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

Kuo Lun Huang1,2*, Meng Yang Ho1,2 and Tsong-Hai Lee1,2*
1Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
2College of Medicine, Chang Gung University, Taoyuan, Taiwan
3Clinical Psychology Program, c/o Department of Occupational Therapy, Chang Gung University, Taoyuan, Taiwan

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 prediction 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 hypoperfusion 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 leuкоaeroidization, 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 hypoperfusion is in the amenable 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.

Acknowledgement

This study was carried out under the grants from Ministry of Science and Technology, Taiwan (Grants MOST 105-2314-B-182A-009 and 103-2410-H-182-002-MY2), and Research Fund of Chang Gung Memorial Hospital (CMRPG3E2131, CMRPG3F2181, CMRPG3F2211, BMRP274 and BMRP611).

References

1. Momjian-Mayor I, Baron JC (2005) The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. Stroke 36: 567-577.
2. Cheng HL, Lin CJ, Soong BW, Wang PN, Chang FC, et al. (2012) Impairments in cognitive function and brain connectivity in severe asymmetric carotid stenosis. Stroke 43: 2567-2573.
3. Wang T, Xiao F, Wu G, Fang J, Sun Z, et al. (2017) Impairments in brain perfusion, metabolites, functional connectivity, and cognition in severe asymmetric carotid stenosis patients: An Integrated MRI Study. Neural Plast 2017: 8738714.
4. Tsai CL, Lee JT, Cheng CA, Liu MT, Chen CY, et al. (2013) Reversal of ophthalmic artery flow as a predictor of intracranial hemodynamic compromise: Implication for prognosis of severe carotid stenosis. Eur J Neurol 20: 564-570.
5. Altinbas A, Hendrikse J, Algra A, van Zandvoort MJ, Brown MM, et al. (2014) Ipsilateral foetal-type posterior cerebral artery is associated with cognitive decline after carotid revascularisation. BMC Neurol 14: 84.
6. Hendrikse J, Hartkamp MJ, Hillen B, Mali WP, van der Grond J (2001) Collateral ability of the circle of Willis in patients with unilateral internal carotid artery occlusion: Border zone infarcts and clinical symptoms. Stroke 32: 2768-2773.
7. Hoksbergen AW, Legemate DA, Csiba L, Csági G, Siro P, et al. (2003) Absent collateral function of the circle of Willis as risk factor for ischemic stroke. Cerebrovasc Dis 16: 191-198.
8. Drakou AA, Koutsiasia AG, Tachmitzi SV, Roussas N, Tsiorni E, et al. (2011) The importance of ophthalmic artery hemodynamics in patients with atherosomatic carotid artery disease. Int Angiol 30: 547-554.
9. Costa VP, Kuzniec S, Molnar LJ, Cerri GG, Puech-Leao P, et al. (1998) Collateral blood supply through the ophthalmic artery: A steal phenomenon color by doppler imaging. Ophthalmology 105: 689-693.
10. Rutgers DR, Klijn CJ, Kapelle LJ, van Huffelen AC, van der Grond J (2000) A longitudinal study of collateral flow patterns in the circle of Willis and the ophthalmic artery in patients with a symptomatic internal carotid artery occlusion. Stroke 31: 1913-1920.
11. Hu HH, Wang S, Chem CM, Yeh HH, Sheng WY, et al. (1995) Clinical significance of the ophthalmic artery in carotid artery disease. Acta Neurol Scand 92: 242-246.
12. Cheng XQ, Tian JM, Zuo CJ, Liu J, Zhang Q, et al. (2012) Quantitative perfusion computed tomography measurements of cerebral hemodynamics: Correlation with digital subtraction angiography identified primary and secondary cerebral collaterals in internal carotid artery occlusive disease. Eur J Radiol 81: 1224-1230.
13. Hofmeijer J, Klijn CJ, Kapelle LJ, Van Huffelen AC, Van GJ (2002) Collateral circulation via the ophthalmic artery or leptomeningeal vessels is associated with impaired cerebral vasoreactivity in patients with symptomatic carotid artery occlusion. Cerebrovasc Dis 14: 22-26.
14. van Laar PJ, van der Grond J, Bremmer JP, Klijn CJ, Hendrikse J (2008) Assessment of the contribution of the external carotid artery to brain perfusion in patients with internal carotid artery occlusion. Stroke 39: 3003-3008.
15. Liu CH, Chang CH, Chang TY, Huang KL, Lin JR, et al. (2015) Carotid artery stenting improves cerebral hemodynamics regardless of the flow direction of ophthalmic artery. Angiology 66: 180-186.
16. Chin SC, Chang CH, Chang TY, Huang KL, Wu TC, et al. (2012) Brain computed tomography perfusion may help to detect hemodynamic reconstitution and predict intracerebral hemorrhage after carotid stenting. J Vasc Surg 56: 1281-1290.
17. Sztriha LK, Nemeth D, Sefcik T, Vecsei L (2009) Carotid stenosis and the cognitive function. J Neurol Sci 283: 36-40.
18. Chang YM, Huang KL, Chang YJ, Chang CH, Chang TY, et al. (2011) Immediate regression of leukoaraiosis after carotid artery revascularization. Cerebrovasc Dis 32: 439-446.
19. Chang YM, Lin CP, Wong HF, Chang YJ, Chang CH, et al. (2009) Plasticity of circle of willis: A longitudinal observation of flow patterns in the circle of willis one week after stenting for severe internal carotid artery stenosis. Cerebrovasc Dis 27: 572-578.
20. Chen YH, Lin MS, Lee JK, Chao CL, Tang GC, et al. (2012) Carotid stenting improves cognitive function in asymptomatic cerebral ischemia. Int J Cardiol 157: 104-107.
21. Bokkers RP, van Laar PJ, van de Ven KC, Kapelle LJ, Klijn CJ, et al. (2008) Arterial spin-labeling MR imaging measurements of timing parameters in patients with a carotid artery occlusion. AJNR Am J Neuroradiol 29: 1698-1703.
22. Kluytmans M, van der Grond J, van Everdingen KJ, Kapelle LJ, Kappelle JJ, et al. (1999) Cerebral hemodynamics in relation to patterns of collateral flow. Stroke 30: 1432-1439.
23. Ishihara H, Oka F, Shirao S, Kato S, Sadahiro M, et al. (2009) Cognitive outcome differences on the side of carotid artery stenting. J Vasc Surg 57: 125-130.
24. Derdeyn CP, Shaibani A, Moran CJ, Cross DT, Grubb RL, et al. (1999) Lack of correlation between pattern of collateralization and misery perfusion in patients with carotid occlusion. Stroke 30: 1025-1032.

25. Kao HL, Lin MS, Wu WC, Tseng WY, Su MY, et al. (2015) Improvement of cerebral glucose metabolism in symptomatic patients with carotid artery stenosis after stenting. Clin Nucl Med 40: 701-707.

26. Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, et al. (2002) Variability of cerebral blood volume and oxygen extraction: Stages of cerebral haemodynamic impairment revisited. Brain 125: 595-607.

27. van Laar PJ, Hendrikse J, Klijn CJ, Kappelle LJ, van Osch MJ, et al. (2007) Symptomatic carotid artery occlusion: Flow territories of major brain-feeding arteries. Radiology 242: 526-534.

28. Yamauchi H, Kudoh T, Sugimoto K, Takahashi M, Kishibe Y, et al. (2004) Pattern of collaterals, type of infarcts, and haemodynamic impairment in carotid artery occlusion. J Neurol Neurosurg Psychiatry 75: 1697-1701.

29. Timait SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, et al. (1992) Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. Stroke 23: 486-491.

30. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, et al. (2004) Reduced neuropsychological test performance in asymptomatic carotid stenosis: The Tromsø Study. Neurology 62: 695-701.

31. Silvestrini M, Paolino I, Vernieri F, Pedone C, Baruffaldi R, et al. (2009) Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. Neurology 72: 1062-1068.

32. Grima P, Fabbiani M, Ciccarelli N, Tana M, Farina S, et al. (2012) Increased ophthalmic artery resistance index is associated with cognitive impairment in HIV-infected patients. J Infect 65: 439-446.

33. Huang KL, Chang TY, Chang CH, Liu HL, Chang YJ, et al. (2014) Relationships between ophthalmic artery flow direction and cognitive performance in patients with unilateral carotid artery stenosis. J Neurol Sci 336: 154-159.

34. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, et al. (2005) Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol 57: 789-794.

35. Rohr L, Oestergaard L, Simonsen CZ, Vestergaard-Poulsen P, Andersen G, et al. (2001) Viability thresholds of ischemic penumbra of hyperacute stroke defined by perfusion-weighted MRI and apparent diffusion coefficient. Stroke 32: 1140-1146.