Evaluation of Diffusion–Perfusion Mismatch in Acute Ischemic Stroke with a New Automated Perfusion-Weighted Imaging Software: A Retrospective Study

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ABSTRACT

Introduction: The aim of this study was to evaluate the accuracy of automated software (iStroke) on magnetic resonance (MR) apparent diffusion coefficient (ADC) and perfusion-weighted imaging (PWI) against ground truth in assessing infarct core, and compare the hypoperfusion volume and mismatch volume on iStroke with those on Food and Drug Administration-approved software (RAPID) in patients with acute ischemic stroke.

Methods: We used the single-volume decomposition method to develop the iStroke (iStroke; Beijing Tiantan Hospital, Beijing, China) software. Patients with ischemic stroke were collected from two educational hospitals in China with MR-PWI performed in the emergency department within 24 h of symptom onset. Infarct core volume was defined as ADC < 620 × 10⁻⁶ mm²/s and hypoperfusion volume was defined as Tmax > 6 s. We compared the accuracy of infarct core volume using iStroke and RAPID (iSchema View Inc, Menlo Park, CA) software with ground truth.

Results: We included 405 patients with acute ischemic stroke with MR ADC and PWI sequences. The infarct core volume on iStroke (median 2.43 ml, interquartile range [IQR] 0.60–10.32 ml) was not significantly different from the ground truth (median 2.89 ml, IQR 0.77–9.17 ml) (P = 0.07); Bland–Altman curves showed that the core volume of iStroke and RAPID software were comparable with each other on individual agreement with ground truth. The hypoperfusion volume and mismatch volume on iStroke were not statistically different from those on the RAPID software, respectively. In patients with large vessel occlusion (n = 74), the agreement between iStroke and RAPID was substantial (kappa = 0.76) according to DEFUSE 3 criteria (infarct core < 70 ml, mismatch volume ≥ 15 ml, and mismatch ratio ≥ 1.8).

Conclusions: The iStroke automatic processing of ADC and PWI is a reliable software for the identification of diffusion–perfusion mismatch in acute ischemic stroke.

Keywords: Infarct; Penumbra; Perfusion-weighted imaging; Stroke; Software analysis
INTRODUCTION

Magnetic resonance perfusion-weighted imaging (MR-PWI) allows noninvasive identification of hypoperfused tissue in patients with acute ischemic stroke (AIS), which may progress to infarction without timely reperfusion. Quick, brief, and accurate assessment of the volume of the hypoperfused brain tissue area on MR-PWI is yielded for optimal management strategy selection for AIS in clinical practice, e.g., endovascular treatment or thrombolysis treatment.

Automatic machine analysis utility in neuroimaging has largely saved time for hemodynamic assessment. Currently, several software packages have been developed and widely used to automatically assess CT perfusion (CTP) to identify the ischemic core [1–3], such as the RAPID software (iSchema View Inc, Menlo Park, CA, USA), and the Olea software (Olea Medical Solutions, La Ciotat, France) (https://www.olea-medical.com/en/), but they were challenged by low sensitivity for infarct core [4]. MR diffusion-weighted imaging (DWI) is the gold standard for infarct core evaluation, and the RAPID software has just been approved by the Food and Drug Administration (FDA) for automatic assessment of MR-PWI [5]. Moreover, MRI use in emergency departments is getting increasingly popular in China but there is a lack of reports of automatic MR-PWI data assessment in the Chinese population, and no relevant automatic assessment software has been approved by the National Medical Products Administration for cerebral perfusion assessment in China.

In this study, we aimed to introduce newly developed automated software that could assess MR-PWI automatically and investigate its accuracy in assessing infarct core volume in AIS by comparing it with manually assessed infarct core volume and comparing hypoperfusion and mismatch volume between the new software and FDA-approved software.

METHODS

Study Design and Subjects

This was a multicenter, retrospective, and observational study. We recruited patients admitted to Beijing Tiantan hospital and Shanghai Fourth People’s Hospital between January 2016 and August 2020 with the
following criteria: (1) adult patients with AIS admitted within 24 h of symptom onset; (2) the patient underwent MR-PWI within 24 h of symptom onset; (3) imaging quality that allowed successful assessment of infarct core volume. We excluded patients being diagnosed as stroke mimics, chronic heart failure, low-quality imaging data (e.g., significant artifacts, etc.), and incomplete/low quality medical records. For eligible patients, we collected the demographics (age and sex), cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, etc.), systolic and diastolic blood pressure at admission, NIHSS at admission, large vessel occlusion (LVO) site by magnetic resonance angiography, prior modified Rankin scale, treatment strategies (intravenous thrombolysis, endovascular treatment) and modified Rankin scale score at 90 days.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. The study was approved by the institutional review board and ethics committee at Beijing Tiantan Hospital (KY2022-029-01) and Shanghai Fourth People’s Hospital (2020066-001) without requirement of patients’ written informed consents.

MRI Protocol

At Beijing Tiantan Hospital, MRI was performed on a single 3.0 Tesla clinical scanner (SIEMENS TrioTim, Siemens Healthineers). DWI sequences were acquired at baseline with two b values of 0 and 1000 s/mm². Scanner parameters for DWI were slice thickness = 5 mm, repetition time = 3000 ms, echo time = 75 ms, number of averages = 2, flip angle = 90°, voxel spacing = 1.80 × 1.80 × 6.5 mm³, matrix = 128 × 128, FOV = 230 × 230 mm². Dynamic susceptibility contrast (DSC) MR-PWI was acquired in the axial direction. Scanner parameters for DSC-MR-PWI were slice thickness = 5 mm, repetition time = 1590 ms, echo time = 32 ms, flip angle = 90°, voxel spacing = 0.90 × 0.90 × 6.5 mm³, axial slices = 20 slices, temporal coverage = 50 time points, matrix = 256 × 256, FOV = 230 × 230 mm².

Image analysis software (iStroke; Beijing Tian-tan Hospital, Beijing, China) is used for the measurement of ischemic lesion volumes and volumes of hypoperfused tissue from the DWI and DSC-MR-PWI sequences. The specific module is divided into four parts: (1) image pre-processing; (2) apparent diffusion coefficient (ADC) lesion segmentation; (3) hypoperfused tissue evaluation; and (4) calculation of perfusion–diffusion mismatch. The main theory methodology is similar as a previously published study [6]. The selection of arterial input and venous output functions was in a fully automatic, operator-free manner according to a detection algorithm [6].

Image Pre-processing

Due to the number of slices of MR-PWI and DWI may be inconsistent; furthermore, the application of the strong motion-probing gradients, the effect of minute motion can lead to erroneous image encoding and substantial artifacts, so a pre-processing step was utilized to enable the consistent analysis of cohorts. Non-linear image registration, a complimentary...
approach to rigid body registration, can accommodate inter-subject differences in brain morphology and can also offer the opportunity to track tissue outcomes more accurately in the same subject where the structure of the brain varies across timepoints. Therefore, we adopted nonlinear image registration to solve slice inconsistency, motion correction, and time point correction. Skull stripping is a crucial pre-processing step incorporated in brain magnetic resonance imaging processing applications. It deals with the removal of non-brain tissues from brain. Although manual segmentation has the highest accuracy, it is a time-consuming task. Therefore, we were composed of adaptive iterative thresholding to analyze and remove of connected components. Finally, morphological operations were carried out to obtain the brain mask [7].

ADC Lesion Segmentation

DWI lesion volumes are assessed on the affected sections with hyperintense areas visible from the $b = 1000 \text{ mm/s}^2$ images. Because a brain tumor and edema also show high signals on the b1000 images, the physician paid particular attention to the typical locations of bilateral artifact and produced ADC maps as necessary to identify positive DWI lesions. In the iStroke, infarct regions are automatically segmented on the ADC maps by applying normalized absolute thresholding. A quantile curve of ADC intensities within the brain mask is constructed for each ADC map of each subject, and an intersection point between two tangent lines with maximum and minimum differential coefficients is identified on each quantile-intensity curve. The ADC maps are normalized by dividing the intensities on each by the intensity at the intersection point. This normalization process results in the intensities of normal white matter tissues converging into one. In this way, white matter can be prevented from being misjudged as an infarct lesion.

Hypoperfused Tissue Evaluation

After the iStroke read all MR-PWI datasets, it automatically gave the first pass curve of the bolus injection contrast agent to determine the first pass time [8]. When confirming the input time, this program can automatically calculate brain perfusion parameter maps with circulant singular value decomposition (cSVD) deconvolution methods to eliminate the effect of tracer-arrival delay [9], including relative cerebral blood flow (rCBF) map, relative cerebral blood volume map, time-to-peak map, and mean transit time map, and time-to-peak impulse response (Tmax) map, which reflects the delay of the bolus agent reaching the ischemic area.

Calculation of Perfusion–Diffusion Mismatch

Perfusion–diffusion mismatch (penumbra) is defined as the difference in the volume of segmented hypoperfused tissue volume and the segmented volume of an ADC lesion. This mismatch may help identify patients for thrombolysis [10]. iStroke quantified the location of hypoperfused tissue and ADC lesion and automatically calculated the volume of perfusion–diffusion mismatch. A delay of 6 s ($T_{\text{max}} > 6 \text{ s}$) of the time to the maximum of the residue function was chosen as a threshold for hypoperfused tissue and ADC ($620 \times 10^{-6} \text{ mm}^2/\text{s}$) volume estimation was also chosen as a threshold for infarct focus.

RAPID Software on MR-PWI

The RAPID software (iSchema View Inc, Menlo Park, CA) was approved by the FDA and was used to automatically measure the infarct core volume and hypoperfusion volume. ADC < $620 \times 10^{-6} \text{ mm}^2/\text{s}$ was considered as infarct core, and $T_{\text{max}} > 6 \text{ s}$ as hypoperfusion volume.
Ground Truth for Infarct Core

A 15-year experienced neurologist (X.Y.) and a 10-year experienced neuroradiologist (W.M.) measured the infarct core volume manually on DWI with corresponding of ADC images using 3D Slicer (https://www.slicer.org/). Twenty cases were randomly selected to test inter-rater reliability and intra-rater reliability 1 month later, which yielded intraclass correlation coefficients 0.956 (95% confidence interval 0.889–0.983) and 0.985 (95% confidence interval 0.964–0.994), respectively.

Statistical Analyses

Chi-square tests and Fisher’s exact tests were used to compare the categorical variables. Inter-rater reliability and intra-rater reliability were evaluated by intraclass correlation tests. Mann–Whitney U tests were used to assess the differences of infarct core ground truth and MR-PWI infarct core volume assessed by the iStroke software and by the RAPID software. Dice value was used to assess the morphological agreement between ground truth of infarct core and iStroke infarct core. In addition, Bland–Altman plots were utilized to assess the agreement of ground truth and MR-PWI infarct core volumes by the iStroke software and by the RAPID software. Statistical analysis was performed using the SPSS version 22 software package (SPSS Inc, Chicago, IL, USA).

RESULTS

Patients’ Characteristics

We enrolled 405 patients with AIS with MR-PWI examination from Beijing Tiantan Hospital and Shanghai Fourth People’s Hospital. Among 405 patients, 74 were diagnosed as LVO patients by magnetic resonance angiography. The occlusion sites were 38 middle cerebral artery, 24 internal cerebral artery, six basilar artery, five vertebral artery, one posterior cerebral artery. Table 1 shows the clinical characteristics of the included subjects and patients with LVO.

Infarct Core Volume on Automated Software and Ground Truth

The infarct core volume on iStroke (median 2.43 ml, IQR 0.60–10.32 ml) was not significantly different from the core infarct ground truth (median 2.89 ml, IQR 0.77–9.17 ml) \( (P = 0.07) \), whereas the infarct core volume on the RAPID (median 0 ml, IQR 0–11.50 ml) was significantly smaller than the core infarct ground truth (median 2.67 ml, IQR 0.73–7.25 ml) \( (P < 0.001) \). In LVO patients, the infarct core volume on iStroke and that on RAPID were not significantly different from the ground truth either (Table 2).

Bland–Altman curves showed that infarct core volume of iStroke and RAPID software were comparable with each other on individual agreement with ground truth in all patients (Fig. 1) and in patients with LVO (Fig. 2). Figure 3 shows one case with similar infarct core volumes on the iStroke, RAPID, and ground truth.

Hypoperfusion and Mismatch Volume on Automated Software

In all subjects, the hypoperfusion volume on the iStroke (median 7.68 ml, interquartile range [0–56.65 ml]) was not statistically different from that on the RAPID software (median 5 ml, interquartile range [0–56.00 ml]) \( (P = 0.87) \). The mismatch volume on the RAPID (median 0 ml, interquartile range [0–34.4 ml]) was not significantly different than that on the RAPID (median 0 ml, interquartile range [0–40.5 ml]) \( (P = 0.15) \).

In LVO patients, the hypoperfusion volume on the iStroke (median 68.09 ml, interquartile range [15.67–128.11 ml]) was numerically larger than that on the RAPID software (median 58 ml, interquartile range [20–149.50 ml]) \( (P = 0.07) \). The mismatch volume on the iStroke (median 16.51 ml, interquartile range [0–80.16 ml]) was numerically smaller than that on the RAPID (median 39.00 ml, interquartile range [0–282.25 ml]) \( (P = 0.10) \).

The intraclass correlation between iStroke core and RAPID core was 0.968 (0.961–0.974),
and the intraclass correlation between iStroke hypoperfusion and RAPID hypoperfusion was 0.916 (0.898–0.931).

### Agreement of Detection Large Infarct Core

Among all patients, 23 of 405 patients had large infarct core (ground truth core volume > 70 ml). The iStroke and RAPID had high agreement with the infarct core ground truth (kappa = 0.82 and kappa = 0.79, respectively). In LVO patients, 14 of 74 patients had large infarct core (ground truth core volume > 70 ml), and the iStroke and RAPID had high agreement with the infarct core ground truth (kappa = 0.86 and kappa = 0.80, respectively) as well.

### Agreement Between iStroke and RAPID According to DEFUSE 3 Criteria

In patients with LVO (n = 74), the agreement between iStroke and RAPID was substantial (kappa = 0.76) according to DEFUSE 3 criteria (infarct core < 70 ml, mismatch volume ≥ 15 ml, and mismatch ratio ≥ 1.8).

### Table 1 The clinical characteristics of subjects in all patients and LVO patients

| Variables                      | All patients (N = 405) | LVO patients (N = 74) |
|-------------------------------|------------------------|------------------------|
| Age, years                    | 67.9 ± 11.9            | 68.8 ± 12.2            |
| Men                           | 298 (73.6%)            | 55 (74.3%)             |
| Coronary artery disease       | 52 (12.8%)             | 7 (9.5%)               |
| Hypertension                  | 265 (65.4%)            | 51 (68.9%)             |
| Diabetes mellitus             | 122 (30.1%)            | 24 (32.4%)             |
| Hyperlipidemia                | 25 (6.2%)              | 6 (8.1%)               |
| NIHSS at admission            | 4 (2–11)               | 12 (4–16)              |
| Stroke symptom onset to MRI time, hours | 20.9 (4.5–71.9) | 4.0 (2.3–25.7) |
| Intravenous thrombolysis      | 111 (27.4%)            | 27 (36.5%)             |
| Endovascular treatment        | 49 (12.1%)             | 45 (60.8%)             |

### Table 2 Correlation of infarct core volume on automated software and ground truth in all subjects and LVO patients

| MR-PWI                        | MR-PWI core volumes | Ground truth | P     |
|-------------------------------|---------------------|--------------|-------|
| All patients (N = 405)        |                     |              |       |
| iStroke infarct core volume   | 2.43 (0.60–10.32)   | 2.89 (0.77–9.17) | 0.10  |
| RAPID infarct core volume     | 0 (0–11.50)         | 2.89 (0.77–9.17) | < 0.001 |
| LVO patients (N = 74)         |                     |              |       |
| iStroke infarct core volume   | 7.67 (2.24–29.07)   | 9.30 (2.69–41.18) | 0.43  |
| RAPID infarct core volume     | 10.50 (0–42.25)     | 9.30 (2.69–41.18) | 0.86  |
Morphological Agreement Between Core Infarct on iStroke and Ground Truth

In all patients, the morphological agreement between iStroke core and ground truth was moderate with a mean dice value of 0.65, while in patients with LVO and in patients with large infarct core (ground truth > 70 ml), the agreement between iStroke infarct core and ground truth was both good with mean dice value 0.77 and 0.79, respectively.

DISCUSSION

We have developed a novel real-time, fully automated software to identify diffusion–perfusion mismatch in patients with AIS in China. With a large sample of datasets, the iStroke core volume was closely correlated with the ground truth, and it was comparable with the RAPID software on agreement with the ground truth infarct core. In patients with LVO, morphological agreement between iStroke and the ground
The current study demonstrated that the core volume on iStroke was closely correlated with the ground truth and had a comparable capacity to assess infarct core volume on MR-PWI as the RAPID software. The iStroke was proved to be able to assess the infarct core volume on MR-PWI. Positron emission tomography (PET) was the most widely used method to measure microcirculation in the past. However, its disadvantages were poor spatial and temporal resolution and patient exposure to ionizing radiation and functional MRI may be a more optimal imaging method [11]. Tissue blood volume, which represents core volume, is easier to compute compared with tissue blood flow [12], especially through MR scan [13].

The development of iStroke provided an option for stroke centers and neurologists to quantify ischemic penumbra rapidly and automatically in China. The mismatch volumes on the iStroke software were numerically smaller than the RAPID software, due to limited sample in patients with LVO, it did not reach statistically significance, however, the relatively smaller mismatch volume may induce restrict patient selection for thrombectomy in China, only large mismatch volume patients on the RAPID software will be candidates for thrombectomy, which may be safer for Chinese patients considering the rate of symptomatic rate intracranial hemorrhage and mortality rate were higher in China than that in the USA [14].

![Fig. 3](image)

A case’s penumbral evaluation on iStroke, RAPID, and DWI source image. A iStroke summary result: infarct core volume 17.3 ml, hypoperfusion volume 137.6 ml. B iStroke artery input function: left middle cerebral artery M1 segment; artery input function and venous output function curves were acceptable. C, D magnetic resonance-diffusion-weighted imaging and apparent diffusion coefficient showed. Centrum semiovale and corona radiata infarct with ground truth 15.8 ml. E RAPID summary result: infarct core volume 13 ml, hypoperfusion volume 141 ml. F RAPID artery input function: left middle cerebral artery M2 segment. G RAPID artery input function and venous output function curves were acceptable as well.
In addition, one of the most important functions for RAPID was case selection for thrombectomy in LVO patients according to the DEFUSE 3 trial criteria, and the iStroke reached high agreement with the RAPID software on case selection based on such criteria.

The patients we included mostly had small infarcts. Although the perfusion mismatch is targeting for case selection for reperfusion therapy, patients with LVO are a perfect group for software comparison, while whether small lesions also have important view of the accuracy of the software from a clinical point of view. Local doctors will challenge the accuracy of the software result if the DWI clearly shows a small lesion but with 0 ml core on the software. The motion, spatial resolution, and machine model affects the result. However, we excluded severe motion, and adjusted the algorithm for different machine model, this factors were adjusted through repeated improvement of the algorithm. We particularly focused on the infarct core detection and improved the model sensitivity to small infarcts, so we did not exclude small lesions in the analyses.

The development of the RAPID software was based on the imaging data from Caucasian people, and iStroke was developed based on the imaging data from Eastern-Asian people. Many regions in East-Asia have a great burden of ischemic stroke and the resources of the health care system are limited, which limits the generalization of reperfusion therapy. Hence, the development and release of iStroke would contribute to the generalization of reperfusion therapy in the late window and reduce the burden of ischemic stroke in East-Asian regions and other developing countries.

The current study has the advantage of a large sample size to test the model in the training set and validation set. Patients with MR-PWI before reperfusion therapy are scarce in clinical practice because an MRI scan is more time-consuming than CT, and prolonged the door-to-needle time and door-to-puncture time. Fortunately, the current study enrolled sufficient patients and had a large sample size to prove the accuracy of iStroke infarct core against the ground truth. In addition, we used circulant singular value decomposition (cSVD), a single global threshold value for truncating the number of small singular values before decomposition, to develop our software. To avoid the leakage of the contrast agent, which leads to CBV underestimation, we increase the step of leakage correction to improve the accuracy of the program.

There are several limitations to our study. First, the current study only included two sites to enroll study participants and collect clinical and imaging data. Few stroke centers could perform MRI scans in the emergency room in China. Both of the sites in our study provided imaging data of high quality to conduct a qualified dataset. Second, the retrospective design of our study limited the generalization of the study conclusion. However, the demonstration of similar results between the iStroke infarct core and ground truth in our study laid a solid foundation for penumbral evaluation between the two software programs. Thirdly, advanced artificial intelligence algorithms including deep learning or machine learning may increase the correlation between perfusion assessment software and ground truth, which warrants further investigations. Finally, we did not analyze the variability of assessment of penumbra. Further studies could determine the intraobserver and interobserver variability in the assessment of penumbra. In addition, further studies could determine the accuracy of the software to determine the presence of hemorrhage, vascular occlusion, and collateral circulation in the acute stroke setting.

CONCLUSIONS

The iStroke automatic processing of ADC and MR-PWI is reliable software for the identification of diffusion–perfusion mismatch in acute ischemic stroke.

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**Author contributions.** Study concept and design: Yongjun Wang and Yunyun Xiong. Acquisition of data: Yu Luo, Mingming Wang, Guangshuo Li. Analysis or interpretation of data: all authors. Yunyun Xiong wrote the first draft of the manuscript. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Kaixuan Yang.

**Disclosures.** Yunyun Xiong, Yu Luo, Mingming Wang, Shih-Ting Yang, Ruiqiong Shi, Wanxing Ye, Kaixuan Yang, Shang Wang, Zixiao Li, and Yongjun Wang have nothing to disclose.

**Compliance with ethics guidelines.** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review committee and the principles of the Declaration of Helsinki. The study was approved by the institutional review board and ethics committee at Beijing Tiantan hospital without requirement of patients’ written informed consents (KY2022-029-01).

**Data availability.** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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