

A Physiological Approach to Prolonged Recovery From Sport-Related Concussion

John Leddy, MD, FACSM, FACP*; John G. Baker, PhD*†; Mohammad Nadir Haider, MBBS§; Andrea Hinds, PhD*; Barry Willer, PhD‡

*UBMD Department of Orthopaedics and Sports Medicine, †Department of Nuclear Medicine, and ‡Department of Psychiatry, §Jacobs School of Medicine and Biomedical Sciences, The State University of New York at Buffalo

Management of the athlete with postconcussion syndrome (PCS) is challenging because of the nonspecificity of PCS symptoms. Ongoing symptoms reflect prolonged concussion pathophysiology or conditions such as migraine headaches, depression or anxiety, chronic pain, cervical injury, visual dysfunction, vestibular dysfunction, or some combination of these. In this paper, we focus on the physiological signs of concussion to help narrow the differential diagnosis of PCS in athletes. The physiological effects of exercise on concussion are

especially important for athletes. Some athletes with PCS have exercise intolerance that may result from altered control of cerebral blood flow. Systematic evaluation of exercise tolerance combined with a physical examination of the neurologic, visual, cervical, and vestibular systems can in many cases identify one or more treatable postconcussion disorders.

Key Words: postconcussion syndrome, exercise intolerance, athlete

New research is challenging the traditional approach of “rest until symptoms resolve” and suggests, in fact, that prolonged rest adversely affects the pathophysiology of concussion, delays the institution of effective therapies, and may be detrimental to recovery. Identifying the symptom generator(s) in the athlete with a prolonged recovery is essential to prescribing appropriate active therapy. This paper presents emerging thought about assessing exercise tolerance as a potential physiological biomarker to establish or confirm the diagnosis of concussion and, perhaps more importantly, to help practitioners decide when the physiological dysfunction of concussion has resolved. We discuss the current best available evidence for the pathophysiology of postconcussion syndrome (PCS) and for the efficacy of subthreshold aerobic exercise and of cervical, ocular, and vestibular rehabilitation for treating the athlete with prolonged recovery after concussion. A case report highlights how athletic trainers can be key members of the medical team in assessing and treating the athlete with prolonged recovery after concussion.

The most recent international consensus statement on concussion in sport, the Zurich guidelines,¹ and the 2014 National Athletic Trainers' Association (NATA) position statement on the management of sport-related concussion (SRC)² define *concussion* as a brain injury resulting from biomechanical forces producing a complex pathophysiological process that typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously. Concussion is a functional disturbance rather than a macrostructural brain injury, the resolution of which requires 7 to 10 days in the typical athlete (80%–90% of cases). The Zurich guidelines¹ state

that persistent symptoms (>10 days) are reported in 10% to 15% of patients with SRC. Thus, although athletes who are symptomatic for more than 10 days may be considered atypical with respect to the expected recovery time, recent investigators,³ using an approach accounting for concussion heterogeneity that incorporates symptoms and neurocognitive and vestibular-oculomotor outcomes, suggested that recovery time for adolescents with SRC may be as long as 3 to 4 weeks. Therefore, for the purposes of this paper, *concussion* refers to the condition that clinically resolves within 30 days of injury, whereas *PCS* is present when symptoms persist for 30 days or longer.

Postconcussion syndrome describes patients who do not recover after concussion within the expected time frame,⁴ which depends on the patient and the circumstances of the injury. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,⁵ *PCS* refers to (1) cognitive deficits in attention or memory and (2) at least 3 or more of the following symptoms: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, or apathy or personality change that persists for 3 months or longer.⁶ Use of a broader definition of PCS (eg, the World Health Organization's *International Classification of Disease-10*⁷ clinical criteria are the persistence of 3 or more of the following symptoms: fatigue, headache, dizziness, irritability, insomnia, concentration difficulty, or memory difficulty) is much more sensitive for identifying PCS patients but does not specify a time frame.⁶ After 3 weeks, patients (and especially athletes) begin to worry about when they will recover, and if symptoms persist for 6 weeks, PCS can alter how individuals live their lives.⁸ The various definitions of PCS reflect a syndrome characterized

by nonspecific cognitive and symptom criteria rather than by a specific diagnosis based on pathophysiological evidence.⁴

The NATA position statement² notes that adult males typically recover within 14 days, whereas females and younger patients may require more time to recover. Precisely when athletes are considered to have moved from a typical concussion recovery to PCS is not specifically defined, but athletes who are symptomatic for more than 4 weeks are considered to be beyond the typical recovery period, particularly if they are older adolescents or collegiate or professional athletes.^{2,9,10} Although some¹ have reported that children recover more slowly than adolescents, recent evidence^{3,11,12} suggested that adolescents take longer to recover than children or adults. Predictors of PCS are not known with certainty because PCS is not a specific diagnosis. The following clinical variables have been associated with increased PCS risk: a history of 3 or more concussions,^{13,14} female sex,¹⁵ younger age,¹⁶ history of cognitive dysfunction,¹⁷ and affective disorders such as depression and anxiety.^{18,19}

The Zurich guidelines¹ and the NATA position statement² noted that persistent symptoms are not specific to concussion, so it is important to consider other conditions such as migraine headaches, mental health concerns, or concurrent injuries (eg, to the cervical spine).²⁰ Practitioners must determine whether prolonged symptoms reflect ongoing concussion pathophysiology or a different process.^{4,21} Therefore, the assessment of PCS requires a careful history and physical examination (including assessment of any history of affective disorders¹⁸ and examination of the cervical spine, vestibular function, and vision^{4,20}). It is becoming evident that vision problems are common after concussion, that vision should be assessed acutely,²² and that treatment is indicated for patients with persistent oculomotor problems.²³ The purpose of this paper is not to present a comprehensive overview of all of the physical and psychological consequences of concussion but to review the emerging evidence on the physiology of concussion, introduce the concept of exercise tolerance as a potential physiological biomarker of concussion and of concussion recovery, describe a physiological approach to the differential diagnosis of PCS, and discuss the management and physiological treatment of the atypical athlete with persistent symptoms after concussion.

LITERATURE REVIEW METHODS

We searched PubMed and MEDLINE for articles using the key words *activity, athlete, autonomic, cervical, concussion, exercise, mild traumatic brain injury (mTBI), mTBI, ocular, physical, physiology, postconcussion syndrome, PCS, sport, therapy, treatment, vestibular, and vision*. Only original and review articles that focused on concussion or mTBI effects and treatment in both the acute and chronic phases after concussion were included. The bibliographies of relevant articles also provided citations.

Exclusion criteria were non-English-language articles, case series, and articles that did not focus on concussion or mTBI (eg, those that addressed seizures or moderate to severe traumatic brain injury [TBI]).

THE PHYSIOLOGY OF CONCUSSION

The Zurich guidelines¹ did not define what specifically constitutes the “complex pathophysiological process” of concussion, but it is considered to include some combination of metabolic,²⁴ physiological,²⁵ and microstructural²⁶ injuries to the brain. Concussion affects the autonomic nervous system (ANS)^{27,28} and the control of both cerebral blood flow (CBF)^{29–32} and cardiac rhythm.^{33,34} The primary ANS control center may be damaged in concussion, particularly if a rotational force was applied to the upper cervical spine,³⁵ as supported by results from a diffusion tensor imaging study³⁶ that showed changes to brainstem white matter neurons after concussion. The metabolic and physiological dysfunction typically but not always resolves within days to weeks after injury.^{24,37} For example, reduced resting CBF has been evident for up to a month postconcussion in some adolescents³¹ and collegiate football players.³² The resolution of this vulnerable period of brain metabolic imbalance after concussion does not necessarily coincide with the resolution of symptoms. Using proton magnetic resonance spectroscopy, Vagnozzi et al³⁸ showed that metabolic dysfunction can last up to 30 days after SRC and up to 45 days if a second injury occurs before the first has resolved. Thus, a second injury before metabolic homeostasis is restored can significantly delay the metabolic and clinical recovery from concussion.

The ANS consists of the sympathetic and parasympathetic branches, which act antagonistically to regulate homeostasis. The sympathetic nervous system (SNS) branch mobilizes the body for action and defense behaviors during times of stress, whereas the parasympathetic nervous system (PNS) branch works to conserve energy.³⁹ The primary ANS control center is in the brainstem, near the cardiorespiratory control center, and sends its nerve fibers out through the spinal cord. Evidence from functional magnetic resonance imaging⁴⁰ suggests that the ANS is distributed beyond the brainstem to include higher cortical (eg, dorsolateral prefrontal, posterior insular, and middle temporal cortices) and limbic-related regions (eg, amygdala, hippocampus, and thalamus). The major parasympathetic output from the brain, the vagus nerve, innervates the visceral organs and is essential for the regulation of cardiac rhythm. Heart-rate variability (HRV) is the physiological phenomenon of variations in the time interval between heartbeats. It is measured in the time domain by the variation in the beat-to-beat interval (the R-R interval on an electrocardiogram) or in the frequency domain by methods that assign bands of frequency and then count the number of R-R intervals that match each band. The bands are typically high frequency (HF), from 0.15 to 0.4 Hz, and low frequency (LF), from 0.04 to 0.15 Hz. The HF component is thought to primarily represent the SNS, whereas the LF component is considered a marker of both SNS and PNS activity. The contribution of each to LF power is controversial and related to the experimental conditions.⁴¹ Under stress, however, an increase in LF power reflects sympathetic activation.⁴¹ The LF:HF ratio is used to represent the sympatho-vagal balance.⁴¹ Low HRV (reflecting a preponderance of SNS activity) is associated with mortality in clinical populations at risk for heart disease,⁴² whereas high HRV is a beneficial adaptation to endurance training (reflecting increased PNS and reduced SNS activity).⁴³

Heart-rate variability has been used to quantify autonomic dysfunction across a broad spectrum of TBI severity, including concussion.^{33,44,45} Autonomic dysfunction after TBI is believed to represent some degree of uncoupling between the brain autonomic centers and the cardiovascular system,⁴⁴ can be precipitated by different types of exercise in patients after concussion,^{28,33} and improves as patients recover from severe TBI⁴⁶ or from concussion.²⁸ One group, for example, showed that concussed athletes who reported recent symptom resolution had abnormal HRV³³ and elevated heart rates (HRs)³⁴ during steady-state exercise (but not at rest) versus healthy controls, which is consistent with increased SNS activation during exercise after concussion. More recent evidence, however, suggests that concussed patients are unable to switch from parasympathetic to sympathetic control of cardiac function at the appropriate time. Symptomatic concussed individuals had lower HRs at exercise initiation and during equivalent exercise intensities on a progressive treadmill test when compared with their HRs once they had recovered; in other words, their HRs were not appropriate for the level of physical work being performed.⁴⁷ Hilz et al⁴⁸ identified orthostatic intolerance in concussed participants when moving from supine to standing. Blood pressure (BP) did not rise appropriately on standing, consistent with lack of withdrawal of parasympathetic influence or augmentation of sympathetic modulation. Clinically, this manifests as symptoms of lightheadedness and dizziness upon sitting or standing, as reported by some concussed patients. These symptoms can reach extreme levels with syncope, as from *postural orthostatic tachycardia syndrome*, which is defined as symptoms or syncope (or both) in association with a tachycardic HR response without a drop in BP.⁴⁹

Autonomic tests may be effective in identifying concussion or PCS. La Fountaine et al^{27,28} showed that 2 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 head 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 HRV in university athletes who were judged to be clinically recovered from concussion (a mean of 95 days postinjury), Abaji et al⁵⁰ found that during the isometric hand-grip exercise, but not at rest, athletes with a history of concussion had less HF power and a greater LF:HF ratio than age- and team-matched controls 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. A recent prospective study⁵¹ of adolescents 13 to 18 years of age with PCS provides an idea of the prevalence of autonomic dysfunction after concussion: 70% of these patients had abnormal cardiac tilt-table results. Thus, symptomatic orthostatic intolerance may be a clinical physiological biomarker of concussion, one that can be assessed in the examination room or on the sideline. A reduction of 20 mm Hg in systolic BP or a reduction of 10 mm Hg in diastolic BP (measured supine and within 3 minutes of standing) is diagnostic of orthostatic hypotension.⁵² Symptoms include lightheadedness, dizziness, blurred vision, and nausea. Because some healthy adolescents meet the diagnostic criteria for orthostatic hypoten-

sion but experience no symptoms, it is not clear whether this reflects physiological dysfunction from concussion or a preinjury physiological state. A rise in HR of 20 beats or more (with or without a drop in BP) can also indicate orthostatic intolerance but is considered more likely to be a hypovolemic response, whereas the absence of an HR response more often indicates a neurogenic cause.⁵² Vital signs need only be obtained in supine and standing positions (not sitting).⁵² These data show evidence of abnormal autonomic function with concussion and PCS; unfortunately, no information is available on the sensitivity or specificity of these tests in concussed patients. Finally, the reactive depression experienced by some athletes after concussion may influence vagal tone and autonomic regulation. Cardiac autonomic regulation is impaired in girls with major depression⁵³ as well as in those with reactive depression (eg, bereavement).⁵⁴ Therefore, exercise treatment (discussed later) may be beneficial from a psychosocial perspective to improve the negative mood driving the autonomic dysregulation in some patients after concussion.

The physiological effects of concussion during exercise are especially important for athletes. Athletes with PCS have exercise intolerance⁵⁵ that may result from altered control of CBF during exercise.²⁹ The CBF response during progressive exercise is opposite to the reduced CBF at rest. In female athletes with persistent symptoms (such as headache and difficulty with concentration) more than 6 weeks after concussion, CBF increased out of proportion to exercise intensity when compared with CBF in those athletes once they recovered and when compared with nonconcussed athletes exercising at the same intensities.²⁹ Elevated CBF was associated with the development of headache and dizziness, which significantly limited exercise tolerance in the PCS patients.⁵⁵ We hypothesize that cerebral autoregulation, which allows the brain to maintain an almost constant perfusion pressure in the face of varying systemic BPs,^{56,57} is abnormal after concussion.⁵⁸ If so, then changes in systemic BP will induce excessive changes in cerebral perfusion pressure in concussed patients and produce symptoms such as headache.⁵⁹ This hypothesis is supported by evidence that PCS patients exercising on a treadmill had abnormally increased BPs at low exercise intensities associated with the appearance or exacerbation of headache.^{55,60} Authors⁶¹ of a recent study also reported that elevated cerebral perfusion pressure caused headache during exercise shortly after SRC.

EXERCISE TOLERANCE

The Zurich guidelines¹ recommended that athletes recovering from a recent concussion return to play (RTP) only after they are asymptomatic both at rest and with provocative exercise. Stages 1 and 2 of the Zurich RTP program consist of low-level aerobic exercise; not until completion of the protocol is maximum exertion required. The inference is that exercise precipitates physiological and metabolic dysfunction that is not apparent while at rest after concussion. This can be reformulated as a question of exercise tolerance. For typical patients recovering from concussion (that is, not a patient with PCS), those who report a normal level of symptoms and who can exercise to exhaustion without symptom exacerbation (ie, normal

exercise tolerance) may, in conjunction with a normal physical examination and normal cognitive function, be sufficiently recovered physiologically to begin the Zurich graduated RTP protocol.¹ Conversely, the concussion patient who demonstrates exercise intolerance during systematic testing is not yet physiologically recovered or ready to begin the RTP protocol. *Exercise intolerance* manifests as a symptom-limited cessation of exercise at a submaximal exercise intensity, before reaching physical exhaustion or the maximum age-predicted HR (or both).⁶² The clinician assessing a concussed patient during an exercise test relies on 2 observations to determine exercise intolerance: the subjective report from the patient of increased or new symptoms plus the presence of signs such as obvious facial expressions of distress, sharply reduced communication with the clinician, or a significant jump in HR, BP, or both from one stage to the next. The patient with physiological intolerance to exercise typically stops well short of the age-predicted maximum HR because he or she simply cannot continue to exercise for reasons other than physical exhaustion. We hypothesize that the exercise intolerance provoked by systematic exercise testing is a proxy for the underlying abnormal physiology of CBF control as a result of concussion.²⁹ The principle of exercise intolerance may therefore be conceptualized as a physiological biomarker to establish or confirm the diagnosis of concussion and, perhaps more importantly, to help practitioners decide when the physiological dysfunction of concussion has resolved (ie, return of normal exercise tolerance).

We developed a systematic approach to assess exercise tolerance in PCS patients and those with acute concussion.⁶⁰ The Buffalo Concussion Treadmill Test (BCTT) is based on the Balke cardiac treadmill stress test and imparts a very gradual increase in workload. The BCTT is safe for use in patients with PCS⁶⁰ to develop a subthreshold exercise treatment prescription and has good test-retest reliability.⁶³ We also modified the BCTT to suit the needs of different populations, including the military.⁶⁴

With respect to the use of the BCTT in patients with acute concussion, we completed a prospective randomized controlled trial of 54 adolescents (66% males, mean age = 15.5 years) within 9 days of SRC (mean = 4.5 days).⁶⁵ On visit day 1, half performed the BCTT and half did not perform any exercise testing. The day 1 symptom severity score on the Sport Concussion Assessment Tool-2 was 35 ± 22 for the exercise-test group and 26 ± 22 for the no-exercise-test group, but the results were not significantly different. All those randomly assigned to the BCTT ($n = 27$) stopped exercise at their symptom-exacerbation threshold,⁶² which was well below their predicted maximum exercise tolerance (mean exercise HR at threshold was 70% of age-predicted maximum). All participants were diagnosed with a concussion as assessed by independent blinded physicians. Thus, acutely concussed adolescents displayed exercise intolerance on the treadmill. It is important to note that those who completed the treadmill test did not report a short-term increase in symptoms (ie, within 24 hours) or experience delayed recovery from SRC when compared with the control group.

The BCTT has also been used to establish physiological recovery from acute concussion. In the study referenced earlier,⁶⁵ all participants ($N = 54$) performed the BCTT 2

weeks after visit day 1. A total of 80% had return of normal exercise tolerance; that is, they achieved a mean exercise HR of 85% of age-predicted maximum. They stopped exercise because of exhaustion, not because of symptoms, and they were independently judged by blinded physicians to be recovered (based upon a normal level of symptoms and a normal physical examination). However, the 20% of participants with persistent exercise intolerance were judged by independent blinded physicians as still being concussed. Thus, the return of exercise tolerance was consistent with physician evaluation and with clinical practice. The benefit of the BCTT is that it may serve as a more objective physiological biomarker of concussion recovery if the clinician has concerns because some athletes intentionally minimize symptoms in order to RTP.⁶⁶ We also evaluated the value of exercise-tolerance assessment versus computerized cognitive testing to establish readiness to RTP acutely after SRC. In a retrospective study conducted to validate the Zurich RTP guidelines,⁶⁷ 117 adolescent athletes with SRC (mean age = 15.4 years) underwent computerized neuropsychological testing before performing the BCTT on the day they reported a baseline level of symptoms (a mean of 24 days after SRC). On passing the BCTT, all athletes began the Zurich RTP protocol. All participants with normal exercise tolerance on the BCTT completed the Zurich RTP protocol without symptom exacerbation and all returned to sport successfully. Computerized neuropsychological test performance did not predict RTP.⁶⁷

THE ATHLETE WITH PROLONGED RECOVERY

Persistent symptoms (>10 days) have been reported in 10% to 15% of collegiate and professional American football players and in Australian footballers with concussions. Greater rates (up to 30% or more) have been reported in ice hockey and high school athletes.²⁰ The Zurich statement¹ recommends an initial period (24–48 hours) of physical and cognitive rest immediately after the concussion and RTP only when the athlete is asymptomatic at rest. The practical consequence of the recommendation to rest until asymptomatic has been that many clinicians advise restricting all physical and cognitive activity because of a theoretical risk that symptoms indicate brain damage and will delay recovery, even in those with PCS who remain symptomatic well beyond the metabolic recovery time frame.⁶⁸ It is true that some animal⁶⁹ and retrospective human⁷⁰ data have shown that uncontrolled exercise or activity delays recovery if instituted too early after concussion. Humans, however, can identify their symptom-limited threshold and stop activity, whereas rats forced to continue to exercise cannot. The findings of recent studies have begun to challenge the use of rest as treatment for patients with concussion and PCS. For example, patients who were advised immediately after concussion to rest for 2 days and then return to normal activities according to their symptoms recovered faster than those who were advised to maintain strict bed rest for 5 days.⁷¹ In another investigation,⁷² concussed patients in a rest group were withheld from activities, including classes, for the remainder of the injury day and the following day, whereas patients in a no-rest group were not provided any postinjury accommodations. The prescribed day of cognitive and

physical rest did not reduce postconcussion recovery time, suggesting that light activity after concussion may not be deleterious to the recovery process. Our group⁶⁰ has shown that in PCS patients, a single bout of controlled exercise using the predetermined cessation criterion of the individual symptom-limited threshold was safe and did not increase symptoms or delay recovery. Moreover, a subthreshold aerobic exercise program using HR data from the initial exercise test safely resolved symptoms in the PCS patients when compared with a period of no intervention.⁶⁰

It is important to acknowledge that self-report of symptoms is problematic because symptoms can be nonspecific and may be reported by healthy athletes at baseline and by patients with other injuries, illnesses, or neuropsychiatric conditions such as anxiety or depression.²⁰ Patients with cervical injury, for example, report cognitive and headache symptoms as frequently as do patients after concussion.⁷³ Postconcussion syndrome is not a diagnosis but a description of patients who report prolonged symptoms.⁴ A focus of our work has been to evaluate PCS more systematically to define a series of specific postconcussion disorders (PCDs). For example, those with physiological concussion are identified by significant exercise intolerance, whereas those with symptoms and signs from cervical, vestibular, or visual dysfunction (or a combination of these) typically do not have early, significant exercise intolerance on the BCTT. We believe that objective physiological measures are required to confirm recovery because self-report of symptoms is confounded by athletes who minimize or hide symptoms in order to expedite RTP⁶⁶ or who lack appropriate knowledge of the symptoms and consequences of concussions.⁷⁴ Conversely, some PCS patients may continue to report symptoms because of either psychological or socio-legal considerations.²⁰

We have found that some PCS patients, particularly athletes, have persistent physiological dysfunction that is revealed by their level of tolerance to exercise and their HR response during systematic exercise testing. Clausen et al²⁹ recently reported persistent exercise intolerance in female collegiate athletes with PCS who had abnormally low sensitivity to arterial carbon dioxide when compared with healthy participants. This resulted in a relative hypoventilation during progressive exercise despite increasing carbon dioxide levels that caused CBF to rise disproportionately to the level of exercise they were performing. The PCS participants stopped exercise at submaximal levels because of symptoms of headache and dizziness. A program of subthreshold aerobic exercise restored their carbon dioxide sensitivity, ventilation, exercise CBF, and exercise tolerance to normal in association with symptom resolution. Others have identified abnormal autonomic regulation of BP⁴⁸ and HR^{33,34} in patients with concussion.

MANAGEMENT OF PERSISTENT POSTCONCUSSIVE SYMPTOMS

Every practitioner caring for the athlete with prolonged recovery from concussion should consider whether persistent symptoms reflect prolonged concussion pathophysiology or a different process.⁴ We have attempted to systematize the approach to PCS by using the response to

exercise and physical assessment of the ANS, the cervical spine, and the visual and vestibular systems that are commonly affected by the injury that produces concussion.^{4,22,23,73,75}

In athletes with prolonged symptoms (>3–4 weeks), it is safe to assess exercise tolerance using the BCTT.^{30,60,62,63} Athletes with a symptom-limited submaximal threshold (those who stop because of symptom exacerbation at a rating of perceived exertion <18 and who do not achieve near-maximum predicted HR) are considered to have a persistently abnormal concussion physiology (which we believe is a dysautonomia that produces abnormally elevated exercise CBF). These patients are candidates for subthreshold progressive aerobic exercise treatment.⁶² Physical examination findings in patients with other PCDs include abnormal visual tracking (saccadic eye motion with symptoms during smooth pursuit testing) or abnormal near point of convergence (normal is 6–10 cm from the nose) or both, cervical tenderness, spasm, reduced proprioception, and abnormal balance (abnormal Balance Error Scoring System or tandem-gait testing).^{76,77} A brief vestibulo-ocular motor-screening examination has demonstrated good sensitivity for identifying patients with concussion.⁷⁸ A physical sign-based approach to PCS reveals that the majority (approximately two-thirds) of patients do not have physiological concussion; rather, symptoms most often result from one of several PCDs, such as isolated or combined cervical, vestibular, or visual system injuries.⁷⁹ Identifying the source of symptoms allows the provider to prescribe specific active forms of therapy such as cervical physical therapy,⁸⁰ vision therapy,²³ or vestibular rehabilitation.⁸¹

MANAGEMENT OF PATIENTS WITH PCDs

The Zurich guidelines¹ acknowledge that more research is needed to evaluate the optimal amount and type of rest after SRC. Practitioners in the field must determine how much rest after concussion is enough to enhance recovery and when it is safe for concussed patients to be active again. The prescription of rest early after concussion has a theoretical basis, given the acute metabolic crisis of high energy demand,²⁴ the vulnerability of the brain to more serious injury and delayed recovery after a subsequent injury,^{80,82} and animal studies showing that premature exercise hinders recovery. Griesbach et al⁸³ found that exercise immediately after a fluid-percussion brain injury in rodents compromised brain-derived neurotrophic factor (BDNF), which is involved in neuron repair after injury as well as in cognitive performance. When exercise was delayed by 2 weeks, BDNF increased in association with improved behavior,^{83,84} suggesting a therapeutic window for the implementation of exercise after concussion. They subsequently analyzed the effects of voluntary versus forced exercise after concussion. Rats forced to exercise after concussion markedly stimulated the corticotrophic axis and did not increase BDNF, whereas BDNF levels increased after voluntary exercise.^{69,85} Thus, the motivation for exercise appears to be important after concussion, and exercise regimens with strong stress responses (ie, forced exercise) are not beneficial shortly after concussion.

Two uncontrolled studies^{86,87} showed that rest improved symptoms in adolescents slow to recover after concussion.

However, no evidence indicates that strict rest for more than 3 days is beneficial to adult recovery from concussion.⁶⁸ Adolescents advised to rest in bed for 5 days after concussion showed increased neurobehavioral symptoms versus those advised to resume normal activity after 2 days of rest. This may reflect a situational depression caused by missing social interactions and falling behind academically, thereby increasing emotional symptoms.⁷¹ Some evidence suggests that reassurance, discussing the expected recovery time, and education about compensatory strategies early in the process can reduce later symptoms.⁸⁸ Two controlled studies of adults showed that brief, early education (an information booklet)⁸⁹ and psychological intervention⁹⁰ reduced PCS symptoms at 3 to 6 months after injury. There is little evidence of efficacy for medications such as antidepressants for treating PCS,⁴ and compensatory strategies for students returning to class have not been explored in prospective trials but certainly merit further study.⁹¹

ACTIVE TREATMENT FOR THE ATHLETE WITH PROLONGED RECOVERY

Subthreshold Exercise

The Zurich guidelines¹ acknowledge that low-level exercise for those who are slow to recover may be of benefit, although the optimal timing to initiate this treatment after injury is currently unknown. This perspective is also supported by the NATA position statement.² In our center, we have demonstrated that the BCTT can reveal physiological dysfunction in patients with concussion,^{29,30,55,60} differentiate concussion from other diagnoses (eg, cervical injury, depression, migraines),^{79,92} and quantify the clinical severity and exercise capacity of concussed patients.⁶² Based on the Balke cardiac protocol, the test begins at a speed of 3.2 to 3.6 mph (5.2–5.8 kph, depending on the patient's age and height) at 0% incline. The speed remains the same, while the incline is increased by 1% each minute thereafter until the patient cannot continue. Our safety protocol dictates that exercise is stopped according to the predetermined criterion of symptom exacerbation.⁶² The HR at threshold forms the basis for an individualized aerobic exercise prescription that we have shown treats the underlying physiological dysfunction of concussion (see following paragraphs).²⁹ Testing requires some experience because neurologic symptoms have been reported by healthy individuals after intense exercise⁹³ 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.⁶²

Once the diagnosis of physiological concussion is established by treadmill testing, each patient is prescribed exercise at 80% to 90% of the achieved HR, which becomes his or her individual target HR. Patients are asked to exercise for 20 min/d (with a 5-minute warm-up to the target HR and a 5-minute cool-down for a total exercise duration of 30 min/d), 6 or 7 days per week. The use of an HR monitor is important to prevent athletes from overexerting (which will precipitate symptoms). Patients are advised to stop exercise at symptom exacerbation or at

20 minutes, whichever comes first. We advise them to exercise first on a bicycle (to minimize any provocation of vestibular symptoms) and then attempt treadmill running. The target HR is increased by 5 to 10 beats/min every 1 to 2 weeks, depending on how fast the patient is responding. Once the athlete can exercise at $\geq 85\%$ of the age-predicted maximum HR for 20 minutes without symptoms for 2 to 3 days in a row, he or she is declared physiologically recovered. Yet this does not necessarily mean the athlete is ready for RTP. Advice on RTP is based on history (eg, depending on the number of prior concussions, it may be wise for the athlete to forgo contact sport because of the risk of further injury) and the presence of other signs and symptoms (ocular or vestibular dysfunction, for example, which must resolve before full RTP is advised). Even if the athlete cannot yet RTP, he or she can begin training to restore aerobic fitness. Our nonrandomized studies showed that in PCS patients, individualized subthreshold aerobic exercise treatment improved symptoms, fitness, and autonomic function during exercise,⁶⁰ and when compared with no intervention, the rate of safe recovery and restoring function (sport and work) improved.^{60,92} Investigators⁹⁴ in a recent study used a standard cycle-ergometer protocol (the McMaster All-Out Progressive Continuous Cycling Test) in 54 youths (age range = 8.5–18.3 years) with PCS (mean symptom duration = 6.3 months). A total of 63% of participants had symptoms during exertion; however, the number and severity of symptoms improved significantly over the ensuing 24 hours in most patients. The authors concluded that exertion testing has an important role in the evaluation of symptoms and readiness to RTP, particularly in youths who are slow to recover, and that a cycle ergometer can be used safely by these patients. Although we demonstrated a benefit of subthreshold exercise treatment on the physiology of female athletes with PCS,²⁹ others have shown that sex may affect the response to exercise treatment. In a study of sedentary, healthy young adults, aerobic conditioning improved autonomic control of the heart only in males.⁹⁵

Treatment of Other PCDs

A proactive approach to treating cervical, vestibular, and ocular PCDs includes cervical physical therapy, vestibular rehabilitation, and vision therapy. The benefits of a combined approach of orthopaedic and vestibular physical therapy after concussion were shown in a randomized clinical trial and a case series.⁸⁰ If persistent headache after concussion suggests a cervicogenic cause, cervical spine manual therapy is effective.⁹⁶ Some patients are diagnosed with a combination of both physiological and cervical or vestibular disorders, based on early exercise intolerance on the BCTT plus cervical and vestibular abnormalities on physical examination.⁷³ By combining cervical and vestibular therapy with sub-symptom threshold aerobic exercise, 64% of these patients returned to full function within 1 year.⁹²

CASE STUDY

For the student-athlete with PCS, a gradual return to full school participation and a graded exercise program have been recommended before return to sport.^{97,98} As noted in the Reduce, Educate, Accommodate, Pace (REAP) pro-

Table 1. Patient's ImPACT Test Results

Test	Weekly Visits: Percentile (Classification)		
	1	2	3
Memory composite—verbal	1 (Impaired)	6 (Borderline)	10 (Low average)
Memory composite—visual	6 (Borderline)	20 (Low average)	25 (Average)
Visual motor speed composite	86 (High average)	90 (High average)	94 (Superior)
Reaction time composite	60 (Average)	69 (Average)	72 (Average)

gram,⁹⁹ the athletic trainer can play a pivotal role in informing school academic personnel that a student-athlete has had a concussion and in working with other school personnel to return the student-athlete to the classroom and to play.

Erik is a 16-year-old football player who suffered a concussion from helmet-to-helmet contact during practice 12 days before the school year began. Erik's athletic trainer recognized his concussion, removed him from play, and referred him to a concussion clinic. Erik reported a persistent headache, dizziness, sensitivity to light, and fatigue. Both Erik and his mother noted he had difficulty concentrating, even on simple tasks such as reading, watching television, or having a conversation. This was Erik's second concussion, and he and his mother described a prolonged recovery after the first injury.

On physical examination, Erik's supine and standing BPs were 119/75 and 127/81, with pulses of 76 and 96 beats/min, respectively. He was a little lightheaded on standing. Ocular convergence was abnormal at 12 cm from his nose, and he became symptomatic with visual tracking. Tandem gait was abnormal. Cervical examination was normal. His cranial nerves were intact, and his fundoscopic examination was normal. Thus, Erik showed signs of vestibular and oculomotor dysfunction and mild orthostasis on his physical examination.

Erik underwent a BCTT at his initial clinic visit, 3 days after injury. He demonstrated exercise intolerance at an HR of 105 beats/min. A second treadmill test 17 days after his injury revealed that his threshold was still 105 beats/min. Eventually, when his HR threshold reached 130 beats/min, he was prescribed subthreshold aerobic exercise at an HR no greater than 110 beats/min. His target HR was increased as his threshold HR increased on subsequent BCTTs. When Erik's balance and visual problems did not improve in the usual time frame, he was referred for vestibular rehabilitation. Erik's prolonged recovery was secondary to combined physiological, vestibular, and oculomotor dysfunction.

Erik was both a very good athlete and a very good student. Although he was still quite symptomatic, he wanted to attend school. Erik's athletic trainer had informed the school nurse, who informed other school academic personnel about his injury. Even though a gradual return to school was recommended, Erik returned to full days and reported that his symptoms worsened significantly. He was instructed to limit the number of hours he spent at school by attending half days, alternating mornings and afternoons. As part of a team approach to returning to school, a brief meeting was held with Erik, his parents, clinic personnel, the school nurse, his athletic trainer, his coach, and his teachers. Recognizing Erik's symptom threshold in class and providing accommodations were discussed. Course objectives and grading were adjusted so

that Erik's prolonged recovery did not affect his overall high school record.

Erik was seen in the concussion clinic for 15 visits over 6 months. After 5 months, he was able to exercise to his maximum HR, and then he began the Zurich RTP protocol. He completed ImPACT testing early in his recovery, as well as brief paper-and-pencil neuropsychological tests of concentration, processing speed, and visual tracking at his third clinic visit. As shown in Table 1, his computerized test results improved over time. It is interesting to note that although Erik was able to perform adequately on most testing (except for 2 relatively lower computerized composite scores; Table 2), he had difficulty sustaining concentration in school and maintaining the cognitive endurance required to process the amount of stimulation involved in a full school day. Pacing himself to take regular breaks before he reached his symptom threshold helped his cognitive recovery.

Erik's athletic trainer played a critical role in his removal from play and prompt referral for evaluation and treatment. As noted, successful completion of return to learn has been recommended before an RTP protocol is initiated.^{97,98} Thus, athletic trainers can contribute to student-athletes' integrated return to full daily functioning during a prolonged course of recovery after SRC.

CONCLUSIONS

The athlete with prolonged recovery after concussion is challenging to manage because of the nonspecificity of symptoms. Symptom reporting can be influenced by other medical conditions, such as migraine headaches, and by psychological factors, such as coexisting anxiety and depression. Practitioners should focus on the physiological signs of concussion to help narrow the differential diagnosis of PCS. In many cases, systematic evaluation of exercise tolerance combined with a physical examination of the neurologic, visual, cervical, and vestibular systems can identify 1 or more treatable PCDs. Identifying the symptom

Table 2. Patient's Additional Cognitive Testing at Week 3

Test	Raw Score	T-Score	Percentile	Classification
Wechsler Intelligence Scales for Children-IV				
Digit Span	35	65	94	Superior
Letter Number Sequencing	24	66	95	Superior
Coding	72	55	70	Average
Trail Making Test ^a				
Part A	16"	60	84	High average
Part B	43"	55	68	Average

^a Trail Making Test part A and B T-scores based on normative data from the age group 18–24 years.

generator(s) in the athlete with prolonged recovery is essential to prescribing appropriate active therapy. We have presented the current best available evidence for the pathophysiology of PCS and for the efficacy of subthreshold aerobic exercise and of cervical, ocular, and vestibular rehabilitation for the treatment of the athlete suffering from prolonged symptoms after concussion. Emerging research is challenging the traditional approach of rest until symptoms resolve and suggests, in fact, that prolonged rest adversely affects the pathophysiology of concussion, delays the institution of effective therapies, and may be detrimental to recovery. Future randomized multicenter trials of exercise treatment that include clinical phenotyping should determine the appropriate mode, duration, intensity, and frequency of exercise during the acute recovery phase of a concussion and establish the efficacy of subthreshold aerobic exercise and other forms of active treatment in those with PCS. The athlete experiencing prolonged symptoms should be encouraged to become active within his or her symptom limitations. Furthermore, the athlete with PCS may benefit substantially from a sub-symptom threshold exercise program that can safely improve activity tolerance, restore aerobic capacity, and prepare the athlete for a safe return to sport.

ACKNOWLEDGMENTS

Financial support for our research has been generously provided by the Ralph C. Wilson Foundation, the Buffalo Sabres Foundation, the Robert Rich Foundation, NFL Charities, and the Program for Understanding Childhood Concussion and Stroke.

REFERENCES

- McCrory P, Meeuwisse W, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Clin J Sport Med*. 2013; 23(2):89–117.
- Broglio SP, Cantu RC, Gioia GA, et al. National Athletic Trainers' Association position statement: management of sport concussion. *J Athl Train*. 2014;49(2):245–265.
- Henry LC, Elbin RJ, Collins MW, Marchetti G, Kontos AP. Examining recovery trajectories after sport-related concussion with a multimodal clinical assessment approach. *Neurosurgery*. 2016; 78(2):232–234.
- Leddy JJ, Sandhu H, Sodhi V, Baker JG, Willer B. Rehabilitation of concussion and post-concussion syndrome. *Sports Health*. 2012;4(2): 147–154.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Boake C, McCauley SR, Levin HS, et al. Diagnostic criteria for postconcussional syndrome after mild to moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2005;17(3):350–356.
- World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization; 1992.
- Willer B, Leddy JJ. Management of concussion and post-concussion syndrome. *Curr Treat Options Neurol*. 2006;8(5):415–426.
- Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med*. 2013;47(1):15–26.
- Pellman EJ, Lovell MR, Viano DC, Casson IR. Concussion in professional football: recovery of NFL and high school athletes assessed by computerized neuropsychological testing, part 12. *Neurosurgery*. 2006;58(2):263–274.
- Carson JD, Lawrence DW, Kraft SA, et al. Premature return to play and return to learn after a sport-related concussion: physician's chart review. *Can Fam Physician*. 2014;60(6):e310, e312–e315.
- Zuckerman SL, Lee YM, Odom MJ, Solomon GS, Forbes JA, Sills AK. Recovery from sports-related concussion: days to return to neurocognitive baseline in adolescents versus young adults. *Surg Neurol Int*. 2012;3:130–136.
- Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*. 2007;39(6):903–909.
- Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003;290(19):2549–2555.
- Preiss-Farzanegan SJ, Chapman B, Wong TM, Wu J, Bazarian JJ. The relationship between gender and postconcussion symptoms after sport-related mild traumatic brain injury. *PM R*. 2009;1(3):245–253.
- Lovell MR, Collins MW, Iverson GL, et al. Recovery from mild concussion in high school athletes. *J Neurosurg*. 2003;98(2):296–301.
- Teasdale TW, Engberg A. Duration of cognitive dysfunction after concussion, and cognitive dysfunction as a risk factor: a population study of young men. *BMJ*. 1997;315(7108):569–572.
- McCauley SR, Boake C, Levin HS, Contant CF, Song JX. Postconcussional disorder following mild to moderate traumatic brain injury: anxiety, depression, and social support as risk factors and comorbidities. *J Clin Exp Neuropsychol*. 2001;23(6):792–808.
- Chamelian L, Feinstein A. The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2006;18(1): 33–38.
- Makdissi M, Cantu RC, Johnston KM, McCrory P, Meeuwisse WH. The difficult concussion patient: what is the best approach to investigation and management of persistent (>10 days) postconcussive symptoms? *Br J Sports Med*. 2013;47(5):308–313.
- Kutcher JS. Management of the complicated sports concussion patient. *Sports Health*. 2010;2(3):197–202.
- Leong DF, Balcer LJ, Galetta SL, Evans G, Gimre M, Watt D. The King-Devick test for sideline concussion screening in collegiate football. *J Optom*. 2015;8(2):131–139.
- Master CL, Scheiman M, Gallaway M, et al. Vision diagnoses are common after concussion in adolescents. *Clin Pediatr (Phila)*. 2016; 55(3):260–267.
- Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train*. 2001;36(3):228–235.
- McKeag DB, Kutcher JS. Concussion consensus: raising the bar and filling in the gaps. *Clin J Sport Med*. 2009;19(5):343–346.
- Bazarian JJ. Diagnosing mild traumatic brain injury after a concussion. *J Head Trauma Rehabil*. 2010;25(4):225–227.
- La Fountaine MF, Gossett JD, De Meersman RE, Bauman WA. Increased QT interval variability in 3 recently concussed athletes: an exploratory observation. *J Athl Train*. 2011;46(3):230–233.
- La Fountaine MF, Heffernan KS, Gossett JD, Bauman WA, De Meersman RE. Transient suppression of heart rate complexity in concussed athletes. *Auton Neurosci*. 2009;148(1–2):101–103.
- Clausen M, Pendergast DR, Willer B, Leddy J. Cerebral blood flow during treadmill exercise is a marker of physiological postconcussion syndrome in female athletes. *J Head Trauma Rehabil*. 2016;31(3): 215–224.
- Leddy JJ, Cox JL, Baker JG, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *J Head Trauma Rehabil*. 2013;28(4):241–249.
- Maugans TA, Farley C, Altaye M, Leach J, Cecil KM. Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics*. 2012;129(1):28–37.

32. Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurol.* 2015;72(5):530–538.
33. Gall B, Parkhouse W, Goodman D. Heart rate variability of recently concussed athletes at rest and exercise. *Med Sci Sports Exerc.* 2004;36(8):1269–1274.
34. Gall B, Parkhouse WS, Goodman D. Exercise following a sport induced concussion. *Br J Sports Med.* 2004;38(6):773–777.
35. Geets W, de Zegher F. EEG and brainstem abnormalities after cerebral concussion. Short term observations. *Acta Neurol Belg.* 1985;85(5):277–283.
36. Polak P, Leddy JJ, Dwyer MG, Willer B, Zivadinov R. Diffusion tensor imaging alterations in patients with postconcussion syndrome undergoing exercise treatment: a pilot longitudinal study. *J Head Trauma Rehabil.* 2015;30(2):E32–E42.
37. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA.* 2003;290(19):2556–2563.
38. Vagnozzi R, Signoretti S, Tavazzi B, et al. Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes—part III. *Neurosurgery.* 2008;62(6):1286–1295.
39. Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med.* 2009;76(suppl 2):S86–S90.
40. Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *Neuroimage.* 2008;42(1):169–177.
41. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J.* 1994;71(1):1–2.
42. May O, Arildsen H. Long-term predictive power of heart rate variability on all-cause mortality in the diabetic population. *Acta Diabetol.* 2011;48(1):55–59.
43. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. *Sports Med.* 2003;33(1):33–46.
44. Goldstein B, Toweill D, Lai S, Sonnenthal K, Kimberly B. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. *Am J Physiol.* 1998;275(4, pt 2):R1287–R1292.
45. King ML, Lichtman SW, Seliger G, Ehert FA, Steinberg JS. Heart-rate variability in chronic traumatic brain injury. *Brain Inj.* 1997;11(6):445–453.
46. Meglic B, Kobal J, Osredkar J, Pogacnik T. Autonomic nervous system function in patients with acute brainstem stroke. *Cerebrovasc Dis.* 2001;11(1):2–8.
47. Hinds A, Leddy J, Sharma T, Willer B. Heart rate in response to exertion after concussion. *J Neurol Neurophysiol.* 2016;7(4):388.
48. Hilz MJ, DeFina PA, Anders S, et al. Frequency analysis unveils cardiac autonomic dysfunction after mild traumatic brain injury. *J Neurotrauma.* 2011;28(9):1727–1738.
49. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic dysfunction presenting as postural tachycardia syndrome following traumatic brain injury. *Cardiol J.* 2010;17(5):482–487.
50. Abaji JP, Curnier D, Moore RD, Ellemberg D. Persisting effects of concussion on heart rate variability during physical exertion. *J Neurotrauma.* 2016;33(9):811–817.
51. Heyer GL, Fischer A, Wilson J, et al. Orthostatic intolerance and autonomic dysfunction in youth with persistent postconcussion symptoms: a head-upright tilt table study. *Clin J Sport Med.* 2016;26(1):40–45.
52. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology.* 1996;46(5):1470.
53. Tonhajzerova I, Ondrejka I, Javorka K, Turianikova Z, Farsky I, Javorka M. Cardiac autonomic regulation is impaired in girls with major depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;34(4):613–618.
54. O'Connor MF, Allen JJ, Kaszniak AW. Autonomic and emotion regulation in bereavement and depression. *J Psychosom Res.* 2002;52(4):183–185.
55. Kozlowski KF, Graham J, Leddy JJ, Devinney-Boymel L, Willer BS. Exercise intolerance in individuals with postconcussion syndrome. *J Athl Train.* 2013;48(5):627–635.
56. Ogoh S, Dalsgaard MK, Yoshiga CC, et al. Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J Physiol Heart Circ Physiol.* 2005;288(3):H1461–H1467.
57. Querido JS, Sheel AW. Regulation of cerebral blood flow during exercise. *Sports Med.* 2007;37(9):765–782.
58. Junger EC, Newell DW, Grant GA, et al. Cerebral autoregulation following minor head injury. *J Neurosurg.* 1997;86(3):425–432.
59. DeWitt DS, Prough DS. Traumatic cerebral vascular injury: the effects of concussive brain injury on the cerebral vasculature. *J Neurotrauma.* 2003;20(9):795–825.
60. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med.* 2010;20(1):21–27.
61. Marsden KR, Strachan NC, Monteleone BJ, Ainslie PN, Iverson GL, van Donkelaar P. The relationship between exercise-induced increases in cerebral perfusion and headache exacerbation following sport-related concussion: a preliminary study. *Curr Res Concussion.* 2015;2(1):17–21.
62. Leddy JJ, Willer B. Use of graded exercise testing in concussion and return-to-activity management. *Curr Sports Med Rep.* 2013;12(6):370–376.
63. Leddy JJ, Baker JG, Kozlowski K, Bisson L, Willer B. Reliability of a graded exercise test for assessing recovery from concussion. *Clin J Sport Med.* 2011;21(2):89–94.
64. Progressive return to activity following acute mTBI/concussion: guidance for rehabilitation providers. Defense and Veterans Brain Injury Center Web site. <http://dvbic.dcoe.mil/resources/progressive-return-to-activity>. Published 2014. Accessed October 2005.
65. Leddy J, Hinds AL, Miecznikowski J, et al. Safety and prognostic utility of provocative exercise testing in acutely concussed adolescents: a randomized trial. *Clin J Sport Med.* In press.
66. McCrory P, Meeuwisse WH, Echেমendia RJ, Iverson GL, Dvorak J, Kutcher JS. What is the lowest threshold to make a diagnosis of concussion? *Br J Sports Med.* 2013;47(5):268–271.
67. Darling SR, Leddy JJ, Baker JG, et al. Evaluation of the Zurich Guidelines and exercise testing for return to play in adolescents following concussion. *Clin J Sport Med.* 2014;24(2):128–133.
68. Silverberg ND, Iverson GL. Is rest after concussion “The Best Medicine?”: recommendations for activity resumption following concussion in athletes, civilians, and military service members. *J Head Trauma Rehabil.* 2012;28(4):250–259.
69. Griesbach GS, Tio DL, Vincelli J, McArthur DL, Taylor AN. Differential effects of voluntary and forced exercise on stress responses after traumatic brain injury. *J Neurotrauma.* 2012;29(7):1426–1433.
70. Majerske CW, Mihalik JP, Ren D, et al. Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train.* 2008;43(3):265–274.
71. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics.* 2015;135(2):213–223.
72. Buckley TA, Munkasy BA, Clouse BP. Acute cognitive and physical rest may not improve concussion recovery time. *J Head Trauma Rehabil.* 2016;31(4):233–241.
73. Leddy JJ, Baker JG, Merchant A, et al. Brain or strain? Symptoms alone do not distinguish physiologic concussion from cervical/ vestibular injury. *Clin J Sport Med.* 2015;25(3):237–242.

74. Cournoyer J, Tripp BL. Concussion knowledge in high school football players. *J Athl Train*. 2014;49(5):654–658.
75. Leslie O, Craton N. Concussion: purely a brain injury? *Clin J Sport Med*. 2013;23(5):331–332.
76. Guskiewicz KM. Assessment of postural stability following sport-related concussion. *Curr Sports Med Rep*. 2003;2(1):24–30.
77. Schneiders AG, Sullivan SJ, Gray AR, Hammond-Tooke GD, McCrory PR. Normative values for three clinical measures of motor performance used in the neurological assessment of sports concussion. *J Sci Med Sport*. 2010;13(2):196–201.
78. Mucha A, Collins MW, Elbin RJ, et al. A brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings. *Am J Sports Med*. 2014;42(10):2479–2486.
79. Leddy J, Hinds AL, Sirica D, Willer B. The role of controlled exercise in concussion management. *Phys Med Rehabil*. 2016;8(3):S91–S100.
80. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med*. 2013;47(5):304–307.
81. Ellis MJ, Leddy J, Willer B. Multidisciplinary management of athletes with post concussion syndrome: an evolving pathophysiological approach. *Front Neurol*. 2016;7:136.
82. Tavazzi B, Vagnozzi R, Signoretti S, et al. Temporal window of metabolic brain vulnerability to concussions: oxidative and nitrosative stresses, part II. *Neurosurgery*. 2007;61(2):390–395.
83. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res*. 2004;1016(2):154–162.
84. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience*. 2004;125(1):129–139.
85. Griesbach GS, Tio DL, Nair S, Hovda DA. Recovery of stress response coincides with responsiveness to voluntary exercise after traumatic brain injury. *J Neurotrauma*. 2014;31(7):674–682.
86. Moser RS, Schatz P, Glenn M, Kollias KE, Iverson GL. Examining prescribed rest as treatment for adolescents who are slow to recover from concussion. *Brain Inj*. 2015;29(1):58–63.
87. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *J Pediatr*. 2012;161(5):922–926.
88. Mittenberg W, Tremont G, Zielinski RE, Fichera S, Rayls KR. Cognitive-behavioral prevention of postconcussion syndrome. *Arch Clin Neuropsychol*. 1996;11(2):139–145.
89. Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome following mild head injury in adults. *J Neurol Neurosurg Psychiatry*. 2002;73(3):330–332.
90. Mittenberg W, Canyock EM, Condit D, Patton C. Treatment of post-concussion syndrome following mild head injury. *J Clin Exp Neuropsychol*. 2001;23(6):829–836.
91. Master CL, Gioia GA, Leddy JJ, Grady MF. Importance of “return-to-learn” in pediatric and adolescent concussion. *Pediatr Ann*. 2012;41(9):1–6.
92. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. *Rehab Res Pract*. 2012;2012:705309.
93. Alla S, Sullivan SJ, McCrory P, Schneiders AG, Handcock P. Does exercise evoke neurological symptoms in healthy subjects? *J Sci Med Sport*. 2010;13(1):24–26.
94. Dematteo C, Volterman KA, Breithaupt PG, Claridge EA, Adamich J, Timmons BW. Exertion testing in youth with mild traumatic brain injury/concussion. *Med Sci Sports Exerc*. 2015;47(11):2283–2290.
95. Sloan RP, Shapiro PA, DeMeersman RE, et al. The effect of aerobic training and cardiac autonomic regulation in young adults. *Am J Public Health*. 2009;99(5):921–928.
96. Jull G, Trott P, Potter H, et al. A randomized controlled trial of exercise and manipulative therapy for cervicogenic headache. *Spine (Phila Pa 1976)*. 2002;27(17):1835–1843.
97. Baker JG, Rieger BP, McAvoy K, et al. Principles for return to learn after concussion. *Int J Clin Pract*. 2014;68(11):1286–1288.
98. Halstead ME, McAvoy K, Devore CD, et al. Returning to learning following a concussion. *Pediatrics*. 2013;132(5):948–957.
99. McAvoy K. REAP the benefits of good concussion management. HealthONE Web site. http://issuu.com/healthone/docs/reap_oct21. Published 2015. Accessed November 1, 2015.

Address correspondence to John Leddy, MD, FACSM, FACP, UBMD Department of Orthopaedics and Sports Medicine, State University of New York at Buffalo, 160 Farber Hall-SUNY, Buffalo, NY 14214. Address e-mail to leddy@buffalo.edu.