Assessment of Cerebral Collateral Circulation in Acute Ischemic Stroke

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Abstract
Collateral circulation has a crucial role in maintaining blood flow to the ischemic area during the acute and subacute phase after acute stroke or transient ischemic attack. Cerebral collateral circulation refers to the network of blood vessels that stabilizes cerebral blood flow when the main blood flow fails. Collateral circulation is related to improved blood flow or revascularization to help perfusion of the ischemic area. Reperfusion is important for predictions of improvement in brain tissue and clinical outcomes. The collateral system is known to differ between patients with acute ischemic stroke. Various imaging techniques are known to provide an initial collateral status assessment. Digital Subtraction Angiography (DSA) is a gold standard examination to evaluate the structure of blood vessels, including collateral status, but because the examination is invasive and not easy, other neuroimaging techniques have also been developed such as ASPECTS scores on CT and CTA, CT Perfusion or MR Perfusion and Arterial Spin Labeling on MRI. More attention is needed in assessing the role of early collateral circulation in patients with acute ischemic stroke for the determination of revascularization therapy candidates.

Keywords: collateral circulation, acute ischemic stroke, neuroimaging technique.

Abstrak
Sirikulasi kollarat memiliki peran penting dalam mempertahankan aliran darah ke area iskemik selama fase akut maupun sub akut setelah serangan stroke akut atau serangan iskemik sepiptas. Sirikulasi kollarat serebral mengacu kepada jaringan pembuluh darah yang menstabilkan aliran darah serebral ketika jalur utama aliran darah mengalami kegagalan. Sirikulasi kollarat berkaitan dengan perbaikan aliran darah atau revaskularisasi untuk membantui perfusi area iskemik. Reperfusi penting untuk prediksi perbaikan jaringan otak dan hasil klinis. Sistem kollarat diketahui berbeda antara pasien dengan serangan stroke iskemik akut. Berbagai macam teknik pencitraan diketahui dapat memberikan penilaian status kollarat awal. Digital Substraction Angiography (DSA) masih merupakan pemeriksaan baku emas untuk mengevaluasi struktur pembuluh darah, termasuk status kollarat, namun karena pemerikasnanya yang bersifat invasif dan tidak mudah, teknik pencitraan otak lain juga banyak dikembangkan seperti skor ASPECTS pada CT dan CTA, CT Perfusi atau MR Perfusi serta Arterial Spin Labelling pada MRI. Diperlukan perhatian lebih dalam menilai peran sirikulasi kollarat awal pada pasien dengan stroke iskemik akut untuk penentuan kandidat terapi revaskularisasi.

Kata kunci: sirikulasi kelateral, stroke iskemik akut, teknik pencitraan.

Introduction
Stroke as part of cardiovascular disease is classified in catastrophic disease because it has wide social and economic impacts. Until now, stroke is still a scourge in Indonesia because the highest mortality and disability rates. Data from Indonesian Ministry of Health shows the prevalence of stroke in Indonesia of 10.9 per mile. Management of
The acute phase of stroke is important to save neurons and prevent other pathological processes that can threaten brain function. Rapid and precise management is needed to improve and maintain optimal brain function.¹

The American Heart Association / American Stroke Association (AHA/ASA) recommends IV thrombolysis within 3-4.5 hours and or using a mechanical thrombectomy that can be performed 6-24 hours from onset in acute ischemic stroke. European Stroke Organization (ESO) in 2019 also recommends mechanical thrombectomy plus best medical management as standard therapy in acute stroke patients associated with occlusion of large blood vessels.²³

Collateral circulation plays a vital role in sustaining blood flow to the ischemic areas in acute, subacute or chronic phases after an ischemic stroke or transient ischemic attack. Good collateral circulation shows a protective effect on beneficial functional outcomes and a lower risk of stroke due to different etiologies or when undergoing medical or endovascular treatment.⁴

Cerebral collateral circulation refers to a network of vascular branches that stabilizes cerebral blood flow when the main channel fails. Arterial insufficiency due to thromboembolism, hemodynamic compromise, or a combination of these factors can cause collateral recruitment. Pathophysiological recruitment of this potential anastomotic connection is often observed in a variety of ischemic conditions, but knowledge of collateral circulation remains limited.⁵

The role of collateral circulation is often used in clinical practice, but apparently seemingly basic relationships related to variables such as age and comorbidity remain unclear. Completion of diagnostic techniques for evaluating collateral circulation can facilitate the anatomic and pathophysiological characterization of these vessels in humans, with potential therapeutic and prognostic applications.

**Anatomy**

The anatomy of collateral circulation includes extracranial cerebral blood flow and additional intracranial perfusion routes which are usually divided into primary and secondary collateral pathways. Primary collaterals include arterial segments circle of Willis, while ophthalmic arteries and leptomeningeal vessels are secondary collaterals. Interhemispheric blood flow across the anterior communicating artery and backflow on the proximal side of the anterior cerebral artery provide collateral support in the anterior part circle of Willis. Posterior communicating arteries supply collateral blood flow on both sides of the anterior and posterior circulation. The other interhemispheric collateral passes through the proximal side of the posterior cerebral artery to the posterior aspect circle of Willis. The anatomy circle of Willis is very varied, asymmetries are often obtained and only a small proportion have an ideal configuration. From the research, it is known that about 30% have hypoplasia or aplasia in the posterior communicating arteries, 10% have hypoplasia or aplasia on the proximal side of the anterior cerebral artery, and 1% have aplasia in the anterior communicating artery.⁶

The largest number and size of anastomotic vessels is between the anterior cerebral artery and the medium cerebral artery, smaller and less in the middle and posterior cerebral artery collaterals and the least anastomotic terminal is between the posterior cerebral artery and the anterior cerebral artery. The distal branches of the major cerebellar arteries together provide collateral connections in the vertebral and basilar segments of the posterior circulation. Leptomeningeal and arterial dural anastomoses with cortical vessels further enhance collateral circulation. Other
collateral routes are rarely encountered in acute strokes, such as the tectal plexus which joins the supratentorial branch of the posterior cerebral artery with the infratentorial branch of the superior cerebellar artery; orbital plexus connecting the ophthalmic artery with facial arteries, meningeal media, maxilla and ethmoidal; which connects the internal and external carotid arteries. The pathways and characteristics of collateral anatomy can vary widely, with atypical collaterals such as the anterior choroidal supply from the posterior circulation caused by pathological conditions. Moyamoya syndrome is a prime example of massive collateralization over chronic time, recruiting various leptomeningeal and deep parenchymal vessels. Deep parenchymal arteries in the basal ganglia are usually not well developed. Collateral vessels form during the prenatal period, although pathological conditions can cause secondary changes. The collateral ability of blood vessels is ultimately determined by luminal caliber.\(^5\)

**Pathophysiology**

The process of collateral recruitment depends on the caliber and patency of the primary pathway which can quickly compensate for the reduction in blood flow and the adequacy of the secondary collateral route. Primary collateral provides immediate diversion of cerebral blood flow to the ischemic area through existing anastomosis. Secondary collaterals such as leptomeningeal anastomosis can be anatomically present, although increasing the capacity of these alternative routes for cerebral blood flow may require time to develop. Although the specific pathophysiological factors that lead to collateral development are uncertain, a decrease in blood pressure in the downstream vessels is considered a critical variable. Collateral opening may depend on several compensatory hemodynamic, metabolic, and neural mechanisms.\(^5\,\!^6\)

Angiogenesis can stimulate collateral growth in the peripheral of ischemic area. Focal cerebral ischemia can cause angiogenic peptide secretion with some potential for collateral formation, although these vessels designed to eliminate necrotic debris instead of increasing cerebral blood flow. Experimental data on occlusion of cerebral media artery in rats showed temporal dependence from collateral development. Clinical observations further emphasize the rate of cerebral ischemia as a critical variable, with collateral capacity increasing over time. The effect of comorbidity and other clinical variables on the development of intracranial collateral in humans is unknown, because no prospective study has been carried out. Hypertension slows collateral development in mice, and anastomosis is significantly narrower, with reduced collateral capacity. 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.\(^5\,\!^6\)

Chronic hypoperfusion due to restriction of arterial flow such as extracranial carotid stenosis or intracranial stenotic disease increases collateral development, although this collateral relationship with cerebral blood flow and clinical symptoms remains unclear. Secondary collateral pathways that require time to develop are considered recruited once the primary collateral in the Willis circle has failed. Although longitudinal studies have not recorded this sequence of collateral failure, the presence of secondary collateral pathways is considered a marker of cerebral hemodynamic disorders. Increased severity of carotid stenosis has been correlated with a greater degree of collateral. Efforts to correlate various collateral patterns with hemodynamic and metabolic parameters have produced conflicting results in several studies. Some of these differences may result from the use of
variable methodologies, including MR spectroscopy, CO2 reactivity with transcranial Doppler ultrasonography (TCD), and positron emission tomography. Inadequate angiographic assessment of all potential collateral routes can also explain this conflicting result. Clinical manifestations of carotid occlusive disease may depend on many variables including time travel, the degree of luminal stenosis, and collateral circulation status which ultimately affect changes in brain perfusion pressure.

Collateral circulation is also an important determinant of brain perfusion pressure in acute cerebral ischemia. The hemodynamic effects of the collateral circulation may be important in maintaining perfusion to the penumbra region, but these collateral vessels can also facilitate the cleansing of fragmented thrombus from a more proximal location. Deep collateral parenchyma in the striatum may be less effective, so that the insoluble thrombus is maintained for a longer period of time. These factors may be involved in the development of large subcortical infarction with cortical sparing of the basal ganglia in occlusion of the middle cerebral artery and limited thalamic infarction in posterior cerebral artery occlusion. Regional brain blood flow studies with various modalities have shown a decrease in regional brain blood flow in peripheral cortical areas to subcortical infarction.5,7

**Diagnostic Studies**

From the study of neuroimaging parameters in the event of an acute stroke, it is known that, extensive core infarction and poor collateral are strong predictors of response to endovascular therapy and functional output. Exclusion of patients with a wide core of infarction and poor collateral can increase the therapeutic benefit of endovascular measures.8

Conventional angiography using Digital Subtraction Angiography (DSA) has been recognized as a gold standard to evaluate the collateral structure. Evaluation using DSA has advantages, including being able to clearly show a total occlusion and subtotal occlusion, assessing the level of recanalization well, and a high resolution leptomeningeal collateral picture. But DSA also has several limitations, among others because it is invasive, requires an expert, requires more time, and a small risk of thrombosis. In addition, the results of assessment of collateral angiography studies are usually incomplete, especially during emergency settings, such as not being able to perform anterior and posterior collateral circulation checks simultaneously.4,8

DSA based scoring systems are widely used by the American Society of Interventional and Therapeutic Neuroradiology / Society of Interventional Radiology (ASITN / SIR) by classifying collateral status using grading 0-4. Grade 0, no collateral is seen in the ischemic area. Grade 1, slow filling of collateral to the ischemic edge with some defects. Grade 2, rapid collateral to the ischemic peripheral area with some defects in some ischemic areas. Grade 3, slow collateral but blood flow in complete angiography from the ischemic area until the end of the venous phase. Grade 4, complete and rapid collateral blood flow to the vascular in all ischemic areas with retrograde perfusion.9

Information obtained about collateral status on anterior and lateral projections via DSA cannot be easily correlated with axial features commonly used on CT or MRI, so that various efforts are made to visualize collateral status using CT or MRI modalities. In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) study, collateral status was measured using multiphase Computed Tomography Angiography (CTA) in most cases to their exclusion criteria.10
ASPECTS – Collateral System Score
In acute ischemic stroke, changes that occur early in infarction and the role of leptomeningeal collateral circulation on CT scans are important considerations for therapeutic decisions of thrombolysis. The assessment uses the Alberta Stroke Program Early CT Score (ASPECTS) score system which can identify the extent of infarction and the degree of cerebral edema. Large infarct prediction using ASPECTS scores is associated with poor outcomes and is a relative contraindication to recanalization therapy.  

ASPECTS scores on non-contrast CT and enhanced contrast CT show a fairly good correlation with collateral levels in conventional angiography. To improve the reliability of ASPECTS scores on non-contrast CT scans, ASPECTS scores were also developed on CT angiography especially in the acute infarction phase. Research conducted by Yeo et al and Tan et al is an example of research using the ASPECTS-collaterals system score methodology. CT angiography is used to evaluate intracranial collaterals using the 20-level ASPECTS scale method. This system assesses contrast filling in the distal occluded artery in 6 areas of the cortical region of ASPECTS (M1-6), caudatus, insular, internal capsula, and lentiform nucleus to compile a score of 0-20 (0, arteries not visible; 1, less visible; 2, looks the same or more clearly than the corresponding region in the contralateral hemisphere). Lenticulostrate arteries in the basal ganglia originating from retrograde filling of the cerebral arteries distal to the side of the occlusion are also included in the scoring system.  

Multiphase CT and CT Angiography
Collateral levels on multiphase contrast CT show a good correlation with leptomeningeal collateral levels in DSA in patients with acute ischemic stroke and can be used as predictors of late infarct volume, infarct growth, development of cerebral edema and clinical response after thrombolysis. Research that uses multiphase CT to assess the collateral system is the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) study. ESCAPE researchers developed a 6-point scoring system for pial arterial filling, which provides reasonably good reliability between assessors, and helps determine clinical outcomes. The first phase is a conventional arch to a vertex CT angiogram. The next two phases are sequential skull base to vertex acquisitions acquired in the mid venous and late venous phase. This technique can be easily and quickly used, minimal radiation levels, no additional contrast material and does not require post-processing procedures.

CT Perfusion
Perfusion CT is known to be able to provide information about collateral status as well as information about the core and penumbra infarction. Perfusion CT has the advantage that it does not require a long time, is available in the emergency room and can be combined with data obtained from CT scans without and with contrast. The combination of CT angiography and CT perfusion is known to be quite accurate in assessing the location of occlusion, core infarction, brain tissue that can still be saved and collateral circulation. Actually CT perfusion and CT angiography, each presents data on anatomic and functional aspects and collateral circulation differently, but it can be understood that an increase in blood volume in the brain (CBV) depends on the effectiveness of the collateral supply. However, more specific CT perfusion criteria for collateral assessment are yet to be determined.

Conventional MRI
The volume and pattern of lesions in the DWI sequence are associated with collateral flow rates in acute ischemic stroke. A large lesion volumes and cortical lesion patterns on DWI are frequently found in patients with
poor collateral. FLAIR overview can also provide information about collateral status. The presence of distal hyperintensity vessels or FLAIR vascular hyperintensity and the absence of perisylvian sulcal effacement are associated with good collateral and favorable outcomes in patients with acute middle cerebral artery stroke. Likewise, conspicuous flow voids, deoxygenation seen as hypointensity, or disappearance of phase mismatch on gradient echo images can also be clues about collateral status. Disadvantages of this technique are collateral may not or poor visualization dan many confounders.15

**MR Perfusion**

Various MR perfusion parameters have been used to measure collateral status. Compared with patients with poor collaterals, those with good collaterals showed less severe Tmax delays and relatively maintained brain blood volume in the ischemic region. Optimal MR perfusion parameters for predicting collateral grade are rarely reported. Collateral status is determined by the presence of delayed perfusion (Tmax of 16-22 s) rather than with a shorter perfusion delay (Tmax ≤10). In addition, collateral circulation can be easily visualized by simple postprocessing using the source data of dynamic susceptibility contrast MRI. A simple semi-automatic collateral map technique (Rapid Analysis System for the Collateral Program [FASTColl]) using perfusion scan source data have implemented to assess collateral levels in acute ischemic stroke. A good correlation was observed between MRI and conventional angiographic based collateral assessment systems. These techniques have the advantage that information about collateral status can be directly compared with MR diffusion and perfusion images, and there is no need for additional acquisition of conventional angiography or MRI dedicated to collateral assessment.16,17

**Arterial Spin Labelling MRI**

Arterial spin labeling (ASL) is a non-contrast perfusion imaging method for measuring cerebral blood flow that depends on magnetic labeling of water in the blood component. ASL is a promising technique for collateral flow assessment that can provide various types of information about collateral status. With ASL, late-flowing appears as a serpiginous high ASL signal in cortical vessels, called arterial transit artifacts. Patients with arterial transit artifacts have an increased outcome, indicating that this signal can represent collateral flow. In addition, flow direction–sensitive phase contrast MR angiography (MRA) and vessel-encoded arterial spin labeling could noninvasively provide information about the origins and distal function of collateral flow comparable with that obtained with conventional angiograms. 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. Disadvantages of this technique is 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.18,19

**Conclusion**

In patients with acute stroke, reperfusion after cerebral ischemia can be achieved via collaterals or through arterial revascularization. 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.

For patients with acute ischemic stroke with cervicocerebral arterial occlusion who
receive recanalization therapies, the pretreatment cerebral collateral status possesses significant prognostic values for the outcomes. Based on current evidence, assessment of the collateral status and infarct core helps identify patients who will benefit from such treatment, especially among those presenting beyond 6 hours after symptom onset.

References

