SVN Stroke & Vascular Neurology

Assessment of Perfusion Volumes by a New Automated Software for Computed Tomography Perfusion

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To cite: Cao Z, Wang D, Feng X, *et al*. Assessment of Perfusion Volumes by a New Automated Software for Computed Tomography Perfusion. *Stroke & Vascular Neurology* 2024;**9**: e002964. doi:10.1136/svn-2023-002964

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/svn-2023-002964).

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Received 2 November 2023
Accepted 7 March 2024
Published Online First
28 March 2024

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ABSTRACT

Introduction To compare the perfusion volumes assessed by a new automated CT perfusion (CTP) software iStroke with the circular singular value decomposition software RAPID and determine its predictive value for functional outcome in patients with acute ischaemic stroke (AIS) who underwent endovascular treatment (EVT).

Methods Data on patients with AIS were collected from four hospitals in China. All patients received CTP followed by EVT with complete recanalisation within 24 hours of symptom onset. We evaluated the agreement of CTP measures between the two softwares by Spearman's rank correlation tests and kappa tests. Bland-Altman plots were used to evaluate the agreement of infarct core volume (ICV) on CTP and ground truth on diffusion-weighted imaging (DWI). Logistic regression models were used to test the association between ICV on these two softwares and functional outcomes.

Results Among 326 patients, 228 had DWI examinations and 40 of them had infarct volume >70 mL. In all patients, the infarct core and hypoperfusion volumes on iStroke had a strong correlation with those on RAPID (ρ=0.68 and 0.66, respectively). The agreement of large infarct core (volume >70 mL) was substantial (kappa=0.73, p<0.001) between these two softwares. The ICV measured by iStroke and RAPID was significantly correlated with independent functional outcome at 90 days (p=0.009 and p<0.001, respectively). In patients with DWI examinations and those with an ICV >70 mL, the ICV of iStroke and RAPID was comparable on individual agreement with ground truth.

Conclusion The automatic CTP software iStroke is a reliable tool for assessing infarct core and mismatch volumes, making it clinically useful for selecting patients with AIS for acute reperfusion therapy in the extended time window.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Automated CT perfusion (CTP) software for evaluating the perfusion volumes is helpful for decision-making for endovascular treatment (EVT) in patients who had a stroke due to large vessel occlusion.

WHAT THIS STUDY ADDS

⇒ A new automated CTP software iStroke demonstrates good agreement with the ground truth and the RAPID software for evaluating infarct core and penumbra.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ iStroke software can be used for measurement of acute infarct core volume, penumbral tissue and case selection for thrombolysis or EVT in the late time window.

INTRODUCTION

Current challenges in the management of acute ischaemic stroke (AIS) mainly include optimising imaging analysis methods for patient selection and predicting the clinical outcome before reperfusion therapy.[1] The DAWN (Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) trials confirmed that mechanical thrombectomy (MT) improved clinical outcome for patients with AIS selected by either CT perfusion (CTP) or MRI.[2 3] Therefore, currently, accurate and reliable measurement of perfusion or diffusion volumes is important for reperfusion therapy decision-making in stroke.

CTP is widely used to estimate the extent of ischaemic core and penumbra by calculating perfusion parameters including cerebral blood flow (CBF), cerebral blood volume, mean transit time and time-to-maximum (Tmax).[4] These perfusion parameters are inferred from CTP images by deconvolution of the concentration–time curves (CTCs)[5] against the arterial input function (AIF). Numerous methods have been developed to deconvolve CTC,[5 6] and the standard approaches are based on circular singular value decomposition (cSVD).[7–9] The RAPID software (iSchema View, Menlo Park,

California, USA) is the most popular software based on cSVD algorithm. Several large clinical studies including the DAWN and DEFUSE 3 trials are also supported by the RAPID software.[2 3] However, cSVD algorithms are notoriously sensitive to noise and can produce varying results depending on their implementation.[10] More recently, numerous attempts have been made to use neural networks for estimating perfusion parameters.[11–14] Furthermore, this technique is more robust to noise and scan artefacts compared with the cSVD software. In a previous study, we demonstrated that the automated software iStroke (Beijing Tiantan Hospital and Biomind, Beijing, China) predicted perfusion parameters on magnetic resonance perfusion-weighted imaging.[15] However, whether iStroke has similar accuracy by measuring perfusion volumes on CTP using deep neural networks to the RAPID software and its predictive ability for clinical functional outcomes are unclear.

Therefore, we sought to compare the agreement of iStroke and RAPID on CTP imaging with ground truth on DWI and the association of infarct core volume (ICV) by softwares with clinical functional outcomes in patients with AIS who underwent endovascular treatment (EVT) with complete recanalisation.

METHODS

Subjects

We retrospectively included patients who were admitted to four teaching hospitals in China between January 2017 and September 2022. The inclusion criteria were as follows: (1) age ≥18 years old; (2) patient with AIS; (4) the patient underwent preprocedure CTP and postprocedure MRI examinations; (4) received EVT within 24 hours of symptom onset and achieved postprocedure complete recanalisation, which was defined as Modified Thrombolysis in Cerebral Infarction Score 3[16]; (5) good imaging quality for evaluation of cerebral perfusion and ICV. Patients with incomplete or low-quality medical imaging were excluded. We collected patients' demographics, clinical medical history (hypertension, diabetes mellitus, atrial fibrillation, etc), baseline National Institutes of Health Stroke Scale, treatment strategies (intravenous thrombolysis, EVT), perfusion imaging parameters and functional outcomes (Modified Rankin Scale (mRS) Score at 90 days). Excellent and favourable functional outcomes were defined as mRS ≤1 and mRS ≤2, respectively.

Automated software on CTP

Preprocedure CTP images of the same patients were processed using the image analysis software iStroke and RAPID independently. Infarct core and hypoperfusion volumes from the CTP data were automatically measured by the two softwares, respectively. Infarct core was defined as a CBF <30% of that in normal tissue, hypoperfusion volume was defined as Tmax >6 s. Large infarct core was defined as volume >70 mL.

ICV and hypoperfusion data of RAPID software were retrospectively collected from local hospitals, while iStroke results were calculated by source imaging with Digital Imaging and Communications in Medicine (DICOMs) in core centre. iStroke uses digital phantoms[17] of haemodynamics constructed from known perfusion parameter values. The architectural foundation of the model relies on recurrent neural networks, specifically implemented as a modified long short-term memory model, followed by a multilayer perceptron. First, a preprocessing pipeline, including motion correction, noise reduction, automatic AIF selection and brain tissue segmentation, is employed before inputting perfusion images into the deep learning model. Second, deep learning model generates the perfusion parameter maps undergoing threshold segmentation, resulting in the identification of regions corresponding to CBF <30% and Tmax >6 s. Third, during deployment, iStroke establishes a direct connection to imaging devices for image retrieval in the native DICOM format. Finally, the analysis results are sent back to the Picture Archiving and Communication Systems (PACS) for real-time review by clinical teams.

Ground truth of infarct core

We used the same method to manually trace the ground truth of infarct core on diffusion-weighted imaging (DWI). A 5-year experienced radiology researcher (YH) measured the infarct volume and was blinded to the patient's medical information. The tracing maps were double-checked by the senior neurologist (YX).

Statistical analyses

The agreement of the two softwares on mismatch volumes was tested by Spearman's rank correlation tests. Kappa tests were used for agreement on large infarct core or mismatch volume ≥15 mL. Bland-Altman plots were used to evaluate the agreement of ICV by each software on CTP and ground truth. Logistic regression models were used to determine the association of the ICV assessed by two softwares on CTP with the functional outcomes. Statistical analyses were performed by the SPSS V.22 software package (SPSS, Chicago, Illinois, USA).

RESULTS

Subjects

We included 326 patients with AIS with preprocedure CTP and complete recanalisation after thrombectomy. Among them, 228 underwent DWI examination and 40 of them had an infarct volume >70 mL. Clinical characteristics of the included patients are shown in table 1.

Head-to-head comparison of perfusion volumes on automated softwares

In all patients, iStroke was strongly correlated with RAPID on ICV (median 20.0 mL, IQR 5.0–35.0 mL vs median 6.0 mL, IQR 0.0–23.0 mL, respectively, ρ=0.68, p<0.001) and hypoperfusion volume (median 131.2 mL, IQR 67.9–183.5 mL vs median 135.5 mL, IQR 83.8–187.5 mL,

Table 1 Clinical characteristics of included patients across different subgroups

Variables	All patients (N=326)	Patients with DWI (N=228)	DWI infarct volume >70 mL (N=40)
Age, years	66.0 (56.8–74.0)	67.5 (57.3–75.0)	66.0 (57.5–76.5)
Men	205 (62.9%)	144 (63.2%)	30 (75.0%)
Hypertension	196 (60.1%)	132 (57.9%)	17 (42.5%)
Diabetes mellitus	72 (22.1%)	43 (18.9%)	6 (15.0%)
Hyperlipidaemia	25 (7.7%)	16 (7.0%)	3 (7.5%)
Atrial fibrillation	74 (22.7%)	51 (22.4%)	7 (17.5%)
NIHSS at admission	15.0 (9.5–20.0)	9.0 (15.0–19.0)	14.0 (17.0–21.0)
Intravenous thrombolysis	95 (29.1%)	75 (32.9%)	19 (47.5%)
Anterior circulation large vessel occlusion	297 (91.1%)	202 (88.6%)	39 (97.5%)
RAPID CBF <30 mL	6.0 (0.0–23.0)	5.0 (0.0–18.0)	40.5 (10.3–71.5)
iStroke CBF <30 mL	22.3 (7.2–37.6)	18.8 (3.9–32.1)	46.7 (20.4–70.1)
RAPID Tmax >6 s	135.5 (83.8–187.5)	121.0 (66.3–177.0)	169.0 (103.7–215.8)
iStroke Tmax >6 s	131.2 (67.9–183.5)	123.9 (57.4–173.6)	165.7 (125.4–219.1)
Onset to first CTP time	231.0 (142.3–408.5)	228.0 (141.8–390.3)	219.0 (105.0–369.0)
CT to first recanalisation time	118.0 (85.0–152.0)	118.0 (85.0–152.0)	125.0 (71.0–153.0)
CT to MRI time	3506.0 (2540.0–5075.0)	3509.0 (2540.0–5079.0)	3639.5 (2583.5–5066.5)
Infarct volume on DWI	23.9 (10.8–52.1)	23.9 (10.8–52.1)	91.6 (77.9–113.9)

Data are described as n (%) or median (IQR) as appropriate.
CBF, cerebral blood flow; CTP, CT perfusion; DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; Tmax, time-to-maximum.

respectively, ρ=0.66, p<0.001) (table 2). Boxplots illustrate the infarct core and hypoperfusion volumes of the two softwares (online supplemental figure 1).

Consistent with the main result, close correlation between iStroke and RAPID softwares was also found on hypoperfusion volume and ICV in anterior and posterior circulation stroke separately (online supplemental table 1).

Substantial agreement was observed between these two softwares for large infarct core (kappa=0.73, p<0.001). While the mismatch volume ≥15 mL on iStroke had a good agreement with that on RAPID (kappa=0.35, p<0.001) (table 2). With regard to the mismatch ratio ≥1.8, 308 patients were consistent on both softwares. One patient was found to have a mismatch ratio <1.8 on both softwares, and other 17 cases had inconsistent findings between RAPID and iStroke. The kappa value was not suitable and the agreement rate was 94.79% (309/326).

Association of ICV with functional outcomes

Shift analysis by ordinal logistic regression revealed that ICV on iStroke and RAPID significantly correlated with 90-day mRS distribution after adjusting for age and sex (p=0.003 and p<0.001, respectively). The ICV on iStroke and RAPID were both significantly associated with an excellent to favourable functional outcomes with age and sex as covariates (table 3).

Agreement of ICV on CTP softwares and DWI

In patients with DWI examination, the ICV on both iStroke and RAPID softwares significantly correlated with the ground truth (ρ=0.43 and ρ=0.62, respectively) (table 4). Furthermore, strong correlation of ground truth with the two softwares was observed in patients with anterior large vessel occlusion (ρ of iStroke=0.43, ρ of RAPID=0.65, respectively), however, was not significant in patients with posterior large vessel occlusion (ρ of

Table 2 Agreement of automated softwares on infarct core volume (ICV) and hypoperfused volume for all patients

	RAPID (N=326)	iStroke (N=326)	ρ/kappa	P value
CBF <30%	6.0 (0.0–23.0)	20.0 (5.0–35.0)	0.68*	<0.001
Tmax >6 s	135.5 (83.8–187.5)	131.2 (67.9–183.5)	0.66*	<0.001
ICV >70 mL	18 (5.5%)	17 (5.2%)	0.73†	<0.001
Mismatch volume ≥15 mL	301 (92.3%)	292 (89.6%)	0.35†	<0.001

Data are described as n (%) or median (IQR) as appropriate.
*Spearman's rank correlation.
†Kappa.
CBF, cerebral blood flow; Tmax, time-to-maximum.

Table 3 The impact of ICV on functional outcomes

ICV on CTP	mRS ≤2				mRS ≤1				mRS distribution			
	OR (95% CI)	P value	Adjusted OR (95% CI)*	P value	OR (95% CI)	P value	Adjusted OR (95% CI)*	P value	OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
iStroke	1.01 (1.00 to 1.02)	0.008†	1.01 (1.00 to 1.02)	0.009†	1.01 (1.00 to 1.03)	0.01†	1.01 (1.00 to 1.02)	0.012†	1.01 (1.00 to 1.02)	0.003‡	1.01 (1.00 to 1.02)	0.003‡
RAPID	1.02 (1.01 to 1.03)	<0.001†	1.02 (1.01 to 1.03)	<0.001†	1.02 (1.01 to 1.04)	<0.001†	1.02 (1.01 to 1.04)	<0.001†	1.02 (1.01 to 1.02)	<0.001‡	1.02 (1.01 to 1.02)	<0.001‡

*OR adjusted for age and sex.
†Binary logistic regression.
‡Ordinal logistic regression.
CTP, CT perfusion; ICV, infarct core volume; mRS, Modified Rankin Scale.

iStroke=0.18, ρ of RAPID=−0.016, respectively) (online supplemental table 2).

In patients with ground truth core volume >70 mL, the ICV on both iStroke and RAPID softwares was strongly correlated with the ground truth (ρ=0.51 and ρ=0.66, respectively) (table 4).

With regards to individual agreement with ground truth, ICV on iStroke and RAPID was comparable to each other in patients with DWI (figure 1 and online supplemental figure 2) and in patients infarct volume >70 mL (figure 2).

DISCUSSION

Our study revealed substantial agreement between iStroke and RAPID in measuring hypoperfusion and ICV on CTP. In patients with DWI, the ICV on both the iStroke and RAPID softwares was comparable in all patients and in large infarct core patients. The ICV on both softwares was significantly correlated with the patients' functional outcomes at 90 days.

Accurate estimation of perfusion volumes is critical to evaluate the amount of potentially salvageable tissue and provide timely treatment. In patients with AIS presenting within 6–24 hours of onset and with a large vessel occlusion in the anterior circulation, EVT is recommended when patients meet DAWN or DEFUSE 3 eligibility criteria.[2 3] With a cut-off ICV of 70 mL per DEFUSE 3, overestimation of an ICV may inaccurately exclude patients from EVT, while underestimating of the ICV may be associated with poor clinical outcome following EVT.[2] Therefore, the accuracy of the automatic image analysis software is crucial for case selection for EVT. In this study, we found that the iStroke had a substantial agreement with the RAPID in measuring the infarct core and hypoperfusion volumes from CTP data, both in anterior and posterior circulation large vessel occlusion. However, the agreement of mismatch volume ≥15 mL was only fair between the two softwares in all patients, probably due to a higher hypoperfusion volume and lower core volume on RAPID compared with those on iStroke. This finding was consistent with previous studies that showed RAPID tended to underestimate the ICV on CTP images compared with the ground truth[4 18 19] and consequently overestimated the size of penumbra compared with iStroke.

In patients with DWI examination, the ICV on both iStroke and RAPID softwares was significantly correlated with the ground truth. However, in the subgroup of posterior circulation arterial occlusion, this correlation was not significant for the two softwares. The contradictory results should be treated with caution. First, a limited sample size of only 29 patients who had a posterior circulation stroke was included. Second, ICV on the RAPID mismatch map tends to be characterised by significant low sensitivity and accuracy values, resulting in less adequate accuracy for detecting ischaemic lesions in posterior circulation regions.[20] iStroke was not sensitive to posterior circulation infarcts either.

Table 4 Correlation of ICV on CTP softwares and DWI

	ICV on CTP	Ground truth on DWI	ρ	P value
Patients with DWI (N=228)				
iStroke ICV	18.8 (3.9–32.1)	23.9 (10.8–52.1)	0.43*	<0.001
RAPID ICV	5.0 (0.0–18.0)	23.9 (10.8–52.1)	0.62*	<0.001
Infarct volume >70 mL (N=40)				
iStroke ICV	46.7 (20.4–70.1)	91.6 (77.9–113.9)	0.51*	<0.001
RAPID ICV	40.5 (10.3–71.5)	91.6 (77.9–113.9)	0.66*	<0.001

Data are described as median (IQR).
*Spearman's rank correlation.
CTP, CT perfusion; DWI, diffusion-weighted imaging; ICV, infarct core volume.

Consistent with Shi *et al* study,[21] we also found that the assessment of ICV measured by the iStroke was important in selecting patients for EVT and predicting their clinical outcome. Additionally, our study included the largest sample size of patients who underwent EVT with complete recanalisation,[22 23] in order to control the possibility of infarct growth, to ensure the accuracy of ICV with the ground truth and to better illustrate the association of preprocedure ICV with postprocedure functional outcomes.

As the most popular image processing platform, the RAPID software has been used for hypoperfusion-infarction mismatches in many large clinical trials and provided evidence for case selection for extended time-window thrombolysis and EVT. In addition, other commercially available CTP automated softwares including MIStar (Apollo Medical Imaging, Melbourne, Australia) and OLEA (Olea Medical Solutions, La Ciotat, France) are widely used in Australia and Europe. The iStroke has been installed in more than 100 clinical centres in China. The cross-comparison of these softwares is essential for future trials case selection and patients' treatment strategies.

Several limitations should be paid attention to. First, patients with AIS with large infarct core were limited, which may account for only a fair agreement between the ICV measured by the softwares and the ground truth, although it remained significant. Second, there was a time delay between the first CT scan and MRI (approximately 58 hours), during which the infarct volume might grow up. This change in volume may potentially lower the agreement of the assessment. Third, retrospective design of the study may limit the generalisability of the findings. Nonetheless, the included centres are large centres in China with common CTP modality parameters, and our

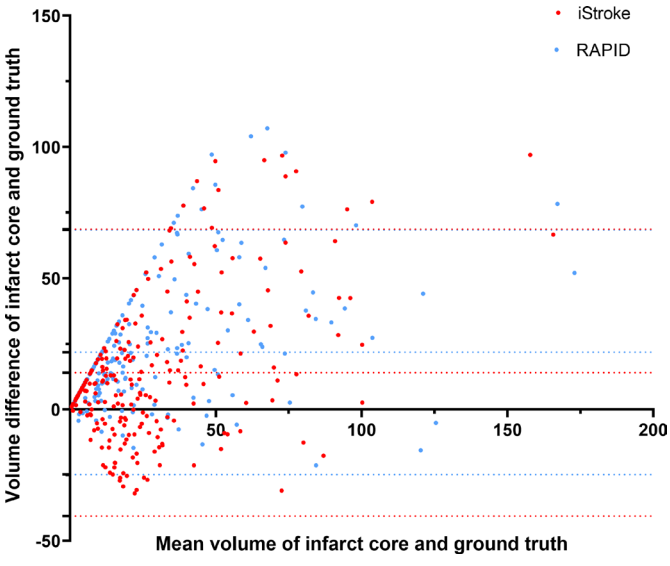

Figure 1 Agreement of infarct core volume between iStroke, RAPID and ground truth in patients with diffusion-weighted imaging. Volume difference between iStroke and ground truth in each patient was present as red dots (the mean volume difference is 14.0 mL, 95% CI −40.6 to 68.7 mL). Volume difference between RAPID and ground truth was present as blue dots (the mean volume difference is 21.8 mL, 95% CI −24.8 to 68.4 mL).

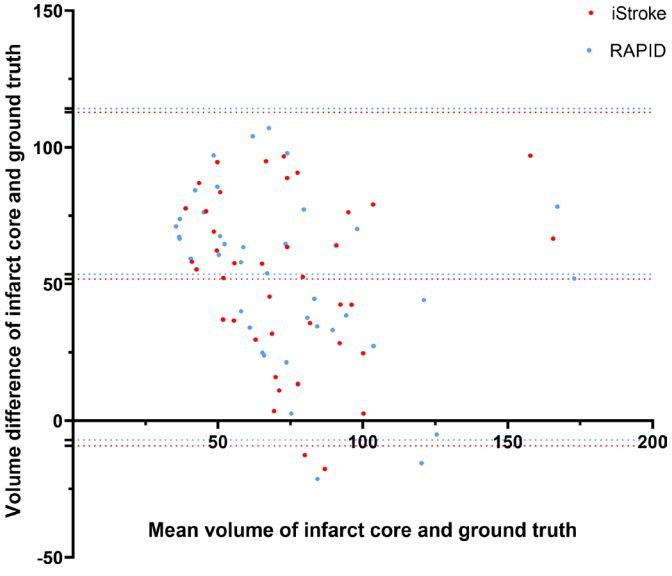

Figure 2 Agreement of infarct core volume between iStroke, RAPID and ground truth in patients with diffusion-weighted imaging infarct volume >70 mL. Volume difference between iStroke and ground truth in each patient was present as red dots (the mean volume difference is 51.8 mL, 95% CI −9.2 to 112.8 mL). Volume difference between RAPID and ground truth was present as blue dots (the mean volume difference is 53.6 mL, 95% CI −7.1 to 114.2 mL).

study provided robust data on the accuracy of the CT perfusion volumes determined by iStroke. Further longitudinal studies with broader centres are needed.

CONCLUSION

The automatic CTP software iStroke is a reliable tool for assessing infarct core and mismatch volumes, making it clinically useful for selecting patients with AIS for acute reperfusion therapy in the extended time window.

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Funding This study is supported by Beijing Municipal Science & Technology Committee (Z211100003521019).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval 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 without the requirement of patients' written informed consents (KY2022-029-01).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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