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The Role of Controlled Exercise in Concussion Management

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Abstract

Concussion affects the autonomic nervous system and its control of cerebral blood flow, which may be why uncontrolled activity can exacerbate symptoms after concussion. Traditionally, patients have been advised to restrict physical and cognitive activity until all symptoms resolve. However, recent research suggests that prolonged rest beyond the first couple of days after a concussion might hinder rather than aid recovery. Humans do not respond well to removal from their social and physical environments, and sustained rest adversely affects the physiology of concussion and can lead to physical deconditioning and reactive depression. Some animal data show that early forced exercise is detrimental to recovery after concussion, but other animal data show that voluntary exercise is not detrimental to recovery. We developed the Buffalo Concussion Treadmill Test to systematically evaluate exercise tolerance in persons with prolonged symptoms after concussion (ie, more than 4-6 weeks, which is called postconcussion syndrome [PCS]). Using a predetermined stopping criterion (symptom-exacerbation threshold), akin to voluntary exercise in animals, the Buffalo Concussion Treadmill Test is the only functional test known to safely and reliably reveal exercise intolerance in humans with PCS. The test data are used to develop individualized subthreshold exercise treatment programs to restore the physiology to normal and enhance recovery. Return of normal exercise tolerance can then be used to establish physiological recovery from concussion. New research suggests that absolute rest beyond the first few days after concussion may be detrimental to concussion recovery. However, further research is required to determine the appropriate mode, duration, intensity, and frequency of exercise during the acute recovery phase of a concussion prior to making specific exercise recommendations. For patients with PCS, subsymptom threshold exercise improves activity tolerance and is an appropriate treatment option for this patient population.

Introduction

The International Concussion in Sport Group currently supports the concept that concussion management should promote physical and cognitive rest until acute symptoms resolve [1]. The rationale for rest as treatment hinges primarily on data from elegant animal experiments that show a cascade of increased metabolic demand acutely after simulated concussion that occurs—paradoxically, it would seem—during a state of reduced cerebral blood flow (CBF) at rest [2]. The clinical inference has generally been that nonessential physical or cognitive activity diverts essential oxygen and glucose away from injured neurons and delays recovery from concussion. A consequence of this inference is that many clinicians advise concussed patients to restrict most if not all physical and cognitive activity, including schoolwork, until all symptoms have resolved because of a theoretical risk that activity-induced exacerbation of symptoms damages the brain and delays recovery. This standard of care has been implemented for many years despite a lack of empirical evidence that such "radical rest" is therapeutic [3,4] and without consideration that symptoms after concussion are protean and not specific to brain injury [5].

Recent studies have begun to challenge the utility of prolonged rest as treatment for concussion. Citing the risk for prolonged and exacerbated symptoms that may not be directly related to the concussive injury, some medical organizations have recommended that athletes be permitted to engage in limited physical and cognitive activity as long as it does not worsen symptoms [6]. In support of this approach, recent studies predominantly focusing on patients with postconcussion syndrome (PCS) have shown that more liberal noncontact activity recommendations [7,8] and controlled, subsymptom threshold aerobic exercise [9-11] may enhance recovery

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after concussion, particularly in persons with PCS. The purpose of this article is to discuss the scientific basis for exercise in the treatment of concussion.

Literature Review Methodology

Inclusion Criteria

For the human studies, we searched PubMed and MEDLINE for articles with key words that included "concussion," "postconcussion syndrome," "mild traumatic brain injury" (mTBI), "exercise," "physical," "activity," "therapy," "treatment," "cerebral blood flow," "carbon dioxide," "cerebrovascular reactivity," "autonomic," and "physiology." For the concept of treatment, we included only the articles that focused on aerobic exercise treatment of concussion or PCS. The search terms for the animal studies included "exercise," "traumatic," "brain," "injury," and "rodent." We included only the studies that focused on concussion/mTBI effects. We included articles that looked at treatment both in the acute and chronic phases after concussion. The bibliographies of relevant articles also provided citations.

Exclusion Criteria

Exclusion criteria were non—English language articles, articles before the year 2000, case series, and review articles (except for review articles that relate to the discussion of more general aspects of concussion and PCS). For the human studies, we read each abstract and excluded any that did not feature aerobic exercise for assessment or as a form of treatment for concussion or PCS or that did not discuss the physiology of concussion or mTBI. For example, articles on moderate or severe TBI or that focused on vestibular or physical therapy modalities were excluded. For the animal studies, we excluded those that did not focus on concussion/mTBI (eg, seizures and moderate to severe TBI effects) or were review articles.

The Physiology of Concussion

Concussion has been described as a metabolic [2], physiological [12], and microstructural [13] injury to the brain. The metabolic cascade of events immediately after TBI involves excitatory neurotransmitter release, abnormal ion fluxes, increased glucose metabolism, lactic acid accumulation, and inflammation. The macrophysiological insult involves the autonomic nervous system (ANS) and its control of both CBF and cardiac rhythm. The primary ANS control center, located in the brainstem, may be damaged in concussion, particularly if a rotational force was applied to the upper cervical spine [14]. This mechanism was confirmed in a recent diffusion tensor imaging study showing changes in brainstem white matter neurons after concussion [15]. Animal and human data suggest that this physiological dysregulation typically resolves, assuming no recurrent insult, within days to weeks after the injury is sustained [2,16]. However, there is evidence of reduced resting CBF for up to a month after concussion both in adolescents [17] and in college football players [18]. Evidence has shown that a vulnerable period of brain metabolic imbalance occurs after concussion, the resolution of which does not necessarily coincide with resolution of clinical symptoms. Measuring N-acetylaspartate using proton magnetic resonance spectroscopy, Vagnozzi et al [19] showed that metabolic dysfunction can last up to 30 days after sport-related concussion (SRC) and up to 45 days in persons sustaining a second injury before resolution of the first injury. Thus, a second concussive event prior to metabolic resolution of the first concussion can significantly delay recovery.

Post-TBI autonomic dysfunction has been proposed as a possible cause for prolonged symptoms of PCS [20]. In studies of moderate to severe TBI, altered ANS 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, the arterial baroreceptors, and the heart [21], is proportional to TBI severity, and improves with TBI recovery [21]. In concussion/mTBI, autonomic dysfunction has been shown to affect cardiac function during exercise. For example, concussed athletes have altered heart rate variability during exercise [22] that is interpreted to reflect altered balance of the sympathetic and parasympathetic input from the ANS to the heart. This interpretation was supported by a study showing elevated heart rates (HRs) during steady-state exercise in concussed patients versus control subjects, suggesting excessive activity of the sympathetic branch of the ANS [23]. Newer evidence, however, suggests that concussed patients may not have the ability to switch appropriately from one branch of the ANS to the other (ie, from the parasympathetic to the sympathetic) at the appropriate time. Hilz et al [24] showed orthostatic intolerance in concussed subjects when moving from supine to standing (ie, blood pressure did not appropriately rise upon standing), consistent with concussed subjects not withdrawing parasympathetic influence or augmenting sympathetic modulation at the right time. In a recent prospective study of adolescents 13-18 years of age who had PCS, 70% of patients had abnormal tilt table results [25].

The physiological effects of concussion during exercise are especially important for athletes and soldiers. Athletes with PCS have been shown to have exercise intolerance, as well as altered control of CBF [26]. The CBF response during progressive exercise appears to be opposite to the reduced CBF measured at rest. CBF in persons with concussion increased out of proportion to exercise intensity compared with when they were

recovered and when compared with nonconcussed subjects exercising at the same intensities [26]. Importantly, the elevated CBF was associated with the development of symptoms of headache and dizziness that limited exercise tolerance in concussed subjects. This response may occur because cerebral autoregulation, the process that allows the brain to maintain an almost constant perfusion pressure in the face of varying levels of systemic blood pressure (BP) [27,28], appears not to function normally after concussion [29]. If cerebral autoregulation does not function normally after concussion, then changes in systemic BP will induce excessive changes in cerebral perfusion pressure, resulting in symptoms such as headache [30]. In support of this finding, patients with PCS exercising on a treadmill had abnormally increased BP at low exercise intensities associated with the appearance or exacerbation of symptoms [11,31].

Dysregulation of resting CBF has been shown in patients soon after concussion by magnetic resonance imaging (MRI) measures of global CBF [17,18], as well as by functional MRI (fMRI) within local brain regions [32]. Abnormal CBF has also been seen in patients with PCS [10,33]. This issue is particularly important in adolescents, in whom abnormally low resting CBF has been reported up to 4 weeks after injury despite reported resolution of resting symptoms [17]. A prospective evaluation of recovery from SRC revealed reduced resting CBF in the dorsal midinsular cortex at 1 month after concussion in slow-to-recover collegiate athletes that was inversely related to the magnitude of initial symptoms, suggesting that CBF could serve as a biomarker for human concussion and subsequent recovery [18].

The primary influence on CBF control is the arterial carbon dioxide tension ($Paco_2$). Depressed $Paco_2$ reduces CBF, and increased $Paco_2$ increases CBF [34]. For a given CO_2 production ($\dot{V}co_2$), the $Paco_2$ is inversely proportional to the pulmonary ventilation ($\dot{V}_E$); that is, as $\dot{V}_E$ increases, $Paco_2$ decreases, and vice versa. Normally, as oxygen consumption ($\dot{V}O_2$) and $\dot{V}Co_2$ increase with exercise intensity, $Paco_2$ increases until the onset of excess blood lactic acid accumulation, at which point there is a hyperventilation, that is, a respiratory compensation for the metabolic acidosis that reduces $Paco_2$ and CBF [27,28,35]. The onset of this compensatory hyperventilation is called the "ventilatory threshold" [36]. The $Paco_2$ where this hyperventilation begins varies among individuals—that is, some persons are more sensitive to the effects of CO_2 than are others. This phenomenon is known as "CO_2 sensitivity" [37]. There is no reason to expect that patients with concussion would have a different $\dot{V}Co_2$ than healthy patients because the $\dot{V}O_2$ for a given exercise intensity is not different [31]. However, it is possible that they have a different sensitivity to the effects of CO_2 if concussion damaged the control centers for the ANS and for $\dot{V}_E$ located in the brainstem. Again, evidence shows that some patients with concussion have injury to the brainstem [15], and a recent controlled study of female athletes with PCS revealed altered CO_2 sensitivity, $\dot{V}_E$, and abnormally elevated CBF during exercise that produced symptoms of headache and dizziness that limited their exercise tolerance [26].

The ability of the cerebral vasculature to maintain a steady supply of oxygenated blood in the face of changing $Paco_2$ is called *cerebral vasoreactivity* (CVR), a critical component of neurophysiological health. Some evidence links mTBI, impaired CVR, and outcome after concussion [38]. Len et al [38,39] showed that after SRC, CVR was not impaired at rest but was impaired in response to a respiratory stress test. Bailey et al [40] showed that boxers had reduced CVR to CO_2 compared with control subjects that correlated with the volume and intensity of sparring during training, suggesting that chronically impaired cerebral hemodynamic function in active boxers was from the repetitive, subconcussive head impacts. Other investigators have recently identified abnormal reactivity to CO_2 challenge after mTBI. Mutch et al [41] showed that both symptomatic and recovered asymptomatic PCS patients had abnormal regional CVR during provocative CO_2 challenge that was not present in healthy control subjects. Thus, accumulating evidence shows that abnormal dynamic control of the cerebral vasculature in response to changes in $Paco_2$ could be a functional biomarker of concussion and perhaps, with return of normal reactivity, of recovery.

Exercise Effects on the Brain

Emerging data suggest that exercise improves brain function via favorable effects on brain neuroplasticity [42] as early as after 6-8 weeks [43]. The rapidity of the beneficial effect of exercise on the brain suggests that the mechanism is not reduced cerebrovascular disease risk but improved neuronal function. Aerobic exercise improves fMRI cortical connectivity and activation [44], is cognitively protective [45], is associated with greater levels of brain-derived neurotrophic factor (BDNF), which is involved in neuron repair after injury, and increases hippocampal volume and improves spatial memory [46].

Physical deconditioning of the cardiovascular system as a result of prolonged rest may be a consequence of TBI. Exercise (or the lack thereof) has effects on the ANS and control of CBF. Deconditioning impairs CBF control [47], whereas exercise training and physical fitness improves CBF control [48] and CVR [49]. The mechanism may relate to improved autonomic function [50], improved CVR [49], and/or a sensitization of the autoregulatory system to gradual increases in systemic BP [51]. fMRI studies show an excess of metabolic activity during simple cognitive tasks, which suggests that the concussed brain is much less efficient acutely [52]

and in persons with PCS [33], which may explain why concussed patients become easily fatigued with sustained cognitive activity. Subthreshold aerobic exercise treatment has been shown to restore fMRI brain activation patterns to normal versus a sham (stretching) program in association with resolution of persistent symptoms, including fatigue [10].

Exercise Effects on the Concussed Brain

Animal Studies

Griesbach et al [53,54] have performed elegant rodent studies using a fluid percussion cortical impact injury model of mTBI. They found that exercise immediately after mTBI compromised BDNF, but if exercise was delayed by 2 weeks, BDNF increased in association with improved behavior [53,54], suggesting that a therapeutic window exists for the implementation of voluntary exercise after mTBI. These investigators also showed that the time window for exercise-induced increases in BDNF is dependent on injury severity [55]. BDNF levels increased in mTBI rats that exercised 14 to 20 days after injury, whereas the moderate TBI rats only showed that response when they exercised 30 to 36 days after injury. Furthermore, blocking BDNF greatly reduced the molecular effects of exercise [56]. These studies suggest that BDNF has a major role in cognitive effects of exercise in the traumatically injured brain.

Cardiac and temperature autonomic regulation are also compromised during exercise within the first 2 weeks after mTBI [57]. Griesbach et al [58] analyzed the effects of voluntary versus forced exercise after concussion. Rats *forced* to exercise 28-32 days and 35-39 days after mTBI markedly stimulated the corticotrophic axis and did not increase BDNF, whereas BDNF levels increased after *voluntary* exercise [58]. Thus the motivation for exercise appears to be important after mTBI. In another study, rats forced to exercise after mTBI had increased stress hormone levels, whereas rats allowed to voluntarily exercise did not have increased levels, suggesting that exercise regimens with strong stress responses (ie, forced exercise) may not be beneficial during the early post-TBI period [59].

In other animal studies, voluntary physical exercise immediately after or within days of TBI has been shown to have beneficial effects. For example, there were reduced interhemispheric differences in hippocampal formation and lateral ventricle volumes and in density of mature neurons in the hilus of the dentate gyrus and the perirhinal cortex [60], increased proliferation of neuronal stem cells [61] and reduced neuronal degeneration and apoptotic cell death around the damaged area [62], increased Purkinje neurons and suppressed formation of reactive astrocytes [63], and better cognitive performance in association with decreased DNA fragmentation in the hippocampus [64]. Furthermore, some rodent studies have shown that voluntary exercise just *prior to* injury is protective after TBI. Three weeks of voluntary exercise prior to injury improved cognitive performance and counteracted neuron and synaptic density loss associated with rodent TBI compared with nonexercising controls [65]. Six weeks of swimming training protected against oxidative damage and adverse neurochemical alterations (reduced activity of the sodium-potassium adenosine triphosphatase) after TBI [66]. These studies support the idea that regular physical training may exert prophylactic effects on neuronal cell dysfunction and damage associated with TBI.

Human Studies

Few clinical studies of the effects of physical activity upon the concussed brain in humans have been performed. A retrospective study of electronic medical records from the office-based practice of one family/sports medicine physician who provided recommendations for cognitive and physical rest based on existing consensus guidelines revealed that, based on the return of symptoms, 43.5% of patients returned to sport too soon and 44.7% returned to school too soon [67]. In another retrospective study, athletes engaging in a medium level of physical and cognitive activity (ie, school activity and light activity at home, such as slow jogging or mowing the lawn) performed better on neurocognitive testing than did those with no activity and those reporting the highest levels of activity [68]. These findings should be interpreted cautiously because activity was self-reported recall, and it is not known at what point after injury the athletes began physical activity.

Experimental studies reveal that some patients with PCS have a symptom-limited response to exercise [31]. In a recent controlled study [26], female athletes with PCS had abnormal CO_2 sensitivity, leading to a relative hypoventilation during exercise that raised CO_2 levels out of proportion to exercise intensity. This response raised exercise CBF disproportionately to intensity and was associated with symptoms of headache and dizziness that limited their exercise tolerance to low levels. A program of subthreshold aerobic exercise treatment restored their CO_2 sensitivity to normal and normalized their $\dot{V}_E$, $Paco_2$ levels, and exercise tolerance. Thus subthreshold aerobic exercise, which is akin to voluntary exercise in rodent concussion studies, can have salutary effects on the concussed brain in active patients with PCS. It has been shown to restore abnormal brain fMRI activation patterns to normal in patients with PCS [10], allowing successful return to sport and work [9,11]. A recent pilot study found that increased CBF velocity was strongly related to headache exacerbation during exercise in concussed athletes, suggesting that exercise-induced alterations in cerebral perfusion may be the mechanism for headache after SRC [69].

Other investigators have examined the cardiac autonomic response to concussion in athletes. La Fountaine et al [70,71] showed that two measures of cardiac vagal modulation, the QT interval variability index at rest and HR complexity during isometric hand grip exercise, were altered within 48 hours of injury, resolved within 1 week, and remained at control levels 2 weeks later, consistent with vagal dysfunction early after concussion. In a controlled study of HR variability in university athletes who were clinically judged to be recovered from concussion (a mean of 95 days after injury), Abaji et al [72] found that during isometric hand grip, but not at rest, athletes with a history of concussion had a significantly lower high frequency power and a significantly higher low frequency/high frequency ratio than did age and team-matched control subjects (with no history of concussion). Thus asymptomatic athletes exhibited modifications in cardiac autonomic modulation weeks to months after concussion that became apparent only during physical exertion.

The Role of Exercise in Concussion Management

The primary forms of concussion treatment have traditionally included rest, education, coping techniques, support and reassurance, neurocognitive rehabilitation, and antidepressants, all with limited evidence of efficacy [73]. When patients present for medical attention after an mTBI/concussion, rest is one of the most common recommendations they receive [74], and rest has also generally been extended to patients with PCS, that is, the persistence of symptoms beyond several weeks or months [75]. Moser et al [76] showed that 61.5% of adolescents with persistent symptoms after concussion improved after receiving education and reassurance and engaging in 1 week of prescribed rest. However, the efficacy of rest in all phases of concussion recovery is being challenged [4]. Persons with more severe TBI who exercise are less depressed and report better health status when compared with those who do not exercise [77]. Inactivity has been shown to prolong recovery from many health conditions, including those most often comorbid with mTBI/concussion such as vestibular disorders, depression, post-traumatic stress disorder, chronic fatigue, and pain disorders [4]. Other investigators suggest that the psychological consequences of removal from validating life activities, combined with physical deconditioning, may contribute to the development and persistence of PCS in some children and adolescents [78]. With respect to acute concussion, although it is generally accepted that children and adolescents require more cognitive and physical rest in the acute phase of recovery, there is no evidence that complete rest beyond 3 days in adults is beneficial, whereas gradual reintroduction of activity appears to be helpful [4]. Prolonged rest, especially in athletes, can lead to physical deconditioning and secondary symptoms such as fatigue and reactive depression [73]. de Kruijk et al [79] randomized adults discharged from the emergency department with acute mTBI to usual care or strict bed rest and found no significant differences in actual amounts of reported rest or in outcomes at 2 weeks, 3 months, and 6 months. In a recent prospective controlled trial in a pediatric emergency department, Thomas et al [8] randomized patients aged 11 to 22 years within 24 hours of concussion to strict rest for 5 days versus 1-2 days of rest followed by stepwise return to activity. The group treated with 5 days of strict rest reported more daily postconcussive symptoms and slower symptom resolution.

The Zurich guidelines advise that concussed patients who are asymptomatic at rest should progress stepwise from light aerobic activity such as walking or stationary cycling up to sport- or work-specific activities [1]. Athletes should not return to sport (RTS) until they can participate to the full extent of their sport without symptoms. We have applied this principle to persons with persistent symptoms. Our nonrandomized studies show that individualized subthreshold aerobic exercise treatment improved symptoms in subjects with PCS in association with improved fitness and autonomic function (ie, better HR and BP control) during exercise [11] and, when compared with a period of no intervention, safely improved the rate of recovery and restored function (sport and work) [9,11]. A similar rehabilitation program has been effective for children with PCS [7]. Recent data suggest that some concussion symptoms may be related to abnormal local CBF regulation that is amenable to individualized aerobic exercise treatment [10], but the mechanism of the effect of subthreshold exercise treatment in patients with PCS requires further study.

In our laboratory and clinic, we have demonstrated that the Buffalo Concussion Treadmill Test (BCTT) is the only functional test thus far shown to safely [11] and reliably [80] reveal physiological dysfunction in concussion, differentiate concussion from other diagnoses (eg, cervical injury, depression, and migraines) [9], and quantify the clinical severity and exercise capacity of concussed patients [11]. The test is based on the Balke cardiac protocol, which imparts a gradual increase in workload. The starting speed is 3.2-3.6 mph (depending on patient age and height) at 0% incline. The incline is increased by 1% at minute 2 and by 1% each minute thereafter while maintaining the same speed until the subject cannot continue. We established our safety protocol such that exercise is stopped using the predetermined criterion of symptom exacerbation [81]. The HR recorded at the threshold of symptom exacerbation forms the basis for the individualized exercise prescription (subsequently described). Testing requires some experience because neurologic symptoms have been reported by healthy persons after intense exercise

[82], and cervical symptoms and migraine headaches occasionally become exacerbated during the final stages of the test. However, the onset of symptom exacerbation in patients with physiological concussion occurs much earlier in the test protocol and well short of predicted maximum exercise capacity [81].

The contraindications to performing the BCTT are those that would typically contraindicate the performance of a cardiac stress test and are presented in Table 1. Using the BCTT, we have shown that it is safe for adult patients with PCS to exercise up to 74% of maximum predicted capacity [31], which provides an evidence base for stage 2 (light aerobic exercise) of the Zurich Conference guidelines' graduated return to play protocol [1].

Diagnosis of Postconcussion Disorders

In our clinic, the BCTT has become an essential component of the diagnostic process, especially for patients with prolonged symptoms. We conducted a retrospective review of 181 consecutive patients referred to our clinic for evaluation of suspected PCS. Referrals came from primary care physicians, neuropsychologists, specialists (neurologists), and self-referral. Each patient underwent a physical examination to evaluate any cervical, oculomotor, vestibular, and balance problems, as well as signs of dysautonomia (such as orthostatic intolerance). The physical examination also determined if patients were healthy enough to exercise on the treadmill. The BCTT was used to determine exercise tolerance. Patients who were symptomatic but could exercise to a state of exhaustion without symptom exacerbation were evaluated further for possible cervical, vestibular, and/or oculomotor injuries.

At the conclusion of the evaluation process, the treating physician evaluated all of the information and made a diagnosis. For the purposes of this retrospective review, a second physician reviewed all of the information and independently established a diagnosis for each patient. In most cases the second opinion was the same as that of the first physician, and when there was disagreement, the case was discussed until consensus on a primary diagnosis was reached. If a patient showed evidence of PCS, PCS was always the primary diagnosis.

The distribution of diagnoses is presented in Figure 1. (Note that many patients had a secondary diagnosis that is not represented in the chart.) The first important observation is that patients with physiological PCS—that is, patients with exercise intolerance and the usual array of symptoms—consisted of only 21% (n = 38) of the group. Furthermore, 13.3% of patients had completely resolved their concussion issues but did not know they had recovered. These recovered individuals were occasionally experiencing symptoms that they attributed to their concussion and were relieved to learn that there was nothing to stop them from returning to work, school, or sport safely. The 5% of patients with mood disturbance (eg, anxiety and depression) is substantially less than some clinician/researchers suggest [83]. However, as with migraine (also 5%), we found this to be an unlikely explanation of prolonged symptoms in our patient population.

The largest group (55.8%) of postconcussion disorders fell into a category we called cervicogenic-oculomotor-vestibular (COV). These patients demonstrated varying degrees of difficulty with dizziness, oculomotor performance, and cervical proprioception. Specific diagnosis within the COV group was beyond the scope of this study, although a review of the mechanism suggests that neck-related injury was the common denominator. The COV group in general tolerated exercise and in some cases experienced fewer symptoms as they approached voluntary exhaustion. Some patients in the COV group, however, stopped exercise

Table 1
Absolute and relative contraindications to the Buffalo Concussion Treadmill Test

Absolute contraindications	
History	Unwilling to exercise
	Increased risk for cardiopulmonary disease as defined by the American College of Sports Medicine*
Physical examination	Focal neurologic deficit
	Significant balance deficit, visual deficit, or orthopedic injury that would represent a significant risk for walking/running on a treadmill
Relative contraindications	
History	β-blocker use
	Major depression (may not comply with directions or prescription)
	Does not understand English
Physical examination	Minor balance deficit, visual deficit, or orthopedic injury that increases risk for walking/running on a treadmill
	Resting systolic BP >140 mm Hg or diastolic BP > 90 mm Hg
	Obesity: body mass index ≥30 kg/m^2

BP = blood pressure.

* Individuals with known cardiovascular, pulmonary, or metabolic disease; signs and symptoms suggestive of cardiovascular or pulmonary disease; or individuals ≥45 years who have more than one risk factor, including (1) family history of myocardial infarction, coronary revascularization, or sudden death before age 55 years; (2) cigarette smoking; (3) hypertension; (4) hypercholesterolemia; (5) impaired fasting glucose level; or (6) obesity (body mass index ≥30 kg/m^2).

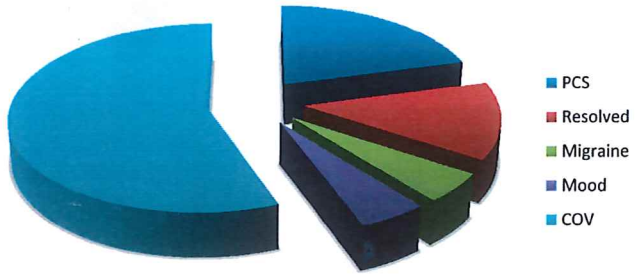

Figure 1. Distribution of patients assessed for postconcussion syndrome according to their primary diagnosis. PCS = postconcussion syndrome; resolved = concussion now resolved, completely recovered; migraine = migraine is the primary diagnosis; mood = depression or anxiety is the primary diagnosis; COV = primary diagnosis is cervicogenic/oculomotor/vestibular dysfunction.

because of significant vertigo and/or imbalance during the treadmill test.

Treatment With Subthreshold Exercise

If a submaximal symptom exacerbation threshold is identified on the BCTT, patients are given a prescription to perform aerobic exercise (on a stationary cycle at first) for 20 minutes per day at an intensity of 80% (90% in elite athletes) of the threshold HR achieved on the BCTT, once per day, for 5 to 6 days per week using an HR monitor. They should terminate exercise at the first sign of symptom exacerbation or after 20 minutes, whichever comes first. Having athletes use an HR monitor is important so they do not exceed the prescribed HR "dose." The BCTT can be repeated every 2-3 weeks to establish a new target HR until symptoms are no longer exacerbated on the treadmill. A more cost-effective approach, however, is simply to establish the subthreshold HR on the initial test and increase the exercise HR target by 5-10 beats per min (bpm) every 2 weeks (via phone call or e-mail), provided the patient is responding favorably [9]. More fit patients and athletes generally respond faster [11] and can increase their HR by 10 bpm every 1-2 weeks, whereas nonathletes typically respond better to 5-bpm increments every 2 weeks. The rate of exercise intensity progression varies, and some patients may have to stay at a particular HR for more than 2 weeks. Physiological resolution of concussion is defined as the ability to exercise at 85%-90% of age-predicted maximum HR for 20 minutes without exacerbation of symptoms for several days in a row [11]. Patients can then begin the Zurich RTS program. Exercise testing should only be considered for patients without orthopedic or vestibular problems that increase the risk of falling off the treadmill and only in patients who are at low risk for cardiac disease [11]. In patients who have a different cause of persistent symptoms (eg, COV disorders) or a combination of disorders (eg, patients with physiological PCS can also have a neck injury), we have found that subthreshold exercise along with specific treatment for the concomitant disorder enhances recovery as well [9].

The concept of return of normal exercise tolerance can also be used to establish physiological recovery from concussion. In a retrospective study of 117 athletes with SRC (75% male, ages 13-19 years), those that reported return to baseline symptoms (3 weeks after injury) had computerized neuropsychological testing (cNP) followed by the BCTT. All athletes returned to sport in the week after successful completion of the BCTT [84]. They then progressed through the Zurich Guidelines RTS program, and none of the athletes experienced exacerbation of symptoms in sport during the 2 months after RTS. The cNP test performance did not relate to RTS. Thus the ability of concussed athletes to exercise to exhaustion on the BCTT better predicted readiness to begin the RTS process than did same-day cNP test performance.

Conclusion

The pathophysiological response to concussion includes a complex neurometabolic cascade of events resulting in a mismatch of energy demand (metabolic crisis of ion fluxes and increased glucose requirement) and supply (low resting CBF). The energy deficit leads to a period of vulnerability during which the brain is at risk for additional injury, explains why symptoms are exacerbated by excessive cognitive and physical exertion early after concussion, and has been used to rationalize the prescription of complete rest until all symptoms have resolved. However, recent clinical and physiological research is showing that prolonged rest beyond the first couple of days might hinder rather than aid recovery because humans do not respond well to sustained removal from their social and physical environments and because prolonged rest adversely affects the physiology of concussion. We are starting to appreciate that introduction of symptom-limited activity, even within the first few days after concussion, is safe and perhaps even therapeutic. With respect to exercise, some animal data show that early forced exercise is detrimental to recovery, but other animal data suggest that voluntary exercise may not be detrimental. We have shown that in humans with postconcussion symptoms for more than 4-6 weeks, exercise using a predetermined stopping criterion (the symptom-exacerbation threshold), which is akin to voluntary exercise in rodents, is safe and can be used to develop individualized subthreshold exercise treatment programs to help these patients regain aerobic capacity and speed recovery. Prudent advice for patients with concussion early after injury is to avoid contact sport and the extremes of activity, that is, excessive physical exertion. Prolonged avoidance of physical exercise and mental activity, however, can also exacerbate symptoms. Persons who have experienced a concussion need guidance to help them avoid triggers of severe symptoms and a plan for gradually increasing

daily activities and exercise tolerance to promote recovery. Athletes who continue to report concussion-related symptoms well beyond the acute stage of injury, which in adolescents is 3-4 weeks [67,85], may benefit from a progressively intensive exercise protocol to return them to their sport.

The emerging data on the timing of return to activity and exercise after concussion are important for clinicians. These data support the hypothesis that patients with concussion and PCS who demonstrate exercise intolerance often have a physiological source for their symptoms. In the case of persons with PCS, individualized subthreshold aerobic exercise treatment or other approaches that improve autonomic function, such as ventilatory biofeedback [86], may address the underlying disease and speed of recovery. Further work should be performed in this area of the role of exercise during the PCS period. For patients in the acute phase of concussion recovery, however, the evidence to support symptom-limited, subthreshold aerobic exercise treatment is still lacking, and further research is required to determine if it is the ideal treatment. It is also important to emphasize that the response to early exercise may be different for different age groups; what is appropriate in an adult may not be appropriate in an adolescent or child. With respect to the determination of when a patient has recovered from concussion, emerging data suggest that return of normal exercise tolerance could be an objective physiological biomarker of recovery, which has implications for establishing prognosis and preventing premature return to sport, activity, or military duty.

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