HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Stroke. 2015 November ; 46(11): 3302–3309. doi:10.1161/STROKEAHA.115.010508.

Collateral Circulation in Ischemic Stroke: Assessment Tools and Therapeutic Strategies

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Keywords

Stroke; Collateral Circulation; MRI; Computed tomography

Importance of Collateral Circulation in Ischemic Stroke

Revascularization encompasses all treatment-related improvements in blood flow, including recanalization of the proximal arterial occlusion and reperfusion of the downstream territory. Recanalization is required for antegrade tissue reperfusion, but recanalization may not necessarily lead to reperfusion in regions where distal emboli or established infarctions are present.[12] On the contrary, acute reperfusion without recanalization may occur in patients who received or did not received endovascular therapies, and reperfusion ≤6 hours was consistently superior to recanalization in predicting tissue and clinical outcome.[3] The cerebral collateral circulation refers to the subsidiary network of vascular channels that stabilize cerebral blood flow when principal conduits fail. Collateral status differs among patients with acute ischemic stroke. Relatively sparse attention has been devoted to the role of baseline collateral circulation in patients with acute ischemic stroke who are candidates for revascularization.

The IMS III,[4] MR RESCUE,[5] and SYNTHESIS Expansion trials[6] were three multicenter, prospective, randomized controlled trials which failed to show a benefit from endovascular intervention for acute ischemic stroke. In addition, successful recanalization failed to improve the functional outcome in a significant proportion of patients, ranging from 26 to 49% (futile and dangerous recanalization), stimulating the need to improve the selection of patients based on individual pathophysiology.[78]

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Among neuroimaging parameters, a large core and poor collaterals are demonstrated to be strong predictors of both response to endovascular therapy and functional outcome,[9, 10111213] and excluding patients with large core and poor collateral circulation may improve the therapeutic benefit from endovascular therapy. In the subgroup analysis of the IMS III trial, more robust collateral grade was associated with better clinical outcomes.[14] Adequate collateral circulation may contribute to the maintenance of tissue viability in the absence of recanalization. In both intravenous thrombolysis and endovascular trials, shorter time to treatment was associated with better odds for positive outcome.[151617] However, stroke patients presenting at later time points may still benefit from endovascular therapy,[18] and the time to treatment was a predictor of outcome only when collaterals were not considered, suggesting the important role of collaterals for the determination of this time window.[19] Good pial or leptomeningeal collateral circulation predicts better clinical responses to intra-arterial treatment even 5 hours after the onset of the stroke, suggesting that collateral status could extend the time window for endovascular procedures.[2021] Therefore, collateral flow to penumbral tissue beyond the clot has clinical implications in the setting of acute endovascular therapy (Figure 1).

With the lessons from the aforementioned randomized clinical trials published 2013, the recent phase III randomized control trials have been conducted; the MR CLEAN,[22] ESCAPE,[23] EXTEND-IA,[24] SWIFT PRIME,[25] and REVASCAT trials.[26] Most studies addressed the large core (as measured by the ASPECT score <5–7 points) and one study (the ESCAPE trial) poor collaterals in their exclusion criteria. In the ESCAPE trial, collateral status was measured in most cases by multiphasic computed tomography (CT) angiography, a dedicated CT technique to exclude patients with absent collateral.[2327] New evidence from these new randomized trials has demonstrated an overwhelming benefit from endovascular intervention, preferably with stent retriever-mediated mechanical thrombectomy, for the treatment of acute ischemic stroke secondary to large arterial occlusion. Beside the endovascular therapy field, the results of recent stroke prevention trials (WASID and SAMMPRIS) and thrombolysis trials (DIAS-2) have also emphasized the importance of collateral circulation.[2829]

Images for Assessment of Collateral Status using CT or MRI

Conventional angiographic evaluation has advantages, including its reliable demonstration of occlusion vs. subtotal occlusion, well standardized recanalization grading, and high resolution visualization of leptomeningeal collaterals.[130] However, it has several limitations. First, because conventional angiography is invasive, it requires more expertise and time to perform and carries a small risk of thrombotic events. Second, the results of angiographic collateral studies would mostly be incomplete (e.g., not including the venous phase, no contralateral or vertebrobasilar view), especially in acute setting. In addition, it is not possible to simultaneously examine both anterior and poster circulation-derived collaterals (Figure 1). Last, the information obtained regarding the effect of collateral status on the anterior and lateral views in conventional angiography cannot easily be correlated with axial images typically used to depict CT or MRI of ischemic injury. Various efforts have been made to visualize collateral flow using CT or MRI (Figure 2).

The Alberta Stroke Program Early CT Score (ASPECTS)

The ASPECTS on baseline imaging is an established predictor of acute ischemic stroke outcome. Both non-enhanced CT and contrast-enhanced CT ASPECTS showed a good correlation with leptomeningeal collateral grade on conventional angiography.[31] Hypoattenuation on non-contrast CT is caused by a shift in brain tissue water content secondary to ischemia, and this process is dependent on the time as well as the degree of ischemia. To increase the interrater reliability of non-enhanced CT ASPECTS, especially in early phase of infarction, ASEPCTS on CT angiography source image has been developed that is less time dependent.[32] The ASPECTS on contrast-enhanced CT or CT angiography source image showed better correlation with baseline stroke severity and infarct growth than non-enhanced CT ASPECTS.[33]

Multiphasic CT and CT angiography

Multiphasic contrast-enhanced CT collateral grades showed a good correlation with leptomeningeal collateral grade on conventional angiography in acute ischemic stroke,[3435] and has been used as a prediction tool for final infarct volume, infarct growth, subsequent brain edema, and clinical response after thrombolysis.[363738] More recently, the ESCAPE trialists developed a six-point score system for pial arterial filling using multiphasic CT angiography, which showed a good interrater reliability and ability to help determine clinical outcome.[27] This technique is a quick and easy-to-use and needs minimal additional radiation and no additional contrast material, and no post-processing.

CT perfusion

CT perfusion may provide information of collateral status as well as core and penumbra. CT perfusion has the advantage of rapidity and wide accessibility in emergency room, and can be combined with non-enhanced CT and CT angiographic data, especially in patients with anterior circulation stroke.[3940] One retrospective study showed that the most accurate assessment of the site of occlusion, infarct core, salvageable brain tissue, and collateral circulation in patients suspected of acute stroke is afforded by a combination of CT perfusion and CT angiography.[39] CT perfusion and CT angiography provide differential assessment of collateral circulation, functional and anatomic aspects, respectively.[41] Cerebral blood volume may be elevated or within the normal range depending upon effectiveness of collateral supply. Moreover, virtual CT perfusion can be obtained utilizing CT angiographic information.[42] CT perfusion-based selection was used in two recent randomized control trials of revascularization therapy (tenecteplase and thrombectomy).[2443] However, more specific CT perfusion criteria for collateral assessment are yet to be determined.

Conventional MRI

The diffusion-weighted image lesion volume and pattern are associated with the degree of collateral flow in acute ischemic stroke.[4445] A large lesion volume and cortical lesion pattern (regardless of the lesion volume) on diffusion-weighted image are frequently found in patients with poor collaterals. Fluid attenuation inversion recovery images can also provide information about collateral status. The presence of distal hyperintense vessels or

fluid attenuation inversion recovery vascular hyperintensities and the absence of perisylvian sulcal effacement are associated with good collaterals and favorable outcome in patients with acute middle cerebral artery stroke.[4647] Similarly, conspicuous flow voids, deoxygenation seen as hypointensity, or disappearing phase mismapping on gradient echo image may also be clues about the collateral status.[48]

Dynamic susceptibility contrast MR perfusion

Various MR perfusion parameters have been used to measure collateral status. Compared with patients with poor collaterals, those with good collaterals show less severe delays in *T*max and relatively preserved (or even increased) cerebral blood volume within ischemic regions.[10] Optimal MR perfusion parameter to predict collateral grade has seldom been reported. In our *T*max severity-weighted probabilistic model, collateral status was determined by a presence of delayed perfusion (*T*max of 16 to 22 sec) rather than by the presence of a shorter delay in perfusion (*T*max ≤10).[49] In addition, collateral circulation can be easily visualized by simple post-processing using the source data of dynamic susceptibility contrast MRI. Christensen et al. reported the potential use of novel post-processing and visualization techniques (subtracting the image of the first movement map) for evaluating collaterals using bolus tracking MRI.[50] Campbell et al. developed collateral vessel grading using a digitally-subtracted perfusion MRI, and showed that deterioration in collateral grade correlated with subsequent infarct growth.[51] We have applied a simple semi-automatic collateral map technique (FAST-Coll program) using perfusion scan source data to assess collateral grade in acute ischemic stroke.[52] A good correlation was observed between MR- and conventional angiography-based collateral assessment systems. These techniques have an advantage in that the information regarding collateral status can be directly compared with MR diffusion and perfusion image, and there is no need for additional acquisition of conventional angiography or MRI dedicated for collateral assessment.

Arterial spin labeling MRI (ASL)

ASL is a non-contrast perfusion imaging method to measure cerebral blood flow that relies on the magnetic labeling of arterial water. ASL is a promising technique for the assessment of collateral flow that can provide various types of information regarding collateral status. With ASL, late-arriving flow appears as a serpiginous high ASL signal within cortical vessels, which has been termed ‘arterial transit artifact’ (ATA). Patients with ATA had improved outcomes, suggesting that this signal may represent collateral flow.[5354] In addition, flow-direction-sensitive phase contrast MR angiography and vessel-encoded arterial arterial spin labeling could noninvasively provide information regarding the origins and distal function of collateral flow comparable to that obtained with conventional angiograms.[5556] Lastly, ASL can provide anatomic (ASL MRA) and dynamic blood flow (time-resolved) information in the circle of Willis, similar to that obtained with conventional angiography without the use of exogenous contrast agents.[5758]

Imaging techniques to visualize collateral arteries

Various modalities have been used to noninvasively measure collateral flow, such as transcranial Doppler, CT angiography, or MR angiography.[59] CT or MR angiography can evaluate the cerebral collateral circulation in the circle of Willis with moderate-to-good diagnostic performance, but has limitation in the evaluation of leptomeningeal collaterals. Recent advances in 7-Tesla MRI have enabled the direct visualization of pial branches in cerebral arterial disease, indicating the possibility of assessing leptomeningeal collaterals with high-resolution MR angiography.[60] However, this technique is not feasible in patients with acute stroke.

Advantages and disadvantages of various neuroimaging techniques

As shown in Table 1, they differ greatly depending on the technique used in the assessment of collateral status. While there are various ways to determine collaterals using MRI, these may have limited usefulness in light of (a) recent trials where mostly CT was used; (2) further overwhelming data for the need for speed. It is unlikely that in the near future MRI images can be obtained at the same efficiency as CT based imaging. MRI techniques for collateral status deserve further investigation but are not yet ready for implementation as a valid predicting neurologic biomarker in stroke reperfusion trials for the following aspects.

a. Availability and scan time: CT-based collateral assessment is faster and more accessible than MRI-based techniques. However, the great potential for improving feasibility and accuracy of MR-based collateral assessment exist. For example, a 6-minute multimodal MRI protocol was proposed recently, which showed a good diagnostic quality and a significant reduction in scan time rivaling that of multimodal CT protocol.[66]

b. Visualization: The ASPECTS scoring system imperfectly accounts for brain eloquence, is limited to the middle cerebral artery territory, is dependent on attention to scan quality and technique, and takes practice to learn and use well. MRI-based or multi-modal CT-based collateral techniques may provide better quantitative and good visualization than simple non-enhanced CT techniques.

c. Evidences: While CT-based collateral assessments have been used in large randomized controlled trials, no studies have been focused on MRI-based collateral assessments vs. standard CT in patient selection for revascularization therapy. Randomized trials are needed to show the same kind of efficiency at CT.

Strategies to enhance Collateral Circulation

Several conditions might adversely affect collateral status, including systemic illness (cardiac or pulmonary illness, dehydration, vascular risk factors, etc), medications that inhibit physiological augmentation of blood pressure (i.e., high-dose antihypertensives or wide fluctuation in blood pressure), and cerebral vascular status (widespread cerebral atherosclerosis or incomplete circle of illness).[67] Optimization of these factors could help to minimize the risk of collateral failure. Beside, non-modifiable factors, such as aging and genetic factors may also influence on the collateral development and rarefaction.[6869]

Collateral enhancing strategies are important ways to restore blood flow within ischemic regions, particularly in patients who are ineligible for revascularization therapy, such as those outside the therapeutic time window for intravenous thrombolysis (4.5 h) or endovascular therapy (6–8 h), or those having poor collaterals in whom unfavorable response to revascularization therapy is expected. Collateral enhancing strategies for hemodynamic manipulations include induced hypertension, lying flat head position, volume expansion, external counterpulsation, partial aortic obstruction diverting splanchnic blood flow to the upper body and brain, and sphenopalatine ganglion stimulation (Table 2).[6770] In the field of neurosurgery, emergent bypass surgery has been applied for patients with acute ischemic stroke.[7172] Application of nitric oxide,[73] albumin,[74] and tumor necrosis factor-α inhibitor[75] has been shown to increase arteriogenesis (collateral formation from preexisting channels) in animal model of stroke. In addition, preclinical and clinical studies have showed that various pharmacological therapies may enhance angiogenesis (capillary formation from preexisting vessels) and vascuologenesis (de novo capillary formation),[677677] which includes sildenafil and phosphodiesterase type 5 inhibitors,[7879] erythropoietin/trophic factors,[808182] and statins with or without cell therapy.[83848586] Large, randomized trials in acute stroke patients have seldom been performed and showed negative results.[87888990] The potential reasons for these failures include inadequate patient selection and lack of assessment of the effects of such interventions on collateral blood vessels and collateral flow. Further studies are needed with optimal patient selection and rigorous assessment of the therapeutic values of collateral enhancing strategies using advanced imaging techniques for collateral flow. There are currently several ongoing clinical trials employing various strategies (Table 2).

Conclusions and perspectives

In acute stroke patients, reperfusion after cerebral ischemia can be achieved via collaterals or through arterial revascularization. Relatively little attention has been paid to the patient's collateral status or therapeutic strategies for collateral enhancement. Growing evidence has demonstrated that it is important to re-estimate the risk-benefits of stroke therapy, such as endovascular therapy for acute ischemic stroke, in consideration of collateral status. Neuroimaging techniques for the assessment of collaterals are rapidly developing and may provide insight on the perfusion of collaterals in patients who may not otherwise be candidates for conventional angiography. Continuous efforts are needed to develop collateral enhancing strategies, and large randomized trials are needed with monitoring their effects using imaging modalities for collateral assessment.

Acknowledgments

Funding sources: This study was supported by the Korea Health Technology R&D Project, the Ministry of Health & Welfare (HI14C1624) to O.Y.B. Dr. Liebeskind has received a research grant from the NIH-NINDS (K24NS072272 and R13NS089280), and Dr. Goyal has received a research support from Covidien.

Disclosure: M.G. has received honoria from Covidien and remuneration from GE Healthcare.

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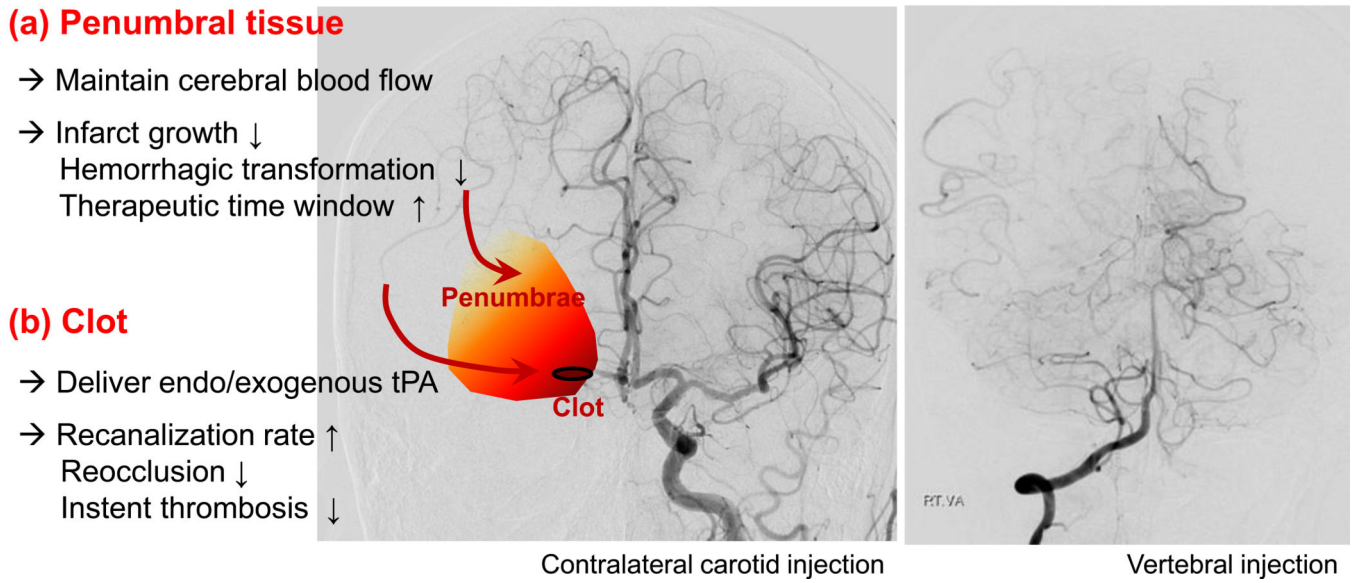

Figure 1.
Impact of collateral flow to penumbral tissue and occluding clot.
tPA, tissue plasminogen activator

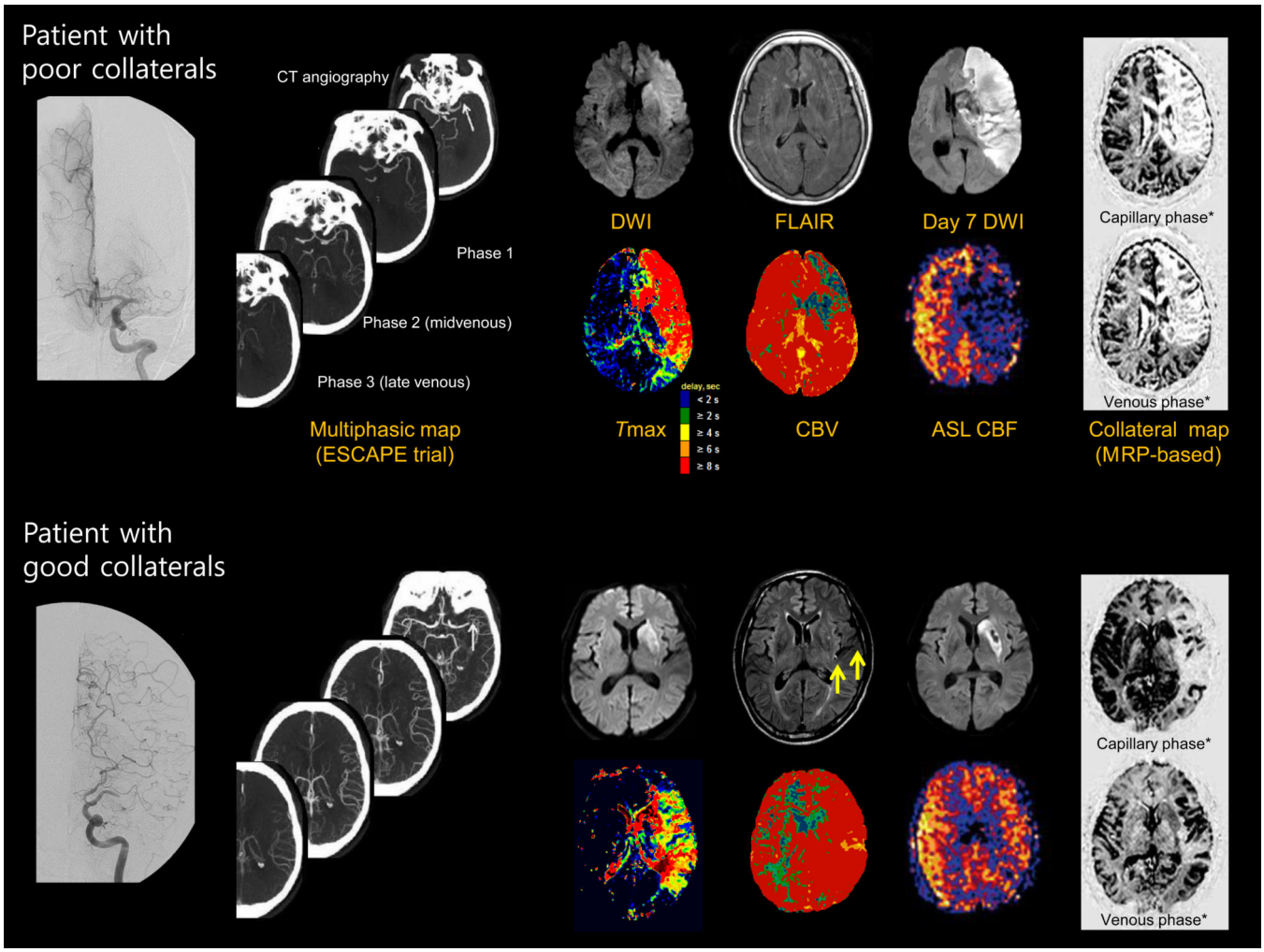

Figure 2.

Various neuroimaging parameters representing the infarcted area and collateral status.

Arrow indicate the distal hyperintense vessels

* based on the contralateral side

Table 1

Advantages and disadvantages of various neuroimaging techniques for collateral assessment.

Images	A good correlation with conventional angiographic collateral grade	Clinical Trials	Advantages	Disadvantages
Conventional angiography		None	Reference standard	Invasive
ASPECTS score	ASPECTS on both contrast-enhanced than non-enhanced CT[31]	ESCAPE[23] SWIFT PRIME,[25] REVASCAT[26]	Easy-to-use Routine study	Relatively low interrater reliability[61] Collaterals not visualized
Multiphasic CT	Multiphasic perfusion CT collateral grades[3435]	ESCAPE[23]	Easy-to-use	Radiation Needs contrast dye
Diffusion-weighted image	Infarct volume[44] Infarct pattern[45]	BRASIL[62] DEFUSE[63]	Routine MRI study	Many confounders Collaterals not visualized
FLAIR and gradient echo image	Distal hyperintense vessel on FLAIR[46]	Observational studies	Routine MRI study	Poor visualization
MR or CT perfusion	*T*max severity[1049]	DEFUSE[63] EPITHET[64] MR RESCUE[5] EXTEND-IA[24] SWIFT PRIME[25]	Quantitative and good visualization	Needs post-processing Needs contrast dye More specific criteria for collateral assessment are needed
MR-based collateral image	Collateral map using DSC PWI source data[65]	Observational studies	Good visualization Simple post-processing performed at workstations; Covers the entire vascular phase	Needs validation
Arterial spin labeling	Vessel-encoded ASL[5655] Arterial transit artifact[53]	iCAS Other ongoing studies*	Vessel selective information No contrast dye	Contamination from the partial labeling of the nearby vessels or antegrade flow T1 decay of the label may limit the extent to which slow inflows can be imaged

ASPECTS, Alberta Stroke Program Early CT Score; ESCAPE, Endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times; SWIFT PRIME, Solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke; REVASCAT, Endovascular revascularization with solitaire device versus best medical therapy in anterior circulation stroke within 8 hours; BRASIL, Bleeding risk analysis in stroke; DEFUSE, Diffusion and perfusion imaging evaluation for understanding stroke evolution imaging before thrombolysis; FLAIR, fluid attenuation inversion recovery; EPITHET, the echoplanar imaging thrombolysis evaluation trial; MR RESCUE, mechanical retrieval and Recanalization of stroke clots using embolectomy; EXTEND-IA, extending the time for thrombolysis in emergency neurological deficits-Intra-arterial; iCAS, imaging collarterals in acute stroke.

*Quantifying collateral perfusion in cerebrovascular disease-Moyamoya disease and stroke patients (NCT01419275), Acute MRI in transient ischemic attack (NCT01531946), and A longitudinal study of multimodal resonance imaging in stroke patients (NCT02024503).

Table 2

Therapeutic strategies for enhancing collateral circulation via arteriogenesis and angiogenesis/vasculogenesis.

Arteriogenesis	Clinical trials	Angiogenesis/ vasculogenesis	Clinical trials
Induced hypertension	SETIN-Hypertension (O)	Erythropoietin	EPO stroke (C)
Head position	HeadPoST (O)	Trophic factors	
Volume expansion		Statins	
Partial aortic occlusion	SENTIS (C), FASTFlo-tPA (C), Flo24 (C)	PDE5 inhibitors	Sildenafil treatment of subacute ischemic stroke (C)
SPG stimulation	ImpACT-24 (O)	Stem/progenitor cells	
External counter pulsation	CUFFS (C), EULIPCCS (O)		
Bypass surgery			
Albumin	ALIAS (C)		
Nitric oxide	ENOS (C)		
TNF-α inhibitor			

SPG, sphenopalatine ganglion; TNF-α, tumor necrosis factor-α; PDE5, phosphodiesterase type 5 inhibitors.

SETIN-Hypertension, Safety and efficacy of therapeutic induced hypertension in acute non-cardioembolic ischemic stroke; HeadPoST, Head position in stroke trial; SENTIS, Safety and efficacy of NeuroFlo technology in ischemic stroke; FASTFlot-tPA, Feasibility and safety of NeuroFlo in stroke patients receiving tissue plasminogen activator; Flo24, Safety and efficacy of NeuroFlo in 8–24 hour stroke patients; ImpACT-24, Implant for augmentation of cerebral blood flow trial, effectiveness and safety in a 24 hour window; CUFFS, Safety study of external counterpulsation as a treatment for acute ischemic stroke; EULIPCCS, Effects of upper limb ischemic postconditioning on collateral circulation after stroke; ALIAS, Albumin in acute ischemic stroke trial; ENOS, Efficacy of nitric oxide in stroke; EPO stroke, Multicenter efficacy study of recombinant human erythropoietin in acute ischemic stroke.

(C) completed trials ; (O) ongoing trials.