Chronic Neurovascular Uncoupling Syndrome

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Our current understanding of the blood supply to the human brain has advanced considerably but is far from complete. Although great progress has been made in determining the relationship between neuroglial activity and blood flow, especially in animal models, this relationship is not as well defined in humans, in particular for diseases that cause chronic compromise of the cervicocerebral vasculature. There is no mystery concerning the ischemic consequences to the brain when there is an acute loss in blood flow. However, there is a major gap in our knowledge concerning the effect of chronic vascular insufficiency on the integrity of the brain and the associated functional consequences. C. Miller Fisher in 1954 was the first to report an association between unilateral/bilateral carotid occlusion and senile dementia. Interestingly, the report references a study from Freyhan et al., in which a decrease in cerebral blood flow observed in patients with arteriosclerotic dementia and senile psychosis was thought to be attributable to increased vascular resistance with vascular changes preventing a "compensatory" increase in blood flow. More recently, a study that compared the effect of increased oxygen extraction fraction and cognition in patients who were enrolled in the National Institute of Neurological Disorders and Stroke sponsored Carotid Occlusion Surgery Study found a significant association between increased oxygen extraction fraction and diminished mental function once covariates, including age, education, side of occlusion, depression, and previous stroke, were controlled.

Therefore, it seems that a relationship between hemodynamic insufficiency and diminished brain function in the absence of clinically expressed ischemic events can occur. This raises important questions concerning the cause of the brain dysfunction in these patients. Is it secondary to inadequate delivery of metabolic substrates with functional impairment alone, or does inadequate blood flow actually result in a physical degradation in the structure of the neuropil or glia, such as a reduction in the complexity of neural networks or more drastically glioneuronal loss? If physical injury occurs, then it becomes imperative that the presence of hemodynamic insufficiency is detected before significant loss in neurological function develops.

The mechanism and effects of hemodynamic insufficiency can only be appreciated through assessment of neurovascular coupling. During the last 20 years, the field of functional brain mapping has shown that MRI can view neural activity by measuring signal changes caused by activity-induced modulation in local blood flow. Blood flow secondary to neuronal activation can increase significantly. In one study, a 45% increase above resting levels was observed during visual stimulation, but oxygen consumption increased by only 16%, indicating that far more oxygen is being delivered than is consumed. This has been termed neurovascular uncoupling by many; however, from a medical perspective, this is a misnomer because this difference between blood flow and oxygen consumption during neuronal activation in healthy individuals is a normal observation. Uncoupling infers disease. It would make more sense to refer to the normal condition as functional hyperemia. When disease of the supplying arteries is present, this normal neurovascular relationship can become uncoupled with diminished or absent blood flow augmentation in response to neural activation. The implication in patients with severe cerebrovascular disease is that the ability to increase blood flow in response to neural activity may be significantly diminished. This raises another set of important questions. Is the marked increase in blood flow in response to neural activity a built-in protective mechanism to guard against vascular diseases that impair blood flow? This seems unlikely. A more plausible explanation is that high flows are necessary for supporting the high metabolic activity of the brain in ways that are not yet completely understood. For example, high flow may be necessary for dissipating metabolic heat. What then happens if blood flow fails to increase appropriately during neuronal activation? We know that this condition can exist in asymptomatic patients with severe vaso-occlusive disease. These patients can have elevated levels of oxygen extraction at rest in the absence of acute ischemic injury. The answer to this important question may be that very little, if anything, is happening to the brain over the short term. Although permanent injury may not be occurring acutely, neurons chronically exposed to inadequate flow during activation may begin to deteriorate secondary to repeated stress (thus, the application of the terminology chronic neurovascular uncoupling syndrome to this condition). Occlusion of both common carotid arteries in rats that have survived for several months has shown significant deficits in memory and object recognition (with preservation of locomotor activity). At pathology, neuronal death and reactive gliosis were observed in the hippocampus. Not only was there evidence of neuronal cell death, but also reduced network complexity was observed indicated by decreased dendritic arborization and fewer synapses.
In humans with advanced unilateral steno-occlusive disease of the cervicocerebral vasculature, but without clinical or imaging evidence of previous cerebral infarctions, a relationship between exhaustion of cerebrovascular reserve and cortical thickness has been established. 

Our study in this group of patients found an 8% reduction in cortical thickness in the area showing exhausted cerebrovascular reserve compared with the normal side. Of significance was that the majority of subjects were found to have thinner cortex in the left hemisphere, which is thicker than that in the right hemisphere under normal conditions. Importantly, we found the thinning to be partially reversible after surgical revascularization. 

Additional studies have shown that revascularization can improve cognitive decline as well as cognitive function. Unfortunately, these optimistic reports are counterbalanced by the negative outcome of the Carotid Occlusion Surgery Study (COSS), which showed that External Carotid to Internal Carotid (EC-IC) bypass surgery plus medical therapy compared with medical therapy alone did not reduce the risk of recurrent ipsilateral ischemic stroke at 2 years. This study has been criticized for using positron emission tomography oxygen extraction fraction thresholds that failed to select the highest risk patients for revascularization. This being true, it would seem that bypass surgery was done in some patients who would not have fully benefited from the procedure. As a result, the overall application of bypass surgery in occlusive conditions will likely decline unless additional studies indicate benefits, such as stabilization or reversal of cognitive decline.

The issue, however, is not as simple as the presence or absence of vascular occlusion. Normal blood flow and normal vascular reserve can be seen in the setting of occlusive disease in the presence of sufficient collateral circulation. On the contrary, loss of vascular reserve can be observed without occlusive disease in the setting of high-grade stenosis and limited collateral supply. For a given blood pressure, blood flow is determined by the overall flow resistance in the vascular system. An increase in vascular resistance attributable to steno-occlusive disease can be compensated by means of vasodilatation elsewhere in the vascular system. Because the compensatory mechanism, that is, vascular reserve, has normal physiological limits, the increases in flow resistance attributable to severe steno-occlusive disease without adequate collateral can go uncompensated. Under these conditions, flow in the vascular system becomes blood pressure dependent. This physiology is associated with an increased risk for acute ischemic injury and, as discussed, chronic ischemic injury. The most appropriate way to detect and quantify loss of vascular reserve is through the measurement of blood flow changes during a vasodilatory stimulus, such as hypotension (not used clinically), or potent vasodilators, such as acetazolamide or carbon dioxide. From a practical perspective, the tools that can make these measurements are available, including ultrasound, single-photon emission computed tomography, xenon computed tomography, blood oxygen level-dependent MRI, and arterial spin labeling MRI, but routine clinical application will require a stronger evidence base proving that revascularization in the setting of significant loss in cerebrovascular reserve, and especially in patients with chronic neurovascular uncoupling, improves outcome. Assessment of the efficacy of revascularization techniques to restore neurovascular coupling is also needed. We have repeatedly observed improved vascular reserve, in terms of magnitude and spatial extent after revascularization (Figure 1), as well as restoration restricted only to a small territory within the larger area of cerebrovascular reserve deficit after EC-IC bypass (Figure 2). This emphasizes the importance of mapping spatial extent when assessing the efficacy of a flow restoration procedure. It also calls into question the manner in which these procedures are deemed effective. Failure to improve vascular reserve both in magnitude and extent would potentially expose the patient to continued risk.

Figure 1. Successful revascularization. Moyamoya disease with bilateral cerebrovascular reserve (CVR) deficits. Blue on CVR map represents areas in the brain where blood oxygen level–dependent signal/blood flow decreases with increasing arterial carbon dioxide (steal physiology). CVR normalizes after successful bilateral EC-IC bypass surgery.
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References

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