Leptomeningeal Collaterals in Acute Ischemic Stroke

Abstract

Introduction: The leptomeningeal collaterals are a subsidiary network of vascular channels that act as anastomotic channels in conditions where cerebral blood flow is pathologically altered. These secondary collateral pathways may be utilized when collateral flow through the circle of Willis is inadequate.

Summary of Review: The review highlights the importance of leptomeningeal (pial) anastomoses in the brain especially in conditions of hemodynamic impairment such as ischemic stroke. The historical perspective regarding the role of these vessels is discussed. New advancements in the diagnostic and treatment modalities for the evaluation and optimization of these vessels are identified.

Conclusion: Evaluation and optimization of the leptomeningeal collaterals in ischemic stroke represents an important venue in prevention and treatment of cerebral ischemia.

Keywords: leptomeningeal collaterals, ischemic stroke, cerebral blood flow

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Abbreviations: DSA, digital subtraction angiography; LMCs, leptomeningeal collaterals; LMAs, leptomeningeal anastomosis; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ICA, internal carotid artery; rCBF, regional cerebral blood flow; MRA, magnetic resonance angiography; TCD, transcranial Doppler; GM-CSF, granulocyte monocyte-colony stimulating factor; CT, computed tomography; CTA, computed tomographic angiography; PET, Positron emission tomography

Historical perspectives of LMCs
The first elaborate description of LMCs was given by Heubner in 1874. In the late 1950s and early 60s, Van der Eecken and Adams later provided a comprehensive anatomic description of LMCs. They performed several studies on cadaveric brains derived from patients suffering from ischemic stroke secondary to MCA occlusion. They observed that the infarcted area in most patients was smaller than actual distribution supplied by the occluded artery. A variable proportion of the MCA territory was spared as a result of LMC filling from the ACA and/or PCA. In recent years, both anatomic and angiographic studies have confirmed the presence of LMCs in patients' brains under normal and diseased states.

The role of various imaging modalities in the evaluation of LMCs
Modern diagnostic imaging techniques, like Xenon enhanced CT, single photon emission CT, PET, CT perfusion, MR perfusion, and TCD, have improved the assessment of cerebral blood flow through collaterals. Relatively subtle findings such as vascular enhancement...
ment on CT and MRI scans may also identify collateral blood flow. LMCs can be directly visualized by conventional angiography, CTA and MRA. Collateral blood flow as assessed by CT angiography, triphasic perfusion CT, Xenon CT, MR imaging, and SPECT has been shown to correlate with the extent of LMC formation seen on conventional angiograms and with clinical outcome. Angiographic scales have attempted to qualitatively classify the extent of collateral blood supply, however, variations in contrast volume and pressure during injection may distort the appearance of distal vessels. Noninvasive techniques including CTA and MRA angiograms have limited resolution, precluding thorough evaluation of LMCs and other secondary collateral pathways. The specific advantages and limitations of each modality must be considered, along with the timing of image acquisition as collaterals evolve with time from the incipient ischemic event.

The role of LMCs in acute ischemic stroke patients
Since their description, the role of LMCs in the pathophysiology of cerebral ischemia has been a matter of debate. From the year 2000 onwards, the role of LMCs in ischemic stroke has again gained substantial attention. The PROACT II trial investigated semiquantitatively analyzed pial collateral formation on angiography and categorized them as full, partial, or none and found that presence of good collaterals influences NIHSS score at initial presentation and infarct volume on 24-hour CT scan in patients with MCA occlusion. The presence of LMCs has also been associated with better outcomes, reduced infarct size, and faster recanalization. After the introduction of the concept of ischemic penumbra by Astrup et al in 1981, Fukuyama et al (1983) studied LMCs by nuclear medicine techniques and concluded that cortical infarction occurs in patients with inadequate development of LMCs despite an angiographically normal circle of Willis. Saito et al (1987) measured the time interval between opacification of the distal internal carotid and the M2 segment via LMCs on 21 angiograms in patients presenting with acute ischemic stroke within 24 hours of symptom onset. The investigators found that a time interval <5 seconds for opacification resulted in better outcomes with reduced infarct size. In another study, (1992) visualization of robust LMCs in CT angiograms was associated with rapid recanalization and possible prevention of large infarcts. Presumably, retrograde collateral filling may permit thrombolytic activity in the distal aspects of the clot and dissolution of fragmented thrombi. Lee et al (2000) correlated triphasic perfusion CT in MCA distribution ischemic stroke with angiographic findings and found a positive correlation between recovery after thrombolytic therapy and the presence of efficient LMCs. Christoforidis et al (2005) reviewed 65 patients retrospectively who underwent thrombolysis for acute ischemic stroke and reported that LMC formation before thrombolytic treatment predicted infarct volume and clinical outcome independent of other predictive factors. The benefit of thrombolytic treatment was augmented in patients with greater LMC formation.

Qureshi et al (2002) devised a grading scheme for angiographic evaluation of patients before and after intra-arterial thrombolysis. The grading scheme was based on anatomic location of occlusion and presence of LMC pathways in the affected distribution. The scheme showed that presence of good collaterals in patients undergoing thrombolytic therapy for stroke correlated with better recanalization rates, and recovery and lower mortality at 7 days. Prediction of these outcome variables in stroke patients using the abovementioned scheme has been established with high confidence in several studies. Yamauchi et al (2004) studied 42 patients and determined that the presence of ophthalmic or leptomeningeal collaterals in patients with symptomatic ICA occlusion was an independent predictor of increased oxygen extraction suggestive of ischemic stress within the brain tissue but this association was confounded by the presence of ischemic lesions in the brain. Mohammad et al (2008) determined the relationship between severity of angiographic occlusion using Qureshi grading scheme and the volume of brain infarction on follow up CT in 55 patients with anterior circulation ischemic stroke who underwent intra-arterial thrombolysis. He found that collateral supply through LMCs was associated with lower volume of brain infarction in patients with proximal MCA occlusion.

Temporal profile of development of LMCs in acute ischemic stroke
LMCs connect arterial watershed territories (eg: ACA and MCA, MCA and PCA territory) and are activated instantly in the presence of a major proximal arterial occlusion. Variable blood flow along these pre-existing connections occurs to fill the territory of the occluded vessel. Martin et al determined the intracranial hemodynamic response to ICA occlusion following clamping by using TCD measurements. Secondary collaterals were detected in 62 of the 85 patients. Yamashita et al (1996) used Xenon enhanced CT rCBF measurement with acetazolamide challenge in patients with ICA stenosis and demonstrated that LMCs develop to some extent immediately after occlusion and continue to develop for some time. Drake et al documented a prominent compensatory potential of LMCs during surgical occlusion of major cerebral arteries for aneurysms based on their findings on conventional angiograms. Enam and Malik (1999) observed refilling of arteriovenous malformations as a result of LMCs subsequent to complete occlusion of major feeding vessels documented on cerebral angiography.

The presence of secondary collateral pathways is usually a marker of impaired cerebral hemodynamics. Secondary collateral pathways that require time to develop are presumed to be recruited once primary collaterals at the circle of Willis are inadequate.

LMC adequacy in maintaining rCBF in patients with major cerebral artery occlusion
Some studies have reported that LMCs are not always adequate in maintaining rCBF. Derdeyn et al (1998) concluded that LMCs are not adequate to maintain normal rCBF in major
cerebral artery occlusion based on conventional angiograms and PET scan findings. It is important to note that the effect of concomitant medications on LMC formation is not known although previous studies have not suggested an acute affect of either antiplatelet agents\textsuperscript{34} or heparin.\textsuperscript{35}

Factors determining functionality and patency of LMCs

From the functional aspect, blood flow can occur in both directions through LMCs depending on the pressure gradient. The functional capacity of LMC vessels is ultimately determined by their lumen caliber\textsuperscript{36}, since it is inversely proportional to hydraulic resistance, ie, the fourth power of the radius. Therefore, size and number of LMCs determine the total capacity to maintain rCBF.\textsuperscript{11} The activation of these collaterals also depend on less well understood compensatory hemodynamic, metabolic, and neural mechanisms. Angiogenesis may result in collateral growth at the periphery of an ischemic region over time.\textsuperscript{37} During the incipient development of secondary collaterals rCBF may vary with hemodynamic fluctuations. Similarly, distal fragmentation of a thrombus within the parent vessel may occlude distal branches supplying retrograde collateral flow from cortical arteries. The efficacy of LMCs also depends upon age, duration of ischemia, and associated comorbidities. Hypertension may impair collateral development in the setting of carotid occlusion and therefore increase stroke risk.\textsuperscript{18} Chronic hypoperfusion due to arterial flow restrictions such as extracranial carotid or intracranial steno-occlusive disease promotes collateral development, although the relationship of these collaterals with rCBF and clinical symptomatology remains unclear.

The role of animal studies in understanding LMCs

Animal experiments provide the possibility of measuring LMCs in vivo and also manipulating them under various experimental conditions. However, there are certain differences between the cerebrovascular systems of humans and animals, the major one being the presence of single ACA in rats and non-human primates. Furthermore, the PI segment of the PCA is narrow, lacking, or variable in diameter. Early studies involving LMCs in animals were mostly performed in cats, canines, and non-human primates. They indicated that rCBF after major cerebral arterial occlusion depends on vessel size and collateral circulation and that rCBF via LMCs is established immediately after occlusion followed by chronic adaptation of LMCs by hypertrophy.\textsuperscript{39, 40} Coyle et al\textsuperscript{41} (1991) reported that LMCs can increase up to 50% in diameter 3 weeks after MCA occlusion in rats. The luminal width of these LMCs was a major determinant of rCBF in the territory of the occluded artery and of subsequent infarction. Maeda\textsuperscript{42} and Nallet et al.\textsuperscript{43} (1999) performed experiments on rats. They found that microvascular perfusion in the penumbra was predominantly preserved by LMCs in MCA occlusion. Recently, a study\textsuperscript{44} found an increase in the diameter of leptomeningeal anasotomoses after hypoxic preconditioning in rats. This change could be attributable to the upregulation of several angiogenic growth factors such as vascular endothelial growth factor and erythropoietin which have been shown to contribute to vascular remodeling after hypoxic preconditioning.\textsuperscript{45, 46} Most recently (2008), Todo et al\textsuperscript{47} observed enhanced LMC growth after giving GM-CSF treatment to mice with chronic unilateral ICA occlusion. After 14 days, the MCA was artificially occluded and a significant reduction in infarct size was observed in the GM-CSF treated mice compared with controls.

**Figure 1A**

![Figure 1A](image1.png)

Figure 1A and B. Left ICA injection, antero-posterior projection, early (A) and late arterial phase.

1A. The left MCA is occluded. There is no filling of the vascular territory.

1B. Leptomeningeal collaterals (arrows) are now filling the MCA territory. The respective supply territories of the vessels are marked.
Conclusions and future prospects

The current review highlights the important research conducted in the last few decades on the role of LMCs in the cerebral circulation. The presence of robust LMCs is associated with rapid recanalization in acute ischemic stroke and reduction of infarct size. The application of nanotechnology has already begun to show promise in imaging LMCs. Three-dimensional MRA techniques using 5-nm particles of contrast material have produced clear images of blood vessels less than 1 mm in diameter allowing quantitative measurements of angiogenesis and microvascular permeability in both healthy and ischemic tissues. Rapid advancements in such diagnostic modalities may allow further elaboration of the role of LMCs under abnormal hemodynamic conditions of the brain. Furthermore, a better understanding of LMCs in acute ischemic stroke might advance knowledge related to mechanism of action and mode of delivery pertaining to thrombolytic drugs.

References

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