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The Benefits of Exercise for Individuals with Concussion Grant Proposal

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PI: **Dundore, Tyler M.**	Title: The Benefits of Exercise for Individuals with Concussion
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Organization: Grand Valley State University	Department: Movement Science
Subtotal Direct Costs: Year 1: $37,193.40 Year 2: $28719.65 Total: $65913.05	Animals: N Humans: Y Clinical Trial: N New Investigator: Y

Senior/Key Personnel	*Organization*	*Role Category*
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NFL Innovative Translational Research on Concussion and Comorbid Conditions

Grant Proposal Table of Contents

Technical Project Summary/Abstract

Concussions are an issue in many sports at both the amateur and professional level. In 2015, 43.5% of athletes across all age groups and sexes that sustained a concussion returned to sport too soon[1]. In the past, patients with a concussion were told to restrict physical and cognitive activities until they are asymptomatic[2]. Recently, research about concussion recovery has shown that a rest period beyond 1-2 days' post-concussion can be more detrimental to recovery than beneficial[3].

The Buffalo Concussion Treadmill Test (BCTT) has been used to study the effects of exercise on individuals with post-concussion syndrome[3]. However, little research using the BCTT or other methods has examined the effect of exercise on recovery from acute concussions. The BCTT is the only method currently available to assess concussion severity, determine exercise tolerance, and predict when an athlete may safely return to play[3].

In addition to human studies, animal models have researched the effect of voluntary exercise on markers of brain health and recovery. These include cerebral blood flow (CBF)[3], blood levels of carbon dioxide (CO_2)[3], adrenocorticotrophic hormone (ACTH)[4], and brain-derived neurotrophic factor (BDNF)[4,5]. When a concussion occurs, blood levels of these hormones decrease, a severe issue in the brain healing process.

This study will examine NCAA Division II varsity and club sport athletes in the acute stages of concussion recovery at a university in the Midwestern United States. Levels of CO_2, ACTH, and BDNF in the blood will be measured as well as CBF. The BCTT will initially be used to identify exercise tolerance and to develop an individualized exercise recovery protocol. Athletes will follow up before returning to practice to repeat the BCTT protocol in order to evaluate if they have recovered. The purpose of this study is to determine if voluntary exercise is more effective than rest for returning athletes to play during the acute stages of a concussion.

Lay research project summary and big picture impact

Exercise has been shown to have a positive impact on concussion recovery in individuals with Post-concussion syndrome (PCS, having concussion symptoms lasting longer than 4-6 weeks)[3]. However, little research has looked at the physiological level on the effect that voluntary exercise has on recovery from a concussion in the acute stages.

This study will examine NCAA Division II varsity and club sport athletes in the acute stages of concussion recovery at a university in the Midwestern United States. Since there is likely a therapeutic window of when exercise can be implemented to help individuals recover from concussion based on severity[4], the BCTT will initially be used to identify exercise tolerance at different time intervals and to develop an individualized exercise recovery protocol. Various physiological markers will be measured throughout the BCTT to monitor exercise tolerance. Athletes will repeat the BCTT protocol to evaluate if they have recovered before returning to practice. The purpose of this study is to determine if voluntary exercise is more effective than rest for returning athletes to play during the acute stages of a concussion.

This project is important because it could revolutionize how recovery from concussion is implemented. If the physiologic markers match the stages of the recovery protocol utilized, the procedure could be used to create a safer and more effective return to play protocol. The procedure used to rehabilitate and monitor individuals in this study is very simple to administer and requires commonplace equipment[3]. Having this screening tool available will allow healthcare providers, coaches, and parents alike to stop guessing when an athlete can return to play after a concussion. Instead, they will be able to closely monitor an athlete's recovery and get them back in the game when it is determined that their brain is physiologically ready to handle their sport.

Research Project Description

Collection of Subjects

This project will examine NCAA Division II athletes and their peers who sustain a concussion that play club sports at a Midwestern university. These athletes will be recruited when a concussion is either self-reported or diagnosed by a health professional within one day of the head trauma. These patients and/or their medical provider will contact the PI directly after the diagnosis for inclusion into the study. Before an athlete may begin the BCTT, they will be examined by the physician on staff to verify that they do have a concussion.

The Buffalo Concussion Treadmill Test (BCTT)

After the individuals have rested for one day and voluntarily want to resume exercise, they will do the BCTT. The BCTT is based on the Balke Protocol which uses a gradual increase in workload over time. The heart rate (HR) and blood pressure (BP) recorded at the threshold of symptom exacerbation becomes the basis of the individualized exercise program for the patient. The contraindications to performing the BCTT are those that typically would contraindicate a cardiac stress test with a couple of additions. Figure 1 shows the absolute and relative contraindications[3].

The speed at the start of the test is 3.6 mph at 0% incline for the first minute. However, the starting speed can be increased to comfort for taller or athletic patients and reduced for shorter or sedentary patients. The incline is increased by 1% at minute 2 and by 1% each minute thereafter while maintaining the same speed until maximum incline is reached or the subject cannot continue. Rating of perceived exertion (RPE, Borg Scale) and symptoms are assessed every minute. HR (measured by Polar HR monitor) and BP (measured by automated BP cuff) are determined every 2 minutes. The test is stopped at a significant exacerbation of symptoms (defined as ≥3 points from that day's pre-treadmill test resting overall symptom score on a 1- to 10-point visual analog scale (VAS), Figure 2) or at exhaustion (RPE of 19 to 20). If the patient reaches maximum incline and can still continue (not at RPE 19 or 20 or exacerbation of symptoms), the speed is increased by 0.4 mph for each subsequent minute until stopping criteria are fulfilled. Patients with significant pretest resting symptoms (i.e., ≥7 on the pretest VAS) may not perform the test[6].

Physiological Markers

Various animal models of experiments studying the effect of exercise on concussions in the acute and long-term stages of injury have measured various hormones/molecules in the blood as well as cerebral blood flow (CBF) to measure the physiological changes that exercise has on the brain after a concussion. Brain Derived Neurotrophic Factor (BDNF) is a hormone that facilitates the synapse and regulates neurotransmitter release, which has been associated with cognitive function enhancements. BDNF has been shown to facilitate recovery from traumatic brain injury in rats after voluntary exercise following a delayed-recovery period[4]. Conversely, adrenocorticotropic hormone (ACTH) is a hormone that regulates cortisol, controls the body's stress response, a mechanism that does not promote healing, and actually suppresses BDNF release. After a traumatic brain injury, animal models show an increase in ACTH if forced to exercise. In those that chose to exercise voluntarily, only an increase in BDNF was seen, and these animals healed promptly[4].

Experimental studies have shown that some patients with Post-concussion syndrome (PCS) have a symptom-limited response to exercise. This was due to several factors, including

disproportionately increased cerebral blood flow compared to the exercise intensity. In addition, female athletes with PCS had abnormal CO_2 sensitivity during exercise that led to hypoventilation and elevated CO_2 levels. However, when a program of subthreshold aerobic exercise treatment was used, CO_2 sensitivity and exercise tolerance normalized compared to a control group[3].

While performing the BCTT, this study will also measure the physiological changes that occur in the athletes during exercise. In addition to HR and BP which must be measured in the BCTT protocol, CBF[7], and blood levels of CO_2, ACTH, and BDNF will be measured throughout the test. This will be done for safety, as well as to make sure that patients have healed when they are retested after they report being symptom free and starting the RTP.

RTP Exercise Prescription

The researchers who developed the BCTT also created an exercise prescription which involves performing aerobic exercise (on a stationary bicycle) at 80% of threshold HR achieved on the BCTT for 20 minutes, once per day, for 5 to 6 days per week using a heart rate monitor to track HR. The individuals are instructed to terminate a session if they become asymptomatic or when they have exercised for 20 minutes, whatever comes first. To progress individuals back to play, patients can increase their HR by 5-10 bpm every 1-2 weeks if asymptomatic throughout. This prescription also gives an objective physiological guideline of when to start the RTP process (Figure 3). Physiological resolution of a concussion is defined as "the ability to exercise at 85-90% of age-predicted maximum HR for 20 minutes without exacerbation of symptoms for several days in a row"[3]. Once this occurs, the individual can begin performing sport-specific exercises and finish the return to sport protocol.

Study Timeline

The following timeline will be followed in this study:

- Following at least 1 day of rest after an athlete sustains a concussion, they may do the BCTT if they choose to volunteer.
- Athlete is given individualized RTP exercise prescription and follows as directed.
- When an athlete can exercise at 85-90% of age-predicted maximum HR for 20 minutes on their own without symptom exacerbation for at least 3 days in a row, they may begin the RTP process (Figure 4).
- Prior to returning to practice, athlete performs BCTT one more time to evaluate recovery.
- If the athlete achieves 85-90% of age-predicted maximum HR on BCTT, CBF, blood CO2 and ACTH levels are at normal ranges, the athlete may fully return to play.

Project Milestones

- April 1, 2018: Information about the study and recruitment of subjects sent out to all varsity athletics coaches as well as club and recreational sports directors, coaches, and players. Referees and medical professionals also notified in surrounding area to report concussions. This reminder is continually sent monthly as a reminder to report.
- April 1, 2018: All lab materials purchased and set up, begin collection of subjects.
- January 1, 2019: 50 athletes tested/returned to play.
- January 1, 2020: 100 athletes tested/returned to play.
- April 1, 2020: Study concludes.
- June 1, 2020: Data analyzed, manuscript of study findings written.

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Biographical Sketch

Name: Tyler Dundore

I am a student at Grand Valley State University (GVSU) and will graduate in April of 2018. I have worked in two different exercise science research labs. I am a co-author of the paper *Effect of Bench Press Load Knowledge on Repetitions, Rating of Perceived Exertion, and Attentional Focus* published in the Journal of Strength and Conditioning. I presented this research at the American College of Sports Medicine national conference in June of 2017. In addition, I have also done research in a microbiology lab on GVSU's campus where I became proficient in bench work. Through a number of classes, I have received training on how to use all equipment in GVSU's Human Performance Lab including all exercise machines, metabolic cart, and blood glucose/lactic acid measurements. I am a member of GVSU's Honors College, and have been awarded several grants and scholarships towards my undergraduate education. I will continue my education during the fall of 2018 working towards a Master's of Science in Exercise Physiology.

Name: Kimbo Yee, Ph.D

Kimbo Yee is a Visiting Professor of Exercise Science at Grand Valley State University. He majored in Kinesiology at Michigan State University and received a PhD in Kinesiology from Michigan State University in 2015 prior to joining GVSU. His research interests include examining the obesogenic family and home environment of children and adolescents, school and family-based healthy lifestyle interventions, and physical activity measurement. He has numerous first author and co-authored publications in several journals across the fields of Exercise Science.

Facilities

Facilities

This study will take place in Grand Valley State University's Human Performance Lab. This is a shared space among all exercise science faculty and is also used for classes. The Exercise Science Department has shared office space available for graduate assistants. Dr. Yee has his own office space in the Exercise Science Department. GVSU's recreation center is included in all student's tuition and has stationary bicycles for use by students participating in this study.

Equipment

The Human Performance Lab contains a Woodway Pro Treadmill with safety harness, its incline and speed are able to be adjusted as needed in the BCTT. There are also three computers available for use in the lab that can be used for the collection of data. The lab also contains a -80°C freezer (ThermoFisher Scientific) to store biological samples as needed. GVSU also owns a microplate reader capable of reading plates at a wavelength of 450nm which is needed for the BDNF assay.

Budget

Item	Company	Use	Number of Units	Cost per Unit	Total Cost
Automated Blood Pressure Monitor	Omron Healthcare, Inc., Lake Forest, IL	Monitor Blood Pressure	1	$50	$50
H10 Heart Rate Sensor	Polar Electro, USA	Monitor Heart Rate	5	$90	$450
Nonin 9843 Handheld Pulse Oximeter with CO_2 detector without alarm	Tiger Medical Inc., Irvington, NJ	Measure Blood CO_2 Levels	1	$1100	$1100
AvaSpec-Mini2048CL-OEM	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$2,280	$2,280
100um slit installed in AvaSpec-Mini Spectrophotometer	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$152	$152
Detector Collection Lens for AvaSpec-Mini Spectophotometer	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$161.50	$161.50
Order sorting filter (600nm) for AvaSpec-Mini Spectophotometer	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$52.25	$52.25
AvaSphere-50-LS-HAL-12V Integrating Sphere with Halogen Light Source	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$2,420	$2,420
FC-UVIR200-2-BX Fiber Optic Cable	Avantes, Louisville, CO	Measure Cerebral Blood Flow	1	$190	$190
Raspberry Pi Zero W	Adafruit, New York City, New York	Measure Cerebral Blood Flow	1	$10	$10
Human BDNF Sandwich ELISA 5 Plate Kit	RayBiotech, Norcross, GA	Measure BDNF Levels	1	$1608	$1608

ACTH Blood Draw + Analysis	Spectrum Health Grand Rapids	Measure ACTH Levels	30	$81.31	$2439.30
Stipend	$25/hr	20 hrs/wk	2 years	$25,000/yr	$50,000
Miscellaneous	Various	nitrile gloves, paper, ink, electricity, etc	N/A	N/A	$5000
Total					**$65,913.05**

Appendix

Figure 1: Abosulte and Relative Contraindications to the Buffalo Concussion Treadmill Test

Absolute and relative contraindications to the Buffalo Concussion Treadmill Test

Absolute contraindications	
History	Unwilling to exercise
	Increased risk for cardiopulmonary disease as defined by the American College of Sports Medicine*
Physical examination	Focal neurologic deficit
	Significant balance deficit, visual deficit, or orthopedic injury that would represent a significant risk for walking/running on a treadmill
Relative contraindications	
History	β-blocker use
	Major depression (may not comply with directions or prescription)
	Does not understand English
Physical examination	Minor balance deficit, visual deficit, or orthopedic injury that increases risk for walking/running on a treadmill
	Resting systolic BP >140 mm Hg or diastolic BP > 90 mm Hg
	Obesity: body mass index ≥30 kg/m^2

BP = blood pressure.

* Individuals with known cardiovascular, pulmonary, or metabolic disease; signs and symptoms suggestive of cardiovascular or pulmonary disease; or individuals ≥45 years who have more than one risk factor, including (1) family history of myocardial infarction, coronary revascularization, or sudden death before age 55 years; (2) cigarette smoking; (3) hypertension; (4) hypercholesterolemia; (5) impaired fasting glucose level; or (6) obesity (body mass index ≥30 kg/m^2).

Figure 2: Symptom Rating Scale

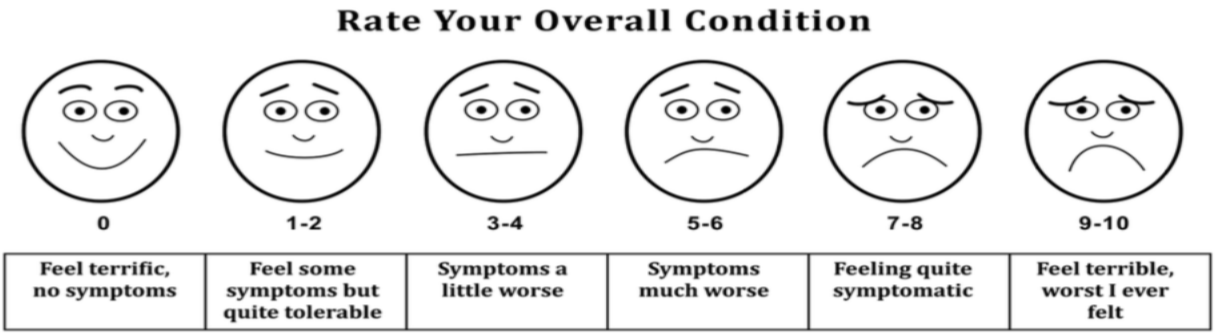
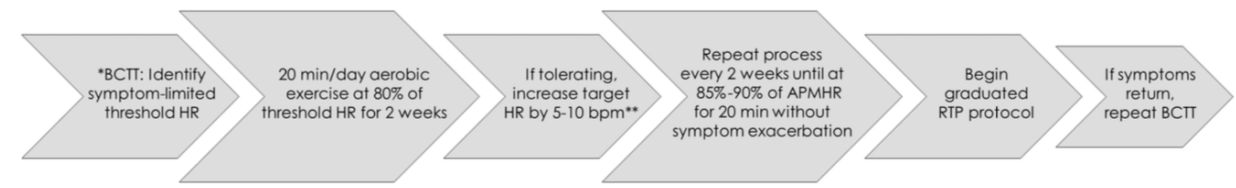


Figure 3: BCTT Subthreshold Exercise Guidelines



Use of the BCTT and exercise prescription for RTA in physiologic PCD. APMHR, age-predicted maximum HR. *After 3 wk of symptoms. **5 bpm for nonathletes; 10 bpm for athletes. To obtain a more precise target HR, consider repeating the BCTT every 2 wk.

Figure 4: Return to Play Guidelines

Rehabilitation Stage	Functional Exercise at Each Stage of Rehabilitation	Objective of Each Stage
1. No activity	Symptom limited physical and cognitive rest.	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling keeping intensity < 70% maximum permitted heart rate.	Increase HR
	No resistance training.	
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities.	Add movement
4. Noncontact training drills	Progression to more complex training drills, eg, passing drills in football and ice hockey.	Exercise, coordination, and cognitive load
	May start progressive resistance training.	
5. Full contact practice	Following medical clearance participate in normal training activities.	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play.	