Cerebrovascular regulation, exercise, and mild traumatic brain injury

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ABSTRACT

A substantial number of people who sustain a mild traumatic brain injury report persistent symptoms. Most common among these symptoms are headache, dizziness, and cognitive difficulties. One possible contributor to sustained symptoms may be compromised cerebrovascular regulation. In addition to injury-related cerebrovascular dysfunction, it is possible that prolonged rest after mild traumatic brain injury leads to deconditioning that may induce physiologic changes in cerebral blood flow control that contributes to persistent symptoms in some people. There is some evidence that exercise training may reduce symptoms perhaps because it engages an array of cerebrovascular regulatory mechanisms. Unfortunately, there is very little work on the degree of impairment in cerebrovascular control that may exist in patients with mild traumatic brain injury, and there are no published studies on the subacute phase of recovery from this injury. This review aims to integrate the current knowledge of cerebrovascular mechanisms that might underlie persistent symptoms and seeks to synthesize these data in the context of exploring aerobic exercise as a feasible intervention to treat the underlying pathophysiology. ***Neurology*®** **2014;83:1665–1672**

GLOSSARY

mTBI = mild traumatic brain injury; **NO** = nitric oxide.

Each year in the United States, as many as 3.8 million individuals sustain a mild traumatic brain injury (mTBI) in sports alone.[1] Furthermore, at least 10% of Iraq/Afghanistan veterans have sustained one or more mTBIs during their military career, and more than a third of them report persistent symptoms.[2] When symptoms persist beyond a month or are present chronically, the cause of these symptoms is likely multifactorial—and comorbidities such as chronic pain, depression, traumatic stress, anxiety, substance abuse, and life stress can mimic or exacerbate these symptoms. It is possible that cerebrovascular dysregulation might underlie initial, subacute, and/or chronic symptoms after mTBI. Moreover, dysregulation could result from the injury itself, or from subsequent deconditioning due to bed rest, or both. Unfortunately, there has been very little research on the degree of impairment in cerebrovascular control that may exist in patients with mTBI, especially in the subacute phase of recovery. This review aims to integrate the current knowledge of cerebrovascular mechanisms that might underlie postacute and chronic symptoms in mTBI and seeks to synthesize these data in the context of exploring aerobic exercise as a feasible intervention to treat the underlying pathophysiology.

Overview. No organ in the body is as dependent as the brain on a steady supply of blood. However, the evolution of the skull to house the brain coupled with 2-legged motion has put fairly complex constraints on the control of cerebral blood flow, and the brain seems to lack the survival advantage of other organs, such as the liver or kidney, that are more tolerant to fluctuations in blood flow. Compensatory mechanisms, however, offset this limited autonomy, ensuring that brain perfusion is well-controlled. These include *neurovascular coupling* to increase flow in response to increased neuronal activity and metabolic demand, *cerebral*

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vasoreactivity to alter flow with changes in carbon dioxide (CO_2) levels, and *cerebral autoregulation* to maintain constant flow despite changing perfusion pressure. Insults to any of these mechanisms may result in impaired cerebrovascular regulation, and might underlie some of the pathophysiologic heterogeneity associated with TBI.

There is some evidence that aerobic exercise training could reduce persistent symptoms by engaging the array of mechanisms for cerebrovascular control. For example, sustained muscle engagement during exercise leads to cortical activation in motor and sensorimotor areas, increasing cerebral metabolism, and thus engaging neurovascular coupling[3] to increase flow. Increased CO_2 production attendant to aerobic exercise is accompanied by greater cerebral vasoreactivity[4] to regulate flow in response to hyper- and hypocapnia. In addition, the increases in systemic pressure with even low-intensity exercise must be counterregulated by effective cerebral autoregulation[5] to constrain flow and prevent overperfusion. Thus, regular exercise and engagement of these mechanisms might result in a "training effect" on cerebrovascular regulation. Moreover, it is known that detraining (i.e., prolonged inactivity) results in significant deficits in cerebrovascular control,[6] and emerging evidence suggests that exercise training reduces symptoms in those with mTBI.[7,8] Thus, there may be beneficial adaptations to exercise training that contribute to symptom reduction via improved cerebrovascular regulation.

Neurotrauma and cerebrovascular control. Symptoms similar to those associated with mTBI (altered cognitive function, headache, and dizziness) can arise as a result of cerebrovascular dysfunction. First, studies suggest that alterations in neurovascular coupling may relate to declines in cognitive function. Retired boxers can show evidence of cerebral hypoperfusion coupled with neurocognitive dysfunction.[9] Second, individuals with migraine demonstrate excessive increases and decreases in cerebral blood flow in response to both hyper- and hypocapnia that might be associated with the development and/or persistence of headaches.[10] Lastly, those with vasovagal syncope, frequently accompanied by dizziness, can demonstrate rapid changes in cerebrovascular autoregulation prodromal to frank syncope, such that autoregulation is virtually lost immediately preceding, during, and after syncope.[11] In fact, there is an association between the presence of syncope, risk of fainting, and impaired autoregulation,[12] and thus, impaired cerebrovascular autoregulation may be an important factor underlying dizziness. Although the mechanisms that underlie these associations are not well understood, taken together, available data suggest that dysregulation of neurovascular coupling, cerebral vasoreactivity, and cerebral autoregulation could contribute to some of the chronic symptoms of mTBI, specifically altered cognitive function, headache, and dizziness.

Neurovascular coupling. Distribution of cerebral flow is regulated in response to the functional activity in different brain regions. That is, when activity in a brain region increases, flow to that region also increases. Evidence indicates that glia, neurons, as well as blood vessels act as an integrated unit and have a crucial role in this process. The term *neurovascular unit* was coined to highlight the intimate functional relationships between these cells and their coordinated pattern of reaction to injury. Moreover, because neuronal activity requires delivery of adequate oxygen and glucose to specific brain regions, cerebral blood flow and cerebral metabolic rate are normally coupled. Alterations of this "neurovascular coupling" can impair the ability of the brain to provide sufficient flow to active regions, leading to neural dysfunction. Neurovascular coupling could derive from several mechanisms. Activity-related ion content shifts, energy substrate changes, or neurotransmitters themselves can influence vasomotor tone.[13] Interneurons may also mediate flow coupling via endings directly on arterioles and by secreting acetylcholine, an endothelial-dependent vasodilator.[14] Alternatively, astrocytes directly contact endothelial cells and can secrete vasodilatory substances, such as epoxyeicosatrienoic acid, adenosine, nitric oxide (NO), and cyclooxygenase-2 metabolites.[15] Although the exact interplay among these potential mechanisms is unclear, vasodilatory effects in the microcirculation are insufficient to effectively increase local blood flow. The vasodilatory signal must be back-propagated to upstream pial arterioles that offer the greatest resistance to flow. The signal appears to be transmitted through gap junctions of neighboring endothelial or smooth vascular muscle cells. The increase in the arterial flow might also induce further dilation as a result of increased shear stress. Hence, vascular endothelial function and smooth muscle responsiveness appear to be critical in transducing the signals into cerebral flow changes orchestrated to the period of neural activation.

Data on alterations in neurovascular coupling after mTBI are limited. Animal data suggest that after moderate to severe TBI, local cerebral blood flow decreases, and as a result of these focal impairments, neurovascular "uncoupling" occurs.[16] These alterations are thought to be primarily due to alterations in neural control[17] and endothelial function[18] in the pial vasculature. Unfortunately, there are no comparable data in humans. One study showed that central acetylcholinesterase inhibitors (which reduce the clearance of acetylcholine, thereby increasing

endothelium-dependent acetylcholine availability) may be a promising treatment to improve vigilance and attention after moderate to severe TBI in humans.[19] If so, endothelial dysfunction may underlie impairment in neurovascular coupling after mTBI in humans. However, this link has not been explored.

Cerebral vasoreactivity. Cerebral blood flow is also highly sensitive to changes in arterial CO_2 level. Cerebrovascular responses to changes in CO_2 are primarily mediated via changes in extracellular pH and subsequent activation of ion channels in the vascular smooth muscle. This is a key mechanism for cerebrovascular control because arterial CO_2 can fluctuate widely from one breath to the next and can change significantly with everyday stressors, such as moving from supine to upright postures. Hypercapnia (i.e., high CO_2) leads to vasodilation and increases in flow, whereas hypocapnia (i.e., low CO_2) leads to vasoconstriction and decreases in flow. The highly sensitive flow responses to changes in CO_2, termed cerebral vasoreactivity, is a vital homeostatic function that helps regulate and maintain central pH. In essence, elevations in flow with hypercapnia "wash out" CO_2 from brain tissue, thereby attenuating the rise in pH, whereas declines in flow with hypocapnia attenuate the fall in brain pH. This response is rapid, occurring with an approximate 6-second delay.[20] Links between systemic endothelial function and cerebral vasoreactivity have been reported,[21] indicating a common pathway between peripheral flow-mediated dilation and vasoreactivity. However, the mechanism of action for CO_2-mediated blood flow changes has not been entirely elucidated. Potassium channel activation may have a role in coordinating vascular tone in upstream and downstream vessels via endothelial and vascular smooth muscle effects.[22] An alternative or complementary mechanism is CO_2/pH-induced alterations in vasoactive factors. Key among these factors is endothelial release of NO. The extent to which NO acts as obligatory or permissive is unknown, but it seems to be an essential vasoactive factor in the response to CO_2.[23] Thus, similar to neurovascular coupling, endothelial function as well as smooth muscle responsiveness may be key factors in cerebral vasoreactivity.

Impaired cerebrovascular response to CO_2 has been shown to predict poor outcomes in patients with severe TBI.[24] CO_2 reactivity is compromised in the initial days postinjury but can return to normal.[25] Of note, a disruption in cerebral vasoreactivity occurs in the days immediately after a mild cortical impact injury in animals,[26] and this has also been observed shortly after sports-related concussion in humans.[27] However, it remains unknown whether alterations in cerebral vasoreactivity also relate to the chronic symptoms after mTBI.

Cerebral autoregulation. A third line of defense, cerebrovascular autoregulation, counteracts the effects of arterial pressure fluctuations occurring with everyday activities. For example, changes in posture can result in as much as a 50% drop in systolic pressure and produce vasovagal syncope with brief loss of consciousness if blood flow to reticular brain cells also rapidly falls. However, this will not occur if effective "autoregulation" results in maintained blood flow via cerebrovascular resistance changes that fully counteract changes in pressure. Cerebral arteries relax when pressure decreases and constrict when pressure increases to maintain stable cerebral perfusion. As with neurovascular coupling and cerebral vasoreactivity, the exact mechanisms are not entirely known, but certain important effectors have recently been demonstrated. Autonomic control appears to be a key mechanism for adequate autoregulation. Ganglionic blockade of cardiovascular autonomic control reduces the ability of the cerebral circulation to counterregulate pressure fluctuations.[28] In fact, intact sympathetic function is critical to normal cerebrovascular responses to changes in pressure[29] and cholinergic control provides a counterregulatory balance to sympathetic effects.[30] In addition, data in humans suggest that myogenic mechanisms counteract pressure-driven flow[31] and have an important role in regulation of pressure–flow relations.[32] Recent work directly addressed how sympathetic, cholinergic, and myogenic systems work in concert to shape cerebral autoregulation in healthy humans, and showed that the 3 mechanisms have distinct contributions that explain the majority of cerebral autoregulatory responses.[33] Lastly, an endothelium-dependent NO mechanism may have a role,[34] although this is not consistently found. Nonetheless, it is likely that adequate function at the neural, smooth muscle, and endothelial levels is required for cerebral autoregulation.

Although severity of injury is not a good predictor of autoregulatory failure,[35] compromised cerebral autoregulation is a significant predictor of poor outcomes in the acute phase of severe TBI.[35] For example, Lam et al.[36] identified 3 distinct TBI groups with intact, transient loss, or persistent loss of cerebral autoregulation; they found that 9 of 11 with persistent loss of autoregulation died and the remaining 2 had severe disability on follow-up. In contrast to the volume of work on severe TBI, there is very limited work on the degree of impairment in cerebrovascular control in patients with mild to moderate TBI, and no work at all on the subacute phase. Early after minor cerebral contusion, global cerebral flow may be reduced, and interhemispheric flow asymmetries appear to be common.[37] In fact, almost 30% of patients with mTBI have impaired or absent cerebral autoregulation within 48 hours of injury.[38] One case

report suggests that very mild injuries may result in sustained loss of autoregulation[39]; a patient who experienced a mild concussion 6 days earlier demonstrated complete absence of cerebral autoregulation. Although data are suggestive of a sustained impairment in cerebrovascular control after mTBI, there have been no systematic studies exploring a possible compromise in control mechanisms underlying symptomatology.

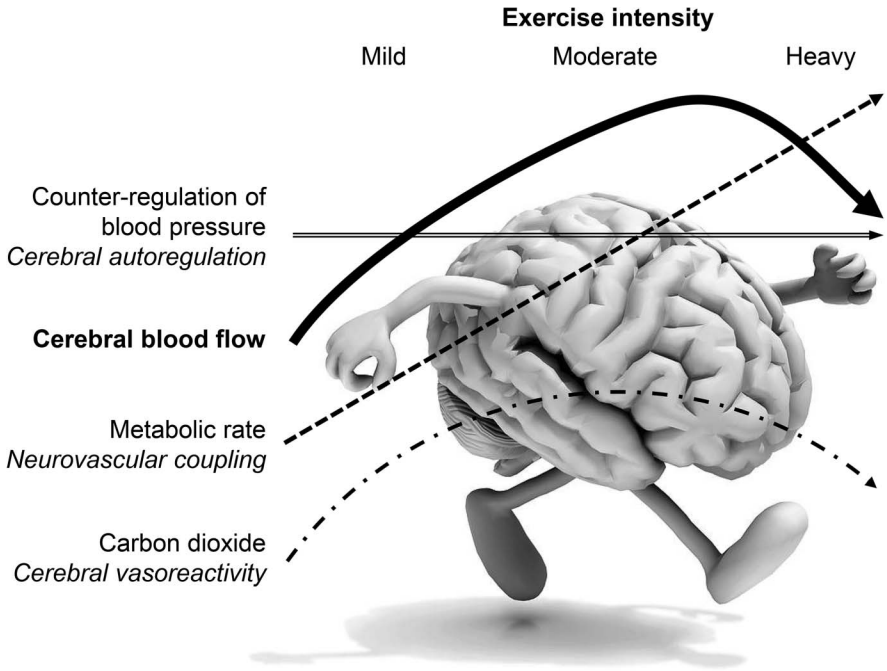
Current approaches to acute management, treatment, and rehabilitation. Currently, clinical management of mTBIs, particularly those sustained by athletes, consists mainly of physical and cognitive rest during the acute phase.[40–42] A primary rationale for rest, especially in the first few days after injury, is that the injured brain is believed to be in a state of neurometabolic crisis[43] and rest might theoretically facilitate recovery. In addition, a rest period reduces the likelihood of another head injury during the recovery period. Although there is evidence in the animal literature that vigorous exercise in the first few days after brain injury suppresses neuromolecular markers of neurogenesis and neuroplasticity,[44] evidence showing that rest and restricted physical activity result in shorter recovery times is limited, and one randomized clinical trial did not find that rest was associated with better clinical outcomes after mTBI.[45] However, there are some observational studies suggesting that higher physical and cognitive activity during the acute recovery period is associated with greater postacute symptoms in concussed athletes.[46] After the acute recovery phase, treatment of patients with persistent symptoms focuses on symptom management via a variety of approaches, such as medications, physical and vestibular therapy, and psychologic treatment.[42]

Increasingly, researchers have encouraged the use of exercise as primary or adjunctive treatment for children, adolescents, and adults who are slow to recover from mTBI,[47] primarily because of the positive effects of exercise on symptom clusters (e.g., headache, fatigue, and sleep disturbance) and comorbid conditions (such as depression and anxiety). Although the biochemical and physiologic impact of mTBI may be different in children vs adults,[48] there is indirect evidence that exercise might be beneficial for those with persistent or chronic symptoms after mTBI: (1) exercise promotes neuroplasticity and neurogenesis in both the healthy and injured brain,[47] (2) exercise is associated with direct changes in neurotransmitter systems,[49] and (3) exercise is an effective adjunctive treatment for depression and anxiety.[50] The timing of exercise as an intervention is likely important: the optimal time window for exercise may differ depending on injury characteristics and symptom severity, and premature exercise may interrupt restorative mechanisms—at least in animal injury models.[44] Unfortunately, the optimal timing for introduction of exercise after mTBI is not yet known. Nonetheless, compared with pharmacologic management, exercise is available at relatively low cost and mostly free of serious adverse effects. Lastly, several lines of evidence suggest a beneficial effect of mild- to moderate-intensity exercise on cerebrovascular function, potentially supporting the utility of exercise training in patients with persistent symptoms.

Exercise and cerebrovascular control. The responses of cerebral blood flow to exercise are driven by neural demand and the marked changes in arterial CO_2 tension and mean arterial pressure. During exercise, increases in cerebral metabolism require increased delivery of oxygen to the brain. During mild to moderate exercise, cerebral flow increases due to cortical activation. It is thought that the vasodilation due to the exercise-induced increase in brain metabolism overrides vasoconstrictor effects of increased pressure on the cerebral vasculature.[3] However, exercise-induced elevations in metabolism do not simply lead to proportional increases in global cerebral flow. Flow increases up to approximately 60% of maximal effort and returns toward baseline values at higher exercise intensities[51] (see the figure). This is due to exercise intensity-dependent effects of CO_2 on cerebral flow. Mild to moderate exercise is associated with a small increase in arterial CO_2 that increases cerebral blood flow[52] in concert with metabolism. However, with intense exercise, there is a reduction in arterial CO_2 because ventilation increases exponentially with exercise intensity as pH decreases. Accordingly, intense exercise is accompanied by decreases in cerebral blood flow that ultimately interfere with adequate oxygenation of the brain and contribute to fatigue[53] (see the figure). In addition to the interacting effects of metabolism and CO_2, the mitigating influence of cerebral autoregulation on cerebral flow during dynamic exercise is considerable. Elevated cerebral blood flow during exercise cannot be explained simply by elevated pressure.[52] It is important to note that the large increase in systolic pressure during intense exercise often exceeds the upper limit of cerebral autoregulation. Nonetheless, dynamic cerebral autoregulation appears sufficient to limit the increase in systolic cerebral blood flow velocity.[54] Thus, the cerebral flow responses to exercise require the integration of the 3 primary controlling mechanisms: neurovascular coupling, cerebral vasoreactivity, and cerebral autoregulation.

Exercise training after mTBI. As noted above, early management of mTBI consists mainly of physical and cognitive rest, with some studies suggesting a benefit.[55] Most major guidelines for management of sport-related concussion call for physical rest acutely after injury, with graded return to exertion after

Figure Cerebral blood flow response to increasing exercise intensity and the engagement and role of the 3 mechanisms that control it



Blood pressure increases proportionally to exercise intensity, engaging autoregulation that serves to maintain constant flow. However, at mild and moderate intensities, both metabolic rate and carbon dioxide increase, hence both neurovascular coupling and cerebrovascular reactivity result in increased cerebral blood flow. With heavy exercise intensities, there is a pronounced hypocapnia, and so the net result of the 3 controlling mechanisms is a decrease in cerebral blood flow.

concussion symptoms resolve.[41] The limited evidence behind the recommendation for physical rest, however, is well recognized.[40,41] In fact, after the acute phase, the introduction of subsymptom threshold exercise appears safe, and may be beneficial in improving symptoms.[8] A 4-week intervention of cycling exercise produced significant improvement in cognitive function in patients with TBI,[56] but it is unclear whether this was attributable to exercise per se or the virtual reality component of this program. Animal models suggest that exercise can promote neuroplasticity, especially in mTBI.[57] However, as yet, there have been no prospective trials examining the effects of a controlled exercise training program on physiologic function and symptoms in patients with TBI. Other groups of people have shown improvements in cerebrovascular control with aerobic exercise training. For example, 7 months of aerobic training improved cerebral vasoreactivity in older (>60 years), healthy individuals.[58] This may have functional significance; increases in maximal exercise capacity relate proportionately to increased cerebral blood volume in the hippocampus in older individuals, and increases in flow volume were reflected in improved cognitive function.[59] Therefore, in adults and older adults with compromised cognitive function, exercise may demonstrate beneficial effects on cerebrovascular control that are reflected in cognitive improvement. However, in young, healthy individuals, exercise training may not have appreciable effects on cerebrovascular control, probably because cardiovascular function is at or near its peak capacity. Thus, the effectiveness of exercise in reducing postconcussion symptoms may be different in older and younger individuals. However, detraining does result in significant deficits in cerebral regulatory control. This may be relevant to those who have sustained mTBIs because prolonged physical rest may lead to extreme deconditioning and resultant cardiovascular declines.[60] This could exacerbate impaired cerebral autoregulation; deconditioning has been shown to reduce cerebral blood flow in humans. In fact, even a single day of bed rest reduces cerebral blood flow for a substantial period of time afterward.[6] Thus, independent of primary cerebrovascular dysfunction due to head injury, it seems feasible that prolonged rest after TBI leads to deconditioning that may induce physiologic changes in cerebrovascular control—and these physiologic changes could contribute to symptoms associated with the postconcussion syndrome.

Perspectives. Persistent symptoms after mTBI in athletes, civilians, active-duty military service members, and veterans can be difficult to effectively treat. The evidence reviewed above suggests that alterations in cerebrovascular function after mTBI might partially

underlie persistent symptoms, and the multifaceted nature of cerebrovascular function (neurovascular coupling, vasoreactivity, and autoregulation) and underlying physiologic mechanisms may contribute to symptom heterogeneity. For example, it is possible that potential differences in etiology of mTBI sustained from different injuries (e.g., sport-related concussion vs blast injuries) may result in different pathophysiologic alterations in cerebrovascular regulatory mechanisms, and thus, in different symptoms. Blast injury is often characterized by a series of primary (blast wave), secondary (rotational acceleration as the head moves), and tertiary (direct contusion/laceration by fragment/shrapnel) injuries, as opposed to a distinct, solitary, independent mechanism. Unfortunately, possible time-limited or persisting alterations in cerebrovascular function after mTBI remain mostly unknown, and future studies are needed to fill this gap in our knowledge.

If persistent symptoms are indeed related to cerebrovascular dysfunction, targeting this underlying pathophysiology may provide an additional treatment strategy. The evidence suggests that active exercise training may be one such strategy, because the cerebral flow responses to exercise require the integration of the major mechanisms that underlie cerebrovascular function. While physical rest initially after an mTBI is currently recommended, preliminary evidence suggests that the introduction of subsymptom exercise after the acute recovery period is safe.[8] Exactly when subsymptom physical activity should be introduced and which patients might benefit most are not yet clear. Furthermore, the effect of subsymptom threshold exercise on cerebral blood flow and the association between cerebral blood flow and postconcussion symptoms, exercise tolerance, neurocognitive performance, and postural stability remain largely unknown. Given the evidence outlined above, further investigations into the effects of concussion on cerebral blood flow and the effects of exercise on patients with mTBI are warranted.

AUTHOR CONTRIBUTIONS

Can Ozan Tan, PhD: drafted and revised the manuscript for content, including medical writing for content. William P. Meehan III, MD: revised the manuscript for content, including medical writing for content. Grant L. Iverson, PhD: revised the manuscript for content, including medical writing for content. J. Andrew Taylor, PhD: drafted and revised the manuscript for content, including medical writing for content. All authors have seen and approved the final version of the manuscript.

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