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MAGNETIC RESONANCE

Impact of perfusion lesion in corticospinal tract on response to reperfusion

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Abstract

Objectives We aimed to examine the impact of corticospinal tract (CST) involvement in acute ischaemic stroke (AIS) patients on functional outcome and the interaction with reperfusion.

Methods We retrospectively examined data in consecutive anterior circulation AIS patients undergoing thrombolysis. MR perfusion (time to maximum of tissue residue function, Tmax) and apparent diffusion coefficient (ADC) images were transformed into standard space and the volumes of CST involvement by Tmax > 6 s (CST-Tmax) and ADC < 620 × 10^{-6} mm^2/s (CST-ADC) lesions were calculated. Good outcome was defined as modified Rankin scale ≤ 2 at 3 months.

Reperfusion was defined as a reduction in Tmax > 6 s lesion volume of ≥70% between baseline and 24 h.

Results 82 patients were included. Binary logistic regression revealed that both CST-Tmax and CST-ADC volume at baseline were significantly associated with poor outcome ($p < 0.05$). The 24-h CST-ADC volume was correlated with baseline CST-ADC volume in patients with reperfusion ($r = 0.79$, $p < 0.001$) and baseline CST-Tmax volume in patients without reperfusion ($r = 0.67$, $p < 0.001$). In patients with CST-Tmax volume > 0 mL and CST-ADC volume < 3 mL, the rate of good outcome was higher in patients with reperfusion than those without (70.4% vs 38.1%, $p = 0.04$).

Conclusions The use of CST-Tmax in combination with CST-ADC provides prognostic information in patients considered for reperfusion therapies.

Key Points
• *Examine the impact of corticospinal tract involvement in acute ischaemic stroke patients.*
• *Spatially registered Tmax images can identify corticospinal tract hypoperfusion injury.*
• *Corticospinal tract salvage through reperfusion is associated with improved outcome.*

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Abbreviations

ADC	Apparent diffusion coefficient
AIF	Arterial input function
AIS	Acute ischaemic stroke
CI	Confidence interval
CRR	Corticospinal tract reperfusion rate
CST	Corticospinal tract

CST-ADC	Volumes of corticospinal tract involvement by apparent diffusion coefficient $< 620 \times 10^{-6}$ mm²/s
CST-Tmax	Volumes of corticospinal tract involvement by time to maximum of tissue residue function > 6 s
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
HT	Haemorrhage transformation
MNI	Montreal Neurology Institute
mNIHSS	Motor subscore of the National Institute of Health Stroke Scale
mRS	Modified Rankin scale
MRP	Magnetic resonance perfusion
NIHSS	National Institute of Health Stroke Scale
OR	Odds ratio
ROC	Receiver operating characteristic
RR	Reperfusion rate
rt-PA	Recombinant tissue-type plasminogen activator
SVD	Singular value deconvolution
SHT	Symptomatic haemorrhage transformation
T1WI	T1-weighted imaging
Tmax	Time to maximum of tissue residue function

Introduction

In acute ischaemic stroke (AIS), penumbra is defined as hypoperfused tissue with loss of electric activity, which is potentially salvageable with timely reperfusion [1, 2]. Successful reperfusion of penumbra is of great significance to reversal of neurological deficits, leading to good outcome [3]. The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) [4] and EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) [5] studies used the perfusion parameter time to maximum of tissue residue function (Tmax) on MRI to identify hypoperfused tissue, and documented that a Tmax > 6 s identified ischaemic tissue that was likely to progress to irreversible injury in the absence of reperfusion.

The majority of current imaging analyses in AIS for reperfusion therapy focus on the overall extent of ischaemic injury. However, infarct localization and fibre tract integrity play critical roles in functional impairment [6, 7]. Studies have demonstrated that the severity of functional motor deficit after AIS is highly dependent on the extent of lesion involved in corticospinal tract (CST), but not the lesion size [7]. In 2010, diffusion tensor imaging (DTI)-derived probabilistic maps of CST were developed, and the extent of lesion along the CST was shown to strongly correlate with motor impairment in chronic stroke patients [8, 9]. Most recently, the volume of diffusion lesion within the CST (defined using a probabilistic atlas derived from healthy elderly control subjects) was shown to strongly correlate with post-stroke motor outcomes at 3 months [10].

We hypothesized that timely reperfusion of hypoperfused but diffusion-negative CST would be associated with improved functional outcome and applied the atlas-based assessment of CST involvement to Tmax maps, in conjunction with assessment of reperfusion.

Materials and methods

Patient selection

We retrospectively reviewed our prospectively collected database for AIS patients who received thrombolytic therapy between March 2009 and December 2014. We included patients who (1) had a diagnosis of anterior circulation AIS confirmed by diffusion-weighted imaging (DWI); (2) received intravenous recombinant tissue-type plasminogen activator (rt-PA) within 6 h of symptom onset; (3) underwent T1-weighted imaging (T1WI), DWI and magnetic resonance perfusion (MRP) before and 24 h after rt-PA infusion; (4) had complete follow-up at 3 months. We excluded patients with poor image quality due to severe head motion, and movement artefacts on MRI were assessed by an experienced neuroradiologist (Z.W.).

Ethics statement

The study was approved by our local human ethics committee. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from all patients.

MR acquisition

All subjects underwent MRI on a 3.0-T system (Signa Excite HD, General Electric Medical System, WI, USA) equipped with an 8-channel phased array head coil. The MRI protocol included an axial isotropic diffusion-weighted echo-planar spin-echo sequence and bolus-tracking MRP. DWI was performed with a spin echo-planar sequence (field of view = 240 mm, slice thickness = 5 mm, number of slices = 18, slice gap = 1 mm, acquisition matrix = 160×160). MRP was performed with gradient echo-planar imaging (field of view = 240 mm, repetition time = 1500 ms, echo time = 30 ms, acquisition matrix = 128×128, total repetitions = 50, gadolinium dose = 15 mL, injection speed = 4–5 mL/s, scan duration = 1 min 15 s). Conventional T1WI parameters were repetition time = 1900 ms, echo time = 25 ms and slice thickness = 5.0 mm.

Image analysis

The CST-Tmax and CST-ADC were assessed using similar approaches to previous publications [8, 10, 11]. The specific

steps were as follows: (1) MIStar (Apollo Medical Imaging Technology, Melbourne, Vic., Australia) was used to generate Tmax from MRP and apparent diffusion coefficient (ADC) images from DWI. The Tmax map was produced using standard singular value deconvolution (SVD) without delay correction (no arterial input function (AIF) delay). The AIF was automatically selected, which should be a global AIF from a normal artery. (2) Both Tmax and ADC images were spatially coregistered with the concurrently acquired high-resolution T1WI for each subject using SPM12 (Wellcome Department of Neurology, University College of London, UK). T1WI was spatially registered into the Montreal Neurology Institute (MNI) standard brain space using the segmentation-based spatial normalization algorithm implemented in SPM12. ADC and Tmax images were subsequently warped into the MNI space using the T1WI-derived spatial normalization transformation. We applied cost function masking (CFM) [12] first and used the state-of-art new segmentation-based brain normalization method, a new upgrade to the unified normalization [13], to register an individual brain into the MNI space. (3) Infarct lesion was defined on the normalized ADC images in MRIcron software (http://www.nitrc.org/projects/mricron) with a threshold of $ADC < 620 \times 10^{-6}$ mm^2/s [14]. Hypoperfusion was identified by MRIcron with a threshold of Tmax > 6 s on the normalized Tmax images. Then the automatically segmented infarct and hypoperfusion lesions were manually checked and corrected [including two steps: (1) correction of non-cerebral parenchyma areas including ventricles and leptomeninges being labelled as hypoperfusion or infarct lesion; (2) correction of cerebral parenchymal areas in the unaffected hemisphere being labelled as hypoperfusion or infarct lesion] by one experienced neurologist (S.Z.) and another radiologist (Z.W.) who were blinded to all other imaging and clinical data. Both lesions were overlaid with the canonical CST [8, 10] to determine CST-ADC and CST-Tmax. The volumes of CST-ADC or CST-Tmax were calculated by adding up the volumes of ADC or Tmax lesions overlaid with the posterior limb of internal capsule and the upper extent of corona radiata.

Outcome measures

The National Institute of Health Stroke Scale (NIHSS) and the motor subscore of the NIHSS (mNIHSS, the limb-related elements of the NIHSS) were collected at baseline, 24 h and 7 days after stroke onset. Overall reperfusion rate (RR) was defined as (baseline hypoperfusion volume − 24-h hypoperfusion volume)/baseline hypoperfusion volume, and overall reperfusion was defined as RR ≥ 70% with baseline hypoperfusion volume ≥ 10 mL [15]. CST reperfusion rate (CRR) was defined as (baseline CST-Tmax volume − 24-h CST-Tmax volume)/baseline CST-Tmax volume, and CST reperfusion was defined as CRR ≥ 70% with baseline CST-Tmax

volume ≥ 0.2 mL. The modified Rankin Scale (mRS) was collected at 3 months after stroke onset, which was used to define good outcome (mRS ≤ 2) or poor outcome (mRS > 2). In the study, we defined good motor outcome as mNIHSS ≤ 4 and poor motor outcome as mNIHSS > 4. Haemorrhage transformation (HT) and symptomatic HT (SHT) were defined according to the European Cooperative Acute Stroke Study (ECASS) II trial [16].

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, USA). All metric and normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables were reported as median (25th–75th percentile). Categorical variables were presented as frequency (percentage). Comparisons between groups were assessed by using Student's t test for data that followed a normal distribution, Mann–Whitney U test for data that did not follow a normal distribution and Fisher's exact test for categorical data. Binary logistic regression analysis was used in analysis of clinical outcome. Patients were divided into reperfusion group and non-reperfusion group for correlation analyses, which also were derived from overall data. Pearson correlation analysis was used to analyse the relationship of volumes between CST-ADC and CST-Tmax. The optimal volume thresholds for CST-ADC and CST-Tmax to define good outcome were calculated using receiver operating characteristic (ROC) analysis, and the threshold was derived from analysis from overall data of the included patients. A p value of less than 0.05 was considered to be statistically significant.

Results

Subject characteristics

A total of 82 patients were included after exclusion of six who had poor image quality. The mean age was 67.5 ± 12.3 years and 55 (67.1%) were male. Baseline NIHSS score was 7.0 (4.0–14.0) and the median time from onset to treatment was 219.5 (174.3–261.5) min. Good motor outcome occurred in 61 (74.4%) patients at 7 days. Good outcome occurred in 55 (67.1%) patients at 3 months. Overall reperfusion was analysed in 58 (70.7%) patients, of whom 33 (56.9%) patients achieved reperfusion at 24 h, 40 (69.0%) patients had good motor outcome and 34 (58.6%) patients had good outcome. CST reperfusion was analysed in 54 (65.9%) patients, of whom 28 (51.9%) patients achieved CST reperfusion at 24 h, 35 (64.8%) patients had good motor outcome and 30 (55.6%) patients had good outcome.

Relationship between CST-Tmax volume and neurological outcome

In univariate analysis, patients with poor outcome were older and had higher baseline NIHSS score, longer time from onset to treatment, larger baseline CST-ADC volume and CST-Tmax volume than the patients with good outcome (Table 1). Binary logistic regression showed that baseline CST-Tmax volume was significantly associated with poor outcome (odds ratio (OR) 1.4, 95% confidence interval (CI) 1.1–1.8, $p = 0.003$) and poor motor outcome (OR 1.5, 95% CI 1.2–1.9, $p < 0.001$) after adjusting for age and onset to treatment time. The areas under the curves in ROC analysis for poor outcome and poor motor outcome were 0.76 (95% CI 0.66–0.87, $p < 0.001$) and 0.79 (95% CI 0.67–0.90, $p < 0.001$), respectively, larger than those of overall hypoperfusion volume which were 0.73 (95% CI 0.60–0.85, $p = 0.001$) and 0.73 (95% CI 0.60–0.87, $p = 0.002$), respectively.

As shown in Table 2, all 16 patients with CST-Tmax volume = 0 mL had good outcome, while only 59.1% (39/66) patients with CST-Tmax volume > 0 mL had good outcome ($p = 0.001$). In contrast, patients with overall hypoperfusion volume < 10 mL on MRP had a lower rate of good outcome (21/24, 87.5%).

We analysed reperfusion status in the patients ($n = 51$) who had baseline CST-Tmax volume > 0 mL and found that the rate of good outcome was significantly higher in patients with overall reperfusion than those without reperfusion (67.9% vs 34.8%, $p = 0.026$).

Relationship between reperfusion and CST-ADC volume and CST-Tmax volume

The baseline CST-ADC volume was correlated with baseline CST-Tmax volume in patients with overall reperfusion ($r = 0.50$, $p = 0.003$) (Fig. 1b) and not correlated with baseline CST-Tmax volume in those without overall reperfusion ($r = 0.31$, $p = 0.134$) (Fig. 1a), as well as in patients without ($r = 0.24$, $p = 0.230$) and with CST reperfusion ($r = 0.33$, $p = 0.088$) (Fig. 1c, d). The 24-h CST-ADC volume was larger than baseline CST-ADC volume (0.334 (0.051–1.430) vs 0.113 (0–0.546) mL, $p = 0.001$; 1.317 (0.334–7.656) vs 0.413 (0.013–1.561) mL, $p = 0.001$) both in patients with and without overall reperfusion. This difference was also found in patients with and without CST reperfusion ($p = 0.027$, $p = 0.001$).

The 24-h CST-ADC volume was correlated with baseline CST-Tmax volume in patients without overall reperfusion ($r = 0.67$, $p < 0.001$) and baseline CST-ADC volume in those with overall reperfusion ($r = 0.79$, $p < 0.001$) (Fig. 1e, j). The 24-h CST-ADC volume was correlated with baseline CST-Tmax volume in patients without CST reperfusion ($r = 0.67$, $p < 0.001$) and baseline CST-ADC volume in those with CST reperfusion ($r = 0.70$, $p < 0.001$) (Fig. 1g, l).

Relationship between CST-ADC volume and neurological outcome

Baseline CST-ADC volume was significantly associated with poor outcome (OR 5.1, 95% CI 2.1–12.8, $p < 0.001$)

Table 1 Univariate comparison of characteristics between patients with good and poor outcome

Variable	Good outcome ($n = 55$)	Poor outcome ($n = 27$)	p value
Age, years	65.5 ± 12.0	71.6 ± 12.1	0.035
Female, n (%)	16 (29.1)	11 (40.7)	0.325
NIHSS	6.0 (4.0–10.0)	14.0 (7.0–17.0)	<0.001
mNIHSS	2.0 (0–4.0)	6.0 (3.0–8.0)	<0.001
Onset to treatment, min	195.0 (154.0–256.0)	249.0 (218.0–275.0)	0.004
Risk factors			
Atrial fibrillation, n (%)	18 (32.7)	12 (44.4)	0.336
Prior stroke or transient ischaemic attack, n (%)	12 (21.8)	4 (14.8)	0.561
Hypertension, n (%)	37 (67.3)	19 (70.4)	1.000
Diabetes, n (%)	10 (18.2)	6 (22.2)	0.769
Smoking, n (%)	23 (41.8)	9 (33.3)	0.483
Imaging data			
Baseline overall hypoperfusion volume, mL	19.500 (3.000–67.200)	76.000 (26.800–130.100)	0.001
Baseline overall infarct volume, mL	1.000 (1.000–5.700)	4.200 (1.000–55.400)	0.012
Baseline CST-Tmax volume, mL	0.337 (0.000–1.834)	2.686 (0.533–5.463)	<0.001
Baseline CST-ADC volume, mL	0.000 (0.000–0.233)	0.871 (0.131–1.670)	<0.001

NIHSS National Institute of Health Stroke Scale, *mNIHSS* motor subscore of the NIHSS, *CST-Tmax* volumes of corticospinal tract involvement by time to maximum of tissue residue function >6 s, *CST-ADC* volumes of corticospinal tract involvement by apparent diffusion coefficient < 620×10^{-6} mm^2/s

Table 2 Effect of definition of minor stroke on outcome

	Good outcome (n = 28)	Poor outcome (n = 3)
Overall hypoperfusion volume on MRP < 10mL and CST-Tmax volume > 0 mL (n = 15)	12	3
Overall hypoperfusion volume on MRP < 10 mL and CST-Tmax volume = 0 mL (n = 9)	9	0
Overall hypoperfusion volume on MRP ≥ 10 mL and CST-Tmax volume = 0 mL (n = 7)	7	0

MRP magnetic resonance perfusion, *CST-Tmax* volumes of corticospinal tract involvement by time to maximum of tissue residue function >6 s

and poor motor outcome (OR 2.9, 95% CI 1.5–5.7, $p = 0.003$) after adjusting for age and onset to treatment time in binary logistic regression. In ROC analysis the area under curve was 0.79 (95% CI 0.68–0.90, $p < 0.001$) for poor outcome and 0.81 (95% CI 0.70–0.92, $p < 0.001$) for poor motor outcome, larger than that of overall infarct volume of 0.66 (95% CI 0.53–0.79, $p = 0.020$) and 0.61 (95% CI 0.45–0.76, $p = 0.147$), respectively. Additionally, the threshold of baseline CST-ADC volume to predict poor outcome was 3 mL, with a specificity of 100% in ROC analysis.

Relationship between the combined CST-Tmax and CST-ADC imaging profiles and good outcome

We analysed the relationship between reperfusion and good outcome (Table 3) and good motor outcome (Table 4). Patients were divided into three groups using CST-Tmax volume and CST-ADC volume at baseline: (1) no hypoperfusion lesion (CST-Tmax volume = 0 mL, $n = 16$), (2) large infarct lesion (CST-ADC volume ≥ 3 mL, $n = 3$) and (3) target lesion profile (CST-Tmax volume > 0 mL combined with CST-ADC volume < 3 mL, $n = 63$). We found that overall reperfusion
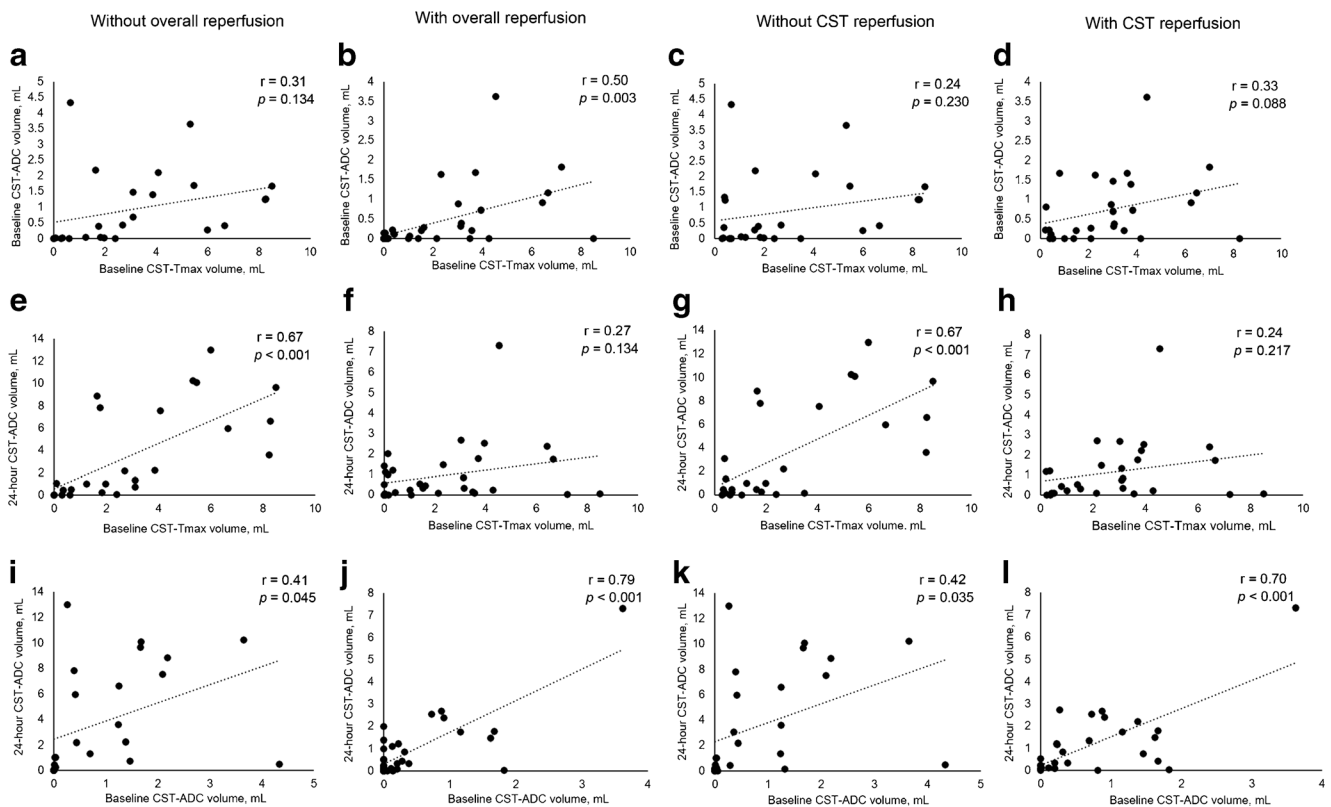

Fig. 1 Relationship between reperfusion and CST-ADC volume and CST-Tmax volume. Scatter plot comparing baseline CST-ADC volume and baseline CST-Tmax volume in patients **a** without and **b** with overall reperfusion; and **c** without and **d** with CST reperfusion. Scatter plot comparing 24-h CST-ADC volume and baseline CST-Tmax volume in patients **e** without and **f** with overall reperfusion; and **g** without and **h** with CST reperfusion. Scatter plot comparing 24-h CST-ADC volume and baseline CST-ADC volume in patients **i** without and **j** with overall reperfusion; and **k** without and **l** with CST reperfusion. *CST* corticospinal tract, *CST-ADC* volumes of CST involvement by apparent diffusion coefficient $< 620 \times 10^{-6}$ mm²/s, *CST-Tmax* volumes of CST involvement by time to maximum of tissue residue function > 6 s

Table 3 Relationship between overall reperfusion and good outcome in different CST-Tmax and CST-ADC groups

	Reperfusion		No reperfusion		p value
	Total	Good outcome (%)	Total	Good outcome (%)	
No hypoperfusion lesion ($n = 7$)	5	5 (100.0)	2	2 (100.0)	-
Target lesion ($n = 48$)	27	19 (70.4)	21	8 (38.1)	0.040
Large infarct lesion ($n = 3$)	1	0 (0)	2	0 (0)	-

CST-Tmax volumes of corticospinal tract involvement by time to maximum of tissue residue function >6 s, *CST-ADC* volumes of corticospinal tract involvement by apparent diffusion coefficient $< 620 \times 10^{-6}$ mm^2/s, *no hypoperfusion lesion* CST-Tmax volume = 0 mL, *target lesion* CST-Tmax volume > 0 mL and CST-ADC volume < 3 mL, *large infarct lesion* CST-ADC volume ≥ 3 mL

(70.4% vs 38.1%, $p = 0.04$) and CST reperfusion (74.1% vs 41.7%, $p = 0.025$) led to higher rates of good outcome than those without CST reperfusion in patients with target lesion profile. Overall reperfusion (85.2% vs 42.9%, $p = 0.005$) and CST reperfusion (85.2% vs 45.8%, $p = 0.006$) also led to higher rates of good motor outcome than those without overall reperfusion or CST reperfusion in patients with target lesion profile. Representative examples are shown in Figs. 2 and 3. Moreover, there was no association between reperfusion and HT or SHT in three groups as shown in Tables 1 and 2 in the Supplemental Material.

Additionally, the areas under the curve in ROC analysis of CST reperfusion rate for good outcome and good motor outcome were 0.71 (95% CI 0.55–0.86, $p = 0.018$) and 0.76 (95% CI 0.60–0.92, $p = 0.005$), respectively, larger than those of overall reperfusion rate which were 0.68 (95% CI 0.51–0.85, $p = 0.042$) and 0.72 (95% CI 0.56–0.87, $p = 0.008$), respectively.

Discussion

This study has demonstrated that CST salvage through reperfusion is associated with improved outcome, independent of overall salvage. We normalized Tmax and ADC images to canonical brain and confirmed that patients with target lesion (CST-Tmax volume > 0 mL and CST-ADC volume < 3 mL) benefit from reperfusion, indicating that an early estimate of potentially salvageable tissue and ischaemic core specifically related to the motor pathway would more accurately predict imaging and clinical outcomes and potentially guide therapeutic interventions.

Minor stroke poses a dilemma for thrombolysis decision-making with many patients deemed "too good to treat" [17]. However, without reperfusion therapy, 25% minor stroke patients deteriorate and are left disabled or even dead [18]. It is difficult to predict which patients will deteriorate [19–21]. Hypoperfusion volume < 10 mL has been proposed as an imaging marker for minor stroke [22, 23]. However, the location of the perfusion lesion is also an important consideration. In our study, the absence of CST involvement in the perfusion lesion (CST-Tmax volume = 0 mL) was associated with good outcome in all patients, compared to only 87.5% good outcome in patients with hypoperfusion volume < 10 mL. Therefore, the use of CST-Tmax volume may provide an important clue for guiding reperfusion therapy in minor stroke patients.

The "mismatch" principle is that baseline ischaemic core volume will approximate the final infarct volume in patients who achieve reperfusion, whilst the baseline hypoperfusion volume will predict the final infarct volume in "non-reperfusers" [24]. We observed that this principle held true when applied specifically to the corticospinal tract. The 24-h CST-ADC volume was well correlated with baseline CST-ADC volume in patients who achieved reperfusion and baseline CST-Tmax volume in patients without reperfusion, indicating that hypoperfused CST tissue may be salvaged by timely reperfusion, whereas CST tissue exhibiting diffusion restriction at baseline was not salvageable. However, without reperfusion, the hypoperfusion CST tissue converted to irreversible injury.

Table 4 Relationship between overall reperfusion and good motor outcome in different CST-Tmax and CST-ADC profiles

	Reperfusion		No reperfusion		p value
	Total	Good motor outcome (%)	Total	Good motor outcome (%)	
No hypoperfusion lesion ($n = 7$)	5	5 (100.0)	2	2 (100.0)	–
Target lesion ($n = 48$)	27	23 (85.2)	21	9 (42.9)	0.005
Large infarct lesion ($n = 3$)	1	0 (0)	2	1 (50.0)	1.000

Abbreviations same as in Table 3

mNIHSS		CST-ADC volume (mL)		CST-Tmax volume (mL)		overall infarct volume (mL)		overall hypoperfusion volume (mL)	
Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour
2	7	1.670	1.763	3.711	0.000	4.200	2.900	39.800	3.000

Before normalization

After normalization

Patient A   Overall reperfusion : Yes   CST reperfusion : Yes   3m-mRS = 4

mNIHSS		CST-ADC volume (mL)		CST-Tmax volume (mL)		overall infarct volume (mL)		overall hypoperfusion volume (mL)	
Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour
5	0	0.008	0.450	0.338	0.206	17.400	44.800	54.100	38.700

Before normalization

After normalization

Patient B   Overall reperfusion : No   CST reperfusion : No   3m-mRS = 1
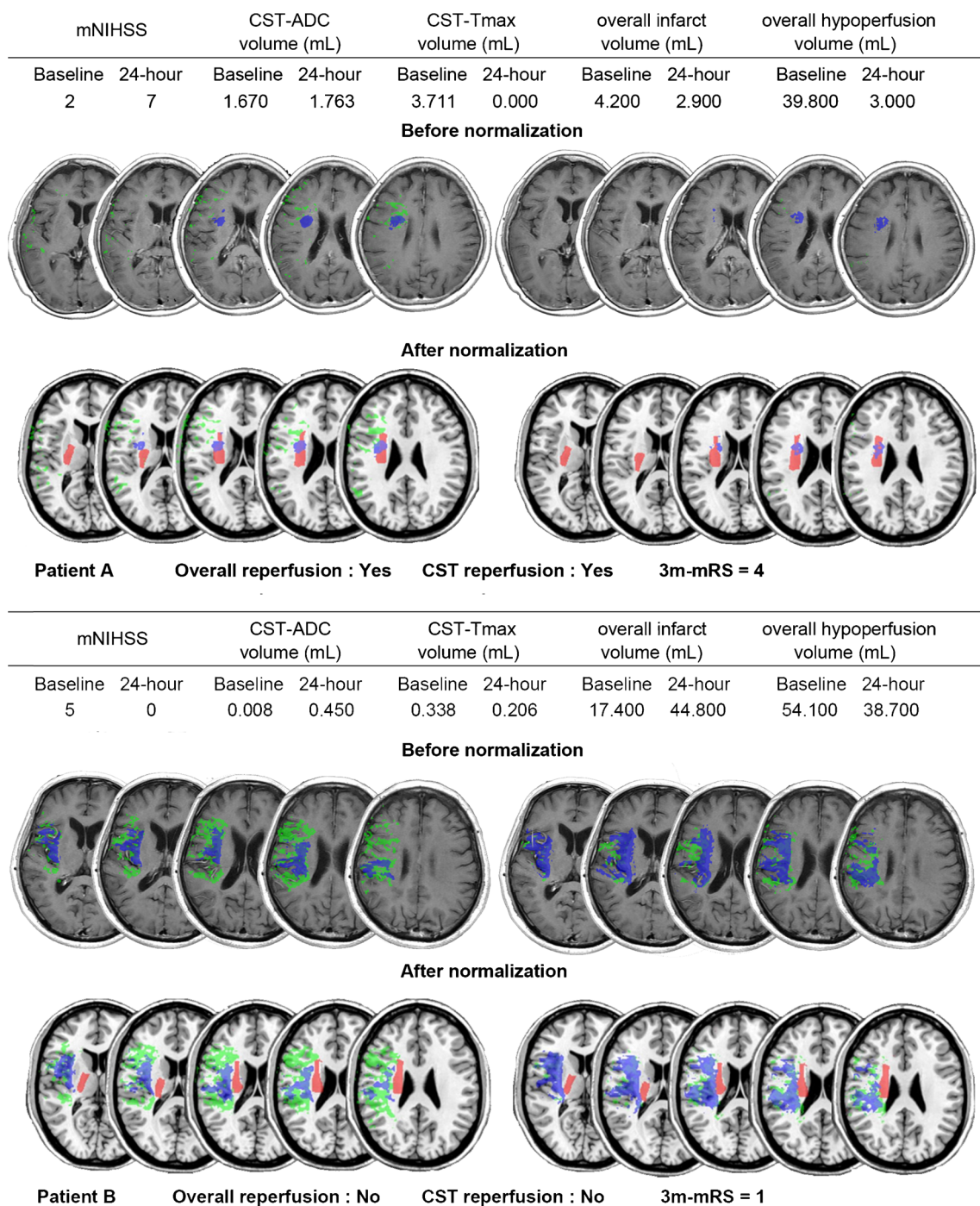
Fig. 2 Representative examples of two patients. Infarct lesion (*violet*) and hypoperfusion lesion (*green*) were overlaid onto the probabilistic fibre map (*red*). The images in the *left column* were obtained at baseline, images in the *right column* were obtained at 24 h after thrombolysis. For each patient, images before and after normalization were presented separately. Patient A had relatively large CST-ADC volume and did poorly despite reperfusion. Patient B had a relatively small CST-Tmax volume and therefore reperfusion status was unlikely to influence motor outcome. *CST* corticospinal tract, *CST-ADC* volumes of CST involvement by apparent diffusion coefficient $< 620 \times 10^{-6}$ mm^2/s, *CST-Tmax* volumes of CST involvement by time to maximum of tissue residue function > 6 s, *mNIHSS* limb-related elements of the National Institute of Health Stroke Scale, *mRS* modified Rankin Scale

Previous studies have demonstrated that the severity of motor function damage after AIS is highly dependent on the volume of CST-ADC rather than the overall lesion size [10], which was also found in our study. Besides, all patients with baseline CST-ADC volume ≥ 3 mL had poor outcome even if reperfusion was achieved. Therefore, we proposed a cut-off of 3 mL for CST-ADC volume, which might be helpful to exclude patients who would not be eligible for
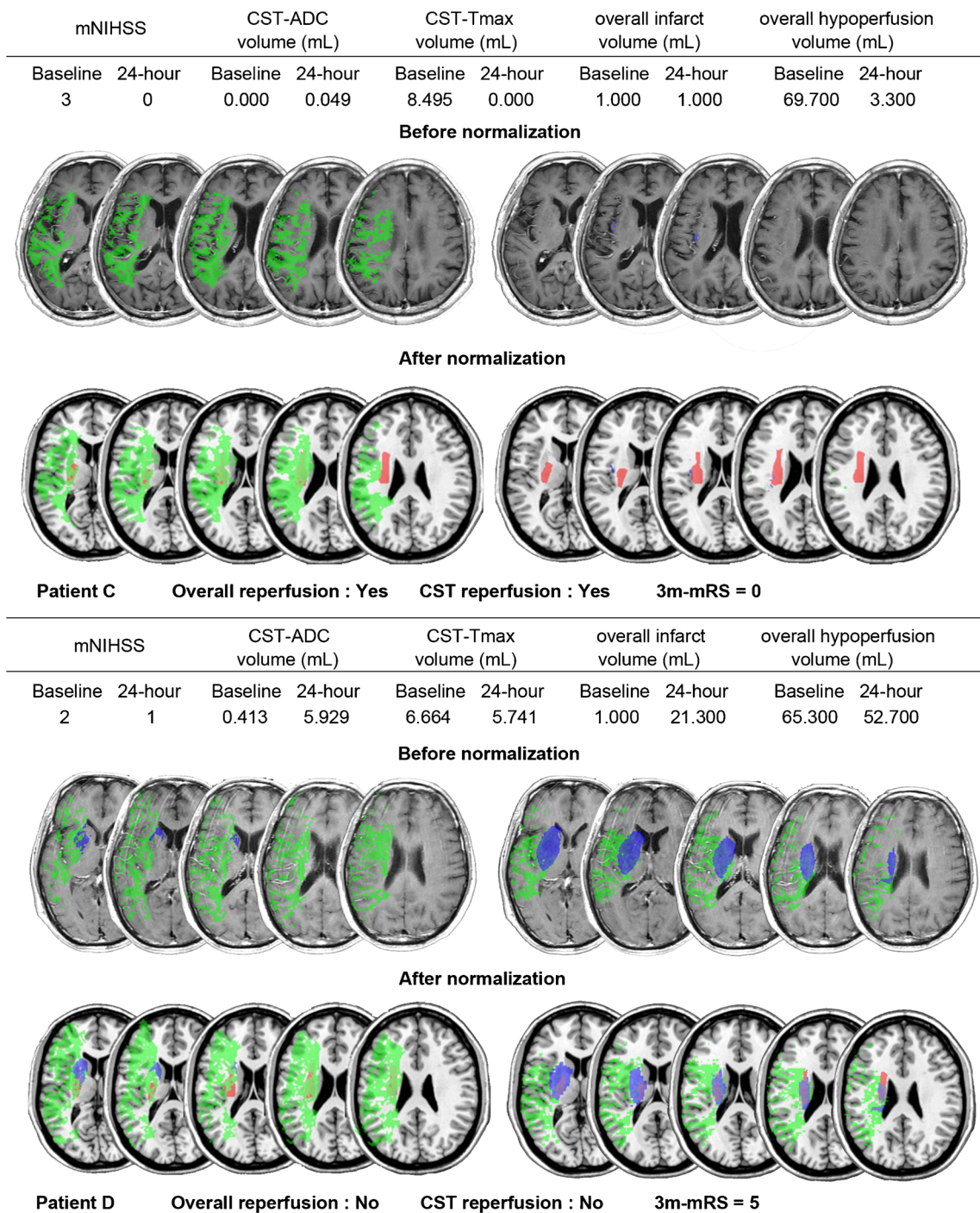
mNIHSS		CST-ADC volume (mL)		CST-Tmax volume (mL)		overall infarct volume (mL)		overall hypoperfusion volume (mL)	
Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour
3	0	0.000	0.049	8.495	0.000	1.000	1.000	69.700	3.300

Before normalization

After normalization

Patient C   Overall reperfusion : Yes   CST reperfusion : Yes   3m-mRS = 0

mNIHSS		CST-ADC volume (mL)		CST-Tmax volume (mL)		overall infarct volume (mL)		overall hypoperfusion volume (mL)	
Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour	Baseline	24-hour
2	1	0.413	5.929	6.664	5.741	1.000	21.300	65.300	52.700

Before normalization

After normalization

Patient D   Overall reperfusion : No   CST reperfusion : No   3m-mRS = 5

Fig. 3 See caption of Fig. 2 for full explanation and abbreviations. Representative examples of two patients. In patients with a target profile (CST-Tmax volume > 0 mL and CST-ADC volume < 3 mL), the outcome at 3 months was significantly better in patients with reperfusion (patient C) than those without reperfusion (patient D)

reperfusion therapy. Since we did not obtain detailed information about the amount or intensity of rehabilitation in our patients and did not use it as a covariate in the multivariate regression analysis, future studies may be needed to determine whether patients with large CST-ADC volume would benefit more from rehabilitation therapy than reperfusion therapy.

On the basis of the above findings, we gave a definition of target lesion and found that the rate of good outcome was higher in patients with reperfusion than those without reperfusion. Patients with target lesion had relatively large CST-Tmax (large hypoperfused tissue which may die without reperfusion) and small CST-ADC lesion (already dead tissue), and might achieve functional recovery from reperfusion

therapy. Therefore, the combination of CST-Tmax and CST-ADC might be useful to select eligible patients who would benefit from reperfusion therapy, and to monitor the therapeutic response to acute interventions.

Our use of CST hypoperfusion and infarct using diffusion and perfusion MR has advantages over other more specialized sequences such as functional MRI and DTI, which can be challenging to acquire in acute stroke patients because of their long acquisition time. Although a decrease in fractional anisotropy derived from DTI was associated with poor motor outcomes in stroke patients at chronic phase [25], it offered minimal predictive value in the acute phase [6]. Some studies also showed that DTI might provide inaccurate assessment of the CST lesion as a tract distal to a lesion may still appear structurally intact in the acute phase, despite already being irreversibly damaged [10]. In future, our method to evaluate CST injury in acute phase would refine selection of reperfusion therapy in AIS patients. Despite of the overall lesion size, it is rational to give reperfusion therapy in patients with target CST lesion. Recent study has showed that it was feasible and practical to achieve the benchmark of door-to-needle time ≤60 min, by using MRI as the routine screening modality before reperfusion therapy. With the post-processing of DWI/PWI, our method provides more details about motor function and could be integrated into acute workflow when waiting for the patient's consent form. In addition, fibre tracts have been suggested to have greater ischaemic tolerance than other regions in recent studies [26]. For example, a recent study demonstrated that immediate remote ischaemic postconditioning after ischaemia could protect cerebral white matter but not grey matter in piglets [27].

Our study had limitations related to its retrospective nature and moderate sample size. Spatially normalized brain images may contain distortions due to large lesions, oedema or cerebral ventricle. However, solutions such as masking large lesions were used to improve the accuracy of spatial normalization. Besides, we had not discussed the involvement of other specific eloquent areas other than CST in this study considering the various complex functional area. Motor function is not the sole determinant of functional outcome and other key abilities such as language could be similarly studied in future analyses. Posterior circulation ischaemic stroke was not included in our study and perfusion parameters may differ from the anterior circulation. Confirmation and extension in larger and multicentre cohorts is needed.

Conclusion

Spatially registered Tmax and ADC images could identify CST hypoperfusion and irreversible injury in the acute phase of ischaemic stroke. The combined information from CST-Tmax and CST-ADC could improve outcome prediction and potentially refine selection of reperfusion therapy.

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