

Chinese Consensus Statement on the Evaluation and Intervention of Collateral Circulation for Ischemic Stroke

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SUMMARY

Background: Collateral circulation is becoming more significant in the individual management strategy of ischemic stroke, there are more data updated recently. **Aim:** To make the further acknowledgment of the evaluation and how to improving collateral flow, for better treatment selection. **Method:** A panel of experts on stroke providing related statement based on review the results from most up-to-date clinical research. **Results:** DSA is the gold standard in evaluating all levels of collaterals. CTA can be used for evaluating leptomeningeal collaterals, MRA for CoW, TCD or TCCS can be used as screening tool for primary evaluation. The treatment modalities include direct interventions, such as Extracranial–Intracranial bypass, and indirect interventions, as External counterpulsation and pressor therapy. The consideration of methodology to augment and improve can be considered on an individual basis. **Discussion:** In this consensus, we interpret the definition, neuroimaging evaluation, intervention and potential strategy on collaterals in the future. **Conclusion:** Assessment of collateral circulation is crucial for selecting therapeutic options, predicting infarction volume and making prognosis after ischemic stroke. Data is still needed to provide therapeutic evidence for many new developed technologies. Until more evidence is available, the clinical significance of applying the new technologies is unclear and perhaps limited.

Introduction

Currently, there are only two therapeutic strategies that are proven to be effective during the acute phase of ischemic stroke. They are as follows: (1) vascular recanalization and (2) antiplatelet therapy. Over 90% of stroke patients cannot get to a hospital in time for acute intervention [1]. Recent studies have shown that improving collateral circulation may reduce infarction volume and risk of stroke recurrence and then lead to better prognosis [2–5]. Complete and full evaluation of collateral circulation is the crucial precondition of planning individualized therapy for ischemic stroke patients. However, consensus is lacking on what the standard methodology should be when evaluating the collateral circulation [6]. Many committees are currently working on finding such consensus so that it can be used to guide clinical practice and research.

Definitions

Collateral branches: Arterial structures that connect to the adjacent arterial network. They exist in most human tissue. They can alter the direction of blood flow to the territories with occluded

arteries. **Collateral circulation:** The subsidiary network of vascular channels that stabilizes cerebral blood flow when the principal conduits fail [5]. It is the main factor that influences infarction volume and size of ischemic penumbra.

Compensatory Mechanism of Brain Collateral Circulation

There are three levels of compensatory collateral circulation in human brain [5]. The first level is by the circle of Willis. It can open channels between anterior and posterior circulation. The second level is through the network such as ophthalmic artery, leptomeningeal collateral vessels, and other smaller collateral arterial connections [7]. The third level is angiogenesis, which is formed shortly after ischemia occurs. Once a cerebral artery is either partially blocked or occluded, collateral circulation begins to form new, or open existing, blood vessels to best improve blood supply to that area of brain. Individual's ability to establish collateral circulation may vary. In general, the main form of arterial compensation comes from the first level of collateral circulation. If it is insufficient to meet the need, then second level of collateral

circulation begins to operate. For example, leptomeningeal arteries may open between the intracranial and extracranial arteries. If this compensation is still insufficient, third level of collateral circulation may begin to operate. However, this process takes time, normally needing several days to complete.

Factors Influencing Brain Collateral Circulation

- 1 Vascular anomalies: It's crucial that the structures of collateral circulation are present. However, a complete circle of Willis circle is only in 42–52% of population [8].
- 2 Risks: Old age, chronic hypertension, hyperlipidemia, and hyperglycemia may impair endovascular function and its self-regulatory ability, which would interfere the process of forming third level collateral circulation [9–11].
- 3 Others: The diameter of the blood vessels and their pressure gradient greatly affect collateral circulation. It is generally accepted that vascular diameters less than 1 mm in the circle of Willis represents an impaired compensatory ability, even though compensation can sometimes be fulfilled at other levels [12,13]. Favorable establishment of collateral circulation is directly related to the severity of low perfusion and speed of forming artery stenosis [5,14]. The collateral circulation is likely to establish whether formation of arterial stenosis is severe but slow. Long-term exposure to brain hypoperfusion may lead to increased concentration of vascular growing Factors, which in turn will promote the process of angiogenesis and building of collateral circulation [15].

Brain Collateral Circulation and Microvasculature

Brain microvasculature and brain collateral circulation are two different concepts. Microvasculature refers to the smaller vessels, those with an internal diameter of at most 100 microns [15]. In physical conditions, 20% of microvasculature opens every 30–60 seconds. In pathological conditions, certain intervention treatments are aimed at microvasculature for the purpose of improving brain perfusion. Microvasculature disorders first appear when brain ischemia occurs. At the onset of ischemia, a cascade of damages occurs, which eventually causes brain cell damage. The existence of a full structure of microvascular bed is crucial to the reconstruction of the brain's blood supply. Improvement in collateral circulation may favor microvascular perfusion, which would preserve brain microstructures and function. There are two possible explanations for this phenomenon: (1) collateral circulation may increase microvascular perfusion in areas of infarction and enhance the ischemic tolerance of microvascular structures, which in turn relieve microvascular disorders. (2) Collateral circulation can improve the delivery of medicine to the ischemic area, thus improving the effects of therapy.

Clinical Significance

Predicting Clinical Outcome

Patients with a complete circle of Willis (CoW) are more likely to have early improvement in National Institute of Health

Stroke Scale (NIHSS) score and be independent at 3 months (odds ratio 2.32; $P = 0.01$) after treated with tissue plasminogen activator (rt-PA) within 3 h of symptom onset [2]. Furthermore, patients with better pial collateral formation appear to have a greater clinical improvement with thrombolytic treatment [3]. For acute ischemic stroke patients with severe intracranial or extracranial carotid artery stenosis or occlusion, the prognosis is better in those with collateral circulation, which can be seen on digital subtraction angiography (DSA) [16]. Warfarin–Aspirin Symptomatic Intracranial Disease trial indicated that the extent of collaterals was an independent predictor for subsequent stroke in the symptomatic arterial territory [4]. The regional leptomeningeal score (rLMC, higher the better outcome) is a strong and reliable imaging predictor of good clinical outcomes ($mRS \leq 2$ at 90 days) in acute anterior circulation ischemic strokes [17].

Predicting Therapeutic Recanalization

Bang *et al.* [18] proposed the angiographic collateral grading system that might help guide the treatment decision-making process in acute cerebral ischemia. They studied 222 patients with acute cerebral ischemia who received endovascular therapy (including intra-arterial thrombolytic therapy, mechanical thrombectomy device, etc.). Angiographic collateral grade was evaluated by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System on pretreatment angiography. Complete revascularization occurred in 14.1% patients with poor pretreatment collateral grades (score = 0–1), while 25.2% patients had good collaterals (score = 2–3) and 41.5% patients had excellent collaterals (score = 4). When revascularization was achieved, greater infarct growth occurred in patients with poor collaterals than in those with good collaterals. Marc *et al.* [19] evaluated 61 stroke patients who received endovascular treatment. They found that identification of good collateral pial circulation might help physicians when considering recanalization therapies in late time windows.

Predicting Hemorrhagic Transformation

Angiographic grade of collateral flow strongly influences the rate of hemorrhagic transformation after therapeutic recanalization for acute ischemic stroke (OR, 2.666; 95% CI, 1.163 to 6.113) [20]. In the group with incomplete CoW, the rate of symptomatic intracerebral hemorrhage (SICH) according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition was almost three times higher [2]. Furthermore, pial collateral formation was a significant predictor of SICH following intra-arterial thrombolysis [21].

Recommendation/Expert Comments

Collateral circulation is not only an important predictor for clinical outcome, but also a factor for decision-making in acute cerebral ischemia. It is valuable to perform a comprehensive evaluation of collateral circulation in patients with cerebral ischemia.

Diagnostic Evaluation

Primary Collaterals (Circle of Willis)

Currently, common ways to evaluate CoW include transcranial Doppler (TCD), computed tomography angiography (CTA), magnetic resonance angiography (MRA), and DSA. They all have their own advantages and shortcomings. Internationally, DSA is considered the gold standard. However, DSA is invasive, expensive, and rarely performed. Variation in contrast volume and pressure during injection may distort the appearance of distal vessels [22].

Transcranial Doppler is a reliable tool to evaluate collateral supply in patients with internal carotid artery occlusions. Its sensitivity and specificity were higher to examine the flow abnormality in anterior communicating artery (ACoA) than posterior communicating artery (PCoA) [23]. Transcranial color-coded sonography (TCCS) is a relatively new, bedside noninvasive technique that shows a real-time two-dimensional depiction of cerebral parenchymal and intracranial vascular structures. Compared with conventional TCD, there is more accurate demonstration of vascular anatomy, because imaging of smaller arterial branches and venous structures is feasible. Contrast-enhanced TCCS may increase the sensitivity [24]. These methods are noninvasive, convenient and inexpensive which can be used for screening purpose and preliminary diagnosis of stroke in primary hospitals. Limitations of these methods include insufficient transtemporal ultrasound beam penetration due to hyperostosis of the skull, and the quality of images obtained is operator dependent.

Computed tomography angiography is highly accurate in the assessment of anatomic variations of the CoW (sensitivity and specificity were more than 90%); however, its sensitivity is limited in depicting hypoplastic segments (sensitivity was 52.6% and specificity was 98.2%) [25].

Magnetic resonance angiography is a sensitive technique for examine the anatomy of the circle of Willis. Maximum intensity projection images are more specific than source images. An arterial segment with a diameter of at least 1 mm on the source image is almost always present and patent [26]. The sensitivity of MRA to detect vascular abnormality was 89.2% for the anterior and 81.3% for the posterior communicating arteries [27].

Secondary Collaterals

Direct visualization of collaterals includes TCD, CTA, MRA, and conventional angiography. Conventional angiography is the gold standard in evaluating secondary collaterals. Noninvasive techniques have limitation in evaluating pial collaterals or other secondary collaterals for their low resolution. Computed tomography angiography source images may contain valuable information regarding collaterals, but systematic review indicated that the usefulness of CTA source images in yielding information about the perfusion state of stroke patients in clinical routine should not be overestimated [28]. Postprocessing of CTA data may be more informative. During the acquisition MRA velocity, encoding allows for flow-sensitive images in three orthogonal planes; however, these images are constrained by anatomic resolution and are therefore only useful in visualizing the proximal segments [29].

Indirect evaluation methods include TCD vasomotor reactivity test, xenon-enhanced CT, single-photon emission CT, positron emission tomography (PET), CT perfusion, MR perfusion, and MR perfusion imaging of arterial spin labeling. These methods assess cerebral blood flow and indirectly infer the status of collaterals. Prolonged transit times of arterial blood flow may indicate the presence of collateral blood supply. However, when the parent vessel is occluded, the arterial source of sustained perfusion may not be evident.

Transcranial Doppler can be used to assess cerebral vasomotor reactivity which provides information regarding cerebral autoregulation and collateral circulation. Three such tests are currently used for this purpose: The apnea test, CO₂ inhalation, and the Diamox test (i.e., acetazolamide) [30]. These vasodilatory stimuli have somewhat different hemodynamic effects, conferring relative advantages and disadvantages of each approach [30,31]. These methods are based on the hypothesis that impaired vasomotor reactivity would correlate with the extent of collateralization. TCD performance and interpretation, however, are subject to considerable variability, and validation of vasomotor reactivity testing has been suboptimal [32].

Other surrogate marker that may represent collateral blood flow includes vascular enhancement on conventional neuroimaging studies (including CT and MRI) [33], vascular hyperintensities on fluid-attenuated inversion recovery (FLAIR) MRI sequences [34]. Although such indirect evaluation of collaterals may be apparent with multiple imaging techniques, only limited information regarding collaterals can be obtained [5].

Collateral Flow Grading Tool

ASITN/SIR Collateral Flow Grading System [35], which is based on DSA and widely used, is as follows. Grade 0: No collaterals visible to the ischemic site; Grade 1: Slow collaterals to the periphery of the ischemic site with persistence of some of the defect; Grade 2: Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory; Grade 3: Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase; Grade 4: Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion.

Moreover, the regional rLMC score [17] and the pial collateral score [3] have been used in some studies. The rLMC score is based on scoring pial and lenticulostriate arteries (0, no; 1, less; 2, equal or more prominent compared with matching region in opposite hemisphere) in 6 ASPECTS regions (M1–6) plus anterior cerebral artery region and basal ganglia. Pial arteries in the Sylvian fissure are scored 0, 2, or 4. Evaluation of pial collateral formation was based on retrograde contrast opacification of vessels within the occluded territory on delayed angiographic images. Collaterals were scored as follows:

Score of 1 was assigned if collaterals reconstituted the distal portion of the occluded vessel segment (i.e., if there was M1 segment occlusion, the M1 segment distal to the occlusion reconstituted); Score of 2 was assigned if collaterals reconstituted vessels in the proximal portion of the segment adjacent to the occluded vessel (i.e., if there was M1 segment occlusion with reconstitution to the

proximal M2 vessel segments); Score of 3 was assigned if collaterals reconstituted vessels in the distal portion of the segment adjacent to the occluded vessel (i.e., if there was M1 segment occlusion with reconstitution to the distal portion of the M2 vessel segments); Score of 4 was assigned if collaterals reconstituted vessels two segments distal to the occluded vessel (i.e., if there was M1 segment occlusion with reconstitution up to the M3 segment branches); Score of 5 was assigned if there was little or no significant reconstitution of the territory of the occluded vessel.

Recommendation/Expert Comments

- 1 TCD or TCCS can be used as screening tools for primary evaluation of collateral circulation in stroke patients.
- 2 DSA is the gold standard in evaluating all levels of collaterals. CTA can be used for evaluating leptomeningeal collaterals, MRA for CoW.
- 3 There is insufficient evidence on how best to study collaterals.

Interventions to Enhance Collateral Circulation in Ischemic Stroke

Direct Interventions: Extracranial–Intracranial Bypass

Extracranial–intracranial (EC-IC) bypass was first reported by Yasargil *et al.* in 1970 [36], who performed anastomosis of superficial temporal artery (STA) and middle cerebral artery (MCA) in the treatment of cerebral ischemia. But early randomized clinical trials failed to show the benefits of EC-IC bypass prior to medical treatment. One of the reasons was the lack of assessment of hemodynamics and collateral circulation [37]. With the development of radiological techniques in recent years, St Louis Carotid Occlusion Study (STLCOS) used quantitative positron emission tomography and oxygen extraction fraction (OEF) to evaluate collaterals and cerebral perfusion. In symptomatic patients with carotid occlusion receiving medical treatment, those with misery perfusion (defined as increased OEF) had significantly higher risk of recurrent stroke compared with those with better perfusion [38]. Based on STLCOS, the Carotid Occlusion Surgery study randomized high risk patients (carotid artery occlusion patients with ipsilateral-to-contralateral hemispheric ratios of mean regional OEF > 1.13) into either surgical intervention with STA-MCA bypass or medical treatment [39]. The original estimated sample size of COSS was 372 patients, but it was prematurely halted after enrollment of 195 patients. The main reason was that interim analysis showed the ipsilateral ischemic stroke rates within 2 years were not significantly different in surgical and medical groups. Subgroup analysis of COSS found mean ipsilateral-to-contralateral OEF ratio in the surgical group significantly improved from baseline at the time of 30-to 60-day follow-up PET [40]. Another larger clinical trial is Japanese EC-IC bypass trial (JET), which used baseline cerebral blood flow and response of cerebral blood flow to vasodilator as entry criteria of patients. Although the second interim analysis of JET reported that the incidence of stroke recurrence in surgical group was significantly lower than that in medical group, the final results of this study have not been subjected to publication

[41,42]. The improvement in cerebral blood flow after EC-IC bypass has been proved, but the benefits of EC-IC bypass in the long term remain under investigation. How to select suitable patients to surgical revascularization may be the key to reach significant clinical benefits.

Indirect Interventions

External Counterpulsation

External counterpulsation (ECP) is a novel noninvasive method similar to intra-aortic pump. The concept of ECP was established by Dr. Soroff and Dr. Birtwell in Harvard University in 1960s [37]. Modern external counterpulsation system with air cuff, called enhanced external counterpulsation (EECP), was reported by Chinese Scientists in 1983 [43]. There are three pairs of pneumatic cuffs applied to the calves, lower thighs, and upper thighs (but-tocks) in EECP system. The electrocardiogram triggers inflation of air cuffs with the pressure up to 250–300 mmHg sequentially from distal to proximal during diastole and releases cuff pressure before the start of systole. Diastolic pressure on the lower extremities improves venous return and cardiac output, while deflation before systole leads to increased systolic unloading. Sequential inflation of air cuffs in early diastole shifts the blood from lower limbs to aortic artery and creates a retrograde pressure wave at the same time, which elevates diastolic blood pressure (BP) as well mean arterial BP, while the deflation at the end of diastole removes the previous externally applied pressure and leaves behind a relative empty vascular bed in the lower extremities to receive cardiac output in the systole, reducing peripheral vascular resistance. ECP increases cardiac output and augments blood flow of vital organs, such as brain, kidney, liver, and myocardium [44–47].

Investigators in China found upper limb ischemic preconditioning improved cerebral perfusion and significantly reduced 1-year stroke recurrence (from 26.7% reduced to 7.9%) [48].

NeuroFlo Catheter is a dual-balloon catheter system with two inflatable balloons placed in the descending thoracic aorta, separately above and below the renal arteries. Inflated balloons partially occlude aortic artery, then increase cerebral blood flow. A large multicenter prospective randomized trial Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) showed NeuroFlo treatment was safe in acute phase of ischemic stroke. The post hoc analysis indicated that for patients randomized within 6 h, patients with disease of moderate severity (NIHSS 8–14), and patients older than 70 years, NeuroFlo-treated patients were more likely to have a good clinical outcome (modified Rankin Scale 0–2) [49,50]. However, the primary efficacy endpoint of SENTIS trial did not reach significant difference, and NeuroFlo treatment requires extensive neuroimaging data to offer important information of cerebral hemodynamics. Therefore, further investigations may confirm the benefits of NeuroFlo treatment from careful patient selection.

Pressor Therapy

Cerebral autoregulation is one of the main regulatory mechanisms of cerebral blood flow. When mean arterial BP varies between

50–150 mmHg, cerebral autoregulation remains and cerebral blood flow is relatively constant. However, cerebral autoregulation is impaired in ischemic stroke patients, and cerebral blood flow may change dependently with variation in systemic BP [50]. Elevation of BP except at malignant range may help to increase cerebral blood flow, open collateral channels and improve cerebral perfusion [51–53]. Clinical trials demonstrated that induced BP elevation in acute ischemic stroke was relatively safe and it could significantly improve neurological deficit as well as stroke prognosis [53–55]. Pressor therapy seems to benefit patients with large extracranial or intracranial artery stenosis the most. Usually, pressor agents used include phenylephrine, norepinephrine, epinephrine, dopamine, dobutamine, and so on. Phenylephrine is the most commonly used pressor with many clinical evidences. It is a selective α_1 -agonist with vasoconstriction but does not have direct substantial effects on cerebral vessels where a low density of α_1 receptors is distributed. Phenylephrine is less likely to cause adverse effects such as cerebral vasoconstriction and tachyarrhythmias.

Clinical applications of pressor therapy are still under investigation, and many questions remain unanswered. For example, theoretically, the earlier treatment patients receive the better clinical outcome they get, as it could save penumbra in early phase of ischemic stroke. In recent pressor studies that reported a clinical benefit, their stroke onset to treatment time ranged from hours up to 7 days, and the durations of pressor stimulus were different. The optimal therapeutic window for pressor therapy and its duration are still uncertain. Also baseline BP levels to start therapy and target levels of BP elevation in those studies were quite distinct, with baseline systolic BP varying from 120–150 mmHg and the majority of target BP aiming to maintain systolic BP > 160 mmHg or increase mean arterial BP by 10–20%. Furthermore, the association between BP elevation and augmentation of cerebral blood flow needs further identification and quantification. More large randomized clinical trials may be warranted to investigate detailed treatment strategy of pressor therapy.

Medical Treatment

Statins play an important role in the primary prevention and secondary prevention of ischemic stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol levels, a large clinical trial of lipid-lowering therapy for stroke prevention, suggested that atorvastatin was effective in the reduction in recurrent stroke and improvement in stroke prognosis [56,57]. Statins lower lipid level, and also the mechanisms of their clinical benefits cover stabilization of atherosclerotic plaques, improvement in endothelial function, augmentation of cerebral blood flow as well as enhancement of collaterals [58,59]. Statins treatment could upregulate the expression of endothelial nitric oxide synthase, promote the differentiation of endothelial progenitor cells, and have dose-dependent neuroprotection effect on animal stroke model [60]. Studies investigated the association between prestroke statin use and pre-treatment angiographic collateral grade showed that, in acute ischemic stroke patients with occlusion of a large cerebral artery, statin users had higher collateral scores than nonstatin users and the use of statins was an independent factor of better collateralization after stroke [61,62].

Human urinary kallidinogenase is a kind of highly purified kininogenase derived from human urine. Kininogenase cleaves kininogen in the body to release kinins, which bind to bradykinin receptors on the vascular endothelial cells, produce nitric oxide and prostacyclin via transduction of second messenger, then trigger a series of biologic effects, such as vasodilatation, neovascularization, and suppression of apoptosis and oxidative stress [63]. In animal experimental stroke model, urinary kallidinogenase enhanced proliferation, migration, and differentiation of neuroblasts, dilated leptomeningeal vessels in ischemic region, significantly increased vascular density in the peri-infarction region and improved cerebrovascular reserve capacity on the ischemic side [64–66]. In acute ischemic stroke patients, there are several reports using clinical and neuroimaging evidences to demonstrate the benefits of human urinary kallidinogenase, such as increasing cerebral perfusion in ischemia area, improvement in cerebrovascular reserve, promotion of collateralization, reduction in neuron death, and improvement in stroke prognosis [67,68].

Albumin therapy has been found to provide neuroprotective effects by expansion of blood volume and augmentation of cerebral perfusion, leading to improvement in intracranial microcirculation [69–71]. Both preclinical and clinical studies of butylphthalide indicated its protective effects on stroke. It could ameliorate local circulation after stroke, reduce infarct volume, attenuate damage of brain tissue, and then maximally improve neurological recovery. The mechanisms of improving microcirculation may involve the relief of microvessel spasm, improvement in functions of vascular endothelial and mitochondrion, and protection of brain–blood barrier [72,73]. Currently, clinical studies and publications of these medical treatments are limited, and they are only recommended at relative low level by international guidelines. Their clinical efficacy and mechanisms need to be further investigated.

Recommendation/Expert Comments

The consideration of methodology to augment and improve can be considered on an individual basis. The treatment modalities include direct interventions, such as extracranial–intracranial bypass, and indirect interventions, such as ECP, and pressor therapy.

Conclusion

Assessment of collateral circulation is crucial for selecting therapeutic options, predicting infarction volume, and making prognosis after ischemic stroke. Data are still needed to provide therapeutic evidence for many newly developed technologies. Until more evidence available, the clinical significance of applying the new technologies is unclear and perhaps limited.

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Conflict of Interest

The authors declare no conflict of interest.

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