Boston Children's Hospital

Protocol:

TITLE: The effects of a sub-maximal exercise program on adolescents who sustained a concussion

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Investigators:
William Meehan, MD
David Howell, PhD
Can Ozan Tan, PhD

A. Specific Aims/Objectives

1. To observe how concussion affects cerebrovascular function and symptoms among adolescents.

2. To investigate the effect of a sub-maximal exercise protocol on cerebrovascular function and concussion symptoms in adolescents who have recently sustained a concussion.

B. Background and Significance

An estimated 1.6 to 3.8 million sport-related traumatic brain injuries occur annually in the United States,[1] the vast majority being concussions. Despite this high prevalence, the clinical management of concussion remains difficult.[2] Recovery of symptoms following a concussion usually occurs within a few days to a few weeks of injury. These symptoms, which include cognitive difficulties, headache, and dizziness, are pervasive, impacting personal relationships, community re-integration, return to sports, and the ability to work or go to school. Unfortunately, the pathophysiology of persistent concussive symptoms remains poorly understood, and very few treatment options are available.

After concussion, optimal cerebral blood flow is necessary to meet the metabolic needs of the injured brain. However, cerebral blood flow is diminished globally after injury,[3] and in fact, there may be an inverse relation between regional flow and symptom burden after concussion.[4] Thus, cerebrovascular dysfunction may play a role in the manifestation of prolonged concussive symptoms.[5] Moreover, alterations in cerebral perfusion may act as a trigger in symptom exacerbation. Even if overt symptoms are mostly gone, strenuous effort may induce symptoms, presenting a major obstacle to return to daily activities.[6] However, prolonged cessation from physical activity may also induce concussion-like symptoms, such as difficulty sleeping, concentration abnormalities, and anxiety.[7]

While high intensity exercise can induce symptoms after a concussion, mild to moderate (so-called sub-maximal) exercise has recently been identified as a safe activity after a concussion.[6,8–10] Recent investigations have supported the use of sub-maximal exercise protocols to improve patient outcomes following concussion,[9,10] and have identified that more physical activity following a concussion is not universally detrimental to the duration of time required for symptom resolution.[11] Therefore, it is conceivable that mild-to-moderate exercise can contribute to symptom resolution by improving cerebrovascular function, while avoiding symptom exacerbation associated with high-intensity exercise. Although the 2013 recommendations for concussion in sport states that individuals should remain at-rest until asymptomatic,[12] these guidelines are expected to change in 2017. This is due to recent evidence regarding exercise after concussion that suggests early exercise may not be detrimental, and perhaps beneficial in the early stages of recovery (i.e. within 10 days of injury).[8,9,11,13,14] Specifically, some researchers and clinicians now suggest tailoring management plans to individual signs and symptoms based on the patient's most bothersome findings in order to move away from "one therapy for all" treatments.[15,16] Therefore, early exercise interventions at a sub-maximal level soon after concussion may be a beneficial strategy in reducing the risk of persistent symptoms.

C. Preliminary Studies

Preliminary data obtained among patients seen at the Boston Children's Hospital Sport Concussion clinic indicate that physical activity level is not associated with symptom duration time (Cox proportional hazard ratio = 1.0008, 95% CI= 0.9994 - 1.0021, p= .261).[11] In fact, when stratified among only adolescents, those who reported more physical activity during recovery reported shorter symptom duration times (Cox proportional hazard ratio = 1.0018, 95% CI= 1.0004 - 1.0031, p = .009).[11] Furthermore, the extent of impairment of cerebrovascular function is directly proportional to symptom burden (0.018+0.007 in controls vs 0.017+0.010 in patients).

D. Design and Methods

(1) Study Design

Prospective, non-blinded, Interventional study

We plan to recruit up to 60 concussed patients, equally randomized to an intervention group who participate in the at home exercise program, or those who undergo the same testing but receive the standard of care given by their physician. Subjects will be recruited from Boston Children's Hospital Sports Medicine Clinic, The Micheli Center for Sports Injury Prevention as well as affiliated schools, clinics and sports organizations. The subjects and parents/guardians who voluntarily agree to participate will be scheduled for three visits. Upon the first visit, a research coordinator will explain the study and have the subject and parent/guardian sign the "Research Consent Form", approved by the Institutional Review Board of Boston Children's Hospital before participating in the study. Subjects will be required to complete three visits to The Micheli Center for Sports Injury Prevention or Spaulding Hospital in Cambridge for testing.

(2) Patient Selection and Inclusion/Exclusion Criteria

Inclusion

- Male or females between 14-21 years of age
- Experienced a concussion within 14 days of testing, defined as a person who has had a traumatically induced physiological disruption of brain function, manifested by at least one of the following:
  - Any period of loss of consciousness;
  - Any loss of memory for events immediately before or after the accident;
  - Any alteration in mental state at the time of the accident (ie., feeling dazed, disoriented, or confused)
  - Symptoms of nausea, dizziness, fatigue, headache, or changes in sleep, cognition or, emotions following the accident
- Low or moderate cardiac risk according to American College of Sports Medicine (11)

Exclusion

- History of neurological surgery
- Seizure disorder
- Use of medication or medical device that would alter heart rate, blood pressure or autonomic function
- Any current, serious, chronic medical or psychiatric disease that, in the Principal Investigator's judgment, may interfere with study participation or data integrity
- Unable or unwilling to provide informed consent

(3) Description of Study Treatments or Exposures/Predictors

Concussion Symptoms will be monitored by the Post-Concussion Symptom Inventory (PCSI), Post-Concussion Symptom Score (PCSS),the abbreviated Concussion Symptom Inventory (CSI), and Visual analog scale (VAS)

Surveys: Dizziness Handicap Scale, Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ) will be completed before each testing visit.

Height and weight will be measured.

Heart rate, cerebral blood flow, and end-tidal CO_2 will be recorded during a one hour session, before graded exercise test, during a graded exercise test on a cycle ergometer, and during 5 minutes of recovery. The branching exercise protocol (shown in Figure 1 below) based on the modified YMCA protocol will progressively increase exercise intensity up to 85% of age-predicted maximum heart rate. Exercise will be stopped at this point or if the volunteer becomes symptomatic.

Single/ Dual-Task Gait: Patients will be instrumented with three accelerometer devices, attached via elastic strap at L5, left, and right feet, which take less than one minute to place on the patient. The devices will be wirelessly connected to a laptop run by the study coordinator to obtain and save motion data. While wearing these devices, they will complete tasks in three different conditions:

- *Standing single-task*: patients will be seated and be asked to complete a mini-mental status examination, adapted from previous investigations and recommendations.[17,36–38] It consists of spelling a five letter word backwards, serial subtraction of 6s or 7s, or reciting the months in reverse order. 8 trials will be completed.
- *Walking single-task*: patients will be instructed to walk down the hall at a length of 10m, turn around and return to the original starting point, with no obstruction or completion of other tasks. 8 trials will be completed.
- *Walking dual-task*: patients will be instructed to walk down the hall at a length of 10m, turn around and return to the original starting point, while completing a mental status examination. The examiner will ask the patient to spell a five letter word backwards, subtract by 6s or 7s from a number, or recite the months in reverse order. The examiner will say, "Ready, go" and the patient will begin walking while completing the mental task. 8 trials will be completed.
- *Static postural stability:* As the Balance Error Scoring System (BESS) test is typically performed as a part of the clinical exam, participant performance will also be documented. During the BESS, three experimental trials are performed with eyes closed in 3 conditions: double-leg stance, single-leg stance, and tandem stance. During double-leg stance, participants are instructed to stand with their feet positioned side by side. For the single-leg stance condition, participants stand on the foot that they identified as their non-dominant kicking leg. The tandem stance condition consists of participants standing with their feet positioned where the non-dominant foot is placed directly behind the dominant foot. Each trial is performed for 20 seconds. When available, participants will perform the test on an instrumented motion capture-force platform system.

Estimated time to complete the single and dual-task balance assessment is approximately 8 minutes. The order of assessments will be rotated for each visit, but consistent for all subjects.

Heart rate will be monitored via a standard 5-lead ECG.

Cerebral blood flow will be monitored via Near-Infrared Spectroscopy (NIRS) and transcranial Doppler ultrasound (TCD). NIRS will be measured with a probe placed on the forehead contralateral to the dominant hand. NIRS-derived blood oxygenation levels will be used as a measure of cerebral blood flow at the prefrontal cortex. TCD will be measured with probes placed bilaterally on both sides of the head slightly behind the temples. TCD derived blood flow velocities on middle cerebral arteries will be used as a measure of global cerebral blood flow. The TCD protocol used will be exactly the same as the active and IRB-approved protocol (Protocol number: 8926) within this study.

Arterial blood pressure will be monitored continuously via a photoplethysmographic finger cuff on the index or middle finger throughout the study session and via a standard oscillometric blood pressure cuff attached to the upper arm. Pressure measurements will be obtained only via oscillometric blood pressure cuff during the graded exercise.

End-tidal CO_2 will be monitored using infrared analyzer (Model 17515A, VacuMed) connected to a nasal cannula.

Rate of Perceived Exhaustion (RPE) will be monitored by a visual Borg rating of perceived exertion during the graded exercise test

All aerobic activity will be monitored by a Polar Wrist Units with Heart Rate Monitors.

YMCA modified branching Exercise Protocol:

The subject will be familiarized with the cycle ergometer if they are not already. They will be properly positioned with an upright posture, proper bend in the knee for maximal leg extension and hands placed on the handle bars. The subject will have a few minutes to become comfortable and warm up before starting the protocol. The first stage of the protocol involves the subject pedaling at a steady state (~100rpm), at 100 watts or 150 kg / m / min for three minutes. As long as the subject reaches a steady state heart rate, defined as a heart rate that does not increase more than 5 beat per a minute in the last minute of the stage, they will move to the next stage. The next stage's intensity will depend on the difference between their warm up heart rate and the heart rate reached during the first stage. They will increase their Watts or kg/ m/ min as shown in Figure 1. Once the subject experiences symptoms the testing will stop. If the subject does not have an increase in symptoms and can reach 85% of their age- predicated heart rate, the testing will stop. Subject will remain on the cycle ergometer for a 2 minute recovery period before getting off.

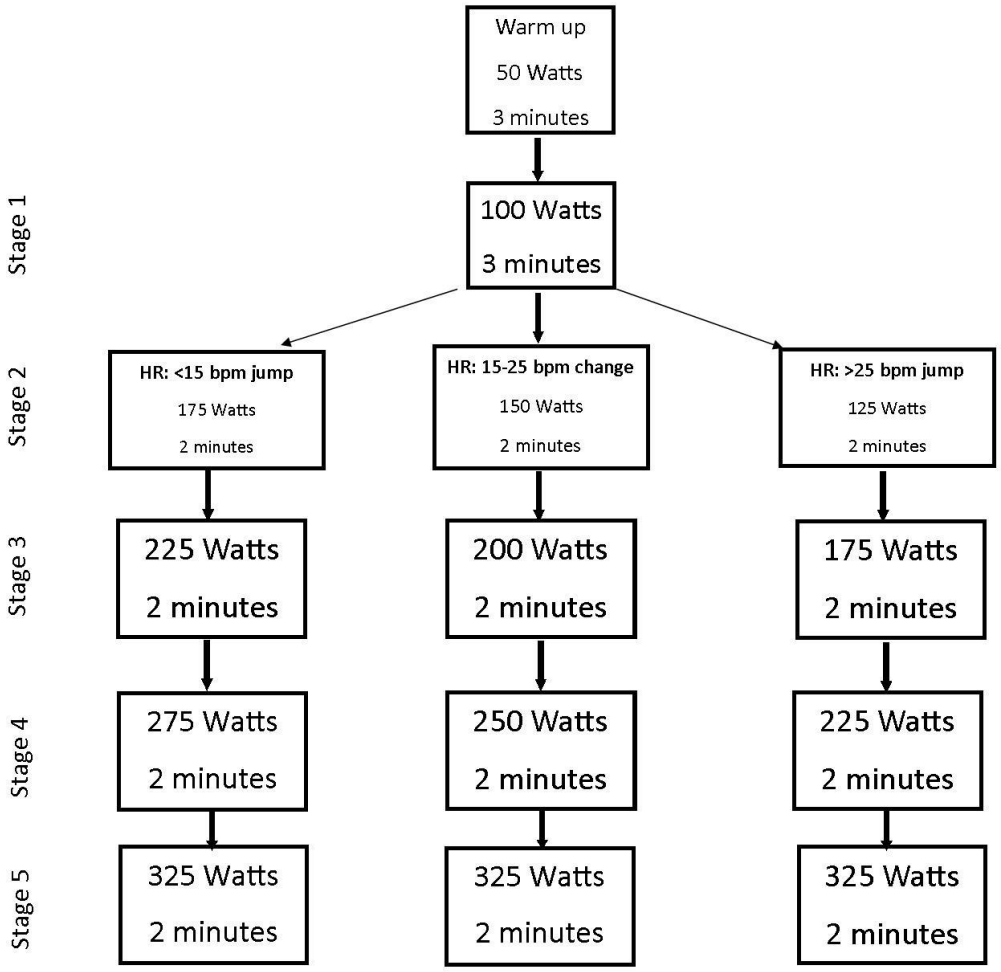

Figure 1: Modified sub-maximal exercise protocol

(4) Definition of Primary and Secondary Outcomes/Endpoints

- Primary: blood oxygenation level in the prefrontal cortex before and after the administration of the exercise protocol.
- Secondary: the proportion of participants who continue to experience symptoms after the 8-week exercise intervention and the potential confounding variables that contributes to this risk of persistent symptoms.

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

Consent process: Research staff from the Division of Sports Medicine will complete the consenting process with the participants and their parents/guardians (if necessary) prior to any testing. The research staff member will explain the project and review the consent/assent form. The subject will review the consent form with their parent/legal guardian. The subjects and their parents will be given adequate time to review the study materials and ask questions. If they choose to participate, the patient and parent will sign the IRB approved consent/assent forms. It will be made clear to the patient and their parents that participation in the study is voluntary. They will be informed during the explanation of the study that their decision to participate or not will not affect their medical treatment at Boston Children's Hospital.

Data collection methods:
Height/Weight
Cerebral blood flow: NIRS and TCD systems
CO2 levels obtained during the study session and exercise
Blood Pressure obtained during the study session and exercise
Heart Rate: 5 lead ECG during the study session and exercise
Rate of Perceived Exhaustion: Borg Scale
Post-concussion symptom inventory: PCSI, PCSS, CSI
Single/ dual-task gait assessments at rest before exercise
Aerobic Activity: Polar Wrist Units with Heart Rate Monitors
Anxiety, Dizziness and patient health surveys are measured by the following scales: Dizziness Handicap Scale (DHS), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ)

The protocol consists of measurements and procedures that have no known risks and have been routinely used in laboratory studies as well as other human physiology and biomechanics labs without any adverse events. Throughout each examination, the electrocardiogram will be monitored using a standard 5-lead ECG via wires attached to the chest via hypoallergenic adhesive electrodes. Blood pressure will be monitored every 2 – 4 minutes via a standard oscillometric blood pressure cuff attached to the upper arm, and monitored continuously via a photoplethysmographic finger cuff on the index or middle finger.

The attachment and removal of ECG electrodes and inflation of the blood pressure cuff may cause mild discomfort (though no more than routine physical examinations), but there are no risks associated with any of these measurements.

Cerebral blood flow will be measured via ultrasound with a Doppler probe placed on the left and right temple and a NIRS probe placed on the forehead contralateral to the dominant hand. There are no known risks associated with transcranial ultrasound or near infrared spectroscopy. We routinely use both (currently, in over 50 young individuals) with no reported discomfort or ill effects.

***Schedule*:**

Recruitment: Potential concussed subjects will be recruited from the sports medicine clinic at Boston Children's Hospital by a research staff member. If the subject is eligible and interested in participating they will schedule study visit 1 with the research staff member.

Study Visit 1 (time of enrollment):
Subjects will come to The Micheli Center for Sports Injury Prevention or Spaulding Hospital in Cambridge for a two hour visit. Once they give consent we can schedule a time for testing.

Subjects will be measured for height and weight. Subjects will complete a short medical history questionnaire, which includes the DHS, HADS, PHQ and a PCSI/ PSCC. Subjects will then be fitted for a Polar Wrist Unit and Heart Rate Monitor. During this time, they will also have a standard 5-lead ECG placed by a trained research member. Additionally, a research member will attach a blood pressure cuff to their non-dominant arm and to their middle finger (for photoplethysmographic measurements) and set up to the TCD and NIRS system. Both the usual care group and intervention group will complete this part of the study.

The first part of the study procedure involves supine rest, performing mental tasks, CO2 rebreathing, and resistance breathing to induce small periodic oscillations in arterial pressure. For resistance breathing, volunteers will breathe through a mouthpiece attached to a standard impedance threshold device made from latex-free PVC (PowerBreathe) set-up to moderate breathing resistance (10-20 cmH20). There are no risks associated with mental or physical tasks (N-Back and finger tapping tasks) or resistance breathing. The CO2 re-breathing may cause slight lightheadedness in some people; however, this can be reversed almost immediately by switching them back to room air. Both usual care and intervention groups will complete this part of the study.

The second part of the procedure involves the branching graded exercise test. Subjects will still be monitored using a standard 5-lead ECG and blood pressure measured by oscillometric blood pressure cuff. Throughout the graded exercise test cerebral blood flow will be monitored via TCD or NIRS. The subjects will also be connected to the metabolic cart to measure VO_2 The exercise test will continue until the subject reports an increase in symptoms, using the abbreviated concussion symptom inventory or to 85% of their age-predicted maximum heart rate determined by the 5-lead ECG. The subject will be taken off the bike and cool down. Measurements will be taken for an additional five minutes. Both the usual care and intervention group will complete this part of the study.

After completion of testing, the subject will have the ECG, blood pressure cuff, metabolic cart, TCD and NIRS system removed. They will be monitored by a trained professional until symptoms ease or subject's heart rate and blood pressure has returned to resting values.

The final part of the procedure includes the single/ dual-task gait evaluation and VOMS.

Weeks 1-4 (at-home exercise):
Subjects in the intervention group will be advised to participate in aerobic exercise five days a week. This includes walking, biking, jogging and running. While participating in these activities, they will be wearing their Polar Wrist Unit and Heart Rate Monitor to help subjects track their exercise intensity. They will exercise for 20 minutes five times a week at 80% of their heart rate reverse, determined by their resting heart rate and maximum heart rate reached during exercise testing.

Usual care subjects will follow their physician's instructions for exercise and rest. They will also wear the Polar Wrist Unit and Heart Rate Monitor to track their exercise intensity, but will not receive a heart rate specific exercise recommendation.

Study Visit 2 (approximately 4 weeks post-enrollment):

All participants will participate in this visit. Subjects will undergo the same procedures as visit one, including the DHS, HADS, PHQ, PCSI/ PCSS, supine rest, graded exercise test, VOMS and

single/dual- task gait. At this time, the target heart rate for exercise will be adjusted to a new symptom limited heart rate for all participants who are still symptomatic based on the same procedure.

Weeks 4-8:
Subjects will continue to participate in aerobic activity as specified above, monitored by their Polar Wrist Unit and Heart Rate Monitor. Usual care subjects will continue to follow their physician's recommendations.

Study Visit 3 (8 weeks post-enrollment):
All subjects will participate in this visit (usual care and intervention). Subjects will undergo the same procedures as visit one, including completing the DHS, HADS, PHQ, PCSI/PCSS, cerebrovascular function tests, graded exercise test, VOMS and single/ dual-task gait.

(6) Study Timeline (as applicable)

Once IRB approval is given we will start the recruitment process. We plan to enroll and complete testing for a total of 60 subjects over the next year.

Timeline for all subjects:
- Recruited from Boston Children's Hospital Sports Medicine clinic
- Comes in within 14 days of injury for study 1 visit
- Comes in 4 weeks later for study 2 visit
- Comes in 4 weeks later for study 3 visit

E. Adverse Event Criteria and Reporting Procedures

There are no known risks associated with near-infrared spectroscopy or transcranial Doppler ultrasound and the anticipated volunteer discomfort due to instrumentation and measurements is not more than that of a routine physical exam. The probability and magnitude of harm or discomfort anticipated during the experimental protocols are not greater than those ordinarily encountered in routine daily life. There is the possibility that exercise triggers concussion symptoms however exercise will be stopped immediately upon reporting of increased symptoms and patients will be monitored until resolution of symptoms. Risk of exercise in concussion may occur in the setting of acute injury (within the first 72 hours), however, there is no known harmful effect of exercise in sub-acute or chronic mild TBI. In fact, recent research suggests that sub-symptom threshold exercise may aid in recovery.[10] If any adverse event occurs, they will be reported immediately to the CCI.

F. Data Management Methods

Medical health information will be saved and input using RedCap survey. There will be an internal RedCap to enter recruitment information and identifying information. It will also include the exercise logs to help blind the PI from knowing which intervention group the subjects are in. The external RedCap will include the surveys, concussion history and test measurements. The information will be stored using the study ID numbers consistent with the rest of the measurements. Data from the heart rate monitors will be securely transferred from the device to a BCH-encrypted computer via USB drive.

G. Quality Control Method

As these studies represent physiologic investigation and not clinical trials, no formal quality assurance programs will be implemented. However, the ongoing results, problems, and limitations of the study will be overseen by the P.I. Studies will be conducted in a well-supervised hospital facility and

subjects will be under constant observation by skilled professionals. Appropriately certified and registered laboratory personnel will be present during the procedure. Procedures will be stopped if the volunteer exhibits any discomfort.

Any adverse events will be promptly reported to the Human Research Committee for review according to HRC guidelines. Serious adverse events either expected or unexpected will be reported immediately (within 24 hours of event) by telephone, fax or email followed by a full written report using the PHRC Adverse Event Form within 10 working days/14 calendar days. Mild to moderate unexpected or expected adverse events will be reported in writing using the PHRC Adverse Event Form within 20 working days/30 calendar days.

Information about particular subjects will be known only by study team. To maintain confidentiality, subject data will be referenced by number and identifying information will not be used during discussion, presentation, or publication. Spaulding Hospital certifies key personnel have completed education on the use of human subjects in compliance with NIH regulations.

H. Data Analysis Plan

This protocol seeks to elucidate the relationship between regional brain blood flow and CO_2 during exercise in individuals who have experienced a mild TBI, and to assess the effect of a standardized exercise protocol on cerebral blood flow.

Total hemoglobin concentration in the pre-frontal cortex will be calculated as the sum of oxygenated and deoxygenated hemoglobin (as measured by NIRS) and will serve as a surrogate for regional cerebral blood flow. The brain blood flow and end-tidal CO_2 data will be aligned in time. The linear relationship between the two time series will be determined and compared across injury duration and symptom severity. We will use a linear mixed effect model akin to a multiple linear regression model where regional cerebral blood flow is used as the dependent variable, end-tidal CO_2 is the independent variable, and symptom duration and amount of exercise are covariates.

I. Statistical Power and Sample Considerations

To estimate the sample size required to achieve our aims, we used R-language statistical software using a p-value cutoff of 0.05 and minimum statistical power of 0.8. To achieve our specific aim, we will compare the relation between regional blood flow and CO_2 responses to a branching exercise protocol, while accounting for injury duration. Given this analysis plan, we estimated that obtaining data from 60 individuals will allow us to detect any relation with an R^2 of 0.31 or higher.

J. Study Organization

Boston Children's Hospital

K. References

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