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Original Article

Effects of Interval-Training Exercise on People Who Have Had Persistent Post-Concussive Symptoms for Less Than One Year: A Pilot Study

Yi-Ning Wu,[1] Caroline Stark,[1] Jessica Gravel,[2] Matthew White,[2] Josh Avery,[2] Terrie Enis,[2] and Robert C. Cantu[2]

Abstract

This study is to examine the effects of a 12-session moderate intensity-interval-training program with blood flow restriction (BFR) and body cooling (BC) on people who have had persistent post-concussive symptoms (PPCS) for <1 year. A single-blind randomized controlled trial of interval-training exercise with BFR and BC was conducted. Twenty-five adults with PPCS were assigned to the experimental group ($n=14$) or the control group ($n=11$). Both groups rode a recumbent elliptical machine for 21 min at moderate intensity (65% predicted maximum heart rate) twice a week for 6 weeks, but only the experimental group received BFR and BC while riding. The variances of overall PPCS scale scores and their sub-domain scores for individuals during the 6-week intervention and 6-week follow-up period were calculated. During the intervention, the fluctuation of overall symptom severity, severity in the cognitive domain and severity in the mood domain were significantly less in the experimental group ($p=0.03$; $p=0.02$; $p=0.02$). During the follow-up period, the number of symptoms remained more stable in the experimental group ($p=0.02$), and a trend toward less fluctuation of symptom severity ($p=0.05$) was also observed. The reduced number of symptoms in the cognitive and sleep domains remained more stable in the experimental group following the intervention ($p=0.007$; $p=0.02$). The severity of mood and sleep symptoms also remained more stable during the follow-up period in the experimental group ($p=0.04$). More stable recovery was found in individuals who exercised using BFR and BC than in those who underwent exercise without BFR and BC. Moderate intensity-interval-training exercise with BFR and BC alleviated post-concussive symptoms in people who have had PPCS <1 year.

Keywords: blood flow restriction; body cooling; exercise; persistent post-concussive symptoms

Introduction

Concussion or a mild traumatic brain injury presents a large risk to public health with 1,600,000–3,800,000 occurrences per year in the United States.[1] Most concussions are resolved within 7–10 days; however, 10–30% of patients remain symptomatic for weeks to years. These symptoms are known as persistent post-concussive symptoms (PPCS).[2,3] Trauma to the brain during a single or multiple concussive events can cause damage to neurons, with cell death initiated from stretching of the cell membranes and axons,[4] resulting in complex symptoms affecting physical, emotional, cognitive, and/or social functioning.[5] Conventional concussion management recommends rest directly after injury until the patient is asymptomatic without medicine, and the concussion is resolved.[2,6,7] Although abstaining from physical and cognitive activities has been the traditional treatment strategy, the American Academy of Neurology has acknowledged that a return to moderate activity could produce lower symptom scores and that a program implementing progressive physical activities could be beneficial for those with PPCS.[6,8]

There is extensive evidence demonstrating that exercise possesses many health benefits. The protective and therapeutic effects of exercise are related to the impact of exercise on the autonomic nervous system (ANS), which leads to improved autonomic functions and cardiovascular functions.[9] Studies also showed the rapid beneficial effect of exercise on neuroplasticity, neuronal functions, attenuating cognitive impairments, and reduced dementia risk in humans. These results are potentially caused by increased brain-derived neurotrophic factor (BDNF) concentration level induced by exercise, which has been reported as early as 5–6 weeks after initiation of aerobic exercise.[10] The beneficial effects of exercise on the ANS through ANS adaptations and neuronal functions through neuroplasticity might be germane to concussion or PPCS intervention.[10,11]

[1]Department of Physical Therapy and Kinesiology, University of Massachusetts Lowell, Lowell, Massachusetts, USA.
[2]Dr. Robert C. Cantu Concussion Center, Emerson Hospital, Concord, Massachusetts, USA.

Although exercise can be beneficial for brain health, it might pose a challenge to people with concussions. PPCS manifest in a variety of ways in patients, and the symptoms can be triggered or worsened by certain events for those individuals. Patients frequently describe that they have good days and bad days, or that symptoms come and go but rarely disappear forever. The worsening symptoms can be the result of the suboptimal way that the brain uses its resources and available oxygen,[12] as well as the altered functional pathways to relay information.[13] Symptom fluctuations can also be caused by brain disturbances after physical activities. It has been suggested that delayed symptom exacerbation in patients with PPCS over time, after participation in a graded exercise test, may occur, and that subjective symptom reporting, the most commonly used clinical measure, should be used for follow-up.[14–16] Therefore, a modality that allows people with PPCS to exercise with no symptom exacerbations before experiencing benefits, in the other words, that allows a stable recovery, will have a significant impact on PPCS recovery.

Exercise intolerance with exacerbation of PPCS may prevent people with unresolved concussions from staying physically active or performing sufficient exercise to receive the exercise-induced health benefits.[16,17] Several recent approaches, such as interval-training exercise and blood flow restriction (BFR), have attracted attention from researchers and clinicians because of their efficiency in generating beneficial health outcomes when compared with conventional exercise protocols.[18–21] Interval training consists of several short bouts of exercise with passive or active rests between each bout at various ratios of exercise bouts to rest intervals.[22] Studies have shown that interval training, but not energy-matched continuous training, increased the nuclear peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) level and total PGC-1α content in muscles.[23,24] PGC-1α is linked to many health benefits including cardiac functions and endurance.[25] Fluctuations in adenosine triphosphate (ATP) turnover during interval training activating signaling pathways might account for this increase in PGC-1α following interval training.[26] BFR is another popular form of exercise, which is applied often with resistance training. BFR works by restricting blood flow to working muscles during exercise, producing hypoxic conditions and forcing the body to utilize anaerobic metabolism of glucose, causing increased lactate levels in the blood.[27–30] With elevated plasma lactate concentrations, lactate becomes a significant fuel source for the brain, providing up to 33% of the brain's energy requirements.[30–33] Lactate metabolism also provides neuroprotection for brain health.[34,35] Further, the hypoxia environment created by BFR might also induce upregulation of BDNF, which promotes brain health and PPCS recovery, as blood BDNF levels and BDNF gene expression are enhanced not only by physical activity but also in response to hypoxia.[36–41] An oxygen deficit caused by intermittent hypoxia induces an increase in hypoxia-inducible factor (HIF-1α)[42] that modulates BDNF gene expressions.[39] All those potential mechanisms suggest that BFR and interval training might be helpful for PPCS recovery. The safety of using BFR has been tested, and it has been shown to present no risk to the participants,[20,28] as is also the case with interval training.[21]

Cerebral blood flow is one essential mediator for dissipating heat in the brain in addition to the heat capacity of the blood and the arteriovenous blood temperature difference. Studies using an arterial spin labeling perfusion functional magnetic resonance imaging technique have shown that people with mild traumatic brain injury demonstrated reduced cerebral blood flow compared with controls.[43,44] Even in controls, reduced global cerebral blood flow during higher intensity exercise was observed.[45] Therefore, exercise potentially imposes a challenge for people with PPCS because of unmet blood (oxygen) demand for cerebral metabolism, and may increase the temperature in the brain (lacking heat dissipation through blood circulation). With the body cooling (BC) modality, we might be able to minimize the impacts of exercise-induced heat production on brain functions. In addition, BC is also thought to create an environment favorable for lactate production.[46] In other words, exercise under BFR and BC triggers physiological responses at a relatively low intensity.

Because of the aforementioned benefits of BFR and interval training, and considering strategies to alleviate hyperthermia in the brain, the combination of interval training exercise with BFR and BC, in theory, enables people with PPCS to better tolerate the exercise and receive its benefits because desired changes can be accomplished at lower intensities. We believe that this concept requires further investigation. Therefore, in this study, we aimed to first demonstrate the safety of exercise intervention in the PPCS population. We then compared the outcomes of interval-training exercise using the conventional recumbent elliptical machine to the outcomes of the same exercise but with BFR and BC. We hypothesized that using BFR and BC could alleviate PPCS in participants in a more favorable way (fewer symptom fluctuations) than the same exercises without using BFR and BC.

Methods

Participants

A convenience sample of 25 adults with PPCS, recruited from a regional medical center, were assigned randomly to the exercise (control) group or the exercise with BFR and BC (experimental) group. Consecutive assignment through random permutation was used to allocate the recruited participants to the groups. Table 1 depicts the characteristics of participants in both groups who completed the study. Inclusion criteria for this study were (1) being diagnosed with PPCS because of having had a concussive event within the past year, (2) with modified Somatic Perceptions Questionnaire score <10, (3) able to follow instructions, and (4) self-reporting ability to ride a stationary bike for $\sim$30 min at a self-selected speed. Exclusion criteria were (1) being diagnosed with other neurological disorders, (2) pregnancy confirmed via participants' medical history, and (3) receiving other research pharmacotherapy for concussion. All participants were required to maintain or reduce the treatments for PPCS during the duration of the study. Participants who were unable to fulfill this requirement would be excluded from the study. The study protocol was approved by Advarra IRB (Protocol no: Pro00027235). All participants gave written informed consent prior to participating in the study. No adverse events were reported. There were five participants who dropped out of the study: one dropout in the experimental group and four dropouts in the control group.

Instrument

A Vasper system (Vasper, Mountain View, CA, USA) consisting of NuStep, a recumbent elliptical machine, and a cooling system were used in this study to provide BFR and BC for the experimental group (Fig. 1). The water was cooled down to 42°F and pumped to the cooling pad and the cuffs by the cooling system. By controlling the amount of chilled water filling the cuffs, the pressure of upper arm cuffs was set between 40 and 50 mm Hg and the pressure of thigh cuffs was set between 65 and 75 mm Hg, according to each participant's tolerance to the pressure. The cooling pad contacted the backs of thighs, buttocks, lower back, and most of the upper back of participants. Two copper plates mounted on each foot pedal cooled the bottom of the participant's feet. For the control group, the cuffs and the cooling pad were removed during the intervention.

Table 1. Characteristics of Participants

Group	*Sex*	*Age (years)*	*PPCS length (days)*	*Sport-related*	*Cervical (C) and vestibular (V)*	*Comorbidities*	*Progressed to higher intensity*
C1	F	49	212		C, V		
C2	F	22	180		C	Anxiety, depression, migraines	
C3	F	53	301		C,V		
C4	F	36	218		C,V		7th visit
C5	M	49	144		C		
C6	F	28	215		C,V	Anxiety, migraines	
C7	M	39	186	Yes, hockey	C,V		
C8	F	39	184		C,V	Anxiety, depression	
C9	F	23	141		C,V		
C10	F	49	153		C,V		3rd visit
C11	F	31	43		C,V	Depression	
$n=11$	9 F; 2 M	38 ± 11	180 ± 64				
E1	F	31	42		C,V		11th visit
E2	F	37	101		C,V		
E3	F	37	211		C,V	Depression, migraines	
E4	M	32	209		C,V		
E5	M	44	297		C,V	Migraines	
E6	F	30	184		C,V	Migraines, anxiety	
E7	M	21	198		C,V		
E8	M	40	313		C,V		
E9	M	20	91	Yes, skiing	C,V		
E10	F	18	183		C,V		
E11	F	18	243		C,V		
E12	M	49	240		C		
E13	F	42	44		C,V		
E14	F	37	127		C		
$n=14$	8 F; 6 M	33 ± 10	178 ± 86				

PPCS, persistent post-concussive symptoms.

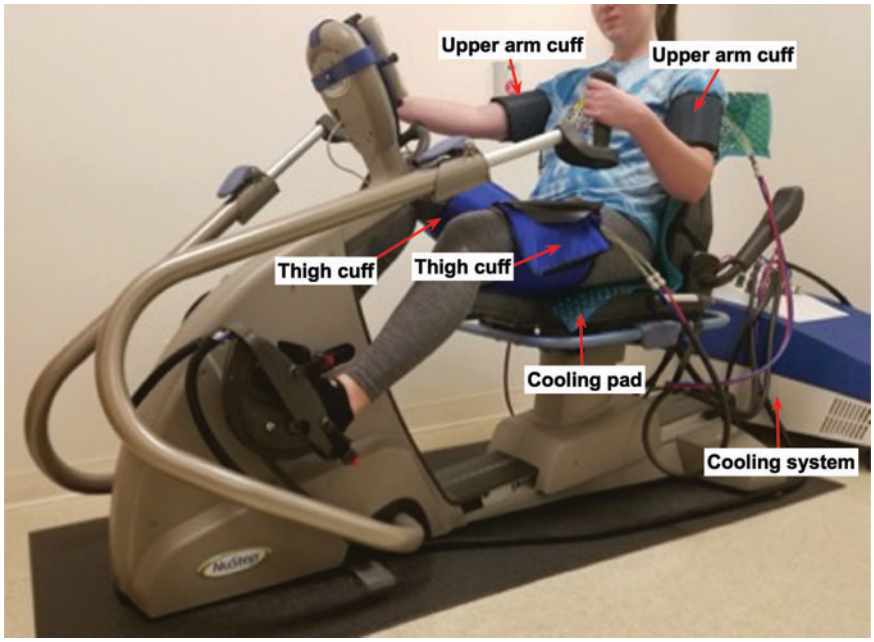

FIG. 1. A Vasper system was used to deliver the exercise. Blood flow restriction (BFR) and body cooling (BC) were on for the experimental group and were off for the control group.

Experimental timeline and protocol

Participants visited the clinics twice a week for 6 consecutive weeks. During each visit, participants in both groups rode the recumbent elliptical machine for 21 min following the interval training protocol (Fig. 2B). Participants were encouraged to reach ~65% of the predicted maximal heart rate during the sprint intervals. The 21-min protocol was chosen according to the instructional guideline of the Vasper system. The guideline is based on studies that demonstrated safety of using the Vasper system on healthy participants and people with Parkinson's disease.[28,47] Further, the total duration of most high-intensity interval training is ~ ≥20 min in the clinical populations, which is comparable to the duration recommended for continuous training.[21] Figure 2B illustrates the interval training profile used in both groups. Each participant started with the introductory protocol (solid lines in Fig. 2B) and only progressed to the next level, a higher intensity (dotted lines in Fig. 2B), based on the participant's perception of difficulty. Three participants (two in the control group and one in the experimental group) progressed to the next level, while the rest of the participants stayed at the same level throughout the 12 sessions. In addition to the interval training, each participant received standardized physical therapy based on their impairments, which may have included stretching and strengthening of neck muscles and vestibular exercises, as part of the 6-week intervention. Table 1 also shows participants who experienced neck and vestibular impairments. The standardized physical therapy was provided by two concussion specialists to control the potential effects of the therapy provided. The participants were asked to maintain their routine and not to change their exercise regimen during both the intervention and the follow-up periods. After the 6-week intervention, participants were asked to receive no additional intervention for 6 weeks while we observed the lasting effects of exercise (6-week follow-up). In addition to training sessions, participants attended evaluation sessions.

Outcome measures

Primary outcome measure. To track the fluctuations of the PPCS, a PPCS scale[48–50] was used daily throughout the period of the 12-week study as the primary outcome measure (Table 2). There are 26 symptom items with self-reported score 0–6, with 6 indicating

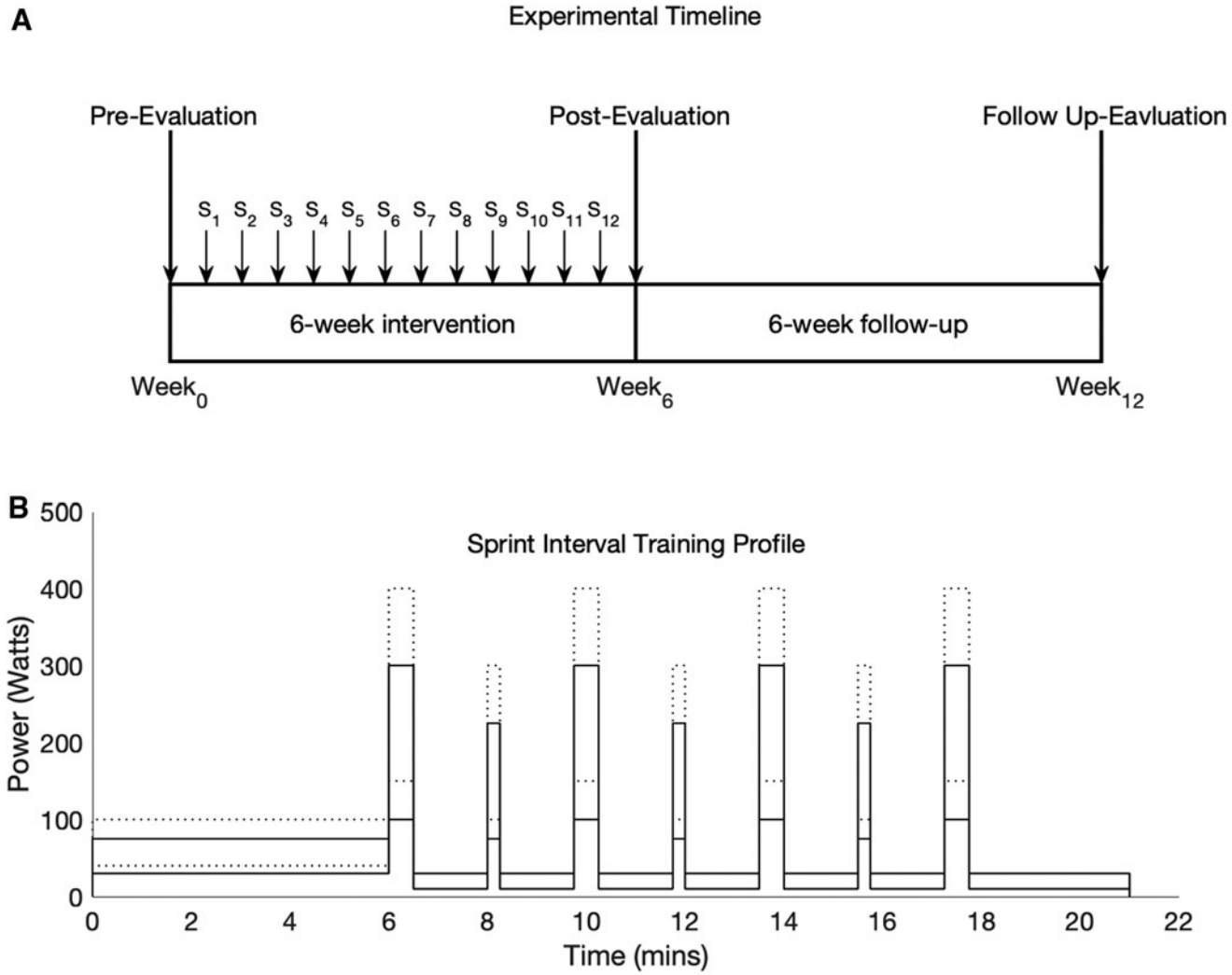

FIG. 2. **(A)** Experimental timeline. Twelve sessions (S1 ~ S12) over the 6-week intervention period followed by no intervention for 6 weeks (6-week follow-up). Three clinical evaluations occurred before (Pre-Evaluation), after (Post-Evaluation) and 6 weeks after (Follow Up-Evaluation) the 6-week intervention. **(B)** Sprint interval training profile; 21-min interval training included a 6-min warmup at 30–75 W, seven sprint intervals (four 30-sec sprints at 100–300 W and three 15-sec sprints at 75–225 W), six 90-sec rest intervals at 10–30 W between each sprint, and a cool-down period at the end (solid lines). Each participant started with the aforementioned protocol and only progressed to the next level, a higher intensity (dotted lines), based on the participants' perception of difficulty.

TABLE 2. PERSISTENT POST-CONCUSSIVE SYMPTOMS SCALE USED TO TRACK DAILY SYMPTOMS

Cognitive	*Emotional*	*Physical*	*Sleep*	*Vestibulo-ocular*
Confusion	Feeling more emotional	Headache/Head pressure	Drowsy	Balance issues
Difficulty concentrating	Irritability	Nausea/Vomiting	Fatigue/Low energy	Dizziness
Difficulty remembering	Nervous/Anxious	Neck pain	Feeling slowed down	Ringing in the ears
''Not feeling right''/Bell rung	Sadness	Numbness/Tingling	Sleeping less than usual	Visual problems/Blurred vision
Feeling in a fog		Sensitivity to light	Sleeping more than usual	
Loss of consciousness		Sensitivity to noise	Trouble falling asleep	

the greatest severity. The scores were analyzed as a whole and as clusters (cognitive, mood, somatic, sleep and vestibulo-ocular domains).[51] The number and severity of overall symptoms and symptoms in each domain were then calculated and compared between the two groups. To examine the fluctuations of symptoms, the variance of number and severity scores of post-concussive symptoms of each participant at the 6-week intervention and 6-week follow-up were calculated. The slope of a fitting line through data points (daily persistent post-concussive symptoms scale score over the 6-week intervention) was derived as the recovery rate for each participant.

Secondary outcome measure. Commonly used clinical measures were included as the secondary outcome measures including the Balance Error Scoring System (BESS), the King-Devick test, the Standardized Assessment of Concussion (SAC), and the Quality of Life after Brain Injury (QOLIBRI) scale. These clinical measures were administered by the blind evaluator at three time points: before the intervention (Pre-Evaluation) as a baseline, right after the intervention period (Post-Evaluation) to examine any immediate effects after training, and 6 weeks after the intervention ended (Follow Up-Evaluation) to examine any lasting effects that might reflect on the changes of commonly used clinical measures.

Statistical analysis

Non-parametric statistics, the Mann-Whitney *U* test, were used because of the non-normal distribution of our sample data examined by the Shapiro–Wilk test. A statistical significance was set at $p < 0.05$ to examine the differences of changes of the abovementioned variables between the two groups. Statistical analyses were performed using SPSS V26. We also used the box plot to display data distributions. The box represents the interquartile range with the median bar within the box. The whiskers extend to the most extreme data points. The outliers are indicated by the '+' symbols.

Results

Symptom recovery during the intervention period

Figure 3 shows an example of daily PPCS scale data of one participant from each group. The slope of the dotted line of each

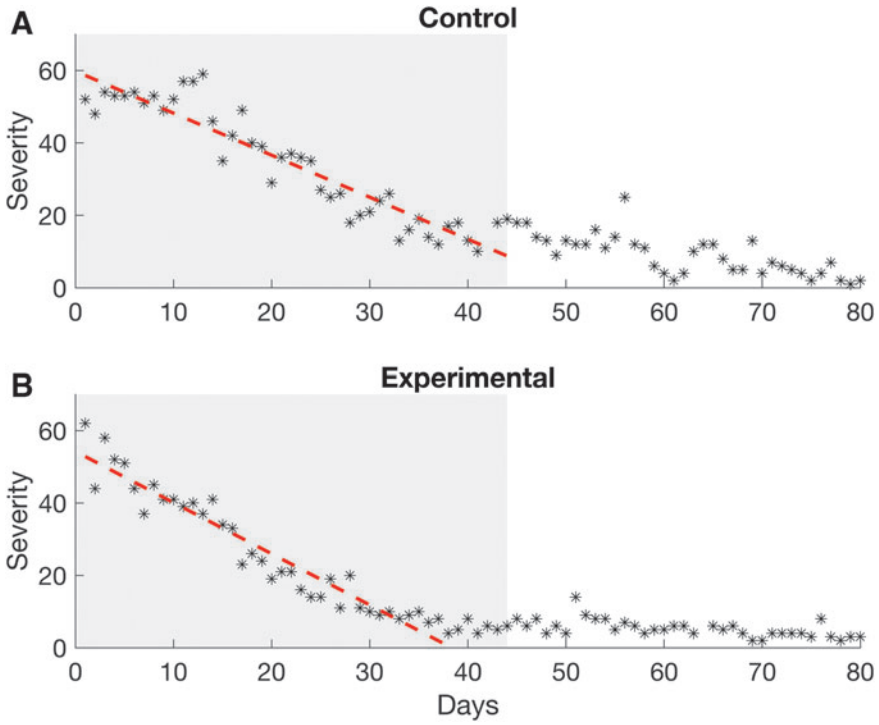

FIG. 3. Examples of individual's daily persistent post-concussive symptoms scale data over the 6-week intervention (shaded area) and 6-week follow-up periods from the control group **(A)** and the experimental group **(B)**. The slope of the severity changes over the intervention period (dotted line) was derived as the recovery rate.

individual was derived as the recovery rate and compared between groups. There was no significant difference between the recovery rates of the experimental group and of the control group (-0.32 ± 0.38 vs. -0.31 ± 0.43, $p = 0.9$). Figure 4A shows the variances of the total number and severity changes, as well as changes in each domain during the intervention period. The fluctuation of overall symptom severity during the 6-week intervention was significantly less in the experimental group ($p = 0.03$). Fewer variations of severity in cognitive and mood domains were observed in the experimental group ($p = 0.02$ respectively).

Fluctuations of symptoms during the follow-up period

Figure 4B shows fluctuations of symptoms during the follow-up period. During the 6-week follow-up period, the number of symptoms remained more stable in the experimental group ($p = 0.02$). There is a trend that after the intervention ended, less symptom severity fluctuation was observed in the experimental group ($p = 0.05$). The number of symptoms in the cognitive and sleep domains reduced after the 6-week intervention ended and remained stable during the 6-week follow-up period ($p = 0.007$ and $p = 0.02$). Further, the severity of mood and sleep symptoms remained more stable in the experimental group ($p = 0.04$ for both domains).

Secondary outcome measures

Both groups demonstrated improvement in secondary outcome measurements after the 6-week intervention, but there was no significant difference between two groups (Fig. 5).

Discussion

Our study has demonstrated the feasibility and safety of implementing moderate intensity-interval-training through the recumbent elliptical machine with BFR and BC on people who have had PPCS for <1 year. The people who exercised with BFR and BC stayed more stable in terms of symptom severity after the intervention ended than did those who underwent training without BFR and BC. We also observed a higher dropout rate in the control group: four dropouts in the control group compared with only one in the experimental group. Those findings and observations suggest that BFR and BC might be a favorable combination to enhance the comfort during interval training intervention for people with PPCS.

The stable recovery pattern we observed in the experimental group might be attributed to the cooling effect. People with PPCS often have poor ANS regulation, including thermoregulation. Physical exercise accelerates the rate of heat production and

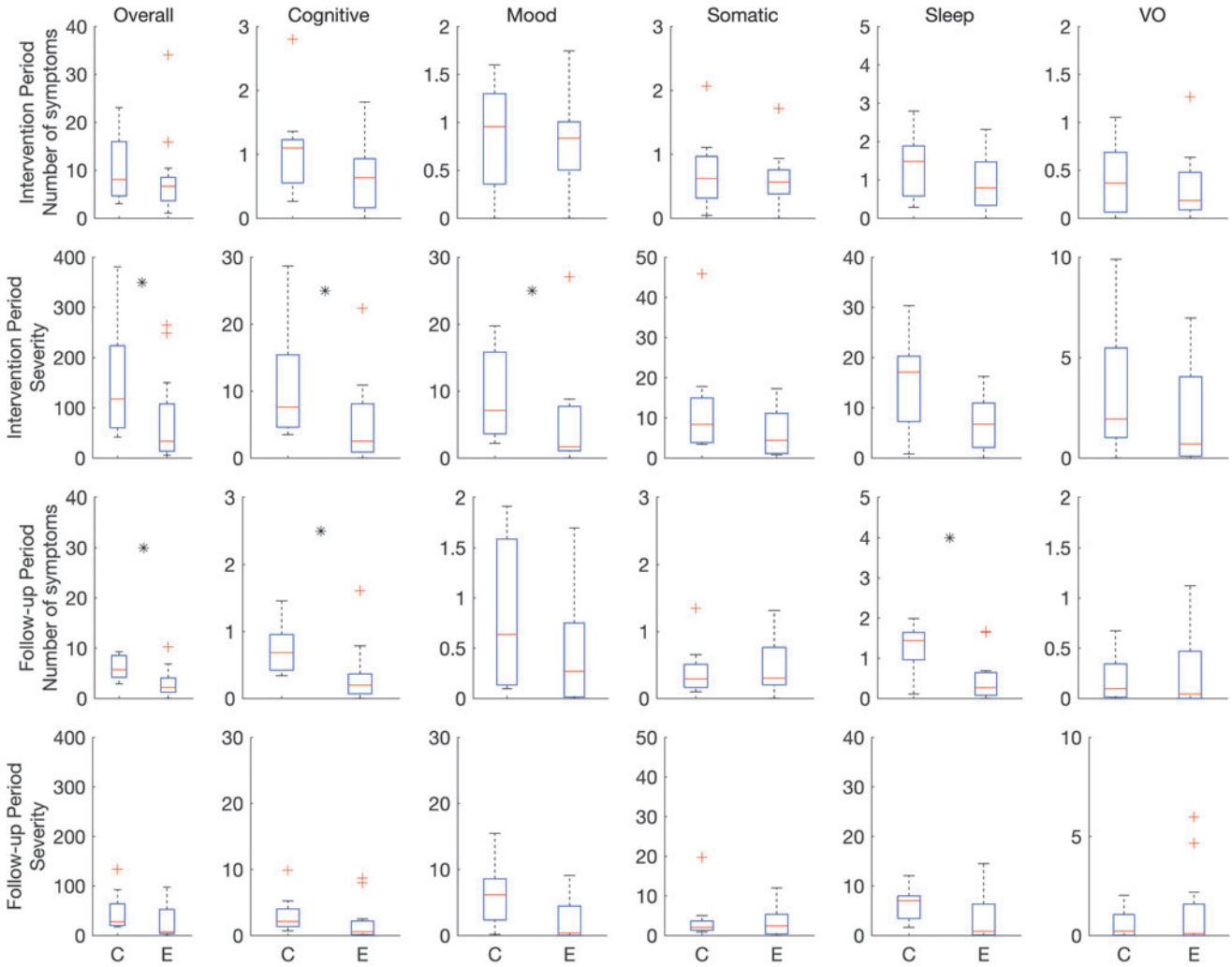

FIG. 4. Number and severity of persistent post-concussive symptoms during the 6-week intervention period and during the 6-week follow-up period. Asterisk indicates statistical significance. C, control group; E, experimental group; VO, vestibulo-ocular.

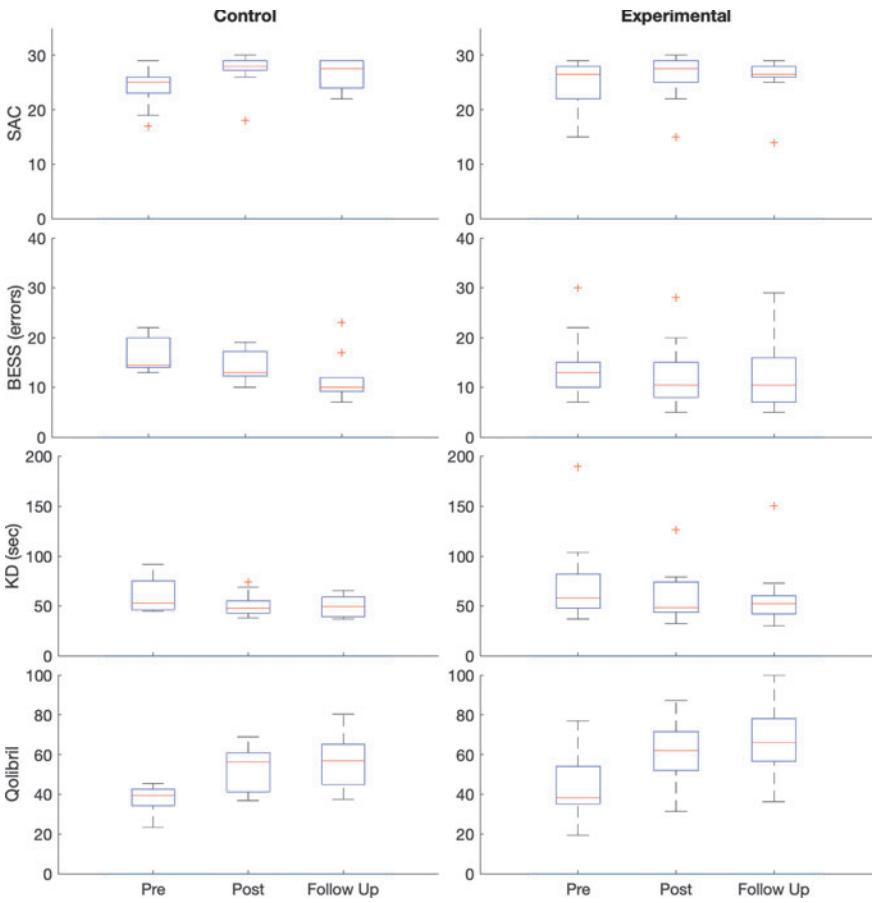

FIG. 5. Group comparisons of the clinical outcomes. Pre, before 6-week intervention; Post, post 6-week intervention; Follow-Up: 6 weeks after the intervention ended.

increases the body temperature, which can lead to increased perceived exertion and decreased cerebral function.[52,53] The reduced cerebral blood flow in people with PPCS impedes the heat dissipation that might exacerbate symptoms temporarily after exercise. In our study, we noticed the statistically significant differences of recovery in the cognitive domain between the two groups. In people with PPCS, emotional symptoms tended to develop later in the recovery period, whereas cognitive symptoms might be present and dominate throughout and even 1 year after the injury.[3,54] According to our results, BC during exercise stabilized cognitive function recovery. This evidence indicates that interval training with BFR and BC can alleviate the most dominant symptoms that people with PPCS face.

The symptoms in each domain often do not exist exclusively and it can be difficult to draw a causality among the symptoms or treat each symptom individually. For example, any intolerance to exercise leads to a reduced physical activity level, which possibly further causes fatigue.[55] Fatigue then impedes the motivation to exercise and starts a vicious circle. Similarly, emotional distress reduces physical activity level such that patients with emotional distress receive less of the benefit of exercise-induced hormone production that could improve their mood. Therefore, implementing an exercise program within the patients' tolerance, and providing an environment where they can exercise safely and efficiently, greatly expands the treatment regimen for PPCS management. We observed the improvement in both groups in our study, which contributes to the current emerging literature[8,15,56–59] that shows that proper exercise alleviates PPCS.

The comparable improvement, except for the more stable recovery in the BFR/BC group, otherwise seen in both groups might be a result of the intensity prescribed for each participant. The current protocol used the predicted heart rate as the intensity indicator; we did not individualize the training parameters according to each participant's capacity to reach the highest sub-symptomatic intensity as suggested by Leddy and coworkers.[10] This limitation might be a reason that we cannot differentiate the outcome between the two groups.

Relatively higher efforts have been put into investigating exercise as a treatment option to manage concussion in youth athletes, and with less focus on the general population or adults. Our study provides evidence of the positive interval training effect on adults with PPCS. Our study did not restrict the cause of the concussion to sport-related injury; in fact, most of our participants (23 among 25) sustained a non-sport-related concussion. The only two sport-related concussions were caused by hockey and skiing. People with a sport-related concussion might have experienced sub-concussive events that can complicate the recovery. Therefore, our results might need to be further investigated before we can generalize the findings to PPCS caused by sport-related concussions.

Another challenge our study encountered was keeping participants blind to the interventions. Unlike pharmaceutical studies, exercise intervention studies require participants to actively engage

in the exercise. Future studies investigating the modalities of BFR and BC should have strategies for a double-blind design to enhance the internal validity of the study. Instead of the sole use of the Vasper system for providing interventions (with BFR and BC or BFR/BC removed) to both groups, we should only use the Vasper system for the experimental group and use a conventional recumbent elliptical machine for the control group in two separate but identical rooms. To mimic the appearance of BFR and BC modalities, we could use arm floaties, which do not compress the limbs, to avoid the BFR effects, and a gel padded seat that is cool but not chilled enough to cool the body during exercise.

Nonetheless, our preliminary finding that utilizing the modalities of BFR and BC can promote PPCS recovery is encouraging. To expand from our findings and to address the limitations of the current study, in the future, studies should include larger samples and consider factors that might affect patients' responses to interventions, such as whether PPCS was sport- related or non-sport-related, gender, age, physical activity level prior to concussive event(s), and a thorough review of participants' medical history, both physical and behavioral. This will allow researchers to investigate (1) the mechanism of PPCS recovery caused by the exercise intervention, (2) the efficacy of the proposed strategy, (3) phenotypes of the responders to the exercise intervention, (4) the optimal prescription/dosage of intervention, and (5) guidelines to individualize the progressive programs with proposed modalities for people with PPCS. Moreover, physiological measurements, such as serum lactates, core body temperature, brain activation and cognitive load, and oxygen utilization, should be included, when permitted, in addition to the self-report post-concussion symptom scales, to help differentiate the human responses to the proposed exercise intervention to which PPCS recovery is attributed.

Conclusion

Our study demonstrates that it is safe and feasible to implement moderate intensity-interval-training exercise as part of PPCS intervention. In our study, exercise alleviated PPCS of people who have had unresolved concussions lasting >1 month but <1 year. A more stable recovery, meaning less fluctuation of symptom severity, was observed in people receiving BFR and BC during exercise.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Langlois, J.A., Rutland-Brown, W., and Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21, 375–378.
2. Baker, J.G., Freitas, M.S., Leddy, J.J., Kozlowski, K.F., and Willer, B.S. (2012). Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. Rehabil. Res. Pract. 2012, 705309.
3. Roe, C., Sveen, U., Alvsaker, K., and Bautz-Holter, E. (2009). Post-concussion symptoms after mild traumatic brain injury: influence of demographic factors and injury severity in a 1-year cohort study. Disabil. Rehabil. 31, 1235–1243.
4. Shrey, D.W., Griesbach, G.S., and Giza, C.C. (2011). The pathophysiology of concussions in youth. Phys. Med. Rehabil. Clin. N. Am. 22, 577–602.
5. Barlow, K.M. (2016). Postconcussion syndrome: a review. J. Child Neurol. 31, 57–67.
6. Giza, C.C., Kutcher, J.S., Ashwal, S., Barth, J., Getchius, T.S., Gioia, G.A., Gronseth, G.S., Guskiewicz, K., Mandel, S., Manley, G., McKeag, D.B., Thurman, D.J., and Zafonte, R. (2013). Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 80, 2250–2257.
7. Corbin-Berrigan, L.A., and Gagnon, I. (2017). Postconcussion symptoms as a marker of delayed recovery in children and youth who recently sustained a concussion: a brief report. Clin. J. Sport Med. 27, 325–327.
8. Leddy, J.J., Kozlowski, K., Donnelly, J.P., Pendergast, D.R., Epstein, L.H., and Willer, B. (2010). A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. Clin. J. Sport Med. 20, 21–27.
9. Fu, Q., and Levine, B.D. (2013). Exercise and the autonomic nervous system. Handb. Clin. Neurol. 117, 147–160.
10. Leddy, J.J., Haider, M.N., Ellis, M., and Willer, B.S. (2018). Exercise is medicine for concussion. Curr. Sports Med. Rep. 17, 262–270.
11. Tan, C.O., Meehan, W.P., 3rd, Iverson, G.L., and Taylor, J.A. (2014). Cerebrovascular regulation, exercise, and mild traumatic brain injury. Neurology 83, 1665–1672.
12. Brooks, G.A., and Martin, N.A. (2014). Cerebral metabolism following traumatic brain injury: new discoveries with implications for treatment. Front. Neurosci. 8, 408.
13. Redell, J.B., Moore, A.N., Grill, R.J., Johnson, D., Zhao, J., Liu, Y., and Dash, P.K. (2013). Analysis of functional pathways altered after mild traumatic brain injury. J. Neurotrauma 30, 752–764.
14. Burke, M.J., Fralick, M., Nejatbakhsh, N., Tartaglia, M.C., and Tator, C.H. (2015). In search of evidence-based treatment for concussion: characteristics of current clinical trials. Brain Inj. 29, 300–305.
15. Leddy, J.J., Haider, M.N., Ellis, M.J., Mannix, R., Darling, S.R., Freitas, M.S., Suffoletto, H.N., Leiter, J., Cordingley, D.M., and Willer, B. (2019). Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. JAMA Pediatr. 173, 319–325.
16. Kozlowski, K.F., Graham, J., Leddy, J.J., Devinney-Boymel, L. and Willer, B.S. (2013). Exercise intolerance in individuals with post-concussion syndrome. J. Athl. Train. 48, 627–635.
17. Fleming, J., Braithwaite, H., Gustafsson, L., Griffin, J., Collier, A.M., and Fletcher, S. (2011). Participation in leisure activities during brain injury rehabilitation. Brain Inj. 25, 806–818.
18. Centner, C., Wiegel, P., Gollhofer, A., and Konig, D. (2019). Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: a systematic review and meta-analysis. Sports Med. 49, 95–108.
19. Loenneke, J.P., Wilson, J.M., Marin, P.J., Zourdos, M.C., and Bemben, M.G. (2012). Low intensity blood flow restriction training: a meta-analysis. Eur. J. Appl. Physiol. 112, 1849–1859.
20. Vanwye, W.R., Weatherholt, A.M., and Mikesky, A.E. (2017). Blood flow restriction training: implementation into clinical practice. Int. J. Exerc. Sci. 10, 649–654.
21. Cassidy, S., Thoma, C., Houghton, D., and Trenell, M.I. (2017). High-intensity interval training: a review of its impact on glucose control and cardiometabolic health. Diabetologia 60, 7–23.
22. Lloyd Jones, M.C., Morris, M.G., and Jakeman, J.R. (2019). Effect of work: rest ratio on cycling performance following sprint interval training: a randomized control trial. J. Strength Cond. Res. 33, 3263–3268.
23. Little, J.P., Safdar, A., Wilkin, G.P., Tarnopolsky, M.A., and Gibala, M.J. (2010). A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. J. Physiol. 588, 1011–1022.
24. Tjonna, A.E., Lee, S.J., Rognmo, O., Stolen, T.O., Bye, A., Haram, P.M., Loennechen, J.P., Al-Share, Q.Y., Skogvoll, E., Slordahl, S.A., Kemi, O.J., Najjar, S.M., and Wisloff, U. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation 118, 346–354.
25. Liang, H., and Ward, W.F. (2006). PGC-1alpha: a key regulator of energy metabolism. Adv. Physiol. Educ. 30, 145–151.
26. Daussin, F.N., Zoll, J., Dufour, S.P., Ponsot, E., Lonsdorfer-Wolf, E., Doutreleau, S., Mettauer, B., Piquard, F., Geny, B., and Richard, R. (2008). Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic perfor-

mance improvements in sedentary subjects. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R264–272.
27. Loenneke, J.P., and Pujol, T.J. (2009). The use of occlusion training to produce muscle hypertrophy. Strength Cond. J. 31, 77–84.
28. Gladden, J., Wernecke, C., Rector, S., Tecson, K., and McCullough, P. (2016). Pilot Safety Study: the use of vasper, a novel blood flow restriction exercise in healthy adults. J. Exerc. Physiol. Online 19, 99–105.
29. Manini, T.M., and Clark, B.C. (2009). Blood flow restricted exercise and skeletal muscle health. Exerc. Sport Sci. Rev. 37, 78–85.
30. Adeva-Andany, M., Lopez-Ojen, M., Funcasta-Calderon, R., Ameneiros-Rodriguez, E., Donapetry-Garcia, C., Vila-Altesor, M., and Rodriguez-Seijas, J. (2014). Comprehensive review on lactate metabolism in human health. Mitochondrion 17, 76–100.
31. Overgaard, M., Rasmussen, P., Bohm, A.M., Seifert, T., Brassard, P., Zaar, M., Homann, P., Evans, K.A., Nielsen, H.B., and Secher, N.H. (2012). Hypoxia and exercise provoke both lactate release and lactate oxidation by the human brain. FASEB J. 26, 3012–3020.
32. Aveseh, M., Nikooie, R., Sheibani, V., and Esmaeili-Mahani, S. (2014). Endurance training increases brain lactate uptake during hypoglycemia by up regulation of brain lactate transporters. Mol. Cell Endocrinol. 394, 29–36.
33. Boumezbeur, F., Petersen, K.F., Cline, G.W., Mason, G.F., Behar, K.L., Shulman, G.I., and Rothman, D.L. (2010). The contribution of blood lactate to brain energy metabolism in humans measured by dynamic 13C nuclear magnetic resonance spectroscopy. J. Neurosci. 30, 13,983–13,991.
34. Jourdain, P., Allaman, I., Rothenfusser, K., Fiumelli, H., Marquet, P., and Magistretti, P.J. (2016). L-Lactate protects neurons against excitotoxicity: implication of an ATP-mediated signaling cascade. Sci. Rep. 6, 21250.
35. Bergersen, L.H. (2015). Lactate transport and signaling in the brain: potential therapeutic targets and roles in body–brain interaction. J. Cereb. Blood Flow Metab. 35, 176–185.
36. Edelmann, E., Lessmann, V., and Brigadski, T. (2014). Pre- and postsynaptic twists in BDNF secretion and action in synaptic plasticity. Neuropharmacology 76 Pt C, 610–627.
37. Hartmann, M., Heumann, R., and Lessmann, V. (2001). Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. EMBO J. 20, 5887–5897.
38. Haubensak, W., Narz, F., Heumann, R., and Lessmann, V. (1998). BDNF-GFP containing secretory granules are localized in the vicinity of synaptic junctions of cultured cortical neurons. J. Cell Sci. 111 (Pt 11), 1483–1493.
39. Helan, M., Aravamudan, B., Hartman, W.R., Thompson, M.A., Johnson, B.D., Pabelick, C.M., and Prakash, Y.S. (2014). BDNF secretion by human pulmonary artery endothelial cells in response to hypoxia. J. Mol. Cell Cardiol. 68, 89–97.
40. Kohara, K., Kitamura, A., Morishima, M. and Tsumoto, T. (2001). Activity-dependent transfer of brain-derived neurotrophic factor to postsynaptic neurons. Science 291, 2419–2423.
41. Vermehren-Schmaedick, A., Jenkins, V.K., Knopp, S.J., Balkowiec, A. and Bissonnette, J.M. (2012). Acute intermittent hypoxia-induced expression of brain-derived neurotrophic factor is disrupted in the brainstem of methyl-CpG-binding protein 2 null mice. Neuroscience 206, 1–6.
42. Wiener, C.M., Booth, G., and Semenza, G.L. (1996). In vivo expression of mRNAs encoding hypoxia-inducible factor 1. Biochem. Biophys. Res. Commun. 225, 485–488.
43. Grossman, E.J., Jensen, J.H., Babb, J.S., Chen, Q., Tabesh, A., Fieremans, E., Xia, D., Inglese, M., and Grossman, R.I. (2013). Cognitive impairment in mild traumatic brain injury: a longitudinal diffusional kurtosis and perfusion imaging study. AJNR Am. J. Neuroradiol. 34, 951–957.
44. Kim, J., Whyte, J., Patel, S., Avants, B., Europa, E., Wang, J., Slattery, J., Gee, J.C., Coslett, H.B., and Detre, J.A. (2010). Resting cerebral blood flow alterations in chronic traumatic brain injury: an arterial spin labeling perfusion FMRI study. J. Neurotrauma 27, 1399–1411.
45. Ogoh, S., and Ainslie, P.N. (2009). Cerebral blood flow during exercise: mechanisms of regulation. J. Appl. Physiol. (1985) 107, 1370–1380.
46. Doubt, T.J. (1991). Physiology of exercise in the cold. Sports Med. 11, 367–381.
47. Byl, N., Byl, N.N., Kretschmer, J., Irina, F., Molli, B., and Maurice, G. (2014). Aerobic exercise enabled with rehabilitation technology improves mobility and balance of patients with Parkinson's disease: a quality assurance report. Int. J. Phys. Med. Rehabil. 2, 1–14.
48. Cantu, R.C. (2003). Recurrent athletic head injury: risks and when to retire. Clin. Sports Med. 22, 593–603.
49. Cantu, R.C. (2017). History of concussion and chronic traumatic encephalopathy, in: *Chronic Traumatic Encephalopathy*. A. Budson, A.C. McKee, R.C. Cantu,.and R.A Stern, (eds.). Philadelphia, PA: Elsevier, pp. 1–18.
50. Wu, Y., Gravel, J., Chatiwala, N., Enis, T., Stark, C., and Cantu, R.C. (2018). Effects of electrical stimulation in people with post-concussion syndromes: a pilot study. Health 10, 381–395.
51. Howell, D.R., O'Brien, M.J., Beasley, M.A., Mannix, R.C., and Meehan, W.P., 3rd (2016). Initial somatic symptoms are associated with prolonged symptom duration following concussion in adolescents. Acta Paediatr. 105, e426–432.
52. Ftaiti, F., Kacem, A., Jaidane, N., Tabka, Z., and Dogui, M. (2010). Changes in EEG activity before and after exhaustive exercise in sedentary women in neutral and hot environments. Appl. Ergon. 41, 806–811.
53. Nybo, L., and Nielsen, B. (2001). Perceived exertion is associated with an altered brain activity during exercise with progressive hyperthermia. J. Appl. Physiol. (1985) 91, 2017–2023.
54. Eisenberg, M.A., Meehan, W.P., 3rd, and Mannix, R. (2014). Duration and course of post-concussive symptoms. Pediatrics 133, 999–1006.
55. van Markus-Doornbosch, F., Peeters, E., van der Pas, S., Vlieland, T.V., and Meesters, J. (2019). Physical activity after mild traumatic brain injury: what are the relationships with fatigue and sleep quality? Eur. J. Paediatr. Neurol. 23, 53–60.
56. Anderson, V., Manikas, V., Babl, F.E., Hearps, S., and Dooley, J. (2018). Impact of moderate exercise on post-concussive symptoms and cognitive function after concussion in children and adolescents compared to healthy controls. Int. J. Sports Med. 39, 696–703.
57. Chrisman, S.P.D., Whitlock, K.B., Mendoza, J.A., Burton, M.S., Somers, E., Hsu, A., Fay, L., Palermo, T.M., and Rivara, F.P. (2019). Pilot randomized controlled trial of an exercise program requiring minimal in-person visits for youth with persistent sport-related concussion. Front. Neurol. 10, 623.
58. Dobney, D.M., Grilli, L., Kocilowicz, H., Beaulieu, C., Straub, M., Friedman, D., and Gagnon, I. (2017). Evaluation of an active rehabilitation program for concussion management in children and adolescents. Brain Inj. 31, 1753–1759.
59. Kurowski, B.G., Hugentobler, J., Quatman-Yates, C., Taylor, J., Gubanich, P.J., Altaye, M., and Wade, S.L. (2017). Aerobic exercise for adolescents with prolonged symptoms after mild traumatic brain injury: an exploratory randomized clinical trial. J. Head Trauma Rehabil. 32, 79–89.

Address correspondence to:
Robert C. Cantu, MD
Emerson Hospital
131 ORNAC, Suite 820
John Cuming Building
Concord, MA 01742
USA

E-mail: RCantu@emersonhosp.org