Mini Review **Open Access**

Ophthalmic Artery Flow and Cognitive Performance in Patients with Carotid Artery Stenosis

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Abstract

The circle of Willis is regarded as the primary collaterals in patients with severe carotid artery stenosis (CAS), while the secondary collaterals from the reversed ophthalmic artery (OA) flow would be recruited when the primary collaterals are inadequate to maintain cerebral perfusion. Even though some reports suggest patients with reversed OA flow are more vulnerable to cerebral ischemic injury, whether reversed OA flow is adequate to maintain cognitive function or can be employed as a surrogate marker of cognitive impairment remains elusive. The purpose of this article is to review the dynamic behavior of collateral flow and to assess the relationship between OA hemodynamics, cerebral perfusion and cognitive performance in patients with CAS.

There is evidence that the OA flow patterns behave dynamically according to the hemodynamic, metabolic, and neural demands. Patients with reversed OA flow have compensatory increased cerebral blood volume and time-related perfusion parameters, while cerebral blood flow usually remains unchanged. Despite of the evidence having been scarce, the associations between hemodynamics of OA flow and cognitive performance have been observed in several recent studies. Furthermore, our previous study demonstrated a tendency for specific cognitive impairment observed in patients with reversed OA flow, depending on the side of reversed OA flow. However, the impacts of the OA flow patterns on cognition may be modified when the other pathogenic factors of stroke are taken into account. Concurrent application of multimodality neuroimaging findings about perfusion status and neural activities will greatly enhance our understanding of the relationships between the hemodynamics of OA flow and cognition.

Keywords: Carotid artery stenosis; Ophthalmic artery; Cognitive function

Abbreviations: CAS: Carotid Artery Stenosis; OA: Ophthalmic Artery; CT: Computed Tomography; CBF: Cerebral Blood Flow; MR: Magnetic Resonance; PCoA: Posterior communicating artery; TTP: Time-to-Peak; CBV: Cerebral Blood Volume; OEF: Oxygen Extraction Fraction

Introduction

Carotid artery stenosis (CAS) is a common finding in the atherosclerosis process. In patients with severe CAS, cerebral perfusion insufficiency not only contributes to the occurrence of ischemic stroke [1], but also insidiously leads to neural disruption and cognitive impairment [2,3]. However, the clinical outcome for patients with CAS cannot be determined by the severity of CAS alone [4] and the collateral circulation also plays a pivotal role in the pathophysiology of cerebral ischemia and cognitive impairment [5]. In patients with severe CAS, the establishment of primary collateral flow is reported to reduce the risk of ischemic stroke [6,7], whereas ophthalmic artery (OA) and leptomeningeal vessels that constitute the secondary collaterals will be recruited when the primary collaterals are insufficient to maintain adequate cerebral perfusion [8,9]. Among these anastomotic connections, reversed OA flow, which can be measured non-invasively by Doppler ultrasound, usually develops in patients with CAS as a steal phenomenon [9]. The prevalence of reversed OA flow ranges from 17.3% to 76% in patients with CAS, especially when there is carotid artery occlusion, high-grade stenosis in bilateral carotid arteries, or a concomitant intracranial artery stenosis [4,9,10].

However, there is controversy about whether the recruitment of secondary collaterals may serve as a protective mechanism or a marker of insufficient overall cerebral perfusion. Previous studies have shown that the presence of secondary collaterals may indicate insufficient collateral blood flow via the circle of Willis with an increased risk of cerebral ischemia. Hu et al. [11] reported more subsequent cerebral ischemic stroke could be seen in patients with reversed OA flow than those with forward OA flow, especially in asymptomatic patients. Cheng et al. [12] found patients with signs of recruiting secondary collaterals had worse cerebral hemodynamic profiles on computed tomography (CT) perfusion imaging compared to those patients only with signs of recruiting primary collaterals from the circle of Willis. Hofmeijer et al. [13] revealed in symptomatic carotid artery occlusion, patients recruiting Willisian collaterals plus reversed OA flow or leptomeningeal collaterals may have a worse vascular reactivity than those with Willisian collaterals alone. The above results suggest patients with reversed OA flow may be more vulnerable to subsequent cerebral ischemic events than those with forward OA flow. On the other hand, the presence of reversed OA flow can supply more blood flow to the brain in patients with unilateral carotid artery stenosis/ occlusion [14] and the intracranial arterial flow velocity and cerebral blood flow (CBF) are maintained symmetrically between the bilateral cerebral hemispheres [12,15]. After carotid revascularization, profound improvement in cerebral hemo dynamics can be reconstituted within a

few days with the normalization of OA flow in patients with reversed OA flow [15,16].

Carotid artery stenosis may cause cerebral hypo perfusion, cerebral ischemia, and leukoaraiosis, which have long been implicated in cognitive impairment [17]. Restoration of cerebral perfusion by carotid revascularization can reduce the severity of leukoaraiosis [18]. Although the OA flow direction is sensitive to the overall cerebral perfusion condition, whether the reconstitution of cerebral perfusion through reversed OA flow is adequate to maintain cognitive function or can be employed as a surrogate marker of cognitive impairment remains elusive. The purpose of this article is to review the dynamic behavior of collateral flow and to assess the relationship between OA hemo dynamics, cerebral perfusion, and cognitive performance in patients with CAS. Better understanding the underlying mechanisms of collateral flow formation would help interpret their influence on clinical and cognitive outcome.

Dynamic Behavior of Collateral Flow after Carotid Revascularization

The circle of Willis is considered to behave in a dynamic manner. In our previous study, 23 of 65 (35%) patients with symptomatic CAS had a significantly altered flow pattern in the circle of Willis on the magnetic resonance (MR) angiography after carotid artery stenting [19]. In summary, segments in the circle of Willis were opened preoperatively but blocked after carotid revascularization in 14 patients, whereas other segments of the circle of Willis were closed initially but reopened postoperatively in 9 patients, leading to the reorganization of Willisian collateralization. The opening and closing of Willisian segments suggests Willisian collaterals may be remodeled in response to carotid revascularization either to relieve the reperfusion pressure or to perfuse the hypo perfused areas. This plasticity of the circle of Willis can be also observed in the anastomotic connections of OA.

Our previous study of OA flow direction, Chin et al. [16] showed that in 78 patients with unilateral CAS, reversed OA flow all returned to forward OA flow within one week after carotid revascularization. Furthermore, patients with reversed OA flow had greater improvement in the perfusion parameter of time-to-peak (TTP) than patients with forward OA flow. More recently, we have also demonstrated that in the 116 patients with unilateral CAS, 42 patients with reversed OA flow were found to have more severe ipsilateral CAS, higher hemoglobin level, and larger cardiac output [15]. After carotid revascularization, the reversed OA flow was normalized to forward flow immediately with recovery of Doppler flow volume in the ipsilateral carotid artery.

Ophthalmic Artery Flow and Cerebral Blood Flow

Cerebral hypo perfusion is one of main clinical manifestations in patients with severe CAS, and can be measured directly by various imaging techniques, such as CT perfusion [12,16,20], MR perfusion [14,21,22], single photon emission computed tomography [23], and positron emission tomography [24,25] imaging. In patients with mildly decreased cerebral perfusion pressure, the overall cerebral perfusion can be maintained by autoregulatory mechanisms; the cerebral blood volume (CBV), TTP and even oxygen extraction fraction (OEF) are gradually increased while the CBF remains unchanged or slightly decreased [26]. Even though the primary collaterals can rapidly compensate for cerebral hypo perfusion, secondary collaterals would be recruited when the primary collaterals are inadequate to maintain brain perfusion.

The detection of reversed OA flow is accessible on clinical transcranial ultrasound examination. With regard to the influence of reversed OA flow on cerebral perfusion, some studies suggest that recruitment of secondary collaterals can protect the brain against further ischemic injury by augmenting blood supply [14,21,27], while others regard secondary collaterals as a marker of insufficient overall cerebral perfusion [4,13,24,28]. The presence of reversed OA flow is beneficial to regional CBF supply in patients with symptomatic unilateral carotid artery occlusion [14]. On the contrary, Yamauchi et al. reported that the presence of reversed OA flow in patients with carotid artery occlusion was a significant predictor of increased OEF, indicating inadequate collateral blood flow distal to the occlusion lesion [28]. Furthermore, patients with reversed OA flow are more vulnerable to impaired vasoreactivity than patients without reversed OA flow [13]. Cheng et al. [12] adopted CT perfusion to investigate the influence of reversed OA flow on various perfusion profiles. They found that the relative CBF did not significantly differ between patients with and without reversed OA flow, but the relative CBV and TTP were increased in patients with reversed OA flow. Increased CBV and prolonged TTP reflect the effect of auto regulated vasodilatation, longer perfusion distance and smaller vessel diameter of collateral pathways and the ability to maintain symmetric CBF suggests adequacy of these compensatory mechanisms. These findings lend support for our previous observation that while there was no post-revascularization change in CBF, patients with reversed OA flow were found to have greater TTP improvement in both middle and posterior cerebral artery territories than patients with forward OA flow after carotid revascularization [16].

The influence of reversed OA flow on cerebral perfusion can be evaluated directly by the brain perfusion imaging as well as indirectly by Doppler ultrasound examination of cervicocranial vessels. Our recent report by Liu et al. [15] has shown that there is regional flow compensation with increased flow volume in the ipsilateral external carotid artery and contralateral internal carotid artery, and a systematic hemodynamic compensation with increased hematocrit and cardiac output in patients with reversed OA flow. Although cerebral perfusion scanning was not conducted in this study, the time average velocity of all the insonated intracranial arteries in patients with reversed OA flow was similar to that in patients with forward OA flow. In summary, although the occurrence of reversed OA flow is subject to insufficient primary collaterals, CBF could still be maintained by auto regulation in most cases with reversed OA flow [26].

Ophthalmic Artery Flow and Cognitive Performance

Carotid artery stenosis is one of the atherosclerosis markers to distinguish ischemic stroke subtypes [29]. In addition to the marker of stroke risk, patients with asymptomatic CAS are found to have a higher proportion of silent magnetic resonance imaging lesions as well as cognitive impairments, including poor performance on attention, psychomotor speed, memory, and motor functioning [30]. Alteration of cerebrovascular reactivity due to cerebral hypoperfusion may be responsible for the reduction in some cognitive abilities involving the function of the hemisphere ipsilateral to CAS [31]. Since cerebral hypo perfusion can be implicated in cognitive impairment in patients with CAS, it is possible that the hemodynamic patterns of OA may be associated with cognitive impairment.

Several reports have been elucidating the influence of OA flow patterns on cognitive performance. Grima et al. [32] found a significant association between hemodynamics of OA flow and cognitive decline in patients with HIV infection, and pathological OA resistance index

seems to reflect diminished arterial compliance caused by systemic atherosclerosis and hemodynamically significant lesions distal to carotid bifurcation. In our previous report, Huang et al. [33] examined 102 patients with severe CAS by allocating these patients into four groups according to the side of CAS and OA flow direction. All patient groups performed worse than the control group on most tests. Interestingly, the characteristics of cognitive performance in each patient group also revealed a predilection for specific cognitive impairment depending on the side of reversed OA flow; patients with right reversed OA flow performed significantly worse on the visuospatial, executive, verbal memory, and category fluency tests, whereas patients with left reversed OA flow had worse scores of fluid intelligence, verbal memory, and executive function. However, when hierarchical regression analyses were applied to disentangle the associations between the cognitive performance and relevant factors, the contribution of reversed OA flow to cognitive performance became negligible when the estimated premorbid intelligence, the degree of CAS, and infarct severity on imaging were taken into account. Despite of the fact that reversed OA flow is a significant marker of insufficient primary collaterals, the lack of significant association between reversed OA flow and cognition under more sophisticated analyses has an important clinical and pathological implication. Reversed OA flow is an indirect marker of insufficient cerebral collateral blood supply and is not necessarily suggestive of critical cerebral hypo perfusion in all patients with CAS. Indeed, compared to the direction of OA flow, regional CBF is more directly related to neuronal vitality and cognitive performance [3,34,35]. In patients with reversed OA flow, CBF is usually maintained stable by auto regulation mechanisms [12,26]. Although there is significant improvement in cerebrovascular reactivity and time-related perfusion parameters after carotid revascularization, no significant change in CBF is observed in CAS patients with reversed OA flow [16,23]. Since reversed OA flow is associated with a higher risk for cerebral ischemia and worse CAS severity, the influence from the other risk factors should always be taken into account when looking at the interaction between OA flow and cognitive performance.

Conclusion

Patients with CAS are found to have impaired cerebral perfusion and increased leukoaraiosis, which may result in cognitive impairment. The presence of reversed OA flow is associated with more severe CAS and can be regarded as a sign of inadequate primary collaterals. However, the influence of reversed OA flow on cognitive performance is limited once the overall cerebral hypo perfusion is in the amendable range by auto regulatory mechanism. Although carotid revascularization can lead to immediate normalization of OA flow and subsequent cognitive benefits, whether the presence of reversed OA flow can be a marker for post-revascularization cognitive changes and clinical outcome requires further investigation in the future.

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