

Improving Collateral Circulation: A Potential Adjunctive Strategy to Prevent or Slow the Progression of Vascular Dementia

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Abstract: Vascular dementia (VaD), a cognitive disorder caused by cerebrovascular pathologies, is the most common cause of dementia in the elderly, being second only to Alzheimer's disease. Researches have shown that adequate cerebral blood flow (CBF) is the first condition for maintaining the structural integrity and normal function of the brain, and VaD is generally considered to be resulted from neuronal loss due to reduced CBF. Collateral circulation, a compensation mechanism for CBF, provides an alternative vascular pathway for blood to reach ischemic tissues, which has been confirmed to be associated with better clinical outcomes of ischemic diseases. At present, considerable effort has been devoted to enhancing the functional prognosis of acute ischemic stroke by improving collateral circulation. Since ischemic stroke is the primary contributor to VaD, it is necessary to explore whether improving collateral circulation is beneficial to prevent or slow the progression of VaD. This article reviews the compensatory characteristics of different levels of cerebral collateral circulation, addresses the relationship between collateral circulation and VaD, and highlights that improving collateral circulation may be a potential adjunctive strategy in preventing and slowing the progression of VaD.

Keywords: vascular dementia, cerebral blood flow, collateral circulation, pathology, precaution, palliation

Introduction

Vascular dementia (VaD), a term used to describe neurocognitive disorder, is widely regarded as a major contributor to the dementia after Alzheimer's disease.¹ Epidemiology shows that VaD accounts for at least 20% of dementia cases worldwide, and even reaches 30% in Asia and developing countries.² VaD results from different vascular etiologies such as cerebral atherosclerosis/artery damage, thrombosis, vascular stenosis, or occlusion, which damage blood vessels in the brain and reduce cerebral blood flow (CBF), leading to secondary focal neuronal injury and tissue loss.³ Although the human brain is only 2–3% of the body mass, its metabolism is vigorous, consuming up to 20% of the total amount of oxygen and glucose contained in the blood.^{4,5} However, the amount of adenosine triphosphate stored in the brain is limited, so it must rely on the oxygen and nutrients delivered by the CBF to produce energy.^{6,7} When chronic hypoperfusion occurs in brain tissue, the rapid decline of CBF causes ischemia, hypoxia, and a series of injuries: (1) Hypoxia-induced oxidative stress leads to mitochondrial dysfunction, which directly damages neurons.⁸ (2) Oxidative stress also causes an imbalance in the ratio of

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antioxidants and reactive oxygen species to damage vascular endothelium, glial and neurons, which leads to endothelial dysfunction, neurovascular decoupling, induced thrombosis and vasospasm, eventually narrowing the blood vessels and further reducing CBF.^{8,9} (3) Chronic cerebral hypoperfusion (CCH) is extremely prone to damage the periventricular white matter (WM), basal ganglia and hippocampus, leading to cognitive impairment.¹⁰ In summary, the continuous reduction of CBF aggravates cerebral ischemia-hypoxic damage, leads to neuronal death and cognitive decline, and ultimately contributes to the occurrence and development of VaD.¹¹ Therefore, adequate CBF is a primary condition for maintaining the structural integrity and normal function of the brain,⁷ and improving CBF may be an effective strategy for the prevention and treatment of VaD.

Collateral circulation is defined as a subsidiary network of vascular channels that provide nutrient perfusion to ischemic areas when the principal conduits cannot stabilize CBF.¹² In recent years, there has been accumulating evidence that collateral circulation is associated with the protection of ischemic brain injury.^{13–15} Enhancing collateral perfusion as an adjunctive strategy combined with thrombolysis and endovascular interventions is considered to play a potentially important role in the treatment of acute ischemic stroke.¹⁶ As we all know, ischemic stroke (IS) is a major risk factor for VaD, and its incidence impairs cognitive function.¹⁷ However, the benefits of collateral blood flow in cognitive function are not fully understood, so few studies have focused on its effect on VaD. In this review, we summarize the relationship between collateral circulation and the common pathological or pathophysiological conditions in the course of VaD, and concentrate on the potential contribution of improving collateral circulation in preventing and slowing the progression of VaD.

Different Levels of Collateral Circulation and Its Compensation Characteristics

Collateral circulation in the brain is usually divided into primary routes, ie, the Circle of Willis, secondary routes, eg, collaterals from the external to the internal carotid artery and leptomeningeal collaterals,¹⁸ and tertiary routes, eg, arteriogenesis and angiogenesis.¹⁹ The Circle of Willis, as the main form of arterial compensation, provides immediate diversion of CBF to ischemic regions through existing anastomoses, which generally occurs after the sudden thrombotic occlusion of the internal carotid artery.²⁰ However,

substantial variability exists in the size and degree of completeness of the Circle of Willis, and a complete circle is only in 42–52% of population.²¹ Secondary collaterals are presumed to be recruited once primary collaterals at the circle of Willis is insufficient to meet the need; for example, in the case of embolic occlusion of the middle cerebral artery, leptomeningeal anastomoses become the principal alternative pathways to supply blood flow.²² If the secondary compensation is still insufficient, arteriogenesis and angiogenesis may begin to operate. Arteriogenesis can compensate for CBF not only acting in time but also more efficiently compared to angiogenesis that occurs in a delayed fashion, while increases the total resistance of the vascular bed of the affected territory.²³

Relevance of the Collateral Circulation to VaD Collateral Circulation and Atherosclerosis

Different from a single disease, VaD is a group of conditions with different pathological correlates, which involve different forms of cerebrovascular diseases, mainly including macrovascular diseases, and small vessel diseases (SVD).²⁴ Atherosclerotic stenosis of large arteries causes macroinfarction, infarction of major arterial territories due to atherosclerotic thromboembolism and induces major stroke, while lacunar infarcts, microinfarcts and WM hyperintensities are mostly explained by progressive SVD.³ Atherosclerosis of the large arteries or SVD accounts for most of the burden of VaD and affects cognitive function.^{25,26} A recent cross-sectional study provides more evidence of a positive correlation between intracranial atherosclerotic stenosis and cognitive impairment after stroke.²⁷ Collateral circulation may counteract the potentially adverse effects of stenosis. In the study of systematic evaluation of collaterals on angiography in Warfarin–Aspirin Symptomatic Intracranial Disease, it was found that collateral circulation is often observed with intracranial atherosclerosis at varying extents, and the extent of collateral flow is correlated with the percentage of stenosis, with more severe stenoses exhibiting greater compensation via collaterals.²⁸ In another retrospective cohort study of patients with symptomatic intracranial stenosis and compromised antegrade flow, the results of composite flow assessment also showed that good collateral circulation was associated with favorable neurological outcomes.²⁹

Collateral Circulation and CCH

CCH, caused by SVD and atherosclerosis, is regarded as a major factor leading to cognitive decline and the degenerative process of VaD.³⁰ In essence, CCH deprives oxygen and nutrients, ultimately leading to synaptic dysfunction and neuronal degeneration/loss.³¹ CCH may stimulate the recruitment and regeneration of collateral circulation. In rats with bilateral common carotid artery occlusion, CCH promoted angiogenesis that paralleled recovery of blood flow in the later stage (from 4 to 6 weeks) of surgery.³² Ipsilateral leptomeningeal collateral growth was observed in normotensive rats with unilateral common carotid artery occlusion.³³ Furthermore, clinically, due to CCH, cervical atherosclerosis may promote more extensive collateral circulation in patients with IS.^{34,35} Effective collateral flow in carotid atherosclerotic stenosis patients was associated with the normalisation of territory arterial spin labelling perfusion territory after carotid endarterectomy.³⁶

Collateral Circulation and Hemodynamic Impairment

Hemodynamic impairment is an important sign of cognitive decline and plays an important role in the process of VaD.³⁷ A meta-analysis of transcranial Doppler studies on cerebrovascular hemodynamics in VaD showed that hemodynamics in patients with VaD had a significant disturbance, compared with healthy elderly subjects.¹¹ Collateral circulation has a significant influence on hemodynamic status.³⁸ In the case of symptomatic intracranial atherosclerotic stenosis, the fractional flow at the lesion in patients with poor collateral circulation was associated with the percentage of stenosis at the lesion, and conversely, with good collateral circulation was not related to the percentage of stenosis.³⁹ In addition, improvement of collateral blood flow contributed to the improvement of increased oxygen extraction fraction in patients with carotid occlusion and no interval stroke during the hemodynamic impairment.⁴⁰

Collateral Circulation and WM Lesions

Diffuse and focal WM lesions are a feature of VaD, which involves myelin loss, axonal abnormalities, arteriolosclerosis, and parenchymal changes resulting from lacunar infarcts, microinfarcts, microbleeds and perivascular spacing.^{41,42} Diffuse and focal WM changes are described in neuroimaging as WM hyperintensities

(WMH) on T2-weighted MRI or leukoaraiosis (LA) on computed tomography.⁴³ LA typically affect the prefronto-subcortical circuits, which may be responsible for some of the cognitive deficits usually associated with executive function.⁴⁴ Poor collateral circulation of periventricular WM combined with diffuse cerebral ischemia seems to be the cause of LA, and poor recruitment of collaterals is also associated with WMH.^{45,46} Studies have shown that the severity of LA is linked to poor collateral grade, and good collateral grade is independently associated with reduced LA volume.⁴⁷

Collateral Circulation and Cognitive Dysfunction

The cognitive dysfunction of VaD is usually manifested as memory loss, attention, executive dysfunction, and so on.⁴⁸ The regulation of CBF may affect cognitive function.⁴⁹ Despite collateral circulation compensated for reduced CBF, its effect on cognitive function remains controversial.^{50,51} Recent studies have shown Prostaglandin E1 treatment can enhance CBF recovery in CCH by dilating blood vessels and sustaining angiogenesis, which is associated with the alleviation of cognitive impairment in bilateral CCA occlusion rats.⁵² Chronic remote limb ischemic conditioning may improve long-term CBF and long-term cognitive and motor functions by inducing angiogenesis and collateral remodeling.⁵³ In addition, a prospective cohort, cross-sectional, single-center study provided more evidence that, during the two-year follow-up period, patients who had severe middle cerebral artery stenosis with “moderate” and “poor” leptomeningeal collateral status had function impairment in at least one cognitive domain, but for patients with “good” leptomeningeal collateral status, the cognitive function was not significantly affected.⁵⁴ Another clinical study has reported that anterior communicating artery collaterals may benefit the selective attention function of patients with severe internal carotid artery.⁵⁵

Potential Contribution of Improving Collateral Circulation in the Course of VaD

Good Prognosis of IS Reduces the Risk of VaD

Stroke can increase the risk of VaD that has been widely discussed.⁵⁶ IS, a typical risk factor for VaD, accounts for 87% of all strokes worldwide.⁵⁷ There is evidence that 25–30% of IS survivors will develop VaD immediately (within

three months after stroke) or delayed (more than three months or after recurrent stroke).⁵⁸ So, the prevention and management of IS are obviously expected to reduce the burden of VaD. At present, studies have confirmed that good collateral circulation can prolong the treatment time window of IS by slowing the loss of penumbra tissue, and decrease the risk of hemorrhagic transformation.⁵⁹ Collateral circulation may also help in delivering more tissue plasminogen activator to the position of occlusion, resulting in improved recanalization.⁶⁰ Furthermore, collateral circulation has been shown to be an important determinant of cortical infarct volume, and good or better collateral circulation can alleviate the injury of hypoperfusion and reduce the infarct volume.^{61,62} Therefore, pretreatment of the collateral state is conducive to maintain the penumbra before recanalization, inhibit the growth of the infarct core area and increase the success rate of recanalization to enhance the prognosis of IS to prevent IS from inducing VaD.^{13,63,64}

Improvement of Pathological Conditions Slows the Progression of VaD

So far, there are still no FDA approved treatment options for VaD. Although measures such as blood vessel expansion, anti-

thrombosis, anti-platelet aggregation, anti-oxidation, and enhancement of cholinergic have shown a certain extent of therapeutic effect, they are far from satisfying the needs of patients.⁶⁵ A review of the above-mentioned convincing literature undoubtedly shows that collateral circulation is strongly associated with atherosclerosis, CCH, hemodynamic impairment, WM lesions and cognitive dysfunction, which are common in the pathophysiology of VaD. Not only that, it also suggests that good collateral circulation may have a positive effect on the fate of these typical pathological conditions of VaD. Therefore, we speculate that enhancing collateral circulation may slow the progression of VaD via improving related pathological states and promoting CBF recovery to protect neurons and cognitive function. There is evidence that in the case of reduced tissue perfusion, inhalation of nitric oxide improves collateral blood flow by dilating cerebral resistance vessels, thereby significantly reducing ischemic brain injury and transforming into significantly improved neurological outcomes.⁶⁶ Of course, merely enhancing collaterals may not be enough to completely save neuron loss and cognitive deficits after permanent ischemia. It may be used as an auxiliary strategy, combined with other strategies to produce cumulative effects in a synergistic form of treatment.

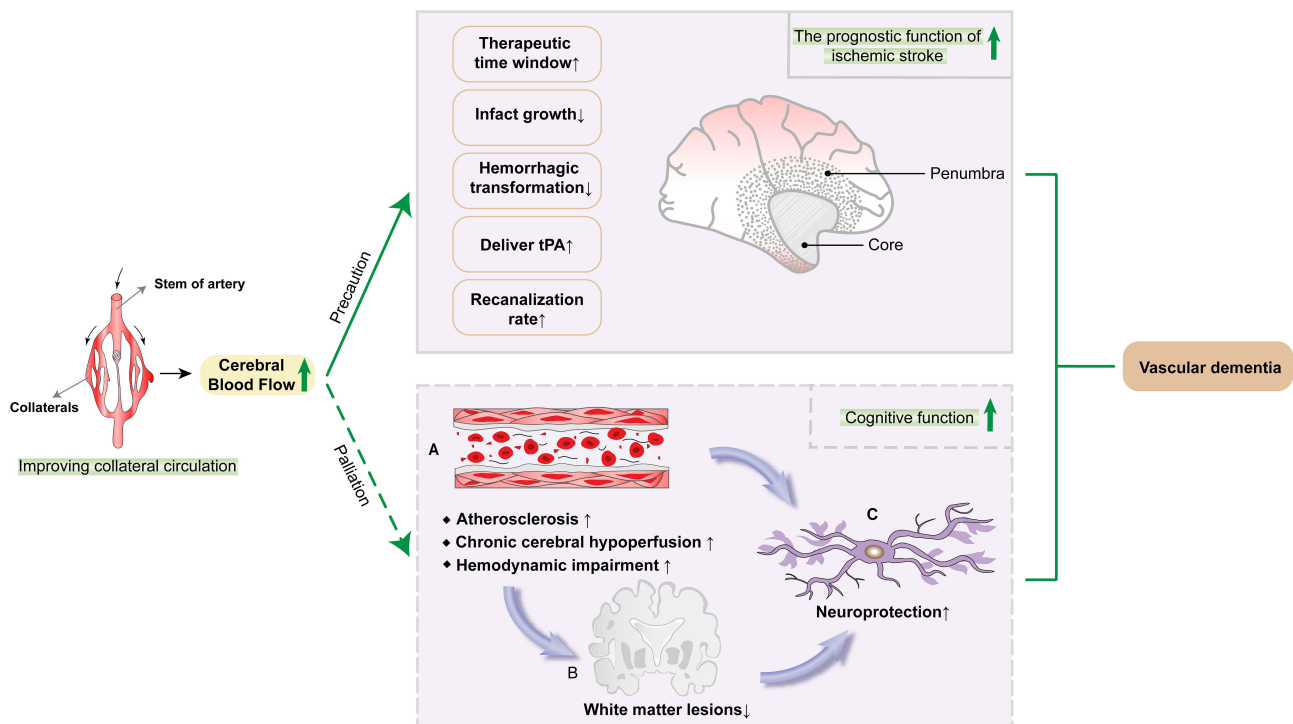


Figure 1 Improving collateral circulation contributes to preventing or slowing the progression of vascular dementia (VaD). On the one hand, improving collateral circulation can prevent VaD via compensating cerebral blood flow and enhancing the prognostic function of ischemic stroke, which involves prolonging the reperfusion treatment time window, reducing the infarct core volume, decreasing the risk of hemorrhagic transformation, delivering more tissue plasminogen activator, and increasing recanalization rate. On the other hand, enhancing collateral circulation can compensate cerebral blood flow to eliminate the adverse effects of atherosclerosis, chronic cerebral hypoperfusion and hemodynamic disorders, reduce white matter lesions, protect neurons, improve cognitive function, and slow the progression of VaD.

Conclusions and Perspectives

Collateral enhancement may not only prolong the reperfusion treatment time window of IS but also improve the therapeutic effect of thrombolytic drugs or intravascular intervention, thereby reducing the risk of IS developing into VaD; it may also reduce the contribution of atherosclerosis, CCH, hemodynamic damage, WM changes, and cognitive dysfunction to VaD (Figure 1). At present, some pharmacological or non-pharmacological interventions have also been developed to improve collateral circulation, such as inhaled nitric oxide,⁶⁶ statins pretreatment,⁶⁷ TAO⁶⁸ and RIPC.⁶⁹ At the same time, the discovery of related targets that promote collateral circulation or induce natural collateral remodeling (eg endocan⁷⁰ and PEDF⁷¹) has expanded the range of strategies to enhance collateral circulation. Considering the chronic development time frame of VaD, efforts are also needed to explore more collateral improvement strategies. More importantly, it is necessary to carefully design reasonable and rigorous trials to determine the contribution threshold of improving collateral circulation combined with other neuroprotective strategies to prevent and slow the progression of VaD.

Abbreviations

VaD, vascular dementia; CBF, cerebral blood flow; CCH, chronic cerebral hypoperfusion; WM, white matter; IS, ischemic stroke; SVD, small vessel diseases; WMH, white matter hyperintensities; LA, leukoaraiosis; TAO, transient aortic occlusion; RIPC, remote ischemic postconditioning; PEDF, pigment epithelium-derived factor.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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