Leptomeningeal Collateral Response and Computed Tomographic Perfusion Mismatch in Acute Middle Cerebral Artery Occlusion

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Abstract

Objective: To identify the relationship between the magnitude of leptomeningeal collaterals (LMC) on digital subtraction angiography (DSA) and regional cerebral blood volume (rCBV)/regional cerebral blood flow (rCBF) mismatch on computed tomography perfusion (CTP) in patients with acute middle cerebral artery (MCA) occlusion.

Design/Methods: We reviewed the clinical records, and neuroimaging studies in consecutive patients with proximal MCA (M1-segment) and proximal branch (M2-segment) occlusion undergoing endovascular treatment following the demonstration of mismatch on CTP. DSA images acquired prior to the treatment were used to grade collateral flow from the anterior cerebral artery to the MCA on a scale ranging from 1 to 5, based on retrograde reconstitution of MCA segments in the late arterial phase. CTP images were reviewed and rCBV/rCBF mismatch was categorized as minor (≤ 1/3 of MCA territory), moderate (1/3-2/3 of MCA territory), or severe (> 2/3 to complete territory). Statistical association was assessed using Pearson exact test.

Results: A total of sixteen patients were studied (10 were men; mean age of 69 years). Mean time from symptom onset to CTP was 146 minutes. Patients with M1-segment occlusion (n=10) had more severe rCBV/rCBF mismatch compared to patients with M2-segment occlusion (p=0.016). There was no association between the magnitude of LMC and severity of rCBV/rCBF mismatch on CTP.

Conclusions/Relevance: The magnitude of LMC on DSA does not correlate with the severity of rCBV/rCBF mismatch in patients with MCA occlusion. This result suggests that additional factors, such as micro vascular failure, may contribute to altered cerebral perfusion.

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Introduction

In acute ischemic stroke (AIS), the collateral circulation reduces ischemic injury to tissue and may maintain the tissue in a state of vulnerability but potentially salvable (penumbra). The absence of angiographic evidence of cerebral collateral circulation is considered a prognostic sign of poor outcome.[1, 2, 3] CT perfusion (CTP) has been used for selecting patients with AIS for endovascular treatments.[4] Patients also undergo digital subtraction angiography (DSA) prior to endovascular treatments. In dynamic CTP, areas with prolonged mean transit time (MTT) are suspected to be hemodynamically compromised. In these area of increased MTT, the regions with increased regional cerebral blood volume (rCBV) represent "tissue at risk", where as regions with decreased rCBV correspond to the infarct core. This increase in rCBV is believed to be a result from vasodilatation and collaterals recruitment including communicating segments of the circle of Willis (primary collaterals) supplemented by collaterals from external carotid artery branches, and leptomeningeal vessels (secondary collaterals).[4-7] Our intent was to study the relationship between the extent of leptomeningeal collaterals seen on DSA and regional cerebral blood volume (rCBV)/regional cerebral blood flow (rCBF) mismatch visible on CTP. We included only acute middle cerebral artery (MCA) occlusion patients to ensure a homogenous population. Our hypothesis was that if LMCs are adequate then rCBV may be preserved and rCBV/ rCBF mismatch may be present. Since this mismatch is usually treated as a surrogate marker of penumbra, an angiographic correlate of such mismatch may be valuable for selecting patients for endovascular treatment in acute ischemic stroke.

Materials and Methods

We conducted a retrospective analysis of consecutive patients with AIS who met our study inclusion criteria at two centers.

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Table 1: Pial Collateral Classification: (modified from Christoforidis et al.)[9]

1	Collaterals reconstituted the distal portion of the occluded vessel segment (reconstitution of distal M1 segment)
2	Collaterals reconstituted the proximal portion of the segment adjacent to occluded vessel (reconstitution of proximal M2 segments)
3	Collaterals reconstituted the distal portion of the segment adjacent to occluded vessel (reconstitution of distal portions of M2 segments)
4	Collaterals reconstituted 2 segments distal to the occluded vessel (reconstitution M3 segments)
5	There was little or no significant reconstitution of the territory of the occluded vessel

Patient selection

We screened consecutive patients admitted with AIS who presented with acute occlusion of M1 or M2 segment of the middle cerebral artery (n= 53) from November 2006 to July 2008 . In all patients, non-contrast baseline cerebral CT scan was immediately followed by CT perfusion (CTP) along with CT angiogram (CTA), which is included in the initial routine survey of AIS patients at our institution (see Figures 1-3). We excluded patients with critical stenosis or occlusion of either internal carotid artery (ICA), remote or acute ischemic stroke in anterior cerebral artery (ACA), or posterior cerebral artery (PCA) territory. None of the patient had hypotension, defined by systolic blood pressure less than 90 mmHg at the time of CTP.

Imaging Techniques and data processing

CT Perfusion:

The CTP examination consisted of two 55-second series at an interval of two minutes, each series consisting of 1 image per second during intravenous administration of iodinated contrast material. The acquisition parameters for both series were 120 kilovolt (peak; kVp) and 150 mAs (300 mA at 0.5 seconds). For each series, CT scanning was initiated immediately after injection of 36 mL iodinated contrast material, Omnipaque, 350 mg/mL iodine, at a rate of 6 mL/s into an antecubital vein with a power injector (Stellant, Medred Co). Multidetector-array technology allowed data acquisition from 4 adjacent 10-mm sections for each series. The two perfusion CT series thus allowed data acquisition in 8 adjacent 10-mm cerebral CT sections. The four studied cerebral sections were selected above the orbits to protect the lenses, running through the basal nuclei and then toward the vertex.

Perfusion CT data consist of time–contrast enhancement curves registered in each pixel, with the curves linearly related to the time-concentration curves for the iodinated contrast material. The perfusion CT data were analyzed by perfusion CT software (Vitrea 2). Images of rCBF, rCBV, and MTT were interpreted together on a workstation permitting the use of visual assessment. MCA territory ischemia was divided on CT perfusion images as minor deficit (≤ 1/3 of MCA vascular territory), moderate deficit (1/3-2/3 territory) and severe deficit (2/3 to complete territory) by one of the investigators (RK).

DSA and leptomeningeal collaterals:

Leptomeningeal collaterals (LMC) are best studied by conventional digital subtraction angiography (DSA) in emergent setting.[8] After initial evaluation and initiation of IV rt-PA therapy in eligible patients; patients were transported immediately to the neuro-angiographic suite. Transfemoral approach was used to access the target artery. Contrast injection using Visipaque 320 in the internal carotid artery was used to visualize and assess leptomeningeal collaterals and site of occlusion. DSA images acquired prior to treatment were used to grade collateral flow from the anterior cerebral artery to the MCA on a scale ranging from 1 to 5, based on retrograde reconstitution of MCA segments in the late arterial phase. This scoring system was adopted from leptomeningeal collaterals classification as described by Christoforidis et al.[9] (see Table 1)

Statistical analysis

We assessed the association between LMC score on digital subtraction angiography (DSA) with various categories of rCBV/rCBF mismatch on CTP in patients with acute occlusion of M1 or M2 segments. We tested this association using Pearson exact test.

Results

We included 16 patients with mean age of 69 years who met our criteria; 10 were men,. Ten patients had M1 segment occlusion; with National Institutes of Health Stroke Scale (NIHSS) score ranging from 6-21 (Median NIHSS score 14). Six patients had M2 segment occlusion with NIHSS score ranging from 9-20. Mean

Table 2: Regional cerebral blood flow/ regional cerebral blood volume mismatch and leptomeningeal collateral score in middle cerebral artery occlusion

	rCBV/rCBV mismatch		
LMC Score	Minor	Moderate	Severe
1	1	None	None
2	None	4	1
3	None	5	3
4	1	1	None
M1 segment	None	6	4
M2 segment	2	4	None

time from symptom onset to CTP acquisition was 146 minutes. Time interval between the first angiographic image acquisition and symptom onset among thirteen patients with known time of symptom onset ranged from 144-525 minutes; remaining three patients had unknown time of symptom onset and received endovascular interventions based on CTP mismatch. Five patients received intravenous recombinant tissue plasminogen activator (rt-PA) within 3-hours of symptom onset, prior to endovascular intervention (intra-arterial thrombolytic and/or mechanical thrombectomy).

A total of five patients were found to have early evidence of infarction in the MCA territory on head CT scan prior to the procedure however all changes were less than 1/3rd of MCA territory and each patient had significant rCBV/rCBF mismatch noted on the CTP. Three out of these five patients with evidence of infarction on head CT scan had unknown time of onset, one event was after 3 hours and another one event was less than 2 hours from the symptom onset. Patients with M1-segment occlusion (n=10) had more severe rCBV/rCBF mismatch compared to patients with M2-segment occlusion (p=0.016). LMC score of 1 had minor mismatch compared to moderate to severe deficit mismatch with LMC score of 2 and 4. However LMC score of 4 (n= 1) did not have severe mismatch as would be expected but had minor to moderate mismatch. Overall there was no clear association between the extent of leptomeningeal collaterals and severity of rCBV/rCBF mismatch on CTP. (see Table 2)

Discussion

Astrup et al[10] tried to differentiate between the areas of severe ischemia (state of energy failure, high extra-cellular potassium, and developing infarction) and areas with less severe ischemia "penumbra" (state of electrical failure but sustained energy metabolism and low extra-cellular potassium) in the animal model. In our series of patients with middle cerebral artery occlusion, residual flow in the MCA territory would be mainly dependent on LMC[2,11] with no contribution from anterior cerebral artery via anterior communicating artery, posterior cerebral artery via posterior communicating artery or external carotid artery collaterals. Our results suggest that the magnitude of LMCs on DSA does not correlate with the severity of rCBV/rCBF mismatch in patients with MCA occlusion. There may be several explanations for this observation including the technical limitations of resolution in both DSA and CTP. rCBF is dependent on both macrovasculature and microvasculature circulation. DSA typically demonstrates arteries with diameter larger than 100 µm. The arterioles that arise from the leptomeningeal arteries are less than 100 µm in diameter and supply the capillary bed of the cerebrum. This extensive microcirculation (< 100 µm) networks provide the actual blood supply to the brain parenchyma and has been proven to be a potential collateral pathway in patients with ischemic cerebrovascular disease may be relatively invisible on DSA.[2,12] The lack of visualization of smaller arteriolar networks may explain the discrepancy between CTP mismatch and LMC score. CTP also has limitations in studying penumbra in brain. Currently, CTP only allows the estimation of rCBF, rCBV, and MTT in a limited volume of brain tissue. Other limitations of our analysis include the inability to study the hemodynamic fluctuations which may influence the magnitude of collaterals, possibly rCBF deficits. Presence of LMC nay be only a marker of impaired hemodynamic status[8] and not compensatory status We did not study this factor in detail in our analysis, however none of our patients had hypotension (systolic blood pressure < 90 mmHg). There was also a time lag between the CTP and DSA during which distal embolism of a thrombus within the parent vessel lead to further occlusion of distal branches, compromising the LMC as well as microcirculation. Moreover, it is not merely the presence of LMC but also efficiency of these vessels tat need to be taken into account. The efficiency of collateral vessels depends on age, duration of ischemia, and associated co-morbidities.[8]

Despite all the technical and procedural limitations, our analysis suggests that the extent of leptomeningeal collaterals per se on DSA does not explain the extent of mismatch noted on CTP and additional factors need to be accounted for and studied in future.

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