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Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: Implications for treatment

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Abstract. Although most patients with concussion recover within days to weeks, a small but significant minority develop persistent signs and symptoms of post-concussion syndrome (PCS). The standard treatments of PCS, rest and cognitive adaptation, have limited effectiveness. PCS patients are advised not to exercise because of the concern for symptom exacerbation. Prolonged rest, however, leads to deconditioning (especially in athletes) and may cause secondary effects including depressive symptoms. Concussion is associated with metabolic and physiological changes in the brain and in other organ systems (for example, autonomic function of the heart and altered cerebral autoregulation, sleep, and circadian rhythms). We propose that PCS results from ongoing central and systemic physiologic regulatory dysfunction after traumatic brain injury (TBI) and we further propose that this physiologic dysfunction may be reduced or alleviated by individualized controlled sub-symptom threshold aerobic exercise rehabilitation.

1. Introduction

It is generally considered that concussion reflects primarily an injury to the brain. However, recent research has demonstrated that the metabolic changes that occur in the brain following a concussion have implications for metabolic and physiologic function of other organ systems. The purpose of this paper is to review these metabolic and physiologic changes and to bring together the available research into a theory to explain why post concussion syndrome (PCS) occurs. We propose that concussion produces a temporary alteration of the central regulatory systems that control, for example, the autonomic nervous system and circadian rhythms, as well as the autoregulatory protection of the brain, which under normal conditions maintains a constant state of cerebral blood flow. We further suggest that PCS represents a condition whereby the regulatory and autoregulatory mechanisms of the brain do not naturally return to normal. Finally, we discuss the implications of this theory of concussion and PCS for treatment and further research.

Concussion is most commonly defined as a trauma-induced alteration of mental status that may or may not involve loss of consciousness [44]. Approximately 1.5 to 2 million people each year sustain brain injuries in the United States, mostly from accidents and sports [48]. Formerly it was thought that some concussions, especially those sustained in sports, were relatively benign (termed a “ding” or “bell ringer”) and that athletes could return to play within the same contest once they reported being symptom free. Subsequent research, however, suggests that even persons who have so-called minor head injuries in sports may experience impaired memory and renewed symptoms

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within 36 hours of the injury [54]. More recent recommendations therefore state that all athletes with concussion, even if they report being symptom free, should be withheld from competition and evaluated by a doctor before return to play [60]. The majority of patients with sports-related concussion recover within a seven to ten day period [5,58]. In non-sports-related mild traumatic brain injury (mTBI), most cases recover completely within the first three months; however, a significant minority experience continued cognitive deficits and symptomatology beyond that point, with prevalence estimates ranging from 7–8% [8] to up to 33% [65], with some individuals reporting distressing symptoms for months or years post-injury [37]. These individuals typically report a constellation of physical, emotional and cognitive symptoms collectively known as PCS [5].

PCS is defined by the World Health Organization as persistence of three or more of the following symptoms after head injury: headache, dizziness, fatigue, irritability, insomnia, concentration or memory difficulty [9]. While concussion effects are assumed to be transient, especially in sports-related concussion, when signs and symptoms persist beyond 3 weeks it has been suggested that patients with PCS have progressed from transient injury to the semi-permanent brain injury reflective of mTBI [76]. The diagnosis of PCS is complicated by the multiplicity of symptoms encompassed within the syndrome and a differential diagnosis that includes among others depression, somatization, and chronic pain [33,56]. Nevertheless, PCS should be considered when patients remain symptomatic for three weeks or more after head injury [76]. The assumption is that metabolic and physiologic changes in the brain of the concussed individual have not returned to homeostasis. Recent research suggests that a significant risk factor for the development of PCS is three or more prior concussions [40,41]. Consistent with this clinical observation, there is evidence of a persistently altered brain physiologic milieu (i.e., blood-brain barrier disruption and reduced global and regional cerebral blood flow) in some patients after mTBI [47]. It can thus be argued that there is no such thing as a "minor" brain injury.

1.1. Physiology of concussion and PCS

There is a metabolic cascade of brain neurochemical changes following concussion that produces an initial hypermetabolic state as the brain attempts to restore homeostasis followed by a state of metabolic depression as cerebral blood flow declines and brain energy demand exceeds supply [25]. This may explain why in humans some symptoms are delayed in onset or worsen over time [60], why some patients report symptom resolution before they demonstrate physical and cognitive homeostasis [53], and why patients who are asymptomatic at rest can become symptomatic during physical or cognitive exertion [60]. Animal research suggests that the concussed brain is in a vulnerable state that places it at increased risk of more debilitating injury should it sustain more trauma before metabolic homeostasis has been restored [25,52]. This vulnerable state can be inferred in humans from the rare but devastating phenomenon of Second Impact Syndrome [11], from evidence that concussion risk increases after having had one or more concussions [34], that previous concussions may be associated with slower recovery of neurological function [34], and that repeated concussions can result in permanent neurocognitive impairment [32,34, 41] and an increased incidence of depression [33].

Concussion is also associated with metabolic and physiological changes in other organ systems. For example, when compared with control subjects, concussed subjects have greater heart rates at rest [45] and after both cognitive [36] and physiological (i.e., exercise) stress [24]. This may be due to disturbed autonomic nervous system (ANS) function after concussion as indicated by altered heart rate variability (HRV). HRV is a measure of the variability in the rhythmic oscillations in heart rate that reflects the brain-heart physiological connection and parasympathetic-sympathetic nervous system balance [64]. Patients with severe TBI [45], cerebral infarction [73], and concussed athletes [23] demonstrate greater sympathetic and lower parasympathetic activity when compared with controls. Altered autonomic regulation is believed to be due to changes in the autonomic centers in the brain and/or an uncoupling of the connections between the central ANS and the heart after TBI, is proportional to TBI severity, and improves during TBI recovery [28]. Cerebral autoregulation (the capacity to maintain cerebral blood flow at a relatively constant level during changes in systemic blood pressure) and cerebral blood flow are also disturbed after concussion [42,69], which may explain why concussion symptoms often re-appear or worsen with physical exertion or other stress, as the brain's ability to maintain constant blood flow in the face of fluctuating mean arterial blood pressure is impaired after concussion [42]. In a similar manner, the cerebrovascular response to arterial carbon dioxide tension ($PaCO_2$), which is a fundamental physiologic mech-

anism to maintain adequate blood flow to the brain, is diminished in severely brain injured humans [18] and early after experimental concussive injury in animals [27]. The major determinant of blood $PaCO_2$ is the pulmonary ventilation (the product of breathing frequency and tidal volume), which may be altered in concussed individuals, especially during exertion. If ventilation is altered after concussion, changes in arterial $PaCO_2$ may cause cerebrovascular constriction leading to reduced cerebral blood flow. It is believed that impairment of the cerebral vasculature after TBI renders the brain at risk to secondary insults such as hypotension, intracranial hypertension, and dehydration [26].

Other "systemic" effects of concussion include altered hepatic and renal cytochrome P450 enzyme activity, which has implications for drug metabolism and clearance after TBI [43], sleep and circadian rhythm disruption [2], and the release of pro-inflammatory cytokines into the circulation after concussion [16]. Concussion is also associated with depressed mood and fatigue [56]. Research indicates that no residual neuropsychological impairments can be measured greater than seven days after sports-related concussion [5], yet some athletes nevertheless go on to develop PCS [76].

We believe that the accumulating evidence suggests that concussion, while initially and primarily a brain injury, involves more than just a disturbance of cerebral cognitive function: it is a systemic injury that affects multiple physiological systems throughout the body. PCS may therefore reflect less a primary cognitive disorder than a manifestation of a persistently altered central and peripheral physiological state after concussion. If so, it may be that some persistent cognitive deficits or symptoms are not directly the result of damage to neurons or their connections but secondary to the physiological dysregulation after concussion, which would have implications for the treatment of PCS.

1.2. PCS treatment: Rest versus exercise

The primary forms of PCS treatment have traditionally included rest, education, neurocognitive rehabilitation, and antidepressants [56]. While there is evidence that simple education and reassurance given shortly after the injury help to reduce somatic and psychological symptoms [15], the few empirical studies of neurocognitive therapy and antidepressants have shown limited effectiveness [14,19,38,78] and there are no controlled trials showing that they improve outcome in PCS patients. One way to conceptualize the variety of PCS symptoms is that they arise from the most injured areas of the brain in a given individual and are capable of being modulated by other factors such as reactive depression, pain or secondary gain [56]. We hypothesize that another modulating factor in PCS may be persistent physiological disequilibrium.

The initial treatment of concussion includes a period of cognitive and physical rest because symptoms can increase with cognitive and physical exertion in the early post-injury period [60]. Theoretically, intense exercise too soon after concussion may increase the risk of cerebral hemorrhage by increasing intracranial pressure [13]. Experimental animal data show that following TBI there is a lower concentration of ATP [50,67] as well as structural alterations of the mitochondria in the brain [51]. Exercise in the acute post concussion period may therefore increase brain metabolic demand at a time when the brain is energy compromised [74] and vulnerable to secondary injury due to premature neuronal activation [50,67]. In animals, for example, forced exercise following a unilateral cortical injury leads to anatomical and behavioral dysfunction [39] and in humans sexual activity has been reported to exacerbate concussion symptoms soon after head injury [68]. Exercise too soon after concussion could also divert the brain from producing neurotrophins, such as brain-derived neurotrophic factor (BDNF), that promote neuronal recovery. BDNF enhances neuronal survival, growth and synaptic plasticity [3] and has been shown to improve cognitive and neurological deficits due to cerebral ischemia [1].

In elegant animal experiments, Griesbach et al. [29, 30] have shown that BDNF and its downstream effectors on synaptic plasticity, cyclic AMP response element-binding-protein (CREB) and synapsin I, increase after physical activity. Concussed animals demonstrate the same response, but only if they rest following concussive injury. Premature voluntary exercise within the first week after concussion interferes with the post-concussion rise of these plasticity molecules and is associated with impaired performance in the acquisition of cognitive memory tasks. Conversely, aerobic exercise performed 14–21 days *after* TBI upregulates BDNF, CREB and synapsin I in association with improved cognitive performance. These results suggest that exercise rehabilitation after brain injury may be beneficial if administered at the appropriate time. The neurochemical and metabolic disruptions require approximately 10 days to normalize after TBI [6]. As cells are in a state of energy crisis and vulnerable to secondary activation, it is possible

that premature exercise reduces the brain's capacity for neuronal differentiation and survival.

PCS patients have traditionally been advised to engage in no exertional activity while still symptomatic. Prolonged rest, however, especially in athletes, can lead to secondary symptoms such as fatigue and reactive depression [7] in addition to physical deconditioning [76] and metabolic disturbances (the so-called "physiology of inactivity") [35]. Current return-to-play guidelines for concussed athletes who become asymptomatic at rest recommend a graduated return to increasing intensities of physical activity [60]. If symptoms recur, then the athlete returns to the prior level of exertion before attempting to advance again. There are, however, no evidence-based criteria for initiating or progressing through this "brain exercise stress test".

Regular physical exercise has been shown to be beneficial to overall human health and has been linked with a decrease in cognitive decline [49] as well as improvements in cognitive function [4,20]. Regular exercise also has beneficial effects upon many of the symptoms and physiological systems adversely affected by concussion. Animal studies, for example, have found that exercise training protects against cerebral ischemia [70], enhances hippocampal neurogenesis [72], and improves learning capabilities [22]. The beneficial effects of exercise training on the brain may be mediated by several mechanisms. A potentially important one is the effect of exercise on brain neurotrophins. Exercise increases BDNF and its downstream effectors on synaptic transmission in select brain regions in animals [61] and in humans BDNF increases acutely after physical exercise [20]. Thus, endogenous upregulation of BDNF and associated molecular systems through exercise training may lead to a better outcome in patients whose physiological milieu remains disturbed after concussion.

Exercise training also has beneficial effects upon the cerbrovascular and cardiovascular systems that are adversely impacted by brain injury. Most studies show reduced cerebral blood flow [16] and altered cerebral autoregulation [42,69] early after TBI that may persist for a long period of time [47]. This could be why both acutely concussed and PCS patients report increasing headache and other symptoms with exertion as the brain is unable to maintain stable intracranial pressure in the face of fluctuating mean systemic arterial pressure during exercise [10]. Failure of central regulation after TBI puts patients in a state of sympathetic overdrive, which causes fatigue and has been associated with the development of negative mood after deprivation of usual exercise activities [75]. Regular aerobic exercise training, however, increases parasympathetic activity and improves autonomic regulation (i.e., HRV) [12] and increases global [17] and regional [31] cerebral blood flow. In addition, regular physical training has well recognized benefits on mood [66], sleep [77], and depression [62], and reduces systemic markers of inflammation [21], which are elevated after brain injury [16].

1.3. Implications for treatment and research

We have proposed that PCS occurs because the disturbances in brain physiology (e.g., central autonomic control and cerebral autoregulation) and whole body physiology (e.g., autonomic influence on the heart) as a result of concussive injury do not return to a state of homeostasis or equilibrium in some persons. The research on physiologic outcomes following concussion provides scientific evidence to support this theory. This human and animal research demonstrates that cerebral concussion negatively impacts multiple physiological systems and that individuals with PCS have continued physiologic dysfunction consistent with regulatory and autoregulatory imbalance, in spite of normal neuropsychological test performance. The current recommended treatment of prolonged rest is detrimental to recovery of autoregulatory function. We propose that whole body aerobic exercise rehabilitation, of progressively increasing intensity that is performed at submaximal intensities so as not to exacerbate symptoms, will improve central regulatory and autoregulatory function and may help to resolve some PCS symptoms, especially in athletes.

Improved PCS symptoms may not result, however, from all forms of physical exercise since there is evidence of disturbed cerebral autoregulation after both maximal aerobic [63] as well as dynamic resistance [46] exercise. The research on animals suggests that a beneficial effect of exercise may be related to the restoration of a normal energetic response following concussion and that a period of at least two weeks is required to allow the brain to recover sufficiently to prevent an exercise-induced exacerbation of metabolic dysfunction and for neurotrophin levels to rise [29,30]. In one animal study, even though a one week exercise training intervention increased neurotrophin levels by post-injury day 21, BDNF in the concussed animals had still not returned to normal levels [30]. Given that the delayed exercise increased BDNF, it is possible that exercise training performed even later post-injury and

for a longer period than one week might result in more robust increases in neurotrophins.

Based upon the research to date, we recommend that the exercise rehabilitation of PCS patients should be an individualized, progressive sub-symptom threshold aerobic exercise program. That is, exercise will exacerbate symptoms in PCS patients at an individualized threshold of exertion (which is determined by the linear rise in blood pressure, heart rate and ventilation as exercise intensity increases). A controlled exercise-based rehabilitation program for PCS should be sub-symptom threshold so as not to exacerbate symptoms while the central regulatory and autoregulatory systems adjust. In addition, the exercise training should be of sufficient duration to allow the regulatory and autoregulatory systems time to both acutely and chronically adapt to the stress of exercise-induced changes in peripheral physiological variables (i.e., blood pressure, heart rate, ventilation and $PaCO_2$) [57] and it should be adjusted on a regular basis to account for a "training effect" on the autoregulatory system. This form of controlled exercise rehabilitation we believe may also have wide application to patients with more severe forms of TBI, whether from sports, motor vehicle accidents or falls.

Exercise is currently recommended as a means of determining when an athlete is symptom free and ready to return to play. The consensus opinion at the Prague Conference was that an athlete is only ready to return when s/he has no symptoms with maximal exercise. We propose that exercise testing can be used as a more comprehensive diagnostic tool to help determine whether some PCS symptoms are due to etiologies other than concussion. For example, headache is a common complaint after concussion [76] that may have etiologies other than from the head trauma (e.g., cervicogenic or related to a prior history of migraines). If a patient is able to attain his or her maximal level of exercise without reproduction of headache or other claimed PCS symptoms and has normal physiological responses to exercise, then it is very likely that the symptom(s) is(are) not related to PCS.

Our theory of regulatory and autoregulatory physiologic dysfunction as a primary explanation of PCS has implications for research. Past research has focused on identifying and treating cognitive variables such as attention, concentration and speed of information processing. The most useful research investigations have controlled for potential confounding variables including history of prior concussions [34], depressive symptoms [32], pre-injury cognitive impairment [55], and stress (e.g., post traumatic stress disorder) [71] since these may have cognitive and mood symptoms similar to PCS. Past research, however, has tended to neglect physiologic variables such as indicators of fitness and of regulatory and autoregulatory function. Future research in PCS patients should measure the effects of regular sub-symptom threshold exercise on cerebral autoregulation and the variables that affect it, i.e., blood pressure, heart rate, cerebral blood flow, pulmonary ventilation and arterial $PaCO_2$; on the systems and symptoms that reflect disturbed central physiological regulation, i.e., HRV, sleep and circadian rhythm disturbance, depressive symptoms, fatigue, etc.; and on neurotrophins and other markers of neural plasticity. The information provided by the animal studies emphasizes the importance of the type and timing of exercise training after brain injury. Any research on treatment should look at the efficacy of a controlled exercise rehabilitation program and the exact conditions required for the optimization of the use of exercise to help the injured brain in patients with PCS.

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