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MAGNETIC RESONANCE

Strategically acquired gradient echo (STAGE)-derived MR angiography might be a superior alternative method to time-of-flight MR angiography in visualization of leptomeningeal collaterals

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Abstract

Objectives This study aimed to compare the performance of strategically acquired gradient echo (STAGE)-derived MR angiography and time-of-flight MR angiography (TOF-MRA) in visualization of leptomeningeal collaterals (LMCs).

Methods Between May 2018 and January 2020, 75 participants (47 healthy volunteers and 28 intracranial atherosclerotic disease [ICAD] patients) undergoing TOF-MRA and STAGE-MRA were prospectively included. Image quality was scored at the internal carotid artery (ICA) terminus, proximal middle cerebral artery (MCA), and LMCs. Quantitative analysis included calculation of contrast-to-noise ratios (CNRs) in the M1–4 segments and number of LMCs counted in the line signal intensity profiles. Comparisons of image qualitative scores, CNRs, and number of LMCs were calculated using the Wilcoxon rank-sum test.

Results Image qualitative scores were significantly higher in STAGE-MRA than in TOF-MRA for the ICA terminus, proximal MCA, and LMCs ($ps < 0.05$) in 75 participants. When referred to digital subtraction angiography (DSA) in 25 ICAD patients, STAGE-MRA showed higher qualitative scores only at LMCs. CNRs in the M1–4 segments were significantly higher in STAGE-MRA than in TOF-MRA (218.7 ± 90.7 vs 176.2 ± 72.6, 195.7 ± 86.0 vs 146.6 ± 71.7, 176.4 ± 71.6 vs 125.8 ± 61.1, 126.2 ± 62.9 vs 78.8 ± 43.6; all $ps < 0.001$). STAGE-MRA showed more LMCs (11.4 ± 3.4) than TOF-MRA (8.4 ± 3.3) with $p < 0.05$.

Conclusions STAGE-MRA might be superior to TOF-MRA in qualitative and quantitative assessment of LMCs in both healthy volunteers and ICAD patients; thus, it may serve as an alternative method in evaluating LMC.

Key Points

- *Strategically acquired gradient echo (STAGE)-derived magnetic resonance angiography is a newly developed sequence with a pair of rephasing/dephasing gradient echoes.*
- *STAGE-MRA enables higher image qualitative score, improves contrast-to-noise ratio, and shows greater number of leptomeningeal collaterals (LMCs) in healthy volunteers and patients with intracranial atherosclerotic disease.*
- *LMC visualization by STAGE-MRA shows good to excellent inter-observer agreement.*

Keywords Magnetic resonance angiography · Collateral circulation · Intracranial arteriosclerosis · Healthy volunteers

Ruowei Tang and Qingqing Zhang contributed equally to this work.

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Abbreviations

APCVs	Asymmetrically prominent cortical veins
ASL	Arterial spin labeling
BA	Basilar artery
BET	Brain extraction tool
CNR	Contrast-to-noise ratio
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
DWI	Diffusion-weighted imaging
EVT	Endovascular treatment
FA	Flip angle
FOV	Field of view
ICA	Internal carotid artery
ICAD	Intracranial atherosclerotic disease
ICC	Intraclass correlation coefficient
LMC	Leptomeningeal collateral
MCA	Middle cerebral artery
MIP	Maximum intensity projection
MPR	Multiple planar reconstruction
PACS	Picture archiving and communication system
QSM	Quantitative susceptibility mapping
ROI	Region of interest
SI_{TH}	Threshold signal intensity
ST	Stationary tissue
STAGE	Strategically acquired gradient echo
ST_{ave}	Average signal intensity in stationary tissue
ST_{SD}	Standard deviation of signal intensity in stationary tissue
SWI	Susceptibility weighted imaging
T2WI	T2-weighted imaging
TE	Echo time
TIA	Transient ischemic attack
TOF-MRA	Time-of-flight magnetic resonance angiography
TR	Repetition time
tSWI	True susceptibility weighted imaging
VA	Vertebral artery
V_{max}	Maximum signal intensity

Introduction

Recently, two multi-center randomized trials have suggested that mechanical thrombectomy results in a more favorable clinical outcome in carefully selected patients up to 24 h after stroke onset [1, 2]. Setting a prolonged time window strongly depends on prompt imaging assessment and the presence of robust collateral circulation, and the latter has been recognized as a protective factor for maintaining blood flow to the ischemic brain parenchyma [3]. Of note, the presence of leptomeningeal collateral (LMC) is a determining factor for the progression of ischemic lesions [4] and recanalization [5]. Therefore, it is essential to evaluate LMC in order to determine therapeutic strategy in patients with intracranial vascular disease.

Although multiple imaging techniques have been applied to evaluate LMC in clinical practice, there is no consensus on the optimal imaging method yet [6]. Digital subtraction angiography (DSA) is considered a gold standard in terms of LMC assessment. However, since it is an invasive procedure, the current clinical application of DSA is limited to patients who are eligible for intravascular intervention [7]; thus, DSA is not commonly used in disease screening. Among the noninvasive methods, computed tomography angiography (CTA) is the most widely used technique in clinical practice but still involves radiation exposure. In contrast, time-of-flight MR angiography (TOF-MRA) is superior to DSA and CTA regarding no ionizing radiation exposure. However, it comes with pulsatile flow which may cause ghosting [8] and vessels with slow flow such as distal collaterals are not strongly enhanced since the signal of background tissue is not completely suppressed.

Meanwhile, a newly developed MRA approach, derived from strategically acquired gradient echo (STAGE) imaging, namely STAGE-MRA, has been proposed recently by Chen et al in 2018 [9]. Unlike TOF-MRA, the STAGE-MRA sequence employs an interleaved rephasing/dephasing scheme that makes it possible to subtract the stationary background tissue, thereby better highlighting signal of small arteries with improved contrast-to-noise ratios (CNRs) [9].

Based on the aforementioned strengths of STAGE-MRA, the aim of the present study was to assess the possibility of depicting LMCs with STAGE-MRA in a qualitative and quantitative manner in healthy volunteers and patients with intracranial atherosclerotic disease (ICAD), and to investigate whether STAGE-MRA could be used as an alternative method to TOF-MRA in LMC visualization. We hypothesized that STAGE-MRA could better evaluate LMCs qualitatively and quantitatively than TOF-MRA in both healthy volunteers and ICAD patients.

Materials and methods

This prospective study was approved by the local ethics committee board of Tianjin First Central Hospital and written informed consent was obtained from all participants as required.

Participants

Volunteers were recruited via a posted advertisement from May 2018 to December 2018. We first screened the volunteers in a telephone interview and those who had the following conditions were excluded: (1) age under 18 years; (2) history of ischemic stroke or symptoms of transient ischemic attack (TIA) including diplopia, hemianopia, paralysis, numbness or weakness of limbs, amaurosis, dysarthria, or altered mental status; (3) history of hypertension, diabetes mellitus, or

hyperlipidemia diagnosed by physical workup, or current antihypertensive, antidiabetic drug, or statin use; (4) systemic cardiovascular, hepatic, or renal diseases; and (5) contraindications to MR examination, such as metal implants in or on the body and claustrophobia. Finally, 47 healthy volunteers were included and the flowchart is listed in Electronic Supplementary Material Fig. 1.

Additionally, in order to compare the performance of the two MRA methods and DSA, a group of 28 ICAD patients from the neurosurgery department at our institution were recruited between May 2018 and January 2020. The eligible patients had either a stenosis of intracranial arteries (the terminal internal cerebral artery [ICA], proximal middle cerebral artery [MCA], vertebral artery [VA], and/or basilar artery [BA]) confirmed by admission MRA or CTA, with or without infarction occurrence. Exclusion criteria were history of previous endovascular therapy (mechanical thrombectomy, carotid endarterectomy, or balloon guided catheter use), and severe motion artifacts (Electronic Supplementary Material Fig. 1).

Imaging protocols

All participants were imaged using a MAGNETOM Prisma 3.0-T scanner (Siemens Healthcare) with a 64-channel head coil. The sequences included diffusion-weighted imaging (DWI), T2-weighted imaging (T2WI), clinically optimized TOF-MRA, and STAGE-MRA using the following parameters:

1. DWI: repetition time (TR)/echo time (TE) = 2630/(55, 93) ms, spatial resolution = 1.3 × 1.3 × 5.0 mm^3, field of view (FOV) = 240 mm × 240 mm, matrix size = 192 × 192, slice thickness = 5.0 mm, flip angle (FA) = 180°, bandwidth/pixel = 766 Hz/px, and acquisition time = 1 min 13 s.
2. T2WI: TR/TE = 3500/89 ms, spatial resolution = 0.6 × 0.6 × 5.0 mm^3, FOV = 240 mm × 195 mm, matrix size = 384 × 384, slice thickness = 2.0 mm, FA = 150°, bandwidth/pixel = 221 Hz/px, and acquisition time = 1 min 2 s.
3. TOF-MRA: TR/TE = 20/3.59 ms, spatial resolution = 0.7 × 0.7 × 0.7 mm^3, FOV = 256 mm × 192 mm, matrix size = 384 × 384, slice thickness = 0.7 mm, FA = 18°, bandwidth/pixel = 165 Hz/px, and acquisition time = 7 min 8 s.
4. STAGE-MRA: TR/TE = 20/(2.5, 12.5) ms, spatial resolution = 0.67 × 0.89 × 2.0 mm^3, FOV = 256 mm × 192 mm, matrix size = 384 × 216, slice thickness = 2.0 mm, FA = 12°, bandwidth/pixel = 650, 240 Hz/px, and acquisition time = 5 min 50 s. Specifically, STAGE-MRA employed a pair of gradient echoes with different phase preparation strategies [10]. The flow rephased echo was achieved by a set of bipolar gradients leading to a bright-blood image, while the dephased echo had strong flow dephasing gradients in front of the readout to acquire a black blood image. These two echoes were acquired with interleaved TR as well as with the same TE and sampling bandwidth. Therefore, the stationary tissue had the same signal intensity in each acquisition and could be completely suppressed on the subtraction image. The recent updated sequence introduced a supplementary short echo to maintain signal from very fast flow vessels that may be dephased on the long TE image [9]. Therefore, it could be used for imaging the small arteries in the brain.

MRA data post-processing

STAGE raw data were processed using STAGE software (SpinTech Inc.) to obtain 64-slice STAGE-MRA images. For overall depiction of the entire brain's vasculature, an axial 90-mm slab maximum intensity projection (MIP) image was generated using the Syngo.via Workstation (Siemens Healthcare) for STAGE-MRA or TOF-MRA. Multiple planar reconstruction (MPR) was used to ensure that the MIP images were placed at the same head level, demonstrating bilateral ICA terminus and MCAs.

Image analysis

Two observers (R.T. with 5 years experience, Q.Z. with 3 years experience), blinded to the clinical data and sequence type, independently performed qualitative and quantitative analyses as proposed by Obara [11] and Togao et al [12].

Qualitative evaluation

STAGE-MRA and TOF-MRA images were displayed on the off-line picture archiving and communication system (PACS) and two observers scored the image quality of the terminal ICAs, proximal MCAs, and LMCs. First, the vessel visualization between STAGE-MRA and TOF-MRA was compared using a 3-point scale in all participants. Then, STAGE-MRA or TOF-MRA images were respectively compared with DSA and graded using a 4-point scale in ICAD patients. The 3-point and 4-point scales are listed in Electronic Supplementary Material Table 2.

Quantitative evaluation

The quantitative analysis, including calculation of CNRs and the number of LMCs, was performed on the MIP images of both STAGE-MRA and TOF-MRA using SPIN software (SpinTech Inc.), as shown in Fig. 1. Eight circular or oval regions of interest (ROIs) were placed on bilateral M1, M2, M3, and M4 segments, respectively. Additional two ROIs were placed on bilateral background stationary tissue (ST) where vessels were carefully avoided. The 10 ROIs were first

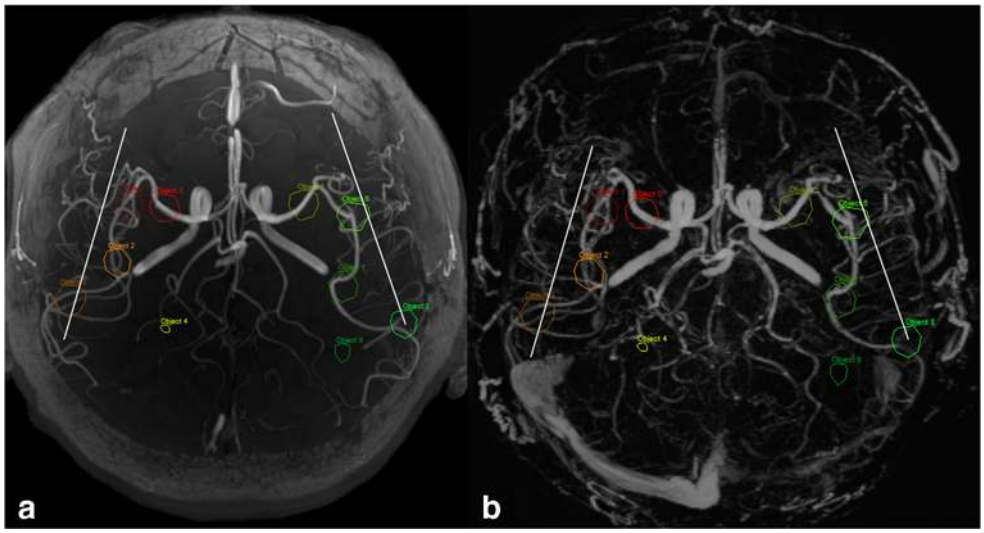

Fig. 1 Quantitative evaluation of leptomeningeal collaterals (LMCs), including measurement of contrast-to-noise ratios (object 0–9) and number of LMCs (straight lines). (**a**) TOF-MRA and (**b**) STAGE-MRA

drawn on the MIP image of one angiographic method and then were copied to the other method. CNRs of the M1–4 segments were calculated as $(V_{max} - ST_{ave})/ST_{SD}$, where V_{max} was the maximal signal intensity within the corresponding ROI, and ST_{ave} (average signal intensity) and ST_{SD} (signal intensity standard deviation) were acquired in the ROI of stationary tissue. Straight lines were drawn in bilateral MCA distal territories and line-signal profiles were obtained. A threshold signal intensity (SI_{TH}) was set as $ST_{ave} + 5 \times ST_{SD}$ and vessels were defined as signal intensity greater than SI_{TH}. The number of LMCs was counted as the number of peaks on the line signal profiles (Electronic Supplementary Material Fig. 2).

Statistical analysis

Statistical analyses were conducted using MedCalc 18.11.3 (MedCalc Software) and GraphPad Prism 7.0 (GraphPad Software). Inter-observer consistencies in qualitative and quantitative analysis were compared using weighted Kappa test and intraclass correlation coefficient (ICC), respectively. Comparisons of image qualitative scores, CNRs, and the number of LMCs between STAGE-MRA and TOF-MRA were performed using a Wilcoxon rank-sum test. A p value less than 0.05 was considered statistically significant.

Results

Demographic data

We prospectively recruited 76 participants, of which one ICAD patient was excluded because of severe motion artifacts. Finally, 75 participants (60 ± 12 years, 33 males and 42 females) were included, which consisted of 47 healthy volunteers and 28 ICAD patients. The clinical and major imaging findings of the 28 ICAD patients are listed in Electronic Supplementary Material Table 1. Among the 28 ICAD patients, 25 underwent DSA examination and the other 3 did not. Therefore, comparison between the two angiographic methods was conducted in all 75 participants, whereas comparison between two angiographic methods and DSA was performed in 25 ICAD patients.

Inter-observer agreement

The two observers showed good to excellent consistency with weighted Kappa coefficients ranging from 0.71 to 0.96 in image qualitative scoring in 75 participants (Table 1; Figs. 2, 3), and 0.77 to 0.89 in 25 ICAD patients with reference to DSA (Table 2). The ICCs of quantitative measurement ranged from 0.83 to 0.90 with STAGE-MRA and 0.84 to 0.94 with TOF-MRA (Table 3).

Qualitative analysis of LMC visualization

In all 75 participants, LMC qualitative scores were higher for STAGE-MRA than for TOF-MRA in three locations of interest ($ps < 0.01$, Table 4). Whereas in 25 ICAD patients, STAGE-MRA only showed higher qualitative scores than TOF-MRA in the location of LMCs (Table 5).

Quantitative analysis of LMC visualization

Mean CNRs in the M1–4 segments were higher with STAGE-MRA (218.7 ± 90.7, 195.7 ± 86.0, 176.4 ± 71.6, 126.2 ± 62.9) than with TOF-MRA (176.2 ± 72.6, 146.6 ± 71.7, 125.8 ± 61.1, 78.8 ± 43.6) as illustrated in Fig. 4 with all $ps < 0.001$. Figure 5 and Electronic Supplementary Material Fig. 3 show improved CNRs and greater number of LMCs for STAGE-MRA in an ICAD patient and a healthy volunteer,

Table 1 Inter-observer agreement of image qualitative score in 75 participants with a 3-point scale

	Observer 1	Observer 2	Weighted Kappa coefficient	95% CI
STAGE-MRA				
ICA terminus	2.4 ± 0.6	2.5 ± 0.6	0.96	0.92–1.00
Proximal MCA	2.4 ± 0.6	2.6 ± 0.6	0.71	0.61–0.82
LMCs	2.6 ± 0.5	2.7 ± 0.5	0.82	0.73–0.91
TOF-MRA				
ICA terminus	2.3 ± 0.7	2.3 ± 0.7	0.89	0.84–0.95
Proximal MCA	2.2 ± 0.8	2.3 ± 0.9	0.90	0.85–0.95
LMCs	2.3 ± 0.7	2.4 ± 0.7	0.92	0.86–0.97

CI, confidence interval; *ICA*, internal cerebral artery; *MCA*, middle cerebral artery; *LMCs*, leptomeningeal collaterals

respectively. The mean numbers of LMCs were 11.4 ± 3.4 for STAGE-MRA and 8.4 ± 3.3 for TOF-MRA, respectively, indicating that STAGE-MRA depicted a significantly greater number of LMCs than TOF-MRA (Fig. 6, $p < 0.001$).

Discussion

In the present study, we introduced STAGE-MRA as a novel method to perform qualitative and quantitative evaluations of LMCs. Compared with TOF-MRA, this technique showed higher image qualitative scores, improved CNRs of the M1–4 segments, and increased number of LMCs in 47 healthy volunteers and 28 ICAD patients. Our study suggested that STAGE-MRA was a reliable technique in evaluating LMC; thus, it might be a potential alternative method to TOF-MRA in the clinical practice, specifically in ICAD patients.

In terms of qualitative scores, STAGE-MRA was higher than TOF-MRA in ICA terminus, proximal MCA, and LMCs, while the advantage to STAGE-MRA was found only in LMCs with reference to DSA. A possible explanation might be the relatively limited sample size of ICAD patients undergoing DSA, with 25 patients not providing sufficient statistics. When compared with DSA, the inter-observer agreements of STAGE-MRA were higher than those of TOF-MRA (weighted Kappa coefficient range 0.80–0.89 vs

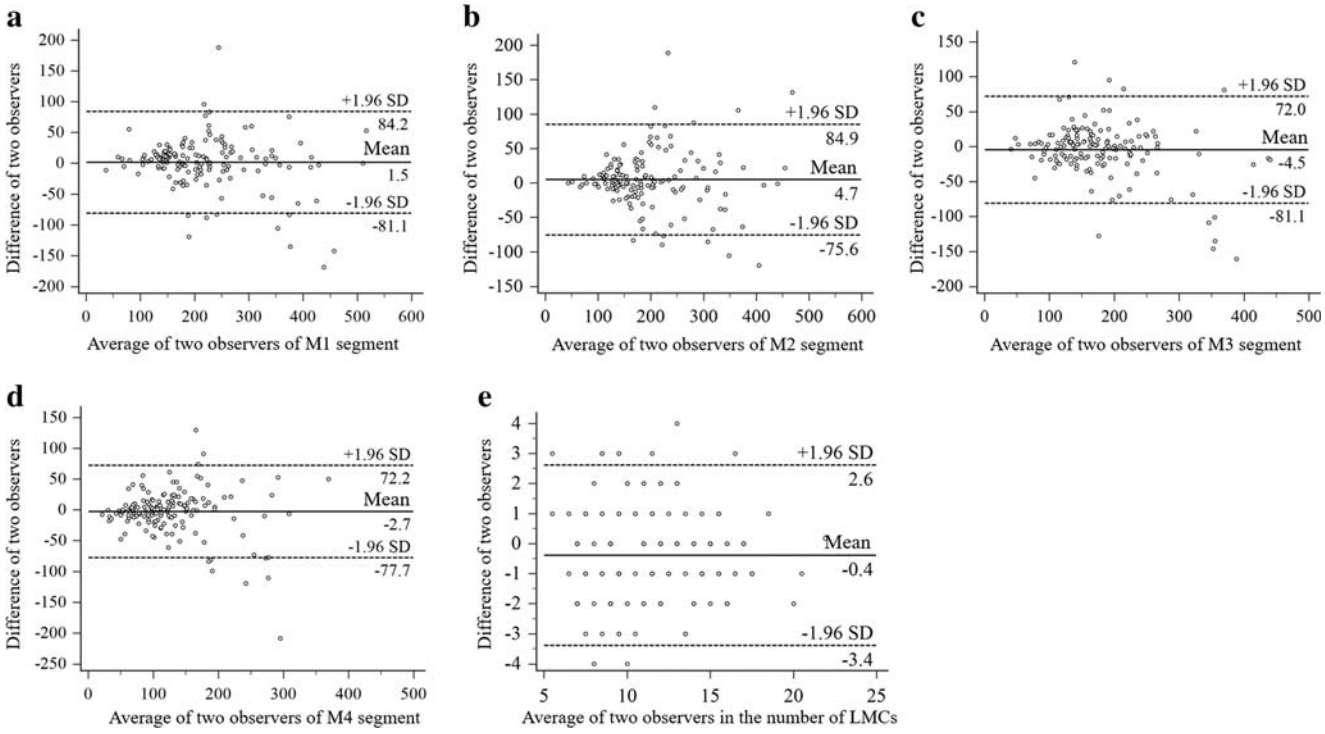

Fig. 2 Bland-Altman plots for inter-observer agreement for STAGE-MRA: (**a**–**e**) represent contrast-to-noise ratios of M1–4 segments and the number of leptomeningeal collaterals (LMCs), respectively. The solid lines and the dashed lines indicate the mean difference and the 95% limits of agreement, respectively. SD, standard deviation

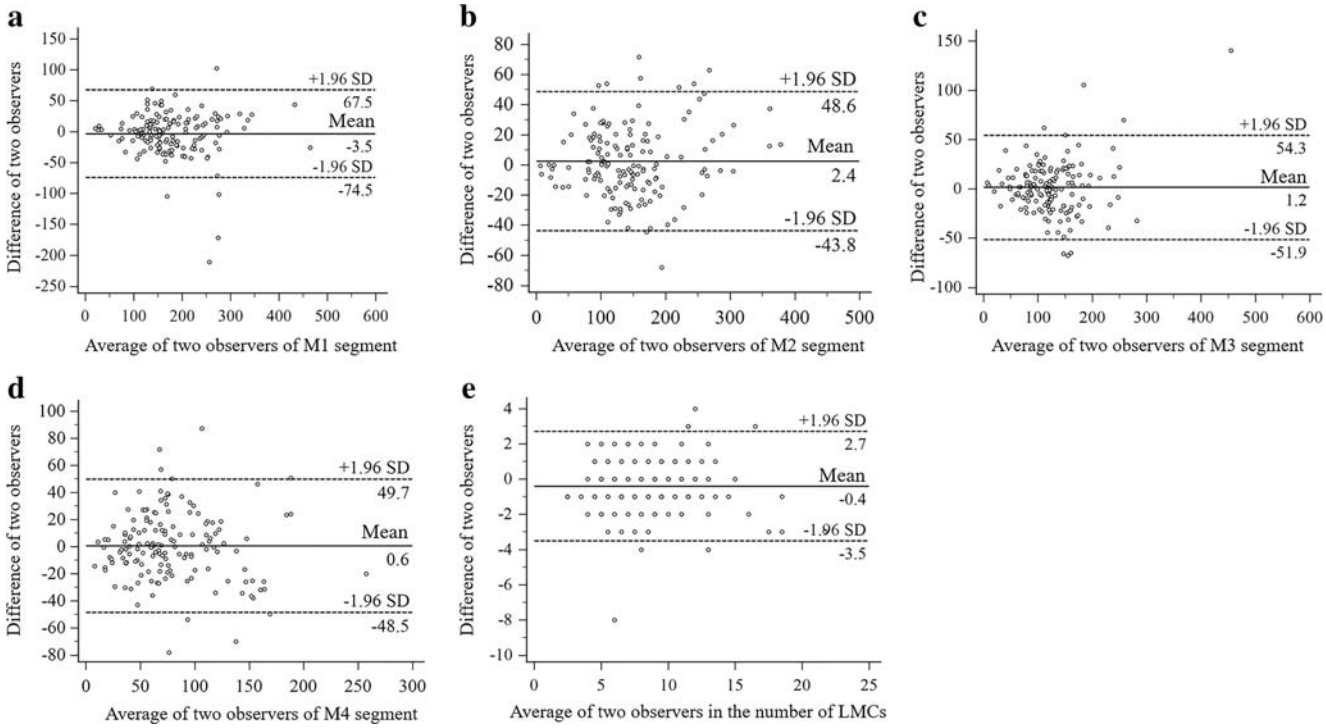

Fig. 3 Bland-Altman plots for inter-observer agreement for TOF-MRA: (**a**–**e**) represent contrast-to-noise ratios of M1–4 segments and the number of leptomeningeal collaterals (LMCs), respectively. The solid lines and the dashed lines indicate the mean difference and the 95% limits of agreement, respectively. SD, standard deviation

0.77–0.87, Table 2), which indicated that STAGE-MRA achieved better inter-observer agreement than TOF-MRA.

The image analysis approach we used was based on prior studies proposed by Obara [11] and Togao [12], where CNRs of M1–4 segments in arterial spin labeling (ASL) were compared with TOF-MRA. They found that ASL was superior to TOF-MRA in the M4 segment in healthy volunteers and patients with moyamoya disease, and ASL showed twice the number of LMCs compared with TOF-MRA. However, occlusion of the ICA terminus was better depicted using TOF-MRA than ASL and the study concluded that ASL was suitable for visualizing distal slow flow while TOF-MRA was better for proximal fast flow. Similar to their findings, our study revealed STAGE-MRA having improved CNRs of M1–4 segments and showing a greater number of LMCs than TOF-MRA, proving the potential application of STAGE-MRA in clinical practice.

As the secondary grade of arterial pathway following the Circle of Willis, LMC improves the delivery of retrograde blood flow to ischemic brain parenchyma where arteries are critically stenosed or occluded. Besides its potential effect on clinical outcomes, LMC plays a useful role in therapeutic decision-making and the choice of individualized treatment. Better collaterals are associated with lower mortality and higher grade of functional independence in stroke patients treated with endovascular treatment (EVT) [13]. Across all collateral subgroups, patients with good collaterals benefited the most from EVT [14]. Therefore, the prognosis and

Table 2 Inter-observer agreement of image qualitative score with reference to DSA with a 4-point scale

	Observer 1	Observer 2	Weighted Kappa coefficient	95% CI
STAGE-MRA				
ICA terminus	3.5 ± 0.8	3.5 ± 0.8	0.89	0.79–1.00
Proximal MCA	3.4 ± 0.6	3.5 ± 0.8	0.82	0.69–0.96
LMCs	3.6 ± 0.5	3.6 ± 0.8	0.80	0.68–0.92
TOF-MRA				
ICA terminus	3.6 ± 0.6	3.6 ± 0.8	0.87	0.76–0.98
Proximal MCA	3.5 ± 0.7	3.5 ± 0.8	0.77	0.62–0.91
LMCs	3.0 ± 0.6	3.0 ± 0.8	0.77	0.62–0.92

CI, confidence interval; *ICA*, internal cerebral artery; *MCA*, middle cerebral artery; *LMCs*, leptomeningeal collaterals

Table 3 Inter-observer agreement of CNRs and the number of LMCs

	Observer 1	Observer 2	Intraclass correlation coefficient	95% CI
STAGE-MRA				
CNR M1	218.7 ± 90.7	217.1 ± 99.4	0.90	0.87–0.93
CNR M2	195.7 ± 86.0	191.0 ± 86.3	0.89	0.85–0.92
CNR M3	176.4 ± 71.6	181.0 ± 83.9	0.87	0.83–0.90
CNR M4	126.2 ± 62.9	128.9 ± 68.7	0.83	0.77–0.87
Number of LMCs	11.4 ± 3.4	11.8 ± 3.4	0.89	0.86–0.92
TOF-MRA				
CNR M1	176.2 ± 72.6	168.4 ± 72.1	0.88	0.84–0.91
CNR M2	146.6 ± 71.7	137.9 ± 70.3	0.94	0.92–0.96
CNR M3	125.8 ± 61.1	129.9 ± 66.7	0.89	0.86–0.92
CNR M4	78.8 ± 43.6	74.9 ± 42.4	0.84	0.79–0.88
Number of LMCs	8.4 ± 3.3	8.8 ± 3.3	0.87	0.83–0.91

CNR, contrast-to-noise ratio; *LMCs*, leptomeningeal collaterals; *CI*, confidence interval

strategic treatment of ICAD patients strongly depend on an accurate assessment of the presence of LMC, especially those presenting with stroke or TIA.

STAGE-MRA sequence used in this study was firstly proposed by Chen et al [9]. In their study, STAGE-MRA did a better job in removing the signal of background tissue than TOF-MRA, thus providing a better depiction of small arteries. The CNR of small arteries (M3 segment) was higher for STAGE-MRA than for TOF-MRA (27.1 ± 7.7 vs. 12.6 ± 5.1). For M1–2 segments, STAGE-MRA showed higher CNRs but the differences did not reach significance [9]. Although both techniques used the in-flow effect to produce hyperintensity of blood lumen, small arteries with slow velocity were typically invisible or had poor contrast to background tissues in conventional TOF-MRA. In contrast, STAGE-MRA used two echoes with identical acquisition parameters but different preparations for rapidly and slowly flowing spins. One echo was fully rephased providing hyperintensity of blood lumen, and the other was strongly dephased in all three orthogonal directions with no blood signals but keeping the stationary tissues the same with the rephased echo. Therefore, STAGE-MRA subtracted the background and thus increased the visibility of small arteries. Over and above this MRA advantage, STAGE-MRA could provide more versatile information than TOF-MRA. The interleaved STAGE-MRA sequence not only provided a good depiction of small vessels, but also offered the potential to create co-registered susceptibility weighted imaging (SWI), quantitative susceptibility mapping (QSM), and true SWI (tSWI) images in just under 6 min with a single scan [9]. QSM with an echo time of 12.5 ms provides improved visualization of tissues with different susceptibilities, including cerebral veins, microbleeds, calcifications, and cortical veins [15]. In addition, both tSWI and QSM images have proven useful in evaluating the presence of asymmetrically prominent cortical veins (APCVs) [16, 17] and iron deposition in the basal ganglia and midbrain [18]. Therefore, combined with the findings of the current study, STAGE-MRA is able to provide different sources of information regarding the morphology of the intracranial vasculature system.

We found high CNRs in both healthy volunteers and ICAD patients, demonstrating that image qualitative score was independent of the participant's pathophysiology. Although this approach is fairly robust to small patient movement, major motion can still be a problem [11]. By fixing the head with side cushions and soothing the participants during the rapid imaging acquisition time, we reduced the possibility of

Table 4 Image qualitative score comparison between STAGE-MRA and TOF-MRA ($n = 75$)

Observer	ICA terminus			Proximal MCA			LMCs		
	STAGE-MRA	TOF-MRA	*p*	STAGE-MRA	TOF-MRA	*p*	STAGE-MRA	TOF-MRA	*p*
1	2.4 ± 0.6	2.3 ± 0.7	< 0.001*	2.4 ± 0.6	2.2 ± 0.8	< 0.001*	2.6 ± 0.5	2.3 ± 0.7	< 0.001*
2	2.5 ± 0.6	2.3 ± 0.7	< 0.001*	2.6 ± 0.6	2.3 ± 0.9	< 0.001*	2.7 ± 0.5	2.4 ± 0.7	< 0.001*

ICA, internal cerebral artery; *MCA*, middle cerebral artery; *LMCs*, leptomeningeal collaterals

*p value significant

Table 5 Image qualitative score comparison of STAGE-MRA and TOF-MRA with reference to DSA ($n = 25$)

Observer	ICA terminus			Proximal MCA			LMCs		
	STAGE-MRA	TOF-MRA	*p*	STAGE-MRA	TOF-MRA	*p*	STAGE-MRA	TOF-MRA	*p*
1	3.5 ± 0.8	3.6 ± 0.6	0.727	3.4 ± 0.6	3.5 ± 0.7	0.250	3.6 ± 0.5	3.0 ± 0.6	< 0.001*
2	3.5 ± 0.8	3.6 ± 0.8	0.125	3.5 ± 0.8	3.5 ± 0.8	1.000	3.6 ± 0.8	3.0 ± 0.8	< 0.001*

ICA, internal cerebral artery; *MCA*, middle cerebral artery; *LMCs*, leptomeningeal collaterals

**p* value significant

motion artifacts and only one ICAD case was excluded because of severe motion artifacts.

There are several limitations in this study. First, the sample size in the ICAD group was relatively small. Although the clinical potential of STAGE-MRA could be inferred through its application in the 28 ICAD patients, increasing of the sample size would better demonstrate its clinical value. Second, STAGE-MRA and TOF-MRA did not have identical resolution with the former having a 2-mm slice thickness and the latter 0.7 mm. There are several reasons to it. First, we chose a slice thickness of 2.0 mm for STAGE-MRA to match that in Chen's study [9]. Since the purpose of this study was to assess the feasibility of using STAGE-MRA as an alternative method to TOF-MRA in a clinical setting, we adopted the slice thickness of 0.7 mm with TOF-MRA, which was optimized for clinical purpose at our institution. Nevertheless, STAGE-MRA still showed higher qualitative scores, improved CNRs, and greater number of LMCs than TOF-MRA. For the purpose of an even more direct comparison, identical resolutions should be used (as in Electronic Supplementary Material Fig. 4). Third, STAGE-MRA had dural sinuses and some superficial veins left on the image.

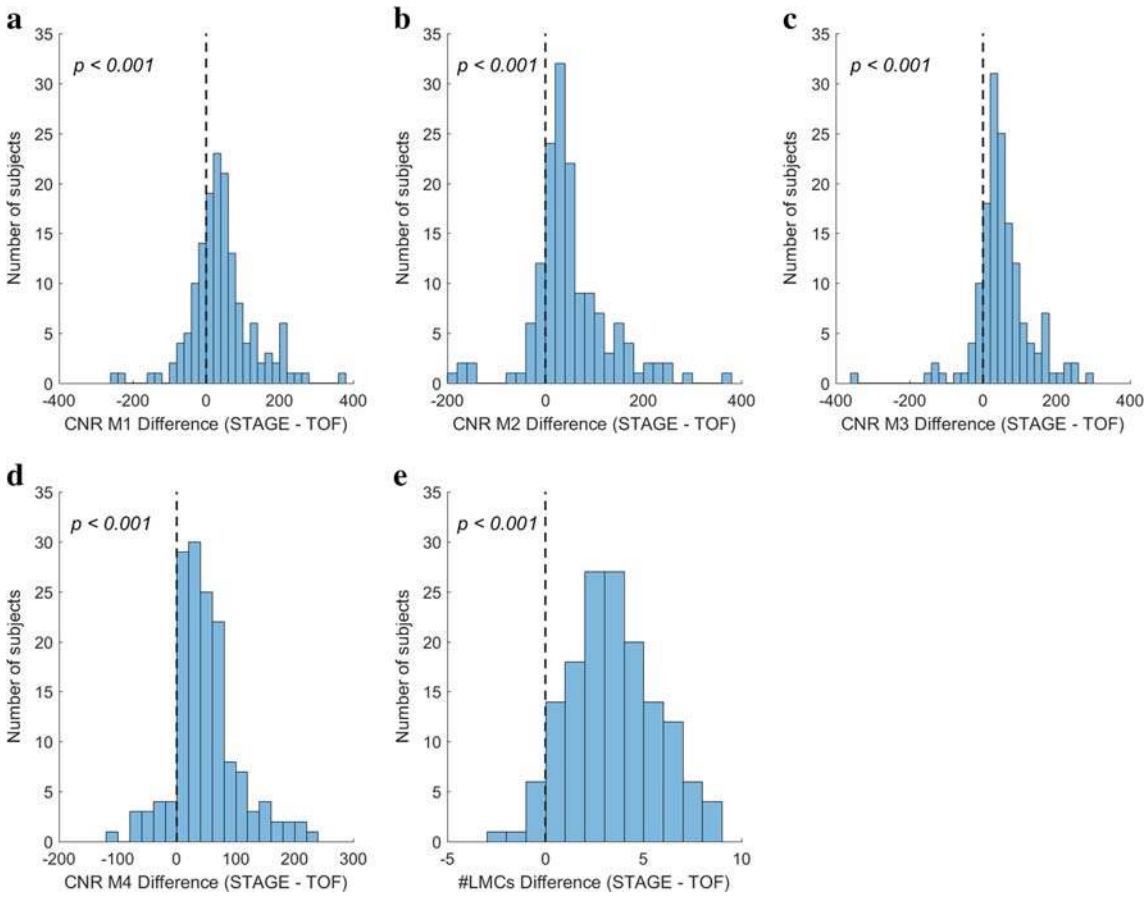

Fig. 4 Contrast-to-noise ratio (CNR) differences in M1-4 segments (**a**-**d**) and the number of leptomeningeal collaterals (LMCs, **e**). CNRs or the number of LMCs are: M1 (STAGE-MRA, 218.7 ± 90.7; TOF-MRA, 176.2 ± 72.6), M2 (STAGE-MRA, 195.7 ± 86.0; TOF-MRA, 146.6 ± 71.7), M3 (STAGE-MRA, 176.4 ± 71.6; TOF-MRA, 125.8 ± 61.1), M4 (STAGE-MRA, 126.2 ± 62.9; TOF-MRA, 78.8 ± 43.6) segments, and the number of LMCs (STAGE-MRA, 11.4 ± 3.4; TOF-MRA 8.4 ± 3.3)

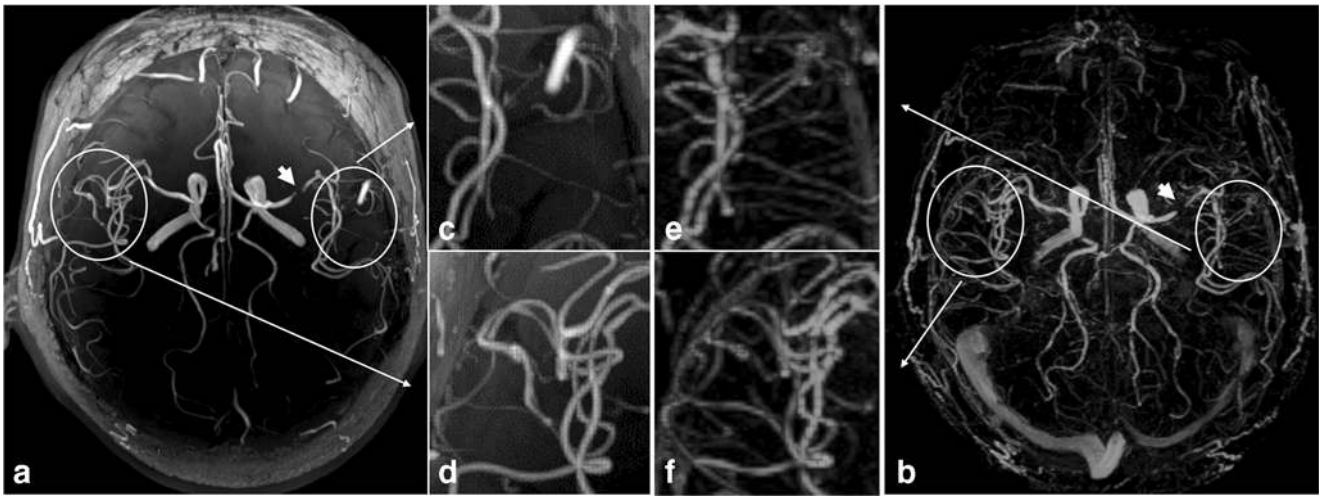

Fig. 5 Images of a 56-year-old male patient with atherosclerotic ischemic stroke. He suffered from left limb weakness for 20 days. The occlusion of the M1 segment (white arrowheads) on the 90-mm maximal intensity projection images of both TOF-MRA (**a**) and STAGE-MRA (**b**) is clearly demonstrated. (**c**, **d**) represent zoomed in images of the lesion side and contralateral side at TOF-MRA, which shows fewer number of LMCs than at STAGE-MRA (**e**, **f**), indicating the patient has robust LMC collaterals and the LMC status might be underrated with TOF-MRA

This is because the rephasing/dephasing strategy used in STAGE-MRA depicts a "flow-only" image which yields MRAV image. To create the final STAGE-MRA image, the venous blood lumen is then suppressed by a QSM mask generated from the same scan [9]. The QSM reconstruction uses the brain extraction tool (BET) which typically excludes the edge of the brain where the dural sinuses and cortical veins appear. Therefore, the pipeline only suppresses venous blood lumen inside the BET mask [19]. In the present study, the appearance of cortical veins might result in excessive counts of LMCs when the cortical veins were adjacent to the cortical LMCs and large dural veins are anatomically distinct from the arteries, and thus could be easily distinguished during image analysis. Knowing the potential bias, the observers avoided placing ROIs near large cortical and dural veins when performing quantitative analysis. In the future, these potential venous confounds could be removed by using an improved QSM reconstruction for dural sinuses and cortical veins. Fourth, qualitative assessment might be biased by recognition of the sequences. STAGE-MRA had a lower resolution with more venous structures and TOF-MRA showed more residual stationary tissue. Therefore, the observers could easily distinguish the two sequences although they were blinded to the type of sequences. Quantitative evaluation was objectively measured and qualitative analysis was potentially biased.

In conclusion, we found that STAGE-MRA was better than TOF-MRA in qualitative and quantitative assessments of LMCs in both healthy volunteers and ICAD patients.

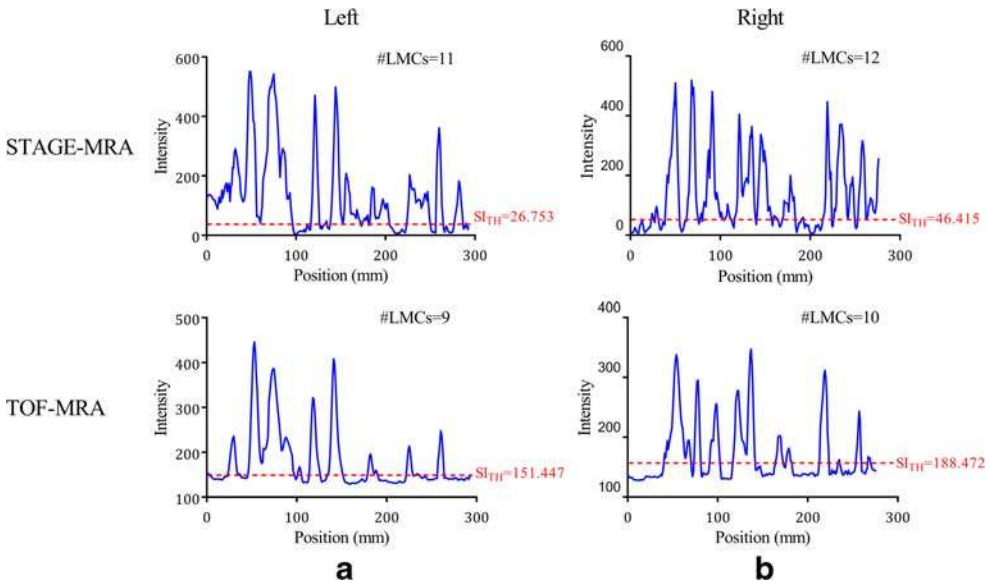

Fig. 6 Line signal profiles of the left (**a**) and right (**b**) hemispheres of a 63-year-old healthy volunteer at STAGE-MRA (upper row) and TOF-MRA (lower row). The number of leptomeningeal collaterals is measured by counting the peaks of the vessel. The threshold signal intensity (SI_{TH}) is calculated (red dotted line) and a signal is defined as coming from a vessel if it is higher than the threshold

STAGE-MRA was a reliable technique in evaluating LMC with good-to-excellent inter-observer agreement and may serve as an alternative method to TOF-MRA in clinical practice.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Shuang Xia.

Conflict of interest EMH works for SpinTech which has a business interest in STAGE and SPIN software. The other authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (healthy volunteers and patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
- Diagnostic or prognostic study
- Performed at one institution

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