Aerobic Training for Management of Post-Concussion Syndrome in Adolescents

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I. Introduction

Pediatric traumatic brain injury (TBI) is among the most common causes of acquired morbidity and mortality in children and results in over 6,000 deaths, 60,000 hospitalizations, and 630,000 emergency department visits annually in the U.S.[1,2] Approximately, 75-85% of these injuries are mild TBIs (mTBI) or concussions.[1] Although most individuals recover within 2-4 weeks after a concussion, an estimated 10-33% of individuals have persistent symptoms beyond 1-3 months after injury.[3-6] Prolonged symptoms beyond four weeks after injury are commonly referred to as post-concussion syndrome (PCS)[7] and children and adolescents have an increased risk for persistent symptoms compared to older adolescents.[8-12] In this study, we examined the efficacy of a sub-symptom exacerbation aerobic exercise intervention for management of PCS in adolescents. Additionally, we used a multi-modal MRI to determine if the aerobic intervention resulted in cerebral blood flow (CBF) changes. We also used diffusion tensor imaging (DTI) and spectroscopy (MRS) to evaluate white matter integrity, structural connectivity of white matter tracts across brain regions, and cellular metabolism.

II. Executive Summary

Background

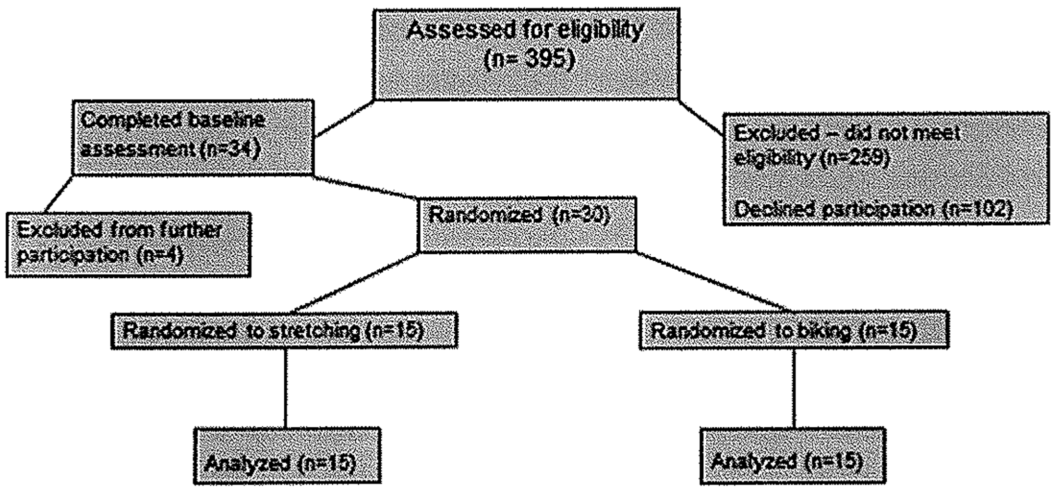
Traumatic brain injury (TBI) is among the leading causes of morbidity and mortality. Direct medical and indirect costs related to TBI total an estimated $76.5 billion annually in the U.S. Pediatric traumatic brain injury (TBI) is among the most common causes of acquired morbidity and mortality in children and results in over 6,000 deaths, 60,000 hospitalizations, and 630,000 emergency department visits annually in the U.S.[1,2] Approximately, 75-85% of these injuries are mild TBIs (mTBI) or concussions.[1] A large proportion of concussions in children are sports-related. Forty-four million children participate in at least one sports team[13], with an estimated 3.8 million sports/recreation-related concussions occurring each year in the U.S.[14] Seventy percent of sports/recreation-TBIs occur in adolescents between ages 10 and 19 years. Although most individuals recover within 2-4 weeks after a concussion, an estimated 10-33% of individuals have persistent symptoms beyond 1-3 months after injury.[3-6] Prolonged symptoms beyond four weeks after injury are commonly referred to as post-concussion syndrome (PCS)[7] and children and adolescents have an increased risk for persistent symptoms compared to older adolescents.[8-12] Because of the high incidence of concussions and the unrecognized potential long-term consequences, concussions are recognized as a serious public health problem.[6,15,16] There is a critical need to develop efficacious interventions for PCS in children and understand the influence of the interventions on the pathophysiology of PCS.

Participants

Adolescents between ages 12 and 17 years of age were recruited from the community via electronic fliers, head injury clinics, and emergency departments across the greater Cincinnati, OH area. Adolescents who sustained a mTBI and had between 4 and 16 weeks of persistent symptoms were potentially eligible for the study. Mild TBI was defined using the American Congress of Rehabilitation Definition: A blow to the head or acceleration/deceleration movement of the head resulting in one or more of the following: *i.* loss of concussions <30 minutes, *ii.* amnesia, *iii.* any alteration in mental state at the time of the injury. Persistent symptoms were defined according to the World Health Organization, ICD-10 criteria for post-concussion syndrome (PCS). Clinical diagnostic criteria for PCS require a history of TBI and the presence of at least three of eight symptoms: 1.) headache, 2.) dizziness, 3.) fatigue, 4.) irritability, 5.) insomnia, 6.) concentration problems, 7.) memory difficulty, or 8.) intolerance of stress, emotion, or alcohol. Additional criteria included endorsement of symptoms that were exacerbated with physical activity. Exclusion criteria included children and/or families who did not speak and/or read English, evidence of more severe brain injury defined as post-resuscitation Glasgow Coma Scale (GCS) score below 13 or evidence of more severe injury on clinically performed neuroimaging (subdural hematoma, epidural hematoma, and contusion), pre-existing neurological impairment, (e.g., stroke, cerebral spinal fluid shunt, brain tumor), cognitive disorders, significant psychological problems, developmental delay, genetic disorder, metabolic disorder, hematologic disorder, cancer, pre-injury diagnosis of attention deficit hyperactivity disorder (ADHD) that requires two or more medications for control or active changing of attention medications recently, history of cardiovascular problem that would preclude participation in an aerobic training protocol, and evidence of neck pain. Participants on beta-blockers, anti-depressants, anti-anxiety, or other mood/behavioral medications, or prophylactic medications were considered for enrollment only if they were on a stable dose, defined as on the medication for at least one month and no medication dose changes planned. Participants were asked not to participate in other therapy programs during the trial,

There were 395 individuals assessed for eligibility, 259 did not meet eligibility criteria and 102 decline participation. A total of 34 individuals that completed a baseline assessment; four were excluded at the baseline assessment and 30 participants were randomized.

Figure 1. CONSORT Flow Diagram



Methodology

This was a randomized controlled trial that examined the efficacy of an aerobic training intervention for the management of PCS in adolescents. The overarching objectives of the project were to 1) systematically evaluate the effects of an aerobic training intervention for management of PCS and 2) evaluate cerebral blood flow correlates of PCS in adolescents. The primary outcomes of this study were the measures of post-concussion symptoms ratings.

Conclusion

This project provides novel information about the efficacy of an aerobic intervention for adolescents with prolonged PCS. Findings will inform the development of larger studies to elucidate the optimal timing of aerobic training for management of PCS and further improve our understanding of the influence of exercise on the pathophysiology of PCS, thus transforming the care and limiting the adverse public impact of this condition.

III. Information/Qualifications – principal and all co-investigators

Principal Investigator—*Brad G. Kurowski, MD, MS*—is an Assistant Professor of Pediatric Physical Medicine and Rehabilitation (PM&R) at Cincinnati Children's Hospital Medical Center (CCHMC) and the University of Cincinnati, College of Medicine. He has subspecialty certification pediatric rehabilitation medicine and brain injury medicine. Dr.

Kurowski's prior research has focused on evaluating predictors and moderators of neurocognitive and behavioral recovery after pediatric traumatic brain injury (TBI), specifically elucidating the association of neuroimaging and genetics with executive function and behavioral outcomes after pediatric TBI. More recently, he has been working with colleagues in the emergency department to pilot a web-based behavioral intervention for children after concussion. From a clinical standpoint, he has spearheaded the development of a multidisciplinary head injury clinic. Through this work, he has developed collaborations with several sports physical therapists to implement a clinical exercise protocol for children with prolonged post-concussion symptoms. Dr. Kurowski's prior research and clinical work has enabled him to develop clinical and research collaborations that span multiple fields (pediatric neuroimaging, clinical trial implementation and analysis, emergency medicine, sports medicine/sports physical therapy, and physical medicine and rehabilitation).These collaborations were integral to the implementation of this pilot project and will be integral to the development of larger studies.

Co-investigator—*Shari Wade, PhD*— Dr. Wade is a Research Professor at CCHMC. She is an experienced pediatric psychologist who has been investigating predictors of family adaptation to pediatric TBI for more than 20 years and has developed and tested web-based interventions to reduce behavioral morbidity and family consequences for the past decade. She is a leader in multi-center clinical trials for pediatric TBI having directed six completed and three ongoing trials. She is the Principal Investigator and Director of the Rehabilitation Research and Training Center (RRTC) for Pediatric Brain Injury Interventions, the only federally-funded center for pediatric TBI. Her prior research experience with clinical trials and multi-site collaborations, and role as the PI for the RRTC for Pediatric Brain Injury Interventions make her ideally suited to serve as a Co-investigator on this project.

Co-investigator—*Kim Cecil, PhD*—Dr. Cecil is an expert in evaluating the association of neuroimaging with cognitive and behavioral outcomes in children. The project builds on her recent concussion study published in Pediatrics, using MRI and spectroscopy techniques to evaluate adolescents following acute and sub-acute concussion. Her study found global changes in cerebral blood flow as the most significant. The current study will determine brain cerebral blood flow with an improved technique as well as provide regional measures. Dr. Kurowski and Cecil have worked together previously, publishing novel analyses of diffusion imaging associated with measures of executive function in children with traumatic brain injury.

Co-investigator—*Gregory Lee, PhD*—Dr. Lee has a decade of experience in MR imaging. He has worked on quantitative perfusion imaging via arterial spin labeling with a spiral imaging protocol and extensively on fast imaging with 3D multi-echo radial pulse sequences. He has published work applying these sequences to both functional neuroimaging and time-resolved contrast-enhanced magnetic resonance angiography. Dr. Lee has developed anatomical and functional magnetic resonance (MR) imaging data processing streams for the Cincinnati MR Imaging of Neurodevelopment project. His thesis work was on the development of rapid, quantitative cerebral blood flow measurements using arterial spin labeling MRI.

Co-investigator—*Mekibib Altaye, PhD*—Dr. Altaye a biostatistician with more than 15 years' experience in designing and analyzing both experimental and observational studies. He has also performed analyses of several neuroimaging projects with investigators in the Imaging Research Center at the sponsoring institution. Specifically, he has worked with co-investigator, Kim Cecil, to analyze the association of cerebral blood flow assessed with neuroimaging with recovery of children after concussion.

Co-investigator—*Jason Hugentobler, PT, DPT*—Jason Hugentobler is a physical therapist who currently focuses on identifying postural control deficits with clinical testing tools, prognostic factors for recovery, physical therapy management, and determining safe return to play guidelines for athletes following concussion. He completed a sport physical therapy residency program at Cincinnati Children's with an area of focus on concussion evaluation and management. He also completed a Point of Care Scholar (POCS) program at Cincinnati Children's to improve clinical practice guidelines regarding the management of patients with concussion.

Consultant—*Catherine Quatman-Yates, PT, DPT, PhD*—Dr. Quatman-Yates is a physical therapist and researcher with expertise in the areas of postural control assessment and rehabilitation with children and adolescents following concussions. Drs. Quatman-Yates, Kurowski, and Hugentobler have successfully collaborated in the past for both patient care and research studies.

Consultant—*Lynn Babcock, MD, MS*—Dr. Babcock is an emergency medicine physician-scientist focused on decreasing morbidity associated with traumatic brain injury (TBI) in children, especially in those with mild TBI by developing empirically-based approaches to injury identification and treatment through translational research. She is working to uncover novel serum markers and radiographic markers to predict the outcomes of children after sustaining a TBI. In addition, with Dr. Kurowski as a Co-I, developed a novel web-based therapeutic intervention to facilitate recovery.

Consultant—*Paul Gubanich, MD, MPH*—Dr. Gubanich is a sports medicine physician at CCHMC. His clinical and research interests include the management of sports concussion, treatment of musculoskeletal and medical problems in athletes, performance optimization, injury prevention, and returning athletes to play.

IV. A review of the literature related to the project topic

Direct medical and indirect costs related to TBI total an estimated $76.5 billion annually in the U.S. Pediatric traumatic brain injury (TBI) is among the most common causes of acquired morbidity and mortality in children and results in over 6,000 deaths, 60,000 hospitalizations, and 630,000 emergency department visits annually in the U.S.[1,2] Approximately, 75-85% of these injuries are mild TBIs (mTBI) or concussions.[1] A large proportion of concussions in children are sports-related. Forty-four million children participate in at least one sports team[13], with an estimated 3.8 million sports/recreation-related concussions occurring each year in the U.S.[14] Seventy percent of sports/recreation-TBIs occur in adolescents between ages 10 and 19 years. Although most individuals recover within 2-4 weeks after a concussion, an estimated 10-33% of individuals have persistent symptoms beyond 1-3 months after injury.[3-6] Prolonged symptoms beyond four weeks after injury are commonly referred to as post-concussion syndrome (PCS)[7] and children and adolescents have an increased risk for persistent symptoms compared to older adolescents.[8-12] Because of the high incidence of concussions and the unrecognized potential long-term consequences, concussions are recognized as a serious public health problem.[6,15,16] There is a critical need to develop efficacious interventions for PCS in children and understand the influence of the interventions on the pathophysiology of PCS.

<u>*Post-concussion syndrome (PCS):*</u> Clinical diagnostic criteria for PCS require a prior history of TBI and the presence of at least 3 of 8 symptoms (1-headache, 2-dizziness, 3-fatigue, 4-irritability, 5-insomnia, 6-concentration, 7-memory difficulty or 8-intolerance of stress, emotion, or alcohol) four weeks after injury.[7,17,18] Animal studies have demonstrated several potential biologic correlates of post-concussion symptoms. Pathologic changes in the hippocampus and disruption of the blood-brain barrier lead to neuronal loss.[19-22] Neurochemical, metabolic, cerebral blood flow, and mitochondrial

dysfunction are also associated with the sequelae of mTBI.[23-27] Neuroimaging studies are beginning to elucidate the mechanism of PCS in humans; however, the majority of these studies have been performed in adults. Using quantitative electroencephalography and single photon emission computer tomography, focal cortical dysfunction, blood-brain barrier disruption, and reduced global and regional cerebral blood flow have been demonstrated in individuals with PCS more than one month after injury.[28] Magnetic resonance spectroscopy (MRS) studies have also shown that metabolic disturbances gradually normalize, but may persist up to 30 days after concussion and that a second concussion may prolong the metabolic disruption.[29,30] Cerebral autoregulation and cerebrovascular reactivity are also impaired after concussion.[31-34] Specifically, reductions in global cerebral blood flow are associated with prolonged post-concussion symptoms in children.[35] Other studies have suggested that regional hypoperfusion in frontal and temporal lobes contribute to post-concussion symptoms.[36,37] Collectively, these studies indicate that anatomic, neurochemical, metabolic, and cerebral blood flow changes may all contribute to PCS, but that primary biologic correlates of PCS are dysregulation in cerebral metabolism and cerebral blood flow. Therefore, an intervention that improves or normalizes cerebral metabolic function and blood flow would potentially be an effective treatment for PCS.

Exercise and brain function: Population-based studies suggest that cognitive decline is reduced in individuals who participate in physical and cognitively stimulating activities throughout life.[38-47] Exercise is purported to contribute to improved cognition through improved cerebral blood flow, oxygen extraction, glucose metabolism and neuroplasticity.[48-51] In animal studies, voluntary exercise stimulates hippocampal neurogenesis and is associated with up or down-regulation of signal transduction, synaptic trafficking, transcriptional regulation, neurotrophins, and neurotransmitter proteins important to brain metabolism and synaptic plasticity.[52-59] These same positive biologic effects of exercise are thought to be beneficial and aid in recovery after TBI.[60,61] However, studies have revealed conflicting results with regard to the benefits and potential detrimental effects of exercise after concussion. In animal models of mTBI, exercise correlates with growth factor upregulation and improved performance on memory tasks;[62] however, the timing of exercise after injury is important.[63,64] Exercise more than 14 days after injury is beneficial, while exercise introduced within 0-6 days after injury was detrimental in animal models.[64] In a retrospective review of student-athletes after concussion, individuals engaging in moderate as compared to no or high intensity physical activity had better neurocognitive outcomes and earlier return to sport.[65] **These findings highlight the need to determine the optimal intensity and timing for introduction of exercise following brain injury.**[66] Based on the potential risk for repeat injury and the potential risk of physical or cognitive activities worsening symptoms and slowing recovery, physical and cognitive rest are commonly recommended initially after concussion.[11,67,68] However, prolonged rest may be detrimental to recovery[69] and the introduction of activity at an optimal time after injury may accelerate recovery.[61] Aerobic exercise performed at an intensity and duration that does not exacerbate symptoms (i.e., sub-symptom exacerbation exercise) is potentially beneficial in adults and children with prolonged post-concussion symptoms. In a case series of 12 adults (mean age 27.9 years, range 16-53 years) with at least 6 weeks of refractory post-concussion symptoms, sub-symptom threshold exercise 5-6 days per week was well-tolerated and improved post-concussion symptoms.[70] In a descriptive study of children and adolescent athletes (mean age 14.25 years, range 8-17 years) with PCS at least 4 weeks post-injury, completion of a combined aerobic and sports-specific training program was associated with the return of all 16 participants to normal lifestyle and full sports participation.[71] To our knowledge, a randomized controlled aerobic intervention study evaluating the efficacy and influence of exercise on biologic correlates of PCS in adolescents has not been performed.

V. Historical perspectives on the topic of this report

Pediatric traumatic brain injury (TBI) is among the most common causes of acquired morbidity and mortality in children.[1,2] Approximately, 75-85% of these injuries are mild TBIs (mTBI) or concussions.[1] Forty-four million children participate in at least one sports team[13], with an estimated 3.8 million sports/recreation-related concussions occurring each year in the U.S.[14] Seventy percent of sports/recreation-TBIs occur in adolescents between ages 10 and 19 years. Although most individuals recover within 2-4 weeks after a concussion, an estimated 10-33% of individuals have persistent symptoms beyond 1-3 months after injury.[3-6] Prolonged symptoms beyond four weeks after injury are commonly referred to as post-concussion syndrome (PCS)[7] and children and adolescents have an increased risk for persistent symptoms compared to older adolescents.[8-12] Because of the high incidence of concussions and the unrecognized potential long-term consequences, concussions are recognized as a serious public health problem.[6,15,16]

VI. A brief review of the current status of the topic in Ohio, the surrounding states, and nationally

Similar to national trends as mentioned above, pediatric TBI is also the leading cause of morbidity and mortality in Ohio. Recent media attention highlighting the potential problems of concussion or mild TBI has also generated awareness of the potential long-term consequences of TBI more broadly. With this increased awareness of the potential impairments, families and practitioners are seeking ways to optimize management and recovery after concussion.

VII. Future trends, both regionally and nationally

Currently, evidence-based treatments for concussion or mild TBI are lacking. There is a critical need to develop standardized, effective treatment protocols for children and adolescents with concussions. Recent consensus guidelines state that rest and pacing return to activity is the cornerstone of management of concussion. However, active interventions are beginning to show evidence of benefit for this condition. With the recent media attention around concussion, a large number of concussion programs are being formed around the country. Therefore, it is critical for develop a strong evidence-base for implementation of treatments within these programs that will potential transform management of this condition.

Financial issues and considerations

TBI in children is associated with a large economic and societal cost. Hospital charges associated with pediatric TBI are over $2.56 billion annually in the United States. Further it is estimated that direct medical and indirect costs related to TBI total $76.5 billion annually in the U.S.[1,2]

VIII. Education and training issues and considerations

Not applicable to this research

IX. Legislative and regulatory issues and considerations

Recently many states, schools, and sports organizations have created policies on pediatric concussion. At this time, all 50 states have passed laws on concussion and sports in youth and teens. These laws are focused on three areas: 1.) coaches, parents/guardians, and athletes must be educated on concussion and given informational handouts, 2.) ensuring removal of the athlete from play after suspected concussion and no return to play on the same day of injury, and 3.) returning to play only after a health care provider evaluation.[72] Although this study did not directly address legislative and regulatory issues, findings will potentially inform future return to activity guidelines and recommendations.

X. Data and information issues and considerations

<u>*Primary Outcome Measures*</u>

Post-concussion symptom ratings: The Post-Concussion Symptom Inventory (PCSI) was used to assess self- and parent/guardian-reported post-concussion symptoms.[73,74] The PCSI was used to obtain symptom ratings pre-injury, pre-intervention (week 0 and 1) at interval visits (weeks 2 – 9) and post-intervention (week 10). The adolescent version of the PCSI is a 7-point Likert scale (0-6) rating 21 items on post-concussive symptoms in physical, cognitive, emotional, and sleep domains. Total scores range from 0 to 126 on the PCSI. The parent version of the PCSI uses the same 7 point Likert scale to rate 20 items in physical, cognitive, emotional, and sleep domains. Total scores range from 0-120 on the parent version of the PCSI. Additionally, there is a 5-point Likert scale (0-4) asking adolescents and parents to rate "In general, to what degree do you (your child) feel (act) 'differently' than before the injury (not feeling (acting) like yourself (himself/herself))?", with "0" indicating no difference and 4 indication a major difference. Because the PCSI was collected during interval visits, in addition to pre- and post-intervention, it was used as the primary outcome measure to monitor recovery trajectory.

In addition to the PCSI, the Health and Behavior Inventory (HBI) was also used to assess concussion related symptoms pre- and post-intervention. The HBI is a 50-item questionnaire which includes a variety of cognitive, somatic, emotional, and behavioral symptoms.[75] The scale requires parents and children to rate the frequency of occurrence of each symptom over the past week on a 4-point scale, ranging from "never" to "often." The HBI is one of the core common data element (CDE) measures for symptom rating for TBI research in children according to the National Institute of Neurological Diseases and Stroke.[73]

<u>*Secondary Outcome Measures*</u>

Quality of life and Participation: The Pediatric Quality of Life Inventory (PedsQL) generic core was used to assess quality of life. The PedsQL is composed of 23 items that measure physical, emotional, social, and school function.[76-78] Child self-report forms are validated for children 5-18 years and parent report forms have been developed for children 2-18 years. The PedsQL has been used in pediatric TBI as a measure of quality of life.[79-82]

The Children's Assessment of Participation and Enjoyment (CAPE) and the Preferences for Activity of Children (PAC) will be used to assess child participation.[83] The CAPE and PAC are validated for children ages 6-21 years with and without disabilities.[84,85] A commercially available device called the FitBit Flex™ was used to objectively measure activity. The FitBit Flex™ uses GPS technology to track steps taken, calories burned, hours slept, distance traveled, active minutes, and quality of sleep. The FitBit Flex™ was used to obtain a more objective measure of daily activities during the run-in and run-out periods of the study. Average steps, calories burned, hours slept, distance traveled, and active minutes per day during the run-in and run-out periods were used as a measure of activity.

Cognitive measures: The National Institutes of Health (NIH) toolbox is a multidimensional set of measures that can be used to assess cognitive, sensory, motor, and emotional function in individuals ages 3-85 years.[86] The toolbox has been validated and normed in a broad sample of the U.S. population. The NIH toolbox cognition battery will be used to assess global cognition.[86] The cognition battery consists of tests of executive function, attention, episodic memory, language, processing speed, and working memory.[86] This battery yields the following summary scores: Cognitive Function Composite Score, Fluid Cognition Composite Score, and Crystallized Cognition Composite Score. Composite scores were used in the analysis. Cognitive measures were assessed pre- and post-intervention.

Adherence: Participants were provided with a log to record the times per week they completed their exercise program. This log was reviewed weekly at the interval visits.

Postural Control Measures: Concussions can disrupt the nervous systems ability to process and integrate sensory information which can lead to difficulty with postural control. The examine changes for enrolled participants two different approaches were used. The first tool used was the Balance Error Scoring System (BESS), which is able to detect post-concussion impairments in older children and adults. The second is The BESS is able to detect post-concussion impairments in older children and young adults.[87-89] The second is force plate assessments of postural control. Force plates have been utilized to detect impairments weeks to months following a concussion.[90,91] The total BESS score and a composite center of pressure (COP) score from the WBB will be used in the analysis.

Fitbit—interval activity: The Fitbit Flex is a commercially available device that was used to objectively measure activity. The FitBit Flex™ uses GPS technology to track steps taken, calories burned, hours slept, distance traveled, active minutes, and quality of sleep. We plan to look at average steps, calories burned, hours slept, distance traveled, and active minutes per day during the run-in and run-out periods as a measure of activity.

MRI—Multimodal: Enrolled participants completed before and after completing the intervention. We will examine whether the intervention results in brain-based changes as seen on the MRI using cerebral blood flow (CBF), diffusion tensor imaging (DTI), and spectroscopy (MRS).

Table X. Measures collected

Measure	**Baseline 1**	**Baseline 2**	**Interval Visits**	**Final Assessment**
PCSI—parent & adolescent report	X			X
HBI—parent & adolescent report	X			X
MRI—multimodal		X		X
Postural Control Measures (BESS and Wii)	X	X		X
NIH Toolbox—cognitive domain	X			X
PedsQL—parent & teen report	X			X
CAPE	X			X
Headache questionnaire	X			X
Adherence Log			X	
Fitbit—interval activity		X	X	X

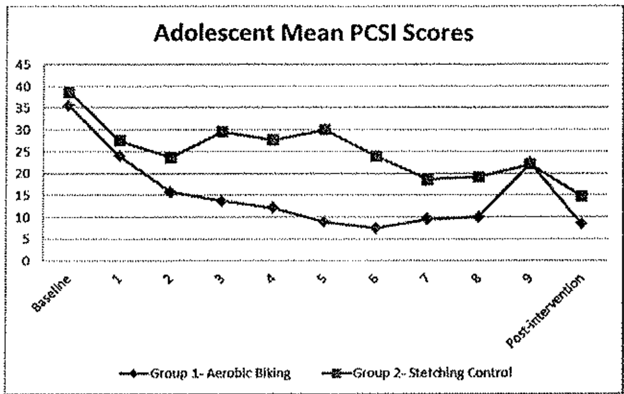
XI. An analysis of the researcher's findings

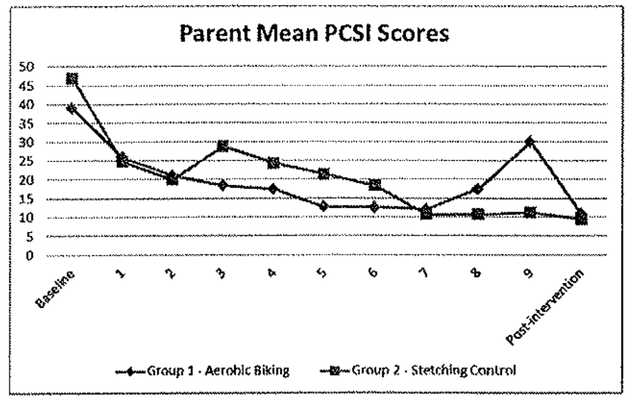
A total of 30 adolescents and teens with mTBI and persistent post-concussive symptoms were enrolled in the study. The distribution of age, sex, race, primary caregiver education, income, time since injury and mechanisms of injury did not differ significantly between groups. The average time since injury for the study population was approximately eight weeks. Additionally, the mean pre-injury, pre run-in-period, and pre-randomization parent and adolescent PCSI scores did not differ between groups.

Table X. Participant Characteristics	Aerobic Biking Group	Stretching Control Group
N	15	15
Age in years, mean (SD)	15.22 (1.37)	15.50 (1.80)
Sex (% male)	33%	53%
Child's race (% non-white)	13%	13%
Primary caregiver education (% bachelor degree or higher)	60%	47%
Income (% above $100,000)	53%	50%
Time since injury in years, mean (SD)	.15 (.05)	.15 (.06)
Mechanism of injury (% non-sport)	53%	20%
Outcomes		
Parent pre-injury PCSI, mean (SD)	7.07 (6.71)	3.6 (4.55)
Parent pre-run in period PCSI, mean (SD)	38.93 (15.13)	46.93 (25.22)
Parent pre-randomization PCSI, mean (SD)	25.86 (19.12)	24.79 (17.54)
Adolescent pre-injury PCSI, mean (SD)	8.33 (8.36)	8.2 (10.10)
Adolescent pre-run in period PCSI, mean (SD)	35.47 (23.47)	38.67(25.95)
Adolescent pre-randomization PCSI, mean (SD)	23.93 (15.10)	27.53 (18.94)

Primary Outcome: symptom scores

Both the aerobic training and stretching groups improved over time on self- and parent-ratings of symptoms. The adolescent ratings demonstrated a trend ($p < .15$) for differences between groups using mixed model analysis. Further analyses will need to be performed to determine whether there are certain individuals more likely to benefit than others.





Secondary Outcome Measures

Paired t-test demonstrated that there was significant ($p<.01$) improvement in symptom ratings on the HBI and quality of life post injury compared to pre-injury in each group. There was not a significant change in balance scores on the BESS post injury compared to pre-injury. Independent t-tests did not demonstrate differences between groups on pre-injury or post-injury ratings of symptoms (HBI), quality of life or balance measures. Future regression and other analyses are planned to better understand the recovery of these factors.

Data for measures of activity (CAPE, PAC, FitBit), cognition, and postural control are in the process of being entered into the dataset. Imaging data is also being processed at this time. Future analyses will evaluate the association of these measures with outcomes as well.

Adverse Events

One participant broke their foot and another had a second head injury. Both of these events were unrelated to study procedures. Additionally, one participant dropped out of the study to start a vestibular therapy while participating in the aerobic training group.

XII. Conclusions

Initiation of an aerobic or generalized stretching program in adolescents with persistent post-concussion symptoms appears to be beneficial. There was a trend for aerobic training to be more beneficial, but it was not statistically significant. Future analyses are planned to better understand the pathophysiology of recovery using multimodal imaging data. Findings from this project will inform the development of larger studies to understand the role of active interventions in facilitating recovery after concussion. More work is needed to determine optimal dose, timing, and intensity of rest and active interventions. In addition, the interface between cognitive and physical activities needs to be better understood. Precision exercise treatments that target specific symptoms or complaints are likely needed. The effect in younger populations is unclear to date. Biological correlates of recovery also need to be better elucidated.

XIII. Recommendations

The optimal management strategies for mild TBI or concussion are unclear. Active interventions, such as aerobic training and stretching evaluated in this study, should be consider as options to facilitate recovery. However, the risk of repeat or worsening injury with any type of active intervention needs to be eliminated or minimized as much as reasonably possible. Future research is needed to definitively understand how aerobic and other active interventions may help recovery after mild TBI or concussion. Findings from this project will inform these larger trials. Additionally, the combined use of active, cognitive, and behavioral interventions also needs to be considered. Research that seeks to identify the optimal type, dose, timing, and intensity of interventions that facilitates recovery is needed. Furthermore, studies that identify imaging related or other types of biomarkers that can be used to follow recovery and track the influence of interventions on biologic factors related to recovery is needed.

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