

The diagnostic value of susceptibility-weighted imaging for ischemic penumbra in patients with acute ischemic stroke

Tianle Wang^{a,b}, Li Zhu^b, Chunhong Hu^{a,*}, Shenchu Gong^b, Hongbiao Jiang^b, Haitao Chen^b and Jia Li^c

^a*Department of Radiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China*

^b*Department of Radiology, The Second Affiliated Hospital of Nantong University, Nantong, Jiangsu, China*

^c*Department of Neurology, The Second Affiliated Hospital of Nantong University, Nantong, Jiangsu, China*

Abstract.

BACKGROUND: The ischemia penumbra area is not easy to be detected accurately using noninvasive imaging methods.

OBJECTIVE: We aim to assess the diagnostic value of susceptibility-weighted imaging (SWI) for ischemic penumbra in patients with acute ischemic stroke.

METHODS: A retrospective analysis was carried out in 47 patients with ischemic stroke involving the middle cerebral artery. Mean transit time (MTT), time to peak, relative cerebral blood flow, and relative cerebral blood volume maps were created after image processing.

RESULTS: No significant difference was found in the mismatch between the SWI and diffusion-weighted imaging (SWI-DWI) or in the MTT-DWI mismatch scores ($P = 0.056$, Kappa = 0.864).

CONCLUSIONS: SWI provides information comparable to PWI and, thus, could serve as a reliable magnetic resonance technique for assessing ischemic penumbras.

Keywords: Susceptibility-weighted imaging, perfusion-weighted imaging, ischemic penumbra

1. Introduction

The ischemic penumbra, first proposed by Astrup et al. [1], initially referred to the area of the brain in which electrical activity disappeared. This disappearance was thought to be caused by maintenance of the membrane potential and transmembrane ion potential during cerebral ischemia. Perfusion abnormalities in brain tissue can be seen clearly with perfusion-weighted magnetic resonance imaging (PWI) following a rapid bolus of a contrast agent. This imaging technique shows four key characteristics: relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), time to peak (TTP), and mean transit time (MTT). Changes in brain tissue hemodynamics can be evaluated visually by combining the values of

*Corresponding author: Chunhong Hu, Department of Radiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China. Tel.: +86 51385061105; Fax: +86 51385061003; E-mail: soochowhch@163.com.

these four characteristics. In previous studies [2,3], investigators reported that the hyperintense lesion seen with diffusion-weighted imaging (DWI) generally indicated the core infarct area. Kamath et al. [4] suggested that MTT was most closely related to the oxygen extraction fraction (OEF). In a study using positron emission tomography (PET), Yata et al. [5] reported that an increase in OEF is closely related to an increase in MTT. Based on the similarity in metabolism data indicated by these two values, MTT was used as the perfusion index for comparison with SWI in their study.

Penumbra has been defined as an area of increased OEF detected by PET-CT [6]. Ischemic penumbra has also been evaluated using CT-PWI. Maija et al. [7] were able to determine a reference value for distinguishing the infarct from the penumbra, but were not able to establish reliable thresholds. While Chen and Ni [8] suggested that PDM could replace PET-CT. Additionally, gadolinium, which is introduced during perfusion scans, can induce an allergic reaction in some patients. Huang et al. [9] believe that gadolinium may cause nephrogenic systemic fibrosis (NSF), which may trigger renal dysfunction. Kuo et al. [10] have also suggested that any contrast agent may cause NSF. In patients who have had an acute ischemic stroke, deoxygenated hemoglobin may serve as a “natural” contrast agent, given that it is hypointense on minimum intensity projection (minIP) imaging.

Therefore, we carried out a prospective study in those patients who had had an acute ischemic stroke using susceptibility-weighted imaging (SWI) and MR PWI as a contrast to detect ischemic penumbras.

2. Materials and methods

2.1. Patients

Patients who had had an acute ischemic stroke between 2013 and 2014 were selected as study subjects. Inclusion criteria were a maximum of 72 hours from time of stroke onset to the time of the MR testing; clinical symptoms that included hemiplegia or hemiparesis, with or without a speech disorder; an abnormal signal within the area served by the middle cerebral artery and identified on the MR-DWI ($b = 1000$) map; decreased apparent diffusion coefficient (ADC) in the ADC map; exclusion of infarction within the encephalon or brainstem; exclusion of hemorrhagic stroke; and no thrombolysis or anticoagulant therapy before the MRI. A total of 47 cases (29 men and 18 women) aged 38 to 84 years (median age: 71 years; average age: 72.3 years) were enrolled. The clinical study protocol underwent an ethics review and was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University in Suzhou City, China. Paraffin-embedded tissue blocks, obtained from our tumor tissue repository, were used in several experiments; patient consent for information provided through these experiments was obtained.

2.2. Image acquisition

The Siemens Verio 3.0-T MRI system used in this study (Siemens; Munich, Germany). Post-MRI processing and image evaluation were carried out in a syngo[®] MR WorkPlace (Siemens) workstation. A LF Optistar[™] LE double-syringe power injector (Mallinckrodt Pharmaceuticals; St Louis, MO) was used. The MRI scanning sequence included conventional T₁WI, T₂WI, fluid-attenuated inversion recovery (FLAIR), DWI, SWI, and PWI, with a test time of about 12 minutes. Scanning parameters for T₁WI, T₂WI, T₁-FLAIR, DWI, and SWI included TR = 1500 ms, TE = 30 ms, FA = 90°, slice thickness = 4.0 mm, slice gap = 5.2 mm, FOV = 230 × 100 mm, and slice number = 950 (single selection). A total of 900 consecutive images were selected from 60 groups. Magnevist (Gd-DTPA; Bayer Schering, Leverkusen, Germany) was used as the MRI contrast agent at a dosage of 0.1 mmol/kg. A bolus injection was administered using the power injector at a rate of 4 ml/s.

2.3. Image processing

Post-imaging SWI processing for the whole-brain vein image involved a 1.2-mm thick slice of the original image. The minIP was carried out on the magnetic torque image using 3DMIP software. A rebuilt slice thickness of 9.6 mm was obtained without any gap. Processing of MRI brain perfusion images involved sending the scanning images to the post-processing syngo[®] MR WorkPlace. rCBV, rCBF, TTP, and MTT maps were created using perfusion software to monitor the cerebral artery and to use as a reference for creating perfusion curves.

2.4. Assessing ischemic penumbra with PWI, SWI

The perfusion-diffusion mismatch (PDM) was determined by superposing the PWI (MTT) map on the DWI image using Fusion software, which was available with the syngo[®] MR WorkPlace; this allowed us to determine whether the signal areas were the same. The susceptibility-diffusion mismatch (SDM) was determined by superposing the minIP map on the SWI with a DWI image using the same software to determine whether the increase in SWI-detected venous area in the epithelial layer is consistent with that indicated by the DWI signal. Two trained physicians blinded to patient information (except clinical history of ischemic stroke) independently and simultaneously assessed the ASPECTS values (SWI, DWI, MTT) of selected images. Disagreements between the raters were resolved by consensus. To compare PDM and SDM scores, we used the ASPECTS method [11], i.e., we divided the area served by the middle cerebral artery into 10 sections – the caudate nucleus, lenticular nucleus, internal capsule, six cortical areas overlying the middle cerebral artery area (Sections M1, M2, M3, M4, M5, and M6) and the insula – and deducted 1 point for each section involved (Fig. 1).

2.5. Statistical analysis

To define ischemic penumbra by PDM, the SDM and PDM were analyzed by chi-square test, with a P value < 0.05 used to indicate a statistically significant difference. A consistent analysis to define the ischemic penumbra range based on any change in size of the area of the epithelial layer occupied by the vein, as detected by SWI, involved the use of statistical software (SPSS 21.0; IBM, New York, NY). A paired t -test was used for statistical analysis, with a P value < 0.05 used to establish statistical significance.

3. Results

3.1. DWI, SWI, and PWI manifestations of acute ischemic stroke

A total of 137 lesions were found in 47 patients with acute ischemic stroke. These lesions demonstrated hyperintensity on DWI ($b = 1000$) and a reduced signal on ADC. Lesions were found within the caudate nucleus ($n = 13$), lenticular nucleus ($n = 26$), insula ($n = 11$), internal capsule ($n = 28$), and all six cortical regions overlying of the middle cerebral artery ($n = 59$). Sixteen patients had prominent veins within the area of the lesion, six demonstrated vein reduction or disappearance around the lesion area; and 25 showed no change in venous area on SWI. An additional 15 patients had microbleeds, each appearing as a round or roundish hypointensity on SWI and hypointensity on the phase detection microscopy image. An intracranial arterial embolus was found in 14 patients, who showed a susceptibility

Table 1
PWI-DWI mismatch, increased cortical veins sign

PWI-DWI	Increased cortical veins sign	
	Positive	Negative
Positive	16	3
Negative	0	28

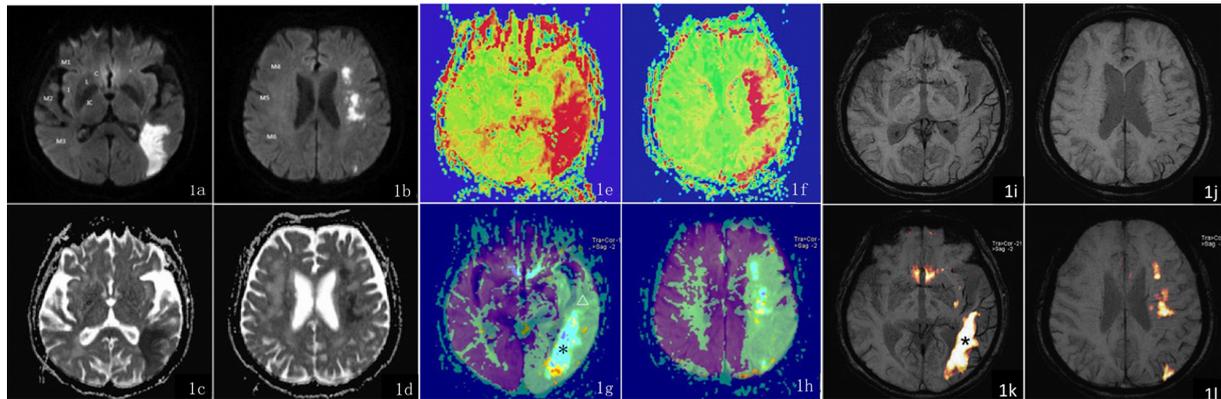


Fig. 1. A female patient, 76 years old, complains of left-sided numbness on when she tries to stand quickly and aphasia over the past 15 hours. Figures 1a and 1c show a patchy hyperintensity on SWI in a single cortical area (Section M3) served by the left middle cerebral artery (area M3). The ADC image shows a reduced ADC value in the left occipital lobe. Figures 1b and 1d show a patchy hyperintensity on SWI in 3 areas served by the left middle cerebral artery (Sections M4-M6) and a decreased ADC signal: ASPECTS = 6 scores. Figures 1e and 1f present a perfusion image (MTT map) with the MTT extending into the left insula and all 6 areas served by the left middle cerebral artery (Sections M1-M6): ASPECTS = 3 scores. Figures 1g and 1h show superimposed DWI and MTT images. Δ indicates an area with an abnormal perfusion signal area; * indicates an area of hyperintensity detected by DWI. The area of abnormal perfusion is clearly larger than the abnormal DWI area in the superposed image. Figures 1i and 1j show a greater number of enlarged small veins in the left insula and in all 6 cortical areas served by the left middle cerebral artery (Sections M1-M6) than are seen on the other side in the SWI minIP image: ASPECTS = 3 scores. Figures 1k and 1l show superposed DWI and minIP images. * indicates an area of DWI-detected hyperintensity. The area containing an increased number of small veins is larger on SWI compared with the abnormal area shown on the DWI. Key: C, caudate nucleus; L, lenticular nucleus; IC, internal capsule; middle cerebral artery cortical areas (Sections M1-M6); I, insula.

vessel sign (SVS). MTT, TTP, CBV and CBF perfusion images were basically the same on both sides of the brain in one patient; MTT and TTP perfusion values were greater on one side than on the other within the middle cerebral artery territory in 46 patients, CBF and CBV were decreased on one side compared with the other in 29 patients, and CBF and CBV were increased on one side compared with the other in 17 patients.

3.2. A consistent analysis for assessing ischemic penumbræ with PWI and SWI

Table 1 shows PWI values that define the ischemic penumbra and signs of an increased number of enlarged veins. The change in these values did not reach statistical significance ($P = 0.250$, Kappa value = 0.864).

An ASPECTS assessment performed on 16 patients revealed both a PWI-DWI and a prominent vein sign. The difference in PWI-DWI versus SWI-DWI scores did not reach statistical significance ($P = 0.056$, Kappa value = 0.508) (Table 2).

Table 2
ASPECTS assessment with different imaging techniques

Case	Imaging techniques		
	SWI	DWI	PWI(MTT)
1	3	6	4
2	3	5	4
3	7	9	6
4	3	8	4
5	5	8	5
6	4	7	3
7	3	7	3
8	6	8	6
9	7	9	6
10	4	7	4
11	5	9	5
12	5	9	5
13	5	8	5
14	3	8	4
15	5	7	5
16	3	8	3

4. Discussion

There are currently three hypotheses for the increase in vein area occupied by an acute ischemic penumbra detected by SWI of the epithelial layer: (1) an increase in deoxyhemoglobin (DHb) levels in venous blood; (2) an increase cerebral blood volume (CBV) facilitated by compensatory vascular dilation; and (3) an increase in the number of veins around the infarct involved in the formation of a compensatory collateral circulation.

Regarding the first hypothesis, the reduced blood supply following the formation of an infarct increases the need for oxygen than normal by affected brain tissue. The relative increase in oxygen required in the artery around the infarct results in a relative increase in DHb in venous blood. Mittal et al. [12] reported that the increase in DHb and decrease in oxyhemoglobin in the capillary and vein may be caused by the uncoupling of oxygen in the hypoperfused tissue. Mammen [13] reported further that the magnetic susceptibility of the tissue could change in response to the reduction in blood flow caused by a thromboembolism, which, in turn could cause an increase in DHb and in the amount of deoxygenated blood. This could lead to the appearance of a cortical vein on SWI. Regarding the second hypothesis, the first compensatory response to a decrease in cerebral perfusion pressure may involve an increase in cerebral blood volume (CBV), which would be facilitated by blood vessel dilation [14]. This could result in the appearance of a prominent vein on SWI with no additional changes. Additionally, 70% to 80% of the total blood volume is venous blood. Therefore, a change in blood volume can result from the dilation of a small vein. Regarding the third hypothesis, the formation of a collateral venous circulation around the infarct may facilitate the restoration of a normal blood supply to the ischemic tissue in the future [15]. The smaller the “new” veins are, the better the collateral circulation is.

Thrombolytic therapy is the most effective treatment currently available for patients who have had an acute ischemic stroke. Our study demonstrates that the selection of patients with an ischemic penumbra and lacking any bleeding risks is the key to a successful outcome with thrombolytic therapy. Thus, a pre-treatment assessment for ischemic penumbræ is of great importance. The internationally recognized therapeutic time window (TTW) for thrombolytic therapy following a stroke is 3 hours [16]. In clinical practice, however, neurologists have found that some patients who are seen within the TTW demonstrate

an infarct on imaging tests. It may still be possible to save cerebral tissue in some patients who are seen well past the TTW using a functional imaging test, and neurological function could be restored satisfactorily using thrombolytic therapy. Some investigators now believe that the TTW can be extended up to 12 hours [17]. If so, thrombolytic therapy that is provided according to the accepted TTW could be ineffective in some patients, whereas other patients who could have benefited from early therapy may “miss the boat.” Thus, determining whether an ischemic penumbra exists could be the most important process in thrombolytic therapy. Parsons et al. [18] compared patients who underwent thrombolytic therapy with those who received the recombinant tissue plasminogen activator (rt-PA) and found that the development of an infarct due to mismatching tissue could be reduced in patients with an acute infarction and PDM. In a multicenter study [19], a significant correlation between early reperfusion and clinical recovery was found for patients with PDM but not for those without PDM. Since the aim of the study was to compare SWI and PWI, no follow-up was provided for patients with increased veins, although three patients demonstrated a final infarcted area that was smaller in size than the abnormal perfusion area initially measured during in the clinical examination. Neurological function in these patients was successfully recovered. Further study should focus on the correlation between the increase in epithelial vessels on SWI and prognosis.

SWI has been drawing an increasing amount of attention from the medical profession as an MRI test that can reflect changes in cerebral blood oxygen levels [20]. In our study, 16 patients showed signs of an increase in vein size and they all had a PDM. Meanwhile, the prolongation of MTT and TTP and the decline in CBF and CBV on the perfusion map indicated a state of hypoperfusion in the infarcted cerebral area. The ASPECTS system was used to assess PDM and evaluate SWI quantitatively in terms of the increased epithelial area occupied by veins. The system provided information about local anatomy, thereby reducing differences among raters or misjudgment caused by tissue atrophy and edema. In a study by Barber and colleagues [21,22], the ASPECTS assessment was also applied in PWI and DWI imaging and found to be related to planimetric volume measurements. Mismatched areas could be predicted by the MR mismatch fraction, which is height-specific. Given that a clinician would probably assess the patient’s medical conditions on a scale, ASPECTS may play an important role in the quantitative evaluation of patients with acute ischemic stroke. ASPECTS is also believed to be an independent factor for predicting the prognosis for patients with an acute ischemic stroke [23]. A comparison of quantitative scores for the MTT-DWI mismatch versus the SWI-DWI mismatch revealed no significant difference and good consistency ($P = 0.056$, $P > 0.05$, Kappa = 0.508). A retrospective analysis was carried out in 31 patients who showed no increased veins sign (Fig. 2), even though the time from stroke onset to MRI testing exceeded 24 hours.

An intracranial artery thrombus was seen as a hypointensity walking along the vessel on an SWI image. It has been reported in the literature [24] that a magnetic resonance angiogram (MRA) and SWI can be used to detect an intracranial artery embolus in a patient with an acute ischemic stroke. Compared with an MRA, however, a susceptibility vessel sign (SVS) is more likely to indicate a clogged artery. A cerebral artery embolus was identified in 14 patients in our study. Moulin et al. [25] reported that more than one-fourth of patients with acute ischemic stroke may present microbleeds compared with no more than 10% of a healthy population. Microbleeds appeared as dispersed hypointensities less than 0.5 cm in diameter in our study. These hypointensities indicated hemosiderin deposits [26]. Multiple microbleeds may indicate an increase in blood vessel fragility. Among patients with an acute infarction, 20% to 40% showed bleeding transitions one week after onset, this introduces a great possibility of serious complications [27]. Studies have suggested a significant correlation between microbleeds and bleeding transitions after infarction [25]. However, the foci of potential microbleeds could not be detected using

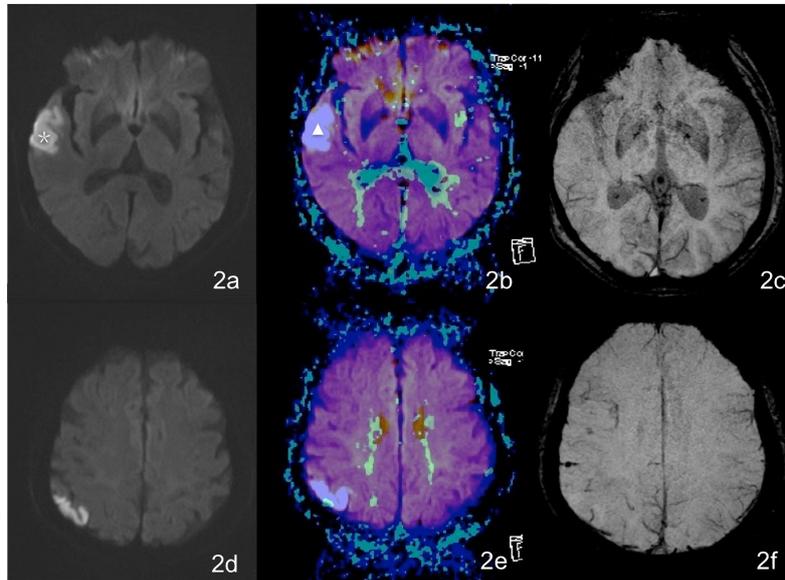


Fig. 2. A female patient aged 76 years complains of vague speech for 46 hours. Figures 2a and 2d show patchy hyperintensity on a DWI of the right temporal lobe and occipital lobe. In Figs 2b and 2e, the white Δ indicates an area with an abnormal MTT signal within an area detected by a DWI superimposed on it. In Figs 2c and 2f, the black \star indicates an area of DWI-detected hyperintensity with no increase in the number of small veins seen on superposed images of the SWI minIP and DWI.

a conventional MRI. The SWI was of great importance as a conventional test sequence for patients with acute ischemic stroke.

The findings of this study are limited due to an inadequate number of study samples and that a relatively long SWI scanning time (5 min 5 s). Some patients with a serious acute ischemic stroke were uncooperative during the examination, and this led to some mobile false images and deviations in judgment. There are some limitations in this study. First, the sample size of this study was small, more samples were required to validate the effect in clinical. Second, the scan time of SWI was long (5'5"), that some patients with serious clinical symptoms cannot remain stationary in the whole examination, it may produce some motion artifacts and then affected the image interpretation. Third, only the MTT maps from PWI were selected for this research, it could not represent all PWI parameters, what roles about the CBV, CBF and TTP maps would play requires further study.

The potential for an effective outcome using the SWI in patients who have had an acute ischemic stroke was demonstrated by the finding that an SWI can detect an intracranial artery embolus or ischemic penumbra, as well as microbleeds, thereby serving as a "one-stop" reference for the selection of clinical therapy and a conventional test sequence. The clinical application of SWI could be improved, however, by reducing the scanning time while maintaining or improving image quality; this possibility is worth of further study. Because of a lack of follow-up in this study for patients with increased veins, we recommend further investigation of the relationship between increased veins and prognosis.

5. Conclusion

SWI and PWI showed excellent consistency in their assessment of ischemic penumbrae. As a simple and feasible imaging test method for ischemic penumbra assessment, SWI may be of significant clinical value.

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Conflict of interest

None to report.

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