceptable time.[10-14,16-20,23,29,33,35] However, this technique is insensitive to a slow or complex flow and can interfere with the visualization of a residual neck or aneurysm (Fig 4).[26] This signal-intensity loss is attributable to intravoxel dephasing and saturation effects. Furthermore, TOF-MRA is more prone to susceptibility artifacts because of coil packing.[51] False-positive examinations were related to the presence of artifacts or intra- or extraluminal blood clot interpreted as flow at MR angiography.[11,17] High signal intensity within a thrombosed aneurysm does not necessarily represent flow but may be due to T1 shortening caused by subacute thrombosis among coil material.[11] However, it is unlikely that this was the cause of a false-positive TOF-MRA result in our series because the minimum follow-up period was 3 months (Fig 3).

Generally, CE-MRA may have potential advantages compared with the 3D TOF technique because the flow within an embolized aneurysm is complex. It is less sensitive to flow turbulences and saturation effects than TOF sequences because of the high signal intensity within the arterial lumen caused by T1 shortening effects. Contrast enhancement allows imaging of low-flow signals with higher conspicuity of a residual aneurysm. This, theoretically, may be especially true for BPCM. Moreover, CE-MRA has demonstrated a relative insensitivity to coil-related artifacts that potentially degrade image quality.[7] Furthermore, the imaging volume may be oriented in the coronal plane, which allows assessment of a larger

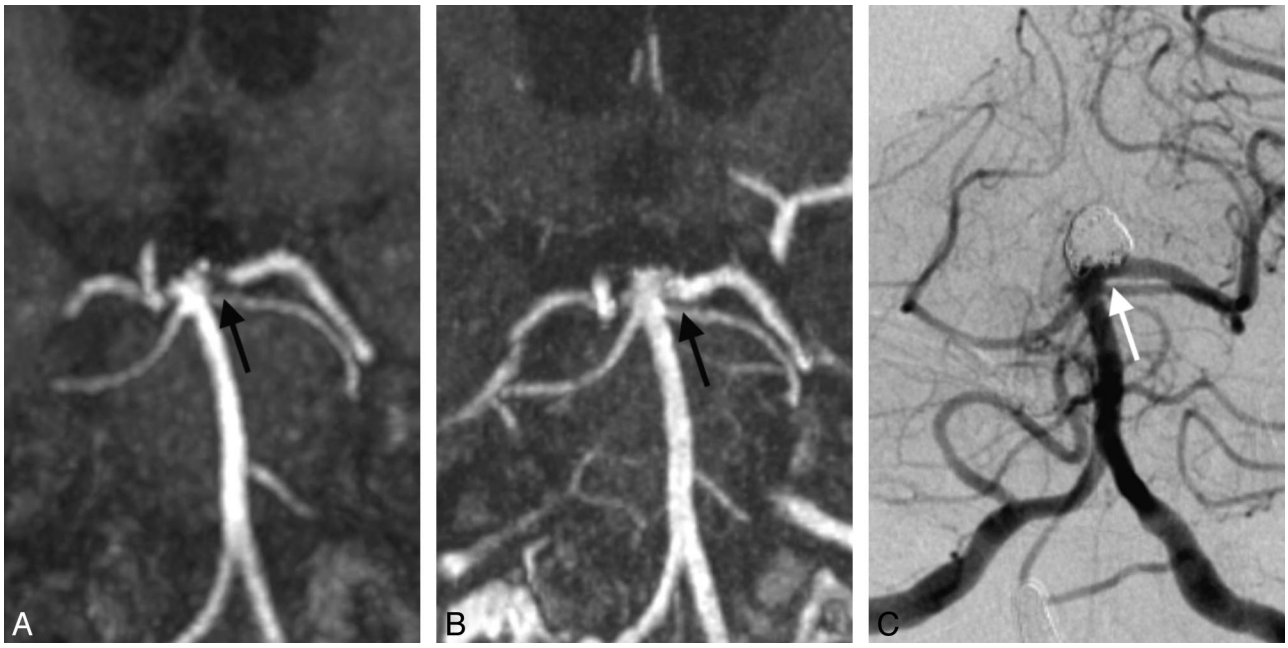

Fig 5. *A,* In the coronal MIP reconstruction of TOF-MRA, signal-intensity loss affecting the origin of the left posterior cerebral artery (*arrow*) simulates significant vessel obstruction after complete embolization of a P1 aneurysm. *B* and *C,* Conversely, BPCE-MRA (coronal MIP, *B*) found a patent parent vessel (*arrow*), which was confirmed by DSA (*arrow, C*).

volume compared with TOF-MRA. A principal disadvantage of steady-state BPCE-MRA with the use of Vasovist is that venous opacification may impede accurate delineation of aneurysm remnants. Indeed, venous overlap might have been responsible for our single false-positive result of BPCE-MRA after coiling of an ICA aneurysm. Gauvrit et al[22] discussed the possible finding of a false neck remnant in standard CE-MRA, which may be explained by peripheral contrast enhancement of the organized thrombus. Using BPCM, we were not confronted with this problem, and there is reason to believe this could be due the prolonged blood-retention time of gadofosveset.

CE-MRA may be useful for the characterization of giant aneurysm recanalization. Our own experience confirmed previous reports that the extent of recanalization was clearer with contrast material.[15,31,32] According to the literature, because of the better visualization of small arteries with CE-MRA, it may preferably be used for distal arterial aneurysms, such as those of the pericallosal artery.[25] Conversely, the only 2 false-negative results of BPCE-MRA in our series affected anterior communicating artery and pericallosal artery aneurysms. The first case might be attributable to misinterpretation of a CE structure that—in synopsis with DSA—represented a class 1 residual filling (Fig 4). In the latter case, the residual neck as confirmed by DSA was <2 mm in diameter. Most probably, a discrete irregularity of the pericallosal artery might have been underestimated during interpretation of Vasovist-enhanced MRA.

Our study hypothesis that early steady-state BPCE-MRA using Vasovist might be considerably more accurate than TOF-MRA in assessing completeness of endovascular aneurysm therapy had to be rejected. With respect to the scale of the 3 classes of Raymond et al, weighted statistical analysis found excellent agreement between TOF-MRA and BPCE-MRA.[48] Albeit showing a tendency toward higher accuracy in differentiating complete occlusion from residual lumen/flow within an aneurysm, early steady-state BPCE-MRA using Vasovist (accuracy, 91.9%) failed to be significantly superior compared with TOF-MRA (accuracy, 83.8%), and DSA was not significantly better than 1 of the 2 MRA techniques in this regard.

There is controversy in the literature about the benefit of contrast material injection for analyzing the patency of parent and adjacent arteries in the vicinity of the aneurysm.[17] Contrary to BPCE-MRA with Vasovist, TOF-MRA failed to delineate the parent vessel of the aneurysm in 2 cases in our series (Fig 5). On the other hand, Vasovist CE-MRA showed a tendency to provide higher signal intensity and a sharper definition of the parent vessel (Figs 1 and 2). Although we did not further evaluate this feature, one may more confidently consider an aneurysm occluded if the parent artery is entirely evident. On the other hand, if images fail to depict the parent vessel, it is impossible to determine aneurysm occlusion or patency. Higher signal intensity and sharper definition of parent vessels may also be achieved by using scanners with higher field strengths.[32] However, Buhk et al[52] found no general advantage of TOF-MRA at 3T compared with 1.5T in the follow-up of coiled cerebral aneurysms.

The present study has several shortcomings, one of which is a general limitation of the classification scale of Raymond et al and its clinical implication.[48] First, an aneurysm may have a worsening degree of occlusion at follow-up, yet it may not change categories on a certain grading scale.[17] Second, there is still no agreement on the definition of recurrence after aneurysm coiling.[42,48] Third, even if one might suspect that an important marker of failure of aneurysm therapy is the need for retreatment, this necessity is currently not something that can be objectively measured. Rather, the decision to retreat is quite subjective in many cases as noted by Cloft et al.[47] Regardless, the aim of our study was to compare 2 imaging techniques

using the scale of Raymond et al and not to evaluate the therapeutic relevance of this classification.

Another limitation is related to aneurysm size, which was reported to have an impact on the sensitivity of TOF-MRA for the detection of reperfusion or residual flow.[29] The study population was not large enough to allow detailed subgroup analysis. However, the size of an aneurysm and its parent vessel was hypothesized to play a minor role in the use of BPCM for CE-MRA.[25,46] As is true for several similar studies in this field, the follow-up period covered a rather wide time span of 3–19 months, and the time interval between DSA and MRA was ≤8 days. This is attributable to the retrospective nature of our study and the fact that there is no commonly accepted follow-up protocol.

There is also considerable uncertainty about the optimal scanning parameters for the use of blood-pool agents in the evaluation of intracranial vessels. First-pass acquisition can be expected to provide a high signal intensity–to-noise ratio (SNR) due to an increased relaxivity of Vasovist, whereas imaging in the steady-state phase will gain a higher spatial resolution, which is its most striking advantage compared with conventional contrast media. Our BPCE-MRA protocol with an acquisition delay of 60 seconds was intended to be a compromise between the benefits of first-pass and steady-state phase imaging. By doing so, we accepted that true steady-state was not yet established; therefore, spatial resolution was not at its maximum. On the other hand, we intended to keep the SNR reasonably high and venous overlap at an acceptably low level. Because only a single false-negative case in our series may possibly be explained by a lack of high and homogeneous intravascular signal intensity, there is no evidence to conclude that the gadolinium dose should be increased for BPCE-MRA in the follow-up of intracranial aneurysms.

Conclusions

In our series of 37 intracranial aneurysms treated with DCs, both 3D TOF-MRA and BPCE-MRA achieved a high diagnostic performance in the detection of incomplete embolization. Except in cavernous ICA aneurysms, Vasovist-enhanced MRA may give more confidence to image interpretation by defining the extent of the residual lumen more clearly and by providing a sharper delineation of the parent vessel. However, the level of agreement between both MRA techniques was excellent in the follow-up assessment according to the criteria of Raymond et al, and BPCE-MRA failed to be significantly more accurate than TOF-MRA. Large studies allowing subgroup analysis with respect to aneurysm size and location are needed to decide whether DSA follow-up can be replaced by MRA, with or without the use of BPCM.

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