Post-Acute Structured Exercise Following Sport Concussion: A Randomized Control Pilot Study

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Exercise Sciences
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Abstract

There is insufficient clinical evidence to recommend prolonged rest following sport-related concussion (SRC), although the optimal timing and nature of activity post-SRC remains poorly understood. The purpose of this study was to determine the safety and feasibility of implementing a standardized aerobic exercise (AE) intervention in a population of adolescent males within the post-acute phase of SRC recovery. Eight participants were administered the intervention beginning on Day 6 post-injury on a stationary bicycle, while seven control participants underwent usual care (i.e. rest followed by a gradual return to activities). Results demonstrate that overall time to medical clearance was not significantly different between groups, although the Exercise Group did achieve a greater trend towards symptom resolution and cardio-autonomic normalization compared to the Usual Care Group. Findings suggest that the AE intervention is safe and beneficial to administer in the post-acute stage of SRC recovery.
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# Table of Contents

Acknowledgments........................................................................................................................................... iii

Table of Contents........................................................................................................................................... iv

List of Tables ..................................................................................................................................................... viii

List of Figures .................................................................................................................................................... ix

List of Appendices ........................................................................................................................................... x

Chapter 1 Introduction .................................................................................................................................... 1
  1.1 Background........................................................................................................................................... 1
  1.2 Etiology of Concussion ......................................................................................................................... 1
  1.3 Autonomic Dysregulation Following Concussion .............................................................................. 3
  1.4 Management guidelines for SRC ....................................................................................................... 3
  1.5 Rationale ............................................................................................................................................ 5

Chapter 2 ......................................................................................................................................................... 6

Review of the Literature ................................................................................................................................... 6
  2.1 Definition of Concussion ....................................................................................................................... 6
  2.2 Key Features of Concussion .................................................................................................................. 7
  2.3 Epidemiology of Concussion ................................................................................................................ 8
  2.4 Evolution of Concussion Management Guidelines ............................................................................... 9
  2.5 Autonomic Dysregulation Following SRC ........................................................................................ 12
    2.5.1 Heart Rate Variability (HRV) ........................................................................................................ 13
    2.5.2 Blood Pressure Variability (BPV) .................................................................................................. 15
  2.6 Effect of Rest on Concussion Rehabilitation ...................................................................................... 17
  2.7 Effect of Exercise on the CNS ............................................................................................................. 18
  2.8 Utility of Exercise in Injuries to the CNS .............................................................................................. 20
    2.8.1 Stroke .......................................................................................................................................... 20
2.8.2 Whiplash .................................................................................................................20
2.8.3 Low Back Pain ...........................................................................................................20
2.8.4 TBI – Animal Studies ...............................................................................................21

2.9 Utility of Exercise Following Concussion ........................................................................22
2.9.1 The Role of Exercise in Post-Concussion Syndrome .................................................23
2.9.2 The Role of Exercise in Adolescent Concussion Rehabilitation .................................25

2.10 Limitations in SRC Management ..................................................................................26
2.10.1 Symptom Causation ...............................................................................................26
2.10.2 Age ........................................................................................................................27

2.11 Gaps in the Literature .................................................................................................28

Chapter 3 .............................................................................................................................30

Methods ................................................................................................................................30

3.1 Rationale ........................................................................................................................30
3.2 Design and Procedures .................................................................................................30
3.3 Outcomes Measures .......................................................................................................31
3.3.1 Feasibility Criteria ....................................................................................................31
3.3.2 Estimate of Treatment Effect ................................................................................31
3.4 Hypotheses ....................................................................................................................31
3.4.1 Hypotheses: Feasibility Outcomes ........................................................................31
3.4.2 Hypotheses: Estimate of Treatment Effect ..........................................................32
3.5 Participant Recruitment and Randomization .................................................................32
3.6 Aerobic Exercise Intervention .......................................................................................34
3.7 Usual Care Group Protocol ..........................................................................................36
3.8 Measures .......................................................................................................................37
3.8.1 Initial Medical Assessment ....................................................................................37
3.8.2 Godin Leisure-Time Exercise Questionnaire .........................................................38
3.8.3 Symptom Assessment .................................................................38
3.8.4 HRV Assessment .................................................................38
3.8.5 BPV Assessment .................................................................39
3.9 Statistical Analyses .................................................................41

Chapter 4 ......................................................................................43
Results .................................................................................................43

4.1 Participant Demographics .................................................................43

4.2 Results: Feasibility Outcomes .................................................................45
  4.2.1 H1\textsubscript{a}: Safety of AE Intervention .................................................................45
  4.2.2 H2\textsubscript{a}: Rates of Participant Recruitment/Retention .........................................46

4.3 Results: Estimate of Treatment Effect .........................................................48
  4.3.1 H1\textsubscript{b}: Time to Medical Clearance .................................................................48
  4.3.2 H2\textsubscript{b}: Symptom Resolution Across the Recovery Timeline ...................................49
  4.3.3 Symptom Resolution Effect Size Calculation .................................................................50

4.4 H3: Autonomic Dysregulation Across the Recovery Timeline ................452
  4.4.1 HRV: Descriptive Statistics and Normality .................................................................52
  4.4.2 BPV: Descriptive Statistics and Normality .................................................................53
  4.4.3 Results of Repeated-Measures ANOVAs .................................................................54
  4.4.4 Within-Group Effects .................................................................................................55
  4.4.5 Group by Time Interaction ..........................................................................................56
  4.4.6 Group by Condition Interaction ...................................................................................57

Chapter 5 ......................................................................................60
Discussion .................................................................................................60

5.1 Dissemination of Findings .................................................................60

5.2 Overall Evidence of Feasibility .................................................................61
  5.2.1 Safety of the AE Intervention ...................................................................................61
List of Tables

Table 1  Standardized Aerobic Exercise Intervention……………………………………49
Table 2  Participant Demographics……………………………………………………58
Table 3  Mean Adjusted PCSS Symptom Severity Scores……………………………66
Table 4  Means and Standard Deviations of all HRV Outcome Measures…………68
Table 5  Means and Standard Deviations of all BPV Outcome Measures………….69
Table 6  P-values of Autonomic Variables Repeated-Measures ANOVAs…………70
Table 7  Proposed Amendments to Standardized AE Intervention…………………..93
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Participant Recruitment and Randomization</td>
<td>47</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Intervention and Assessment Timeline</td>
<td>54</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Participant Recruitment and Retention</td>
<td>60</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Pre- and Post-Exercise Acute Symptom Severity Scores</td>
<td>62</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Mean Symptom Severity Scores</td>
<td>65</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Within-Group Trends in Overall Mean Adjusted Total Power</td>
<td>71</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Group by Time Interaction Trend for Mean DBP</td>
<td>72</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Group by Condition Interaction for Mean RRI</td>
<td>73</td>
</tr>
<tr>
<td>Figure 9</td>
<td>Trend Towards Significance for the Mean Transformed LF/HF Ratio</td>
<td>74</td>
</tr>
</tbody>
</table>
List of Appendices

A Initial Medical Assessment Form .................................................................111

B Permission to Contact Form ........................................................................119

C Primary Informed Consent ...........................................................................121

D Child Assent Form .......................................................................................131

E Parental Informed Consent ..........................................................................139

F Post-Concussion Symptom Scale (PCSS) .....................................................148

G Script for Monitoring Symptoms During Exercise (Session 1) .................149

H Script for Monitoring Symptoms During Exercise (Sessions 2-8) ..............151

I Godin Leisure-Time Exercise Questionnaire ..............................................154

J Individual and Overall Time to Medical Clearance Data and Descriptive Statistics  .................................................................156

K Shapiro-Wilks Test of Normality for Symptom Severity Across the Recovery Timeline ........................................................................157

L Results from Shapiro-Wilks Test of Normality for HRV Across the Recovery Timeline ........................................................................158

M Results from Shapiro-Wilks Test of Normality for BPV Outcome Measures Across the Recovery Timeline ...................................................160
Chapter 1
Introduction

1.1 Background
Concussion is a form of mild traumatic brain injury (mTBI) induced by acceleration/deceleration forces from a blow to the head or body, which produce biomechanical and neurometabolic changes in the brain\(^1\). It is commonly defined as a trauma-induced alteration of mental status, which may or may not involve a loss of consciousness\(^2\).

In recent years, concussions occurring within the context of collision sport have become an increasingly significant concern within the medical community\(^3\). Recent estimates suggest that the annual incidence of sport-related concussion (SRC) ranges from 1.6-3.8 million within the United States alone, but given that many SRC remain undiagnosed and/or unreported, these figures likely underestimate the actual frequency of this injury\(^3\). At the National Collegiate Athletic Association (NCAA) level, concussions account for approximately 5.8% of all injuries sustained in practice and competition\(^4\). However, the majority of SRC occur in people under 20 years of age, and it is estimated that nearly 9% of all high school athletic injuries are concussions\(^4\). Moreover, the annual incidence of concussions in 10-19 year olds in the US has increased by approximately 100,000 from 2001 to 2009\(^5\).

1.2 Etiology of Concussion
A number of pathophysiological alterations have been shown to occur in animal models of concussion, including ion channel disturbances, altered cerebral blood flow, and abnormal neural activation\(^6\). Following biomechanical injury to the brain, there is widespread neuronal depolarization, characterized by a marked efflux of potassium ions and a concurrent influx of
calcium ions\textsuperscript{7}. This potassium ion efflux is further exacerbated by the release of excitatory amino acid and glutamate, which binds to the N-methyl-D-aspartate (NMDA) receptor, contributing to a state of “hypermetabolism” where the sodium-potassium pump must work overtime in order to ensure that an abnormally high ATP supply can be met\textsuperscript{7}. This increased energy demand occurs in the context of diminished cerebral blood flow (CBF) and impaired mitochondrial function due to sequestered calcium ions, leading to an energy crisis and further contributing to impairments in neural connectivity\textsuperscript{7}. Once cerebral oxidative metabolism reaches its peak, anaerobic respiration is employed in an effort to sustain ATP production. This leads to lactate accumulation and further contributes to neuronal dysfunction by inducing acidosis, membrane damage, altered blood brain barrier permeability, and cerebral edema\textsuperscript{7}.

These impairments to neurological function typically evolve in the minutes to hours following concussion and are thought to reflect a disturbance to the neurometabolic processes of the brain\textsuperscript{2}. Consequently, concussion is associated with a wide range of clinical signs and symptoms, including behavioural changes, emotional symptoms, cognitive impairment, somatic symptoms, and sleep disturbance\textsuperscript{2,8}. It is suggested that the dysregulation of cerebrovascular control mechanisms contributes to some of the persistent concussion symptoms, such as cognitive impairment\textsuperscript{9}, headaches\textsuperscript{10}, and dizziness\textsuperscript{11}.

The majority of concussion-associated symptoms tend to resolve spontaneously within 7-10 days in most adult athletes\textsuperscript{1}, although adolescent who sustain SRC have been reported to take longer to achieve asymptomatic status\textsuperscript{12}. Furthermore, approximately 10-15\% of all concussion patients experience a constellation of prolonged concussion symptoms that can persist for weeks to even months following the initial insult\textsuperscript{13}. Recent estimates suggest that 31-33\% of youth (5-18 years
of age) presenting to the emergency department with concussion experience persistent post-concussion symptoms persisting longer than 28 days following the concussive event\textsuperscript{14}.

1.3 Autonomic Dysregulation Following Concussion

It has been suggested that the initial insult may lead to subtle structural alterations within the reticular formation of the brainstem, which is suggested to be responsible for regulation of the autonomic nervous system (ANS)\textsuperscript{15-17}. As such, concussion is associated with physiological dysfunction of the ANS, characterized by dysregulation of the balance between the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS), which can lead to an elevated resting heart rate \textsuperscript{18,19}. Furthermore, disruptions to cerebral autoregulation and cerebral blood flow (CBF) following concussion may contribute to the emergence of concussion-associated symptoms, particularly during exercise or other stressful stimuli that cause increases in blood pressure\textsuperscript{20}.

1.4 Management guidelines for SRC

Historically, medical guidelines for the clinical management of SRC have advised complete physical and cognitive rest following SRC until the achievement of asymptomatic status, followed by an exercise progression standardized according to intensity, duration, and complexity, until the athlete is medically cleared to return to play (RTP)\textsuperscript{2}. This recommendation was largely based on findings from animal models of mTBI, which demonstrated a cascade of increased metabolic demand in the context of decreased energy availability in the early stages following concussion\textsuperscript{6,21}. These studies led clinicians to infer that any activity during this post-concussion state of hypermetabolism will divert glucose and oxygen away from the injured neurons, thereby delaying the recovery process and potentially inducing exacerbation of post-concussion symptoms\textsuperscript{22,23}. 
While this post-injury rest period was generally assumed to be beneficial in the past, it was unsupported by scientific evidence and there was no consensus as to its appropriate nature or duration\(^24\). Furthermore, the notion of complete rest is now being challenged in the literature\(^22\), as prescribed rest has been shown to actually worsen symptoms across a variety of medical conditions\(^25\). With respect to brain injury, it has been suggested that if mTBI-associated symptoms have not been ameliorated following three days of complete rest, any further rest has no beneficial effect and may actually lead to adverse outcomes\(^22\). Furthermore, a growing body of literature has demonstrated the efficacy of early-onset, graded aerobic exercise (AE) interventions in expediting recovery and improving functional outcomes following injury to the central nervous system (CNS) across various conditions such as stroke\(^26-32\), whiplash\(^33-35\), and low back pain\(^36-38\). Furthermore, when compared to rest, early-onset AE interventions have also demonstrated efficacy in facilitating recovery in animal models of mTBI\(^39\).

This emerging body of literature favouring activity over rest in the acute stages of concussion recovery has been reflected in the most recently published consensus statement on concussion in sport following the fifth international conference on concussion in sport held in Berlin, Germany (October 2016), which acknowledged that there is currently insufficient evidence for the benefits of rest following SRC\(^40\). These guidelines suggest that following a brief rest period in the acute phase of injury (i.e. within 24-48 hours), patients may be encouraged to become “gradually and progressively more active while staying below their cognitive and physical symptom-exacerbation thresholds” (McCrory et al., 2017, page 5)\(^40\). While these guidelines encourage athletes to avoid vigorous exertion while recovering, the exact intensity and duration of the post-concussion rest period remains poorly defined.
1.5 Rationale

Given the emerging evidence demonstrating the efficacy of AE in treating various human CNS injuries and animal models of mTBI, as well as the lack of any observable benefit from rest following concussion, there is a need to explore the potential of AE interventions in expediting recovery times and improving physiological outcomes following SRC. The purpose of this study was two-fold: (1) to examine the feasibility (i.e. safety and logistics) of implementing a standardized, graded AE intervention in the post-acute stage of SRC, and (2) to determine the efficacy of a standardized, graded AE intervention administered in the post-acute stage of SRC for improving measures of clinical and physiological recovery compared to usual care.
Chapter 2
Review of the Literature

2.1 Definition of Concussion

Concussion is defined as “a complex pathophysiological process affecting the brain, induced by biomechanical forces”\(^{41}\). All concussions fall under the ‘mild’ end of the TBI spectrum based on the TBI severity classification system\(^{42,43}\). TBI severity is classified as mild, moderate, or severe based on three categories which make up the Glasgow Coma Scale (GCS): 1) degree of injury severity, 2) presence and length of loss of consciousness (LOC), and 3) number and degree of post-traumatic symptoms\(^{44}\). While all concussions are classified as mTBI, not all mTBI are concussions; however, the terms concussion and mTBI are often used interchangeably throughout the literature, and therefore pertain to the same operational definition\(^{45,46}\).

Historically, concussion has not been well defined within the literature.\(^{45,47}\) In 1993, the American Congress of Rehabilitative Medicine defined mTBI as “a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: (1) any period of loss of consciousness (LOC), (2) any loss of memory for events immediately before or after the accident, (3) any alteration in mental state at the time of the accident (i.e. feeling dazed, disoriented, or confused), and (4) focal neurological deficit(s) that may or may not be transient.”\(^{48}\)

This definition was challenged as emerging research began to demonstrate that LOC is not a universal criterion of concussion, as it only occurs in less than 10% of cases\(^{3,49}\). A new definition was proposed by the WHO Collaborating Task Force on Mild Traumatic Brain Injury in 2004,
which defined concussion as “an acute brain injury resulting from mechanical energy to the head from external physical forces.” According to this definition of mTBI, operational criteria for clinical identification include: (1) one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery, and (2) Glasgow Coma Scale (GCS) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare.

2.2 Key Features of Concussion

The most recent consensus statement on concussion in sport from the Fifth International Conference on Concussion in Sport held in Berlin, Germany in 2016 defines SRC as “a traumatic brain injury induced by biomechanical forces” (McCrory et al., 2017, page 2). The concussion definition put forth by the Berlin consensus statement is associated with a number of key clinical, pathological, and biomechanical features:

1. SRC may be caused by either a direct blow to the head, face, or elsewhere on the body with an “impulsive” force transmitted to the head.
2. SRC typically results in the rapid onset of short-lived impairments to neurological function that resolve spontaneously. In some cases, these symptoms may evolve for minutes to hours following the initial insult.
3. SRC may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies.
4. SRC results in a range of clinical and cognitive symptoms that may or may not involve loss of consciousness (LOC). Resolution of clinical and cognitive features typically follows a sequential course. However, in some cases symptoms may be prolonged.
2.3 Epidemiology of Concussion

Recent estimates suggest that the annual incidence of SRC ranges from 1.6-3.8 million within the United States alone, but given that many SRC remain undiagnosed and/or unreported, these figures likely underestimate the actual rate of this injury. At the National Collegiate Athletic Association (NCAA) level, concussions account for approximately 5.8% of all injuries sustained in practice and competition.

Within the youth population (less than 18 years of age), concussion is one of the most commonly reported injuries. The majority of SRC occur in people under 20 years of age, and it is estimated that nearly 9% of all high school athletic injuries are concussions. Moreover, the incidence of concussion in 10-19 year olds in the US has increased by approximately 100,000 between 2001 and 2009. In fact, the incidence of TBI among adolescents aged 14-19 tripled from 1997 to 2007. This is significant given that recovery for high school-aged youth tends to be slower than for college-age and adult individuals.

Canadian statistics demonstrate that mTBI is the most prevalent type of injury across the TBI spectrum within the province of Ontario, comprising 70-90% of all TBI cases. There were an estimated 176,685 pediatric visits (5-18 years of age) to the emergency departments across the province of Ontario between 2003 and 2013, representing a four-fold increase in visits for every 100,000 members of this population over this 10-year period and a five-fold increase in the adolescent population specifically (aged 13-19 years). There was also a steep increase observed in concussion-related visits from 2010 onwards, with nearly 35,000 visits in total occurring in 2013 alone.
2.4 Evolution of Concussion Management Guidelines

The first international conference on concussion in sport, held in Vienna, Austria in 2001, proposed a graduated, six step rehabilitation program, and stated that the athlete must undergo a rest period until they are completely asymptomatic prior to initiating it\textsuperscript{58}. The guidelines go on to say that the longer the symptoms persist, the longer the athlete must rest\textsuperscript{58}. The RTP protocol proposed in these guidelines consists of a graduated six-stage program, with duration and intensity gradually increasing incrementally from one stage to the next\textsuperscript{58}. These guidelines suggest that each step take a minimum of one day, and should symptoms become exacerbated at any point, backtracking to the previous stage is recommended until the patient is able to complete the same stage without exacerbation of symptoms\textsuperscript{58}. If the athlete’s symptoms do not become exacerbated at any point, the protocol should take approximately one week to complete.

The summary and agreement statement of the second international conference on concussion in sport, held in Prague, Czech Republic in 2004, reiterated the previous statement’s emphasis on complete physical and cognitive rest until the patient is completely asymptomatic\textsuperscript{59}. This statement proposes the same supervised, graded six-stage protocol to be initiated once the athlete has achieved asymptomatic status\textsuperscript{59}. It explicitly states that both physical and cognitive rest is required in the first few days of recovery following injury\textsuperscript{59}. In both this publication and the 2001 guidelines, it also states: “when in doubt, sit them out!” (McCrory et al., 2005, page 41).\textsuperscript{59}

One notable difference between these guidelines and the previous consensus statement pertains to cases of complex concussion (i.e. those with PCS). While the 2001 guidelines explicitly stated that patients with prolonged symptoms should be made to sit out from activity and sport for a longer duration, these guidelines simply state that: “in such cases, the rehabilitation will be more prolonged and RTP advice will be more circumspect.” \textsuperscript{59} They go on to say that such
complex cases should be managed by physicians with specific expertise in the management of such injuries, with no further specification of what this might look like in a clinical setting59.

Updated guidelines were published following the third international conference on concussion in sport held in Zurich in 2008, which proposed the same six-stage RTP protocol as the previous two consensus statements60. These guidelines state: “the cornerstone of concussion management is physical and cognitive rest until symptoms resolve and then a graded program of exertion prior to medical clearance and RTP.” 60 However, these guidelines demonstrate significant progress from those published previously by discussing the possibility of same-day RTP in specific cases involving adult athletes whose team physicians have the sufficient resources and access to sideline neurocognitive assessment60. This addition is based on evidence suggesting that some professional American football players are able to RTP more quickly, sometimes even on the same day as the injury, without a risk of recurrence or sequelae61.

It is important to note that the guidelines go on to warn that athletes at the collegiate and high school level may experience neuropsychological deficits post-injury that may not be evident on the sidelines, and are therefore more likely to have a delayed onset of symptoms62-67. The recognition that young elite athletes (i.e. those under the age of 18) require a different approach that adult athletes is another important advancement observed in these guidelines from the previous consensus statements.

In the consensus statement from the fourth international conference on concussion in sport held in Zurich in 2012, rest is still recommended to be the cornerstone of concussion management2. While the authors do note that the body of evidence evaluating the effect of rest on concussion recovery is extremely limited, they propose that a period of rest lasting 24-48 hours in duration may be of benefit to recovery2. While these guidelines still propose the same six-stage RTP
protocol as the three previous statements, they offer more concrete parameters in regards to their implementation. For example, stage two of the graduated RTP protocol, which is comprised of light aerobic exercise, includes examples of appropriate types of exercise (walking, swimming, stationary cycling) and provides an optimal intensity level (less than 70% maximum heart rate).

A notable advancement presented in these guidelines from the previous statement in 2008 is the suggestion that low-level exercise may be of benefit to those who are slow to recover from concussion, although the authors note that the optimal timing of exercise following injury is still unknown. This is an important update from the first consensus statement, which stated that those with prolonged symptoms must rest undergo a prolonged period of rest. It is also important to note that the authors discuss the possibility that the prolonged symptom presentation experienced with PCS may not necessarily be indicative of concussion pathology, and that it is important to consider other possible pathologies. Despite these progressions, these guidelines offer no insight into the appropriate nature of the rest period following SRC, and highlight the fact that there is a dearth of literature on the topic of graded exercise following concussion.

Since the publication of the 2012 guidelines, some promising studies have emerged from the University of Buffalo Concussion Clinic demonstrating the clinical utility of active rehabilitation strategies, often in the form of graded AE interventions, in treating concussion patients with persistent symptoms. For example, results from a preliminary study by Leddy and colleagues in 2010 showed that the implementation of progressive sub-symptom threshold AE rehabilitation in a controlled and individualized manner is not only safe to employ in patients with PCS, but is also associated with significant physiological recovery and successful RTP. It is important to note that the participants in this study had all been symptomatic for at least six weeks post-injury at the time of the exercise intervention. Despite the promise of these findings, the literature
investigating the efficacy of graded AE rehabilitation strategies in concussion patients within the post-acute phase of recovery (i.e. within 7-10 days of the initial injury) remains extremely limited.

The most recent consensus statement was published in 2017 based on the Concussion in Sport Group’s 2016 meeting in Berlin. In these guidelines, authors acknowledge that there is currently insufficient scientific evidence to suggest that rest beyond the initial 24-48 hours of injury provides any beneficial effect following concussion. Following this brief rest period, these guidelines encourage patients to be “progressively and gradually more active while staying below their cognitive and physical symptom exacerbation thresholds”. While these guidelines suggest that athletes should avoid vigorous exertion during the recovery period, they go on to state that “the exact amount and duration of rest is not yet well defined in the literature and requires further study”. While the recognition that rest is of no benefit to concussion recovery is a significant step forward from previous consensus statements, the acknowledged lack of understanding as to the appropriate parameters of rest following this type of injury highlights the need for future studies in this field.

2.5 Autonomic Dysregulation Following SRC

The physiological insult of concussion involves disruptions to the autonomic nervous system (ANS), particularly with respect to its control over the cerebrovascular autoregulation. This dysfunction of the central ANS is suggested to result from subtle structural alterations in regions of the central nervous system (CNS) responsible for regulating autonomic modulation under normal circumstances, which are housed in the reticular formation of the brainstem. These regions are thought to be particularly vulnerable to alterations if the mechanism of injury involves rotational shear force applied to the upper cervical spine. Because of this disturbance
to the reticular formation following concussion, sympathovagal balance may become dysregulated following mTBI, leading to alterations in cardiovascular modulation. As such, normalization in measures of cardio-autonomic dysregulation following concussion has potential utility as an indicator of physiological recovery from this type of injury.

2.5.1 Heart Rate Variability (HRV)

HRV is an objective measure of ANS function based on the fluctuations in mean HR on a beat-to-beat basis, which reflect the balance of sympathetic and parasympathetic influences at the sinoatrial node. An overall higher HRV is reflective of greater flexibility in HR, allowing individuals to adapt to various environmental demands and stressors, and is therefore associated with normal neurophysiological functioning. Conversely, a lower overall HRV is reflective of more uniform time intervals between successive heart beats and is thought to be reflective of less flexibility in the heart rate response to various environmental stressors and demands. As such, a lesser overall HRV is associated with a heightened state of physiological stress and sympathetic nervous system dominance. Evidence suggests that impairments to ANS dysregulation can be improved through AE training, which may be reflected by increases in HRV via greater vagal modulation and diminished sympathetic influence.

Decreased HRV is characteristic of TBI patients, which is thought to reflect the impaired ability of the cerebrovascular system to buffer the increased sympathetic dominance and decreased parasympathetic influence following this type of injury. Within the young adult athletic population, reduced HRV has been observed in individuals suffering from persistent concussion symptoms compared to healthy controls. Impairments in HRV have been observed in mTBI patients during exercise, an observation which is thought to reflect the uncoupling between the parasympathetic branch of the ANS and the cardiovascular system (CVS) post-concussion.
That is, when sympathetic tone is consistently dominant, the cardiovascular response to exercise may be indicative of overall stress, promoting symptoms of fatigue at a heart rate that is significantly lower than pre-morbid performance.\textsuperscript{72}

For example, results from a 2004 study by Gall and colleagues demonstrated significant decreases in various measures of HRV (including mean R-R interval, as well as LF and HF power) in concussed athletes compared to their non-concussed controls during a bout of low-moderate intensity AE.\textsuperscript{18} However, these authors found no difference in HRV parameters between the concussed athletes and their matched controls while at rest, leading them to conclude that exercise induces ANS and CVS uncoupling following SRC, and the effects of this uncoupling were found to persist at 10 days post-injury.\textsuperscript{73}

These results were challenged by a 2011 study by La Fountaine and colleagues, which demonstrated impairments to physiological indicators of sympathetic activation other than HRV both at rest and during exercise using two different measures of cardio-autonomic modulation in recently concussed athletes.\textsuperscript{74} These authors found that both the QT interval variability index (the time interval between electrical depolarization and repolarization of the ventricles during the heart’s electrical cycle) at rest, as well as heart rate complexity during an isometric hand grip exercise, were significantly altered within 48 hours following mTBI. However, these values resolved to normal levels within one week post-injury.\textsuperscript{74}

These results are supported by a 2016 study by Hutchison and colleagues, which also identified significant impairments to HRV in a cohort of concussed athletes compared to matched controls at rest.\textsuperscript{75} Specifically, the standard deviation of R-R intervals (RR\textsubscript{std}) and high frequency (HF) power were both lower in concussed athletes than their matched controls, indicating abnormally low levels of vagal influence, even in a resting state. These impairments were still observed
even after asymptomatic status was achieved and the athletes had received medical clearance to RTP, supporting previous findings which demonstrate the persistence of physiological abnormalities beyond symptom resolution\textsuperscript{76-78}.

Interestingly, these authors found significant interactions between HRV following concussion and other personal characteristics, such as sex and mood state\textsuperscript{75}. Female athletes in this study experienced greater reductions in HRV compared to their male counterparts, leading authors to infer that the female PSNS is particularly susceptible to impairment by concussion\textsuperscript{75}. Moreover, the authors reported that more negative mood states were associated with an abnormally low LF/HF ratio, indicating excessive sympathetic withdrawal\textsuperscript{75}. This effect was more pronounced in males than females. Overall, these results are supported by previous findings, which suggest that males tend to be more sensitive to SNS dysfunction, whereas females tend to be affected more by impairments to the PSNS\textsuperscript{79}.

Overall, while evidence does exist to suggest that HRV and HR complexity is diminished following concussion, both at rest and during exercise, a limited number of studies exist that examine the effect of SRC on measures of HRV across the recovery timeline, particularly within the adolescent population. Furthermore, while AE has demonstrated efficacy in facilitating vagal dominance over the ANS, the utility of exercise in promoting more desirable values of various outcome measures of HRV following this type of injury remains largely unexplored.

2.5.2 Blood Pressure Variability (BPV)

A growing body of literature has examined the relationship between TBI and arterial blood pressure, which suggests that the autonomic disequilibrium following mTBI is associated with reductions to baroreflex sensitivity (BRS). This is thought to be due to the impaired quality of the open-loop interaction between heart rate and blood pressure resulting from the traumatic
event. It is suggested that this dysregulation contributes to the abnormally high resting BP values observed in patients with mTBI, as well as difficulties in modulating blood pressure fluctuations, resulting in undesirable increases to BPV at rest.

This process was observed in a 2011 study by Hilz and colleagues, in which a group of individuals with a history of mTBI demonstrated orthostatic intolerance when moving from a supine position to upright standing. While the authors reported that there were no differences observed in measures of systolic or diastolic BP, or the LF and HF powers of systolic BP oscillations in the resting supine position, these values were shown to increase significantly upon standing upright. Despite the increasing demands of standing upright compared to lying supine, results suggest that these individuals were not able to alter BP appropriately upon changing position. The authors inferred that this response was likely due to an impaired ability to withdraw parasympathetic influence and/or activate sympathetic modulation when necessary as a result of the mTBI.

Hilz et al. further explored the relationship between mTBI and various measures of cardiovascular-autonomic dysregulation in a 2016 study examining HR and BP outcomes at rest and in response to a stimulus of physiological exertion (the Valsalva maneuver) in patients with mTBI compared to healthy controls. The authors reported that patients with a history of mTBI exhibited significantly lower levels of systolic LF power at rest in the supine position compared to healthy controls. Furthermore, following execution of the Valsalva maneuver, the time it took for SBP to normalize to 90% of its resting state was significantly longer in participants with a history of mTBI compared to controls.

More recently, Dobson and colleagues (2017) compared the HR and BP responses to various stressful stimuli (including supine-to-standing, forced breathing, and the Valsalva maneuver) in a
cohort of acutely concussed athletes and matched controls\textsuperscript{84}. Authors reported that at 48 hours post-injury, the concussed group exhibited significantly greater mean SBP at rest than the control group, as well as in response to upright standing. The concussed group also experienced significantly longer SBP normalization times following the Valsalva maneuver than the control group at this time point. However, significant differences between groups in these measures were reported to subside 24 hours later\textsuperscript{84}.

Very few studies have explored the effect of concussion (particularly within the context of sport) on outcome measures of BPV across the timeline of recovery. Given the link between this type of injury and reductions to baroreflex sensitivity, it may be worthwhile to develop a more advanced understanding of the clinical utility of BPV in detecting physiological dysregulation across the timeline of recovery in this population. Furthermore, no study to date has explored the effect of an AE intervention on facilitating normalization of various measures of BPV across the recovery timeline following SRC.

### 2.6 Effect of Rest on Concussion Rehabilitation

While rest is widely recommended for a number of medical conditions, including brain injury, the benefits of rest are largely assumed rather than evidence-based\textsuperscript{22}. Across a variety of injuries and illnesses, it has been demonstrated that rest provides no beneficial effect, and may actually cause harm in some instances\textsuperscript{25}. Sedentary behavior following injury or illness is the most consistent risk factor for chronic disability\textsuperscript{85}. In fact, prescribed rest begins to adversely affect the cardiopulmonary and musculoskeletal systems in healthy people within just three days\textsuperscript{86}.

There are also known mental health consequences of inactivity, particularly depression, which can arise in conjunction with a lack of behavioral activation of regular, reinforcing activities\textsuperscript{87}. 


Furthermore, inactivity can exacerbate and/or prolong recovery from other medical conditions, including those most often comorbid with mTBI, such as vestibular disorders, mental health disorders, chronic fatigue syndrome, and pain disorders. Athletes in particular are vulnerable to the deleterious effects of prolonged rest with respect to physical deconditioning, as well as secondary symptoms arising from fatigue and reactive depression.

While rest has historically been the primary recommendation for patients diagnosed with mTBI/concussion, its efficacy during all phases of recovery is beginning to be challenged. In a randomized trial by de Kruijk and colleagues (2002), no differences in outcomes were observed between mTBI patients who were given usual care compared those who were prescribed strict bed rest for six days post-injury. These results remained consistent at two weeks, three months, and six weeks following discharge from the emergency room, suggesting that bed rest provides no beneficial effect over other rehabilitation strategies. Similar results were reported in a 2009 study by McCrea and colleagues, in which a symptom-free waiting period following SRC was not found to influence clinical recovery or reduce the risk of a repeat concussion in a cohort of high school and collegiate level athletes with SRC.

2.7 Effect of Exercise on the CNS

In contrast to rest, there is evidence of the positive effects of AE on recovery from a number of injuries. In terms of benefiting the CNS, exercise has been shown to influence multiple neurotransmitter systems and promote neuroplasticity, neurogenesis, and angiogenesis following a traumatic event. As such, AE interventions have been associated with positive outcomes across a variety of neurological and mental disorders, including chronic fatigue syndrome, depression, and anxiety. The implementation of AE has also been shown to improve cognitive ability in patients with stroke, dementia, and TBI.
Research in the field of neurorehabilitation suggests that moderate-intensity AE, which is defined as exercise at approximately 65% of an individual’s maximal oxygen consumption, may provide the optimal level of stimulus to safely, effectively, and non-invasively promote recovery following concussion. The suggested mechanism through which this process is thought to occur is via increased synthesis and secretion of specific neurotransmitters and neurotrophic factors (i.e. neurotrophins) elicited by moderate AE, which lead to increases in neurogenesis, angiogenesis, and neuroplasticity following injury.

Neurotrophins are activity-dependent proteins that mediate synaptic plasticity and axonal branching within the brain, thereby protecting and restoring neurons in response to injury. Neurotrophic factors stimulated by exercise include insulin-like growth factor I, fibroblast growth factor II, and brain derived neurotrophic factor (BDNF). Of these trophic factors, BDNF is suggested to be particularly susceptible to regulation by physical activity in terms of both its expression and its release. In fact, AE has been shown to induce the expression of BDNF mRNA and protein in the cerebral cortex, cerebellum, and spinal cord.

In a 2014 review by Ploughman and colleagues on the benefits of AE on stroke recovery, it was concluded that moderate to high intensity AE leads to increased levels of BDNF, IGF-1, nerve growth factor (NGF), while also promoting synaptogenesis in multiple regions of the brain. However, it is important to note that across the literature, dendritic branching was reported to be most responsive to moderate, rather than high intensity AE.
2.8 Utility of Exercise in Injuries to the CNS

2.8.1 Stroke

Very early mobilization (VEM) following stroke (i.e. within 24-36 hours post-injury) has been found not only to be safe and feasible following injury, but it also leads to more positive outcomes for patients compared to standard care\(^{27,109}\). In fact, a shorter time to mobilization following stroke was found to be the most important factor associated with discharge home from a hospital setting\(^{28}\), and patients who began exercise earlier in the recovery process showed greater improvements in functional ambulation compared to those who began later\(^{29}\).

Furthermore, stroke patients who engaged in VEM were shown to have significantly higher odds of independence at three months post-stroke compared to patients who received standard care\(^{30}\). Additionally, it is suggested that reducing activity restrictions in stroke patients and initiating VEM leads to positive mental health outcomes, as it has been shown to decrease the symptoms of depression and anxiety associated with this type of injury\(^{32,110}\).

2.8.2 Whiplash

Research in the field of whiplash rehabilitation suggests that exercise programs are the most effective non-invasive treatment for patients with chronic whiplash associated disorder (WAD)\(^{33}\). While rest and collar restraint were previously the standard mode of treatment for whiplash, more recent evidence suggests that early mobilization and exercise is not only safe following injury, but achieves superior functional outcomes and decreased pain intensity compared to more traditional rehabilitation strategies for patients, even in the acute stages of recovery\(^{34,111}\).

2.8.3 Low Back Pain

Across the literature, consistent findings demonstrate that bed rest is a less effective treatment for low back pain compared to resuming regular activities\(^{37,112}\). In fact, research suggests that bed
rest may actually delay recovery from acute low back pain, and recommendations to resume regular activities as soon as possible following injury result in faster recovery times, less chronic disability, and fewer recurrent problems\(^3\).

### 2.8.4 TBI – Animal Studies

The initiation of exercise training shortly after the administration of fluid percussion injury (FPI) in rats has been shown to be an important facilitator of recovery from cerebral dysfunction induced by TBI\(^1\). A 2011 study by Itoh and colleagues found that 30 minutes of AE per day, for seven consecutive days, following FPI-induced TBI in rats led to significant increases in the proliferation of neuronal stem cells surrounding the damaged area of the brain compared to non-exercising controls\(^1\). Similar results were reported in a 2015 study by Jacotte-Simancas et al., in which there were significant increases in cell proliferation and neurogenesis observed in the granular cell layer of the dentate gyrus of rats with TBI who began exercising at four days post-injury, compared to non-exercising controls\(^1\).

In addition to its beneficial effects on cell proliferation and neuronal regeneration following TBI, voluntary exercise (VE) initiated immediately following injury has been shown to significantly inhibit apoptosis of neurons surrounding the damaged area of the brain in rats with FPI-induced TBI, thereby inducing significantly greater improvements in cognitive function compared to non-exercising controls\(^2\). Treadmill AE initiated two days post-injury has also been shown to significantly decrease DNA fragmentation and caspase-3 expression (a known mediator of apoptosis) in the hippocampal region of rats induced with TBI, thereby alleviating short-term memory loss while also suppressing the expression of pro-apoptotic factor Bax, compared to non-exercising controls\(^3\). VE following TBI has also been associated with enhanced survival of Purkinje fibres and the suppression of reactive astrocyte formation\(^4\).
It is important to note that some animal studies examining VE following FPI-induced TBI suggest that there is an ideal temporal window that occurs around two to three weeks post-injury, during which time exercise exerts its beneficial effects on recovery\textsuperscript{118}. VE initiated between 14 and 21 days post-injury has been shown to facilitate the up-regulation of endogenous BDNF, as well as synapsin-1 and cyclic AMP response element binding protein (CREB), thereby enhancing mTBI recovery in rats\textsuperscript{119}. However, VE initiated prematurely in the recovery process (i.e. within six days of injury) has been associated with delayed recovery as it has been shown to compromise neuroplasticity and suppress BDNF up-regulation, while increasing glucocorticoid expression, which is a known inhibitor of BDNF expression\textsuperscript{120}. Overall, these studies demonstrate the important role of BDNF in neurological recovery following TBI.

These studies by Griesbach and colleagues are some of the main sources of evidence supporting the existing SRC management guidelines, which advise complete rest until symptoms resolve\textsuperscript{119-121}. However, it is important to consider the type of exercise being implemented, as these authors have also demonstrated that the use of forced exercise (FE) is associated with a higher stress response than that of VE, causing this type of exercise to be more strongly correlated with compromised autonomic and cardiovascular function when implemented sub-acute following FPI compared to VE\textsuperscript{122}.

### 2.9 Utility of Exercise Following Concussion

Findings from a recent systematic review and meta-analysis by Lal and colleagues, which spanned a total of 14 studies (including five randomized control trials), suggest that physical exercise following concussion significantly decreases overall symptom burden in patients undergoing such interventions (as reported on the PCSS), compared to controls\textsuperscript{123}. This meta-analysis also demonstrated a statistically significant decrease in the percentage of recently
concussed patients (within five days or fewer) who remained symptomatic following exercise, compared to controls\textsuperscript{123}. Furthermore, a subgroup analysis of two RCTs demonstrated a statistically significant improvement in the reaction time component of the commercially available cognitive test, Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), in patients who underwent exercise compared to controls\textsuperscript{124,125}. However, these authors go on to highlight the need for the development of high-quality RCTs evaluating a greater range of exercise intensities at various time points throughout the recovery process following concussion in order to have a more comprehensive understanding of the effect of exercise on recovery\textsuperscript{123}.

2.9.1 The Role of Exercise in Post-Concussion Syndrome

Traditional treatment programs for PCS typically involve rest, education, neurocognitive rehabilitation, and antidepressant administration, none of which have proven to be particularly effective management strategies\textsuperscript{88}. However, emerging research is beginning to demonstrate that sub-threshold AE training (i.e. AE below the threshold of symptom exacerbation) can exert positive effects on the concussed brain of patients with PCS, thereby facilitating recovery from post-concussion physiological dysregulation and consequent symptom presentation\textsuperscript{68}. For example, Leddy and colleagues (2010) found that the implementation of a controlled, graded AE program involving treadmill exercise for five to six days per week at 80\% of the individual’s pre-determined symptom exacerbation threshold led to significantly more rapid recovery, as well as significantly fewer post-concussion symptoms, compared to rest\textsuperscript{68}.

A 2015 study by Clausen and colleagues examined the effect of sub-threshold AE in a cohort of female athletes with PCS who exhibited abnormal carbon dioxide (CO\textsubscript{2}) sensitivity, which caused relative hypoventilation within these patients. This lead to disproportionately high CO\textsubscript{2}
levels relative to exercise intensity, which was associated with symptoms of headache and dizziness and a lower overall exercise tolerance. However, following the implementation of a sub-symptom threshold AE intervention, the authors reported that CO$_2$ levels and exercise tolerance normalized to pre-injury values, as did minute ventilation and partial pressure of arterial CO$_2$. The use of controlled and closely monitored exercise rehabilitation in the post-acute period has also been shown to help with other populations who are slow to recover following concussion, including youth athletes. A 2009 study by Gagnon and colleagues found that a closely supervised and controlled rehabilitation program helped expedite the recovery process of all 16 athletes (aged 10-17 years old) recruited for this study who were slow-to recover following SRC. This treatment intervention, known as the Montreal Children’s Hospital Rehabilitation After Concussion (MCH-RAC) program, consisted of gradual, closely monitored AE, general coordination exercises, visualization, as well as education and motivation activities. A more recent study by these authors (2015) found that the implementation of this same active rehabilitation intervention was associated with significant decreased post-concussion symptoms, as well as decreased fatigue and improved mood in a group of adolescent athletes who were still symptomatic at four weeks post-SRC. These improvements were still observed at six weeks after the initiation of the intervention.

Graded, sub-threshold AE interventions have also been efficacious in restoring brain fMRI activation patterns back to normal among PCS patient populations. Sub-threshold AE has also been suggested to help normalize cerebral autoregulation in patients with PCS. Overall, these results suggest that sub-symptom threshold AE, which is similar to the VE examined in rodent studies, can have positive effects on the concussed brain in patients with PCS.
2.9.2 The Role of Exercise in Adolescent Concussion Rehabilitation

There are currently very few studies investigating the effect of exercise in adolescent-aged subjects following concussion. Of the limited number of studies that have explored the utility of AE interventions in adolescent SRC recovery, none to date have explored the implementation of activity in the post-acute phase of recovery (i.e. prior to full symptom resolution). One study by Carson and colleagues (2014) retrospectively reviewed the electronic medical charts of youth SRC patients seen in a family and sport physician’s office over a five-year period. The authors noted that there was a relapse of symptoms in 48.2% of patients, as well as recurrence and/or worsening of symptoms in 48.2% of patients, following RTP and 44.7% of patients following return to learn (RTL). These results led clinicians to infer that these patients were returning to their regular activity levels prematurely following concussion. However, these results are limited by the fact that the level of intensity of this post-concussion exertion was not reported.

The results of another retrospective cohort study by Majerske and colleagues (2008) suggest that it is in fact the intensity level of this post-SRC exertion that is significantly correlated with potentially deleterious outcomes. Their results demonstrate that adolescent athletes who engaged in moderate levels of physical and cognitive activity following SRC performed significantly better on neurocognitive measures of verbal memory and reaction time at one month post-injury, compared to athletes who engaged in either no activity or high levels of activity. These results provide further evidence in support of the clinical utility of moderate AE in injury rehabilitation.

Additional evidence favouring the utility of AE interventions for patients with SRC comes from a recent randomized control trial by Thomas and colleagues (2015), which explored the utility of early mobilization in the sub-acute stage of concussion recovery within an adolescent population. The authors found that patients who underwent strict rest for five days post-injury reported more
symptoms and experienced these symptoms for a longer duration compared to patients who underwent a standard rehabilitation program consisting of 24-48 hours of strict rest followed by a step-wise progression of light physical and cognitive activity\textsuperscript{125}.

### 2.10 Limitations in SRC Management

#### 2.10.1 Symptom Causation

A limitation in establishing the parameters of what could be considered safe post-concussion exertion levels is that post-concussion symptoms are not necessarily reflective of the underlying neuropathology associated with sustaining a concussion\textsuperscript{22,132}. On the contrary, the presence of concussion-like symptoms are state-dependent, and can fluctuate depending on a number of variables, such as the time of day of measurement, emotional status, motivation, and willingness of the individual to fully report symptoms\textsuperscript{133}. Furthermore, an increase in concussion-like symptoms concurrent with an increase in activity levels may not necessarily be indicative of exacerbated neuropathology, but instead may be a normal response to the stress of exercise. In fact, a 2010 study by Alla and colleagues found that a 15 minute bout of high intensity exercise elicited a significant increase in concussion-like symptoms in a healthy, active, and non-concussed population\textsuperscript{134}.

Conversely, it is also possible for concussion patients who are symptom-free to have underlying pathophysiology associated with the injury. For example, abnormally low resting CBF can be observed via MRI imaging up to four weeks post-concussion in adolescent patients, despite the resolution of symptoms\textsuperscript{135}. Furthermore, a 2015 study by Meier and colleagues showed decreased resting CBF in the dorsal midinsular cortex at one month post-concussion in a group of slow-to-recover collegiate athletes, which was found to be inversely related to the magnitude of the initial symptoms reported by these individuals\textsuperscript{136}. In other words, the athletes who reported the lowest
magnitude of symptoms experienced the greatest declines in resting CBF. Moreover, abnormally low levels of HRV have even been found to persist for weeks to months in a cohort of collegiate athletes, despite the resolution of concussion symptoms in these individuals.\textsuperscript{72,137} Taken together, these results suggest that symptomology and underlying neuropathology are not necessarily related.

2.10.2 Age

It is also important to consider the fact that the timeline for symptom resolution appears to be different for various populations based on age. While concussion symptoms tend to resolve spontaneously within 7-10 days in the majority of adult athletes at the collegiate and professional levels\textsuperscript{1}, high school aged athletes are known to take longer to achieve asymptomatic status\textsuperscript{12}. This was acknowledged in the most recently published consensus statement from the Concussion in Sport Group’s 2016 meeting in Berlin, Germany, which stated that adolescent patients with SRC experience symptom presentation for a longer duration than their adult counterparts, lasting up to four weeks post-injury\textsuperscript{40}. A recent meta-analysis found that high school athletes’ self-reported symptoms resolve around 15 days post-concussion, compared to six days in collegiate athletes\textsuperscript{138}. McCrea and colleagues (2009) reported that approximately 80% of youth concussion cases involved symptom resolution lasting at least two to three weeks in duration\textsuperscript{90}. Furthermore, neurocognitive deficits have been shown to persist within this population even after asymptomatic status has been achieved\textsuperscript{63,139}.

There are number of suggested explanations as to why adolescent patients seem to take longer to recover from concussion than their adult counterparts. These include: immaturity of the developing CNS, a larger head-to-body ratio, a larger subarachnoid space in which the brain can move freely, as well as differences in cerebral blood volume\textsuperscript{140}. Furthermore, the incomplete
mylenation of neurons combined with excessive elasticity of the cranial vault may place the developing adolescent brain at greater risk for shear injury\textsuperscript{141-143}. Lastly, the natural timeline of neuronal maturation may be altered because of the disturbances associated with concussion, thereby prolonging recovery for this population further\textsuperscript{144}.

For these reasons, adolescent athletes need to refrain from sport and other regular activities for significant periods of time, which may impede recovery and lead to secondary problems (particularly with respect to mental health) which are known to arise in conjunction with a lack of regular, reinforcing activities\textsuperscript{87,145}. This is particularly significant given that the proportion of SRC sustained by high school athletes is greater than that of collegiate athletes with respect to total injuries sustained in sport\textsuperscript{4}.

2.11 Gaps in the Literature

While some progress has been made in the literature with respect to our general understanding of the pathophysiological processes responsible for concussion, particularly using animal models of injury, gaps still remain in terms of our understanding of how to manage this type of injury in the acute stage of recovery. Despite the emerging evidence demonstrating the efficacy of exercise interventions in the treatment of various injuries of the CNS (i.e. stroke, whiplash, low back pain, dementia), there are very few studies examining the clinical utility of alternative rehabilitation strategies other than rest following concussion, particularly in the post-acute stage of recovery.

The majority of existing studies that do investigate the effect of activity post-concussion involve animal models of brain injury, which limits their clinical generalizability to humans. While a very limited body of literature does exist which investigates the effect of acute activity following concussion in humans, the validity (and subsequent clinical utility) of these studies is challenged
by the fact that they all involve retrospective study designs. Furthermore, these studies rely
mainly on subjective reports of concussion-associated symptoms as an indication of impairment
and generally do not involve objective biological markers of underlying pathological processes.
As such, it is important that future studies aim to understand the relationship between subjective
measures of clinical recovery from concussion (i.e. symptom severity/duration) and objective
measures of physiological recovery from concussion (i.e. measures of HRV and BPV) in the
adolescent population across the recovery timeline.

There are also gaps in the literature with respect to the nature and duration of rest following
SRC, especially in the adolescent population, as this demographic generally experiences a longer
period of symptom presentation compared to adults. Given that adolescent athletes sustain a
disproportionately high rate of SRC incidence compared to collegiate and/or professional level
athletes\textsuperscript{12} and that adolescents tend to experience a greater level of impairment following this
type of injury compared to their older counterparts\textsuperscript{146}, the development of a safe, effective, and
evidence-based rehabilitation strategy is imperative for this population. Therefore, the potential
utility of structured AE exercise in the post-acute stage of SRC in adolescents must be explored
in order to understand its efficacy on facilitating clinical and physiological recovery compared to
usual care.
Chapter 3
Methods

3.1 Rationale
Due to the emerging evidence that structured, standardized AE improves outcomes for individuals with persistent symptoms following concussion, and that conversely, prolonged rest or inactivity may be detrimental to recovery, the potential benefits of earlier mobilization through a standardized AE protocol warrants investigation. Therefore, the purpose of this study was two-fold: (1) to examine the feasibility of implementing a standardized, graded AE intervention in the post-acute stage of SRC recovery in the adolescent population with respect to safety and logistics, and (2) to determine the efficacy of a standardized, graded AE intervention administered in the post-acute stage of SRC for expediting overall time to medical clearance and improving measures of clinical and physiological recovery compared to usual care in adolescents.

3.2 Design and Procedures
This study was a prospective randomized control trial that employed a sample of adolescent patients (14-18 years of age) presenting to the University of Toronto’s David L. Macintosh Sport Medicine Clinic with SRC between January 9th and June 30th, 2017. SRC was diagnosed by a staff physician, based on clinical presentation and mechanism of injury using the Macintosh
Clinic Initial Assessment of Injury form (Appendix A). The study was approved by the University of Toronto Research Ethics Board (REB #33459) and registered with ClinicalTrials.gov (also #33459).

3.3 Outcomes Measures

3.3.1 Feasibility Criteria

The feasibility of the structured AE intervention was determined based on two criteria. First, the intervention was considered to be safe if it was not associated with deleterious effects, including worsening of symptom outcomes and/or prolonged clinical recovery compared to usual care. Second, the intervention was determined to be feasible based on rates of participant recruitment and retention.

3.3.2 Estimate of Treatment Effect

The feasibility of the structured AE intervention was also determined based on preliminary estimates of the treatment effect of structured AE on various outcome measures of physiological and clinical recovery as opposed to usual care. Physiological recovery from concussion was determined using various outcome measures of HRV and BPV at Week 1 and Week 4 post-injury. Clinical recovery from concussion was determined based on overall time to medical clearance to RTP (in days), as well as resolution in symptom severity across the recovery timeline (using the PCSS of the SCAT3).

3.4 Hypotheses

3.4.1 Hypotheses: Feasibility Outcomes

**H1a:** Participants in the Exercise would not experience deleterious safety outcomes, including exacerbation of symptoms and/or prolonged clinical recovery, compared to participants in the Usual Care group.
H2s: At least 50% of eligible patients would consent to participate in the study. Participant attrition in both the Exercise Group and the Usual Care Group would be no greater than 20%.

3.4.2 Hypotheses: Estimate of Treatment Effect

H1b: Participants in the Exercise Group would require a significantly shorter time to medical clearance compared to participants in the Usual Care Group.

H2b: Participants in the Exercise Group would demonstrate significantly greater resolution of symptom severity at Weeks 1, 2, 3, and 4 post-concussion compared to participants in the Usual Care Group.

H3b: Participants in the Exercise Group would demonstrate significantly more normalized values of HRV and BPV at Weeks 1 and 4 post-concussion compared to participants in the Usual Care Group.

3.5 Participant Recruitment and Randomization

Participants were informed of the study upon their initial medical assessment at the Macintosh Clinic following concussion diagnosis. Individuals were eligible to participate if they were enrolled in a high school (14-18 years of age) and initial medical assessment occurred within five days of injury. Potential participants were excluded from participating if they had suffered a previous concussion within two weeks of the presenting concussion, and/or if they had any pre-existing cardiovascular, musculoskeletal, or neurological condition(s). Patients who met the inclusion criteria were informed of their eligibility to participate by their attending physician, who presented them with the Permission to Contact form. Eligible participants who were interested in the study could then sign this form, thereby allowing a member of the research team to contact them by phone and educate them on the study in greater detail (Appendix B). Once a patient consented to participate in the study, they were required to sign the Primary Informed
Consent document (see Appendix C). Participants under the age of 16 were required to sign the Child Assent Form (Appendix D), while their parent/guardian was required to sign the Primary Informed Consent document on their behalf, as well as the Parental Informed Consent (Appendix E).

Participants were divided into two groups based on their reported symptom severity score on the Post-Concussion Symptom Scale (PCSS), administered on day five post-concussion (Appendix F). Asymptomatic status was operationally defined as a reported PCSS symptom severity score that was equal to or less than 5, based on the cut-off score determined by Alla and colleagues (2012) which seems to effectively differentiate between individuals who have suffered a concussion versus healthy individuals in the general population experiencing concussion-like symptoms\(^\text{133}\). Participants who reported a total symptom severity score on the PCSS that was greater than 5 were defined as being symptomatic, and were randomized into one of two groups:

1. **Exercise Group** (n=8): Participants in this group were guided through a graded exercise program beginning on day six post-concussion. See section 3.3 for details.

2. **Usual Care Group** (n=7): Participants in this group were instructed to follow the activity recommendations provided to them by their attending physician. These individuals were assessed using the same measures and at the same time intervals as the Exercise Group. See section 3.4 for details.
Figure 1. Participant Recruitment and Randomization

3.6 Aerobic Exercise Intervention

Table 1 below explains the AE protocol in full, which consisted of eight sessions that proceeded in a stepwise fashion with respect to both duration and intensity over the course of 11 days. All exercise sessions were supervised by a member of the research team, and included a five-minute warm-up period as well as a five-minute cool-down period. All exercise was completed on the Velotron Pro stationary cycle ergometer (RacerMate Inc., WA, USA), which ensured that the participant’s head and neck remained stable throughout the protocol, thereby minimizing risk of symptom exacerbation and/or re-injury. This stationary bicycle was digitally connected to a heart rate monitor (Polar Electrol, Kemple, Findland), which allowed the research supervisor to
ensure that the participant maintained a safe and appropriate exercise intensity that corresponded with their age and stage in the recovery timeline.

The first session of the protocol occurred on day six post-injury. The session comprised of 10 minutes of steady-state exercise at 50% of the participant’s age-predicted maximal HR, plus the five-minute warm-up and cool-down periods (total time of 20 minutes). The next session consisted of 20 minutes of steady-state exercise, plus the warm-up and cool-down periods, at the same intensity level (total time of 30 minutes). The remaining sessions consisted of same duration of exercise (20 min), including the warm-up and cool-down periods (total time of 30 minutes), however exercise intensity increased by 5% of their age-predicted maximal HR per session until they achieved 70% of their age-predicted maximal HR. This intensity (70%) was maintained for an additional two sessions.

Symptoms were recorded before and after each exercise session using the PCSS of the SCAT3, and were monitored throughout the exercise session by the supervising researcher using a prepared script (see Appendices G and H). Symptom exacerbation was operationally defined as an increase of three or more on the total symptom severity score of the PCSS, based on the operational definition of exercise-induced symptom exacerbation provided by Willer and Leddy (2013)\textsuperscript{147}. If a participant reported symptom exacerbation at any point during or after the exercise session, the session was terminated. The participant then attempted the same duration and intensity of exercise at the subsequent session. If a participant’s symptoms become exacerbated again at the subsequent session, their participation in the intervention portion of the study was terminated. Exercise sessions occurred on two consecutive days, followed by one day of rest, for a total of eleven days.
Once participants in this Exercise Group achieved asymptomatic status, they continued to progress through the AE intervention until they completed all eight sessions, or until they received full medical clearance to RTP. Time to medical clearance was tracked for all participants.

### 3.7 Usual Care Group Protocol

Participants in the Usual Care Group were advised of activity recommendations set for them by their attending physician. Based on current clinical guidelines, this typically included a brief period of rest, followed by some light-moderate level aerobic activity on a stationary cycle ergometer, without symptom exacerbation. If any activity was recommended for participants in the Usual Care Group, it was completed in an unsupervised setting. Once patients in this group achieved asymptomatic status (i.e. a score of less than 5 on the SCAT3), they were directed

<table>
<thead>
<tr>
<th>Days Post-Injury</th>
<th>Session</th>
<th>Intensity</th>
<th>Duration</th>
<th>Symptom exacerbation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1</td>
<td>50% age-predicted maximum HR</td>
<td>10 minutes</td>
<td>No → proceed to Session 2 on Day 10 Yes → repeat Session 1 on Day 10</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>50% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 3 on Day 12 Yes → repeat Session 2 on Day 12</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>55% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 4 on Day 13 Yes → repeat Session 2 on Day 13</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>60% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 5 on Day 15 Yes → repeat Session 4 on Day 15</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>65% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 6 on Day 16 Yes → repeat Session 5 on Day 16</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>70% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 7 on Day 18 Yes → repeat Session 6 on Day 18</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>70% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>No → proceed to Session 8 on Day 19 Yes → repeat Session 8 on Day 19</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>70% age-predicted maximum HR</td>
<td>20 minutes</td>
<td>Complete</td>
</tr>
</tbody>
</table>

**Table 1. Standardized, graded AE protocol**
through stages three to six of the six-stage RTP guidelines, and their time to medical clearance was recorded.

3.8 Measures
The primary outcome measure of this study was the feasibility of the intervention, which was assessed based on the feasibility criteria outlined in section 3.3. Additional outcome measures of this study were based on the hypotheses stated in section 3.4, including: (1) time to medical clearance (tracked in days from the date of the concussive incident until the date at which the participant was medically cleared to resume pre-injury levels of physical and cognitive activity), (2) symptom resolution, measured at Weeks 1, 2, 3, and 4 post-injury using the symptom severity score of the PCSS (taken from the SCAT3), and (3) physiological indicators of autonomic dysregulation, including various outcome measures of heart rate variability (HRV) and blood pressure variability (BPV), taken in both the supine and upright-seated postures at rest at Week 1 and Week 4 post-injury. Additional measures included questionnaires pertaining to pre-injury activity levels and health history, administered at the initial medical assessment.

3.8.1 Initial Medical Assessment
At the first medical visit post-injury, patients were administered an official assessment of acute injury by the treating physician (Appendix A). This included information about the mechanism of injury, features of the injury (i.e. LOC, amnesia), post-injury activity, concussion history, pre-existing mental/neurological disorders, and medications currently prescribed to the patient. It also included the SCAT3, which allowed the physician to assign the patient a symptom score.
3.8.2 Godin Leisure-Time Exercise Questionnaire

Patients were administered the Godin Leisure–Time Exercise Questionnaire at the initial medical assessment in order to gauge their pre-injury activity levels (see Appendix I). This questionnaire quantified the frequency of regular physical activity an individual engages in on a weekly basis, by asking them to estimate how many times per week they engage in strenuous, moderate, or mild exercise for more than 15 minutes during their free time. Each engagement in strenuous, moderate, or mild activity was multiplied by metabolic equivalents (METs) of nine, five, and three, respectively. The sum of all products was then calculated to produce a total leisure activity score. This questionnaire has been found to be clinically valid and reliable in the adult population\textsuperscript{148}.

3.8.3 Symptom Assessment

All participants were assessed for symptom status using the PCSS of the SCAT3, which was administered on day 5 post-injury, and then again on days 7, 14, 21, and 28 post-injury. If participants were not able to attend assessments on days 14 or 21 post-injury, this data was obtained from their electronic medical records (EMR) at the Macintosh Clinic, where they were assessed by a sport medicine physician on a weekly basis throughout the recovery period. If symptom severity was not assessed at a certain time point by either the research team or a clinician, symptom severity scores were maintained from the previous assessment session. Participants in the Exercise Group were also administered the symptom evaluation component of the SCAT3 to track their symptoms before and after each exercise session.

3.8.4 HRV Assessment

Short-term resting HRV was measured using the RR Interval test setting of the Polar heart rate V800 sports watch and corresponding chest strap (Polar ®, QC, Canada), in accordance with the
guidelines set forth by the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology\textsuperscript{149}. This data was then uploaded and processed using Kubios ® software (Biosignal Analysis & Med Imaging Group, Kuopio, Finland). The mean RR interval (RRI) and the standard deviation of the normal-to-normal intervals (SDNN) were calculated using the time domain method of HRV analysis\textsuperscript{149}. Additionally, frequency domain outputs within the low frequency (LF) and high frequency (HF) components of the power spectral density were calculated (defined as those ranging between 0.04-0.15 Hz and 0.15-0.4 Hz, respectively) \textsuperscript{149}. Frequency domain measures of HRV analysis included in this study were the LF/HF ratio of power (ms\textsuperscript{2}), as well as HF power (analyzed in normalized units, or n.u.).

For the first five minutes of collection, participants underwent a static rest period in the supine position to allow for acclimation to the equipment as well as quieting of the ANS. Following this 5-minute rest period, participants remained in the supine position as their HRV was assessed for 5 minutes. Participants were then asked to assume an upright-seated position, and underwent a one-minute acclimation period before their HRV was measured for an additional five minutes in the upright-seated position. HRV was recorded and digitally uploaded for each posture (not including the rest periods) at Week 1 and Week 4 post-injury. Statistical analysis of HRV included outcome measures from both the time domain (RRI, SDNN) and the frequency domain (HF power [normalized units, or n.u.], LF/HF power ratio).

### 3.8.5 BPV Assessment

Short-term resting BPV data was collected non-invasively on a beat-to-beat basis using continuous finger plethysmography on the middle finger of the participants’ non-dominant hand (Finapres NOVA, Finapres Medical Systems, Amsterdam, Netherlands). Derived BP waveforms
and parameters were digitally processed in real-time using BeatScope ® software (ADInstruments Inc., Colorado Springs, CO, USA). Participants underwent a five-minute rest/acclimation period, at which point their BPV was assessed for 5 minutes in the supine position. After this, participants were asked to assume an upright-seated posture, followed by a one-minute acclimation period and an additional five-minute assessment period in the upright-seated posture. Mean systolic blood pressure (SBP) and mean diastolic BP (DBP) were calculated on a beat-to-beat basis over 30 second epochs as an indicator of sympathetic outflow to the vasculature using the time domain method of analysis. Additionally, frequency domain measures of the power spectral density of BPV were calculated, including LF power of systolic BP oscillations (n.u.). BPV was assessed on days 7 and 28 post-injury.

<table>
<thead>
<tr>
<th>Day post-injury</th>
<th>Intervention/Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 6 post-injury</td>
<td>Session 1 of graded AE protocol for Exercise Group</td>
</tr>
<tr>
<td>Day 7 post-injury</td>
<td>All participants are assessed for symptoms and HRV/BPV</td>
</tr>
<tr>
<td>Day 8 post-injury</td>
<td>Rest day for Exercise Group</td>
</tr>
<tr>
<td>Days 9 - 10 post-injury</td>
<td>Sessions 3-4 of graded AE protocol for Exercise Group</td>
</tr>
<tr>
<td>Day 11 post-injury</td>
<td>Rest day for Exercise Group</td>
</tr>
<tr>
<td>Days 12-13 post-injury</td>
<td>Sessions 5-6 of graded AE protocol for Exercise Group</td>
</tr>
<tr>
<td>Day 14 post-injury</td>
<td>All participants are assessed for symptoms</td>
</tr>
<tr>
<td>Days 15-16 post-injury</td>
<td>Sessions 7-8 of AE protocol for Exercise Group (final)</td>
</tr>
<tr>
<td>Day 21 post-injury</td>
<td>All participants are assessed for symptoms</td>
</tr>
<tr>
<td>Day 28 post-injury</td>
<td>All participants are assessed for symptoms and HRV/BPV</td>
</tr>
</tbody>
</table>

**Figure 2.** Full intervention and assessment timeline
3.9 Statistical Analyses

Normality of the data was determined using the Shapiro-Wilks Test, as well as through visually inspection of boxplots. Independent t-tests were used to determine differences in baseline demographic variables.

To test H1b (which stated that the Exercise Group would experience a faster overall time to medical clearance compared to the Usual Care Group), a linear regression analysis was run to examine between-group differences with respect to overall time to medical clearance (days), including both RTP and RTL, while adjusting for acute symptom severity (i.e. PCSS symptom severity score at Day 5 post-injury). This hypothesis was further tested using an independent samples t-test, a non-parametric approach (Mann-Whitney U Test), and a categorical approach (chi-square test of independence).

To test H2b (which stated that the Exercise Group would experience a greater resolution of symptom severity across the recovery timeline compared to the Usual Care Group), a one-way, repeated-measures analysis of variance (ANOVA) with a Bonferroni correction was run using both raw and logarithmically (log10) transformed PCSS symptom severity scores at Weeks 1, 2, 3, and 4. The main effects of time and group were examined, as well as the interaction between groups over time, to explore differences between groups with respect to overall change in symptom resolution across the recovery time.

To test H3b (which stated that the Exercise Group would demonstrate values of HRV and BPV that were more indicative of parasympathetic dominance and sympathetic inhibition compared to the Usual Care Group across the timeline of recovery), outcomes measures of HRV and BPV were analyzed using a repeated-measures ANOVA with three factors: time (repeated-measures factor with two levels: Week 1 and Week 4), condition (repeated-measures factor with two
levels: supine position and seated position, and group (between-subjects factor with two levels: Exercise Group and Usual Care Group). An effect was also examined for all two-way interactions to determine if the combination of these three factors are associated with different outcomes. Specific interactions of interest included the group by time and group by condition interactions.

Specific HRV outcome measures examined in these analyses included mean RRI, mean SDNN, the LF/HF ratio, LF power, HF power, and total power. Measures of BPV included in the analyses were mean oscillations of SBP and DBP, standard deviation (STD) of SBP and DBP oscillations, as well as oscillations of SBP power in the LF range (n.u.).

Statistical analyses were conducted using IMB® SPSS® Statistics, Version 22 (IBM Corporation, Armonk, NY, USA). Statistical significance was set to an alpha level of 0.05 (5%). P-values less than 0.05 were considered statistically significant, and p-values between 0.05-0.10 were considered to be trending towards significance.
Chapter 4

Results

4.1 Participant Demographics

The study sample consisted of 15 high school-aged, male participants with SRC, all of whom were symptomatic at Day 5 post-injury (PCSS score of $\geq 5$). Of these 15 participants, eight were randomized into the Exercise Group, while the remaining seven were randomized into the Usual Care Group. Independent t-tests revealed no significant differences between groups with respect to demographic and anthropometric variables, including age, height, mass, concussion history, the presence of pre-existing conditions (including anxiety, depression, migraine, and/or attention deficit hyperactivity disorder), pre-injury exercise levels, and the number/severity of PCSS scores on day 5 post-injury. A detailed description of these demographic variables, as well the results from a series of independent t-tests between groups, can be found in Table 2 below.
Table 2. Participant characteristics (mean and standard deviation) stratified by group randomization. T-test statistic and t-test significance were corrected for unequal variance when Levene Test was significant ($p < .05$).

<table>
<thead>
<tr>
<th></th>
<th>Exercise Group ($n=8$)</th>
<th>Usual Care Group ($n = 7$)</th>
<th>T-Test Statistic</th>
<th>T-Test Significance ($p$-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>15.8 ± 1.2</td>
<td>15.6 ± 1.0</td>
<td>0.32</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>179.7 ± 8.3</td>
<td>176.7 ± 3.6</td>
<td>0.88</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Mass (kg)</strong></td>
<td>74.9 ± 12.8</td>
<td>82.0 ± 11.0</td>
<td>-1.15</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Number of Previous Concussions</strong></td>
<td>0.6 ± 0.9</td>
<td>1.0 ± 0.8</td>
<td>-0.57</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Number of Pre-Existing Conditions</strong></td>
<td>2.0 ± 0.0</td>
<td>1.3 ± 0.6</td>
<td>2.00</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Weekly Leisure Activity Score</strong></td>
<td>79.9 ±7.4</td>
<td>78.4 ± 27.2</td>
<td>0.14</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Acute PCSS Symptom Severity Score</strong></td>
<td>32.0 ±13.0</td>
<td>24.4 ± 18.7</td>
<td>0.92</td>
<td>0.37</td>
</tr>
</tbody>
</table>

The mechanism of injury in all of these cases involved collision to the head or body resulting from player-to-player interactions or individual interactions with the sporting environment. Five of these concussions (33.3%) resulted from rugby, while hockey and basketball each accounted for three concussions (20%, or 40% of total concussions). Soccer, snowboarding, lacrosse, and cycling resulted in one concussion each (6.7%, or 26.7% of total concussions). The majority of participants (n=12, or 80%) attended private high schools, while the remaining three participants
(20%) were students at inner city public high schools. None of the participants had sustained a previous concussion with two weeks of their most recent concussive event, nor did they have any pre-existing musculoskeletal, cardiac, or neurological condition(s). However, four participants reported the presence of one or more mood/developmental disorder(s), including anxiety, depression, and/or attention deficit hyperactivity disorder (ADHD). In addition, two participants also reported a history of headaches/migraines.

4.2 Results: Feasibility Outcomes

4.2.1 H1a: Safety of AE Intervention

Results suggest that the structured AE intervention was safe to administer to the adolescent cohort in the post-acute stage of SRC recovery, as it was not found to be associated with worsening of symptom outcomes (either during/immediately after exercise or across the recovery timeline) or prolonged clinical recovery compared to Usual Care.

None of the participants in the Exercise Group reported an increase in symptom severity greater than three points on the PCSS during exercise or 10 minutes after the completion of an exercise session compared to their pre-exercise levels at any of the eight sessions throughout the standardized AE protocol. In fact, Figure 4 below demonstrates that average post-session symptom severity scores were generally lower than average pre-session symptom severity scores at seven of the eight sessions throughout the AE protocol, although differences were not found to be statistically significant ($p = 0.26$).
Figure 3. Pre- and Post-Exercise Symptom Severity Scores on the PCSS throughout Standardized AE Intervention (Exercise Group only)

4.2.2 H2a: Rates of Participant Recruitment/Retention

Recruitment of participants occurred between 9 January 2017 and 30 June 2017 at the David L. Macintosh Sport Medicine Clinic. A total of 21 patients who met the eligibility criteria consented to be contacted by a member of the research team to learn more about the study. Of these 21 patients, \( n = 16 \) (76%) of them went on to participate in the study. Therefore, the participant recruitment rate hypothesis outlined in section 3.4 (H1a) was exceeded, which is promising as it suggests that this intervention is worth pursuing on a larger scale, and that a statistically powered sample size could be achieved.
None of 16 participants were lost to follow-up (100% retention rate). All of the participants who were randomized into the Exercise Group completed the full AE intervention and all four assessment sessions on days 7, 14, 21, and 28 post-injury; three participants in the Usual Care Group who missed one session each (either at Week 2 or Week 3). However, these participants were all present for the assessments which took place at Week 1 and Week 4 post-concussion. The sole female participant was removed from analysis, leaving the remaining sample size at \( n = 15 \). This satisfied the participant retention rate hypothesis stated in section 3.4 (H2\(_a\)), suggesting that this intervention is logistically worthwhile to pursue on a larger scale as part of a full clinical trial.

**Figure 4.** Participant recruitment and retention
4.3 Results: Estimate of Treatment Effect

4.3.1 H1b: Time to Medical Clearance

Individual time to medical clearance data across all participants, including descriptive statistics, can be found in Appendix J. The average (mean) time to medical clearance was 36.1 ± 18.5 days in the Exercise Group, compared to 29.6 ± 15.8 days in the Usual Care Group, indicating that the Usual Care Group achieved a more rapid overall time to medical clearance than the Exercise Group. However, independent samples t-test did not find this difference to be statistically significant, \(t(13) = .03; p = .87\). This finding was consistent with results from a non-parametric approach (Mann Whitney U Test), which showed that there was not a statistically significant difference in median rank between the two groups at any of the four time points (\(U = 20.5, p = .38\)).

Time to medical clearance was also categorized into two groups based on the overall median time to medical clearance: (1) less than 28 days or (2) more than 28 days. A Chi-square test of independence was conducted to explore the difference between the two groups in terms of percentage of participants who achieved an overall time to medical clearance ≤ 28 days. Results from the Chi-square test indicate that there was not a statistically significant difference between groups \(X^2(1) = 1.73, p = .19\). However, fewer participants in the Exercise Group achieved medical clearance within 28 days compared to the Usual Care Group (\(n = 3\) or 38% of Exercise Group versus \(n = 5\) or 71% of Usual Care Group).

Finally, a multiple linear regression analysis was used to explore the between-group difference in overall time to medical clearance while controlling for acute symptom severity (i.e. symptom severity at Day 5 post-injury). The model overall was not statistically significant \(F(2,14) = 3.2, p = .08\), \(R^2 = 0.35\) and the between-group difference was also not found to be significant (\(p\)
= .82). However, linear regression analysis did reveal a significant association between time to medical clearance and acute symptom severity (i.e. symptom severity score on the PCSS at day five post-injury), which yielded a beta coefficient score of 0.57 ($p = .04$), suggesting that a greater acute symptom severity score is predictive of a longer overall time to medical clearance.

4.3.2 H2b: Symptom Resolution Across the Recovery Timeline

Results from a series of Shapiro-Wilks test determined that PCSS symptom severity data was not normally distributed across the overall cohort at any of the four time points of analysis. However, following logarithmic transformation, normality (or approximate normality) was achieved. The results of the Shapiro-Wilks test for symptom severity at all four time points can be found in Appendix K.

A repeated-measures ANOVA with a Greenhouse-Geisser correction (following violation of the assumption of sphericity, $p < .01$) determined that there was a statistically significant decrease in mean transformed PCSS symptom severity scores over time for both groups overall from Week 1 to Week 4 [$F(2.33, 30.23) = 15.10, p < .001$]. However, between-group differences at all four time points were not found to be statistically significant [$F(1, 13) = .001, p = .97$]. Similarly, the group by time interaction was not found to be statistically significant for either the Exercise Group or the Usual Care Group, $F(2.33, 30.23) = 2.40, p = .10$.

The resolution in mean unadjusted symptom severity for both groups across the first month of recovery can be observed in Figure 5 below. Visual inspection of the data demonstrates that the decline in mean PCSS symptom severity over time was noticeably more pronounced in the Exercise Group compared to the Usual Care Group, particularly between Week 1 and Week 3, as well as Week 1 and Week 4. Specifically, the decline in mean symptom severity from Week 1 to Week 3 was $15.8 \pm 1.9$ points on the PCSS in the Exercise Group compared to $6.7 \pm 4.1$ points in
the Usual Care Group across this same time interval. Between Week 1 and Week 4, there was a
decrease of $18.8 \pm 4.9$ points in the Exercise Group, as opposed to $10.0 \pm 6.1$ in the Usual Care
Group. While these differences were not statistically significant, they do indicate that the
Exercise Group experienced a more rapid resolution of symptoms compared to the Usual Care
Group.

Figure 5. Mean symptom severity scores (as reported on the PCSS component of the SCAT3)
across the recovery timeline. Error Bars: +/- 1 Standard Error

4.3.3 Symptom Resolution Effect Size Calculation

To further explore the trend towards significance for the between-group effect in symptom
resolution from Week 1 to Week 3 and Week 1 to Week 4, a series of independent samples t-
tests were conducted on the change scores between groups to compare the decline in symptom
severity across these two time intervals using mean adjusted symptom severity scores. Results of these t-tests demonstrate that symptom severity was not significantly different between the two groups at any of the four time points of analysis. Results and descriptive statistics are listed in Table 3 below.

**Table 3.** Adjusted PCSS symptom severity scores (means and standard deviation) stratified by group randomization. T-test statistic and t-test significance were corrected for unequal variance with a significant Levene Test ($p < .05$).

<table>
<thead>
<tr>
<th>Time</th>
<th>Exercise Group</th>
<th>Usual Care Group</th>
<th>Levene’s Significance</th>
<th>T-Test Statistic</th>
<th>T-Test Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>1.33 ± 0.18</td>
<td>1.06 ± 0.45</td>
<td>0.06</td>
<td>1.53</td>
<td>0.15</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.96 ± 0.46</td>
<td>0.80 ± 0.61</td>
<td>0.39</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>Week 3</td>
<td>0.54 ± 0.57</td>
<td>0.76 ± 0.60</td>
<td>0.87</td>
<td>-0.73</td>
<td>0.48</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.43 ± 0.49</td>
<td>0.60 ± 0.57</td>
<td>0.99</td>
<td>-0.62</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Based on these results, an a-priori power analysis was run to determine the sample size needed for the follow-up study in order to observe a statistically significance effect for symptom resolution across these time intervals. G*Power Version 3.1.9.3 (Heinrich-Heine University, Dusseldorf, Germany) was used to determine this sample size from Week 1 to Week 3 using the following parameters: $M_1 = 0.79, M_2 = 0.31, SD_1 = .46, SD_2 = 0.44$; two-tailed independent samples t-test, alpha = .05, power = 0.80 (Exercise Group = 1, Usual Care Group = 2). Results from the effect size calculation indicated that the overall sample size required across this interval...
for future studies using this protocol is $n = 30$ (15 in each group), which is twice as many participants as there are in the present study.

The following parameters were used to determine the necessary sample size to observe a significant effect from Week 1 to Week 4: $M_1 = 0.90$, $M_2 = 0.47$, $SD_1 = .39$, $SD_2 = 0.39$; two-tailed independent samples t-test, alpha = .05, power = 0.80 (Exercise Group = 1, Usual Care Group = 2). Results indicated that the overall effect size across this interval for future studies using this protocol is $n = 28$ (14 in each group).

4.4 H3: Autonomic Dysregulation Across the Recovery Timeline

4.4.1 HRV: Descriptive Statistics and Normality

Table 4 below displays the means and standard deviations of all HRV outcome measures analyzed for both groups. Results from a series of Shapiro-Wilks tests of normality determined that mean RRI and HF Power were normally distributed across both time points and conditions, while SDNN and the LF/HF ratio consistently demonstrated abnormal distribution. Normalization of SDNN and the LF/HF ratio was achieved for both variables following log transformation. The transformed data was included in the general linear model for these particular variables. Results from the Shapiro-Wilks test, before and after data transformation, can be found in Appendix L.
### Table 4. Means and standard deviations of all HRV outcome measures analyzed, stratified by group randomization, time, and condition.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week</th>
<th>Position</th>
<th>Exercise Group (n = 8)</th>
<th>Usual Care Group (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RRI</td>
<td>1</td>
<td>Supine</td>
<td>918.6 ± 128.4</td>
<td>906.6 ± 59.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>780.7 ± 98.2</td>
<td>867.4 ± 86.1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>953.5 ± 154.2</td>
<td>902.2 ± 104.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>781.1 ± 128.3</td>
<td>787.8 ± 75.6</td>
</tr>
<tr>
<td>†SDNN</td>
<td>1</td>
<td>Supine</td>
<td>1.8 ± .16</td>
<td>1.9 ± .25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>1.8 ± .14</td>
<td>1.8 ± .12</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>1.9 ± .24</td>
<td>1.9 ± .20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>1.8 ± .28</td>
<td>1.9 ± .24</td>
</tr>
<tr>
<td>†LF/HF Ratio</td>
<td>1</td>
<td>Supine</td>
<td>.97 ± .10</td>
<td>.97 ± .16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>1.3 ± .18</td>
<td>1.1 ± .08</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>1.0 ± .13</td>
<td>1.0 ± .08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>1.2 ± .22</td>
<td>1.1 ± .07</td>
</tr>
<tr>
<td>LF Power (n.u.)</td>
<td>1</td>
<td>Supine</td>
<td>43.7 ± 15.9</td>
<td>44.8 ± 22.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>78.5 ± 18.3</td>
<td>64.9 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>47.9 ± 20.1</td>
<td>55.3 ± 14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>67.3 ± 22.4</td>
<td>71.8 ± 10.0</td>
</tr>
<tr>
<td>HF Power (n.u.)</td>
<td>1</td>
<td>Supine</td>
<td>56.1 ± 16.1</td>
<td>55.0 ± 22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>21.5 ± 18.4</td>
<td>35.0 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>52.0 ± 10.1</td>
<td>44.6 ± 14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>32.7 ± 22.3</td>
<td>71.8 ± 10.0</td>
</tr>
<tr>
<td>†Total Power</td>
<td>1</td>
<td>Supine</td>
<td>3.5 ± .35</td>
<td>3.8 ± .49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>3.5 ± .23</td>
<td>3.6 ± .27</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>3.7 ± .47</td>
<td>3.8 ± .42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>3.6 ± .47</td>
<td>3.8 ± .50</td>
</tr>
</tbody>
</table>

†Indicates that variable has undergone log transformation

#### 4.4.2 BPV: Descriptive Statistics and Normality

Table 5 below displays the means and standard deviation of all BPV outcome measures analyzed for both groups. Mean SBP and DBP, as well as systolic LF power, were determined to be normally distributed based on results of Shapiro-Wilks test and visual inspection of histograms. Conversely, the STD of mean SBP and DBP were not normally distributed; therefore, log
transformation was performed. Results of the Shapiro-Wilks tests, both before and after transformation, can be found in Appendix M.

Table 5. Means and standard deviations of all BPV outcome measures analyzed, stratified by group randomization, time, and condition.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week</th>
<th>Position</th>
<th>Exercise Group (n = 7)</th>
<th>Usual Care Group (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP</td>
<td>1</td>
<td>Supine</td>
<td>111.9 ± 24.2</td>
<td>105.3 ± 17.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>143.6 ± 11.3</td>
<td>136.8 ± 17.2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>115.4 ± 24.7</td>
<td>110.4 ± 16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>147.0 ± 12.0</td>
<td>141.3 ± 14.8</td>
</tr>
<tr>
<td>Mean DBP</td>
<td>1</td>
<td>Supine</td>
<td>70.7 ± 14.6</td>
<td>56.6 ± 9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>99.2 ± 9.1</td>
<td>82.1 ± 8.4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>65.4 ± 15.6</td>
<td>62.5 ± 14.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>94.3 ± 12.6</td>
<td>94.6 ± 14.6</td>
</tr>
<tr>
<td>†STD of SBP</td>
<td>1</td>
<td>Supine</td>
<td>.87 ± .19</td>
<td>.98 ± .21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>1.1 ± .46</td>
<td>.93 ± .23</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>.87 ± .16</td>
<td>.91 ± .28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>.99 ± .16</td>
<td>1.1 ± .30</td>
</tr>
<tr>
<td>†STD of DBP</td>
<td>1</td>
<td>Supine</td>
<td>.68 ± .15</td>
<td>.70 ± .16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>.82 ± .15</td>
<td>.64 ± .22</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>.70 ± .16</td>
<td>.63 ± .19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>.86 ± .22</td>
<td>.90 ± .30</td>
</tr>
<tr>
<td>LF Power</td>
<td>1</td>
<td>Supine</td>
<td>65.0 ± 11.9</td>
<td>66.8 ± 9.9</td>
</tr>
<tr>
<td>(systolic)</td>
<td></td>
<td>Seated</td>
<td>51.8 ± 23.7</td>
<td>52.9 ± 10.1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Supine</td>
<td>71.3 ± 7.70</td>
<td>68.7 ± 8.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated</td>
<td>54.1 ± 8.3</td>
<td>63.2 ± 16.0</td>
</tr>
</tbody>
</table>

†Indicates that variable has undergone log transformation

4.4.3 Results of Repeated-Measures ANOVAs

A summary of the ANOVA results detailing p-values for overall within- and between-group effects, overall condition effects, as well as group by time and group by condition interactions for all of the HRV and BPV measures analyzed, can be found in Table 6 below. Significance was set to an alpha level of $p < .05$, and variables were operationally defined as “trending” towards significance at threshold $p$-value $\leq .10$. 
**Table 6.** Significance (p-values) of overall effects and interactions from series of repeated-measures ANOVAs across all HRV and BPV outcome measures of interest.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within-Group Effect (Overall)</th>
<th>Between-Group Effect (Overall)</th>
<th>Condition Effect (Overall)</th>
<th>Time x Group Interaction</th>
<th>Condition x Group Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RRI</td>
<td>p = .70</td>
<td>p = .87</td>
<td>p &lt; .001**</td>
<td>p = .35</td>
<td>p = .02**</td>
</tr>
<tr>
<td>†SDNN</td>
<td>p = .18</td>
<td>p = .39</td>
<td>p = .13</td>
<td>p = .51</td>
<td>p = .95</td>
</tr>
<tr>
<td>‡LF/HF Ratio</td>
<td>p = .67</td>
<td>p = .43</td>
<td>p &lt; .001**</td>
<td>p = .16</td>
<td>p = .08*</td>
</tr>
<tr>
<td>LF Power</td>
<td>p = .48</td>
<td>p = .99</td>
<td>p &lt; .001**</td>
<td>p = .11</td>
<td>p = .30</td>
</tr>
<tr>
<td>HF Power</td>
<td>p = .49</td>
<td>p = .99</td>
<td>p &lt; .001**</td>
<td>p = .11</td>
<td>p = .31</td>
</tr>
<tr>
<td>‡Total Power</td>
<td>p = .10*</td>
<td>p = .30</td>
<td>p &lt; .001**</td>
<td>p = .93</td>
<td>p = .73</td>
</tr>
<tr>
<td><strong>BPV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP</td>
<td>p = .56</td>
<td>p = .40</td>
<td>p &lt; .001**</td>
<td>p = .93</td>
<td>p = .97</td>
</tr>
<tr>
<td>Mean DBP</td>
<td>p = .57</td>
<td>p = .11</td>
<td>p &lt; .001**</td>
<td>p = .07*</td>
<td>p = .98</td>
</tr>
<tr>
<td>‡STD of SBP</td>
<td>p = .82</td>
<td>p = .92</td>
<td>p &lt; .001**</td>
<td>p = .47</td>
<td>p = .25</td>
</tr>
<tr>
<td>‡STD of DBP</td>
<td>p = .11</td>
<td>p = .59</td>
<td>p = .01**</td>
<td>p = .37</td>
<td>p = .62</td>
</tr>
<tr>
<td>LF Power of SBP</td>
<td>p = .16</td>
<td>p = .53</td>
<td>p = .01**</td>
<td>p = .81</td>
<td>p = .49</td>
</tr>
</tbody>
</table>

**Indicates statistical significance (p < 0.05)
*Indicates a trend towards significance (p < 0.10)
†Indicates that variable has undergone log transformation

### 4.4.4 Within-Group Effects

Analyses did not reveal any statistically significant within- or between-group effects for any of the HRV or BPV variables examined. However, there was a trend towards significance identified for the overall within-group effect of adjusted total power ($p = .10$), indicating that both groups experienced an increase in overall total power over time from Week 1 to Week 4 (see Figure 6 below). Mean adjusted total power increased from $3.48 \pm 0.12$ ms$^2$ to $3.65 \pm 0.16$ ms$^2$ within the Exercise Group, while in the Usual Care Group, mean adjusted total power increased from $3.69 \pm 0.13$ ms$^2$ to $3.79 \pm 0.18$ ms$^2$. 
Figure 6. Within-Group trends in overall mean adjusted Total Power from Week 1 to Week 4 in the Exercise Group versus the Usual Care Group. Error Bars: +/- 1 Standard Error.

4.4.5 Group by Time Interaction

A group by time interaction trending towards significance was identified for mean DBP ($p = .07$). Figure 7 below demonstrates this trend, whereby the Usual Care Group experienced a marked and potentially meaningful increase in mean DBP of 12.50 mmHg from Week 1 to Week 4 in the seated position. Across the same time interval in the seated position, the Exercise Group experienced a noticeably smaller change in mean DBP in the opposite direction (a decrease of 4.85 mmHg). Independent t-test results revealed a significant difference in seated mean DBP between the two groups at Week 1 post-injury ($p = .01$) which was no longer observed by Week 4 post-injury ($p = .97$). This trend was not observed in the supine position.
Figure 7. Trend towards significance observed in the group by time interaction for mean DBP in the seated position from Week 1 to Week 4 post-injury ($p = .07$), Error Bars: +/- 1 Standard Error.

4.4.6 Group by Condition Interaction

See Table 6 for results of Group by Condition analyses. Results demonstrate that all but three (adjusted SDNN, adjusted total power, and mean adjusted STD of SBP) of the autonomic measures analyzed displayed a significant overall effect of condition as participants transitioned to an upright seated position following supine rest ($p \leq .01$). Interestingly, the ANOVA did reveal a significant group by condition interaction for mean RRI ($p = .02$), as well as a trend towards significance for the mean transformed LF/HF ratio ($p = .08$).

Figure 9 below displays the significant group by condition interaction observed for mean RRI at Week 1 as participants transitioned from the supine to seated position. There was a decline in mean RRI observed in both groups as participants upon sitting upright, although this decline was greater within the Exercise Group than the Usual Care Group (137.9 ms versus 39.2 ms, ...
By Week 4 post-injury, the interaction was no longer statistically significant, as the decline in mean RRI upon sitting upright experienced by the Usual Care Group more closely resembled that experienced by the Exercise Group at this time point (114.4 ms versus 171.4 ms, respectively).

Figure 8. The significant group by condition interaction observed at Week 1 for mean RRI as participants transitioned from the supine position to the seated position ($p = .02$), Error Bars: +/- 1 Standard Error.

A trend towards significance was observed in the group by condition interaction for the mean transformed LF/HF ratio at Week 1, which can be visualized in Figure 10 below. At this time point, both groups experienced an increase in the mean transformed LF/HF ratio as participants transitioned from the supine to seated position. However, the Exercise Group experienced a noticeably steeper increase in this variable upon transitioning upright compared to the Usual Care Group (0.33 ms$^2$ versus 0.13 ms$^2$, respectively). By Week 4 post-injury, the group by condition interaction was no longer trending towards significance, as the increase in the LF/HF ratio in the Usual Care Group upon transitioning into the upright seated position was noticeably more similar to that of the Exercise Group at this time point (0.10 ms$^2$ versus 0.20 ms$^2$,
respectively). The slopes of the increase in both groups were also noticeably more similar at Week 4 compared to Week 1.

**Figure 9.** Trend towards significance for the mean transformed LF/HF ratio for the group by condition observed at Week 1 as participants transitioned from the supine position to the seated position ($p = .08$). Error Bars: +/- 1 Standard Error.
Chapter 5  
Discussion  

5.1 Dissemination of Findings  
The purpose of this pilot study was two-fold: (1) to examine the feasibility of implementing a standardized, graded AE intervention in the post-acute stage of SRC recovery in the adolescent population with respect to safety and logistics, and (2) to determine the efficacy of a standardized, graded AE intervention administered in the post-acute stage of SRC for expediting overall time to medical clearance and improving measures of clinical and physiological recovery compared to usual care in adolescents. This study is the first randomized controlled trial to investigate the effect of a standardized, graded AE intervention on SRC recovery in adolescents within the post-acute stage of the injury compared to usual care.  

Evidence of feasibility will be discussed with respect to the Feasibility Criteria outlined in Section 3.3.1, including participant safety and recruitment/retention rates. Furthermore, estimation of treatment effect and its variance will be discussed in relation to the hypotheses stated in Section 3.3.2, including time to medical clearance, symptom severity across the recovery timeline, and measures of cardiac autonomic dysregulation (i.e. HRV and BPV) from Week 1 to Week 4 post-injury. Therefore, this discussion will focus on both the results of statistical analyses of these objective measures of recovery, as well as on the feasibility of this protocol with regards to its clinical potential on a larger scale with a statistically powered sample size.
5.2 Overall Evidence of Feasibility

Based on the criteria outlined in Section 3.3, it is reasonable to conclude that this pilot study demonstrated feasibility with respect to participant safety, as well as participant recruitment/retention rates. While statistical power cannot be expected with such a limited sample size, the lack of statistically significant differences between the Exercise Group and the Usual Care Group with respect to the variables of interest (including time to medical clearance, symptom resolution, and HRV/BPV) is meaningful from a safety perspective. Specifically, it provides evidence that the administration of a structured, graded AE intervention on a stationary cycle ergometer, initiated in the post-acute stage of SRC recovery, is not associated with any deleterious effects. Therefore, future studies can build upon these results by implementing this intervention with a statistically powered sample size to determine if it is associated with improved outcomes following SRC.

5.2.1 Safety of the AE Intervention

Evidence demonstrating the safety of the study’s AE intervention is provided in the mean pre- and post-exercise PCSS symptom severity scores reported by participants in the Exercise Group immediately before and 10 minutes after the administration of exercise (see Figure 4). Results indicate that none of the participants experienced symptom exacerbation during or after the administration of exercise. On the contrary, mean post-exercise PCSS symptom severity scores were actually slightly lower than pre-exercise levels for the majority of exercise sessions throughout the intervention (although this difference was not significant at any time point). This is a meaningful finding in light of previous literature involving animal models of mTBI which report that AE initiated prematurely in the recovery timeline is associated with negative outcomes39. Such findings in animals models have historically been one the reasons for
prescriptions of “rest” following concussion and likely have contributed to the lack studies exploring the effect of AE in the sub- and post-acute stages of concussion recovery in human subjects. However, results from the present study demonstrate that low-to-moderate AE initiated on Day 6 post-injury is not associated with symptom exacerbation in human patients with SRC, and may actually be associated with improvements in symptomatology.

5.2.2 Participant Recruitment/Retention Rates
Another domain in which this pilot study demonstrated success is that of participant retention. While the rate of recruitment was only 76% (only 16 out of 21 eligible patients consented to participate), the participant drop-out rate in this study was zero in both the Exercise and Usual Care Groups, which suggests that participants felt safe throughout the protocol and perceived that they were benefiting from the intervention. Regardless of the reasons for retention, the fact that participant retention was 100% supports the feasibility of this study on a larger scale, and suggests that the implementation of this protocol with a statistically powerful sample size is a worthwhile investment of resources.

5.3 Time to Medical Clearance
Contrary to the hypothesis stated in section 3.3, no differences in time to medical clearance between groups for either RTP or RTL were found. Interestingly, regression analysis did reveal a significant correlation between acute symptom severity (i.e. symptom severity on the PCSS at Day 5 post-injury) and time to medical clearance across both experimental groups. That is, individuals reporting a higher PCSS symptom severity score at this time point took significantly longer to obtain medical clearance to return to their pre-injury participation levels compared to those with a lesser symptom severity score at five days post-injury. This finding suggests that
acute symptom burden may be a meaningful predictor of time to medical clearance, regardless of group placement.

This finding is supported by a recent systematic review by Iverson et al. (2017), which reported that the severity of an individual’s acute and subacute symptoms is the most consistent predictor of slower recovery from concussion\textsuperscript{150}. A number of previous studies have also identified baseline and/or acute symptom burden as a powerful predictor of prolonged recovery within the adolescent SRC population. For example, a 2009 case-control study by Lau and colleagues involving 108 recently-concussed high school football players identified specific symptom clusters which demonstrated significant predictive value with respect to time to medical clearance. The categories found to be predictive of the duration of the RTP period included migraine, sleep, and cognitive symptoms\textsuperscript{151}. Similar results were reported in a prospective cohort study by McCrea et al. (2012) involving 570 high school and college student-athletes with SRC, which found a significant correlation between symptom severity within the first 24 hours of the concussion and prolonged recovery time (i.e. an RTP period lasting longer than seven days in duration)\textsuperscript{152}. Overall, these results illustrate the importance of considering additional factors that may influence time to medical clearance beyond the scope of the AE intervention.

### 5.4 Symptom Resolution

The repeated-measures ANOVA did not identify any significant within group differences in mean symptom severity scores at any of the four time points in either the Exercise or Usual Care Groups. Between-group differences in symptom severity across the four time points were also not found to be statistically significant. However, as Figure 5 shows, the Exercise Group does appear to have experienced a more rapid resolution of symptoms than the Usual Care Group, particularly between Week 1 and Week 3 post-injury (15.75 ± 2.08 points versus 6.85 ± 4.4
points, respectively). Furthermore, a priori effect size calculations show promise for future studies utilizing this protocol, as they demonstrated that in order for a significant between-group effect for symptom resolution to be observed from Week 1 to Week 3, there needs to be a total population of \( n = 30 \), which is only 15 more individuals greater than what was included in the present study. The a-priori effect size for the between-group difference in symptom severity from Week 1 to Week 4 was even more promising at \( n = 28 \) (14 in each group). Overall, these findings provide evidence in favour of implementing the standardized AE intervention in the post-acute phase of SRC recovery as opposed to usual care, as they suggest that the structured AE intervention may have a beneficial effect on SRC recovery with respect to the resolution of concussion-associated symptoms.

The clinical determination of recovery still largely relies on symptom status of the individual; therefore, the results are promising of a potential benefit associated with an AE intervention. However, the lack of significant group differences observed in symptom severity at the four time points of analysis in the present study may be related to data acquisition time points. It is possible changes in symptom resolution following SRC may have occurred more rapidly and earlier in the recovery timeline than could be observed using these limited time points of analysis.

Given the timeline of the neurometabolic cascade of mTBI\(^{153}\), which has been shown to be correlated with the presentation of subjective symptoms following SRC\(^{154}\), the implementation of more serial assessment points for the analysis of symptom resolution may be required in order to obtain a more accurate reflection of the underlying changes occurring at the neuropathophysiological level following injury, and how these changes are affected by the administration of structured AE as opposed to usual care.
A number of previous studies also reported a trend towards greater symptom resolution in concussion patients undergoing more active rehabilitation protocols as opposed to rest. For example, Thomas and colleagues (2015) utilized a randomized control trial design to examine the effect of five days of strict rest immediately following the concussion compared to usual care (i.e. 24-48 hours of strict rest followed by a stepwise return to activity), in a population of 11-22 year olds presenting to the pediatric emergency department within 24 hours of sustaining their injury. Fifty percent of participants in the strict rest group took approximately three days longer to achieve symptom resolution (defined as a PCSS symptom severity score of ≤7) compared to those in the usual care group. Furthermore, the strict rest group reported a significantly higher overall PCSS symptom score over the 10 day follow-up period, a greater number of total symptoms on the PCSS during the follow-up period, and a higher average daily PCSS score clustered around day 4 post-injury compared to those in the usual care group.

Collectively, these results support the author’s recommendation to administer the structured AE intervention in the post-acute stage of SRC recovery, as the findings demonstrate that activity during this period appears to be associated with significant improvements in symptom burden within the adolescent SRC population. However, it is recommended that future studies use more frequent time points for the collection of self-reported symptom metrics early on following SRC. Given the importance of symptom resolution as a predictor of clinical recovery from SRC, as well as the economic feasibility of collecting self-reported symptom data, utilizing more frequent time points of analysis in future studies may offer a deeper understanding into the trends in clinical recovery following SRC within this population in alignment with the underlying neuropathophysiology, and how these trends may be affected by the administration of the AE intervention compared to usual care.
5.5 Trends in Autonomic Dysregulation Following SRC

Results from the repeated-measures ANOVAs failed to reveal any significant effects, either for any of the HRV or BPV measures analyzed. However, the model did reveal a number of trends towards significance in a few of the variables examined, as well as some significant interaction effects. These results are generally suggestive that autonomic dysregulation may have worsened across the recovery timeline in the Usual Care Group, while the Exercise Group was able to more effectively modulate (i.e. “buffer”) this dysregulation over time through an attenuation of sympathetic modulation and/or a greater degree of parasympathetic influence.

The complex nature of both concussion and cardio-autonomic control has led to some ambiguity in our understanding of the dynamics of sympathetic versus parasympathetic influences on the ANS following this type of injury. For example, evidence of reduced HRV following mTBI has been reported by a number of studies, which is generally understood to be an indication of upregulation of sympathetic modulation following concussion\textsuperscript{18,69,155-157}. The interpretation of many of these findings have been challenged, however, as they were based on the LF/HF ratio (which is understood to reflect changes in sympathetic activation) and recent evidence suggests the LF component of HRV reflects baroreflex function rather than sympathetic influence over the heart\textsuperscript{158-161}. Despite this, evidence of disproportionately high SNS activity has been identified following concussion using parameters outside of HRV measures (and the LF/HF ratio in particular), such as a presence of postural tachycardia syndrome\textsuperscript{162,163} and arterial pulse contour analysis\textsuperscript{164}. Other studies indicate that SNS activation may actually be reduced in response to mTBI, through the investigation of the pupillary light reflex\textsuperscript{165}, CV functioning during upright standing\textsuperscript{166}, and tilt-table testing\textsuperscript{167}. Moreover, the diversity of study designs,
clinical populations, and sample sizes has further contributed to these contrasting interpretations of the trends in autonomic dysregulation following concussive injuries.

Vagal withdrawal has also been identified as a potential contributor to the trends in HRV responses observed following concussion. For example, La Fountaine et al. (2011) reported transient increases to the QT interval variability index following concussion, further supporting the hypothesis that concussion is associated with an impairment to vagal modulation\textsuperscript{168}. More recently, Abaji and colleagues (2015) noticed that the HF power bands were significantly lower in concussed collegiate athletes compared to healthy controls within the first week of injury, leading to a higher LF/HF ratio\textsuperscript{137}. Based on these findings, it may be possible that the trends towards significance for the group by time and group by condition interactions observed in the present study for the LF/HF ratio were related to a greater withdrawal of parasympathetic activation in the Usual Care Group over time compared to the Exercise Group.

5.5.1 Trend Towards Significance: Within-Group Effect of Total Power

Results showed a trend towards significance for the overall within-group effect of total power, whereby both groups displayed an increase in total power across the recovery timeline (see Figure 6). Total power, which is related SDNN, reflects all possible cyclical components responsible for variability in the recording period, encompassing all of the NN intervals ranging in frequency \( \leq 0.4 \text{ Hz} \) (including both LF and HF components)\textsuperscript{149}. Whether this indicates an increase in the SNS or PSNS activations levels is unclear. While HF power is generally well-established as an indicator of parasympathetic activation, the origin of LF power remains ambiguous, as it is suggested to be influenced by both sympathetic and parasympathetic factors\textsuperscript{169}. Therefore, it is difficult to ascertain how these trends in total power reflect changes to underlying cardio-autonomic physiology across the recovery timeline. The increased overall variability in the
system over time observed in both groups suggests that all participants experienced some degree of resolution of autonomic dysregulation following SRC, although it is difficult to determine whether this is attributable more to changes sympathetic or parasympathetic modulation over time, especially given that the ANOVA failed to demonstrate significance differences or trends towards significance for the individual contributions of either the LF or the HF components individually to total power.

5.5.2 Group by Time Interaction: Mean DBP

Across the recovery timeline from Week 1 to Week 4, the Exercise Group demonstrated a small but noticeable decline in seated mean DBP, whereas the Usual Care Group experienced a steep increase in mean seated DBP across this same time interval. This trend suggests the Usual Care Group may have experienced an increase in sympathetic activation compared to the Exercise Group in the upright seated posture. Possible biological mechanism of these results may include the release of catecholamines that acted to increase total peripheral resistance in the seated position, causing mean DBP to rise in this group compared to the Exercise Group\textsuperscript{170}.

The mean SBP and DBP values obtained in the present study, averaged across groups and time in the resting supine position (110.7 + 20.7 mmHg and 63.8 + 13.5 mmHg, respectively), were not significantly different than the most recently established normative values for the general adolescent population of 13-17 year olds (109.4 ± 0.34 mmHg and 63.5 ± 0.49 mmHg, respectively)\textsuperscript{171}. However, in the upright seated position, mean SBP and DBP values increased on average to 142.2+ 16.1 mmHg and 92.6 + 11.2 mmHg, respectively (averaged again across groups and time points, collectively). While BP is expected to increase in response to a physiological stressor such as the orthostatic challenge, the SBP and DBP values yielded in the present study seem elevated considering that the sample population was comprised of active,
adolescents who were generally healthy aside from their concussion. Furthermore, the values yielded in the present study seem abnormal even in comparison to other SRC populations. For example, Dobson and colleagues (2017) reported mean standing SBP and DBP values of approximately $132.3 \pm 13.4$ mmHg and $81.7 \pm 7.8$ mmHg, respectively, in a cohort of concussed university-aged athletes at one week post-injury$^{84}$.

It is possible the high values observed in the seated position in the present study may reflect an measurement error, possibly due to a lack of correction for the hydrostatic pressure by the finometer as participants assumed the upright position. Given the systolic and diastolic BP values appear to be relatively regular in the supine position based on established population norms, the abnormally high values yielded in the seated position may reflect the fact that the height correction unit for the finometer was not used, and therefore the system was unable to properly account for the change in the location of the heart in relation to the rest of the body, in particular the hand upon which the finger cuff was attached, as patients assumed the upright seated position. However, despite the potential inaccuracies of the mean seated SBP and DBP values due to measurement error, the pulse pressure observed in the present study in the seated position ($49.6 \pm 4.9$ mmHg) still remain in the normal range$^{171,172}$. This suggests that the relative values of SBP and DBP across positions and groups may still provide valuable information about trends in cardio-autonomic modulation in this population, and therefore the trend towards significance observed for the Usual Care group by time interaction of mean DBP warrants future investigation using a statistically powered sample size.

5.5.3 Group by Condition Interaction: Mean RRI

Further evidence in support of a potential buffering effect of autonomic dysregulation following SRC can be found in interaction effect of group and condition revealed by the ANOVAs for
mean RRI and mean transformed LF/HF ratio, which were found to be significant and trending towards significance, respectively. With respect to mean RRI, both groups demonstrated a decrease in this variable upon transitioning from the supine to seated position at Week 1, with the slope of this decline being significantly steeper in the Exercise Group compared to the Usual Care Group at this time point. This suggests that the Exercise Group may have experienced a greater degree of sympathetic activation compared to the Usual Care Group in response to the physiological stress associated induced by this transition. However, by Week 4 post-injury, the slope of the decline in mean RRI within the Usual Care Group upon sitting upright more closely resembled that of the Exercise Group (which was relatively consistent with what it was at Week 1), indicating that the Usual Care Group experienced an exacerbation, or worsening, of autonomic dysregulation over the course of the recovery timeline, whereas the Exercise Group was able to maintain a consistent level of autonomic activity.

5.5.4 Group by Condition Interaction: Mean Transformed LF/HF Ratio

A trend similar to found for mean RRI was observed for the mean transformed LF/HF ratio, which increased in both groups upon transitioning positions. At Week 1, the slope of the increase was noticeably greater for the Exercise Group compared to the Usual Care Group, which suggests that the Exercise Group experienced a greater degree of sympathovagal dysregulation at this time point. However, by Week 4, the Usual Care Group demonstrated a slope of increase that was similar to that of the Exercise Group, which maintained a similar rate of increase at this time point as was observed at Week 1. While this interaction did not achieve statistical significance (as was the case for the interaction observed for mean RRI), this trend towards significance does suggest that the Usual Care Group may have experienced a worsening of sympathovagal dysregulation over the course of the recovery timeline, while the Exercise Group
maintained consistent levels of dysregulation, providing further support of the buffering hypothesis of autonomic dysregulation following SRC.

5.5.5 Effect of Physical Deconditioning on Autonomic Dysregulation Following SRC

Physical activity, particularly AE, is a well-established cardio-protective agent thought to exert beneficial effects on the CV system via attenuations to SNS activation along with augmentations to PSNS influence\(^1\). Conversely, physical inactivity leading to deconditioning has been linked to a number of poor cardiovascular outcomes, which can be attributed in part to the ensuing autonomic imbalance resulting from it. Deconditioning has been associated with a reduction in total blood volume, requiring increased submaximal HR at the sinoatrial node through greater SNS activation and less PSNS activation in order to compensate for lowered stroke volume levels\(^2\). A possible mechanism for this trend in autonomic dysregulation reported consistently in the bed rest and space flight literature is an increase in norepinephrine concentration following deconditioning\(^3\). Altered autonomic balance is thought to be determined in part by the duration and intensity of the detraining period, and as little as 24 hours of bed rest has been associated with modifications to central neural responses to an orthostatic challenge\(^4\).

It is not entirely clear whether the trends in autonomic dysregulation observed in the present study, particularly within the Usual Care Group, are attributable to alterations of cerebrovascular control mechanisms following concussion or the possible effect of physical deconditioning. There is evidence to suggest that there are underlying mechanisms that may cause autonomic dysregulation beyond physical deconditioning. For example, in an cohort of adolescent patients with chronic symptoms of postural orthostatic tachycardia syndrome (or POTS, a condition associated with autonomic dysfunction) versus healthy controls, alterations in HR responses to
the orthostatic challenge observed in the POTS group were not found to be solely due to the
effect of deconditioning, as the proportion of deconditioned subjects was similar in this group as
it was in the control group\textsuperscript{179}. This suggest that underlying autonomic dysregulation in the
present study may not be fully explained by potential effects of deconditioning. The difficulty in
determining the underlying cause of possible autonomic dysregulation following SRC in the
present study is further complicated by the fact that physical activity performed outside of the lab
setting was not controlled for in either group, so it is not entirely clear if physical deconditioning
actually occurred, or the extent to which it did.

5.6 Limitations

One limitation of this study is the small sample size, which is a reflection of the nature of its
feasibility design. Power analyses estimated that an adequate sample size to observe a
significant effect for this protocol is $n = 40$, and the current study had a sample size of $n = 15$.
However, as mentioned previously, the principle aim of this study was to obtain preliminary
evidence on the practical and clinical feasibility of implementing this type of protocol on a larger
scale as part of Phase III clinical trial. Therefore, while the statistically underpowered sample
size does limit the ability to determine the scientific and clinical efficacy of this protocol with
respect to its effect based on objective measures of recovery, it is critical to note that this was not
the primary purpose of the study.

Another limitation of this study is the lack of generalizability of the sample population to the
adolescent population as a whole. As mentioned previously, the sample population included
male participants only. There are a number of sex-related variables that may affect the course of
recovery from SRC, and thereby may affect the efficacy of this intervention. Future research
must aim to recruit both male and female participants equally in order to fully understand the
efficacy of this type of protocol within the adolescent SRC population as a whole.

The external validity of this study was further limited by the fact that socioeconomic status
(SES) was not evenly distributed throughout the sample population. As mentioned previously,
80% (n=12) of the participants in this study came from private schools, while only 20% (n=13)
came from inner city public schools in the city of Toronto. This is significant, as the participants
coming from private schools generally had access to resources that aided them in the RTL/RTP
process, and participants who came from a public school background may not have received
access to these resources. For example, 10 participants included in the sample population came
from a private school which has a long-standing partnership with the MacIntosh Clinic, which
provides students with access to concussion-related resources included education, baseline
testing, individualized learning accommodations following SRC, and a comprehensive RTP/RTL
protocol for students and parents to follow. The participants included in this study coming from
public school backgrounds did not necessarily have access to these kind of resources. Therefore,
access to educational resources through school programming is an important consideration in this
type of research, and future studies must aim to recruit a sample population from a greater mix of
school types (public and private) with varying levels of concussion-related resources offered to
students.

The final limitation of this study is the variability with which the team of sport medicine
physicians at the MacIntosh Clinic assessed, treated, and cleared patients with SRC, particularly
with respect to the variability of exercise prescription that may have occurred for participants in
the usual care group in line with the general trend towards active rehabilitation. It is possible
that some physicians may have prescribed structured AE for participants in the usual care group
early on in the recovery timeline, which may have had an effect on the outcome measures of recovery that were observed. Furthermore, while the clinical decision to medically clear a patient is well-understood, that is, asymptomatic status following a graded exertional protocol, variability in individual physician practices still exist. This is an important limitation to consider when interpreting the results, and future research may want to consider limiting the number of physicians to ensure management consistency. Furthermore, future research should aim to assess inter-rater reliability of physicians with respect to their RTP/RTL decisions in order to obtain a more accurate understanding of the true efficacy of the AE intervention.

5.7 Future Directions/Recommendations

This study is the first of its kind to demonstrate that a standardized, graded AE intervention (low-to-moderate intensity) is safe to administer within adolescent SRC patients in the post-acute stage of recovery (i.e. beginning on Day 6 post-concussion). Despite the promise of this pilot study, there are a number of changes to the methodology and protocol that are recommended for future studies intending to implement this intervention and study design. These recommendations include changes to recruitment strategies, adjustments to the duration/intensity of the AE intervention, and efforts to control physical activity outside of the lab in an unsupervised setting.

5.7.1 Changes to the Recruitment Strategy

Future studies using this protocol should attempt to broaden recruitment with respect to both the volume and diversity of participants. Outreach efforts should be made to various community sport organizations, schools, and local emergency departments in order to obtain a larger and more diverse sample population that includes individuals from the various demographic backgrounds that were underrepresented in the current study, such as female participants and participants from a broader range of SES backgrounds. This would include targeting a wider
geographic radius that includes some of the less advantaged neighbourhoods of the greater Toronto Area. Furthermore, the inclusion criteria should be open to all adolescent-aged patients of SRC (i.e. ages 13-18), rather than simply individuals who are in high school, in order to obtain a larger sample size.

5.7.2 Modifications to the AE Intervention

The AE intervention implemented in the present study was conservatively designed, with the primary emphasis being placed on participant safety and the avoidance of exercise-induced symptom exacerbation. Participant feedback was that Sessions 1-3 were “too easy” in terms of intensity (ranging between 50-55% of the individual’s age-predicted maximal HR), and that it was actually more of a challenge for research assistants to maintain heart rate at such low levels. Furthermore, many of the participants reported performing more demanding physical activity outside of the lab setting than what they were doing in the intervention, sometimes at the instruction of their physician (who was blinded to the group placement of the individual). Given that none of the participants in the present study experienced symptom exacerbation associated with the exercise intervention at any point, it may be prudent to revisit the range of intensities of the intervention, particularly towards the start, in order to determine the most effective dose-response relationship.

The Macintosh Clinic RTP protocol suggests that during Stage 2, or the return to light aerobic activity, patients should aim to cycle at an intensity that brings their HR up to 120 beats per minute (bpm). This corresponds to approximately 60% of the individual’s age-predicted maximal HR. Given that 88% of the participants in the Exercise Group were cleared to begin Stage 2 within the first week of sustaining their concussion, it would make sense to begin the AE intervention at 120 bpm (i.e. 60% of the age-predicted maximal HR), as opposed to 50%, which
is what they would be doing outside of the lab setting as per physicians’ recommendation. Furthermore, the most recently published consensus statement from the Concussion in Sport Group’s 2016 meeting in Berlin stated that rest beyond the initial 48 hours of concussion is not recommended. Therefore, it is suggested that the structured AE intervention is amended in future to begin on Day 3 post-injury as opposed to Day 6 post-injury, which is when it was initiated in the present study.

The AE intervention used in the present study reaches its maximum intensity level at 70% of the individual’s age-predicted maximal HR. This was chosen as a conservative approach based on findings from the University of Buffalo concussion research group, which demonstrated that it is safe for patients with PCS to exercise up to 74% of their age-predicted maximal HR using the Buffalo Concussion Treadmill Test. Given that none of the participants in our study experienced symptom exacerbation resulting from any of the three exercise sessions at 70% of their age-predicted maximal HR, and also that the University of Buffalo group suggests that it is safe for concussion patients to exercise up to 74% of their maximal HR, we propose that there should be an additional two sessions to complete the intervention at 75% of the participants’ age-predicted maximal HR. This would bring the adjusted intervention to a total of eight sessions, and would provide evidence to determine if a slightly more aggressive AE intervention is associated with more favourable outcomes. The frequency of the exercise sessions will remain the same in the proposed intervention, with two days of consecutive exercise followed by one day of rest. The adjusted protocol can be found in Table 7 below.
Table 7. Proposed amendments to standardized AE protocol

<table>
<thead>
<tr>
<th>Days Post-Injury</th>
<th>Session</th>
<th>Intensity</th>
<th>Duration (minutes)</th>
<th>Symptom exacerbation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>60% age-predicted maximum HR</td>
<td>10</td>
<td>No → proceed to Session 2 on Day 4&lt;br&gt;Yes → repeat Session 1 on Day 4</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>60% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 3 on Day 6&lt;br&gt;Yes → repeat Session 2 on Day 6</td>
</tr>
<tr>
<td>5</td>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>65% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 4 on Day 7&lt;br&gt;Yes → repeat Session 3 on Day 7</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>70% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 5 on Day 9&lt;br&gt;Yes → repeat Session 4 on Day 9</td>
</tr>
<tr>
<td>8</td>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>70% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 6 on Day 10&lt;br&gt;Yes → repeat Session 5 on Day 10</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>70% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 7 on Day 12&lt;br&gt;Yes → repeat Session 6 on Day 12</td>
</tr>
<tr>
<td>11</td>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>75% age-predicted maximum HR</td>
<td>20</td>
<td>No → proceed to Session 8 on Day 13&lt;br&gt;Yes → repeat Session 7 on Day 13</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>75% age-predicted maximum HR</td>
<td>20</td>
<td>Complete</td>
</tr>
</tbody>
</table>

5.7.3 Controlling for Unsupervised Exercise Outside of the Laboratory Setting

Future studies using this protocol should make an attempt to control for activity performed outside of the laboratory setting in order to determine if unsupervised exercise acts as a confounding factor with respect to time to medical clearance. In order to do so, the authors of the
present study recommend using the 7-Day Activity Diary, which estimates total daily energy expenditure, activity-related energy expenditure, physical activity levels, and mental activity in one hour intervals throughout a seven day period. This diary has been clinically validated in an adolescent population as an accurate measure of physical activity levels and total energy expenditure. Commercially available wireless tracking devices containing pedometers, accelerometers, and HR sensors could also be utilized to quantify activity-related energy expenditure outside of the lab setting. One such device is the FitBit® (San Francisco, California, USA), which has been shown to be a clinically valid and reliable tool for objectively determining physical activity levels and energy expenditure in unsupervised conditions.

5.8 Conclusion

This study is the first attempt to utilize a randomized controlled trial design to investigate the effect of a standardized, graded AE intervention on SRC recovery in the post-acute stage of the injury. The study found that the standardized AE intervention (implemented beginning on Day 6 post-injury) was not associated with any harmful outcomes, such as worsening of symptoms and/or prolonged time to medical clearance. These results suggest that participants in the Exercise Group experienced a trend towards greater symptom resolution and restoration of autonomic dysregulation compared to those in the Usual Care Group. Overall, these are meaningful results that provide significant and promising evidence in support of the paradigm shift in the general concussion management strategy towards active rehabilitation, as opposed to the historically prescribed rest as treatment in the early stages of injury.

The protocol outlined in this study offers a foundational framework upon which to further explore the clinical utility of structured AE in the management of SRC in human subjects within the post-acute, and possibly even the acute stage of injury. Given the novelty of this protocol
and the feasibility nature of the present study, a conservative approach was taken in developing the timing and intensity of the structured AE intervention. Future studies building upon the protocol outlined in the present study should experiment with greater intensities of exercise at earlier stages in the recovery timeline from SRC in order to determine the optimal parameters for the administration of exercise in treating this type of injury. Furthermore, given the ease of assessing symptom resolution following SRC using the PCSS, symptom assessments should occur on a more frequent basis, especially in the first two-weeks after injury, in order to obtain a more precise understanding of symptom resolution in the adolescent population in the immediate stages following injury, particularly in association with the administration of exercise. Lastly, future studies building on this study should aim to include a more diverse sample population and monitor activity and compliance outside the research setting.
References


Mitka M. Reports of concussions from youth sports rise along with awareness of the problem. JAMA. October 27, 2010:1775-1776.


89. de Kruijk JR, Leffers P, Meershoff S, Rutten J, Twijnstra A. Effectiveness of bed rest


91


163. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic dysfunction presenting as


176. Engelke KA, Convertino VA. Catecholamine response to maximal exercise following 16


Appendices

Appendix A: Initial medical assessment form

Office Assessment of Acute Concussion – Initial Physician Form EMR V.1

00: Encounter Information

Patient Label

Date of Assessment: ____________________________

Other individuals present during assessment: ____________________________

Date of Injury: ____________________________

01: Past History

1. Have you ever in the past been diagnosed as having had a head injury, brain injury, or concussion? ☐ Yes ☐ No

<table>
<thead>
<tr>
<th>Injury #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date (month/day/year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident (e.g., sport, activity, fall etc.) associated with the injury?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you sustain loss of consciousness (i.e., ‘knocked out’)? If yes, please estimate duration</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
</tr>
<tr>
<td>Have you had any memory loss associated with the injury? (Circle yes/no)</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
<td>Yes/No/Unsure</td>
</tr>
<tr>
<td>Symptom duration (days):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time out of sport/activity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other details/notes of note:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* If more than four (4) concussions, note the number of previous diagnoses: ____________ **Complete additional details on back of this form**

2a. Have you ever been ‘dazed’ or had your ‘bell rung’ when it was not diagnosed as a concussion, head injury, or anything else? ☐ Yes ☐ No

2b. If yes, estimate the number of times this has occurred: ____________

3. Details of 2a and 2b (Physician will complete): ____________

4a. Have you ever had or been diagnosed as having any of the following medical conditions: ____________

- ADHD/HDD: ☐ Yes ☐ No
- Sleep disorder: ☐ Yes ☐ No
- Migraine: ☐ Yes ☐ No
- Headache: ☐ Yes ☐ No
- Schizophrenia: ☐ Yes ☐ No
- Depression: ☐ Yes ☐ No
- Encephalitis: ☐ Yes ☐ No
- Epilepsy: ☐ Yes ☐ No
- Panic disorder: ☐ Yes ☐ No
- Meningitis: ☐ Yes ☐ No
- Concussions: ☐ Yes ☐ No
- Phobia: ☐ Yes ☐ No
- Other: ____________

4b. If yes to any of the above medical conditions, please specify details:

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

5. Medications (i.e., antidepressants, anti-epileptics, migraine, psychostimulants, thyroid, etc.): ____________
**Supplemental Form**

*Please complete if suspected concussion occurred more than 3 days ago*

**Overall Trend of Symptoms since Suspected Concussion:**
- Steadily better
- No change
- Steadily worse
- Better, then worse
- Worse, then better
- Other [describe]

**Symptoms Peaked on Date:**

**Cognitive:** i.e. school or occupational workload, reading, writing etc.

**Physical:** i.e. activity level, attendance at school or occupation etc.

**Sensory:** i.e. use of computers, T.V.'s, phones, music etc.

Please rate your activity levels in the various domains since your injury:

<table>
<thead>
<tr>
<th></th>
<th>N/A</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Physical</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Sensory</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Overall Symptom Magnitude in Response to Stressors:

<table>
<thead>
<tr>
<th></th>
<th>none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
</tr>
</tbody>
</table>

Details of Stressors & Responses:

_____________________________________________________________________
|                                                                      |
|_____________________________________________________________________
|                                                                      |
|_____________________________________________________________________
|                                                                      |
|_____________________________________________________________________
|                                                                      |
|_____________________________________________________________________
|                                                                      |
|_____________________________________________________________________
|                                                                      |
05: Cognitive

Standardized Assessment of Concussion (SAC)

A. Orientation (1 pt. for each correct response)

- What month is it? 1
- What is the date today? 0
- What is the day of the week? 0
- What year is it? 0
- What time is it right now? (within 1 hour) 0

Orientation Score Total ______ of 5

B. Immediate Memory

List | Trial 1 | Trial 2 | Trial 3 | Alternative word list
--- | --- | --- | --- | ---
short | 1 | 0 | 1 | candle baby finger
bicycle | 1 | 0 | 0 | paper monkey penny
carpet | 0 | 1 | 0 | 1 sugar perfume basket
saddle | 0 | 1 | 0 | lemon sunset sandwich
bubble | 0 | 0 | 1 | wagon hot insect

Total Immediate memory score total ______ of 15

C. Concentration: Digits Backwards

<table>
<thead>
<tr>
<th>List</th>
<th>Trial 1</th>
<th>Alternative Digit list</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-9-3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3-8-1-6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6-2-3-7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7-1-4-6-2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Total ______ of 4

D. Concentration: Months in Reverse Order (1 pt. entire sequence correct)

Dec-Nov-Oct-Sep-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan ______ 0

Total Concentration Score ______ of 5

06: Physical Exam

Neck:
- Range of Motion: Normal
- Scapular: Normal
- Anterior Shoulder: Normal
- Upper Limb Coordination (Test Both)
- Coordination score: ______ of 1

Additional Comments:

07: Delayed SAC Recall

Delayed recall score ______ of 5

08: Cranial Nerve

- Not warranted

09: Balance

Modified Balance Error Scoring System (BESS) Testing

Condition
- Double leg stance: ______ errors
- Single leg stance (non-dominant foot): ______ errors
- Tandem stance (non-dominant foot at base): ______ errors

And / Or Tandem gait (5 steps)

Time (best of 4 trials): ______ seconds
### 10: Disposition/Treatment

#### How to complete form:

- **Symptom State:**
  - [ ] Asymptomatic
  - [ ] Symptomatic
  - [ ] < 2 weeks or greater

- **Example:**
  - Stage: 1, 2, 3, 4, 5
  - This means patient can progress from stage 1 to a maximum level of stage 4.

#### Plan:

<table>
<thead>
<tr>
<th>Stressors</th>
<th>Action</th>
<th>Stages</th>
<th>Medical Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
<td>1 2 3 4 5</td>
<td>Yes Date:</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td>1 2 3 4 5</td>
<td>Yes Date:</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td>1 2 3 4 5</td>
<td>Yes Date:</td>
</tr>
</tbody>
</table>

**Additional/Domain-Specific Notes:**

### 11: Recommended Management

#### Health Program

- **Therapist referral:** Neck pain or dysfunction, balance symptoms, maintain exercise progression.
- **NP referral:** Clearance to RTP, symptoms > 4 weeks, emotional overlay, multiple concussions, questions regarding long term risk and functioning.
- **Optometry referral:** Abnormal visual symptoms or signs (diplopia > 10 cm).

**Note:** Other health professionals may include a counseling psychologist, neurologist, etc.

<table>
<thead>
<tr>
<th>MD</th>
<th>Yes</th>
<th>When:</th>
<th>Who/Where:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>Yes</td>
<td>When:</td>
<td>Who/Where:</td>
</tr>
<tr>
<td>Therapist</td>
<td>Yes</td>
<td>When:</td>
<td>Who/Where:</td>
</tr>
<tr>
<td>Optometrist</td>
<td>Yes</td>
<td>When:</td>
<td>Who/Where:</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional Comments:**

**Summary For Follow-up:**

- SCAT 3 %
- SCAT 3 % Score

- # of Prior Concussions: ______ Predisposing Conditions: ____________________________
- Positive Exam findings (e.g., Neck pain, BESS) ____________________________
### Additional Injuries

<table>
<thead>
<tr>
<th>Injury #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date [month/day/year]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident (e.g. sport, activity, fall, etc.) associated with the injury?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you sustain loss of consciousness (i.e., &quot;knocked out&quot;)?</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
</tr>
<tr>
<td>If yes, please estimate duration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had any memory loss associated with the injury? (circle yes/no)</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
</tr>
<tr>
<td>Symptom duration [days]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time out of sport/ activity:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Other details/items of note:</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
02: Mechanism of Injury and Details

1. Where and how did the injury occur?

2. Sport or Physical Activity & Level of Competition:

3. Information Sources (witness, subjects, self, other-who?):

4. Loss of consciousness ("knocked out")?  ○ Yes  ○ No  Duration: __________
   Any memory loss associated with the event?  ○ Yes  ○ No  Duration: __________

5. When did you first notice symptoms after the concussion?

6. What symptoms did you notice then?

03: Initial Management

Date of injury: __________, Exposed time since injury: __________

At the time of the suspected concussion, were you:

1. Immediately removed from the sport or physical activity?  ○ Yes  ○ No
   a. If no, how long did you continue to participate? __________
   b. If no, reason(s) for continued participation?

2. Assessed for suspected concussion?  ○ Yes  ○ No, if yes, by whom?

04: Symptom Evaluation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Data (0-6)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Pressure in head&quot;</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck Pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Blurred Vision</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
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<td></td>
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<tr>
<td>Balance problems</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sensitivity to light</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity to noise</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Feeling Stewed Down</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling like &quot;in a fog&quot;</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
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</tbody>
</table>

Details of symptoms:

If headaches: "location of headache? duration? factors?"
If dizziness:  "head or room spinning? affected by position?"
If sleep troubles: "time to fall asleep? restless or vivid dreams? time to wake?"
<table>
<thead>
<tr>
<th>Injury #:</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date (month/day/year):</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you sustain loss of consciousness (i.e., “knocked out”)? If yes, please estimate duration</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
</tr>
<tr>
<td>Have you had any memory loss associated with the injury? (include: yes/no)</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
<td>Yes / No / Unsure</td>
</tr>
<tr>
<td>Symptom duration (days):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time out of sport/ activity:</td>
<td></td>
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<tr>
<td>Other details/items of note:</td>
<td></td>
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</tbody>
</table>
Appendix B: Permission to Contact Form

Participant Recruitment: Permission to Contact Form

Study Title: A Randomized Control Trial to Investigate Post-Acute Exercise Compared to Rest Following Sport Concussion

We are currently recruiting participants for an exciting new study that will investigate the use of aerobic exercise for treating concussions among high school aged athletes who have recently sustained a sports-related concussion. The results of this study have the potential to significantly improve the way this type of injury is managed, and your participation in this study will likely result in better care for all athletes in the future. It will also provide you with an exciting opportunity to learn more about concussion and the various assessment measures associated with it.

You are receiving this form because you meet the criteria to be a participant in this study. By signing this form, you are consenting to be contacted by a member of the research team by phone or email within the next 24 hours. This individual will provide you with more information about the study and what it will entail. Please note that by signing this form, you are not consenting to participate in the study. Furthermore, your decision to participate in this study will have no effect on the medical care you receive at the David L. MacIntosh Clinic, nor will it affect your academic and/or athletic career in any way.

Name (PRINT NAME): __________________________________________________________

A) I hereby consent to be contacted by a member of the research team by phone or email to learn more about this study. Please note that participants under the age of 16 must have their parent or guardian sign on their behalf.

Signature: ___________________________ Date: ______________

Phone number to be reached at: ________________________________

B) I **do not consent** to be contacted by a member of the research team by phone or email to learn more about the study at this time. Please note that participants under the age of 16 must have their parent or guardian sign on their behalf.

Signature: ___________________________   Date: ________________
Appendix C: Primary Informed Consent

ETHICS REVIEW INFORMATION SHEET/CONSENT FORM

Title of research project: Post-acute structured exercise following sport concussion: a randomized controlled study.

Investigators:
Michael Hutchison, PhD. (Principal Investigator)
Faculty of Kinesiology and Physical Education
University of Toronto
Rachel Micay, BKin., University of Toronto
Scot Thomas, Ph.D., University of Toronto
Doug Richards, M.D., University of Toronto

Background & Purpose of Research:

A number of physical, cognitive, somatic, and emotional symptoms commonly occur following sports-related concussion (SRC). The current return to play (RTP) protocol advises complete physical and cognitive rest following SRC until patients are completely free of these symptoms (i.e. asymptomatic) in order to avoid making symptoms worse and further injury. While this initial, post-injury rest period is generally assumed to be beneficial, there is currently no scientific evidence supporting this recommendation. In fact, a growing body of evidence suggests that prolonged rest may actually hinder the recovery process.

Emerging research is beginning to show that light-to-moderate aerobic exercise (AE) actually provides a positive benefit on the injured brain, thereby helping the recovery process. Research has shown this benefit from other injuries such as stroke, whiplash, low back pain, and even traumatic brain injury. In fact, a standardized aerobic exercise protocol has been shown to improve recovery for individuals with concussion symptoms for an extended period of time, a
disorder known as Post-Concussion Syndrome. However, the utility of this type of intervention remains largely unexplored in the early stages of concussion recovery.

Therefore, the purpose of this study is to determine if a standardized, graded AE protocol introduced in the post-acute stage of recovery from SRC will reduce the time to medical clearance, as well as improved concussion recovery, compared to the current RTP protocol of rest. The findings of this study will provide an important understanding of how to manage future SRC in the post acute phase of recovery.

Eligibility:

To participate in this study you must be a high school student (grades 9-12) and a patient of the David L. MacIntosh Sport Medicine Clinic with a medically diagnosed sport concussion.

Procedures:

Based on your symptom status at your first visit with physicians at the clinic, you will be placed in one of two groups: the Symptomatic Group or the Asymptomatic Group. If you are assigned to the Asymptomatic Group, you will be guided through the clinic’s current standard of care through a six-stage RTP protocol until you are cleared to return to play. You will be assessed on various measures including heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers at days 7, 14, 21, and 28, and your time to medical clearance will also be recorded.

If you are assigned to the symptomatic group, you will be randomly assigned to either the Rest Group or the Exercise Group. If you are assigned to the Exercise Group, you will undergo a standardized, graded aerobic exercise protocol consisting of eight sessions that will occur over the course of 11 days, beginning on the Day 6 following your concussion. You will continue to progress through the exercise program until completion. Should your symptoms resolve prior to completion of the program, you will continue to progress through it while concurrently being guided through the clinic’s RTP protocol, beginning at stage 2 of 6. You will be assessed on various measures including heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers at days 7, 14, 21, and 28, and your time to medical clearance will also be recorded.
If you are assigned to the **Rest Group**, you will continue to rest and refrain from participating in physical activity of any kind until your symptoms completely resolve. Once this occurs, you will be guided through the clinic’s existing six-stage RTP protocol until you are medically cleared to return to play. You will be assessed on various measures including heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers at days 7, 14, 21, and 28, and your time to medical clearance will also be recorded.

The days to medical clearance, as well as measures of heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers will be compared between the rest and exercise groups in order to determine whether a controlled AE program leads to a shorter overall time to medical clearance and improved physiological measures of recovery compared to the existing guidelines of rest.

**Standardized AE Protocol:**

The proposed AE protocol will consist of eight sessions that proceed in a stepwise fashion with respect to both duration and intensity over the course of 11 days. All exercise sessions will be supervised by a member of the research team, and will begin with a five-minute warm-up period and conclude with a five-minute cool-down period. All exercise will be performed on the Velotron Pro stationary cycle ergometer (RacerMate Inc., WA, USA), which will ensure that the participant’s head and neck remain stable throughout the protocol, thereby minimizing risk of symptom exacerbation and/or re-injury. This stationary bicycle has the capability to be digitally connected to a heart rate monitor, which will be programmed to monitor the wattage of the bike based on the participant’s heart rate (HR). Heart rate data will be collected via the Polar RS800CX watch and chest strap (RS800cx; Polar Electro, Kemple, Finland). This device will be connected to the participant using an adjustable strap and secured on top of the rip cage, allowing the researchers to monitor individual heart rate in real time throughout each testing session. This will ensure that participant maintains a safe level of exercise intensity throughout each session.

The first session of the protocol will take place on Day 6 post-injury. The duration of this session will be comprised of 10 minutes of steady-state exercise at 50% of the participant’s age-predicted maximal HR, plus the five-minute warm-up and cool-down periods (total time of 20 minutes). The next level consists of 20 minutes of steady-state exercise, plus the warm-up and
cool-down periods, at the previous intensity level of 50% of their maximum age-predicted HR (total time of 30 minutes). The patient will continue to progress through the exercise protocol, maintaining the same duration of exercise, including the warm-up and cool-down periods (total time of 30 minutes), while increasing exercise intensity by 5% of their age-predicted maximal HR per session until they achieve 70% of their age-predicted maximal HR. This intensity will be maintained for the final two sessions.

HR and Blood Pressure (BP) will be recorded before and after each exercise session. Symptoms will also be recorded using the Post-Concussion Symptom Scale (PCSS) from the SCAT3 before and after each exercise session, and they will also be continuously monitored throughout the exercise session by the supervising researcher. Should your symptoms become exacerbated at any point during or after the exercise session, the session will be terminated, and you will resume this same duration and intensity of exercise at the subsequent session. Should your symptoms become exacerbated again at the subsequent session, their participation in the study will be terminated. Exercise sessions will take place on two consecutive days, followed by one day of rest, for a total of eleven days.

**Assessment Battery**

All participants will be guided through a battery of assessment measures lasting approximately 45 minutes in duration on days 7, 14, 21, and 28 post-concussion. This battery includes a symptom assessment, heart rate variability and blood pressure variability assessments, peripheral blood serum samples, as well as a balance, reaction time, and processing speed assessment. Additionally, all participants will have a follow-up appointment with a sport-medicine physician at the MacIntosh Clinic on these same days in order to gauge their progress in the course of recovery.

**Symptoms:**

Concussion-related symptoms will be assessed using the Post-Concussion Symptom Scale (PCSS) of the SCAT3.

**Heart Rate Variability (HRV):**
HRV is an objective measure of autonomic nervous system (ANS) functioning that is reflective of an individual’s ability to respond and adapt to various demands and stressors (such as exercise). It is calculated by measuring the time intervals between an individual’s heartbeats. This will be measured using a Polar heart rate V800 sports watch and corresponding wireless heart rate monitor chest strap, which is a non-invasive tool that poses no risk to you as a participant. HRV will be assessed for approximately 15 minutes.

**Blood Pressure Variability (BPV) Assessment:**

BPV is an objective measure of autonomic nervous system (ANS) functioning that is reflective of an individual’s ability to keep their blood pressure regular in the face of various demands and stressors. BPV will be measured using the Finapres MIDI figure cuff device (Finapres Medical Systems, Amsterdam, Netherlands). This is a non-invasive tool that poses no risk to you as a participant. BPV will be assessed for approximately 15 minutes, and will measured at the same time as HRV.

**Blood Serum Sample:**

A physician or research staff member with venipuncture (blood-drawing) training will collect a small amount of blood (approximately 40 mL) using a needle and vacutainer tubes. This process normally takes approximately 5 minutes.

**Balance, Reaction Time, and Processing Speed Assessment:**

Using an iPad-based assessment tool, participants will complete a series of tests designed to measure reaction time, information processing speed, visual acuity, and postural stability. To assess postural stability, participants will perform two conditions with the iPad secured to the lower back: 1) standing with feet together, eyes open and 2) standing with feet together, eyes closed. In both cases, participants will be asked to maintain the stance for 30 seconds. The entire process takes approximately 15 minutes to complete.

**Voluntary Participation & Early Withdrawal:**

Your participation in this study is voluntary and you may withdraw from this study at any time by notifying the investigator. Your withdrawal from this study or your refusal to participate in
no way affects your care or access to medical services and in no way will affect your academic
and/or athletic career.

**Risks/Benefits:**

**Benefits:**

Participation in this study will provide you with an opportunity to be closely monitored by highly
trained individuals throughout recovery and opportunity to learn more about concussion and the
various assessment measures associated with it. It will also give you the opportunity to be seen
by a sport-medicine physician every week for four weeks following your initial injury, which is
more far medical attention than a concussion patient would receive under normal circumstances.
This study will also likely inform future care for individuals who sustain a concussion, as a result
of better knowledge from research. Finally, participants in the **Exercise Group** will receive
access to exercise equipment and supervision that they otherwise would not be able to make use
of.

**Risks:**

Participants in the exercise group may experience an increase in their symptoms due to physical
exertion. Should symptoms increase during a session, the session will be terminated
immediately. If a participant in the exercise group experiences an increase in their symptoms
over the course of two consecutive sessions, then their participation in this study will be
terminated. In order to ensure the safety of all participants, there will be an on-call physician at
all times available at the David L. McIntosh Sports Medicine Clinic, which is located directly
next to the lab space in which the exercise sessions will take place.

Participants in the Exercise Group may also experience symptom exacerbation later in the day
following the exercise intervention, even after they have left the testing facility. In order to
minimize this risk, participants will be kept at the facility for an additional 10 minutes following
the completion of the entire exercise session (including the 5 minute cool-down period) in order
for the supervising researcher to monitor their symptoms and ensure that they their HR and BP
have returned to what they were prior to the initiation of the exercise session. Additionally,
participants in this group will be provided with the contact information for the David L.
MacIntosh Clinic, where a sports-medicine physician will be available on-call at all times should the participant require urgent care after they have left the facility.

There may be minor and temporary discomfort associated with the blood-drawing procedure. This may include soreness or bruising of the skin in area of the blood-draw. This should resolve within a few days after the blood draw. Risks of experiencing infection or irritation of the skin surrounding the site of the blood acquisition will be minimal due to the training of the phlebotomist on site.

There is also a chance that you may become upset or frustrated if you lack progress in your perceived recovery time. In order to mitigate the mental health related risks that may be associated with participation in this study, you will be given access to mental health treatment through referrals by your attending physician at the MacIntosh Clinic, should you need it. There are also additional mental health resources in the area that you can access at the following location:

Centre for Addiction and Mental Health (CAMH)
33 Russell Street
Toronto, ON
M5S 2S1

Privacy & Confidentiality:

Your medical files in the MacIntosh Clinic at the University of Toronto are kept private and confidential in keeping with the laws of Ontario (the Medicine Act, and the Regulated Health Professions Act). They will be used by health professionals at the MacIntosh Clinic in the normal ways for your clinical care, whether you consent to participate in this study or not. Your medical data will not be released to the investigators in this study for research purposes unless you consent to participate in this study. If you consent, the relevant medical records only (those pertaining to concussion or other minor injury used as a control case in this study) will be made anonymous by stripping your name and all other identifying features from them and replacing them with a subject code that will be kept confidential. Please note that a member of the University of Toronto Research Ethics Board (REB) may be given access to your data for quality assurance purposes.
Please note that confidentiality can only be guaranteed to the extent permitted by law.

**What are the costs of participating in this study?**

Participating in this study may result in costs to you for parking and transportation. You will be compensated $10 for each exercise and $20 for each assessment session at the David L. MacIntosh Clinic to cover these expenses.

**Publication of Research Findings:**

Following the conclusion of this study the results may be published. No information that could reveal you as a participant will be disclosed in any publication.

**New Findings:**

If anything comes to light during the course of this research, which may influence your decision to continue, you will be notified.

**Rights of Subjects:**

You waive no legal rights by participating in this trial. If you have any questions regarding your rights as a participant you may contact:

Office of Research Ethics, Health Sciences  
2nd Floor, McMurrich Building  
12 Queen's Park Cres W  
Toronto, Ontario, M5S 1S8  
Tel: 416-946-3273

**Dissemination of Findings:**

The results of this study will be presented or published in collective form. Your personal information will not be used and as such, any published results cannot identify you as an individual. As a research participant you have the right to request a copy of the final report of the findings of this research study.
Study Title: Post-acute structured exercise following sport concussion: a randomized controlled study

By signing this form, I agree that:

- The study has been explained to me.            Yes  No
- All of my questions were answered.             Yes  No
- The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me. Yes  No
- I understand that I have the right not to participate and the right to stop at any time. Yes  No
- I understand that I may refuse to participate without any problems. Yes  No
- I have a choice of not answering any specific questions. Yes  No
- I am free now, and in the future, to ask any questions about the study. Yes  No
- I understand that there is a risk that my symptoms will be exacerbated by exercise. If this happens, I am aware of the steps the researchers will take to ensure I remain safe and that my symptoms do not worsen. Yes  No
- I have been told that my personal records will be kept confidential. Yes  No
- I understand that I will receive a copy of this consent form. Yes  No
- I agree that my data may be used for future analysis in other research projects not specific to this particular study. Yes  No
- I understand that a member of the University of Toronto’s Research Ethics Board may access my data for quality assurance purposes. Yes  No

Name (PRINT NAME): ____________________________________________
C) I hereby \textbf{consent} to participate in the study. Please note that participants under the age of 16 must have their parent or guardian sign on their behalf.

Signature: _______________________________ Date: ________________

D) I \textbf{do not consent} to participate in the study at this time. However, during the season, if I sustain a concussion, I give my permission for the sport medicine personnel at the University of Toronto to report the injury to one of the investigators of the research team and contact me then to ask if I would like to participate in the research and post-injury testing at that time.

Signature: _______________________________ Date: ________________

I, the undersigned, have fully explained the study to the above participant.

Investigator/Designate Name: ________________________________

Investigator/Designate Signature: _______________________________ Date: ________________

\textbf{Study Contact:}

If you have any questions about this study now or in the future, or in the case of a study-related injury please call Dr. Michael Hutchison at (416) ___-___
Appendix D: Child Assent Form (Under 16 years of Age)

ETHICS REVIEW INFORMATION SHEET:

CHILDREN’S ASSENT (CONSENT FORM FOR PARTICIPANTS UNDER 16 YEARS OF AGE)

Title of research project: Post-acute structured exercise following sport concussion: a randomized controlled study.

Investigators:
Michael Hutchison, Ph.D. (Principal Investigator), Faculty of Kinesiology and Physical Education, University of Toronto
Rachel Micay, B.Kin
Scott Thomas, Ph.D.
Doug Richards, M.D., Dip. Sport Med.

Background & Purpose of Research:

Concussions are linked with a number of signs and symptoms. Medical guidelines advise concussion patients to rest until these symptoms disappear in order to avoid making these symptoms worse and prolonging recovery time. While this rest period is thought to be useful, there is little evidence backing this up. In fact, recent research suggests that too much rest may actually do more harm than good following concussion.

Emerging research suggests that aerobic exercise (AE) has a positive effect on the injured brain. However, the benefits of AE on concussion recovery are still unknown. The purpose of this
study is to understand the effect of AE on concussion recovery within the early phases of injury. Specifically, we want to know if an AE program will allow athletes with concussion to return to sport faster than rest.

**Eligibility:**

To participate in this study you must be a high school student in grades 9-12. You must also be a patient of the David L. MacIntosh Sport Medicine Clinic with a medically diagnosed sport concussion.

**Procedures:**

Within 5 days of your concussion, you will be seen by a doctor at the MacIntosh Clinic. At this time, you will be asked to complete the Post-Concussion Symptom Scale (PCSS). Based on your score on this scale, you will be placed in one of two groups: the Symptomatic Group or the Asymptomatic Group. If you are placed in the Asymptomatic Group, you will be guided through the clinic’s six-stage return-to-play (RTP) protocol until you are cleared to return to play (RTP). On days 7, 14, 21, and 28 post-injury, you will be tested on different measures of concussion recovery. Your time to medical clearance (i.e. RTP) will be measured.

If you are assigned to the symptomatic group, you will be randomly assigned to either the Rest Group or the Exercise Group. If you are placed in the Exercise Group, you will be guided through a standardized AE program. This will consist of 8 sessions over 11 days, starting on the Day 6 after your concussion. You will continue through this exercise program until completion. After this, you will be guided through the clinic’s existing RTP protocol. On days 7, 14, 21, and 28 post-injury, you will be tested on different measures of concussion recovery. Your time to medical clearance will be measured.

If you are assigned to the Rest Group, you will continue to rest and avoid physical activity of any kind until your symptoms completely resolve. Once this occurs, you will be guided through the clinic’s existing six-stage RTP protocol until you are medically cleared to RTP. On days 7, 14, 21, and 28 post-injury, you will be tested on different measures of concussion recovery. Your time to medical clearance will be recorded.
Time to medical clearance (in days), as well as the other measures of concussion recovery, will be compared between the Rest Group and the Exercise Group. This will help us determine if a controlled AE program leads to a faster RTP compared to rest.

**Exercise Protocol:**

The AE program will consist of 8 supervised sessions. Each exercise session will be more difficult than the last one. Exercise sessions will take place for 2 days straight, followed by 1 day of rest, for a total of 11 days. Each session will begin with a 5 minute warm-up period and end with a 5 minute cool-down period. All exercise will be performed on the Velotron Pro stationary bicycle (RacerMate Inc., WA, USA). This will ensure that your head and neck will not move around during exercise, which will minimize the chance that your symptoms will become worse after the session. This bicycle will be connected to a digital heart rate monitor, which will be programmed to monitor the wattage of the bike based on your heart rate. Heart rate data will be collected via the Polar RS800CX watch and chest strap (Polar Electro, Kemple, Finland). This device will be connected to you using an adjustable strap and secured on top of your rip cage. This will ensure that you exercise at a safe intensity level throughout the session.

The first session of the program will take place on Day 6 post-injury. This session will include 10 minutes of exercise at 50% of your age-predicted maximal heart rate (HR), plus the 5 minute warm-up and cool-down periods. The session will be 20 minutes in total. The next session will consist of 20 minutes of exercise, plus the warm-up and cool-down periods, at the same intensity level as the last session. The exercise session will be 30 minutes in total. The duration of exercise for the remainder of the protocol will 30 minutes in total, while exercise intensity will increase by 5% of your age-predicted maximum HR per session. Exercise intensity will be capped at 70% of your age-predicted maximal HR. This intensity will be maintained for the final two sessions.

Heart rate, blood pressure, and symptoms will be tested before each exercise session. These measures will be taken again after each session to make sure that you have safely returned to your pre-exercise state. Additionally, your symptoms will be checked throughout the exercise session by the supervising researcher to make sure they are not worsening with exercise. Should your symptoms worsen at any point during the exercise, the session will be stopped. At the next exercise session, you will attempt the same duration and intensity of exercise as the last one.
Should your symptoms worsen again over the course of two back-to-back sessions, your participation in the exercise portion of the study will be finished. However, you will still remain in the study and continue with the tests on days 7, 14, 21, and 28 post-injury.

**Assessments:**

You will be guided through a series of assessments, which will take around 45 minutes to complete. These assessments will be repeated on days 7, 14, 21, and 28 after your concussion. On these days, you will also have a follow-up appointment with one of the doctors at the MacIntosh Clinic. The doctor will examine your progress in the course of recovery and determine if you are ready to RTP.

**Symptoms:**

Concussion-related symptoms will be assessed using the Post-Concussion Symptom Scale (PCSS) of the Sideline Concussion Assessment Tool, Version 3 (SCAT3).

**Heart Rate Variability (HRV) Assessment:**

HRV is a measure of one’s ability to maintain a constant heart rate in response to various demands and stressors, such as exercise. It is calculated by measuring the time intervals between heartbeats. This will be measured using a Polar heart rate V800 sports watch and corresponding chest strap. This is a non-invasive tool that poses no risk to you as a participant. This test will take approximately 15 minutes.

**Blood Pressure Variability (BPV) Assessment:**

BPV measures one’s ability to maintain their blood pressure within a normal range in the face of various demands on the body. BPV will be measured on days 7, 14, 21, and 28 post-injury using the Finapres device (Finapres Medical Systems, Amsterdam, Netherlands). This is a non-invasive tool that poses no risk to you as a participant. This test will take approximately 15 minutes, and will measured at the same time as HRV.

**Blood Serum Sample:**
A physician or research staff member with venipuncture (blood-drawing) training will collect a small amount of blood (approximately 40 mL) using a needle and vacutainer tubes. This process normally takes approximately 5 minutes.

**Balance, Reaction Time, and Processing Speed Assessment:**

Using an iPad-based assessment tool, you will complete a series of tests designed to measure reaction time, information processing speed, visual acuity, and postural stability. The entire process takes approximately 15 minutes to complete.

**Voluntary Participation & Early Withdrawal:**

Your participation in this study is voluntary. You may withdraw from this study at any time by notifying the investigator. Your withdrawal from this study or your refusal to participate will not affect your care or access to medical services. It will in no way affect your academic and/or athletic career.

**Risks/Benefits:**

**Benefits:**

Participation in this study will give you the benefit of being closely monitored by highly trained individuals as you recover from your concussion. It will also give you an opportunity to learn more about concussions and how they are assessed. You will also see a sport-medicine doctor every week for four weeks following your concussion. This is more far medical attention than a concussion patient would receive under normal circumstances. This study will also likely inform future care for concussion patients, as a result of better knowledge from research. Finally, participants in the Exercise Group will receive access to exercise equipment and supervision that they otherwise would not be able to make use of.

**Risks:**

Participants in the Exercise Group may experience an increase in their symptoms due to physical exertion. Should symptoms worsen during a session, the session will be stopped immediately. If symptoms worsen over the course of two back-to-back sessions, that participant will be removed
from the exercise portion of the study. In order to ensure the safety of all participants, there will be an on-call physician at all times available at the MacIntosh Clinic. This clinic is conveniently located directly next to the lab space in which the exercise sessions will take place.

Participants may also find that their symptoms worsen after exercise, even after they have left the facility. To minimize this risk, participants will stay at the facility for an additional 10 minutes after the exercise session. The supervising researcher will then monitor their symptoms and ensure that their HR and BP have returned to pre-exercise levels. Participants will also be given contact information for the MacIntosh Clinic, where a doctor will be available on-call at all times should they need urgent care after leaving the facility.

There may be minor and temporary discomfort from the blood-drawing procedure. This may include soreness/bruising of the skin around the area of the blood-draw. This should resolve within a few days. Risks of infection or irritation of the skin after the blood-draw will be minimal.

There is also a chance that you may become upset or frustrated you are not progressing as quickly as you thought you might. Your physician at the MacIntosh Clinic will monitor you for possible mental health symptoms that may arise from a lack of perceived progress in your recovery. There are also local mental health resources you can access at the following location:

Centre for Addiction and Mental Health (CAMH)
33 Russell Street
Toronto, ON
M5S 2S1

Privacy & Confidentiality:

Your medical files in the MacIntosh Clinic at the University of Toronto are kept confidential in keeping with the laws of Ontario (the Medicine Act, and the Regulated Health Professions Act). They will be used by health care professionals at the MacIntosh Clinic in the normal ways for your clinical care, whether you consent to participate in this study or not. Your medical data will not be released to the investigators in this study for research purposes unless you consent to participate in this study. If you consent, the relevant medical records only (those pertaining to your concussion) will be made anonymous by stripping your name and all other identifying
features from them. This information will be replaced with a subject code that will be kept confidential. Please note that your data can be accessed to a member of the University of Toronto’s Research Ethics Board (REB) for quality assurance purposes.

Please note that confidentiality can only be guaranteed to the extent permitted by law.

**What are the costs of participating in this study?**

You will be compensated $10 for each exercise and $20 for each assessment session completed for this study.

**Publication of Research Findings:**

Following the conclusion of this study the results may be published. No information that could reveal you as a participant will be disclosed in any publication.

**New Findings:**

If anything comes to light during the course of this research, which may influence your decision to continue, you will be notified.

**Rights of Subjects:**

You waive no legal rights by participating in this trial. If you have any questions regarding your rights as a participant you may contact:

Office of Research Ethics, Health Sciences
2nd Floor, McMurrich Building
12 Queen's Park Cres W
Toronto, Ontario, M5S 1S8
Tel: 416-946-3273

**Dissemination of Findings:**

The results of this study will be presented or published. Your personal information will not be used. Any published results cannot identify you as an individual. As a research participant you have the right to request a copy of the final report of the findings of this research study.
Study Title: Post-acute structured exercise following sport concussion: a randomized controlled study

I hereby consent to participate in this study.

NAME OF CHILD PARTICIPANT:

________________________________________________

______________________________

Signature

Date

I, the undersigned, have fully explained the study to the above participant.

Investigator/Designate Name:

____________________________________________________

______________________________

Signature

Date
**Study Contact:** If you have any questions about this study now or in the future, please contact Michael Hutchison at 416-946-4050

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**Appendix E:** Parental Informed Consent

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**UNIVERSITY OF TORONTO**

ETHICS REVIEW INFORMATION SHEET/CONSENT FORM

**Title of research project:** Post-acute structured exercise following sport concussion: a randomized controlled study.

**Investigators:**

- Michael Hutchison, PhD. (Principal Investigator)
  - Faculty of Kinesiology and Physical Education
  - University of Toronto
- Rachel Micay, BKin., University of Toronto
- Scot Thomas, Ph.D., University of Toronto
- Doug Richards, M.D., University of Toronto

**Background & Purpose of Research:**

A number of physical, cognitive, somatic, and emotional symptoms commonly occur following sports-related concussion (SRC). The current return to play (RTP) protocol advises complete physical and cognitive rest following SRC until patients are completely free of these symptoms (i.e. asymptomatic) in order to avoid making symptoms worse and furthering the injury. While rest period is generally assumed to be beneficial, there is currently no scientific evidence supporting this recommendation. In fact, a growing body of evidence suggests that prolonged rest may actually hinder the recovery process.
Emerging research is beginning to show that light-to-moderate aerobic exercise (AE) actually exerts a positive effect on the injured brain, thereby helping to speed up the recovery process. Previous research has demonstrated this phenomenon in other injuries such as stroke, whiplash, low back pain, and even traumatic brain injury. In fact, a standardized aerobic exercise protocol has been shown to improve recovery for individuals with concussion symptoms for an extended period of time, a disorder known as Post-Concussion Syndrome. However, the utility of this type of intervention remains largely unexplored in the early stages of concussion recovery.

Therefore, the purpose of this study is to determine if a standardized, graded AE protocol introduced in the post-acute stage of recovery from SRC will reduce the time to medical clearance compared to the current RTP protocol of rest. This study also aims to understand the effect of aerobic exercise compared to rest on various measures of concussion-related physiology. The findings of this study will provide an important understanding of how to manage future SRC in the post-acute phase of recovery.

**Eligibility:**

To participate in this study your child must be a high school student (grades 9-12) and a patient of the David L. MacIntosh Sport Medicine Clinic with a medically diagnosed sport concussion.

**Procedures:**

Based on your child’s symptom status at their first visit with physicians at the clinic, your child will be placed in one of two groups: **Symptomatic Group** or **Asymptomatic Group**. If your child is assigned to the **Asymptomatic Group**, they will be guided through the clinic’s current standard of care through a six-stage RTP protocol until they are cleared to return to play. On days 7, 14, 21, and 28 post-injury, your child will be assessed on various measures, including their heart rate variability, blood pressure variability, symptoms, cognition, balance, and blood serum biomarkers, and their time to medical clearance will be recorded.

If your child is assigned to the symptomatic group, they will be randomly assigned to either the **Rest Group** or the **Exercise Group**. If your child is assigned to the **Exercise Group**, they will undergo a standardized aerobic exercise intervention consisting of eight sessions over the course of 11 days, beginning on Day 6 following their concussion. Your child will continue to progress through the exercise program until completion. Should your child’s symptoms resolve prior to completion of the program, they will continue to progress through it while concurrently being guided through the clinic’s RTP protocol, beginning at stage 2 of 6. Your child will be assessed on various measures including heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers at days 7, 14, 21, and 28, and their time to medical clearance will also be recorded. On these days, your child will be re-assessed by a sport-medicine physician at the MacIntosh Clinic who will be able to gauge their progress in the recovery process.
If your child is assigned to the **Rest Group**, they will continue to rest and refrain from participating in physical activity of any kind until their symptoms completely resolve. Once this occurs, they will be guided through the clinic’s existing six-stage RTP protocol until they are medically cleared to return to play, beginning two weeks after their concussion. Your child will be assessed on various measures including heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers at days 7, 14, 21, and 28, and their time to medical clearance will also be recorded.

The time to medical clearance, as well as measures of heart rate variability, blood pressure variability, symptoms, cognition, and blood serum biomarkers, will be compared between the rest and exercise groups in order to determine whether a controlled AE program leads to a shorter overall time to medical clearance and improved physiological measures of recovery compared to the existing guidelines of rest.

**Standardized AE Protocol:**

The proposed AE protocol will consist of eight sessions that proceed in a stepwise fashion with respect to both duration and intensity over the course of 11 days. All exercise sessions will be supervised by a member of the research team, and will begin with a five-minute warm-up period and conclude with a five-minute cool-down period. All exercise will be performed on the Velotron Pro stationary cycle ergometer (RacerMate Inc., WA, USA), which will ensure that the participant’s head and neck remain stable throughout the protocol, thereby minimizing risk of symptom exacerbation and/or re-injury. This stationary bicycle has the capability to be digitally connected to a heart rate monitor, which will be programmed to monitor the wattage of the bike based on the participant’s heart rate (HR). Heart rate data will be collected via the Polar RS800CX watch and chest strap (RS800cx; Polar Electro, Kemple, Finland). This device will be connected to the participant using an adjustable strap and secured on top of the rip cage, allowing the researchers to monitor individual heart rate in real time throughout each testing session. This will ensure that participant maintains a safe level of exercise intensity throughout each session.

The first session of the protocol will take place on Day 6 post-injury. The duration of this session will be comprised of 10 minutes of steady-state exercise at 50% of the participant’s age-predicted maximal HR, plus the five-minute warm-up and cool-down periods (total time of 20 minutes). The next level consists of 20 minutes of steady-state exercise, plus the warm-up and cool-down periods, at the previous intensity level of 50% of their maximum age-predicted HR (total time of 30 minutes). The patient will continue to progress through the exercise protocol, maintaining the same duration of exercise, including the warm-up and cool-down periods (total time of 30 minutes), while increasing exercise intensity by 5% of their age-predicted maximal HR per session until they achieve 70% of their age-predicted maximal HR. This intensity will be maintained for the final two sessions. Exercise sessions will take place on two consecutive days, followed by one day of rest, for a total of eleven days.
HR and blood pressure (BP), and symptoms will be recorded before and after each exercise session to ensure that the participant has safely returned to their pre-exercise values following each exercise bout. Additionally, participants’ symptoms will be continuously monitored throughout the exercise session by the supervising researcher. Should your child’s symptoms become exacerbated at any point during or after the exercise session, the session will be terminated, and your child will resume this same duration and intensity of exercise at the subsequent session. Should your child’s symptoms become exacerbated again at the subsequent session, their participation in the intervention portion of the study will be terminated, although they will remain in the study to undergo the assessments on days 7, 14, 21, and 28 post-injury. Exercise sessions will take place on two consecutive days, followed by one day of rest, for a total of eleven days.

**Assessment Battery**

Your child will be guided through a battery of assessment measures lasting approximately 45 minutes in duration on days 7, 14, 21, and 28 post-concussion. This battery includes a symptom assessment, heart rate variability and blood pressure variability assessments, peripheral blood serum samples, as well as a balance, reaction time, and processing speed assessment. Additionally, your child will have a follow-up appointment with a sport-medicine physician at the MacIntosh Clinic on these same days in order to gauge his/her progress in the course of recovery.

**Symptoms:**

Concussion-related symptoms will be assessed using the Post-Concussion Symptom Scale (PCSS) of the SCAT3.

**Heart Rate Variability (HRV):**

HRV is an objective measure of autonomic nervous system (ANS) functioning that is reflective of an individual’s ability to respond and adapt to various demands and stressors (such as exercise). It is calculated by measuring the time intervals between an individual’s heartbeats. This will be measured using a Polar heart rate V800 sports watch and corresponding wireless heart rate monitor chest strap, which is a non-invasive tool that poses no risk to your child as a participant. HRV will be assessed for approximately 15 minutes.

**Blood Pressure Variability (BPV) Assessment:**

BPV is an objective measure of autonomic nervous system (ANS) functioning that is reflective of an individual’s ability to keep their blood pressure regular in the face of various demands and stressors. BPV will be measured using the Finapres MIDI figure cuff device (Finapres Medical Systems, Amsterdam, Netherlands). This is a non-invasive tool that poses no risk to your child as a participant. BPV will be assessed for approximately 15 minutes, and will measured at the same time as HRV.

**Blood Serum Sample:**
A physician or research staff member with venipuncture (blood-drawing) training will collect a small amount of blood (approximately 40 mL) using a needle and vacutainer tubes. This process normally takes approximately 5 minutes.

**Balance, Reaction Time, and Processing Speed Assessment:**

Using an iPad-based assessment tool, participants will complete a series of tests designed to measure reaction time, information processing speed, visual acuity, and postural stability. To assess postural stability, your child will perform two conditions with the iPad secured to the lower back: 1) standing with feet together, eyes open and 2) standing with feet together, eyes closed. In both cases, participants will be asked to maintain the stance for 30 seconds. The entire process takes approximately 15 minutes to complete.

**Voluntary Participation & Early Withdrawal:**

Your child's participation in this study is voluntary and he/she may withdraw from this study at any time by notifying the investigator. Your child’s withdrawal from this study or their refusal to participate in no way affects their care or access to medical services and in no way will affect their academic and/or athletic career.

**Risks/Benefits:**

**Benefits:**

Participation in this study will provide your child with an opportunity to be closely monitored by highly trained individuals throughout recovery and the opportunity to learn more about concussion and the various assessment measures associated with it. It will also give your child the opportunity to be seen by a sport-medicine physician every week for four weeks following your initial injury, which is more far medical attention than a concussion patient would receive under normal circumstances. This study will also likely inform future care for individuals who sustain a concussion, as a result of better knowledge from research. Finally, participants in the **Exercise Group** will receive access to exercise equipment and supervision that they otherwise would not be able to make use of.

**Risks:**

Participants in the Exercise Group may experience an increase in their symptoms due to physical exertion. Should symptoms increase during a session, the session will be terminated immediately. If a participant in the exercise group experiences an increase in their symptoms over the course of two consecutive sessions, then their participation in the intervention portion of this study will be terminated. In order to ensure the safety of all participants, there will be an on-call physician at all times available at the David L. MacIntosh Sports Medicine Clinic, which is located directly next to the lab space in which the exercise sessions will take place.

Participants in the Exercise Group may also experience symptom exacerbation later in the day following the exercise intervention, even after they have left the testing facility. In order to minimize this risk, participants will be kept at the
facility for an additional 10 minutes following the completion of the entire exercise session (in addition to the 5 minute cool-down period) in order for the supervising researcher to monitor their symptoms and ensure that they their HR and BP have returned to what they were prior to the initiation of the exercise session. Additionally, participants in this group will be provided with the contact information for the David L. MacIntosh Clinic, where a sports-medicine physician will be available on-call at all times should your child require urgent care after they have left the facility.

There may be minor and temporary discomfort associated with the blood-drawing procedure. This may include soreness or bruising of the skin in area of the blood-draw. This should resolve within a few days after the blood draw. Risks of experiencing infection or irritation of the skin surrounding the site of the blood acquisition will be minimal due to the training of the phlebotomist on site.

There is also a chance that your child may become upset or frustrated if they lack progress in their perceived recovery time. In order to mitigate the mental health related risks that may be associated with participation in this study, your child will be given access to mental health treatment through referrals by their attending physician at the MacIntosh Clinic, should you need it. There are also additional mental health resources in the area that you can access at the following location:

Centre for Addiction and Mental Health (CAMH)
33 Russell Street
Toronto, ON
M5S 2S1

Privacy & Confidentiality:

Your child’s medical files in the MacIntosh Clinic at the University of Toronto are kept private and confidential in keeping with the laws of Ontario (the Medicine Act, and the Regulated Health Professions Act). They will be used by health professionals at the MacIntosh Clinic in the normal ways for your child’s clinical care, whether your child consent to participate in this study or not. Your child’s medical data will not be released to the investigators in this study for research purposes unless he/she consents to participate in this study. If your child consents, the relevant medical records only (those pertaining to concussion or other minor injury used as a control case in this study) will be made anonymous by stripping their name and all other identifying features from them and replacing them with a subject code that will be kept confidential. Please note that your child’s data may be made accessible to a member of the University of Toronto’s Research Ethics Board for quality assurance purposes.

Please note that confidentiality can only be guaranteed to the extent permitted by law.

What are the costs of participating in this study?

Participating in this study may result in costs to you for parking and transportation. You will be compensated $10 for each exercise session at the David L. MacIntosh Clinic to cover these expenses.
Publication of Research Findings:

Following the conclusion of this study the results may be published. No information that could reveal you as a participant will be disclosed in any publication.

New Findings:

If anything comes to light during the course of this research, which may influence your decision to continue, you will be notified.

Rights of Subjects:

You waive no legal rights by participating in this trial. If you have any questions regarding your child’s rights as a participant you may contact:

Office of Research Ethics, Health Sciences
2nd Floor, McMurrich Building
12 Queen's Park Cres W
Toronto, Ontario, M5S 1S8
Tel: 416-946-3273

Dissemination of Findings:

The results of this study will be presented or published in collective form. Your child’s personal information will not be used and as such, any published results cannot identify you as an individual. As a research participant you have the right to request a copy of the final report of the findings of this research study.

Study Title: Post-acute structured exercise following sport concussion: a randomized controlled study

By signing this form, I agree that:

- The study has been explained to me. \[\text{Yes} \quad \text{No}\]
- All of my questions were answered. \[\text{Yes} \quad \text{No}\]
- The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me. \[\text{Yes} \quad \text{No}\]
- I understand that my child has the right not to participate and the right to stop at any time. \[\text{Yes} \quad \text{No}\]
- I understand that my child may refuse to participate without any problems. Yes No
- I have a choice of not answering any specific questions. Yes No
- I am free now, and in the future, to ask any questions about the study. Yes No
- I understand that there is a risk that my child’s symptoms will be exacerbated by exercise. If this happens, I am aware of the steps the researchers will take to ensure my child remains safe and that my symptoms do not worsen. Yes No
- I understand that a member of the University of Toronto’s Research Ethics Board may be given access to my child’s data for quality assurance purposes. Yes No
- I understand that I will receive a copy of this consent form. Yes No
- I agree that my child’s data may be used for future analysis in other research projects not specific to this particular study. Yes No

I hereby consent to participate in this research study.

NAME OF CHILD PARTICIPANT:

________________________________________________

I hereby consent to have my son/daughter participate in this study.

______________________________
Signature

______________________________
Date
I, the undersigned, have fully explained the study to the participant above and their parent/guardian.

Investigator/Designate Name:

_________________________________________________

_______________________________

Signature

__________________________

Date

**Study Contact:** If you have any questions about this study now or in the future, please contact Michael Hutchison at 416-
## Appendix F: Post-Concussion Symptom Scale (PCSS)

### SYMPTOM EVALUATION

#### How do you feel?

*You should score yourself on the following symptoms, based on how you feel now.*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>none</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>“Pressure in head”</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Balance problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity to light</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity to noise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling slowed down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling like “in a fog”</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>“Don’t feel right”</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty remembering</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue or low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble falling asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>More emotional</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sadness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nervous or Anxious</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Total number of symptoms (Maximum possible 22)

#### Symptom severity score (Maximum possible 132)

<table>
<thead>
<tr>
<th>Do the symptoms get worse with physical activity?</th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do the symptoms get worse with mental activity?</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

#### Overall rating: If you know the athlete well prior to the injury, how different is the athlete acting compared to his/her usual self?

- no different
- very different
- unsure
- N/A
Appendix G: Script for Monitoring Symptoms During Exercise (Session 1)

The member of the research team who is responsible for supervising the participant during the exercise session will monitor their symptoms throughout (including the warm-up and cool-down periods) at pre-determined checkpoints using a prepared script. The specific check-in time points and corresponding scripts are as follows:

1. Pre Warm-Up Check-In

**Supervisor:** *Hello, we will begin the session today with a 5 minute light warm-up on the stationary bicycle in order for you to get used to the feel of it and for your cardiovascular system to prepare itself for the work out. Please let me know if your symptoms worsen at any point throughout this warm-up period. Remember that you can end the session at any point if you feel like it.*

2. Mid-way check-in during warm-up (2.5 minutes into warm up)

**Supervisor:** *How are you feeling so far? Have your symptoms changed at all since beginning the warm-up? Do you still feel like you can continue through the remainder of the warm-up portion of the session? Please let me know if your symptoms worsen at any point in the remainder of the warm-up period.*

3. End of warm-up check-in point (5 minutes into warm-up)

**Supervisor:** *The warm-up is now over, how are you feeling now? Have your symptoms changed at all? Do you feel up to starting the exercise portion of the session today? Please let me know if your symptoms worsen at any point throughout the work out and/or if you wish to end the session.*

4. Exercise check-in #1 (5 minutes into exercise session)
**Supervisor:** You are now halfway through today’s exercise session. How are you feeling so far? Have your symptoms changed at all since you started? Do you feel any differently than you normally would while exercising? Please let me know if your symptoms worsen at all as we progress through the remainder of the session and/or if you would like to stop.

5. **Exercise check-in #2** (10 minutes into exercise session)

**Supervisor:** The exercise session is now complete. How did that feel? Are your symptoms still feeling the same as when you started? Do you feel any differently than you normally after finishing a work out? Are you ok to continue with the cool-down session now?

6. **Cool-down check-in** (2.5 minutes into cool-down session)

**Supervisor:** How are you feeling now? Are you experiencing any unusual symptoms? Do you feel any differently when you began the session? You are halfway through your cool-down, are you ok to continue with it?

7. **Final check-in** (end of cool-down session)

**Supervisor:** You are now finished with the cool-down session. How do you feel after completing today’s full exercise session? Please fill out this symptom scale from the SCAT3 like you did before you started today.
Appendix H: Script for Monitoring Symptoms During Exercise (Sessions 2-8)

The member of the research team who is responsible for supervising the participant during the exercise session will monitor their symptoms throughout (including the warm-up and cool-down periods) at pre-determined checkpoints using a prepared script. The specific check-in time points and corresponding scripts are as follows:

1. **Pre Warm-Up Check-In**

   **Supervisor:** Hello, we will begin the session today with a 5 minute light warm-up on the stationary bicycle in order for you to get used to the feel of it and for your cardiovascular system to prepare itself for the workout. Please let me know if your symptoms worsen at any point throughout this warm-up period. Remember that you can end the session at any point if you feel like it.

2. **Mid-way check-in during warm-up (2.5 minutes into warm up)**

   **Supervisor:** How are you feeling so far? Have your symptoms changed at all since beginning the warm-up? Do you still feel like you can continue through the remainder of the warm-up portion of the session? Please let me know if your symptoms worsen at any point in the remainder of the warm-up period.

3. **End of warm-up check-in point (5 minutes into warm-up)**

   **Supervisor:** The warm-up is now over, how are you feeling now? Have your symptoms changed at all? Do you feel up to starting the exercise portion of the session today? Please let me know if your symptoms worsen at any point throughout the workout and/or if you wish to end the session.

4. **Exercise check-in #1 (5 minutes into exercise session)**
**Supervisor:** You are one quarter of the way through today's exercise session. How are you feeling so far? Have your symptoms changed at all since you started? Do you feel any differently than you normally would while exercising? Please let me know if your symptoms worsen at all as we progress through the remainder of the session.

5. **Exercise check-in #2** (10 minutes into exercise session)

**Supervisor:** You are half way through today's exercise session. How are you feeling now? Have your symptoms changed at all since I last checked in? Are you ok to continue with the exercise session? Please let me know if your symptoms worsen at all as we progress through the remainder of the session.

6. **Exercise check-in #3** (15 minutes into exercise session)

**Supervisor:** You are three quarters of the way through today's exercise session. How are you feeling now? Have your symptoms changed at all since I last checked in? Are you ok to continue with the exercise session? Please let me know if your symptoms worsen at all as continue through the remaining 5 minutes.

7. **Exercise check-in #4** (20 minutes into exercise session)

**Supervisor:** The exercise session is now complete. How did that feel? Are your symptoms still feeling the same as when you started? Do you feel any differently than you normally after finishing a work out? Are you ok to continue with the cool-down session now?

8. **Cool-down check-in** (2.5 minutes into cool-down session)
Supervisor: How are you feeling now? Are you experiencing any unusual symptoms? Do you feel any differently when you began the session? You are half way through your cool-down, are you ok to continue with it?
Appendix I: Godin Leisure-Time Exercise Questionnaire

Godin Leisure-Time Exercise Questionnaire

Considering a 7-Day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time (write on each line the appropriate number)

<table>
<thead>
<tr>
<th>Times Per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

a) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY)
(i.e. running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE
(NOT EXHAUSTING)
(i.e. fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE
(MINIMAL EFFORT)
(i.e. yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. Considering a 7-Day period (a week), during your leisure-time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

<table>
<thead>
<tr>
<th>OFTEN</th>
<th>SOMETIMES</th>
<th>NEVER/RARELY</th>
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INSTRUCTIONS

The individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three METs, respectively (5). Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

Weekly leisure activity = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

The second question is used to calculate the frequency of responses to the question regarding the frequency of weekly leisure-time activity “long enough to work up a sweat” (see questionnaire).

EXAMPLE

Strenuous = 3 times/wk
Moderate = 6 times/wk
Light = 14 times/wk

Total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99
Appendix J: Individual and Overall Time to Medical Clearance Data and Descriptive Statistics

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Mean 33.07
Standard Deviation 16.98
25th Percentile 20
Median (50th Percentile) 28
75th Percentile 41.5
Maximum 70
Minimum 15
**Appendix K:** Results from Shapiro-Wilks Test of Normality for Symptom Severity Across the Recovery Timeline

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**Appendix L**: Results from Shapiro-Wilks Test of Normality for HRV Across the Recovery Timeline

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**Appendix M**: Results from Shapiro-Wilks Test of Normality for BPV Outcome Measures Across the Recovery Timeline

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