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RESEARCH ARTICLE

Computed tomography perfusion and computed tomography angiography for prediction of clinical outcomes in ischemic stroke patients after thrombolysis

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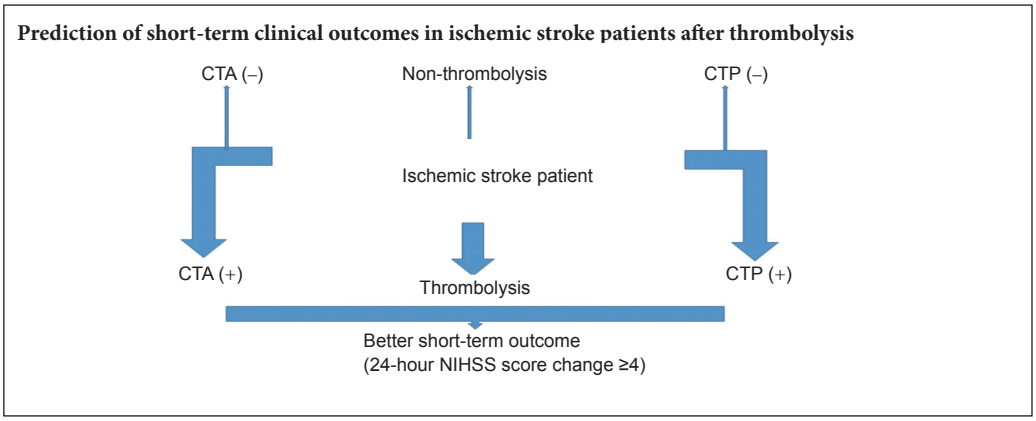
Graphical Abstract



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Abstract

Cerebral blood perfusion and cerebrovascular lesions are important factors that can affect the therapeutic efficacy of thrombolysis. At present, the majority of studies focus on assessing the accuracy of lesion location using imaging methods before treatment, with less attention to predictions of outcomes after thrombolysis. Thus, in the present study, we assessed the efficacy of combined computed tomography (CT) perfusion and CT angiography in predicting clinical outcomes after thrombolysis in ischemic stroke patients. The study included 52 patients who received both CT perfusion and CT angiography. Patients were grouped based on the following criteria to compare clinical outcomes: (1) thrombolytic and non-thrombolytic patients, (2) thrombolytic patients with CT angiography showing the presence or absence of a vascular stenosis, (3) thrombolytic patients with CT perfusion showing the presence or absence of hemodynamic mismatch, and (4) different CT angiography and CT perfusion results. Short-term outcome was assessed by the 24-hour National Institution of Health Stroke Scale score change. Long-term outcome was assessed by the 3-month modified Rankin Scale score. Of 52 ischemic stroke patients, 29 were treated with thrombolysis and exhibited improved short-term outcomes compared with those without thrombolysis treatment (23 patients). Patients with both vascular stenosis and blood flow mismatch (13 patients) exhibited the best short-term outcome, while there was no correlation of long-term outcome with CT angiography or CT perfusion findings. These data suggest that combined CT perfusion and CT angiography are useful for predicting short-term outcome, but not long-term outcome, after thrombolysis.

Key Words: *nerve regeneration; ischemic stroke; 256-slice whole-brain CT perfusion; infarct core; penumbra; CT perfusion mismatch; CT angiography; vessel stenosis; intravenous thrombolysis; 24-hour National Institution of Health Stroke Scale; 3-month modified Rankin Scale; neural regeneration*

Introduction

Computed tomography (CT) perfusion (CTP) and CT angiography (CTA) imaging techniques are widely used for diagnosis of ischemic stroke as they are safe, convenient, and accurate (Vagal et al., 2014; Yew et al., 2015). Cerebral blood flow perfusion and vascular conditions are critical for choice of optimal clinical treatment. However, although patients and their families are mostly concerned with clinical outcomes after thrombolysis, doctors are usually unable to make outcome predictions. Numerous studies have focused on improving the accuracy of imaging examination before treatment (Seeters et al., 2013; Smit et al., 2015), while the prognosis after thrombolysis in patients with long-term follow-up evaluation is poorly understood. In the present study, we examined role of combined CTP and CTA imaging in predicting clinical outcomes after thrombolysis in ischemic stroke patients.

Subjects and Methods

Subjects

This study was approved by the local ethical committee (Institutional Review Board of Huashan Hospital, Fudan University, IRB number KY2013-332), and written informed consent forms were obtained directly from patients or the next of kin. Patients were continuously collected in the Neurological Emergency Department of Huashan Hospital of China from December 2011 to September 2012.

Inclusion criteria

According to China Cerebrovascular Disease Prevention and Control Guidelines (2nd Edition) (Rao, 2010), patients who met all the following factors were enrolled in this study: (1) sudden onset, focal, or comprehensive loss of neurological function and (2) symptoms lasted for 24 hours.

Exclusion criteria

Exclusion criteria included: (1) patients who did not meet one of the above two factors or refused to have the two exams; (2) patients with non-vascular cerebral disease, and (3) patients with cerebral hemorrhage or other diseases by CT scan.

Criteria of the enrolled patients with thrombolytic therapy

(1) CT showed no sign of cerebral hemorrhage; (2) physical exam did not show active bleeding or acute trauma (fracture); (3) no use of oral anticoagulants or international standard ratio ≤ 1.5 if the patient had used oral anticoagulants; (4) activated partial thromboplastin time within normal limits; (5) platelet count ≥ 100×10^9/L, blood sugar concentration ≥ 2.7 mM; (6) infarct size on CT less than 1/3 of the cerebral hemisphere; and (7) informed consent of the patient or family members.

Criteria of enrolled patients without thrombolysis

(1) Met all the diagnostic criteria of acute ischemic stroke and (2) inconformity with one of the thrombolytic therapy criteria.

CTP and CTA scans

Every patient included in this study received a 256-detector CTP and CTA scan (Brilliance iCT; Philips Medical Systems, Cleveland, OH, USA). A dual-head power injector (Stellant Injection System; Medrad Inc., Indianola, PA, USA) was used to inject 40 mL of a nonionic contrast medium (Ultravist, iodine 370 mg/mL; Bayer Healthcare, Berlin, Germany) at a rate of 5 mL/s, followed by a 20-mL saline flush at a rate of 5 mL/s into an antecubital vein. CT scanning was initiated at 5 seconds after the start of the injection with the following acquisition parameters: Jog mode, 80-kV tube voltage, 150 mAs, 5-mm slice thickness, 128 × 0.625-mm collimation, 0.4-second rotation time, 1.9-second cycle time, 22-cm field of view, 512 × 512 image matrix size, 25 slices, and 120-mm scan length. Helical scanning was not performed. A total of 325 slices were obtained with a scan time of approximately 50 seconds. Brain standard reconstruction was performed with the CT system. The gantry angle was parallel to and above the orbital roof to avoid radiation exposure to the lens.

Thrombolysis therapy

Recombinant tissue plasminogen activator (0.9 mg/kg) was mixed with 100 mL normal saline. Ten percent of the solution was intravenously injected, and the rest was intravenously dripped over 1 hour (recombinant tissue plasminogen activator maximum dose: 90 mg).

Image post-processing

Post-processing software (MIStar, Apollo Medical Imaging Technology Pty. Ltd., Melbourne, Australia) (Yang, 2005, 2010; Bivard et al., 2011) was used for deconvolution of the tissue enhancement curve and the artery input function by model-free singular value decomposition with a delay and dispersion correction (see appendix for more detail). CTP penumbra and infarct core parameters were set according to our previous research (Pan et al., 2013). The penumbra scale (a relative mean transfer time ≥ 150%) and the infarct core scale (relative cerebral blood volume ≤ 40%) were calculated by the software.

Group assignment

(1) All patients were divided into two groups based on their acceptance of thrombolytic treatment. (2) All thrombolytic patients were divided into two groups according to whether CTA results showed a vascular stenosis. (3) All thrombolytic patients were divided into two groups according to whether CTP results showed a blood flow mismatch. (4) All thrombolytic patients were divided into three groups according to both CTA and CTP findings (vascular stenosis and blood flow mismatch, vascular stenosis without blood flow mismatch, or blood flow mismatch without occlusive vascular stenosis).

CTP blood flow mismatch

A CTP penumbra volume and infarct core volume ratio ($V_{penumbra}/V_{infarct}$) ≥ 0.2 indicates a mismatch, while a ratio < 0.2 represents no mismatch (infarct core, red; penumbra, green;

Table 1 General information for thrombolytic and non-thrombolytic patients

	Thrombolytic	Non-thrombolytic
n	29	23
Age (mean [range], year)	62(41–81)	66(46–90)
Gender (male/female, *n*)	20/9	18/5
Onset time (hour)		
0–3	14	9
3–6	11	9
> 6	4	5
Location		
Basal ganglia (*n*)	11	9
Cerebral cortex (*n*)	15	12
Brain stem (*n*)	3	2
Risk factors (*n*)		
Hypertension (*n*)	16	10
Heart disease (*n*)	2	3
Diabetes (*n*)	9	10
Anticoagulant or antiplatelet treatment (*n*)	1	2
Baseline NIHSS (mean ± SD, score)	7.9±3.8	5.6±2.9
24-hour NIHSS (mean ± SD, score)	5.7±3.4 (24 hours after thrombolysis)	4.9±2.6
#Short outcome (better/worse, *n*)	(1)12/17*	(2)3/20
&Long outcome (better/worse, *n*)	(3)17/12	(4)15/8

For short-term outcome, better indicates a 24-hour National Institution of Health Stroke Scale (NIHSS) score change ≥ 4, while worse indicates a 24-hour NIHSS score change < 4. For long-term outcome, better indicates a 3-month modified Rankin Scale (mRS) score ≤ 2, while worse indicates a 3-month mRS score > 2. *P < 0.05, *vs.* non-thrombolytic (chi-square test, 95% confidence interval: 1.137–19.484).

Table 2 General information of thrombolytic patients divided by CT angiography (CTA) and CT perfusion (CTP) results

	CTA (+)/ CTP (+)	CTA (+)/ CTP (–)	CTA (–)/ CTP (+)	CTA (–)/ CTP (–)
n	13	5	7	4
Age (mean, range, year)	62(45–80)	64(55–76)	66(46–90)	60(56–72)
Gender (male/ female, *n*)	9/4	4/2	5/2	2/1
Onset time (hour)				
0–3	6	4	4	0
3–6	6	1	2	2
> 6	1	0	1	2
Hypertension (*n*)	6	3	5	2
Heart disease (*n*)	1	0	1	0
Diabetes (*n*)	3	3	3	0
Anticoagulant or antiplatelet treatment (*n*)	0	0	1	0

There were no differences in age, sex, or onset time between the first three groups. CTA vascular stenosis (CTA+) was defined as the degree of arterial stenosis > 50% (< 50% is CTA–). The CTA vascular stenosis formula is: diameter of the narrowest part of the artery / diameter of the normal part of the artery × 100%. A CTP penumbra volume and infarct core volume ratio ($V_{penumbra}/V_{infarct}$) ≥ 0.2 indicates the existence of a mismatch (CTP+), while a value < 0.2 represents no mismatch (CTP–).

Figure 1). This definition is analogous to the magnetic resonance perfusion weighted imaging (MR-PWI) and diffusion weighted imaging (MR-DWI) mismatch, where the CTP infarct core is equivalent to MR-DWI while the CTP penumbra is equivalent to MR-PWI. Thus, the standard of an MR-PWI and MR-DWI mismatch is also applied to a CTP blood flow mismatch (Schlaug et al., 1999).

CTA evaluation

CTA vascular stenosis was defined as the degree of arterial stenosis > 50%, using the following formula: diameter of the narrowest part of the artery/diameter of the normal part of the artery × 100%. We selected the following arteries for evaluation: bilateral intracavernous internal carotid artery, supraclinoid portion of the internal carotid artery, A1 and A2 portion of the anterior cerebral artery, M1 and M2 portion of the middle cerebral artery, P1 and P2 portion of the posterior cerebral artery, and the intracranial sector of the vertebral artery and basal artery. Evidence of stenosis was independently diagnosed by two radiologists, with positive findings from both required for final confirmation (**Figure 2**).

Outcome measures

Each patient received two follow-up assessments: a 24-hour National Institution of Health Stroke Scale (NIHSS) (Thomas et al., 1989) and a 3-month modified Rankin Scale (mRS) (Swieten et al., 1988). These two criteria are the most common methods used by neurological physicians to evaluate patient prognosis. For the NIHSS, the total score indicating-was calculated by adding each item score, with higher score indicating worse patient condition. When comparing at 24-hour NIHSS score with baseline NIHSS score, a reduction ≥ 4 indicates improved short-term outcome, while a reduction < 4 indicates a worse short-term outcome. For the mRS, patients were asked what ranking they conformed to, with a higher score indicating a worse condition. A 3-month mRS score ≤ 2 indicates improved long-term outcome, while a 3-month mRS score > 2 indicates worse long-term outcome.

Statistical analysis

Data were analyzed using SPSS 20.0 software (IBM, Armonk, NY, USA). All data were tested for normality. A chi-square Armonk test was used to compare clinical outcomes (count data were calculated as a ratio) between the groups (inter-group differences). An independent sample *t*-test was used to compare the general information (data were calculated as means) between the groups (inter-group differences). A value of P < 0.05 was considered statistically significant.

Results

Among the 52 ischemic stroke patients, 29 received thrombolytic therapy and 23 did not (baseline information of these two groups are shown in **Table 1**). Thrombolytic patients exhibited better short-term outcomes than those without therapy (**Table 1**). The thrombolytic effect was not different between the various locations (**Figure 3**).

Baseline information of the thrombolytic patients is

Table 3 Chi-square test results of different CTP and CTA examination results and clinical outcomes of thrombolytic patients

Group	24-hour NIHSS score change		3-month mRS score		Compared groups	*P* value	95%*CI*
	≥ 4	< 4	≤ 2	> 2			
(1) CTA (+)	11	7	10	8		0.466	[0.413, 8.611]
(2) CTA (–)	5	6	9	2	(1) *vs.* (2)	0.234	[0.046, 1.667]
(3) CTP (+)	11	9	12	8		0.427	[0.473, 2.629]
(4) CTP (–)	3	6	7	2		0.431	[0.070, 2.614]
(5) CTA (+)/CTP (+)	10	3	8	5	(5) *vs.* (6)	0.047*	[1.048, 169.557]
						0.608	[0.291, 19.784]
(6) CTA (+)/CTP (–)	1	4	2	3	(5) *vs.* (7)	0.017*	[1.676, 238.630]
						1.000	[0.185, 7.770]
(7) CTA (–)/CTP (+)	1	6	4	3	(6) *vs.* (7)	1.000	[0.071, 31.575]
						1.000	[0.049, 5.154]

*$P < 0.05$. CTA: Computed tomography angiography; CTP: computed tomography perfusion; NIHSS: National Institution of Health Stroke Scale; *CI*: confidence interval; mRS: modified Rankin Scale.

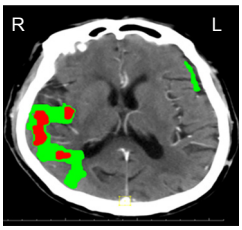

Figure 1 CTP post-processed image.

The patient was a 48-year-old man, with no history of hypertension, diabetes, or heart disease. The onset time was 4 hours, with a lesion detected in the right temporal lobe. The baseline NIHSS score was 15. After thrombolytic therapy, the 24-hour NIHSS score was 9. Red areas represent the infarct core. Green areas represent the penumbra. R: Right; L: left; CTP: computed tomography perfusion; NIHSS: National Institution of Health Stroke Scale.

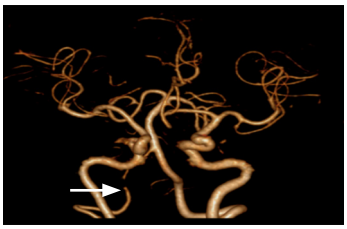

Figure 2 Computed tomography angiography post-processed picture.

The patient was a 64-year-old man, with no history of hypertension, diabetes, or heart disease. The onset time was 3 hours, with stenosis detected in the intracranial section of the right vertebral artery (arrow). The baseline National Institution of Health Stroke Scale score was 12. After thrombolytic therapy, the 24-hour National Institution of Health Stroke Scale score was 7.

shown in **Table 2**. The group of patients with both CTA vascular stenosis and a CTP blood flow mismatch exhibited a better short-term clinical outcome than patients in other groups. There were no other differences between the groups (**Table 3**).

Discussion

Relationship between thrombolysis and clinical outcomes

We found that patients who received thrombolysis had a better short-term clinical outcome than those without thrombolysis, with no effects of onset time or ischemic location. These data suggest that thrombolytic therapy can rapidly help to recover brain perfusion and maintain neurological

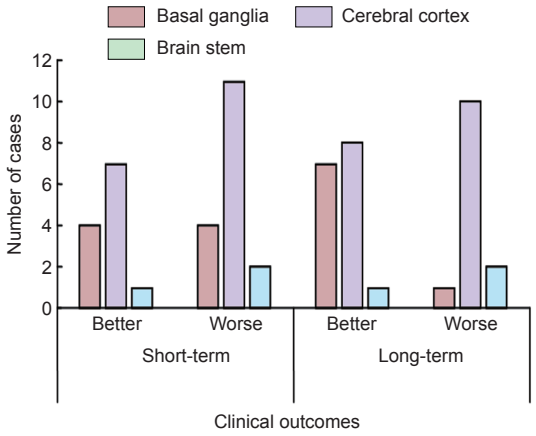

Figure 3 Thrombolytic effects for lesions at different locations.
For short-term outcome, better indicates a 24-hour National Institution of Health Stroke Scale score change ≥ 4, while worse indicates a 24-hour National Institution of Health Stroke Scale score change < 4. For long-term outcome, better indicates a 3-month modified Rankin Scale score ≤ 2, while worse indicates a 3-month modified Rankin Scale score > 2. There were no differences in short-term and long-term outcomes in the various locations (short term: $P = 0.831$; long term: $P = 0.115$).

function. However, there were no differences in long-term outcomes between the two groups.

Relationship between CTA findings and clinical outcomes after thrombolysis

As the target of thrombolytic therapy is the embolus or the *in situ* thrombosis, patients with occlusive vessels should theoretically benefit more from thrombolysis than those with vascular stenosis. However, we found no difference in short-term or long-term clinical outcomes between these patients. These unexpected findings may relate to the affected brain region and the degree of embolism (Porelli et al., 2013; Sillanpaa et al., 2013). For cases with proximal obstructions of large blood vessels such as the internal carotid artery or the M1 segment of the middle cerebral artery, recanalization by intravenous thrombolysis is difficult, especially when the embolus is greater than 5 mm in length (Kimura et al., 2011;

Riedel et al., 2011). Clogging of larger blood vessels suggests a larger embolus volume, which would limit delivery of recombinant tissue plasminogen activator at the infarct site. Thus, our findings may relate to thrombolytic failure in some occlusive vessels.

In addition, recanalization does not imply reperfusion, although these two concepts are often used interchangeably (Tomsick et al., 2008; Soares et al., 2009). Recanalization is more focused on the vascular lumen, while reperfusion is largely related to blood supply to the brain (Tomsick, 2007). There is some evidence that a large embolus can decompose into smaller emboli after thrombolysis and block smaller downstream vessels. Thus, the brain remains ischemic despite appearance of recanalization of the original occlusive large vessels (Janjua et al., 2008). Finally, it is possible that despite the extinction of ischemic brain edema, no blood flow will reach the affected area (Zoppo, 2008). Thus, the presence of blood flow reperfusion rather than recanalization is more widely used as a predictor of clinical outcomes.

Relationship between CTP findings and clinical outcomes after thrombolysis

In the present study, there were no differences in the short-term and long-term outcomes with respect to the presence of a blood flow mismatch. These data are consistent with other studies suggesting that the use of CTP findings to assess the efficacy of thrombolytic therapy remains unclear (Hassan et al., 2012). As the volume of the penumbra that can be saved by thrombolysis is related to the admission time and the selection of CTP parameters (Garcia et al., 2012), the safety and efficacy of CTP require further confirmation (Michel et al., 2012).

Alternatively, it is possible that the blood flow mismatch was not caused by an acute vascular occlusion, but rather by an old infarction. Thus, the mismatch area may have existed for a long time, with no improvement in clinical symptoms following thrombolysis. The brain function in the mismatch area may also be compensated by other parts of the brain. Thus, despite positive imaging findings, there are no differences in clinical function scores. Finally, the blood flow mismatch may be caused by a transient ischemic attack without vascular occlusion. As such, thrombolysis will not be associated with clinical outcomes.

The similar short-term and long-term outcomes in terms of blood flow mismatch in the present study may explain why short onset time patients did not achieve the desired outcomes after thrombolysis, but exhibited serious side effects such as intracranial hemorrhage. Some of these patients may have had relatively larger emboli, with thrombolysis unable to recanalize the occlusive vessels, resulting in persisting cerebral ischemia and neuronal death. For patients with a blood flow mismatch area but no vascular embolism, thrombolysis may cause a hemorrhage in non-obstructive vessels and then aggravate the illness.

Relationship between CTA and CTP findings and clinical outcomes after thrombolysis

By comparing both CTA and CTP results in thrombolytic patients with clinical outcomes, we found that patients with both vascular stenosis and a blood flow mismatch had better short-term outcomes after thrombolysis, but no differences in long-term outcomes. An association between CTP and CTA examination and prognosis of ischemic stroke patients was recently reported (Eckert et al., 2011; Suzuki et al., 2011). For patients with onset times longer than 3 hours, both CTP and CTA findings should be considered to determine whether thrombolysis can significantly improve prognosis (Obach et al., 2011). Our findings of no differences between CTA and CTP data and long-term outcomes after thrombolysis may be caused by a number of factors. (1) If patients have new infarct attacks over the period of 24 hours to 3 months, which they are unaware of (representing a second-time ischemic stroke), the mRS score at 3 months will be significantly reduced. (2) The improved short-term outcome may result from timely compensation of brain tissue and potential collateral circulation opening, rather than vascular recanalization. Neurons subjected to this collateral circulation decompensation would quickly die, eventually leading to a poor long-term outcome. (3) Other factors may influence the cerebrovascular status and cerebral blood flow dynamics within the 3-month time window, including blood pressure, blood sugar, triglycerides, and cholesterol. (4) The mRS score used to measure neural functional recovery in stroke patients considers all aspects of life, including dressing, walking, eating, traveling, studying, and working. The mRS score is divided into six classes according to the severity of impairment. A patient's condition is considered to be improving if there is at least a 2-point difference in the activities in which the patient was competent before the onset of ischemia. However, for patients who can only complete a portion of the activities, the scoring criteria may vary relative to the narrator's recall bias and the rater's subjective judgment. (5) Some low 24-hour NIHSS score patients exhibited spontaneous recanalization after 24 hours, which would improve the long-term outcome and influence the differences among groups.

Conclusions

Ischemic stroke patients with both vascular stenosis and blood flow mismatch have the best short-term clinical outcomes following thrombolysis. However, the long-term outcome is affected by multiple other factors, and is not related to CTA or CTP results. These findings may also be attributable to the small sample size of this study.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

Author contributions: *DYG, QD and JZ designed this study. JWP, SYZ, JHW, YFL, XC and TYZ performed experiments. JWP, JHW and XRY analyzed data. JWP wrote the paper. All authors approved the final version of the paper.*

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verify originality before publication.
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