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Time-resolved imaging of contrast kinetics does not improve performance of follow-up MRA of embolized intracranial aneurysms

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The use of contrast media and the time-resolved imaging of contrast kinetics (TRICKS) technique have some theoretical advantages over time-of-flight magnetic resonance angiography (TOF-MRA) in the follow-up of intracranial aneurysms after endovascular treatment. We prospectively compared the diagnostic performance of TRICKS and TOF-MRA with digital subtracted angiography (DSA) in the assessment of occlusion of embolized aneurysms.

Material/Methods: Seventy-two consecutive patients with 72 aneurysms were examined 3 months after embolization. Test characteristics of TOF-MRA and TRICKS were calculated for the detection of residual flow. The results of quantification of flow were compared with weighted kappa. Intraobserver and interobserver reproducibility was determined.

Results: The sensitivity of TOF-MRA was 85% (95% CI, 65–96%) and of TRICKS, 89% (95% CI, 70–97%). The specificity of both methods was 91% (95% CI, 79–98%). The accuracy of the flow quantification ranged from 0.76 (TOF-MRA) to 0.83 (TRICKS). There was no significant difference between the methods in the area under the ROC curve regarding both the detection and the quantification of flow. Intraobserver reproducibility was very good with both techniques (kappa, 0.86–0.89). The interobserver reproducibility was moderate for TOF-MRA and very good for TRICKS (kappa, 0.74–0.80).

Conclusions: In this study, TOF-MRA and TRICKS presented similar diagnostic performance; therefore, the use of time-resolved contrast-enhanced MRA is not justified in the follow-up of embolized aneurysms.

key words: intracranial aneurysms • embolization • follow-up studies • magnetic resonance angiography

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Background

Endovascular embolization has become a method of choice for the treatment of intracranial aneurysms in many centers [1,2]. However, an important disadvantage of aneurysm coiling is the observed significant rate of recanalization that occurs on average in 20% of patients [3,4]. Therefore, follow-up imaging of coiled aneurysms is recommended to prevent aneurysm recurrence and possible subsequent subarachnoid hemorrhage [5–7].

The role of intra-arterial digital subtraction angiography (DSA) as a standard follow-up method for embolized aneurysms has been questioned [6] because of its invasiveness, need for hospitalization and relatively high cost. Instead, magnetic resonance angiography (MRA) has been proposed for this purpose as being less invasive and presenting very good accuracy in detecting residual flow in aneurysms [8–10].

The question of whether time-of-flight MRA (TOF-MRA) or contrast-enhanced MRA (CE-MRA) is a better method for aneurysm follow-up remains unresolved [11]. Despite a higher signal intensity and a higher signal-to-noise ratio of CE-MRA, both techniques present similar specificity and sensitivity in detecting residual flow in aneurysms [8,10]. The most common disadvantages of CE-MRA include vessel overlapping and venous enhancement [8,10,12]. These drawbacks may be overcome by using time-resolved CE-MRA, which enables imaging of cerebral vessels in several consecutive phases of contrast medium inflow.

This study was a prospective comparison of the diagnostic value of TOF-MRA and time-resolved CE-MRA at follow-up of embolized intracranial aneurysms regarding the determination of aneurysm occlusion.

Material and Methods

Population

The study was approved by the university institutional review board and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study was based on a population of patients that participated in a prospective single-center study comparing the diagnostic value of DSA and MRA in the follow-up of ruptured intracranial aneurysms (Serafin Z. et al., unpublished data, 2011).

Patients treated for subarachnoid hemorrhage due to aneurysm rupture, who presented for the first follow-up imaging at 3 months after the procedure, were included in the study. The exclusion criteria were: (a) age under 18 years; (b) contraindications to MR imaging, including severe claustrophobia, ferromagnetic foreign bodies or electronic implants; (c) the presence of neurosurgical clips; and (d) estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.

Embolizations were performed using platinum coils (GDC Detachable Coils, Boston Scientific, Natick, USA; Axium and Nexus, ev3 Corporate, Plymouth, USA; MicroPlex, MicroVention, Inc., Tustin, USA) and hydrogel coils (HydroCoil and HydroSoft, MicroVention, Inc., Tustin, USA). In 8 patients with broad-neck aneurysms, intracranial stents (Neuroform3, Boston Scientific, Natick, USA) were implanted prior to the coiling to achieve a better packing density and to prevent coil prolapse to the parent artery. After the embolization, the baseline status of the aneurysm was documented by DSA, including both 2-dimensional (2D) and 3-dimensional (3D) acquisitions.

Follow-up technique

Follow-up DSA was performed using a monoplane angiographic unit (Axiom Artis dTA, Siemens Medical Systems, Erlangen, Germany) by means of transfemoral catheterization. The examination included 4-vessel 2-D DSA and 3-D DSA of an artery with an embolized aneurysm. The contrast agent (iopromide, Ultravist 300 mg-I/mL, Bayer Schering Pharma AG, Berlin, Germany) was administered with a power injector through a 5-F catheter. Images were analyzed on a dedicated workstation (Syngo XVP VA72B, Siemens AG, Berlin, Germany) using InSpace 3-D software.

MR angiography was performed with a 1.5 T Signa HDx unit, using an 8-channel HD Brain Coil (GE Medical Systems, Waukesha, WI, USA) within 24 hours after DSA. The examination consisted of 2 sequences: TOF-MRA and time-resolved imaging of contrast kinetics (TRICKS). TOF-MRA was performed with a 3-D TOF ASSET Multislab technique in an axial plane (TE 2.7 ms, TR 30 ms, flip angle 20°, bandwidth 31.25 kHz, section thickness 1.2 mm, matrix 320×224). TRICKS acquisition consisted of 6 3-D phases in a coronal plane (TE 1.5 ms, TR 3.5 ms, flip angle 25°, bandwidth 83.33 kHz, section thickness 2.2 mm, matrix 288×192, temporal resolution 3 s). Contrast medium (gadobenate dimeglumine, Gd-BOPTA, MultiHance, 0.5 mmol/mL, Bracco Imaging Deutschland GmbH, Konstanz, Germany) was administered by a power injection in a dose of 0.1 mmol/kg b.w. at 2 mL/s and was followed by a saline flush. The final analysis was based on a phase that presented optimal delineation of arteries without significant contamination by venous enhancement (Figure 1). Angiograms were evaluated with Advantage Workstation 4.4 and Volume Share 8.4.3 software (GE Medical Systems, Waukesha, WI, USA). The analysis included non-reconstructed images, as well as MPR, MIP and VR reconstructions.

Image analysis

The examinations were independently assessed by 2 interventional neuroradiologists (Z.S, P.S.) with 10 years of experience in the field. The observers evaluated blinded data, and were unaware of the other imaging results of the patient. Discordant results were resolved by means of joint reassessment. Images were evaluated for the detection of residual flow in the aneurysm, quantification of the flow (ie, classification of the degree of aneurysm occlusion (class 1-3 according to Roy et al. [13]), and possibility of retreatment.

Index tests included TOF-MRA and TRICKS. The reference result was established retrospectively when results of index tests were set in all the study participants. The reference test was DSA, which constituted a simultaneous analysis of 2-D DSA images, 3-D DSA VR reconstructions, and source rotational DSA images. All discrepancies between DSA images were resolved by consensus.

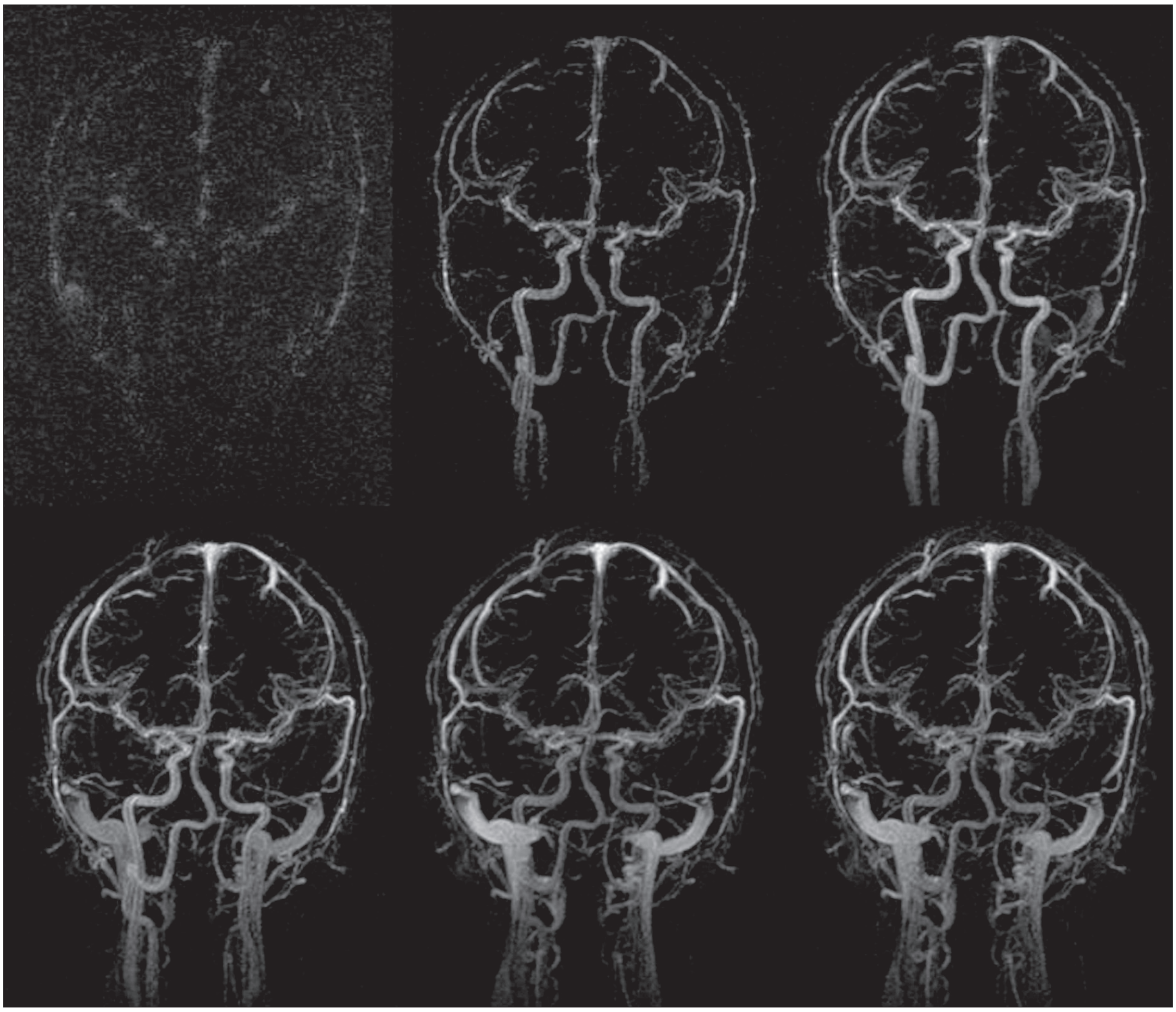

Figure 1. Consecutive phases of cerebral TRICKS angiography.

Calculations and statistical analysis

Parametric variables were expressed as mean values ± standard deviation (SD). The quality of visualization was graded using a subjective semiquantitative scoring method that was proposed by Gibbs et al. [14]. The TOF-MRA and TRICKS examinations were evaluated for overall quality of parent artery delineation, distal vessel identification, vascular signal intensity, and motion artifacts. Each examination was given a score on a 5-point scale: 5 signified excellent quality; 4, more than adequate quality for diagnosis; 3, adequate quality for diagnosis; 2, less than adequate quality for diagnosis; and 1, non-diagnostic. The result was a mean score given by 2 observers. The Wilcoxon signed-rank test was used to determine any statistically significant difference in image quality.

The quantitative assessment of image quality was based on calculation of contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR). Arterial signal intensity (SI_A) of the mid-segments of basilar arteries was measured on non-reconstructed images in regions of interest (ROI) of 2–3 mm^2, depending of the artery diameter. Background signal intensity (SI_B) was measured in the brain stem in ROIs of 20 mm^2 on average. The image noise was measured as the SD of air signal intensity (SD_N) outside the skull in ROIs of 20 mm^2 on average. SNR and CNR for each examination were calculated as follows: $SNR=SI_A/SD_N$; $CNR=(SI_A–SI_B)/SD_N$.

Test characteristics of TOF-MRA and TRICKS *vs.* DSA as a reference were calculated with corresponding 95% CI and expressed the ability of index tests to properly detect residual flow in the aneurysm. The test characteristics included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy. The areas under the receiver operating characteristic curves (AUCs) with their 95% CIs were also calculated. Significance of the AUC values and significance of differences between them was tested with the z-test. The ability of TOF-MRA and TRICKS to properly classify the degree of aneurysm occlusion (class 1–3) was assessed with concordance correlation coefficient (CCC) with its 95% CI and weighted Cohen's kappa (κ). Intraobserver agreement and interobserver agreement were measured with Cohen's κ with its 95% CI. A P-value of <0.05 was considered significant. Statistical analyses were performed using MedCalc 11.6.0 (MedCalc Software, Mariakerke, Belgium) and Statistica 9 (StatSoft Inc., Tulsa, USA).

Table 1. Baseline characteristics of included patients with percentages in parentheses.

Characteristic		Value	
Aneurysm location	ICA	40	(55.6%)
	ACoA/ACA	17	(23.6%)
	MCA	10	(13.9%)
	BA/VA	5	(6.9%)
Largest aneurysm diameter	small (≤5 mm)	26	(36.1%)
	medium (5.1–15 mm)	42	(58.3%)
	large (15.1–25 mm)	5	(6.9%)
	giant (>25 mm)	0	(0.0%)
Sack-to-neck ratio	≤1.5	15	(20.8%)
	1.6–2.5	36	(48.6%)
	>2.5	21	(29.2%)
Number of coils placed	≤3	15	(20.8%)
	4–6	25	(34.7%)
	> 6	32	(44.4%)
Coiling method	Platinum coils	48	(66.6%)
	Mixed coils*	24	(33.3%)
	Stent-assisted	8	(11.1%)
Result of embolization**	Class 1	64	(89.9%)
	Class 2	8	(11.1%)
	Class 3	0	(0.0%)
Vasospasm after embolization		9	(12.5%)

ICA – internal carotid artery; ACoA – anterior communicating artery; ACA – anterior cerebral artery; MCA – middle cerebral artery; BA – basilar artery; VA – vertebral artery.
* Platinum and hydrogel coils; ** according to Roy at al. [13].

Results

Between November 2009 and March 2011, 74 patients with 74 aneurysms were included in this prospective study. Two patients were excluded from the MRA group because of severe claustrophobia. Thus, 72 patients (mean age 51.5±12.4 years), including 24 men and 48 women, were finally analyzed (Table 1). There were no adverse reactions to contrast media during follow-up and there were no adverse events specifically related to DSA. All the follow-up examinations were interpretable in all the cases. The reference test revealed residual flow in 26 aneurysms (36.1%) (Figure 2). The flow area was classified as class 2 (residual neck) in 8 cases (11.1%) and as class 3 (residual aneurysm) in 18 cases (25.0%).

TOF-MRA examinations presented significantly higher quality of images compared to TRICKS examinations. The mean quality score for TOF-MRA and TRICKS images was 4.08±0.64 and 3.88±0.67, respectively (P<0.03). On the other hand, both SNR and CNR of TRICKS images were significantly higher than those of TOF-MRA – 140.5±45.8 and 84.6±28.8 compared to 200.2±146.3 and 182.0±124.3, respectively (P<0.002).

Table 2. Comparison of test characteristics of TOF-MRA and TRICKS in the detection of residual flow in the aneurysm; values with 95% CIs in parentheses.

Characteristic	TOF-MRA	TRICKS
Sensitivity (%)	84.6 (65.1–95.5)	88.5 (69.8–97.4)
Specificity (%)	91.3 (79.2–97.5)	91.3 (79.2–97.5)
PPV (%)	84.6 (65.1–95.5)	85.2 (66.3–95.7)
NPV (%)	91.3 (79.2–97.5)	93.3 (81.7–98.5)
LR+	9.7 (8.1–11.7)	10.2 (8.6–12.0)
LR-	0.17 (0.05–0.60)	0.13 (0.03–0.50)
Accuracy (%)	88.9 (81.6–96.2)	90.3 (83.3–97.1)
AUC	0.88 (0.78–0.94)	0.90 (0.81–0.96)

PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR– – negative likelihood ratio; AUC – area under the receiver operating characteristic curve.

Characteristics of TOF-MRA and TRICKS examinations are presented in Table 2. The TOF-MRA correctly diagnosed complete occlusion in 42 patients and residual flow in 22 patients, while 4 diagnoses were false-positive and 4 were false-negative (Figure 3). The class of occlusion was incorrectly determined in 11 patients. No significant susceptibility artifacts related to the coils were observed. However, in all cases treated with stent-assisted coiling, the signal intensity was slightly decreased within the stent lumen. The decrease of the signal intensity was less pronounced on TRICKS images than on TOF-MRA images and did not influence the evaluation of aneurysms. Detection of the residual flow in TRICKS was true-positive in 23 cases, false-positive in 4 cases, false-negative in 3 cases, and true-negative in 42 patients. Estimation of the occlusion class was incorrect in 8 patients.

The quantification of the occlusion status of an aneurysm was more accurate with TRICKS (κ=0.83; CCC=0.86; 95% CI: 0.79–0.91) than with TOF-MRA (κ=0.76; CCC=0.80; 95% CI: 0.70–0.87), while AUC values were not significantly different between the 2 methods (0.90, 95% CI: 0.81–0.96 and 0.88, 95% CI: 0.78–0.94, respectively).

Both TOF-MRA and TRICKS presented good or very good reproducibility for detecting the residual flow. Intraobserver agreement was 0.86 (95% CI: 0.74–0.98) for TOF-MRA and 0.89 (95% CI: 0.78–0.99) for TRICKS. Different results were noted in 6.9% and 5.6% of cases, respectively. Interobserver agreement was 0.74 (95% CI: 0.59–0.90) for TOF-MRA and 0.80 (95% CI: 0.67–0.94) for TRICKS. Different results were noted in 12.5% and 9.7% of cases, respectively.

Discussion

Despite the fact that for many years DSA has been a standard diagnostic method for follow-up of embolized aneurysms

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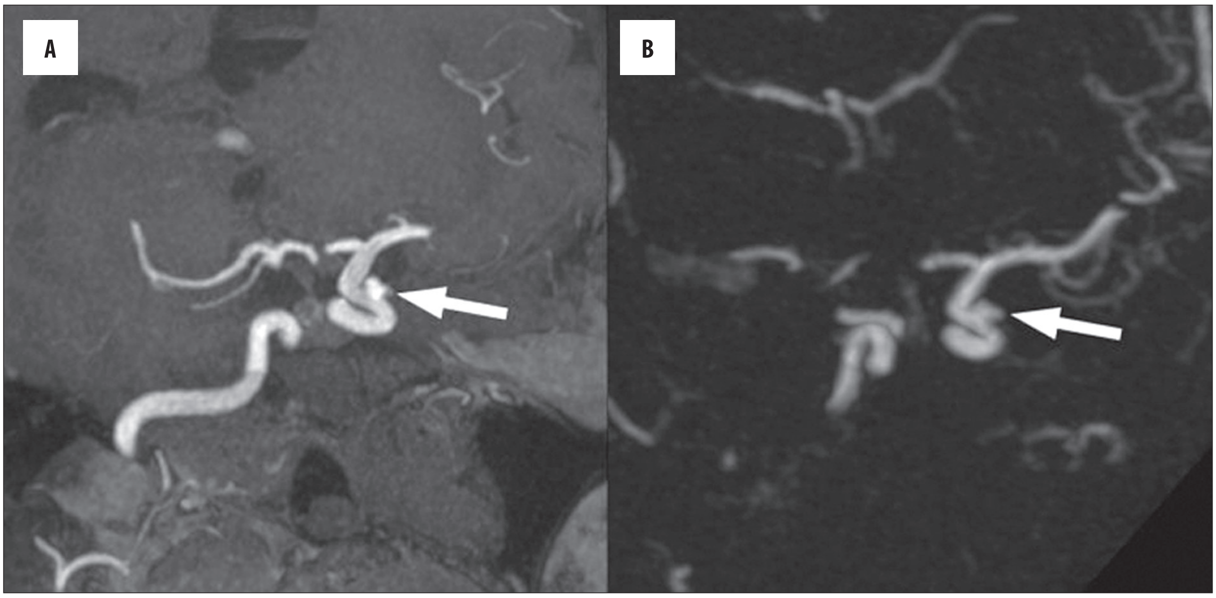

Figure 2. Follow-up MRA after embolization of the left internal carotid artery aneurysm. The residual aneurysm neck (arrows) has similar morphology in TOF-MRA (**A**) and TRICKS (**B**).

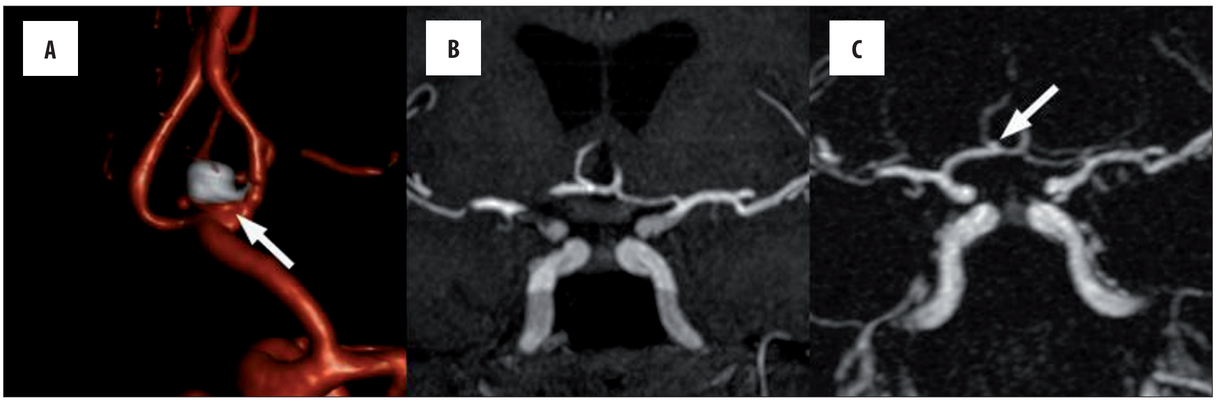

Figure 3. Follow-up angiography with 3D-DSA (**A**), TOF-MRA (**B**), and TRICKS (**C**). The residual flow area (arrows) in the anterior communicating artery aneurysm was not detected by TOF-MRA.

[7,13], MR examination has become an accepted comprehensive alternative to invasive imaging, especially in outpatient practice [6,8,10,15]. However, the most advantageous MRA technique for follow-up remains the subject of debate. A meta-analysis by Kwee and Kwee, which included 16 primary studies, revealed no statistically significant differences in pooled sensitivity and specificity between TOF-MRA and CE-MRA in detecting residual flow in the aneurysm [11]. Similarly, in the largest recently published prospective study with 311 patients by Schaafsma et al., the areas under the receiver operating characteristic curves of the 2 methods were not statistically different [8]. On the other hand, Kaufmann et al recommend performing both CE-MRA and TOF-MRA to increase the accuracy of the examination [10]. TOF-MRA is easy to perform and does not require any contrast media. The main disadvantage of TOF-MRA is its low sensitivity to slow and turbulent blood flow because of intravoxel dephasing and spin saturation [8,11]. Therefore, the slow residual flow within the coil mesh and tortuous remnants may not be detected due to signal loss, resulting in false-negative results [8,10]. CE-MRA better depicts areas of slow and turbulent flow and results in fewer flow-related artifacts [8,10,16]. On the other hand, the use of contrast medium may cause an enhancement of the vasa vasorum and an organized thrombus, which is likely to produce false-positive results [17]. Finally, if a single long CE-MRA acquisition is performed without well-timed contrast triggering, venous enhancement can significantly reduce image quality [13,14]. In both TOF-MRA and CE-MRA, a subacute thrombus, which has a high signal on T1-weighted images, may simulate the residual flow [8,10,16].

Theoretically, the use of the 4-dimensional TRICKS technique may help to overcome some shortcomings of the conventional static first-pass CE-MRA in the follow-up of embolized aneurysms. Since TRICKS offers dynamic images of blood flow, it may be more sensitive to areas of residual filling within the coil mesh. Moreover, image contamination by venous enhancement may be avoided by selecting a proper inflow phase through comparison of consecutive phases. Similarly, enhancement of the vasa vasorum and organized thrombus should be more clearly distinguished from aneurysm remnants. In our study TRICKS presented some advantage in the imaging of aneurysms coiled with stent assistance. We noted a decrease of signal intensity in stented segments of parent arteries, which was related to susceptibility artifacts. The decrease was less pronounced on TRICKS images than on TOF-MRA images. Similar artifacts have already been observed by several authors [18,19] and the intensity of such artifacts seems to depend on the type of stent used for embolization [18].

The application of time-resolved contrast-enhanced MRA has been reported in the investigation of extracerebral aneurysms, arteriovenous malformations and dural arteriovenous fistulas, and as a cerebral venography technique [20–23]. It was also tested as a method for imaging guidance in experimental aneurysm embolizations under MR control [24]. To our knowledge, the diagnostic value of TRICKS and TOF-MRA in the follow-up of embolized intracranial aneurysms has not been previously compared. We found that although TRICKS images had significantly higher SNR and CNR than TOF-MRA, which was a result of contrast medium administration, their quality scored lower. This may be explained by a lower spatial resolution of TRICKS. More importantly, TRICKS was only slightly more accurate in detecting the residual flow and in quantifying the status of aneurysm occlusion with AUC values not statistically different. The received values of sensitivity and specificity of TRICKS (88.5%, 95% CI: 69.8–97.4% and 91.3%, 95% CI: 79.2–97.5%) are comparable to those of the conventional static CE-MRA reported in the literature [8–12].

There are limitations to this study that should be noted. Firstly, the sample size appears to be insufficient to demonstrate the significance of the difference between the diagnostic value of TRICKS and TOF-MRA. It still may be hypothesized that the demonstrated small difference in AUC might appear significant in a larger population. Secondly, there was a possibility to increase spatial resolution of TRICKS examinations; however, this would result in a decrease of temporal resolution. Since both parameters were considered important to our study, the applied settings present, in our opinion, a reasonable compromise.

Conclusions

Our results indicate that the use of time-resolved imaging of contrast kinetics does not improve the diagnostic value of MRA in the follow-up of embolized intracranial aneurysms. Because TOF-MRA has a similar diagnostic performance and does not expose patients to contrast media, it should be considered a first-line alternative to DSA in routine outpatient follow-up.

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