Review Article

Assessment of Arterial Collateralization and Its Relevance to Intra-arterial Therapy for Acute Ischemic Stroke

Siva Seeta Ramaiah, MBBS, MMed,*† Peter Mitchell, FRANZCR,‡ Richard Dowling, FRANZCR,‡ and Bernard Yan, FRACP†‡

Evidence from recent randomized controlled studies comparing intra-arterial (IA) therapy with intravenous tissue plasminogen activator highlighted the mismatch between recanalization success and clinical outcomes in patients presenting with acute ischemic stroke. There is emerging interest in the impact of arterial collateralization, as determined by leptomeningeal anastomoses (LMAs), on the treatment outcomes of IA therapy. The system of LMA constitutes the secondary network of cerebral collateral circulation apart from the Circle of Willis. Both anatomic and angiographic studies confirmed significant interindividual variability in LMA. This review aims to outline the current understanding of arterial collateralization and its impact on outcomes after IA therapy for acute ischemic stroke, underpinning the possible role of arterial collateralization assessment as a selection tool for patients most likely to benefit from IA therapy. **Key Words:** Leptomeningeal anastomoses—acute ischemic stroke—intra-arterial therapy—mismatch.

Brief Overview of Revascularization for Acute Ischemic Stroke: Intravenous Thrombolysis and Intra-arterial Therapy

Intravenous Thrombolysis

The guiding principle of acute stroke treatment is the timely recanalization of occluded arteries, leading to restoration of cerebral blood flow. Intravenous tissue plasminogen activator (IV-tPA) is shown to improve outcomes as shown by the National Institute of Neurological Disorders and Stroke trial and the Safe Implementation of Thrombolysis in Stroke Monitoring Study registry.[1-3] Following the European Cooperative Acute Stroke Study III trial and pooled data from the large IV-tPA trials, IV thrombolysis up to 4.5 hours from stroke symptom onset is now accepted as the standard of care.[4-6] However, recanalization rates with IV-tPA are low in the setting of large artery occlusion with rates ranging from 4% to 68% depending on the location of occlusion.[7-9]

Intra-arterial Therapy

Alternative strategies to intravenous thrombolysis have been developed to address the low recanalization rates of IV-tPA. These strategies, termed intra-arterial (IA) therapy, include a myriad of techniques: IA thrombolysis, percutaneous transluminal angioplasty, aspiration thrombectomy, and mechanical thrombectomy.[10-13] In the recently concluded Interventional Management of Stroke III[14] trial, the investigators randomized acute ischemic stroke (AIS) patient who had received IV-tPA

From the *Department of Neurology, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia; †Melbourne Brain Centre, Royal Melbourne Hospital, Melbourne, Australia; and ‡Neurointervention Service, Department of Radiology, Royal Melbourne Hospital, Parkville, Victoria, Australia.

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Address correspondence to Bernard Yan, FRACP, Melbourne Brain Centre, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia. E-mail: bernard.yan@mh.org.au.

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within 3 hours after symptoms onset to receive additional IA therapy or IV-tPA alone. The study demonstrated equivalent, favorable clinical outcomes (40.8% in IA therapy group and 38.7 in IV-tPA alone) despite a higher recanalization rate in the endovascular group.[14] In another long-awaited randomized trial, Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial,[15] the investigators assigned 362 patients with AIS, within 4.5 hours after onset to IA therapy or IV-tPA alone. The clinical outcomes were similar in both treatment groups (42% favorable clinical outcome in IA therapy and 46.4% in IV-tPA alone) though median time from stroke onset to the start of treatment was only 1 hour longer in the former.[15]

In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)[16] trial, the investigators randomly assigned 127 patients between the ages of 18 and 85 years, with National Institutes of Health Stroke Scale scores of 6-29 who had a anterior circulation ischemic stroke within 8 hours after the onset of symptoms to undergo either mechanical embolectomy (MERCI Retriever or Penumbra System) or standard medical care.[16] The rate of revascularization at 7 days was 71% for endovascular therapy group and 87% for the standard care group.[16] The reported rate of disability-free survival at 90 days was 14% in penumbral group and 9% in non-penumbral group for endovascular therapy and 23% in penumbral group and 10% in non-penumbral group for standard care group.[16] The proposed explanation for better outcomes of patients with an ischemic penumbra than patients without a penumbral pattern was the ability of collateral vessels to maintain sufficient perfusion to limit the infarct size.[17]

Poor Clinical Outcomes Despite Good Recanalization

Although endovascular techniques have shown better recanalization rates than intravenous thrombolysis, this has not been matched by a corresponding improvement in clinical outcomes (Table 1). In the MultiMERCI trial, recanalization rate of 69.5% was achieved, but good clinical outcome remained 36% with a mortality rate of 34%.[10] The Penumbra Pivotal Stroke trial demonstrated an 81.6% recanalization rate with only 25% positive clinical outcome.[11]

Several possible mechanisms have been put forward to explain the mismatch between recanalization success and clinical sequelae: (1) the presence of an incomplete microcirculatory reperfusion after focal cerebral ischemia,[22] (2) the presence of an already infarcted ischemic core,[17] and (3) inadequate arterial collateralization.

Recent advances in imaging of patients undergoing IV thrombolysis and IA therapy suggested the role of arterial collateralization as a significant prognostic factor. A favorable arterial collateralization profile may enhance recanalization, improve downstream reperfusion, reduce the extent of infarct core and ischemic lesion growth, decrease hemorrhagic transformation, and improve outcome after revascularization.[23-25]

Cerebral Collateral Circulation

Human

The development of the cerebral collateral circulatory channels during embryonic stages parallels development of the nervous system. At the fifth week of gestational age, 4 pairs of presegmental arteries originate from the primitive internal carotid artery (ICA): the trigeminal arteries, the otic arteries, the hypoglossal arteries, and the proatlantal intersegmental arteries. By the sixth gestational week, dorsal to the presegmental arteries, bilateral longitudinal neural arteries unite to form the basilar artery.[26] The posterior communicating arteries (PCoAs) develop from caudal division of the ICA at the same period and begin to serve as a communication between the ICA and the arteries of the primitive hindbrain.[27-29] In the early eighth gestational week, the posterior cerebral artery (PCA) develops during the posterior expansion of the forebrain as a posterior continuation of the PCoA and the ICA. Early in development, the PCoA and the proximal branches of the PCA (posterior choroidal, diencephalic, and mesencephalic arteries) are prominent.[27-29] During embryogenesis, the distal PCA elongates and increases in caliber as the occipital lobes expand, outgrowing the once prominent proximal branches. The PCoA undergoes relative regression. This shift in dependence from the carotid to the basilar system in the final stages of embryonic development is not constant. In some adult brains, the embryonic pattern persists, with the PCA remaining a branch of the ICA, which occurs in approximately 20%-30% of cases.[28,29]

The system of leptomeningeal anastomoses (LMA), which was first described by Heubner in 1874,[30] constitutes the secondary network of the cerebral collateral circulation apart from the Circle of Willis (primary network). LMAs (or pial collaterals) are anastomotic connections between distal branches of the cerebral arteries found along the surface of the brain that permit blood flow from the territory of an unobstructed artery into the territory of an occluded artery.[31] The most significant anastomoses are between anterior cerebral artery (ACA) and middle cerebral artery (MCA) (Fig 1), in terms of number and size with smaller and fewer connections between MCA and PCA (Fig 2) and even less prominent terminal anastomoses between PCA and ACA.[32] In recent years, both anatomic and angiographic studies confirmed the presence of LMA in every brain.[33,34] Great interindividual variability in distribution, size, and number of LMA existed, but the range and compensatory capacity still remained unanswered.[35]