A Preliminary Study of Subsymptom Threshold Exercise Training for Refractory Post-Concussion Syndrome

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Objective: To evaluate the safety and effectiveness of subsymptom threshold exercise training for the treatment of post-concussion syndrome (PCS).

Design: Prospective case series.

Setting: University Sports Medicine Concussion Clinic.

Participants: Twelve refractory patients with PCS (6 athletes and 6 nonathletes).

Intervention: Treadmill test to symptom exacerbation threshold (ST) before and after 2 to 3 weeks of baseline. Subjects then exercised 5 to 6 days per week at 80% ST heart rate (HR) until voluntary peak exertion without symptom exacerbation. Treadmill testing was repeated every 3 weeks.

Main Outcome Measures: Adverse reactions to exercise, PCS symptoms, HR, systolic blood pressure (SBP), achievement of maximal exertion, and return to work/sport.

Results: Pretreatment, ST occurred at low exercise HR (147 ± 27 bpm) and SBP (142 ± 6 mm Hg). After treatment, subjects exercised longer (9.75 ± 6.38 minutes to 18.67 ± 2.53 minutes, P = .001) and achieved peak HR (179 ± 17 bpm) and SBP (156 ± 13 mm Hg), both P < .001 versus pretreatment, without symptom exacerbation. Time series analysis showed significant change in rate of symptom reduction for all subjects and reduced mean symptom number in 8/11. Rate of PCS symptom improvement was related to peak exercise HR (r = −0.55, P = .04). Athletes recovered faster than nonathletes (25 ± 8.7 vs 74.8 ± 27.2 days, P = .01). No adverse events were reported. Athletes returned to sport and nonathletes to work.

Conclusions: Treatment with controlled exercise is a safe program that appears to improve PCS symptoms when compared with a no-treatment baseline. A randomized controlled study is warranted.

Key Words: traumatic brain injury, exertion, symptoms, physiology, blood pressure

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INTRODUCTION

The majority of patients with sport-related concussion recover within 7 to 10 days1 and nonathletes within the first 3 months.2 There is, however, a significant minority of athlete3 and nonathlete4 patients who continue to experience symptoms beyond this, called post-concussion syndrome (PCS). The World Health Organization defines PCS as persistence of 3 or more of the following after head injury: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, or memory difficulty.5 The primary forms of PCS treatment have traditionally included rest, education, neurocognitive rehabilitation, and antidepressants, with little evidence of success.3

Concussion affects not only cognitive function but also other physiological systems to include the heart and the autonomic nervous system.6–8 Concussed athletes have exaggerated sympathetic nervous activity and increased heart rates (HRs) when compared with controls.6,9 Cerebral autoregulation (the ability of the brain to maintain constant perfusion pressure in the face of changing systemic arterial pressure during exertion) and cerebral blood flow are disturbed after concussion,10 which may explain why symptoms reappear or worsen with physical exertion or other stressors that increase blood pressure (BP).

Patients are generally advised to not engage in exertion while symptomatic from a concussion.11,12 Prolonged rest, however, can lead to secondary symptoms of fatigue and reactive depression and physiological deconditioning.3 The Prague11 and Zurich12 guidelines on the evaluation and treatment of concussion in athletes recommend that the concussed athlete not return to play until asymptomatic at rest and is able to exercise to maximum without exacerbation of symptoms. This requirement recognizes the physiologic component of concussion. The guidelines do not, however, describe an evidence-based approach to the evaluation of the patient’s response to exercise and do not address the problem of patients with prolonged symptoms. The concept of returning athletes to play once asymptomatic at rest and who demonstrate a normal
response to exercise makes sense; however, there is no known intervention to assist individuals who do not recover spontaneously.

We have proposed that one fundamental cause of refractory PCS is physiologic dysfunction that fails to return to normal after concussion. The primary physiologic issues, we suggest, are altered autonomic function and impaired cerebral autoregulation. Aerobic exercise training may help concussion-related physiological dysfunction because exercise increases parasympathetic activity, reduces sympathetic activation, and improves cerebral blood flow. We therefore hypothesized that a progressive sub symptom threshold exercise training (SSTET) program would ameliorate PCS by restoring autonomic balance and improving cerebral autoregulation and that there would be a relationship between improved exercise capacity and symptom reduction. The goals for this study were to establish the safety and potential effectiveness of SSTET. We recognize that an exercise program for individuals still experiencing symptoms is contrary to expert consensus, and we were especially attentive to the potential ill effects of exercise in patients with PCS.

METHODS

A consecutive enrollment of 13 PCS subjects was obtained at the University at Buffalo Concussion Clinic. The diagnosis of PCS required 2 elements: fulfill the World Health Organization’s International Classification of Diseases, Tenth Revision, criteria of symptoms at rest for ≥6 weeks but <52 weeks (by study physician interview) and demonstrate symptom exacerbation during a graded treadmill exercise test (below). Only subjects at low cardiac risk according to the American College of Sports Medicine were deemed eligible. All 40 patients with PCS seen during the year 2007 were considered for eligibility. Twenty-seven patients were ineligible because they lived too far from the clinic (n = 8), had been injured more than 1 year prior (n = 6), did not show for evaluation (n = 4), had a psychiatric diagnosis (n = 4), could not exercise for health reasons (n = 4), and 1 was involved in litigation. Thirty of 40 patients qualified. One subject dropped out (female nonathlete who stated that she did not like exercise). The remaining 12 subjects (7 men, 5 women) were 27.9 ± 14.3 years old (range, 16–53) and were an average of 19 weeks post injury (range, 6–40 weeks). Six of the 12 were athletes (3/6 athletes and 3/6 nonathletes had a history of 1 or more prior concussions). Five athletes sustained their concussion in sport and 1 in a car accident. Nonathletes sustained their injuries in motor vehicle accidents or falls at work. The study was approved by the University at Buffalo Health Sciences Institutional Review Board, and all subjects signed a written informed consent form. Subjects provided contact by phone 3 months later for follow-up.

Safety Assessment

Subjects were instructed to have a person with them each time they exercised and not to exercise if they felt ill or had severe symptoms. They were instructed to report any adverse reactions to the study physician, investigator, and their primary physician. At the regularly scheduled treadmill tests, they were asked if any of the prescribed exercise sessions within the prior 3 weeks could not be completed and why. Treadmill exercise testing posed the greatest risk for adverse reactions, so subjects were assessed for symptom exacerbation before, during (every 2 minutes), and after exercise testing. They remained with the examiner for 60 minutes upon completion. The protocol required that all reported adverse reactions be immediately assessed by a physician from the Sports Medicine Service. Subjects were provided with investigator emergency phone numbers and e-mail addresses.

Subjects performed an incremental treadmill exercise test according to a standard Balke protocol to the first sign of symptom exacerbation. The treadmill speed was set at 3.3 mph at 0.0% incline. After 1 minute, the grade was increased to 2.0% while maintaining the same speed. At the start of the third minute and each minute thereafter, the grade was increased by 1.0%, maintaining speed at 3.3 mph. Blood pressure (sphygmomanometer) was measured every 2 minutes, and HR (Polar 810i T61 HR Monitor; Kempele, Finland) and ratings of perceived exertion (Borg scale) were measured every minute. The test was terminated at report of exacerbation of PCS symptoms. After test termination, subjects were monitored for 60 minutes. Oxygen consumption (VO₂) was estimated from the treadmill speed and grade.

Subjects were exercise tested at baseline and again after the 2- to 3-week baseline period for 2 treadmill tests before intervention. They were randomly assigned to get the second exercise test either 2 or 3 weeks after starting the study. Subjects had already been symptomatic at rest for 6 weeks or more (mean symptom duration was 19 weeks). Subjects were instructed to record symptoms just before exercise at the same time each day using the Graded Symptom Checklist (GSC). The total GSC score indicated the number of concussion symptoms experienced for the prior 24 hours. After the second exercise test, subjects did aerobic exercise for the same duration that they had achieved during the prior treadmill test but at an intensity of 80% of the maximum treadmill HR (the sub symptom threshold heart rate), once per day for 5 to 6 days per week using an HR monitor. They were required to have someone present during exercise for safety monitoring and were instructed to terminate exercise at the first sign of symptom exacerbation or when the sub symptom threshold duration was reached, whichever came first. Subjects had exercise tests every 3 weeks until their symptoms were no longer exacerbated on the treadmill. Compliance was confirmed in athletes via the team athletic trainer and in nonathletes by reviewing the GSC reports and via confirmation by the identified observer. Subjects then saw the study physician for a reevaluation. Physiologic resolution of PCS was defined as the ability to exercise to voluntary exhaustion without exacerbation of PCS symptoms. Subjects were contacted by phone 3 months later for follow-up.
Statistical Analysis

Daily Symptoms

The daily symptom reports are well represented as individual time series because they vary in terms of the number of baseline and treatment observations and rates of change over time. The inclusion of baseline and treatment phases allows analysis of change in both the rate of improvement (slope) and level of change (total symptoms) at the level of the individual case. A recently developed method known as Simulation Modeling Analysis (SMA)\textsuperscript{19} enables study of shorter series that often arise in clinical settings by modeling key characteristics of the time series (number of observations in baseline and treatment and degree of correlation in each phase via autocorrelation [AR]) combined with modern bootstrapping techniques that estimate exact \( P \) values. Simulation Modeling Analysis generates treatment effect estimates and exact probabilities by comparing the observed data with thousands of simulations that match the AR and phase lengths of the case data.\textsuperscript{21} The effect is calculated as the correlation between the baseline and treatment phases controlling for AR in the baseline and treatment series. The SMA program (version 8.4.11, available at: http://www.clinicalresearcher.org/) allows the researcher to set the number of simulations. In this study, the number of simulations was set to 10,000. The level vector (total daily symptoms) was tested for each individual case so that baseline mean was compared with treatment mean. In addition, the slope vector was tested as a constant baseline against an increasing treatment period. A negative correlation with this vector would indicate improvement, defined as a pattern of decreasing symptoms. Thus, we compared baseline with treatment for change in both level (mean) and slope (rate). Program output includes graphic plots, the effect size (correlation coefficient ranging from \(-1\) to 1) for change in level and slope, and an exact \( P \) value test statistic.

Change in Exercise Time

Exercise duration until appearance of symptoms is another indicator of clinical improvement. Exercise time from baseline assessment to the conclusion of treatment was examined using repeated measures analysis of variance (ANOVA). The small sample size and sparse data across subjects (ie, 7 cases had only 1 or 2 follow-up assessments) precluded more complex modeling of the data.

Physiological Data

Physiological data were analyzed by repeated measures ANOVA at 3 time points: pre and post baseline and at the end of treatment. Significance was set at \( P < .05 \). Paired \( t \) tests were used to compare differences between baseline and treatment means and independent group \( t \) tests for differences among athletes and nonathletes.

Relationship of Symptom Reduction to Physiological Changes

The relationship of exercise intensity to symptom reduction was examined by first calculating the difference between baseline and final maximal systolic blood pressure (SBP), HR, and treadmill time. Second, a standardized change in symptom score was computed via the formula for Cohen’s \( d \) effect size statistic (baseline mean-treatment mean/baseline SD). The 3 physiological variables were then correlated with each other and with the \( d \) estimate of symptom reduction.

RESULTS

Safety and Adverse Events

All 12 subjects reached physiologic criterion for treatment success, that is, they exercised at or near to age-predicted HR maximum without symptom exacerbation (exercise stopped because of exhaustion). There were no occasions where we had to terminate or postpone a testing session because of an adverse reaction and no occasion where a subject could not resume exercise the following day because of symptom exacerbation. No subjects had to see the study or family physician because of an adverse reaction. No adverse events were reported other than one subject who reported a temporary increase in symptoms early in the treatment phase, and only during 1 of the 3-week treatment periods. This slight increase in symptoms did not truly qualify as an adverse reaction but was monitored. He maintained his exercise regimen and did not report any symptom exacerbation to exercise after that.

PCS Symptoms

The descriptive data and SMA results are presented in the Table. One subject (12, nonathlete) was excluded from SMA because he did not provide enough symptom data for analysis, but his physiological data were included, as he completed all tests. The mean GSC total for the sample at baseline was 9.67 ± 5.87 (range, 2.39–18.46). The baseline mean for total symptoms was slightly but not significantly lower for athletes versus nonathletes (8.57 ± 6.21 vs 10.99 ± 5.83, \( P = .53 \)). The mean symptom total for the overall treatment period was 5.42 ± 4.54 (range, 0.58–12.41). A paired \( t \) test indicated that there was a significant reduction in overall mean symptom score between the baseline and treatment periods (\( P = .002 \)).

The analysis of individual time series includes examination of AR and graphic plots. Autocorrelation was estimated separately for the baseline and treatment phases because there was not only sufficient data to do so, but also because we assumed that the symptom reports during the 2 phases represent distinct subjective experiences for subjects and that separate estimates of serial correlation is a more valid way to control for this aspect of scores rather than assuming that one process underlies the entire series from beginning to end. Examination of the AR values in the Table shows that the degree of correlation varies in strength from baseline to treatment within and across subjects. The range of AR values includes a few small negative ARs, suggesting little serial dependence from one day to the next to very high dependence (ie, the treatment phase AR for subject 3 is 0.93, near the maximum value of 1, meaning that each day’s symptom report is very predictable from the prior day’s report for this subject).

The SMA analysis showed that 8 of the 11 subjects significantly improved in symptom level and that all improved significantly in slope. The distribution of effect sizes for the
11 cases ranged from moderate to large. Subject 1, for example, evidenced large effect sizes for both the amount of symptom improvement (the effect size for change in symptom level from baseline was very strong: −0.79) and the rate of improvement when baseline slope was contrasted with the treatment phase slope (the effect size correlation for rate of change was −0.66, a strong effect size). The effect size indicates how much of the change in the time series mean and slope is related to treatment, controlling for the baseline, and for the correlation within each phase of the time series. We calculated a second kind of effect size to summarize across the entire sample, Cohen’s $d$ statistic, which represents standardized mean change. This was 2.50, meaning that on average the degree of symptom improvement across all cases was 2.5 SD. The range of days treated was 11 to 112 (mean = 47.6 ± 27.2 days, median = 36 days). Athletes completed treatment in about one-third the amount of time compared with nonathletes (paired $t$ test, 25 ± 8.7 vs 74.8 ± 27.2 days, $P = .01$). A plot of the mean number of daily symptoms in athletes versus nonathletes across time of exercise treatment is given in Figure 1. In the figure, the number of weeks shown was determined by the number of weeks of complete data. That is, all the nonathletes were in treatment for at least 13 weeks and the athletes were in treatment for at least 4 weeks (2 weeks of baseline are shown). The correlation between improved exercise capacity (maximal treadmill HR) with improvement in symptoms (Cohen’s $d$) over time is shown in Figure 2.

After SSTET, subjects achieved significantly greater peak HR (179 ± 17 bpm) and SBP (156 ± 13 mm Hg), both $P < .001$ versus pretreatment, without symptom exacerbation (Figure 3).

### Relationship of Symptom Reduction and Physiological Changes

Improvement scores from baseline to conclusion of treatment for maximal exercise HR, SBP, and exercise time were highly correlated with each other ($r = 0.56–0.84$, $P < .03$). The correlation between improved exercise capacity (maximal treadmill HR) with improvement in symptoms (Cohen’s $d$) over time is shown in Figure 4.

At follow-up, 10 of 12 subjects reported being symptom free at rest. One had cognitive and visual symptoms, and 1 had migraine headaches (with a pre-injury history of migraine). At study entry, all the athletes were in school but were not

### Exercise Time

Exercise time improved significantly from a baseline mean of 9.75 ± 6.38 minutes to 18.67 ± 2.53 minutes at treatment termination ($P = .001$). There was no difference in improvement for athletes versus nonathletes ($P = .96$).

### Physiological Changes

There were no significant differences in resting HR or BP before and after intervention. During submaximal exercise, there were no significant differences in the HR:VO$_2$ or SBP:VO$_2$ slopes before versus after treatment (Figure 2). Before treatment, symptom exacerbation occurred at low exercise HR (147 ± 27 bpm) and SBP (142 ± 6 mm Hg).

### FIGURE 1

Athlete versus nonathlete improvement in mean number of daily symptoms (with 95% confidence intervals) by weeks of exercise treatment. Athletes completed treatment significantly faster than nonathletes.

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**TABLE.** Summary Statistics for SMA Analysis of SSTET in PCS Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Athlete</th>
<th>n</th>
<th>M (SD)</th>
<th>AR</th>
<th>n</th>
<th>M (SD)</th>
<th>AR</th>
<th>Level</th>
<th>P</th>
<th>Slope</th>
<th>r</th>
<th>P</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
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<td>13</td>
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<td>0.17</td>
<td>28</td>
<td>3.43 (1.15)</td>
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<td>−0.79 .0001</td>
<td>−0.66 .0001</td>
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<tr>
<td>2</td>
<td>M</td>
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<td>18</td>
<td>2.39 (2.16)</td>
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<td>19</td>
<td>0.583 (0.394)</td>
<td>0.07</td>
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<tr>
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<td>13</td>
<td>18.46 (1.28)</td>
<td>0.19</td>
<td>28</td>
<td>7.61 (8.72)</td>
<td>0.93</td>
<td>−0.57 .26</td>
<td>−0.93 .002</td>
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<td>15</td>
<td>13.07 (1.88)</td>
<td>0.32</td>
<td>28</td>
<td>3.92 (4.77)</td>
<td>0.64</td>
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<td>−0.71 .0002</td>
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<td>22</td>
<td>6.77 (3.70)</td>
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<td>11</td>
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<td>0.41</td>
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<td>No</td>
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<td>0.09</td>
<td>112</td>
<td>8.51 (3.01)</td>
<td>0.34</td>
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<tr>
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<td>M</td>
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<td>16</td>
<td>11.34 (1.96)</td>
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<td>8.68 (4.36)</td>
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<tr>
<td>9</td>
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<td>14</td>
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<td>0.88 (0.63)</td>
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<tr>
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<td>F</td>
<td>No</td>
<td>16</td>
<td>16.13 (2.03)</td>
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<td>57</td>
<td>11.82 (2.87)</td>
<td>0.31</td>
<td>−0.55 .0002</td>
<td>−0.52 .0001</td>
<td></td>
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</table>

AR, autocorrelation; F, female; M, male; M, mean number of symptoms; n, days of baseline or treatment; PCS, post-concussion syndrome; r, correlation coefficient; SD, standard deviation; SMA, Simulation Modeling Analysis; SSTET, subsymptom threshold exercise training.
participating in sport. Five of 6 of the nonathletes were not working or going to school. At follow-up, all subjects had returned to full work, school, and athletic activities.

DISCUSSION

The primary purpose of this study was to determine whether controlled exercise was safe to employ in patients with PCS. This was a necessary first step because this form of treatment is contrary to current expert guidelines that recommend no exercise for those who remain symptomatic from a concussion. This study shows for the first time that PCS may be safely treated using a program of quantitative, individualized, and progressive subsymptom threshold aerobic exercise rehabilitation.

The second objective was to determine if PCS improved during SSTET. We found that, when compared with the baseline period of no intervention, patients with PCS performing SSTET significantly improved symptomatically and were able to achieve maximum exertion without symptom exacerbation and so satisfy expert consensus recommendations on readiness to return to sport. By definition, these patients had been symptomatic at rest and were not improving for months and did not improve over a 2- to 3-week period of symptom reporting only. The rate of symptom improvement was related directly to the exercise intensity achieved. Only after the exercise intervention did athletes with PCS return to play and nonathletes return to work. Post-concussion syndrome subjects had low exercise tolerance because their symptoms during exertion were exacerbated at a critical SBP. At this point, they typically reported an increase in headache, dizziness, and/or pressure, that is, a sensation that their head

![FIGURE 2. Heart rate (HR, upper panel) and SBP (lower panel) responses to submaximal exercise in PCS subjects before and after treatment. There were no significant differences in the HR:VO2 or SBP:VO2 slopes before versus after treatment. Base, baseline pre-intervention period; post, postintervention; SBP, systolic blood pressure; PCS, post-concussion syndrome.](image1)

![FIGURE 3. Heart rate (HR) and systolic blood pressure (SBP) responses at maximal exercise in PCS subjects. +Subjects had significantly greater HR and SBP after SSTET (P < .001 for both). Pre, pre-intervention period; post, postintervention; PCS, postconcussion syndrome.](image2)

![FIGURE 4. Scatterplot of heart rate improvement by symptom improvement in PCS subjects (r = -.55, p = .04). PCS, postconcussion syndrome.](image3)
was “full.” After SSTET, subjects reached a peak level of exertion (and SBP) without symptom exacerbation. The data suggest that some PCS symptoms are related to disturbed cerebral autoregulation and that after SSTET the brain was able to regulate blood flow when the BP rose during exercise. Progressive stepwise aerobic training may improve cerebral autoregulation by conditioning the brain to gradually adapt to repetitive mild elevations of SBP.

Because patients with concussion are in a state of sympathetic nervous system predominance, we hypothesized that PCS subjects would demonstrate evidence of autonomic imbalance at rest and that exercise would restore autonomic balance. We did not, however, observe evidence of a significant change in resting or submaximal exercise autonomic balance after exercise treatment, only at peak levels of exertion. We propose that this is because of the long period of inactivity before study entry and the relatively low volume and intensity of the aerobic training, which was below the threshold required to significantly improve aerobic fitness.

Although the mean daily resting symptom reports diminished over time in conjunction with improved exercise capacity, they remained highly variable. This degree of variability was present during the baseline period as well. Thus, daily symptom variability is a part of PCS, with or without exercise. The fact that a few subjects exercised to exhaustion without symptom exacerbation yet did not report resolution of resting symptoms suggests that the exercise test and symptom reports gauge different aspects of PCS. Two nonathletes in our study had persistent cognitive/visual symptoms and migraine headache after being involved in motor vehicle accidents. Their other somatic and affective PCS symptoms resolved, however, suggesting that SSTET may benefit affective and somatic symptoms preferentially or that some concussion injuries also require cognitive behavioral or visual therapy. Exercise is a recognized treatment for depression, and although many of the subjects reported symptoms of depression that improved after SSTET, all subjects in this study had a primary diagnosis of PCS. After SSTET, all subjects returned to work, school, and athletic activities. Thus, this form of exercise rehabilitation may have significant economic and productivity benefit for some patients with refractory PCS.

Experimental animal data show that premature voluntary exercise within the first week after concussion impairs, whereas aerobic exercise performed 14 to 21 days after concussion improves, cognitive performance. Thus, the animal and some human data suggest that uncontrolled activity too soon after concussion is detrimental to recovery. Our results suggest that exercise treatment for PCS is beneficial if the exercise program is individualized, if its progression is controlled in a quantitative manner, and provided it is administered at the appropriate time after brain injury.

Although each concussion should be considered a “unique injury,” a randomized trial with a PCS control group is needed because it is possible that PCS symptoms would have resolved spontaneously without intervention. We think spontaneous recovery is unlikely, at least during the same time frame, because subjects were symptomatic for months and did not improve after 2 to 3 weeks of a period of no intervention. Moreover, the physiological and symptom data improved concurrently after SSTET. The study would have been improved by including measures of cognitive performance and measures of cerebral blood flow and cerebral autoregulation.

The athletes responded to SSTET faster than nonathletes. It is possible that the athletes had less severe trauma, that the treatment is more effective if administered early, that athletes are more responsive to exercise training, or that nonathletes had secondary gain issues. Subsymptom threshold exercise training allowed athletes to start the process of regaining physical fitness after the injury. Differences between athlete’s and nonathlete’s response to exercise-based treatment for PCS warrant further investigation.

Our study suggests that some patients with PCS have a persistent physiological disequilibrium and that controlled aerobic exercise training assists in the recovery of physiological homeostasis. We propose that symptom-limited exercise testing and progressive subthreshold aerobic exercise training are safe and, as opposed to treatments that modify symptoms (eg, pain or antidepressant medications), address a fundamental physiological dysfunction in some patients with PCS. Given that there is evidence of physiological dysfunction in concussion and in PCS, physiological assessment should be studied further for a potential role in the diagnosis of concussion and PCS and for helping to determine when patients are ready to resume school, work, and athletic activities.

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Exercise for Post-Concussion Syndrome