ORIGINAL ARTICLE

The Current Role of 1.5T Non-contrast 3D Time-of-flight Magnetic Resonance Angiography to Detect Intracranial Steno-occlusive Disease

Cindy Sadikin,[1,2] Michael Mu-Huo Teng,[2,3] Ting-Yi Chen,[3] Chao-Bao Luo,[2,3] Feng-Chi Chang,[3] Jiing-Feng Lirng,[2,3] Ying-Chou Sun[2]*

Background/Purpose: This study was performed to evaluate the role of non-contrast 3D time-of-flight (TOF) magnetic resonance angiography (MRA) to detect and quantify intracranial steno-occlusive disease.
Methods: Between April 2004 and January 2006, 45 patients with both 1.5T TOF MRA and digital subtraction angiography (DSA) performed within a 30-day interval were included. We evaluated the following intracranial arterial segments: petrous internal carotid artery (ICA), cavernous ICA, supraclinoid ICA, M1 of middle cerebral artery, A1 of anterior cerebral artery, P1 of posterior cerebral artery, basilar artery, and distal vertebral artery. In total, 675 arterial segments were evaluated and categorized as negative, moderate-1 (30–49% stenosis), moderate-2 (50–69%), severe (70–99% stenosis, including gap sign on MRA), and occlusion.
Results: The sensitivity and specificity of TOF MRA for >29% stenosis and >49% stenosis were 94%, 96% and 95%, 96%, respectively; while sensitivity and specificity for occlusion lesions were both 100%. However, 44 segments (37% of diseased segments) were overestimated by MRA, including 20 false-positive stenoses (which occurred in 10 [22%] patients) and 24 overestimated stenosis degree. The gap sign as severe stenosis only showed about 21% sensitivity and 41% specificity. Seven lesions were underestimated by MRA: three arterial segments were out of the field of MRA examination, and four were moderate-1 stenosis on DSA.
Conclusion: TOF MRA has high sensitivity and specificity in detecting all categories of stenosis degree and occlusion. However, it tends to overestimate lesions. Therefore, MRA can be considered as a screening study. Confirmation with other studies is recommended in doubtful cases. [*J Formos Med Assoc* 2007; 106(9):691–699]

Key Words: digital subtraction angiography, intracranial vessels, occlusion, stenosis, time-of-flight magnetic resonance angiography

Atherosclerotic narrowing of the major intracranial arteries is associated with a risk of stroke.[1] Studies have shown potential benefit of angioplasty, with or without stent placement, in symptomatic stenotic intracranial arteries.[2,3] Digital subtraction angiography (DSA) has long been considered the reference standard for intracranial steno-occlusive disease evaluation. It provides excellent visualization of intracranial vasculature. However, DSA is invasive and carries some risk for patients.[4]

[1]Department of Radiology, Dokter Soetomo Hospital, Surabaya, Indonesia, [2]Department of Radiology, Taipei Veterans General Hospital, and [3]School of Medicine, National Yang-Ming University, Taipei, Taiwan.

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***Correspondence to:** Professor Michael Mu-Huo Teng, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan.
E-mail: mhteng@mail2000.com.tw

Time-of-flight (TOF) magnetic resonance angiography (MRA) is a noninvasive method of evaluating intracranial vasculature, and it has been used in daily practice. Improvements in MRA technology and imaging resolution may parallel improving sensitivity and specificity rates in intracranial steno-occlusive disease. However, despite the ongoing evolution of positive correlation between MRA and DSA in depicting intracranial vasculature, there is still a big issue about the tendency of TOF MRA to overestimate stenosis.[5,6]

Interested by the facts above, we performed this study to re-evaluate the role of non-contrast 3D TOF MRA to detect and quantify intracranial steno-occlusive disease compared with DSA, and its value in providing pre-stenting evaluation of intracranial stenosis.

Material and Methods

We retrospectively compared TOF MRA and DSA images of 45 patients selected from a series of 195 patients who underwent these two examinations between April 2004 and January 2006. Patients with interposed intra-arterial or intravenous thrombolysis or clot therapies were not included. Female to male ratio was 15:30, and age range was 45–91 years with a mean age of 68 years. Time interval between MRA and DSA was 0–30 days. MRA was done earlier than DSA in 29 patients, DSA preceded MRA in 11 patients, and both studies were done on the same day in five patients.

The other 150 patients who also had TOF MRA and DSA examinations within 30 days were excluded because of vascular malformations in 92 patients, aneurysms in 15, mass lesions in 10, normal intracranial vasculature in 24, no selective intracranial DSA image in three, and poor quality of MRA image mostly caused by motion artifact in six.

Image acquisition

Standard clinical protocols were used for 3D TOF MRA and DSA according to the procedures described below.

The MRA protocol was non-contrast 3D TOF MRA technique performed with three 1.5-T MR scanners: Vision (Siemens, Erlangen, Germany), Excite-Twin (GE Medical Systems, Milwaukee, WI, USA) and CV/i (GE Medical Systems). The following parameters were used in each machine: Vision—39/7 ms (TR/TE), 512 × 195 matrix, and 22 × 16.5 cm^2 field of view (FOV), 25° FA, 2 mm slice thickness interpolate to 1 mm slice interval; Excite-Twin—39/6.9 ms (TR/TE), 320 × 192 matrix interpolate to 512 × 512, and 24 × 18 cm^2 FOV, 20° FA, 1.4 mm slice thickness interpolate to 0.7 mm slice interval; and CV/i—39/6.9 ms (TR/TE), 224 × 224 matrix interpolate to 512 × 512, and 22 × 18 cm^2 FOV, 20° FA, 1.8 mm slice thickness interpolate to 0.9 mm slice interval. Spatial saturation pulse was employed at a small distance to the superior end of the 3D slab in order to suppress venous flow. To reduce saturation effects, TONE (Tilted Optimized Non-saturating Excitation)/ramped pulse were applied in all MRA studies. Source images were generated using Spoiled GRASS (Spoiled Gradient Recalled Acquisition in the Steady State) in the GE machines and FLASH (Fast Low Angled Shot) in the Siemens machine. Post processing was performed using a maximum intensity projection (MIP) with the following protocol: carotid artery horizontal and vertical rotation (9.5°–15°), basilar artery horizontal rotation (9.5°–15°), and sagittal right-left brain, coronal carotid and basilar arteries.

The DSA protocol involved femoral puncture and selective injection of cervical vessels employing the Seldinger technique, by using 6–12 mL of iopamidol per injection. The DSA runs were obtained at 2.5 frames per second to late venous phase, by using a matrix of 1024 × 1024, 22-cm FOV, pixel size 0.21 × 0.21 mm^2. Anterior–posterior, lateral and oblique projections were acquired in all cases. Magnification views were acquired when needed to clarify significant findings.

Image analysis

The presence or absence of steno-occlusive disease and its grading on DSA were performed by consensus of two experienced reviewers, who did

not participate in the interpretation of the TOF MRA. TOF MRA interpretation (MIP and source image) was done by two other experienced reviewers who were blinded to the results of DSA. Kappa statistic was used to measure agreement between the two reviewers. In cases with incoherent interpretation, a consensus was made for the overall statistical analysis study.

We classified stenosis according to the following criteria: moderate-1 (30–49% stenosis), moderate-2 (50–69% stenosis), severe (70–99% stenosis), and occlusion. In determining the normal value, we adopted the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) method.[7] Percentage stenosis was defined as severe stenosis when a gap sign was present on MRA (short flow void segment). A lesion was defined as occluded if no flow was seen in a portion of a vessel segment either with anterograde injection or via reflux on DSA images, and if a long flow void segment was seen on TOF MRA.

We included the following intracranial arterial segments for assessment: bilateral petrous internal carotid artery (ICA), bilateral cavernous ICA, bilateral supraclinoid ICA, bilateral middle cerebral artery (M1), bilateral anterior cerebral artery (A1), bilateral posterior cerebral artery (P1), the basilar artery and bilateral distal vertebral artery. Therefore, a total of 675 vessel segments were examined in 45 patients. These arterial segments were chosen because they are large and medium-sized arterial segments generally visualized with both imaging modalities. In addition, stenoses of these arterial segments may be treated with angioplasty and stenting.

Because MR images were obtained from three different machines with varying degrees of image parameters, we studied the sensitivity, specificity, positive predictive value and negative predictive value for each machine. Kappa statistic was performed to test agreement among the three machines. Agreement on the stenosis grading (including occlusion), between TOF MRA and DSA, was also measured. Kendall's tau b and Spearman test were also performed to determine their association.[8]

Results

Of the 675 intracranial arterial segments examined, 118 (17%) segments had stenosis of more than 29% or occlusion on DSA. Each patient had a mean of three diseased vessel segments (range, 1–7). These diseased segments were distributed in the following regions: ICA (47), vertebral (8), A1 (12), M1 (32), P1 (10), basilar (9). Interobserver agreement in the TOF MRA interpretation showed almost perfect agreement (Kappa, 0.892; $p < 0.0001$).

Results of MR images from the three MR machines were obtained. The sensitivity, specificity, positive predictive value, negative predictive value and Kappa value for each machine are shown in Table 1. These three machines showed no significant differences in performance; in addition, they showed almost perfect agreement with each other (Kappa, 0.8–1.0).

Statistical analysis on the degree of stenosis (including occlusion) from DSA and TOF MRA based on Table 2 show that the Kappa value was 0.778, meaning that both examinations had a good agreement. Kendall's tau b and Spearman's correlation were 0.878 and 0.863 ($p < 0.0001$), respectively, which signified a positive correlation between TOF MRA and DSA. Raw data and statistical analysis of TOF MRA versus DSA are presented in Tables 2–4. If we consider > 49% stenosis as our critical cut-off point for stenosis, then the overall sensitivity and specificity of TOF MRA were

Table 1. Comparison of statistical values for each magnetic resonance angiography machine

Performance	Excite-Twin	Vision	CV/i
Sensitivity	95%	94%	95%
Specificity	96%	96%	98%
Positive predictive value	82%	86%	90%
Negative predictive value	99%	98%	99%
Accuracy	96%	96%	97%
Kappa	0.85	0.87	0.91

Table 2. Intermodality discrepancies*

MRA classifications	DSA				
	Negative†	Moderate-1	Moderate-2	Severe	Occlusion
Negative†	530	4	1	2	0
Moderate-1	7	31	0	0	0
Moderate-2	6	9	34	0	0
Severe–no gap sign	0	2	7	11	0
Severe–gap sign (+)	7	1	5	3	0
Occlusion	0	0	0	0	15

**Kappa = 0.778, Kendall's tau b = 0.863, Spearman's correlation = 0.878, $p < 0.0001$; †negative was defined as < 30% stenosis or normal. MRA = (time-of-flight) magnetic resonance angiography; DSA = digital subtraction angiography.*

Table 3. Case number of true and false MRA diagnoses using digital subtraction angiography as the gold standard*

	True positive	False positive	False negative	True negative
MRA > 29% stenosis	103	20	7	530
MRA > 49% stenosis	60	25	3	572
MRA occlusion	15	0	0	530

**Gap sign on MRA is considered severe stenosis. MRA = (time-of-flight) magnetic resonance angiography.*

Table 4. Standard contingency table of 3D time-of-flight magnetic resonance angiography compared with digital subtraction angiography*

	Stenosis > 29%	Stenosis > 49%	Occlusion
Sensitivity	94%	95%	100%
Specificity	96%	96%	100%
False positive rate	4%	4%	0
False negative rate	6%	5%	0
Positive predictive value	84%	70%	100%
Negative predictive value	99%	99%	100%

**Gap sign on time-of-flight magnetic resonance angiography is considered severe stenosis.*

95% and 96%, while it had 100% sensitivity and specificity for occlusion lesions.

However, we found 44 overestimated lesions (37%) on TOF MRA compared with DSA. These included 20 false-positive stenotic segments (7 segments had gap sign) and 24 overestimated stenosis degree (6 segments had gap sign) (Figures 1–4). True negative finding was defined as normal vasculature or mildly luminal stenosis (< 30%) (Table 2). These 20 false-positive stenotic segments on TOF MRA belonged to 13 patients (29%). Their locations were posterior cerebral artery in five, petrous ICA in four, anterior cerebral artery in four, middle cerebral artery in three, supraclinoid in two, cavernous ICA in one, and vertebral artery in one. If we consider that > 49% stenosis is positive stenosis, excluding the moderate-1 group, then 10 (22%) of 45 patients had false-positive results on MRA.

Results of DSA examinations from the 16 segments that showed gap sign in TOF MRA were negative finding (< 30% stenosis or normal) in seven (44%), moderate-1 stenosis in one (6%), moderate-2 stenosis in five (31%), and severe stenosis in three (19%) (Figures 3 and 4).

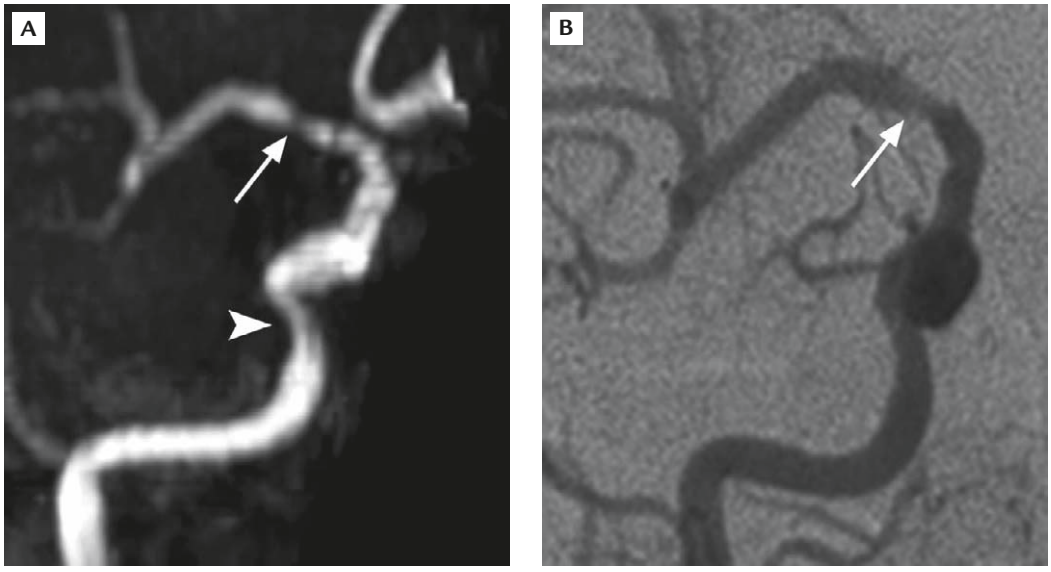

Figure 1. (A) Time-of-flight magnetic resonance angiography (TOF MRA) shows severe stenosis at the proximal right middle cerebral artery (arrow). (B) Digital subtraction angiography (DSA) shows a moderate-2 stenosis (arrow). TOF MRA also shows moderate-2 stenosis at the proximal cavernous segment of the internal carotid artery (arrowhead in A), while DSA shows normal appearance.

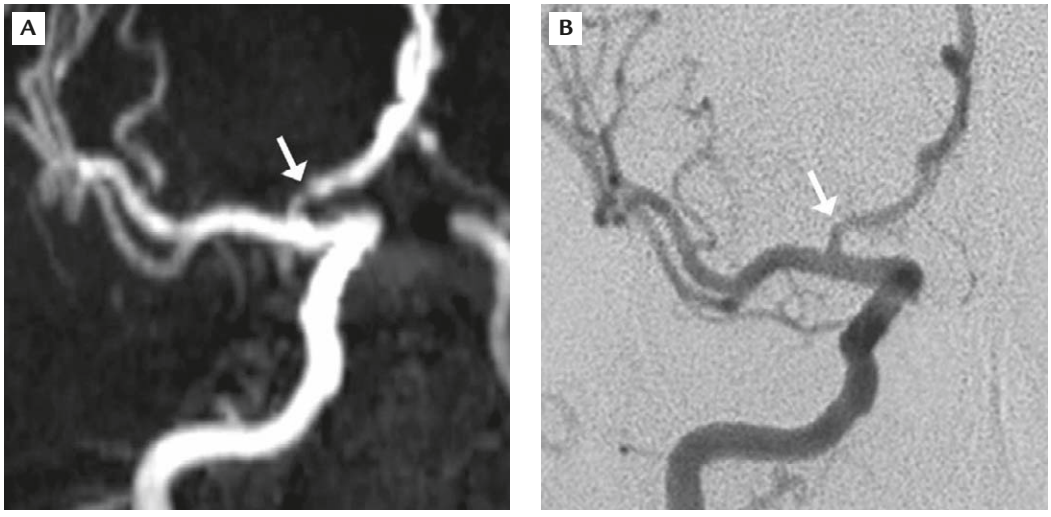

Figure 2. (A) Time-of-flight magnetic resonance angiography shows a moderate-2 stenosis (arrow) at the proximal right anterior cerebral artery. (B) Digital subtraction angiography shows < 30% stenosis (arrow).

In the 15 occlusions on DSA, TOF MRA also showed occlusions. There was no false-positive or false-negative TOF MRA for cases with occlusion.

We also found seven underestimated lesions on TOF MRA. Four of them showed moderate-1 stenosis on DSA. The locations of these lesions were basilar artery (2 segments) and cavernous ICA (2 segments). Two severe stenosis and one moderate-2 stenosis lesions were also found at distal intracranial vertebral arteries on DSA examinations, but MRA failed to show them because these lesions were outside the field of the MRA studies.

Discussion

DSA has long been considered the reference standard imaging for intracranial steno-occlusive

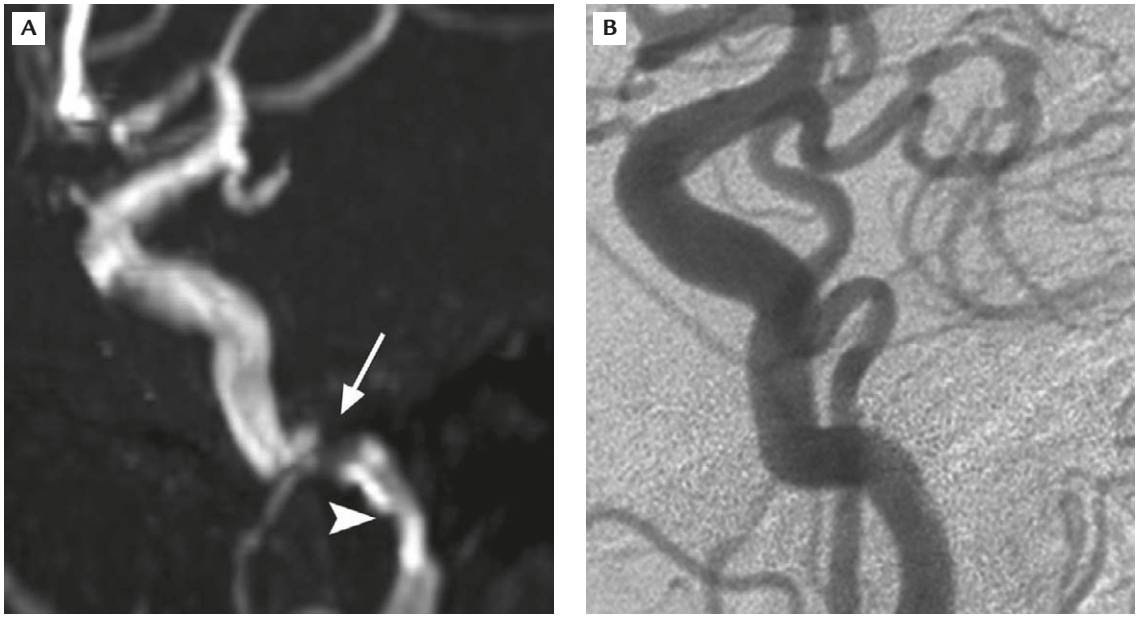

Figure 3. (A) Time-of-flight magnetic resonance angiography shows a gap sign at the horizontal portion of the petrosal segment of the left internal carotid artery (arrow) and a moderate-1 stenosis at the vertical portion of the petrosal segment (arrowhead). (B) Digital subtraction angiography shows normal caliber at these segments.

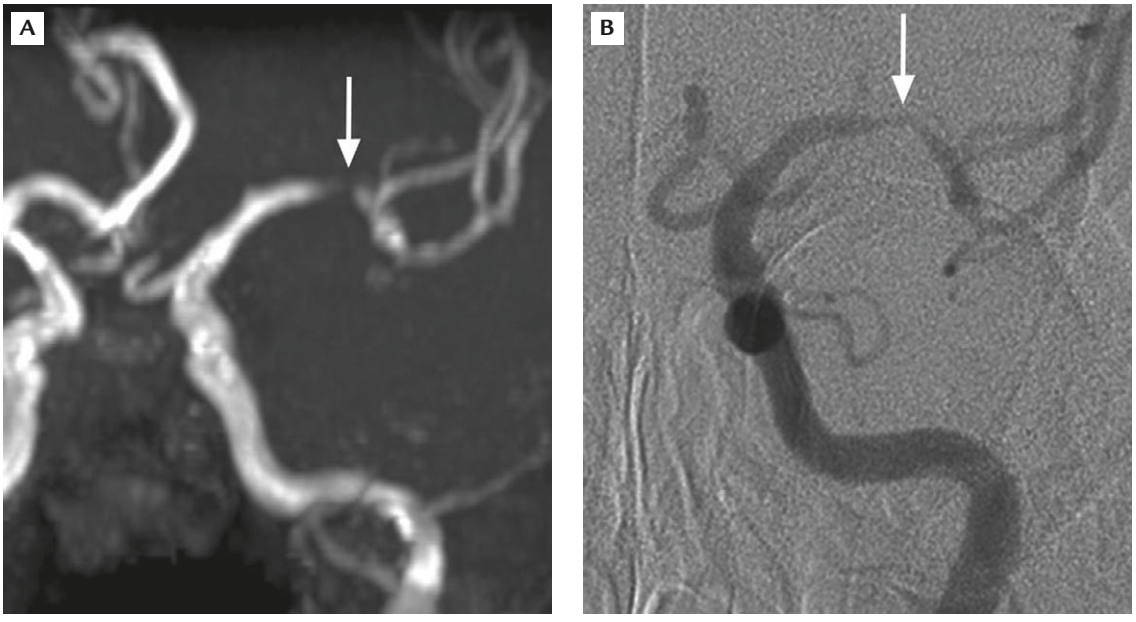

Figure 4. (A) Time-of-flight magnetic resonance angiography shows a gap sign at the left distal middle cerebral artery (arrow). (B) Digital subtraction angiography demonstrates severe stenosis (arrow).

disease. DSA provides excellent visualization of the intracranial vasculature. Dynamic flow information of cerebrovascular segments is provided within each injection. However, its limitations, including requiring great skill to perform and its necessity for intra-arterial catheterization, result in increased morbidity and mortality for patients, with a 0.7% risk of stroke associated with each procedure.[4]

Previous authors have studied the importance of endovascular treatment in symptomatic intracranial stenosis with >70% luminal stenosis. Their studies showed that endovascular treatment had a high success rate and revealed low symptomatic recurrence rate.[9,10] A recent study showed that the general indication for intracranial stent placement in atherosclerotic lesions was >50% stenosis of

the intracranial ICA, the M1 segment of the middle cerebral artery, and the intracranial vertebral arteries or the basilar artery.[11] A stenosis of 50–99% was defined as significant.[12] Therefore, in this study, we classified the degree of stenosis by modifying the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria to the following grading scale: moderate (30–69%) was divided into moderate-1 (30–49%) and moderate-2 (50–69%); severe (70–99%), and occlusion (if no flow was detected). We assumed that this classification is practically applicable for treatment planning and follow-up. In severe cases, endovascular treatment is strongly needed. Patients with moderate-1 stenosis need to be treated medically and followed intensively to evaluate the clinical response and imaging progressiveness of stenosis severity. Intravascular intervention may be considered for recurrent symptomatic patients of moderate-2 stenosis that does not respond to medical treatment and in symptomatic patients with severe stenosis.

Our TOF MRA results showed tendency of overestimation by TOF MRA, similar to previous research.[6] There are several reasons for these stenoses being overestimated. Accelerated flow through stenotic areas may lead to dephasing and overestimate the degree of stenosis.[5] At bifurcation area, there will be flow separated from the main streamline and somehow cause turbulent flow. Turbulent flow contains different velocity components with different phases that tend to cancel each other out and result in no signal.[13]

Hirai et al reported that the use of MIP views alone obtained from TOF MRA were mostly accurate for normal and mildly stenotic arteries, but less useful in stenosis > 50%.[14] In the MIP method, the value of the brightest pixel along the ray line is assigned to that pixel of the MIP image. It is possible for small, lower intensity details to be overwhelmed by larger, brighter structures.[15] Therefore, in this study, we evaluated both MIP and source images.

In this study, we divided the discontinuity of flow image on TOF MRA into two parts, the short segment was the gap sign and the long segment was the occlusion one. The gap sign was defined as 99% stenosis in a previous report.[7] Our study showed that gap sign as severe stenosis only showed about 21% sensitivity and 41% specificity. It is mostly failed in the carotid siphon and more reliable in the M1 branch of the middle cerebral artery or other large intracranial vessels. This may result from complex flow in the carotid siphon region and close anatomic relation with the sphenoid sinus with large susceptibility gradient, leading to dephasing of spins and artifactual signal loss.[16,17]

One study by Wardlaw et al revealed the general inaccuracy of conventional MRA, estimating that 23% of their study patients would have received non-indicated surgery.[18] Our study showed that the false-positive value is higher based on patient number because the result was considered false-positive if the patient had any one false-positive lesion, while the average number of diseased segments in our patients was one to seven lesions.

Lewin and Laub were the first to report the limitations of 3D TOF MRA in slowly flowing blood. 3D TOF MRA may indicate that a vessel is completely occluded when it is in fact patent, but contains slowly flowing blood.[19] They suggested that to maximize flow-related enhancement, the imaging volume should be perpendicularly oriented to inflowing blood, with an optimized flip angle and TR. There are several methods commonly used to reduce saturation effects, one of them is TONE,[13] which we have applied in the current study. TONE uses lower flip angle at the entry side to minimize saturation effects and higher flip angle at the exit side to maximize blood signal. This technique allows better visualization of distal vessels and slow-flowing vessels. In comparison to previous studies,[5,14] we also used higher matrix and thinner slice thickness to reduce the voxel size, which reduced the possibility of intravoxel dephasing. Although high TE is prone to false stenosis, in the current study, we used a specific TE (6.9 ms) to perform the out-of-phase stage in order to suppress fat signals in the surrounding skull base and increase contrast-to-noise ratio.[15]

Huston et al proposed the underestimated stenosis degree of carotid in TOF MRA due to short T1 of plaque that cause a high signal and masks signal loss on MIP display images.[20] In our study, the false-negative for non-contrast 3D TOF MRA for > 49% stenosis would have become 0% if all of the arterial segments were included in the MRA field of study. In previous studies,[5,14] they reported their TOF MRA tendency to underestimate stenosis because their reviewer tended to interpret signal loss as artifact.

Statistical values in previous studies by Bash et al were 70% sensitivity and 97% specificity for stenosis, and 87% sensitivity and 99% specificity for occlusion.[21] Hirai et al reported 92% sensitivity and 91% specificity for stenosis.[6] These previous studies used rather different sample sizes and stenosis criteria. In Bash et al's study, they included 28 patients with a total of 672 vessel segments evaluated for stenosis > 30%, while Hirai et al included 18 patients with a total of 198 vessel segments evaluated for stenosis > 50%. Our statistical results showed good agreement and positive correlation between TOF MRA and DSA.

One limitation of this study was retrospective comparison between studies, and inclusion criteria for the study were not prospectively established, possibly introducing a selection bias. Another promising TOF MRA technique is multiple overlapping thin slab acquisition (MOTSA). MOTSA offered longer coverage and higher contrast-to-noise ratio due to higher flow-related enhancement.[13] In the current study, we used the single slab technique instead of MOTSA due to the longer acquisition time needed in MOTSA and the possibility of Venetian blind artifacts, which may interfere with clinical interpretation in some circumstances.

In conclusion, TOF MRA has high sensitivity and specificity in detecting all categories of stenosis degree and occlusion. However, a high overestimation of stenosis degree (37%) remains. The classical MRA finding for severe stenosis, the gap sign, only showed about 21% sensitivity and 41% specificity; moreover, it is rather insensitive in carotid siphon segments. Therefore, MRA can be considered as a screening study. But confirmation with other studies is recommended in doubtful cases.

Acknowledgments

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