Collateral Circulation
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Background—The collateral circulation plays a pivotal role in the pathophysiology of cerebral ischemia. Current knowledge of the collateral circulation remains sparse, largely because of prior limitations in methods for evaluation of these diminutive routes of cerebral blood flow.

Summary of Review—Anatomic descriptions of the collateral circulation often focus on more proximal anastomoses at the circle of Willis, neglecting secondary collateral pathways provided by leptomeningeal vessels. Pathophysiological recruitment of collateral vessels likely depends on the temporal course of numerous compensatory hemodynamic, metabolic, and neural mechanisms. Subsequent endurance of these protective vascular pathways may determine the severity of ischemic injury. Characterization of the collateral circulation with advanced neuroimaging modalities that provide angiographic information and perfusion data may elucidate critical determinants of collateral blood flow. Such information on the status of the collateral circulation may be used to guide therapeutic interventions. Prognostication and risk stratification may also be improved by routine evaluation of collateral blood flow.

Conclusions—Contemporary understanding of the collateral circulation may be greatly enhanced through further refinement of neuroimaging modalities that correlate angiographic findings with perfusion status, providing the basis for future therapeutic and prognostic applications. (Stroke. 2003;34:2279-2284.)

Key Words: cerebral blood flow ■ cerebral ischemia ■ collateral circulation ■ magnetic resonance imaging ■ stroke ■ tomography, x-ray computed

The cerebral collateral circulation refers to the subsidiary network of vascular channels that stabilize cerebral blood flow when principal conduits fail. Arterial insufficiency due to thromboembolism, hemodynamic compromise, or a combination of these factors may lead to the recruitment of collaterals. Pathophysiological recruitment of these potential anastomotic connections is frequently observed in various ischemic conditions, yet knowledge of the collateral circulation remains limited. Extrapolation of animal research on collaterals is limited by anatomic differences among species, and clinical research on the topic is hampered by inadequate diagnostic methods. The role of the collateral circulation is frequently invoked in clinical practice, yet seemingly basic relationships with regard to variables such as age and comorbidities remain undefined. Refinement of diagnostic techniques for evaluation of the collateral circulation may facilitate anatomic and pathophysiologic characterization of these vessels in humans, with potential therapeutic and prognostic applications.

Anatomy
The arterial anatomy of the collateral circulation includes extracranial sources of cerebral blood flow (Figure 1) and intracranial routes of ancillary perfusion (Figure 2) that are commonly divided into primary or secondary collateral pathways. Primary collaterals include the arterial segments of the circle of Willis, whereas the ophthalmic artery and leptomeningeal vessels constitute secondary collaterals. Interhemispheric blood flow across the anterior communicating artery and reversal of flow in the proximal anterior cerebral artery provide collateral support in the anterior portion of the circle of Willis. The posterior communicating arteries may supply collateral blood flow in either direction between the anterior and posterior circulations. Additional interhemispheric collaterals include the proximal posterior cerebral arteries at the posterior aspect of the circle of Willis. Considerable variability exists in the anatomy of the circle of Willis, with frequent asymmetry and an ideal configuration in only a minority of cases. Anatomic studies note absence of the anterior communicating artery in 1% of subjects, absence or hypoplasia of the proximal anterior cerebral artery in 10%, and absence or hypoplasia of either posterior communicating artery in 30%.

Reversal of blood flow within the ophthalmic artery may provide secondary collateral support. Anastomoses between distal segments of the major cerebral arteries also contribute ancillary collateral blood flow. The number and size of these anastomotic vessels are greatest between anterior and middle cerebral arteries, with smaller and fewer connections between middle and posterior cerebral arteries and even less prominent terminal anastomoses between posterior and anterior cerebral arteries. Distal branches of the major cerebellar arteries similarly provide collateral links across the vertebral
and basilar segments of the posterior circulation. Leptomeningeal and dural arteriolar anastomoses with cortical vessels further enhance the collateral circulation. Other collateral routes are less commonly encountered in acute stroke, such as the tectal plexus joining supratentorial branches of the posterior cerebral artery with infratentorial branches of the superior cerebellar artery; the orbital plexus linking the ophthalmic artery with facial, middle meningeal, maxillary, and ethmoidal arteries; and the rete mirabile caroticum connecting internal and external carotid arteries. The course and anatomic characteristics of collaterals may vary extensively, with atypical collaterals such as anterior choroidal supply from the posterior circulation induced by pathophysiological conditions. Moyamoya syndrome represents the ultimate example of excessive collateralization over a chronic time course, recruiting a wide range of leptomeningeal and deep parenchymal vessels. The deep parenchymal arteries of the basal ganglia are normally poorly developed. Collateral vessels are formed during the prenatal period, although pathophysiological conditions may cause secondary changes. The collateral ability of a vessel is ultimately determined by luminal caliber.

Venous collaterals augment drainage of cerebral blood flow when principal routes are occluded or venous hypertension ensues. The anatomy of venous collateral circulation is highly variable, allowing diversion of blood through numerous routes when exiting the brain (Figure 3).

**Pathophysiology**

The process of collateral recruitment depends on the caliber and patency of primary pathways that may rapidly compensate for decreased blood flow and the adequacy of secondary collateral routes. Primary collaterals provide immediate diversion of cerebral blood flow to ischemic regions through existing anastomoses. Secondary collaterals such as leptomeningeal anastomoses may be anatomically present, although enhanced capacity of these alternative routes for cerebral blood flow likely requires time to develop. Although the specific pathophysiological factors leading to the development of collaterals are uncertain, diminished blood pressure in downstream vessels is considered a critical variable.

The opening of collaterals likely depends on several compensatory hemodynamic, metabolic, and neural mechanisms.
Angiogenesis may stimulate collateral growth at the periphery of an ischemic region. Focal cerebral ischemia may lead to the secretion of angiogenic peptides with some potential for collateral formation, although these vessels may be designed for removal of necrotic debris rather than augmentation of cerebral blood flow. Experimental data on middle cerebral artery occlusion in rats demonstrates the temporal dependence of collateral development. Clinical observations further emphasize the pace of cerebral ischemia as a critical variable, with collateral capacity improving over time. The influence of comorbidities and other clinical variables on the development of intracranial collaterals in humans is unknown, as no prospective studies have been conducted. Hypertension decelerates the development of collaterals in rats, and the anastomoses are significantly narrower, with diminished collateral capacity. Extrapolation from rats to humans is limited, however, by anatomic and likely pathophysiological differences.

The incipient development of collaterals does not guarantee their persistence. Hemodynamic fluctuations may influence the endurance of collaterals, possibly threatening cerebral blood flow. Similarly, distal fragmentation of a thrombus within the parent vessel may occlude distal branches supplying retrograde collateral flow from cortical arteries. The efficacy of collateral vessels likely depends on age, duration of ischemia, and associated comorbidities.

Chronic hypoperfusion due to arterial flow restrictions such as extracranial carotid stenosis or intracranial stenotic disease promotes collateral development, although the relationship of these collaterals with cerebral blood flow and clinical symptomatology remains unclear. Secondary collateral pathways that require time to develop are presumed to be recruited once primary collaterals at the circle of Willis have failed. Although longitudinal studies have not chronicled this sequence of collateral failure, the presence of secondary collateral pathways is considered a marker of impaired cerebral hemodynamics. Increasing severity of carotid stenosis has been correlated with a greater extent of collateralization. Attempts to correlate various collateral patterns with hemodynamic and metabolic parameters have yielded conflicting results across several studies. Some of these discrepancies may result from employing variable methodology, including MR spectroscopy, CO₂ reactivity with transcranial Doppler ultrasonography (TCD), and positron emission tomography. Inadequate angiographic assessment of all potential collateral routes may also account for these conflicting results. The clinical manifestations of carotid occlusive disease likely depend on multiple variables including time course, degree of luminal stenosis, and status of the collateral circulation ultimately effecting changes in cerebral perfusion pressure. The definition of a “hemodynamically significant” carotid stenosis must therefore account for the status of collaterals.

The collateral circulation is also a critical determinant of cerebral perfusion pressure in acute cerebral ischemia. The hemodynamic effects of the collateral circulation may be important in maintaining perfusion to penumbral regions, but these collateral vessels may also facilitate clearance of fragmented thrombus from more proximal locations.

**Figure 4.** Delayed arterial transit effects (arrow) associated with prolonged transit times of collateral flow on continuous arterial spin-labeled perfusion MRI.

Deep parenchymal collaterals within the striatum may be less effective, allowing undissolved thrombus to be retained for longer periods of time. These factors may be involved in the development of large subcortical infarcts with cortical sparing of the basal ganglia in middle cerebral artery occlusion and limited thalamic infarction in posterior cerebral artery occlusion. Studies of regional cerebral blood flow with various modalities have demonstrated decreased regional cerebral blood flow in cortical areas peripheral to subcortical infarcts. Although metabolic factors and diaschisis may account for these findings, diminished regional cerebral blood flow may simply be the result of marginal collateral blood flow.

**Diagnostic Evaluation**

Numerous techniques, including xenon-enhanced CT, single-photon emission CT, positron emission tomography, CT perfusion, and MR perfusion, assess cerebral blood flow and thereby infer the status of collaterals. These diagnostic modalities provide information regarding the amount of blood flow to specific regions of the brain, although the arterial source of sustained perfusion may not be evident when the parent vessel is occluded. Prolonged transit times of arterial blood flow may be indicative of collateral blood supply on perfusion studies (Figure 4). Relatively subtle findings such as vascular enhancement on conventional neuroimaging studies, including CT and MRI, may also be representative of collateral blood flow. Vascular enhancement may persist for several weeks after the onset of ischemia. Vascular hyperintensities on fluid-attenuated inversion recovery (FLAIR) MRI sequences may be another relatively subtle manifestation of collateral flow (Figure 5).

Although such indirect evidence of collaterals may be apparent with multiple imaging techniques, only limited information regarding collaterals can be accrued. Direct visualization of collaterals is limited to angiographic methods including TCD, CT angiography (CTA), MR an-
gigraphy (MRA), and conventional angiography. Technical aspects of each of these diagnostic modalities confer specific advantages as well as limitations. Conventional angiography is considered the gold standard, although objective evaluation of collaterals is rarely performed. Variation in contrast volume and pressure during injection may distort the appearance of distal vessels. Angiographic scales incorporating aspects of collateral blood supply are considerably subjective, with inconsistent use across studies. Incomplete information regarding collaterals is obtained unless multivessel injections are performed. Noninvasive techniques have limited resolution, precluding evaluation of leptomeningeal and other secondary collateral pathways. TCD is used primarily for evaluation of collateral routes at the circle of Willis, although inadequacy of transtemporal bone windows frequently limits evaluation. Transcranial color-coded duplex ultrasonography identifies vessels on color-coded B-mode images, which may be improved with contrast administration. Cerebral vasomotor reactivity testing with TCD may provide information on autoregulation and collateral status, employing serial evaluation of blood flow in response to a vasodilatory stimulus, such as CO₂ inhalation, acetazolamide injection, or apnea. These vasodilatory stimuli have somewhat different hemodynamic effects, conferring relative advantages and disadvantages of each approach. TCD vasomotor reactivity testing with CO₂ has been correlated with stroke risk in carotid stenosis and the need for shunting during carotid endarterectomy. Impaired vasomotor reactivity has also been correlated with the extent of collateralization. TCD performance and interpretation, however, are subject to considerable variability, and validation of vasomotor reactivity testing has been suboptimal. CTA source images may contain valuable information regarding collaterals, but systematic review of these raw images has met limited success. Postprocessing of CTA data may be more informative (Figure 6), but use of these images is far less practical. Collateral assessment with MRA is generally limited to proximal arterial segments at the circle of Willis. MRA velocity encoding during acquisition allows for flow-sensitive images in 3 orthogonal planes; however, these images are constrained by anatomic resolution and are therefore only useful in proximal segments as well.

Figure 5. Collateral blood flow distal to an occlusion of the middle cerebral artery manifest as vascular enhancement (A, arrow) and FLAIR vascular hyperintensity (B, arrow).

Inconsistency in the results of studies focused on collaterals may be due in part to variability in the diagnostic evaluation. Although both approaches provide information regarding collaterals, perfusion techniques cannot be directly compared with angiographic modalities. The specific advantages and limitations of each modality must be considered, and the timing of studies is crucial as collaterals evolve with time from the incipient ischemic event. The contribution of all potential collateral routes must be considered, and objective scales, rather than the presence or absence of specific arterial segments, must be employed to adequately formulate conclusions regarding the role of collaterals.

Therapeutic Considerations

Although numerous theoretical arguments suggest a putative beneficial effect of improved collateral blood flow to the brain, current therapy of cerebrovascular disease is immature in this regard. Systematic evaluation of collaterals in all patients with cerebrovascular disease is not practical with the use of current diagnostic methods. Until noninvasive diagnostic approaches for evaluation of collaterals are refined, conventional angiography remains the gold standard. The risks of conventional angiography may not be warranted unless objective diagnostic criteria for collaterals are formulated and applicable to specific therapeutic interventions for improving blood flow. Empirical approaches for augmentation of collateral blood flow have met limited success. Theoretical arguments support elevation of systemic blood pressure and vasoconstriction during acute stroke, but clinical trials have not demonstrated unequivocal beneficial results in long-term neurological outcome, and the detrimental effects of such interventions are unclear. Hypervolemic-inotropic support, cerebral vasoconstriction, and hyperventilation are unproven in the acute stroke patient. Further clinical research in this area may elucidate the role of collaterals in acute stroke. Robust leptomeningeal collaterals have been linked with rapid recanalization of middle cerebral artery occlusion and possible prevention of larger infarcts. Although this observation may be interpreted simply as the result of collateral sparing of penumbral regions because of enhanced blood flow, retrograde collateral filling may allow thrombolytic access to distal aspects of the clot. Improved collateral flow may also be important for dissolution of fragmented proximal thrombi. Until therapeutic strategies...
for acute stroke incorporate proven approaches for improvement of collateral blood supply, diagnostic evidence of secondary collateral vessels may be interpreted only as a marker of impaired hemodynamic status. In chronic ischemic conditions, such as moyamoya syndrome and steno-occlusive carotid disease, adequacy of collaterals may be used to guide therapy, although further investigation is warranted. Surgical revascularization with encephaloduroarteriosynangiosis with bifrontal encephalotgageo(periosteal)synangiosis for pediatric moyamoya disease has recently been shown to be more effective in improving cerebral blood flow by supplying collateral support to both anterior and middle cerebral artery territories. Current treatment approaches for carotid stenosis emphasize clinical symptomatology and the degree of luminal stenosis, although the role of collaterals is likely embedded in the relationship of these 2 variables. The selection of carotid endarterectomy candidates may be refined with consideration of collaterals. Operative management may also be influenced, as inadequacy of collateral pathways on angiography and TCD correlates with intraoperative electroencephalographic changes.

**Prognostic Implications**

The status of collaterals in acute stroke may have several prognostic implications. Numerous studies have shown that residual perfusion in an ischemic region of the brain is an important determinant of clinical recovery and hemorrhagic transformation. Although the extent of collateral blood supply affects residual perfusion in ischemic territory, the exact relationship of these variables and the relative impact of all collateral vessels are unclear. Early clinical improvement during the first 48 hours of ischemia may be linked to the presence of collaterals. Systematic angiographic evaluation of collaterals before thrombolysis suggests an increased mortality in the absence of significant collateralization. The presence of leptomeningeal collaterals is also predictive of improved long-term clinical outcome in patients treated with and without thrombolysis for middle cerebral artery occlusion. Reperfusion of ischemic regions by collaterals may improve blood flow and minimize the extent of infarction, but collateral flow may also promote hemorrhagic transformation.

The presence of collaterals on conventional angiography has been associated with a lower risk of hemispheric stroke and transient cerebral ischemia in patients with carotid stenosis. This finding promotes the use of angiography for prognostication and risk stratification in carotid endarterectomy candidates. Studies of carotid artery occlusion have suggested that individuals with impaired collaterals suffer from an increased incidence of stroke. Border zone infarcts have been associated with absence of anterior communicating artery flow and hypoplasia or absence of the posterior communicating artery. Others have suggested that cerebral metabolism and hemodynamics may be normal as long as one of the primary collateral pathways is present, although complete absence of the primary collateral pathways has pathophysiological consequences. Hypertension may impair collateral development in the setting of carotid occlusion and therefore increase stroke risk.

**Conclusions**

The collateral circulation constitutes an important aspect of cerebrovascular disease that remains largely unappreciated. Diagnostic modalities for the detection and characterization of collaterals require further refinement. As multivessel conventional angiography is impractical for all subjects, the development of noninvasive approaches that combine angiographic information with perfusion data would promote our understanding of the collateral circulation considerably. Objective scales for assessment of collateral perfusion need to be practical, with proven reliability and validity. Clarification of the relationship between collaterals and perfusion mismatch may advance development of an image-based thrombolytic window for acute stroke. Further understanding of collaterals may also explain differences in clinical outcome, enable risk stratification for individual subjects, and expand treatment options for acute stroke and chronic cerebrovascular disorders.

**References**


