Dear reviewers

Re: Manuscript NO: 69503 and Title: Application of Synthetic MRI Magnetic Resonance Angiography in Acute Stroke

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Application of Synthetic MRI Magnetic Resonance Angiography in Acute Stroke"(69503). Those comments are valuable and very helpful. We have read through comments carefully and have made corrections. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciate your time and consideration.

Sincerely.

Wang Qi.

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Retrospective Cohort Study
Application of Synthetic MRI Magnetic Resonance Angiography in Acute Stroke

Qi W et al. Synthetic MRI in Acute Stroke

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Author Contributions: Qi Wang, Gang Wang designed and coordinated the study; Qiang Sun and Hedi Sun treated the patients.

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Abstract

AIM
To explore the application value of vascular images obtained by synthetic MRI in diagnosing acute ischemic stroke.

METHODS
A total of 64 patients with acute ischemic stroke were selected and examined by MRI in the current retrospective cohort study. The scanning sequences included traditional T1, T2, and T2-FLAIR (fluid-attenuated inversion recovery), three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA), diffusion-weighted imaging (DWI), and synthetic MRI. Conventional contrast images (T1, T2, and T2-FLAIR) and intracranial vessel images (MAGiC [MAGnetic resonance Imaging Compilation] phase-sensitive inversion recovery [PSIR] Vessel) were automatically reconstructed using synthetic MRI raw data. The contrast-to-noise ratio (CNR) values of traditional T1, T2, and T2-FLAIR images and MAGiC reconstructed T1, T2, and T2-FLAIR images in DWI diffusion restriction areas were measured compared. MAGiC PSIR Vessel and TOF MRA images were used to measure and calculate the stenosis degree of bilateral middle cerebral artery stenosis areas. The consistency of MAGiC PSIR Vessel and TOF MRA results displaying the degree of vascular stenosis with computed tomography angiography (CTA) test results were compared.

RESULTS

Among the 64 patients with acute ischemic stroke, 79 vascular stenosis areas showed that the correlation between MAGiC PSIR Vessel test results and CTA ($r=0.90$, $p<0.01$) was higher than that between TOF MRA test results and CTA ($r=0.84$, $p<0.01$). With a degree of vascular stenosis >50% assessed by CTA as a reference, the area under the receiver operating characteristic (ROC) curve of MAGiC PSIR Vessel (AUC [area under the curve]=0.906, $p<0.01$) was higher than the area under the ROC curve of TOF MRA (AUC=0.790, $p<0.01$). Among the 64 patients with acute ischemic stroke, 39 patients were scanned for traditional T1, T2, and T2-FLAIR images and MAGiC images simultaneously, and CNR values in DWI diffusion restriction areas were measured, which were traditional T2=21.2, traditional T1=-6.7, traditional T2-FLAIR=11.9; MAGiC T2=7.1, MAGiC T1=-3.9, MAGiC T2-FLAIR=4.5.

CONCLUSION
The synthetic MRI vascular screening scheme for patients with acute ischemic stroke can accurately evaluate the degree of bilateral middle cerebral artery stenosis, which is of great significance to early thrombolytic interventional therapy and improving patients' quality of life.

Keywords: acute ischemic stroke, magnetic resonance imaging, magnetic resonance angiography.

Core Tip:
This study evaluated the application value of vascular images obtained by synthetic MRI in diagnosing acute ischemic stroke. Synthetic MRI can obtain vascular images simultaneously as T2, T1, T2Flair and other contrast images. Compared with the results of CTA examination, we found that the vascular images can be used to positively evaluate the degree of intracranial bilateral middle cerebral artery stenosis, which is of great significance to early thrombolytic interventional therapy and improving patients' quality of life.

INTRODUCTION

Cerebrovascular disease is the second deadliest disease globally, and acute cerebrovascular disease also has the highest disability rate than any other single disease, which brings heavy burdens to society [1-4]. In recent years, imaging has played an increasingly prominent key role in preventing and treating cerebrovascular disease [5]. For example, in treating acute stroke, the treatment time window of some patients with macrovascular diseases can be extended by 6–24 hours using image evaluation [6, 7]. The long-term survival rate and recurrence rate after acute ischemic stroke also vary significantly with the different causes of the first stroke. The five-year survival rate of small vessel disease is the highest in both males and females, and the five-year recurrence rate is lowest in female patients with small vessel disease and male patients with large vessel diseases [8]. The traditional magnetic resonance imaging technology, three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) has been widely used in screening cerebrovascular diseases because of its advantages, including non-invasiveness, non-radiation, and no need to inject contrast media [9,10]. However, in the imaging examination of patients with acute stroke, saving time can

save the brain, so the shorter the examination process, the better outcome. Traditional sequences such as T1, T2, T2-FLAIR (fluid-attenuated inversion recovery), TOF MRA, and diffusion-weighted imaging (DWI) require separate scanning, so it usually takes more than 10 minutes to complete all the examinations. Furthermore, 3D TOF MRA may overestimate the degree of vascular stenosis due to the hemodynamic changes in stenotic vessels.

Synthetic MRI MAGiC (MAGnetic resonance Imaging Compilation), is a newly emerging magnetic resonance imaging technology. While completing one scan, the technician can acquire conventional T1, T2, T2-FLAIR, and other contrast images, T1 mapping and T2 mapping quantitative images, as well as MAGiC phase-sensitive inversion recovery (PSIR) Vessel cerebrovascular images simultaneously through post-processing, which significantly shortens the scanning time required for magnetic resonance examination [11-14]. In recent years, some researchers reported that MAGiC can reconstruct various contrast images that can be applied in patients with acute ischemic stroke, and T2mapping images acquired by MAGiC can more accurately evaluate stroke onset time [15, 16]. However, evaluating the clinical application value of the intracranial vascular images acquired by MAGiC has not been reported.

This study aims to compare the accuracy of MAGiC PSIR Vessel and TOF MRA in evaluating the stenosis degree of bilateral middle cerebral arteries. Moreover, to further explore the application value of synthetic MRI MAGiC in acute ischemic stroke.

MATERIALS AND METHODS

General information

A total of 64 patients with acute ischemic stroke diagnosed by the neurology department of our hospital (The Stroke Hospital of Liaoning Province, Liaoning Province, China) from November 2020 to May 2021 were retrospectively analyzed (all conforming to the 2018 edition of Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke), including 44 males and 20 females, aged from 41 to 78 years(average age: 58 years). Upon admission, all patients underwent multi-sequence brain MRI scanning (including DWI, TOF MRA, and synthetic MRI MAGiC), and CTA scanning was performed within three days after MRI examination. The post-processing images of DWI, TOF MRA, synthetic MRI, and computed tomography angiography (CTA) were retrospectively analyzed. All patients signed the informed consent form before examinations.

Scanning equipment and parameters

In this study, SIGNAPioneer 3.0T MR scanner (GE, USA) with 21-channel head phased-array coil was used. The main scanning sequences are shown in Table 1.

Image post-processing and analysis

MAGiC original image and images (T1, T2, T2-FLAIR, T2 mapping, and MAGiC PSIR Vessel) automatically generated by the post-processing software supplied with the GE host after scanning, as shown in Figure 1.

The 3D TOF MRA and MAGiC PSIR Vessel images were post-processed by Reformat software of GE ADW4.7 workstation. The two examination methods obtained the consistency between the degrees of intracranial vascular stenosis and CTA evaluation was evaluated, respectively.

Degree of vascular stenosis = (1-diameter of the lumen at stenosis/diameter of the lumen of an adjacent normal blood vessel) × 100%

With CTA vascular stenosis degree greater than 50% as the classification point, receiver operating characteristic (ROC) curves were plotted for the two examination methods, and measured TOF MRA and MAGiC PSIR Vessel, and the areas under the curves.
The method for measuring contrast-to-noise ratio (CNR) values in DWI diffusion restriction areas of traditional T1, T2, and T2-FLAIR images as well as MAGiC T1, T2, T2-FLAIR images was as follows:

CNR = (mean intensity of stroke lesion - mean intensity of thalamus)/standard deviation of the thalamus

Statistical analysis
All quantitative data were analyzed and processed by SPSS25.0 statistical software.
With CTA as the control, the consistency and correlation of the two examination methods TOF MRA and MAGiC PSIR Vessel with CTA in evaluating the degree of vascular stenosis were evaluated by Bland-Altman plots and Spearman correlation analysis, respectively. The significant difference was set as $p<0.05$.

RESULTS
Figures 2-3 show the evaluation of intracranial vascular stenosis degree by 3D TOF MRA, MAGiC PSIR Vessel, and CTA. The correlation between MAGiC PSIR Vessel and CTA ($r=0.90$, $p<0.01$) was higher than that between TOF MRA and CTA ($r=0.84$, $p<0.01$). The area under the ROC curve of MAGiC PSIR Vessel (AUC=0.906, $p<0.01$) was higher than that of TOF MRA (AUC=0.790, $p<0.01$), as shown in Figure 4.
MAGiC-reconstructed multi-contrast images had reduced CNR values of DWI diffusion restriction areas than the traditional multi-contrast images, with traditional T2=21.2, traditional T1=-6.7, and traditional T2-FLAIR=11.9; MAGiC T2=7.1, MAGiC T1=-3.9, and MAGiC T2-FLAIR=4.5, as shown in Figure 5. In addition, two experienced diagnosticians respectively evaluated whether the images obtained by the two methods could meet the clinical diagnostic requirements of stroke. The results showed that both methods could meet the clinical diagnostic requirements.

DISCUSSION
Synthetic MRI MAGiC is a quantitative magnetic resonance imaging technique, which can generate a variety of conventional contrast images (T1, T2, T2-FLAIR, etc.), quantitative images (T1 mapping and T2 mapping), and intracranial vessel images (PSIR Vessel) simultaneously in single scan by acquiring the T1 relaxation rate, T2 relaxation rate, and PD density value of tissues, and has been applied in many sites such as nerves and joints [17-27]. Among them, research has been conducted on the application of T2 mapping in the nervous system, such as the evaluation of edema around tumors and showed epileptic lesions. In recent years, in the imaging diagnosis of stroke, many studies have been conducted to apply

synthetic MRI imaging technology. For example, T2 mapping quantitative images acquired by MAGiC could more accurately evaluate stroke onset time [28, 29, 30].

Magnetic resonance imaging can provide important imaging evidence in the prevention, diagnosis, and treatment of cerebrovascular diseases. However, its long scanning time, especially in patients with hyperacute stroke, contradicts the clinical need to carry out treatment as soon as possible. For example, the evaluation of vascular stenosis degree in acute stroke is of great value in defining the etiology, responsible vessels and guiding the selection of subsequent clinical treatment regimens. However, traditional TOF MRA scanning usually takes 3 to 5 minutes; therefore, a vascular imaging technique with a shorter scanning time is needed in magnetic resonance imaging examination. MAGiC PSIR Vessel intracranial blood vessel images are generated simultaneously with conventional T1, T2, and other contrast images, as well as T1 mapping, T2 mapping, and other quantitative images, which can be initially used for screening intracranial blood vessels without occupying additional scanning time. Its imaging principle is based on the use of difference in phase information between flowing blood flow and stationary tissues to image blood vessels, reducing the influence of hemodynamics on blood vessel imaging. In contrast, traditional TOF MRA imaging technology uses the enhancement effect of blood inflow to obtain blood vessel images, which will be affected by changes in hemodynamics. In the area of vascular stenosis, the degree of stenosis may be overestimated due to turbulent or slow blood flow [31-36]. This study revealed that with CTA results as a reference, the areas under ROC curves of MAGiC PSIR Vessel examination were higher than traditional TOF MRA examinations in patients with vascular stenosis greater than 50%. Some patients diagnosed with vascular occlusion due to intracranial vessels not displayed by TOF MRA only showed moderate to severe stenosis on MAGiC PSIR Vessel and CTA images. In terms of scanning time, the scanning time of synthetic MRI MAGiC was about 4.5 minutes, and the scanning time of MAGiC combined with DWI was about 5 minutes, which was significantly less than that of the traditional scanning scheme of TOF MRA and DWI combined with T1, T2, and T2-FLAIR (usually more than 10 minutes), which is conducive to improving the MRI examination efficiency for patients with acute stroke and treatment window for clinical thrombolytic intervention as soon as possible.

To obtain a clear enough blood vessel display, the slice thickness of the MAGiC scan image was set at 1.6 mm, which made the CNR values of T1, T2, and T2-FLAIR images generated by MAGiC decrease compared with traditional images due to the influence of the decrease in image signal-to-noise ratio. However, the overall display of lesions could meet the diagnostic needs of stroke. In addition, the slices in the MAGiC image were thinner.

There were some limitations to this study. First, this is a retrospective study, and some patients needed to complete CTA and MRI examinations simultaneously, which might result in selection bias. Meanwhile, due to this reason, not all the patients could be scored by the National Institute of Health stroke scale (NIHSS). Second, the number of cases was relatively small, which was mainly because MRI is not widely used in the diagnosis and treatment of acute stroke in clinical departments, as it is considered that the scanning time of this technique is relatively long, which may delay the diagnosis and treatment time of patients. Third, this study did not evaluate the long-term outcomes of patients, e.g., the proportion of recurrent stroke in patients treated with vascular recanalization. The evaluation of long-term outcomes of patients can further clarify the relationships of vascular stenosis degree judgment with

cerebrovascular recanalization treatment and stroke recurrence.

In conclusion, synthetic MRI quantitative and multi-contrast imaging technology MAGiC can simultaneously obtain a variety of conventional contrast images (T1, T2, T2-FLAIR, etc.), intracranial vessel images (MAGiC PSIR Vessel) and both T2 and T1 relaxation time quantitative images (T2 mapping, T1 mapping) in one scan, which can accurately determine the onset time of stroke, preliminarily screen intracranial vessels, and further shorten the magnetic resonance imaging examination time of patients with acute stroke, thereby guiding clinical thrombolytic intervention as early as possible and improve patients' quality of life.

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