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PREDICTION OF THE LONG-TERM EFFICACY OF STA-MCA BYPASS BY DSC-PI

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Abstract

Superficial temporal artery-middle cerebral artery (STA-MCA) bypass [1,2] is an important and effective type of surgical revascularization that is widely used in the treatment of ischemic cerebral artery disease. However, a means of predicting its postoperative efficacy has not been established [3,4]. The present study analyzes the correlation between preoperative perfusion parameters (obtained using dynamic susceptibility contrast-enhanced perfusion imaging, DSC-PI) and postoperative long-term prognosis (using modified Rankin Scale, mRS scores). The preoperative perfusion parameters were defined by a combination of perfusion-weighted imaging and the Alberta Stroke Program Early Computerized Tomography Score (PWI-ASPECTS) and included cerebral blood flow (CBF)-ASPECTS, cerebral blood volume (CBV)-ASPECTS, mean transit time (MTT)-ASPECTS, and time to peak (TTP)-ASPECTS. Preoperative and postoperative scores were determined for 33 patients that received a unilateral STA-MCA bypass in order to discover the most reliable imaging predictive index as well as to define the threshold value for a favorable clinical outcome. The results showed that all of the PWI-ASPECTS scores were significantly negatively correlated with clinical prognosis. Receiver operating curve (ROC) analysis of the preoperative parameters in relation to long term prognosis showed the area under curve (AUC) was maximal for the CBF-ASPECTS score (P = 0.002). A preoperative score of less than six indicated a poor postoperative prognosis (sensitivity = 74.1%, specificity = 100%, AUC = 0.843). In conclusion, preoperative PWI-ASPECTS scores have been found useful as predictive indexes for the long-term prognosis of STA-MCA bypass patients, with higher scores indicating better postoperative long-term outcomes. As the most valuable prognostic indicator, the preoperative CBF-ASPECTS score has potential for use as a major index in screening and outcome prediction of patients under consideration for STA-MCA bypass surgery.

Keywords

Alberta Stroke Program Early Computerized Tomography score (ASPECTS) • Long-term prediction • Magnetic resonance imaging (MRI) • Perfusion imaging • Superficial temporal artery - middle cerebral artery (STA-MCA) bypass

Introduction

Morbidity due to ischemic cerebral artery disease caused by atherosclerosis is increasing. Ischemic cerebral artery disease is treated by various methods including aggressive medical management, intracranial angioplasty, stenting and cerebrovascular bypass surgery [1-4]. In 2014, the results of a randomized clinical trial by Derdyn *et al*. (SAMMPRIS) [5] were published showing evidence that supported the use of aggressive medical treatment rather than percutaneous transluminal angioplasty and stenting (PTAS) in high-risk patients with atherosclerotic intracranial arterial stenosis. In that study, patients were enrolled based solely on morphological lesion severity. However, most researchers acknowledge that stroke patients with intracranial and extracranial artery stenosis or occlusions can additionally exhibit poor blood perfusion caused by abnormal hemodynamics (impaired autoregulation) beyond the lesion [6]. Extracranial to intracranial (EC-IC) bypass surgery is a type of surgical revascularization used for ischemic cerebral artery disease that is due to conditions that progressively decrease cerebral blood flow in the absence of compensatory collateral circulation. Superficial temporal artery - middle cerebral artery (STA-MCA) bypass, the most classical operation, revascularizes the ischemic region of MCA by rerouting blood flow from the STA through the skull to join the MCA, bypassing the stenotic lesion. Traditionally, the acetazolamide challenge test has been used to evaluate cerebral vascular reactivity (CVR) in patients who will potentially undergo STA-MCA bypass in order to predict whether or not they will benefit from surgery [7]. This test can be combined with a variety of medical imaging technologies, including positron emission tomography (PET), single photon emission computed tomography (SPECT), and Xe-CT (xenon-enhanced computerized tomography) [8, 9, 10]. The validity of the test has been extensively confirmed but results are affected by factors such as age and dosage [11]. Additionally, the acetazolamide challenge test may lead to adverse cardiovascular events and temporary neural dysfunction in some subjects [10].

Dynamic susceptibility contrast enhanced perfusion imaging (DSC-PI) is a new tool, with high safety and feasibility, that can be utilized in consideration of patients for direct bypass surgery as well as in evaluation of long-term prognosis. Extensively used in clinical settings, dynamic susceptibility contrast - magnetic resonance imaging (DSC-MRI) is a common

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method of perfusion-weighted imaging (PWI). Parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) are derived from PWI. The combination of the Alberta Stroke Program Early CT Score (ASPECTS) (which achieves a rapid and effective assessment of ischemia extent) and PWI (which can estimate hemodynamics accurately through the parameters mentioned above) is an innovative and quantized grading standard useful for patients with ischemic cerebral artery disease.

Material and methods

Subjects

A retrospective analysis was conducted on 33 patients admitted to the Tianjin Huanhu Hospital from Jan, 2011 to Dec, 2013, who received a unilateral STA-MCA bypass. The mean age was 59.5 years (range: 38-71 years); 29 patients were male and four were female. Before bypass surgery, digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA) showed that all patients had a stenosis or occlusion on one side of the internal carotid or cerebral artery. The arteries on the opposite side were relatively normal, with no abnormality in cerebral blood flow as demonstrated by skull dynamic susceptibility contrast-enhanced perfusion imaging (DSC-PI). Clinical long-term follow up was performed for all patients with a postoperative follow-up time of 2 to 4 years, averaging 33.9 months. Patient symptoms and risk factors are listed in Table 1.

Methods

A Siemens 3.0 T Trio TIM system MRI scanner was used to carry out the preoperative DSC-PI studies. MRI scanning included the area from the base of the skull to the parietal cortex. After scanning, a dose of 0.1 mmol/kg of contrast gadolinium with diethylenetriaminepetacetate DTPA (Gd-DTPA) was injected at a speed of 3 ml/s. Perfusion source images were acquired by scanning the full brain using a gradient-echo - echo-planar imaging (GRE-EPI) sequence, with the following scanning parameters: repetition time (TR) = 2500 ms, echo time (TE) = 80 ms, flip angle = 90°, field of view (FOV) = 230 × 230 mm, layer thickness = 6 mm, interlayer spacing = 1.8 mm. Analysis of cerebral blood flow perfusion was conducted on the perfusion source images, and four color maps displaying perfusion parameters were reconstructed: CBF, CBV, MTT, and TTP.

ASPECTS [12] was determined by evaluation of the middle cerebral artery territory in two standardized regions (at the level of the basal ganglia and the supraganglionic level). The territory was divided into ten parts: C, L, IC, I, M1, M2, and M3 were found on the level of the basal ganglia and M4, M5, and M6 were located rostral to the basal ganglia in the supraganglionic region (Fig. 1). The above-mentioned four color maps derived from DSC-PI could also be scored in this way. That is, if a perfusion abnormality took place in one of the ten MCA blood supply areas, one point was subtracted from the score. An ASPECTS of ten points indicates that there is no ischemic change in the MCA territory, whereas a score of one indicates severe ischemia and occlusions. CBF-ASPECTS, CBV-ASPECTS, MTT-ASPECTS, and TTP-ASPECTS were measured prior to surgery. An example of the preoperative perfusion map of a STA-MCA bypass patient is shown in Fig. 2.

The patients were divided into a good prognosis group (mRS score of 0 to 2) and a poor prognosis group (mRS score of 3 to 6) according to the results obtained during long-term follow up [13, 14].

Statistics

Statistical analysis was performed using the SPSS 17.0 statistical software package (SPSS Inc., released 2008, Chicago, IL, USA). The correlation between the PWI-ASPECTS and the mRS score was evaluated by Spearman correlation analysis. The difference in PWI-ASPECTS score between the good prognosis group and the poor prognosis group was assessed by the Mann-Whitney test; Receiver Operating Characteristic (ROC) analysis of the PWI-ASPECTS score was performed in order to seek out the best predictive index for long-term prognosis. A P-value of less than 0.05 was defined as a difference with statistical significance. The data above were independently evaluated by two experienced physicians without prior knowledge of the patients' medical conditions. Subjects on whom both physicians' assessments agreed were recorded; cases without agreement were reassessed.

Table 1. Major symptoms, neurological status (mRS score), DSA/CTA/MRA diagnosis and risk factors of 33 patients with ischemic cerebral artery disease.

	No. of patients	%
Major symptoms		
TIA	18	54.5
Acute ischemic stroke	15	45.5
Neurological status (mRS score)		
0-2	27	81.8
3-6	6	18.2
DSA/CTA/MRA diagnosis		
ICA occlusion or stenosis	19	57.6
MCA occlusion or stenosis	11	33.3
Both ICA and MCA occlusion or stenosis	3	9.1
Risk factors		
Hypertension	25	75.6
Diabetes	20	60.6
Smoking	29	87.9
Age (≥ 55 years)	24	72.7

Legend: CTA, computed tomography angiography; DSA, digital subtraction angiography; ICA-internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; TIA, transient ischemic attack.

Results

Correlation between baseline preoperative PWI-ASPECTS score and long-term prognosis

Preoperative CBF-ASPECTS, CBV-ASPECTS, MTT-ASPECTS, and TTP-ASPECTS scores were significantly negatively correlated with postoperative long-term mRS scores ($P < 0.05$). The P-values were 0.002, 0.032, 0.026, and 0.039 respectively; the correlation coefficients were -0.523, -0.375, -0.387, and -0.360, respectively.

Difference in PWI-ASPECTS score between the good prognosis group and the poor prognosis group

Thirty-three patients were divided into good and poor prognosis groups. In terms of CBF-ASPECTS ($Z = -2.627$, $P = 0.009$), CBV-ASPECTS ($Z = -2.078$, $P = 0.038$), MTT-ASPECTS ($Z = -2.547$, $P = 0.011$), and TTP-ASPECTS ($Z = -2.146$, $P = 0.032$) scores, there was a statistically significant difference between the groups ($P = 0.009$, 0.038, 0.011, and 0.032 respectively), and scores in the poor prognosis group were lower than those in the good prognosis group. This indicates that unfavorable cerebral hemodynamics tend to result in poor clinical outcomes (Table 2).

ROC curve analysis on long-term prognosis predicted by preoperative PWI-ASPECTS score

ROC curve analysis was performed on CBF-ASPECTS, CBV-ASPECTS, MTT-ASPECTS, and TTP-ASPECTS scores. The results showed that the AUC values were 0.843, 0.750, 0.833, and 0.781 respectively; CBF-ASPECTS was maximal ($P = 0.01$, Fig. 3). It was noted that the preoperative CBF-ASPECTS score was the most reliable index for determining the postoperative clinical outcome. A score of 6 was the best cut-off point for prediction value. CBF-ASPECTS ≤ 6 indicated a poor prognosis with a sensitivity and specificity of 74.1% and 100%.

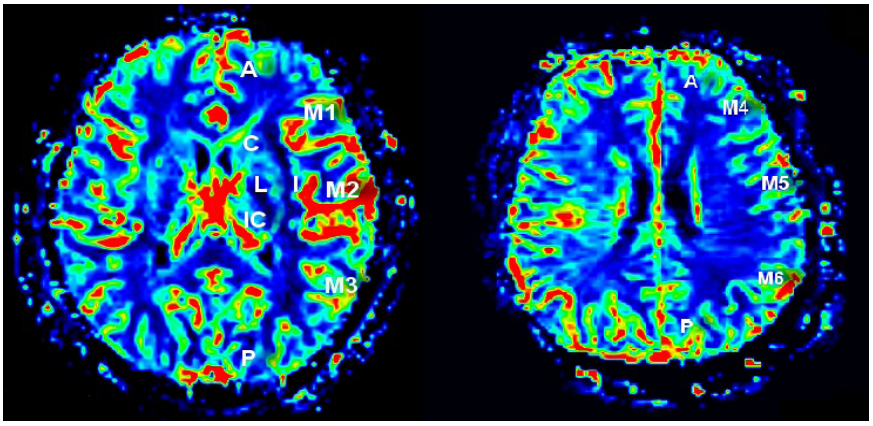

Figure 1. According to the Alberta Stroke Program Early Computerized Tomography Score (ASPECTS) study [12], a normal CT scan of the territory of the middle cerebral artery (MCA) is allotted ten points: cortical regions supplied by the MCA are allotted seven points (one point for insular cortex, M1, M2, M3, M4, M5, and M6), whereas subcortical structures are allotted with three points (one point for C, L, and IC). One point is subtracted for an area of early ischemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A score of zero indicates diffuse ischemia throughout the territory of the MCA. Legend: A, anterior cerebral circulation (blood supplied by anterior cerebral artery); P, posterior cerebral circulation (blood supplied by posterior cerebral artery); C, caudate; L, lenticular nucleus; IC, internal capsule; I, "insular ribbon"; M1, anterior MCA cortex; M2, MCA cortex lateral to the insular ribbon; M3, posterior MCA cortex; M4, M5 and M6 correspond to the anterior, lateral and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

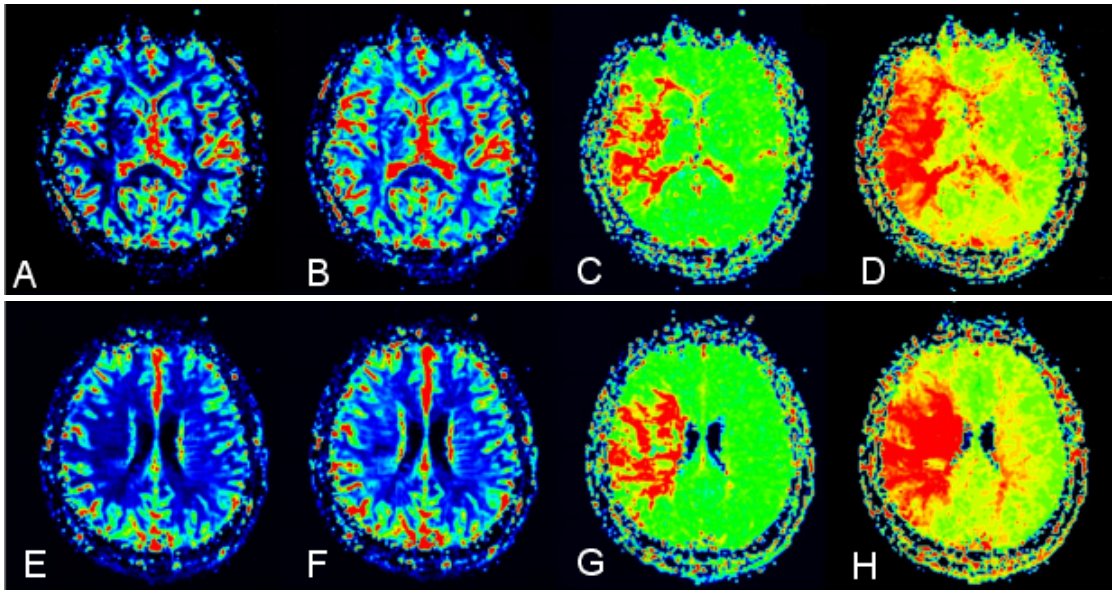

Figure 2. Preoperative perfusion map of a STA-MCA bypass patient. A-D, the preoperative perfusion images of CBF, CBV, MTT, and TTP at the basal ganglia level, respectively; E-H, the preoperative perfusion images of CBF, CBV, MTT, and TTP at the level of the semioval center, respectively. This patient has the CBF-ASPECTS score of nine points, the CBV-ASPECTS score of ten, the MTT-ASPECTS score is six, and the TTP-ASPECTS score is four points. ASPECTS, Alberta Stroke Program Early Computerized Tomography Score; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; STA-MCA, superficial temporal artery - middle cerebral artery; TTP, time to peak.

Table 2. Difference in baseline PWI-ASPECTS score between the good prognosis group (0-2 mRS points) and poor prognosis group (3-6 mRS points).

	Good prognosis group (0-2 mRS points)			Poor prognosis group (3-6 mRS points)			Z	P
	M	P_{25}	P_{75}	M	P_{25}	P_{75}		
CBF-ASPECTS	8.00	6.50	9.00	5.50	3.50	6.75	-2.627	0.009*
CBV-ASPECTS	10.00	9.00	10.00	8.50	7.25	9.00	-2.078	0.038*
MTT-ASPECTS	6.00	4.50	7.50	3.50	3.00	4.00	-2.547	0.011*
TTP-ASPECTS	7.00	4.00	8.00	4.00	2.25	5.00	-2.146	0.032*

Note: * denotes statistically significant differences (P < 0.05)

Discussion

In order to determine the most useful preoperative index for prediction of clinical outcomes after STA-MCA bypass, an analysis of the correlation between preoperative PWI-ASPECTS and postoperative long-term mRS scores was carried out using a combination of medical imaging, clinical symptoms and neural function outcomes.

The mRS classifies the outcome of cerebral ischemic strokes into seven grades with a high grade indicating a poor outcome [13]. The scoring criteria are shown in Table 3.

The mRS is an effective tool to describe health status, and as such, is widely applied in evaluating the clinical outcome of patients with cerebrovascular diseases. It is the most widely used clinical outcome measure in clinical trials of stroke. According to current international practice, an mRS score of 0 to 2 points is considered a good outcome, and 3 to 6 points, a poor outcome [14]. Based on these criteria, the 33 patients were divided into a good prognosis group (0 to 2 points) and a poor prognosis group (3 to 6 points).

ASPECTS [12] was initially used as a scale to decide whether thrombolytic therapy was feasible during acute cerebral infarction. It was used for semi-quantitative evaluation of the degree and range of MCA ischemia. Combining ASPECTS with other more sensitive imaging methods enhances its sensitivity, specificity, and reliability. In addition to its role in determining the degree and extent of cerebral infarction, ASPECTS is being explored as a tool for prediction of clinical prognosis. Several studies have already been published on this subject. For example, in the super-acute stage of fetal cerebral infarction, CBV-ASPECTS tested by CT perfusion scan has been shown to be the most powerful predictive index of clinical outcome [15]. Also, MRI is highly sensitive to early cerebral ischemia, so MRI-ASPECTS is an even more accurate and reliable tool. As has been shown in several studies, DWI-ASPECTS can be taken as an independent predictive index for the early prognosis of patients with acute cerebral infarction due to occlusion of the internal carotid artery [16]. Verma *et al*. conducted a

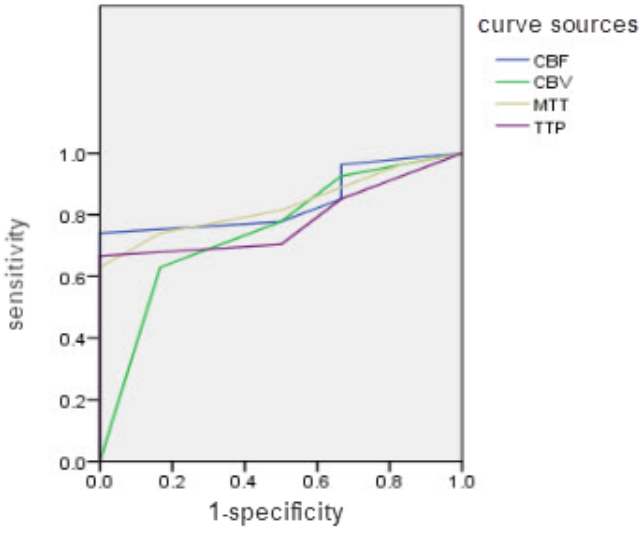

Figure 3. ROC curve of preoperative PWI-ASPECTS (CBF-ASPECTS, CBV-ASPECTS, MTT-ASPECTS, and TTP-ASPECTS) score and long-term prognosis. AUC were 0.843, 0.750, 0.833 and 0.781, respectively. CBF-ASPECTS had maximal AUC; with a threshold of six points the sensitivity and specificity were 74.1% and 100%, respectively (P = 0.01). ASPECTS, Alberta Stroke Program Early Computerized Tomography Score; AUC, area under curve; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; PWI, perfusion-weighted imaging; ROC, receiver operating characteristic; STA-MCA, superficial temporal artery - middle cerebral artery; TTP, time to peak.

Table 3. The modified Rankin Scale.

Grade	Description
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend own bodily needs without assistance, and unable to walk without assistance.
5	Severe disability. Requires constant nursing care and attention. Bedridden, incontinent.
6	Dead.

study on collateral circulation of the pia mater in patients with cerebral infarction. Their results showed that the MTT-ASPECTS score was the most sensitive measure of change in collateral circulation of pia mater [17].

A wealth of clinical research with a strong theoretical basis now exists to aid in exploration of the application of PWI-ASPECTS to STA-MCA bypass, as well as to provide reference for both selection of case studies and evaluation of postoperative efficacy through patients' functional recovery.

The results of the correlation between the preoperative PWI-ASPECTS score and long-term prognosis showed that the former is significantly negatively correlated to the latter, and that there is a significant difference between the good prognosis group and the poor prognosis group. The higher the preoperative PWI-ASPECTS score was, the less the cerebral hemodynamics were impaired, and the better the long-term prognosis. Thus, patients with a small area of perfusion abnormality were preferred when selecting those who would benefit maximally from surgical treatment. DSC-PI produced four parametric images, each of which has a different significance in cerebral hemodynamics as well as different sensitivity and specificity to blood flow perfusion abnormalities. Therefore, it is necessary to select the most reliable image in order to achieve an optimal prediction of postoperative long-term prognosis. This was accomplished by retrospective ROC curve analysis of all preoperative scores for postoperative long-term prognosis. The results showed that CBF has the maximal AUC, indicating that the CBF-ASPECTS score is the parameter most closely associated with postoperative long-term prognosis. Therefore, CBF-ASPECTS, with a threshold of six points, is the most effective predictive index for long-term prognosis following STA-MCA bypass. When the score was equal or less than six points, patients had a poor long-term prognosis.

In our analysis, the MTT-ASPECTS and TTP-ASPECTS scores were far below the CBF-ASPECTS score regarding accuracy of prediction of postoperative long-term prognosis. MTT and TTP are widely recognized as the most sensitive indices of cerebral perfusion changes, and abnormalities of their scores will be observed even in cases of mild impairment of cerebral hemodynamics. This heightened sensitivity raises the possibility that these measurements exaggerate the level of perfusion abnormalities and in doing so, reduce test sensitivity and reliability when attempting to predict long term prognosis. In contrast, CBF is the most representative index of cerebral ischemia because reduction of CBF leads to slowing of cerebral oxygen metabolism which, if continued, results in symptoms of cerebral ischemia and cerebral infarction.

Limitations of the study include a small sample size and limited follow-up time, both of which should be increased to reproduce and improve the study results. Another limitation is that the divisions within the ASPECTS system are subjective and lack a strict definition. The subareas lie in different areas of blood supply and cerebral function, so clinical symptoms and outcomes of patients with the same PWI-ASPECTS scores may differ. In this regard, further improvement of ASPECTS scoring criteria is needed.

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