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REVIEW ARTICLE

A Physiologically Based Approach to Prescribing Exercise Following a Sport-Related Concussion

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Abstract

Clinical management of concussion has evolved over the last 20 years, and complete cognitive and physical rest remains a common clinical recommendation. The duration of rest may vary widely, from 24–48 h to several weeks or until the patient's symptoms have resolved or returned to near baseline levels. Following a period of rest, a stepwise progression of exercise is used for gradual return to play or to work. Previous research in healthy people suggested that prolonged periods of physical inactivity consistently induced deleterious physiological and psychological effects. A growing body of evidence indicates that initiating exercise earlier in the recovery process following a concussion may reduce symptom burden and lower the incidence of post-concussion syndrome. Preliminary findings appear promising, but data on the appropriate exercise prescription for patients who recently sustained a concussion are limited. We reviewed the literature in healthy individuals and patients with concussion and post-concussion syndrome to develop a physiologically based exercise prescription for the days following a concussion. Using this, practitioners may shorten the rest period and initiate controlled exercise earlier during the recovery process following a concussion.

Key Points

Prolonged periods of strict rest are likely detrimental to concussion recovery.

Therapeutic aerobic exercise can elicit positive physiological responses across multiple organ systems that may enhance recovery following a concussion.

Low-intensity, controlled aerobic exercise is likely well-tolerated in acutely concussed patients when appropriately prescribed.

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1 Introduction

It is estimated that upwards of 3.8 million concussions occur annually in the USA from sports participation or recreational activities, and nearly 30% of all concussions treated in emergency departments are due to a sport or recreational activity [1, 2]. A concussion can cause neuropathologic and neurometabolic changes in the brain that may reflect a functional impairment rather than a structural injury [3]. These changes may result in the immediate or delayed onset of symptoms, clinical signs, balance impairment, behavioral alterations, cognitive dysfunction, sleep irregularities, cardiac autonomic dysfunction, or visual disturbances [4–6]. After a concussion occurs, and following a brief period of rest, patients can initiate a stepwise progression of exercise that is used for gradual return to play (RTP) or return to activity and guided by symptom provocation and clinical judgement.

The scientific community's understanding of concussion has vastly improved over the last 20 years, but clinical management of the subacute phase (72 h to 7 days) of recovery still lacks consistent data to support specific strategies in regards to physical activity [7]. Studies that used a "rest" treatment for concussions have reported prolonged symptoms over the observation period [8, 9] but demonstrated improvements in neurocognitive performance [10,

11]. However, prolonged periods of physical rest in healthy, trained populations induce depression, anxiety, and insomnia and negatively impact the cardiovascular system, all of which may impede concussion recovery [12–14]. Nonetheless, recent work suggests that the clinical presentation of concussed patients may influence the efficacy of rest as a treatment [15]. Interestingly, prescribed rest is commonly described as the ideal intervention because rest could lower energy demands, reduce patient discomfort, and limit the risk of subsequent head trauma [16]. Rest is the most widely used treatment for concussion, but a recent systematic review stated that evidence is insufficient that prescribed rest facilitates recovery following a sport-related concussion (SRC) [16–18].

Unfortunately, prescribed rest inhibits the beneficial effects of controlled aerobic exercise, including improved depression and anxiety [19–23], reduced persistent post-concussion symptoms [20, 24–26], improved exercise tolerance [20–22, 24, 26], and enhanced brain function [20, 24, 25, 27]. Several reviews suggested that the early initiation of exercise following a concussion was advantageous. However, only one paper offered recommendations for a specific exercise prescription [28]. Therefore, the purpose of this manuscript was to review and evaluate the available empirical evidence to provide appropriate recommendations for prescribed therapeutic exercise following concussion.

2 Methodological Considerations

2.1 Study Selection

We searched PubMed and Google Scholar for published full manuscripts in English that included the terms low-intensity, light, moderate-intensity, vigorous, or high-intensity, or maximal and physical activity, aerobic exercise, endurance exercise, aerobic training, resistance training, resistance exercise, or strength training. Studies that used healthy human subjects and measured cerebral blood flow (CBF), blood pressure (BP), cerebral glucose, brain-derived neurotrophic factor (BDNF), cortisol, oxidative stress, or heart rate variability (HRV) during a single bout of exercise were included. Protocols that used graded intensities needed exertional stages lasting at least 5 min to be included so that a near steady state may have been achieved, more accurately reflecting the conditions of the proposed therapeutic exercise. The search terms concussion and post-concussion syndrome were used for studies that involved clinical populations. Inclusion required an intervention, such as prescribed rest, bed rest, exercise, or physical activity. Both prospective and retrospective studies were included. References from the originally collected articles were also examined.

2.2 Determination of Benefit or Detriment

Individuals who recently (≤ 7 days post-injury) experienced a concussion display impaired CBF, cerebral oxygenation, or cerebrovascular reactivity [29–34], abnormal BP responses [4, 35], or dysautonomia [4, 35–42]. It was suggested that cerebral hypoperfusion might be responsible for the provocation or worsening of concussion symptoms or reported exercise intolerance [43]. An acute bout of exercise was determined to be potentially beneficial or potentially detrimental based on a statistically significant increase in favorable biomarkers or a reduction in or maintenance of detrimental biomarkers listed in Sect. 2.1. Increases in CBF, cerebral glucose, BDNF, and HRV were considered favorable. Increases in systolic BP (SBP), mean arterial pressure (MAP), cortisol, and oxidative stress and reductions in diastolic BP (DBP) were considered detrimental. Furthermore, the authors considered how biomarker changes may affect impaired physiological systems following a concussion. For example, a significant increase in SBP during exercise may elicit a myogenic response in the cerebral arteries, thus stimulating reflexive cerebral vasoconstriction, resulting in reduced CBF in an already impaired state.

3 Findings

When determining the subacute prescription of exercise for patients who experienced an SRC, clinicians must consider exercise type, intensity, and duration, as each variable can drastically affect exercise tolerance, physiological responses, and patient safety. The goal of the exercise prescription recommendation is to provide an adequate stimulus to facilitate a positive physiological response that may improve cognitive function or patient mood and enhance immune and endocrine signaling while also restoring cardiac autonomic function and CBF. Previous research has suggested that long-duration aerobic exercise, high-intensity aerobic exercise, and resistance exercise may be detrimental for recently concussed patients when considering the physiological impairments associated with the injury. Therefore, an emphasis was placed on the physiological effects of short-duration, low-intensity, and moderate-intensity aerobic exercise [28, 44–46].

3.1 Low-Intensity Aerobic Exercise

Low-intensity aerobic exercise was defined as 30–40% of heart rate reserve (HRR), 37–45% of maximal oxygen consumption (VO_{2max}), 57–63% of maximal heart rate (HR_{max}), 28–69 watts (W), 1.6–3.9 metabolic equivalents (METs), or 9–11 on Borg's rating of perceived exertion (RPE) scale

[47, 48]. A short duration of exercise was defined as an exercise bout of ≤45 min. These measures provided guidelines for classifying the exercise intensities in this paper. When recreationally active adults participated in a steady-state exercise session at low intensity for 15–30 min, significant increases in HR were reported, but SBP, DBP, MAP, and CBF did not differ [49, 50]. The absence of pressure and CBF changes during low-intensity exercise suggested that CBF was not compromised. Concussed individuals displayed reduced CBF, which was present within 24 h post-injury and continued for more than 30 days [30–32, 34, 51]. Ide et al. [52] reported unchanged cerebral glucose uptake but increased CBF and cerebral oxygen (O_2) during cycling exercise at 30% of VO_{2max} in healthy adults, reflecting a positive physiological response [52]. Another study reported that MAP and CBF increased during low-intensity exercise. The mixed results may have been due to differences in ultrasound devices, participant positioning during exercise, or fitness status of participants since fitness ranged from fair to excellent and some studies were performed in a semi-recumbent or upright position [49, 50, 52–54].

BDNF assists with energy metabolism within the neuron, which is vital for differentiation and maintenance of neuronal ion concentrations, suggesting it could play an important role in recovery following a concussion [55]. However, during low-intensity aerobic exercise, the authors reported unchanged BDNF levels in healthy subjects [56, 57]. Similarly, no changes in BDNF concentrations were reported during a submaximal cycling session, although there was a significant reduction from pre-exercise to the 10-min recovery period [56]. Schmidt-Kassow et al. [58] reported similar findings during exercise, but there were no significant differences in BDNF levels between baseline and the 30-min of recovery concentrations. A subgroup analysis in two studies showed that males had significantly higher serum BDNF levels than females, and individuals with the Val/Val BDNF polymorphism had significantly higher serum BDNF levels than the Val/Met or Met/Met polymorphism groups [56, 58]. Sex or genetic factors may have influenced BDNF levels in studies when the samples were not sex or polymorphism matched. Furthermore, spikes in BDNF may have also been transient, and infrequent collection intervals (i.e., ≥20 min) possibly masked acute fluctuations because BDNF changes were identified at shorter intervals during exercise [59]. While there is a lack of human clinical data supporting low-intensity exercise having a positive effect on BDNF concentrations, there are sparse data demonstrating a negative impact. BDNF is commonly reported in animal models of traumatic brain injury, but peripheral levels typically reported in human studies may not represent levels present in the brain [60, 61]. Furthermore, BDNF is secreted by and acts on peripheral tissue such as skeletal muscle, making interpreting sources of change and targets of BDNF action difficult. Therefore, BDNF may not be an appropriate biomarker to determine the success of therapeutic interventions in human participants [62].

During exercise, some endocrine responses may be detrimental rather than beneficial. Cortisol, for example, has previously shown the ability to attenuate neuroplasticity and is an inhibitor of the neuronal glucose transporter (GLUT3), which impairs the metabolic action of BDNF [63]. Thus, if BDNF is a targeted biomarker, concurrently measuring cortisol may provide greater physiological insight into exercise efficacy [64–66]. Young, healthy, active adults showed significant reductions in cortisol levels following low-intensity exercise [56]; however, one study reported no significant changes between pre- and post-exercise cortisol levels [67]. These differences in findings may have been due to variations in methods of collecting cortisol (saliva vs. serum) or the frequency of collections post-exercise (5- or 10- vs. 20-min) [56, 68]. The findings, while inconsistent, do not suggest that low-intensity exercise would result in elevated levels of cortisol or have a detrimental effect on neuronal metabolism and function.

Oxidative stress can also have negative effects on neuron function, such as initiating apoptosis [69, 70] and reducing DNA binding and cell viability [71]. Interestingly, increased oxidative stress can occur following a brain injury [72, 73]. Only one study has examined oxidative stress during low-intensity exercise, and the authors reported no significant changes from rest to exercise or exercise to recovery, which suggested low-intensity exercise may be safe for patients with concussion [50]. It is generally accepted that HR increases at lower exercise intensities predominantly because of parasympathetic (vagal) withdrawal [74]. However, parasympathetic influence, as measured by high-frequency (HF) power, was relatively unchanged up to 70% of VO_{2max} [75–78]. In one other study examining low-intensity exercise, the authors reported a reduction in HF power and an increase in sympathetic activity, as measured by low-frequency (LF) power, suggesting some sympathetic influence may be present, even at lower intensities [79]. It should be mentioned that, unless LF power is transformed to normalized units (nu), LF power is influenced by both sympathetic and parasympathetic control [80]. Without appreciable changes in BP, CBF, or hormone levels, clinicians may not need to worry about detrimental changes in autonomic function. In young, healthy, active populations, low-intensity aerobic exercise displayed no adverse effects on exercising BP, CBF, cortisol, or BDNF levels [49, 52, 56, 58, 67, 68]. Additional work is needed to examine cardiac autonomic modulation in concussed individuals participating in low-intensity aerobic exercise to determine whether the physiological responses are consistent with previous studies of

Table 1 Physiological responses in healthy humans participating in low-intensity exercise

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Bernardi et al. [75]	15	Sedentary and trained cyclists	Sedentary 23.1 ± 0.7; athletic 17.8 ± 1.1	1. 20 min BL 2. Incremental increases of 30 W every 5 min 3. 15 min recovery	HRV	Sedentary 30 W, 60 W, 90 W, 120 W exercise vs. BL: ↑ HR Sedentary 30 W, 60 W, 90 W exercise vs. BL: LFnu, HFnu Sedentary BL = 4 min recovery: LFnu, HFnu Sedentary BL vs. 8 min recovery: ↑ LFnu, ↓ HFnu Active 30 W, 60 W, 90 W, 120 W, 150 W, 180 W, 210 W exercise vs. BL: ↑ HR Active 30 W, 60 W, 90 W, 120 W, 150 W exercise = BL: LFnu, HFnu Active BL = 4 and 8 min recovery: LFnu, HFnu
Perini et al. [77]	7	Average VO_{2max} 44.4 ± 1.6 ml/kg/min	23.7 ± 0.8	1. 5 min seated rest 2. 5 min @ 50 W, 100 W, or 150 W 3. 5 min recovery	HRV	50 W exercise = rest: LFnu 50 W and 100 W exercise = rest and recovery: LF:HF 50 W, 100 W, 150 W exercise = rest: HFnu
Rimoldi et al. [79]	12	Champion swimmers	16 ± 2	1. BL 2. Modified Bruce protocol (extended to 5 min stages) 3. Recovery	HRV	Stage 2, 3, 4 vs. BL: ↓ RR interval Stage 2 vs. BL: ↑ LFnu Stage 2 and 3 vs. BL: ↓ HFnu, ↑ LF:HF Stage 3 = BL: LFnu Stage 4 = BL: LFnu, HFnu
Ide et al. [52]	12	Average VO_{2max} 43 ± 2 ml/kg/min	23 ± 1	1. 10 min rest 2. 10 min @ 30% of VO_{2max} 3. 10 min @ 60% of VO_{2max}	HR MAP CBF Cerebral O_2 Cerebral glucose	Rest vs. 30% exercise: ↑ HR, MAP, $MCAV_{mean}$, HbO_2 Rest = 30% exercise: (a–*v*)Glucose Rest vs. 30% exercise: ↓ (a–*v*)O_2
Jacks et al. [68]	10	Average VO_{2max} 44.5 ± 6.6 ml/kg/min	25.6 ± 4	1. 60 min of 45%, 60%, or 75% VO_{2peak}, or rest 2. 20 min recovery	Cortisol	45%, 60%, 75% BL = 10 min, 20 min, 40 min exercise cortisol
Ogoh et al. [91]	7	Not reported	25 ± 2	1. 10 min rest 2. Progressed up to 39 W, 93 W, or 142 W for 6–8 min 3. 10 min recovery 4. ~ 30–40 min of recovery until HR and MAP returned to BL 5. Process repeated for all intensities	HR BP CBF Pa_{CO_2}	39 W, 93 W, 142 W exercise = rest: Pa_{CO_2}
Goto et al. [50]	8	Not reported	26.3 ± 2.3	1. 5 min BL 2. 30 min @ 25%, 50%, or 75% VO_{2max} 3. 10 min recovery	HR BP Oxidative stress	25%, 50%, 75% exercise vs. rest and recovery: ↑ HR 50%, 75% vs. 25% exercise: ↑ HR, ↑ MAP 75% vs. 25% and 50% recovery: MAP 25% exercise = rest: MAP 25% and 50% exercise = rest: 8-isoprostane

Table 1 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Fisher et al. [49]	9	Recreationally active	24 ± 3	1. 3–5 min warm-up until target HR obtained (30% or 50% of HRR) 2. 15 min steady-state exercise 3. ~30 min of recovery until BL HR and MAP obtained 4. 3–5 min warm-up until target HR obtained (30% or 50% of HRR) 5. 15 min steady-state exercise	HR BP CBF	Rest vs. 30% exercise: ↑ HR Rest = 30% exercise: SBP, DBP, MAP, PP, $MCAV_{mean}$, CVCi, Pa_{CO_2}
Hill et al. [67]	12	Average VO_{2max} 65.5 ± 0.1 ml/kg/min	26 ± 3	1. 5 min @ 10–20% of VO_{2max} 2. 30 min @ 40%, 60%, or 80% of VO_{2max} 3. 20 min rest	Cortisol	Rest pre vs. post: ↓ cortisol 40% pre = post: cortisol 60%, 80% vs. 40%, 20 min rest: ↑ cortisol
Sato et al. [54]	10	Average VO_{2max} 46.2 ± 7.2 ml/kg/min	24 ± 5	1. 3 min BL 2. 5 min @ 40%, 60%, and then 80% of VO_{2peak}	HR BP CBF	40%, 60% exercise vs. rest: ↑ HR, MAP, $MCAV_{mean}$
Nofuji et al. [57]	16	Average VO_{2max} Sedentary 34.7 ± 4.0 ml/kg/min; active 42.3 ± 4.5 ml/kg/min	Sedentary 22.8 ± 1.9; active 21.6 ± 3	1. 30 min @ 40% or 60% of VO_{2peak} 2. 15 min seated rest	BDNF	40% BL = post and recovery: BDNF
Schmidt-Kassow et al. [58]	40	Men 44.4 ± 29.1 MET-h/wk; women 41.6 ± 21.5 MET-h/wk	Men 23 ± 2.9; women 22 ± 2.2	1. 5 min exercise intensity calibration 2. 25 min constant exercise (low or high intensity) 3. 2 min cool down 4. Recovery	HR BDNF	High- vs. low-intensity exercise: ↑ HR, BDNF Male vs. female during exercise: ↑ BDNF High = low intensity: BL BDNF, recovery BDNF
McDonnell et al. [56]	25	Val/Val 31.1 ± 13.1 MET-h/wk; met allele: 23.2 ± 17.2 MET-h/wk	Val/Val 27.8 ± 7.9; met allele: 26.1 ± 8.4	1. 15 min of 75% of age-predicted HR_{max} or 30 min of 38% or age-predicted HR_{max}, or 30 min seated rest 2. 10 min recovery	BDNF Cortisol	MET vs. Val/Val BL: ↓ BDNF 75 and 38%, control pre vs. 10 min recovery: ↓ BDNF 38% pre vs. post: ↓ cortisol Control pre vs. post: ↓ cortisol 75 vs. 38% 10 min recovery: ↑ cortisol

a–v arteriovenous difference, *BDNF* brain-derived neurotrophic factor, *BL* baseline, *BP* blood pressure, *CBF* cerebral blood flow, *CVCi* cerebral vascular conductance index, *DBP* diastolic blood pressure, *h* hour, HbO_2 oxygenated hemoglobin, *HFnu* high frequency normalized units, *HR* heart rate, HR_{max} maximal heart rate, *HRR* heart rate reserve, *HRV* heart rate variability, *LF:HF* low frequency to high frequency ratio, *LFnu* low frequency normalized unit, *MAP* mean arterial pressure, $MCAV_{mean}$ mean middle cerebral artery velocity, *MET* metabolic equivalents, *min* minutes, O_2 oxygen, Pa_{CO_2} arterial partial pressure of carbon dioxide, *PP* pulse pressure, *SBP* systolic blood pressure, VO_{2max} maximal oxygen uptake, VO_{2peak} peak oxygen uptake, *W* watts, *wk* week(s), ↓ and ↑ indicate decrease and increase, respectively

[a]Age is presented as year, mean ± standard deviation

healthy individuals [75, 77, 79]. Research on oxidative stress at lower levels of exercise intensity also requires further investigation as data are limited. Table 1 summarizes the low-intensity exercise results.

3.2 Moderate-Intensity Aerobic Exercise

Moderate-intensity aerobic exercise was defined as 40–59% of HRR, 46–63% of VO_{2max}, 64–76% of HR_{max}, 70–104 W, 4.0–5.9 METs, or 12–13 on Borg's RPE scale [47, 48]. During continuous, moderate-intensity aerobic exercise, participants displayed significantly increased HR, increased SBP, and decreased DBP when compared with rest, but CBF remained unchanged [49], whereas Goto et al. [50] reported increased MAP. In contrast, two other studies reported increased CBF during moderate-intensity aerobic exercise [52, 54] and increased oxygenated hemoglobin, glucose uptake, and cerebral perfusion [52], suggesting positive physiological responses during exercise. Bernardi et al. [75] reported a significant increase in HR but no changes in LFnu or HFnu power when the 90 W stage of a graded cycling protocol was compared with baseline. When different graded exercise protocols were used, the authors reported increases in LFnu, which suggests that sympathetic activity increases during moderate-intensity exercise [77, 79]. Interestingly, Raczak et al. [81] reported increased parasympathetic activity and decreased SBP 60 min after exercise, indicating that moderate-intensity exercise may be beneficial to autonomic and cardiovascular function. It is expected that, as exercise participation stops, sympathetic activity reduces and parasympathetic activity returns as the predominant tone at rest, which is called parasympathetic reactivation [82]. When compared with rest, moderate-intensity exercise appeared to increase or maintain CBF and consistently increase MAP; findings regarding autonomic function varied, but it may be minimally affected.

Endocrine responses during moderate-intensity aerobic exercise were inconsistent in terms of BDNF concentrations, as four studies reported significant increases [58, 83–85] and two reported no change [56, 86]. Given the transient nature of BDNF, collection intervals of 10–15 min were preferred as concentrations dropped dramatically after 20 min [84], peaked between 15 and 20 min [58], and may appear unchanged when only collected immediately before and after exercise [83]. Cortisol responses after moderate-intensity aerobic exercise were also inconsistent, with two studies reporting no change and one reporting an increase in concentrations [56, 67, 68]. Discrepancies may have been due to variable sample collection frequencies or the use of saliva versus blood [56, 67, 68]. When considering endocrine responses of both BDNF and cortisol, it appears that cortisol may attenuate some of the neurotrophic effects of BDNF, but it was difficult to say for sure as the studies presented with mixed results [65, 66].

In addition to cortisol, oxidative stress as exercise intensity increases is a concern because of the possibility of inducing neuronal apoptosis [69, 70]. Goto et al. [50] reported no change in markers of oxidative stress, and Tozzi-Ciancarelli et al. [87] reported no change in oxidative stress or antioxidant concentrations. Conversely, a significant increase in oxidative stress was found when immediately before and after exercise was compared [83]. Without concurrently measuring levels of antioxidants, which could attenuate the negative effects, increases in oxidative stress concentrations are difficult to interpret. Therefore, even though the evidence is somewhat conflicting, it is unlikely that moderate-intensity exercise increases oxidative stress to a level that overpowers the buffering capacity of antioxidants and endangers neuron health.

In young, healthy, active populations, moderate-intensity aerobic exercise had generally positive effects on CBF [49, 52, 54], cortisol [56, 67, 68], oxidative stress [50, 83, 87], and BDNF levels [57, 85, 86, 88] and induced variable changes in BP [49, 50, 52, 54, 81] and autonomic function [75, 77, 79, 81]. This combination of physiological effects may provide therapeutic benefits for recently concussed patients. Moderate-intensity exercise may also induce negative physiological consequences, although the evidence is inconclusive. It should be noted that SBP increases during moderate-intensity aerobic exercise, which is most likely due to vagal withdrawal and increases in sympathetic tone; however, when MAP was reported, it did not exceed the cerebral pressure threshold of > 150 mmHg that could reduce CBF [89]. In healthy populations, it appears that moderate-intensity aerobic exercise would provide sufficient stimuli to elicit changes in cardiovascular and endocrine function. The determination of whether or not moderate-intensity aerobic exercise is too great a physiological stress for recently concussed patients is less certain and warrants exploration. Table 2 provides a summary of moderate-intensity exercise results.

3.3 High-Intensity Aerobic Exercise

High-intensity aerobic exercise was defined as 60–89% of HRR, 64–90% of VO_{2max}, 77–95% of HR_{max}, 105–174 W, 6.0–9.9 METs, or 14–17 on Borg's RPE [47, 48]. The effects of high-intensity aerobic exercise included researchers primarily reporting increased BP [50, 54, 75, 90, 91], variable findings for CBF [54, 90, 91], increased free radical production [50, 83, 87] and cortisol synthesis [67, 68], dangerous increases in MAP [50, 92], and reductions in cerebral glucose [93]. It should be mentioned that Goto et al. [50] reported upper limits of MAP exceeding the threshold of 150 mmHg, which could impair CBF [89]. Additionally, a recent review stated that CBF begins to plateau after exercise intensity surpasses 60% of VO_{2max} and ultimately

decreases as intensity increases, depending on the severity of hyperventilation-induced hypocapnia [94]. These findings in young, healthy individuals suggest that high-intensity aerobic exercise would likely be detrimental for physiologically compromised concussed patients. Furthermore, it is unlikely that patients with SRC could tolerate this level of intensity, thus making high-intensity aerobic exercise a poor candidate for therapeutic prescription during the subacute phase of recovery. Table 3 summarizes the high-intensity exercise results.

3.4 Long-Duration Aerobic Exercise

For this review, long-duration aerobic exercise was classified as an exercise session lasting longer than 45 min, as the proposed therapeutic exercise session would not exceed this length of time. The detrimental effects of long-duration aerobic exercise include increased oxidative stress [45], increased cortisol secretion [68, 95, 96], impaired CBF [97, 98], decreased cerebral glucose [97, 98], and altered cardiovascular [99] and autonomic function [100]. The combined effects of long-duration aerobic exercise have the potential to increase neuronal apoptosis via free radical production, attenuate the effect of BDNF by increasing cortisol, and reduce cerebral substrate availability, which may already be impaired [99, 101–103]. Although the intensity of long-duration aerobic exercise is likely a contributing factor, extended periods of sustained physiological stress in recently concussed patients do not appear to be beneficial for recovery and may not be well-tolerated.

3.5 Resistance Exercise

The detrimental effects of resistance exercise include cerebral vasoconstriction via the myogenic mechanism in response to substantial increases in BP [44, 104–106], increased oxidative stress [107, 108], delayed vagal reactivation [82, 109], increased sympathetic activity [82, 109], and increased cortisol [110]. Intensity [percentage of one repetition maximum (1RM)] of resistance exercise may be the primary factor in eliciting changes in BP and autonomic modulation, as low-intensity resistance exercise (30% 1RM) did not significantly increase SBP or HR or decrease CBF, whereas resistance exercise at 40% and 80% of 1RM resulted in impaired cardioautonomic function [106, 111, 112]. Further, cortisol appeared unchanged at 30% of 1RM but significantly increased at 75% of 1RM [110]. It should be noted that 50% of 1RM with normal and slow movement significantly increased SBP, but MAP and CBF were not reported [113]. Considering the possible balance and coordination problems exhibited by patients with concussion, resistance training may not be appropriate for patients with subacute concussion [6]. When combined, the adverse effects may result in decreased cerebral perfusion and substrate delivery, increased neuronal apoptosis, and attenuated BDNF action, all of which may negatively impact recovery from a sport-related concussion.

3.6 Exercise in Concussed Populations

An active treatment model for brain injuries dates back over 40 years when Relander et al. [114] used biweekly physical therapy and patient engagement and reported a significant improvement in the time by which patients returned to school or work compared with routine care. Several studies provided evidence that exercise (aerobic or aerobic + coordination) was an effective treatment for patients with persistent post-concussion symptoms, and the treatment was well-tolerated [20, 24–26, 115–120] (Table 4). Neurocognitive scores were better in patients who participated in light activity following their concussion [121]. Retrospective reviews found lower risks of prolonged symptoms in patients who participated in low to full activity following a concussion [122]. In fact, two studies reported 100% RTP when using a provocative, graded exercise test [Buffalo Concussion Treadmill Test (BCTT)] to aid in concussion management [123, 124]. The BCTT identifies a symptom provocation threshold during treadmill testing. Following the initial test, a progressive aerobic training program is created based on 80% of the patient's HR at the time of symptom provocation. This exercise programming reduced symptom reporting for patients who exercised 5–6 days per week, and it appears that athletes experienced quicker symptom resolution than nonathletes [26]. Results from the BCTT may also provide prognostic value, as patients with a symptom threshold < 135 beats per minute were 45 times more likely to have a recovery that lasted longer than 21 days [125]. While the evidence is quite clear on the efficacy of therapeutic exercise for patients with prolonged symptoms, less is known about patients exercising during the subacute phase of their injury.

When patients exercised after recently sustaining a concussion, they displayed higher HRs [39], lower RR intervals [40], and lower heart rate complexity [38] during exertion than healthy controls at similar workloads (Table 5). Additionally, symptomatic patients reported a higher RPE than their asymptomatic self at similar workloads [41]. Studies that used symptom monitoring reported an acute decrease or no change in symptom severity following exertion in most cohorts [39, 126–128]. Overall, for recent concussions or prolonged recoveries, it appears that controlled exercise would be advantageous to improve autonomic function, symptom reporting, and perceived exercise tolerance and would possibly reduce the risk of a prolonged recovery.

Table 2 Physiological responses in healthy humans participating in moderate-intensity exercise

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Bernardi et al. [75]	15	Sedentary and trained cyclists	Sedentary 23.1 ± 0.7; athletic 17.8 ± 1.1	1. 20 min BL 2. Incremental increases of 30 W every 5 min 3. 15 min recovery	HRV	Sedentary 30 W, 60 W, 90 W, 120 W exercise vs. BL: ↑ HR Sedentary 30 W, 60 W, 90 W exercise vs. BL: LFnu, HFnu Sedentary BL = 4 min recovery: LFnu, HFnu Sedentary BL vs. 8 min recovery: ↑ LFnu, ↓ HFnu Active 30 W, 60 W, 90 W, 120 W, 150 W, 180 W, 210 W exercise vs. BL: ↑ HR Active 30 W, 60 W, 90 W, 120 W, 150 W exercise = BL: LFnu, HFnu Active BL = 4 min and 8 min recovery: LFnu, HFnu
Perini et al. [77]	7	Average VO_{2max} 44.4 ± 1.6 ml/kg/min	23.7 ± 0.8	1. 5 min seated rest 2. 5 min @ 50 W, 100 W, or 150 W 3. 5 min recovery	HRV	50 W, 100 W exercise = rest and recovery: LF:HF 50 W, 100 W, 150 W exercise = rest: HFnu 100 W, 150 W exercise vs. rest: ↑ LFnu
Rimoldi et al. [79]	12	Champion swimmers	16 ± 2	1. BL 2. Modified Bruce protocol (extended to 5 min stages) 3. Recovery	HRV	Stage 2, 3, 4 vs. BL: ↓ RR interval Stage 2 vs. BL: ↑ LFnu Stage 2 and 3 vs. BL: ↓ HFnu, ↑ LF:HF Stage 3 = BL: LFnu Stage 4 = BL: LFnu, HFnu
Ide et al. [52]	12	Average VO_{2max} 43 ± 2 ml/min/kg	23 ± 1	1. 10 min rest 2. 10 min @ 30% of VO_{2max} 3. 10 min @ 60% of VO_{2max}	HR MAP CBF Cerebral O_2 Cerebral glucose	Rest vs. 60% exercise: ↑ HR, MAP, $MCAV_{mean}$, HbO_2 Rest vs. 60% exercise: ↑ (a-v) Glucose Rest = 60% exercise: (a-v)O_2
Tozzi-Ciancarelli et al. [87]	15	Average VO_{2max} 39.5 ± 1.0 ml/kg/min	20–28	1. 30 min @ 60% VO_{2max} 2. 24-h recovery	Oxidative stress Antioxidants	60% post = pre and recovery: TBARS, TEAC, SOD
Jacks et al. [68]	10	Average VO_{2max} 44.5 ± 6.6 ml/kg/min	25.6 ± 4	1. 60 min @ 45%, 60%, or 75% VO_{2peak}, or rest 2. 20 min recovery	Cortisol	45%, 60%, 75% BL = 10 min, 20 min, 40 min exercise cortisol
Gold et al. [88]	20	Not reported	40.5 ± 2	1. 30 min @ 60% VO_{2max} 2. 30 min recovery	BDNF	60% exercise vs. BL and recovery: ↑ BDNF

Table 2 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Raczak et al. [81]	18	Not reported	20 ± 2	1. 3 min warm-up 2. 3 min stages up to 65% HR_{max} 3. 30 min @ 65% HR_{max} 3. 60 min recovery	BP HRV	Recovery vs. BL: ↓ SBP Recovery vs. BL: ↑ SDNN Recovery = BL: RR interval, RMSSD, pNN50
Ferris et al. [86]	15	Average VO_{2max} 39.5 ± 2.3 ml/kg/min	25.4 ± 1	1. 30 min @ (V_{TH} − 20%) or (V_{TH} + 10%)	BDNF	V_{TH} - 20% pre = post: BDNF
Goto et al. [50]	8	Not reported	26.3 ± 2.3	1. 5 min BL 2. 30 min @ 25%, 50%, or 75% VO_{2max} 3. 10 min recovery	HR BP Oxidative stress	25%, 50%, 75% exercise vs. rest and recovery: ↑ HR 50%, 75% vs. 25% exercise: ↑ HR, ↑ MAP 75% vs. 50% exercise: ↑ HR, ↑ MAP 75% vs. 25% and 50% recovery: MAP 25% and 50% exercise = rest: 8-isoprostane
Ogoh et al. [91]	7	Not reported	25 ± 2	1. 10 min rest 2. Progressed up to 39 W, 93 W, or 142 W for 6–8 min 3. 10 min recovery 4. ~ 30–40 min of recovery until HR and MAP returned to BL 5. Process repeated for all intensities	HR BP CBF Pa_{CO_2}	39 W, 93 W, 142 W exercise = rest: Pa_{CO_2}
Fisher et al. [49]	9	Recreationally active	24 ± 3	1. 3–5 min warm-up until target HR obtained (30% or 50% of HRR) 2. 15 min steady-state exercise 3. ~ 30 min of recovery until BL HR and MAP obtained 4. 3–5 min warm-up until target HR obtained (30% or 50% of HRR) 5. 15 min steady-state exercise	HR BP CBF Pa_{CO_2}	Rest vs. 50% exercise: ↑ SBP, MAP, HR Rest = 50% exercise: DBP, PP, $MCAV_{mean}$, Pa_{CO_2}
Hill et al. [67]	12	Average VO_{2max} 65.5 ± 0.1 ml/kg/min	26 ± 3	1. 5 min @ 10–20% of VO_{2max} 2. 30 min @ 40%, 60%, or 80% of VO_{2max}	Cortisol	60%, 80% pre vs. post: ↑ cortisol 60%, 80% vs. 40% and rest post: ↑ cortisol 80% vs. 60% post: ↑ cortisol

Table 2 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Sato et al. [54]	10	Average VO_{2max} 46.2 ± 7.2 ml/kg/min	24 ± 5	1. 3 min BL 2. 5 min @ 40%, 60%, and then 80% of VO_{2peak}	HR BP CBF	40% and 60% exercise vs. rest: ↑ HR, MAP, $MCAV_{mean}$
Nofuji et al. [57]	16	Average VO_{2max} Sedentary 34.7 ± 4.0 ml/kg/min; active 42.3 ± 4.5 ml/kg/min	Sedentary 22.8 ± 1.9; active 21.6 ± 3.0	1. 30 min @ 40% or 60% of VO_{2peak} 2. 15 min seated rest	BDNF	60% post vs. BL: ↑ BDNF 60% BL = recovery: BDNF
McDonnell et al. [56]	25	Average VO_{2max} Val/Val 31.1 ± 13.1 MET-h/wk; met allele: 23.2 ± 17.2 MET-h/wk	Val/Val 27.8 ± 7.9; met allele: 26.1 ± 8.4	1. 15 min @ 75% of age-predicted HR_{max} or 30 min @ 38% or age-predicted HR_{max}, or 30 min seated rest 2. 10 min recovery	BDNF Cortisol	MET vs. Val/Val BL: ↓ BDNF 75%, 38%, control pre vs. 10 min recovery: ↓ BDNF 75% pre = post exercise: cortisol Rest pre vs. post exercise: ↓ cortisol 75% vs. 38% 10 min recovery: ↑ cortisol
Tsai et al. [85]	40	Average VO_{2max} Low fitness 36.0 ± 3.6 ml/kg/min; high fitness 58.0 ± 6.7 ml/kg/min	Low fitness 23.1 ± 2.2; high fitness 22.2 ± 2.2	1. 3 min warm-up 2. 30 min @ 60% VO_{2max} 3. 3 min cool-down	BDNF	60% low and high fitness post exercise vs. pre: ↑ BDNF
Roh et al. [83]	15	Average VO_{2max} 55.1 ± 4.0 ml/kg/min	20.8 ± 1.1	1. 43 min @ 50% VO_{2max} or 35 min @ 65% VO_{2max} or 28 min @ 85% VO_{2max} 2. 60 min recovery	HR BDNF Oxidative Stress	85% vs. 65%, 50%: ↑ HR 65% vs. 50%: ↑ ROS 50%, 65%, 85% post vs. pre: ↑ ROS 85% vs. 50% post and recovery: ↑ ROS 50%, 65% pre = recovery: ROS 65%, 85% vs. 50% post: ↑ BDNF 50%, 65%, 85% pre = recovery: BDNF

a–v arteriovenous difference, *BDNF* brain-derived neurotrophic factor, *BL* baseline, *BP* blood pressure, *CBF* cerebral blood flow, *DBP* diastolic blood pressure, *h* hour, HbO_2 oxygenated hemoglobin, *HFnu* high frequency normalized units, *HR* heart rate, HR_{max} maximal heart rate, *HRR* heart rate reserve, *HRV* heart rate variability, *LF:HF* low frequency to high frequency ratio, *LFnu* low frequency normalized unit, *MAP* mean arterial pressure, $MCAV_{mean}$ mean middle cerebral artery velocity, *MET* metabolic equivalents, *min* minutes, O_2 oxygen, Pa_{CO_2} arterial partial pressure of carbon dioxide, *pNN50* percentage of adjacent RR intervals differing more than 50 ms, *PP* pulse pressure, *RMSSD* square root of the mean of squared differences between successive intervals, *ROS* reactive oxygen species, *SBP* systolic blood pressure, *SDNN* standard deviation of normal-to-normal RR intervals, *SOD* superoxide dismutase, *TBARS* thiobarbituric acid reactive substances, *TEAC* Trolox equivalent antioxidant capacity, VO_{2max} maximal oxygen uptake, VO_{2peak} peak oxygen uptake, V_{TH} ventilatory threshold, *W* watts, *wk* week(s), ↓ and ↑ indicate decrease and increase, respectively

[a]Age is presented as year, mean ± standard deviation

Table 3 Physiological responses in healthy humans participating in high-intensity exercise

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Bernardi et al. [75]	15	Sedentary and trained cyclists	Sedentary 23.1 ± 0.7; athletic 17.8 ± 1.1	1. 20 min BL 2. Incremental increases of 30 W every 5 min 3. 15 min recovery	HRV BP	Sedentary 30 W, 60 W, 90 W, 120 W exercise vs. BL: ↑ HR Sedentary 30 W, 60 W, 90 W exercise vs. BL: LFnu, HFnu Sedentary 120 W exercise vs. BL: ↑ LFnu, HFnu Sedentary BL = 4 min recovery: LFnu, HFnu Sedentary BL vs. 8 min recovery: ↑ LFnu, ↓ HFnu Active 30 W, 60 W, 90 W, 120 W, 150 W, 180 W, 210 W exercise vs. BL: ↑ HR Active 30 W, 60 W, 90 W, 120 W, 150 W exercise = BL: LFnu, HFnu Active 180 W and 210 W exercise vs. BL: ↑ LFnu Sedentary 120 W exercise vs. BL: ↑ LFnu, HFnu Active BL = 4 min and 8 min recovery: LFnu, HFnu Sedentary 120 W vs. BL: ↑ SBP Sedentary 120 W = BL: DBP Active 210 W vs. BL: ↑ SBP Active 210 W vs. BL: ↓ DBP
Perini et al. [77]	7	Average VO_{2max} 44.4 ± 1.6 ml/kg/min	23.7 ± 0.8	1. 5 min seated rest 2. 5 min @ 50, 100, or 150 W 3. 5 min recovery	HRV	50 W, 100 W, and 150 W exercise = rest: HFnu 100 W and 150 W exercise vs. rest: ↑ LFnu 150 W rest vs. recovery: ↑ LF:HF
Rimoldi et al. [79]	12	Champion swimmers	16 ± 2	1. BL 2. Modified Bruce protocol (extended to 5 min stages) 3. Recovery	HRV	Stage 2, 3, 4 vs. BL: ↓ RR interval Stage 2 vs. BL: ↑ LFnu Stage 2, 3 vs. BL: ↓ HFnu, ↑ LF:HF Stage 3 = BL: LFnu Stage 4 = BL: LFnu, HFnu
Jacks et al. [68]	10	Average VO_{2max} 44.5 ± 6.6 ml/kg/min	25.6 ± 4	1. 60 min of 45%, 60%, or 75% VO_{2peak}, or rest 2. 20 min recovery	Cortisol	45%, 60%, 75% BL = 10, 20, and 40 min exercise cortisol

Table 3 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Ogoh et al. [91]	7	Not reported	25 ± 2	1. 10 min rest 2. Progressed up to 39, 93, or 142 W for 6–8 min 3. 10 min recovery 4. ~30–40 min of recovery until HR and MAP returned to BL 5. Process repeated for all intensities	HR BP CBF	39 W, 93 W, 142 W exercise = rest: Pa_{CO_2} 142 W exercise vs. rest: ↑ HR, SBP, DBP, MAP, $MCAV_{mean}$
Ferris et al. [86]	15	Average VO_{2max} 39.5 ± 2.3 ml/kg/min	25.4 ± 1	1. 30 min @ (V_{TH} − 20%) or (V_{TH} + 10%)	BDNF	V_{TH} + 10% pre vs. post: ↑ BDNF
Goto et al. [50]	8	Not reported	26.3 ± 2.3	1. 5 min BL 2. 30 min @ 25%, 50%, or 75% VO_{2max} 3. 10 min recovery	HR BP Oxidative stress	25%, 50%, 75% exercise vs. rest and recovery: ↑ HR 50%, 75% vs. 25% exercise: ↑ HR, ↑ MAP 75% vs. 50% exercise: ↑ HR, ↑ MAP 75% vs. 25%, 50% recovery: MAP 75% exercise vs. rest: ↑ 8-iso-prostane
Ogoh et al. [90]	8	Not reported	22 ± 1	1. 10 min rest 2. Progressed up to 105 W or 162 W and maintained steady state for 6–8 min 3. ~30–40 min of recovery until HR and MAP returned to BL 4. Process repeated for all intensities	BP CBF HR	162 W exercise vs. rest: ↑ HR, SBP, DBP, MAP, $MCAV_{mean}$ 162 W exercise = BL: Pa_{CO_2} 105 W exercise vs. rest: ↑ HR, SBP, MAP, $MCAV_{mean}$ and Pa_{CO_2} 162 W exercise vs. 105 W: ↑ HR, SBP, DBP, and MAP 162 W exercise vs. 105 W: ↓ $MCAV_{mean}$
Hill et al. [67]	12	Average VO_{2max} 65.5 ± 0.1 ml/kg/min	26 ± 3	1. 5 min @ 10–20% of VO_{2max} 2. 30 min @ 40%, 60%, or 80% of VO_{2max}	Cortisol	Rest pre vs. post: ↓ cortisol 60% and 80% pre vs. post: ↑ cortisol 60% and 80% vs. 40% and rest post: ↑ cortisol 80% vs. 60% post: ↑ cortisol
Sato et al. [54]	10	Average VO_{2max} 46.2 ± 7.2 ml/kg/min	24 ± 5	1. 3 min BL 2. 5 min @ 40%, 60%, then 80% of VO_{2peak}	HR BP CBF	80% exercise vs. rest: ↑ HR, MAP 80% exercise = rest: $MCAV_{mean}$

Table 3 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Schmidt-Kassow et al. [58]	40	Average VO_{2max} Men 44.4 ± 29.1 MET-h/wk; women 41.6 ± 21.5 MET-h/wk	Men 23 ± 2.9; women 22 ± 2.2	1. 5 min exercise intensity calibration 2. 25 min constant exercise (low or high intensity) 3. 2 min cool down 4. Recovery	HR BDNF	High- vs. low-intensity exercise: ↑ HR, BDNF Male vs. female during exercise: ↑ BDNF High- = low-intensity: BL BDNF, recovery BDNF High-intensity exercise vs. BL: ↑ BDNF
Schmolesky et al. [84]	45	Not reported	18–25	1. 20 min @ 60% or 80% of HRR or 40 min @ 60% or 80% of HRR or seated control	BDNF	20 min and 40 min @ 80% post vs. BL and control: ↑ BDNF 20 min @ 60% post vs. BL: ↑ BDNF 40 min @ 60% post = BL and control: BDNF
Saucedo Marquez et al. [59]	Experiment 1: 18; experiment 2: 21	Average VO_{2max} 56.6 ml/min/kg	Experiment 1: 28 ± 5; experiment 2: 27 ± 4	Experiment 1 and 2 1. 30 min rest 2. 2 min rest 3. 3 min warm-up @ 60 W 4. 20 min of 1 min:1 min intervals @ 90% max work load or 20 min continuous @ 70% max work load 5. 20 min recovery	HR BDNF Cortisol	Experiment 1 0 min, 10 min, 14 min, 18 min, 20 min exercise vs. BL: ↑ BDNF Continuous = intervals: rest, exercise, recovery BDNF Continuous = intervals: VO_2, HR, cortisol Experiment 2 Intervals vs. continuous: ↑ BDNF, W Intervals vs. rest: ↑ BDNF Continuous vs. rest: ↑ BDNF Intervals = continuous: cortisol

Table 3 (continued)

Study	Sample size	Fitness status	Age[a]	Exercise protocol	Outcome measure	Results
Roh et al. [83]	15	Average VO_{2max} 55.1 ± 4.0 ml/kg/min	20.8 ± 1.1	1. 43 min @ 50% VO_{2max} or 35 min @ 65% VO_{2max} or 28 min @ 85% VO_{2max} 2. 60 min recovery	HR BDNF Oxidative stress	85% vs. 65%, 50%: ↑ HR 65% vs. 50%: ↑ ROS 50%, 65%, 85% post vs. pre: ↑ ROS 85% vs. 50% post and recovery: ↑ ROS 85% recovery vs. pre: ↑ ROS 50%, 65% pre = recovery: ROS 65%, 85% post vs. pre: ↑ BDNF 65%, 85% vs. 50% post: ↑ BDNF 50%, 65%, 85% pre = recovery: BDNF

BDNF brain-derived neurotrophic factor, *BL* baseline, *BP* blood pressure, *CBF* cerebral blood flow, *DBP* diastolic blood pressure, *h* hour, *HFnu* high frequency normalized units, *HR* heart rate, *HRR* heart rate reserve, *HRV* heart rate variability, *LF:HF* low frequency to high frequency ratio, *LFnu* low frequency normalized unit, *MAP* mean arterial pressure, $MCAV_{mean}$ mean middle cerebral artery velocity, *MET* metabolic equivalents, *min* minutes, Pa_{CO_2} arterial partial pressure of carbon dioxide, *ROS* reactive oxygen species, *SBP* systolic blood pressure, VO_{2max} maximal oxygen uptake, VO_{2peak} peak oxygen uptake, V_{TH} ventilatory threshold, *W* watts, *wk* week(s), ↓ and ↑ indicate decrease and increase, respectively

[a] Age is presented as year, mean ± standard deviation

4 Recommended Exercise Prescription

When making a recommendation for exercise in patients with subacute concussion, the patient's fitness level should be considered. Ventilatory threshold (V_{TH}) occurs at roughly 55% ± 8 of VO_{2max} in untrained participants and at 70–90% of VO_{2max} in well-trained participants [129, 130]. To avoid hypercapnia-induced hyperventilation, resulting in cerebral vasoconstriction and reduced CBF, the prescribed exercise intensity should be below the estimated V_{TH} [24]. Therefore, a conservative exercise prescription for untrained or deconditioned patients would be initiating aerobic exercise at 40–50% of HR_{max} and 60–70% of HR_{max} in well-trained patients [131]. The preferred method for estimating age-predicted HR_{max} is 208 − 0.7 (age), as a meta-analysis reported a strong inverse correlation ($r = -0.90$) with age and HR_{max}, independent of sex and physical activity status [132]. Exercise bouts of 15–20 min were well-tolerated in concussed athletic populations with at least 90% completion rates [127, 133]. The inclusion of a brief warm up and cool down as part of the exercise session would allow the patient to become acclimated to exercise and would also smoothly transition the patient to exercise termination. Untrained or deconditioned patients may prefer 10–15 min, depending on their level of exercise tolerance and symptom provocation. An allowable symptom provocation threshold should be established, as healthy individuals report concussion-like symptoms during high-intensity exercise [134]. For example, using a 10-point visual analog scale, the symptom-limited threshold on the BCTT is reached when the patient reports a ≥ 3-point increase from the pre-test overall symptom severity value; a point is allocated for any worsening of symptoms or the appearance of a new symptom [26]. The clinician should closely monitor the bout of exercise. The use of heart rate monitoring or RPE during exercise is recommended to accurately gauge the exercise intensity. In patients with concussion who exercised within the first week of their injury, heart rate and RPE both tracked linearly over the course of their exercise bout [41].

The initial session of exertion should likely be completed in an unstimulating environment (e.g., quiet office space) to avoid provocation of visual/vestibular symptoms, which may make it difficult for the clinician or patient to discriminate between exertion-related symptom provocation or visual/vestibular-related symptom provocation. A treadmill would be the preferred mode of exercise, as it most closely reflects the patient's daily activity. However, if a lower extremity injury or severe vestibular dysfunction restricts treadmill exercise, a stationary bike or upper body ergometer may be more appropriate. The number of days post-injury when aerobic exercise should be initiated is of great interest. When

Table 4 Characteristics of prospective post-concussion syndrome studies utilizing exercise

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Gagnon et al. [118]	16	75% athletes	8–17	Concussion (7.0 ± 4.1 wk post-injury)	Up to 15 min of 50–60% of HR_{max}	Symptoms Recovery	Pre vs. post treatment: ↓ symptom severity at post Post treatment: 100% return to activity
Leddy et al. [26]	12	55% athletes	27.9 ± 14.3	Concussion (6–51 wk post-injury)	BCTT 1. 1 min @ 3.3 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR	Symptoms BP BCTT tolerance	Pre vs. post treatment: ↓ symptom severity at post Pre vs. post treatment: ↑ exercise time to exhaustion Pre vs. post treatment: ↑ HR_{max} and SBP
Kozlowski et al. [119]	56 (34 PCS, 22 MC)	Not reported	PCS 25.9 ± 10.9; MC 23.3 ± 6.2	Concussion (226.2 ± 219.3 days)	BCTT 1. 1 min @ 3.3 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR	Symptoms HR BP BCTT tolerance RPE	PCS = MC: resting HR and BP MC vs. PCS: ↓ exercise duration, ↓ HR_{max}, RPE, SBP and DBP
Leddy et al. [25]	12 (4 AE, 4 ST, 4 HC)	50% athletes	18–33	Concussion (6–51 wk post-injury); testing repeated	BCTT 1. 1 min @ 3.3 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR 5. Train 6 days/wk	Symptoms HR ANAM fMRI	AE vs. ST: ↓ symptoms at time 2 AE vs. ST: ↑ HR at time 2 exercise termination AE = ST = HC at time 1 and 2 for average accuracy and reaction time AE + ST vs. HC: HC ↑ brain activation at time 1 AE + ST = HC: brain activation at time 2
Dematteo et al. [126]	37	73% athletes	8.5–18.3	PCS (0.7–35 mo post-injury)	McMaster All-Out Progressive Continuous Cycling Test 1. 25–85 W @ 60 rpm to exhaustion/symptoms	Symptoms	↓ symptom severity and number @ 5 min, 30 min, and 24 h post-exercise

Table 4 (continued)

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Clausen et al. [24]	22 (9 PCS, 13 MC)	Collegiate athletes	PCS 21 ± 3; MC 23 ± 6	PCS (> 6 to < 12 wk)	BCTT 1. 1 min @ 3.3 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR 5. Train 5–6 days/wk and retest every 3 wk	VO_2 HR CBF BP V_E $PETCO_2$ Symptoms	PCS pre vs. post: ↓ VO_2 at pre PCS pre vs. MC: ↓ VO_2 in PCS PCS pre vs. post: ↑ HR and SBP at exercise termination at post PCS pre vs. MC: ↑ HR and SBP at exercise termination in MC PCS pre vs. post: ↓ CBF at pre PCS pre vs. MC: ↓ CBF at pre PCS pre vs. MC: ↓ V_E at pre PCS pre vs. MC: ↑ $PETCO_2$ at pre PCS pre vs. post: ↓ symptoms at post PCS pre vs. MC: ↓ symptoms in MC
Gagnon et al. [20]	10	High school athletes	14–18	PCS (3.6–26.2 wk)	Active rehabilitation program 1. Up to 15 min of aerobic exercise @ 60% of HR_{max} 2. Up to 10 min of coordination exercise 3. Imagery and visualization techniques 4. Daily exercise log	Post-concussion Scale, anxiety, ImPACT, balance	Pre vs. post: ↓ all components of Post-concussion Scale Pre = post: anxiety Pre vs. post: ↑ visual motor speed performance Pre = post: balance
Kurowski et al. [120]	26 (12 AE, 14 ST)	69% athletes	AE 15.2 ± 1.4; ST 15.5 ± 1.8	PCS (AE: 52.3 ± 19.9 days post-injury; ST: 56.0 ± 22.2 days post-injury)	Aerobic exercise program 1. 3–29 min of aerobic exercise until symptomatic 2. 5–6 days/wk at home at 80% of symptom threshold for ≥ 6 wk	Post-concussion Symptom Inventory	AE vs. ST: ↑ rate of improvement for self-reported symptoms AE = ST: caregiver-rated symptoms
Dobney et al. [117]	677 AR: 26 started @ < 2 wk, 33 started at 2 wk, 175 started @ 3 wk, 183 started @ 4 wk, 62 started @ 5 wk, 198 started @ ≥ 6 wk	Not reported	14.3 ± 2.3	Concussion (45 days mean time to initial visit)	Active rehabilitation program 1. Up to 15 min of aerobic exercise @ 60% of HR_{max} 2. Up to 10 min of coordination exercise 3. Imagery and visualization techniques 4. Daily exercise log	Post-concussion Scale-Revised	Patients experienced a 6.5–13 improvement in symptoms at follow-up

Table 4 (continued)

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Chan et al. [116]	19 (10 AR, 9 TAU)	High school athletes	15.5 ± 1.47	PCS (132 ± 52 days post-injury)	Active rehabilitation program 1. Up to 15 min of aerobic exercise @ 60% of HR_{max} 2. Up to 10 min of coordination exercise 3. Imagery and visualization techniques 4. Daily exercise log	PCSS	AR vs. TAU: ↑ reduction pre-post PCSS

AE aerobic exercise, *ANAM* Automated Neuropsychological Assessment Metrics, *AR* active rehabilitation, *BCTT* Buffalo Concussion Treadmill Test, *BP* blood pressure, *CBF* cerebral blood flow, *DBP* diastolic blood pressure, *fMRI* functional magnetic resonance imaging, *h* hour, *HC* healthy control, *HR* heart rate, HR_{max} maximal heart rate, *ImPACT* Immediate Post-concussion Assessment and Cognitive Testing, *MC* matched controls, *min* minutes, *mo* month(s), *mph* miles per hour, *PCS* post-concussion syndrome, *PCSS* Post-Concussion Symptom Scale, $PETCO_2$ end-tidal CO_2, *RPE* rating of perceived exertion, *RPM* revolutions per minute, *SBP* systolic blood pressure, *ST* stretching, *TAU* treatment as usual, V_E minute ventilation, VO_2 oxygen consumption, *W* watts, *wk* week(s), ↓ and ↑ indicate decrease and increase, respectively

[a]Age is presented as year, mean ± standard deviation

considering the delayed onset of symptoms, initiating exercise by the third day is likely prudent but warrants investigation. It is important to consider the limitations of the present review as exercise protocols often vastly differed depending on the biomarkers, cohorts were predominantly males and aged < 30 years, and the fitness status of the participants ranged from sedentary to elite.

5 Conclusions

According to the available evidence, low-intensity aerobic exercise does not appear detrimental for concussed individuals and may provide some therapeutic benefits. While preliminary evidence provides less certainty, it does suggest that patients with concussion may also tolerate moderate-intensity aerobic exercise. Given that patients with concussion have higher heart rates, report higher levels of perceived exertion [39, 41], and present with cardiovascular dysfunction [4, 29–42], a prescription of 40% of HR_{max} for 10–15 min in untrained or deconditioned patients or 60% HR_{max} for 15–20 min in well-trained patients would be a conservative approach. The subacute phase of concussion recovery may be the ideal time to initiate aerobic exercise, but the current status of the patient should be considered when making that determination.

Exertional testing, such as the BCTT has proven safe and efficacious, but bringing patients to volitional fatigue or provoking symptoms could potentially be avoided if controlled, low-intensity aerobic exercise is used as an alternative. Further, low-intensity aerobic exercise is recommended as a treatment and could be considered as part of the patient's graded RTP protocol. Operationally, it appears that exertional testing takes a day and then the patient may be able to initiate their individualized RTP the following day. Future studies should aim to determine the optimal exercise prescription to improve cardiovascular, psychological, endocrine, and cognitive function following an SRC. Determining the timing of exercise initiation is of great importance and should be explored. Additionally, comparing an exertional testing prescription to an age-predicted HR prescription may prove useful to clinicians as both approaches might provide similar benefit to the patient. In summary, closely monitored, well-controlled, and accurately prescribed aerobic exercise will likely be tolerated and provide therapeutic benefits for patients who have recently experienced a concussion.

Table 5 Characteristics of prospective concussion studies utilizing exercise

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Relander et al. [114]	178 (96 AC, 82 RC)	Not reported	21–65	Concussion (≤36 h after admission)	AC: Physical therapy 2/wk + encouraged activity + follow-up clinic visits RC: Voluntary activity + voluntary follow-up visits	Time in bed Time in hospital Time off work/school	AC = RC: duration of bed rest AC = RC: length of stay AC vs. RC: ↓ time off work/school
Gall et al. [39]	28 (14 SRC, 14 MC)	Junior hockey players	SRC 18.1 ± 0.4; MC 18.8 ± 0.4	Concussion (1.8 ± 0.2 days post-injury); exercise bout repeated 5 days later	Constant load cycle ergometer: 1. 2 min warm-up: 40 W @ 50–60 rpm 2. 10 min steady state: 1.5 W/kg @ 80–90 rpm 3. Intervals to exhaustion: 40 min 4.7 W/kg @ 90–100 rpm followed by 20 min free pedal 4. Recovery: 1 min free pedal 30 W + 4 min rest	HR Lactate Symptoms	SRC vs. MC: ↑ HR on both trials SRC vs. MC = ↑ lactate on both trials SRC = MC: symptom change post exertion
Gall et al. [40]	28 (14 SRC, 14 MC)	Junior hockey players	SRC 18.1 ± 0.4; MC 18.8 ± 0.4	Concussion (5.0 ± 1.4 days post-injury); exercise repeated 5 days later	Constant load cycle ergometer: 1. 2 min warm-up: 40 W @ 50–60 rpm 2. 10 min steady state: 1.5 W/kg @ 80–90 rpm 3. Intervals to exhaustion: 40 min 4.7 W/kg @ 90–100 rpm followed by 20 min free pedal 4. Recovery: 1 min free pedal 30 W + 4 min rest	HRV	SRC = MC: resting HRV SRC vs. MC: ↓ RR interval during steady-state SRC vs. MC: ↓ LF power at both trials SRC vs. MC: ↓ HF power at both trials
La Fountaine et al. [38]	6 (3 SRC, 3 MC)	Collegiate athletes	SRC 19 ± 2; MC 19 ± 2	Concussion (≤48 h post-injury); exercise repeated 14 days later	IHGT 1. 5 min quiet rest 2. 3 min IHGT @ 30% MVC	HR HRV HRC	MC: 48 h = 2 wk HR, HRV, HRC SRC vs. MC: ↓ HRC at 48 h SRC: ↓ HRC at 48 h than at 2 wk

Table 5 (continued)

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Gay et al. [127]	18 (9 SRC, 9 MC)	Collegiate athletes	College age	Concussion (asymptomatic and cleared for sport)	YMCA Bike Protocol 1. 2 min of accommodation 2. 4×3 min progressive intensity up to 70% HR_{max}	HR EEG	SRC = MC: HR during exercise SRC = MC: EEG during rest SRC vs. MC: power ↑ during exercise SRC vs. MC: power ↑ 30 min post-exercise
Maerlender et al. [133]	28 (9 SRC, 9 MC)	Collegiate athletes	College age	Concussion (median time to evaluation 2 days)	1. 20 min of RPE-based mild to moderate exertion on stationary bike or until "uncomfortable"	ImPACT RPE Symptoms Recovery	SRC = MC: recovery duration SRC = MC: ImPACT composites SRC: 90% exercise completion rate SRC: symptom ↑ post-exercise
Grool et al. [122]	2413 (1677 PA, 736 CR)	68% athletes	5–18	Concussion (seen in ED ≤ 48 h post-injury)	Self-categorized activity within 7 days No activity Light aerobic exercise Sport-specific exercise Non-contact training drills Full-contact Return to competition	PPCS	PA: ↓ risk for PPCS PA vs. CR: light, moderate, and full activity ↓ risk for PPCS
Abaji et al. [36]	22 (11 SRC, 11 MC)	Collegiate athletes	SRC 21.4 ± 1.1; MC 22.1 ± 1.6	Concussion (asymptomatic and cleared: 95 ± 63 days post-injury)	IHGT 1. 5 min resting measurements 2. 3 min IHGT @ 30% MVC	HRV	SRC = MC: NN, HR, SDNN, RMSSD, LF, ApEn during IHGT and rest SRC vs MC: ↓ HF and ↑ LF/HF during IHGT
Hinds et al. [41]	70 (40 AC, 30 NIC)	Not reported	AC 15.5 ± 0.9; NIC 15.9 ± 0.5	Concussion (5.0 ± 1.1 days post-injury); testing repeated once patient was deemed asymptomatic and similar retest interval for NIC	BCTT 1. 1 min @ 3.2–3.6 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR	HR RPE	AC concussed = recovered: resting HR while AC was symptomatic AC concussed vs. recovered: ↓ HR @ 0 min of exercise AC concussed vs. recovered: ↑ RPE during exercise NIC time 1 = time 2: HR and RPE

Table 5 (continued)

Study	Sample size	Fitness status	Age[a]	Disease state	Exercise prescription	Outcome measure	Results
Manikas et al. [128]	30	90% athletes	14.0 ± 2.1	Concussion (tested on days 2 and 10 post symptom resolution)	McMaster All-Out Progressive Continuous Cycling Test 1. 2 min warm-up 2. 25 to 85 W @ 60 rpm to exhaustion/symptoms	CogSport	Day 2 vs. day 10: ↓ detection and identification performance Pre vs. post-exercise: ↓ detection, and identification performance Pre = post-exercise: one back Day 2 = day 10: one back Day 2 pre vs. post: ↑ one card learning performance Day 10 pre vs. post: ↓ one card learning performance Day 2 vs. day 10: ↓ symptoms at day 10
Leddy et al. [125]	54 (27 TT, 27 NT)	High school athletes	TT 15.2 ± 1.5; NT 15.6 ± 1.4	Concussion (1–9 days post-injury)	BCTT 1. 1 min @ 3.2–3.6 mph and 0% incline 2. 1 min @ maintain mph and 2% incline 3. 1 min stages @ maintain mph and +1% incline to exhaustion/symptom exacerbation 4. Progress up to 80% of tested HR	HRt Symptoms Recovery	TT: HRt predicted > 21-day recovery TT = NT: daily symptoms TT = NT: recovery

AC active care, *ApEn* approximate entropy, *BCTT* Buffalo Concussion Treadmill Test, *CR* conservative rest, *ED* emergency department, *EEG* electroencephalogram, *h* hour, *HF* high frequency, *HR* heart rate, *HRC* heart rate complexity, HR_{max} maximal heart rate, *HRt* heart rate threshold, *HRV* heart rate variability, *IHGT* isometric handgrip test, *ImPACT* Immediate Post-Concussion Assessment and Cognitive Testing, *LF* low frequency, *MC* matched controls, *min* minutes, *mph* miles per hour, *MVC* maximal voluntary contraction, *NIC* non-injured controls, *NN* normal-to-normal intervals, *NT* no treadmill, *PA* physical activity, *PPCS* persistent post-concussion symptoms, *RC* routine care, *RMSSD* root mean square of successive differences, *RPE* rating of perceived exertion, *RPM* revolutions per minute, *SDNN* standard deviation of N-N intervals, *SRC* sport-related concussion, *TT* treadmill test, *W* watts, *wk* week(s), ↓ and ↑ indicate decrease and increase, respectively

[a]Age is presented as year, mean ± standard deviation

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