The effect of maximal exercise on cerebral oxygenation.

By

Travis Hrubeniuk

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements to the degree of

MASTER OF SCIENCE

Faculty of Kinesiology and Recreation Management

University of Manitoba

Winnipeg

Abstract

PROBLEM: Expanding knowledge of how the brain responds to various exercise types may allow for investigation and development of individualized methods of concussion management.

PURPOSE: Identify differences in cerebral oxygenation recovery following bouts of maximal anaerobic, resistance and aerobic exercise.

METHODS: Twenty-eight active adults were recruited, each partaking in two sessions. At the first, anthropometric measures and leg press 1-RM were determined. During the second session, cerebral oxygenation and ventilatory gas exchange variables were recorded while participants completed maximal anaerobic, resistance, and aerobic tests, and for 15-minutes of recovery.

RESULTS: Anaerobic (637.41s ± 330.42s) and aerobic (689.29s ± 311.05s) exercise resulted in longer durations of time to return to baseline compared to resistance (363.07s ± 366.34s).

CONCLUSION: Anaerobic and aerobic exercise taking longer than resistance to return to baseline indicates prolonged activity. Expecting equivalent outcomes as concussion management tools from differing exercise methods may be misguided and requires additional research.

Acknowledgements

I would like to take this opportunity to acknowledge and express my deepest appreciation to the following, who in one way or another contributed great value to the completion of this project and made the study possible:

My Co-Supervisors, **Dr. Jeff Leiter and Dr. Todd Duhamel**. Their encouragement, innovative spirits, constant support, and ability to challenge me academically have greatly bolstered my capabilities for research and outlook on life. Without them, neither my personal development nor this thesis would have been possible.

My examination committee members, **Dr. Sari Hannila and Dr. Steven Passmore**, for their expertise, constructive comments and suggestions.

My co-worker, co-student, and friend **Marc Morissette**, who provided constant and immeasurable support, guidance, advice and leadership.

The **Pan Am Clinic Foundation**, **The Canadian Graduate Scholarship-Master's Program**, and **The Ruth Asper Scholarship in Physical Education and Kinesiology** for providing the financial assistance necessary to complete this project.

Dedication

I dedicate this thesis to my Mom and Dad for doing anything and everything in their power to support, encourage, and provide me with opportunities to succeed throughout my life.

Table of Contents

List of Tables

List of Figures

Chapter One: Introduction

Research has shown that exercise is a beneficial prescription for the prevention, treatment, and rehabilitation from a variety of medical conditions, ranging from type-2 diabetes and cardiovascular disease[1,2], to mental well being[3]. Despite growing evidence of medical benefits for this vast array of diseases concussion management has maintained the status-quo. The consensus recommended treatment continues to be rest[4], despite preliminary research showing slight increases in patient activity levels to be beneficial[5]. Moreover, physician visits and return to work or sport decisions are made in a sedentary state within a quiet office rather than in an environment similar to that which the patient is returning. As research continues to support the benefits of exercise on neural growth and enhancement[6–8], it is possible that introducing activity to a concussed brain could propel and expedite recovery. Research is beginning to support the ideology of effective utilization of exercise as a treatment and evaluation tool for return to play, school, or work[9–11]. While these projects represent positive progress, this research focuses solely on using aerobic exercise, which is insufficient in the context of a manual labour worker returning to a job requiring heavy lifting, or an athlete returning to an anaerobically-based sport such as hockey or football. Therefore, it would be of benefit to examine the potential benefits of expanding this practice to a variety of exercise types, thus furthering the individualization of concussion management. Notwithstanding, to ensure the safety of patients it is necessary to expand on the paucity of literature investigating the neural response to exercise before such implementation can occur. As such, the following work will attempt to determine differences in how the brain responds and recovers from bouts of maximal aerobic, anaerobic, and resistance-type exercise.

Literature Review

Overview of Cerebral Blood Flow Neuroanatomy and Control

The brain relies heavily on an undisturbed, regulated supply of oxygenated blood in order to function optimally. This undisturbed supply is vital to the point that loss of consciousness will occur in 15 seconds following the loss of blood supply, with irreversible damage setting in within minutes[12]. As a result of this, in combination with a high metabolic demand, the brain receives approximately 18% of total blood circulation, despite it contributing to only 2% of total body mass[12].

Cerebral blood flow (CBF) is the measure of the volume of blood passing through a specified point of the brain circulation, per unit time, with the standard measurement reflecting the mL of blood/100g of brain tissue/minute[13]. In the average human brain, the gray matter will circulate approximately 65mL/100g/min, while the white matter requires approximately 50mL/100g/min[13]. Arterial blood enters the cranium through two distinct pairs of vessels, referred to as the internal carotid arteries and the vertebral arteries. Originating as the common carotid arteries arising from the aortic arch on the anatomical left and from the bifurcation of the brachiocephalic artery on the right; each separates into internal and external carotid arteries in the neck with the two respective internal carotid arteries entering the cranium[12,14]. The vertebral arteries originate in the neck area as the third branch of the subclavian artery on both the right and left sides, before uniting near the inferior border of the pons to constitute the basilar artery[12,14].

Each set of major supply arteries breaks into multiple branches to ensure perfusion throughout the entire brain. The internal carotid system supplies much of the anterior circulation of the brain, consisting of the forebrain and 80% of the cortex, with major

branches including the ophthalmic artery, anterior choroidal arteries, anterior cerebral arteries, and middle cerebral arteries[12,14]. The vertebral artery system supplies the posterior circulation of the brain, including the brain stem, cerebellum, thalamus, and the remaining 20% of the cortex, with major branches off of the vertebral arteries including the paired posterior spinal arteries, the anterior spinal artery, and posterior inferior cerebellar artery. Once conjoined, the major branches from the basilar artery include the anterior inferior cerebellar artery, the superior cerebellar artery, and the posterior cerebral artery[12,14]. Specific regions of perfusion for each of the aforementioned arterial branches can be viewed in Table I.

Table 1. Major Neural Supply Arteries

Artery	**Region Supplied**
Ophthalmic	The eyeball
Anterior Choroidal	The internal capsule, choroid plexus and diencephalon
Anterior Cerebral	The medial surface of the frontal and parietal lobes
Middle Cerebral	Cortical and subcortical sections of the frontal, parietal and temporal lobes
Posterior Spinal	Posterior third of the spinal cord, dorsolateral medulla
Anterior Spinal	Anterior two-thirds of the spinal cord, medial medulla
Posterior Inferior Cerebellar	Dorsolateral medulla, posterior-inferior cerebellum
Anterior Inferior Cerebellar	Anterior-inferior cerebellum, caudal pons and small section of medulla
Superior Cerebellar	Superior cerebellum, deep cerebellar nuclei
Posterior Cerebral	Inferior-medial surfaces of temporal and occipital lobes, thalamus and midbrain

At the base of the brain, encircling the stalk of the pituitary gland, lies the circle of Willis. The circle of Willis anatomically connects many of the cerebral arteries, fed by a 'coming together' of the internal carotid arteries and the basilar artery. It is composed of the two internal carotid arteries, the anterior cerebral arteries, the anterior communicating artery, the posterior communicating arteries, the posterior cerebral arteries, and the basilar artery[12–14]. The circle of Willis allows for a connection between the anterior and posterior neural circulation, however in typical situations there tends to be minimal interchange. That being said, if one of the major supply arteries becomes occluded, the circle allows for partial compensation from the restricted supply[12] in an attempt to maintain as much flow as possible.

The cerebral venous system differs from the peripheral venous system, since cerebral veins do not possess valves and rarely accompany corresponding cerebral arteries[12,14]. External venous drainage of the brain is accomplished via a network of superficial vertebral veins located within the pia mater. These veins drain blood from the cerebral cortex and subcortical white matter to either the superior sagittal sinus or the superficial middle cerebral vein[12,14]. Internally, deep cerebral veins drain the brain including structures such as the diencephalon, basal ganglia, choroid plexus, and the deep white matter to the great cerebral vein, internal cerebral vein and the basal vein, which will flow into the straight sinus[14]. Venous drainage flows to the respective sinuses located within the dura matter, then to the confluence of sinuses at the posterior aspect of the brain. From here, right and left transverse sinuses carry the venous blood laterally and inferiorly to the S-shaped sigmoid sinuses, which continue inferiorly to the internal jugular veins of the neck[12,14]. Alternatively, internal drainage may occur to the cavernous

sinus which will drain almost directly to the internal jugular veins, via the superior and inferior petrosal sinuses[12].

The brain is not as tolerant as other organs to alterations in blood flow and as a result, alterations to oxygen delivery to the brain. Compensatory systems controlled by the autonomic nervous system (ANS), namely cerebral vasoreactivity and cerebral autoregulation, accomplish much of the work needed to dynamically adjust CBF in response to metabolic needs and changes in perfusion pressure[15]. Cerebral vasoreactivity is the process by which blood flow changes occur in response to changes in carbon dioxide (CO_2) levels[112]. The brain is sensitive to variations in the arterial partial pressure of CO_2 ($PaCO_2$) to the extent where every mmHg increase in $PaCO_2$ is accompanied by a 2-15% increase in cerebral blood flow, and depressed $PaCO_2$ levels result in decreases in cerebral blood flow[16]. While the exact mechanism of action for these changes requires additional research, it is believed that the cerebrovascular response is regulated by modifications in depression and elevation of pH levels and resultant vascular smooth muscle constriction (in response to hypocapnia) or vasodilation (in response to hypercapnia), respectively[15]. Cerebral autoregulation on the other hand maintains consistent blood flow to the brain despite changes in pressure, allowing consistency and protection when faced with variability in mean arterial pressure (MAP) in addition to $PaCO_2$ [15,17,18]. As a result of this system, when blood pressure decreases cerebral arteries dilate and when pressure increases the arteries constrict. The mechanisms responsible for this phenomenon have not been entirely elucidated, but a recent study by Hamner and Tan concluded that sympathetic, cholinergic and myogenic mechanisms work in collaboration to control approximately 62% of the MAP-flow responses[17]. Additionally,

endothelium-dependent release of nitric oxide in response to shear stress has been found to contribute to the autoregulatory response[19].

The respective delivery of oxygen to the brain is highly dependent on these factors controlling CBF, and the presence of arterial oxygen[20,21]. As a result, while CBF may become reduced for short durations, oxygen consumption can be somewhat maintained through increases in extraction by the cerebral tissue[20–22].

Concussion/ Minor Traumatic Brain Injury

The brain is a vital human organ, responsible for regulating the vast majority of daily processes in order to maintain basic survival. While proper function of the brain is critical for life, it is vulnerable to a variety of injuries following trauma affecting the head and/or skull. One such injury can be referred to as concussion or minor traumatic brain injury (mTBI). While concussion has become a popular term throughout media, current literature is lacking a proper, consistently applied definition. For example, a recent review completed by Donovan et al. identified over fifty unique definitions for the injury[23]. This has led to concussion and mTBI being interpreted as clinically different injuries in some instances[4], as the definitions and classifications have changed over time. In the 1960's an Ad Hoc Head Injury Committee first developed a grading system to define and evaluate concussion, using a graded scale based upon the presence, duration, or lack of, loss of consciousness[24]. In 1974 it was shown that while concussion may be the result of a blow to the head, this biomechanical event is not always necessary; as forces can be transmitted to the head from other parts of the body[25]. The concussion evaluation scale was further evaluated and adjusted to include amnesia and confusion as classic indicators of concussion by the Colorado Medical Society in 1991[26], which was

further supported by Kelly et al[27] before becoming denounced as a useful tool at the Second International Conference on Concussion in Sport[28]. In 2012 the 'Fourth International Conference on Concussion in Sport' was held in Zurich, which resulted in a widely, but not universally, accepted definition of concussion and a vast array of potential indicators including; clinical symptoms, physical signs, cognitive impairment, neurobehavioural features and sleep disturbance[4]. The resultant definition of concussion reads as follows: "Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic, and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

1. Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an 'impulsive' force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
3. Concussion may result in neuropathologic changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies.
4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases symptoms may be prolonged."[4]

The historical definitions of mTBI refer to nearly identical physical mechanisms of injury and resultant symptoms as concussion, with the main difference requiring the injury manifestation to include but not exceed one or more of the following:

1. Loss of consciousness of approximately 30 minutes or less;
2. Posttraumatic amnesia not greater than 24 hours;
3. After 30 minutes, an initial Glascow Coma Scale (GCS) of 13-15
4. Any alteration in mental state at the time of the accident; and
5. Focal neurological deficits that may or may not be transient.[29]

It is clear that there are many similarities in the definitions of concussion and mTBI, which has led to a countless number of publications using the two terms reciprocally. As such, in order to avoid confusion, the current document will accept and use the terms interchangeably.

Concussion Incidence

While there have been many attempts to identify a true and accurate incidence rate for concussion, it has proven to be a difficult task. The inability to properly identify a universally accepted definition of concussion has been a factor in this issue. Authors regularly use different definitions of concussion, thus creating distinct samples based on varying inclusion and exclusion criteria. This problem is emphasized as each of these chosen criteria exposes the samples to individualized levels of bias and misclassifications.

Poor knowledge translation in regards to recommended definitions, management, and care for concussions has proven to be an additional limitation, leading to a variety of reported incidence rates. This lack of proper translation was highlighted by Stoller et

al.[30], who identified that 49% of family physicians, 52% of emergency department personnel, and 27% of paediatricians surveyed within southern Ontario were unaware of the existence of concussion consensus statements[30]. This creates large discrepancies in assessment methods, diagnosis criteria, and utilized management methods for those individuals who present with concussion-like symptoms, making it difficult to rely on physician reporting of concussion.

Supplementing this issue is a general reluctance from the population to seek proper medical care for a concussive injury. Sosin et al.[31] highlighted this issue through a National Health Interview Survey investigation which found that 25% of individuals who reported a potential concussion did not seek any form of medical care[31].

Further to the limitations imposed by inaccurate education and ignorance, information biases introduced by organizational methods and policy changes within hospitals creates added accuracy issues. Originally Thurman and Guerrero[32], and more recently Fu et al.[33] identified changes in hospital policies referencing the admittance of individuals with varying levels of brain/head-related injury that may have had an effect on the perceived incidence rates of concussion. Moreover, multiple studies[34–36] have investigated International Classification of Diseases (ICD) records in an attempt to identify codes that may be associated with concussion. Kristman et al.[34] completed a critical review and identified over 10 different ICD codes that had been used to identify or define concussion in the literature, with one study finding that ICD-850 (concussion) only captured 23.1% of concussed patients whilst ICD-854 (intracranial injury of other unspecified nature) captured 71%[36]. While developing a standardized definition of concussion and improving knowledge transfer would likely provide solutions to many of these problems, at the

current time the lack of standardization imposes great limitations to any researcher attempting to identify an incidence rate for concussion.

Despite these limitations, Cassidy et al.[37] performed a review of the literature in an attempt to accurately identify an incidence rate for concussion. The critical review accepted 121 studies on the incidence, risk factors and prevention of concussion from around the world. The included studies reported a wide variety of concussion incidence, ranging from as low as 51 occurrences per 100,000 population[32] to as high as 782/100,000[38]. Ultimately the authors concluded that the incidence of hospital-treated patients with concussion is approximately 100-300/100,000 population[37]. However, acknowledging that many concussive injuries are not reported to, or treated within, hospitals the authors adjusted the rate to likely being above 600/100,000 population[37] and that between 70-90% of all treated brain injuries are mild (concussions)[37].

Falls and motor vehicle collisions have routinely been identified as two of the leading causes for concussion. A study completed by Peloso et al.[39] reviewed hospital records from all hospitals in Sweden between the years 1987 and 2000, and concluded that falls were responsible for 50-60% of the total concussions, with traffic collisions responsible for 25% of the total[39]. Moreover, Langlois et al.[40] reported that in the United States from 1995-2001 falls led to 28% of brain-injury related hospital visits, with motor vehicle traffic accidents accounting for 20%[40]. Finally, Cassidy et al. provided a Canadian perspective, identifying the annual incidence of motor vehicle collision concussions during the 1998-1999 year to be 109/100,000 adults, accounting for 24% of all traffic injuries[41].

Summary of findings. The historical definition of concussion has remained fluid, as researchers are still lacking a universally accepted definition of the injury. The lack of an adequate definition has been a contributing factor to the inability to successfully identify an accurate incidence rate, compounded by poor knowledge translation efforts, a hesitation by the population to seek medical treatment when a potential injury is experienced, and hospital organizational issues. Regardless, it is estimated that concussions occur at a rate of approximately 600/100,000 population, with falls and motor vehicle collisions contributing largely to that total.

Incidence of Sports-Related Concussion

While falls and motor vehicle collisions are a common mechanism for concussion, sports injuries are also a main contributor. In 1996 it was reported that sports-related concussions (SRC) followed only motor vehicle collisions for the cause of brain injury[31], and it appears as if prevalence is only increasing. The trend of increased SRC incidence was first acknowledged by Lincoln et al.[42] who examined the electronic medical records of an American school district between the 1997-98 and 2007-08 academic years. During that time span, SRC incidence increased from 0.12 per 1000 athlete exposures (AE), defined as one athlete's participation in either a practice or competition, to 0.49 per 1000 AE[42]. This study was followed up by Rosenthal et al.[43] who expanded the sample to a national level. Utilizing the National Athletic Therapy Association's High School Reporting Information Online database (HS RIO), the authors compiled athlete injury data from nine sports across a representative sample of 100 American schools. It was concluded that the SRC incidence rate increased from 0.23/1000 AE in 2005-06 to 0.51/1000 AE[43] in 2011-12, reflecting rates similar to those reported by Lincoln et al.

These rates represent approximately 8.9-13.2% of all sport-related injuries that occurred[44,45]. Although the reason for this increase is hard to identify there are a variety of explanations that may exist. First, an increase in concussion awareness and more high profile SRC cases may be causing athletes, coaches, and parents alike to react to a potential injury and respond accordingly. This could mean that while the actual incidence rate isn't increasing, a higher proportion of those that actually occur are being reported and recorded. Another factor that may be having an influence is the recently passed legislation throughout many states in the United States that address the return to play guidelines for youth. Most of these laws promote some level of education and define who is allowed to release an athlete back to play following a concussion[43]. These laws are built to protect athletes and, similarly to increase awareness, possibly leading to a higher rate of SRC reporting. A final explanation could be that the rate of SRC incidence simply is increasing. Bigger, stronger, faster athletes and changes towards harder, less forgiving equipment could be contributing to higher impact forces during sport and, as a result, more concussions.

While population-based concussion studies often report incidence statistics as a percentage or rate of the population, SRC studies express findings in relation to the number of times or the total time an athlete participates in a practice or competition[37,42–50]. This allows for more accurate reporting in an overall sporting context, but various sports do not contribute to these rates equally, nor do all athletes spend the same amount of time participating in an event. Therefore, it is important to identify the key contributors to concussion rates. In the work completed by Rosenthal et al.[43] the rates of 9 different sports were identified with boys' football reporting the highest incidence of SRC at

0.94/1000 AE, followed by girls' soccer at 0.73/1000 AE[43]. A study by Marar et al[45] expanded the search to a variety of 20 high school sports using the HS RIO, including lacrosse, hockey, cheerleading and track & field, and found concussions accounted for 13.2% of all reported injuries[45]. Football was again the leading culprit for SRC at a rate of 0.64/1000 AE, followed by male ice hockey (0.54/1000 AE) and male lacrosse (0.40/1000 AE)[45]. The leading causes for female SRC were lacrosse (0.35/1000 AE), soccer (0.34/1000 AE) and basketball (0.21/1000 AE)[45]. In every sport except for cheerleading SRC was more prevalent during competitions than practices. Findings from Cassidy[37], Gessel[44] and Meehan[51] support those by Marar in that football has the highest incidence of SRC, followed closely by male ice hockey. Dompier et al.[46] recently took this information to identify how football SRC rates change throughout age groups and apply context using three large injury surveillance programs, namely the Youth Football Safety Study; the National Athletic Treatment, Injury and Outcomes Network; and the National Collegiate Athletic Association Injury Surveillance Program. The authors reported that concussions accounted for 9.6% of injuries in youth football players, 4.0% of injuries in high school players, and 8.0% of injuries in college-level players[46]. In practice alone, SRC rates for youth, high school and college players were 0.59/1000 AE, 0.66/1000 AE, and 0.53/1000 AE respectively, which were higher than knee sprains and fractures[46]. Based on these numbers it was calculated that as many as 182,000 players may sustain at least one SRC annually, equating to as high as one of every thirty youth, one in fourteen high school and one in twenty NCAA football players[46].

It is important to note that when looking at comparable sports, thereby meaning sports in which both males and females compete under the same rules such as soccer and

basketball, females regularly report higher rates of SRC[37,43–45]. This could indicate that females are more predisposed to suffering from, or are more willing to report symptoms from, a concussion.

In combination with the aforementioned concussive injury reporting issues regarding an improper definition and poor knowledge transfer, accurate SRC reporting represents an additional challenge. Most notably, it has been well established that athletes at all levels of competition drastically underreport SRC[47–50,52]. A study completed by Register-Mihalik et al.[50] surveyed 167 high school athletes competing in 6 sports from 28 high schools through the 2008 to 2010 academic years, and found that only 48.8% of athletes claiming to have suffered at least one potential SRC actually reported the injury to a coach or medical worker[50]. Llewellyn et al.[48] surveyed 161 NCAA athletes who completed student-athlete careers following the 2011-12 season and found that 11.8% knowingly did not report a SRC, with an additional 26.1% not reporting due to not recognizing the signs and symptoms[48]. Meanwhile, Delaney et al.[47] surveyed 154 professional football players who played in the Canadian Football League during the 1997 season and found that only 18.8% of players who suffered signs and symptoms of a concussion, reported the injury. While similar issues with a lack of knowledge are commonly reported as potential explanations for these staggering numbers[47–50,53,54], alternative reasoning has also been cited. The study completed by Register-Mihalik et al. found that 36.5% of respondents indicated 'not wanting to be removed from competition' as the reason for not reporting the SRC, with 27.0% stating 'not wanting to let teammates down'. McCrea et al.[49] completed a similar study with a focus on football players, surveying a total of 1,532 varsity players from 20 high schools in Wisconsin with similar

results. The authors found that 41.0% of the players did not report the SRC because they 'did not want to leave the game', and 22.1% because they 'did not want to let down teammates'. Similar numbers were also found by Llewellyn et al.[48] and Kaut et al.[53] in collegiate athlete populations. Finally, Martin et al.[55] surveyed 1,437 high school and senior level rugby players in Manitoba in an attempt to understand their knowledge and attitudes towards concussions. The authors found that despite 94% of their sample claiming to understand the inherent risks of participating in rugby while suffering a concussion, 42.0% of the high school players and 29.0% of the senior-level players would continue participation despite suffering signs and/or symptoms[55]. Additionally, 52.3% of the high school and 38.0% of the senior players indicated that they would feel more obligated to continue playing despite signs and/or symptoms during the playoffs[55].

This lack of reporting makes it increasingly difficult for coaches, trainers, and other medical personnel to adequately remove a potentially injured athlete from sport participation. The results by Martin et al.[55] indicate that increases in education and advocacy for better safety may not be sufficient to change the attitude and approach to concussive injury in athletes. This could be due to a variety of factors, such as players not wanting to disappoint others, a desire to further themselves professionally, or potentially not wanting to be removed from play for a full week in accordance with the current return to play guidelines[4]. As such, athletes are returning to participation while suffering from a SRC, and leaving themselves vulnerable to further injury.

Summary of findings. While falls and motor vehicle collisions have long been major contributors to the occurrence of concussion, rates of athletes suffering the injury due to sport participation have been steadily increasing. Violent sports such as football and

hockey are the leading contributors to the rate of SRC, and are much more likely to occur during competition than practice. In similarly officiated sports, females regularly report a higher incidence of concussion than males. In addition to the reporting problems that have hampered efforts to calculate population-wide incidence rates, researchers of SRC have faced new barriers. Athletes have regularly been shown to be dishonest and have a resistance to be forthcoming about concussive symptoms, which makes it incredibly difficult to identify all cases and puts the athlete at risk.

Molecular Changes and Related Symptoms

Many theories exist in regards to the biomechanical mechanisms that result in concussion, with none being universally accepted[51]. Increasingly, it is believed that a concussion is caused by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force being transmitted to the head[4]. This force then results in strain to the underlying neural elements, resulting in molecular damage that could manifest as various symptoms[51,56–58].

Ionic Flux and Energy Crisis

The biomechanical insult to the brain causes the neuronal membrane to be disrupted, resulting in the mechanical opening of otherwise voltage-gated K^+ channels[57–60], and a rapid efflux of potassium into the extracellular space[60–62]. This forces a sudden depolarization of the cells and an early, indiscriminate release of glutamate neurotransmitters, as shown by Katayama et al[62]. This study induced a concussive injury in rats finding that it caused a significant elevation in $[K^+]$ within the hippocampus, which was postulated to be in response to the mechanical deformation of the neural tissue[62]. These findings were complimentary to an early study by Takahashi et al.[61] who

induced a closed-head injury in rats. Katayama et al. expanded on the study by Takahashi et al. and found that the concentration of the neurotransmitter glutamate elevates concomitantly with the large increase in $[K^+]$[62], which has been described elsewhere[57–59,63]. The released glutamate then binds to kainate, N-methyl-D-aspartate (NMDA), and D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ion channel receptors, developing a feed-forward control loop of continued K^+ efflux, and introducing an influx of calcium (Ca^{2+}) and sodium (Na^+)[62–65]. This massive cellular excitation is followed by what was first described by Leao[66] as a 'spreading depression', in which a wave of relative neuronal suppression occurs[57,59,63,67].

In an attempt to restore the cells to normal functioning state, energy dependent pumps (particularly the Na^+/K^+ pump) work at an exhaustive rate[57,58,63,68–70]. Yoshino et al.[63] utilized a rat model that was subject to a concussive blow to display this phenomenon, and found that the cerebral cortex and hippocampus entered a state of hypermetabolism for at least a 30-minute duration[63]. This ionic pump activation quickly reduces the intracellular energy stores and the neurons work via glycolysis, resulting in increased lactate production and accumulation[69–71], along with a state of hypometabolism[63]. This accumulation is intensified by a concurrent impairment of oxidative metabolism caused by the initial biomechanical trauma and the excessive influx of Ca^{2+} [64,65,72]. The elevated lactate levels can result in further neuronal dysfunction by inducing acidosis, causing membrane damage, altering blood brain barrier permeability and cerebral edema[57,59,73,74].

This cascade of events leads to a variety of potential symptoms that are commonly experienced by those who may be suffering from a concussion. First, the 'spreading depression' that occurs following the ionic flux was first described in terms of migraine[66].

As such, it is believed that this event is linked to migraine and headache symptoms following onset[57,58,75]. Next, while multiple neurons enter a state of energy crisis the brain is left vulnerable to subsequent injury known as second impact syndrome[76]. For at least 30 minutes following injury, the metabolism of the traumatized brain is working at its absolute maximum, and any supplementary demand may result in irreversible neuronal injury or cell death[57,58,63,77]. Moreover, the sudden influx of Ca^{2+} impairs mitochondrial metabolism when the cell is desperate for energy[65]. Once again, any physiological event that would lead to further Ca^{2+} influx, such as a repeated brain injury or increased stimulation could lead to cell death[57].

Cytoskeletal Damage and Neurotransmitter Alterations

The cytoskeleton and axons of neurons have proven to be susceptible to biomechanical stretch, resulting in cell membrane disruption[78]. This disruption is a major contributor to the initiation of the aforementioned ion fluctuations and causes increases to the neuron's membrane permeability[78,79]. As a result of the Ca^{2+} influx, neurofilaments that compose the cytoskeleton, and thus provide structural support for the cell, become compacted[79] and microtubules become destabilized[79–81]. These processes lead to an accumulation of organelles at the location of axonal damage and unnecessary axonal transport, resulting in conglomeration and axonal swelling, which can develop into axonal bulbs and potential disconnection[79,81–83].

In addition to cytoskeletal changes, an alteration in excitatory and inhibitory neurotransmission occurs following concussion. Miller et al.[84] utilized a rat model to show that brain injury causes a decrease in glutamate binding to its NMDA receptor, leading to a decrease in the generation of excitatory neuronal signals[84], which has since

been repeated by Sihver et al[85]. This phenomenon causes changes in the Ca^{2+} influx, which can hamper signal transmission[86]. Inhibitory neurotransmission is also hampered following concussion, as GABA producing neurons are lost[57,87].

These physiological abnormalities are manifested as symptoms commonly reported with concussion. Neuronal cytoskeletal damage has been commonly associated with various cognitive impairments using Diffusion Tensor Imaging in humans[77,88,89]. Additionally, Spain et al.[90] showed that mice with a concussive injury and axonal damage had an impaired ability to learn the Morris Water Maze test, indicating a hampered learning ability following concussion. Concurrently, disturbances in neurotransmission have been associated with neurological complications such as deficits in long-term potentiation, learning, and memory[58,90–92].

Repeated Concussion and Second Impact Syndrome

The decision of when to return an individual to normal activity, work, or sport after suffering a concussion, and whose brain may still be experiencing the aforementioned physiological distress, is not to be taken lightly. While in this state, physiological conditions are abnormal, the brain is less functional, and the cerebral tissue is vulnerable[59]. Thus any further demand or reduction in energy, such as that caused by further biomechanical disturbance, can cause severe strain on the brain. Vagnozzi et al.[93] displayed this with a rat model, where a second concussive-like injury was administered to an already injured rat at different time points. The researchers found that administering a second concussion within a short time interval (three days) resulted in a summation-like response, producing damage similar to a severe traumatic brain injury and doubling the neuronal damage and metabolic impairments. However when a sufficient recovery time

(five days) was offered, the injuries acted as two independent events[93]. Similarly, Longhi et al.[94] administered multiple concussive injuries to mice and found that the occurrence of a second concussion three days apart resulted in drastic increases in cytoskeletal damage and axonal injury when compared to a single concussion[94].

A major concern following an early return to activity is second impact syndrome (SIS). SIS was first described by Richard Schneider in 1973, where he identified two young football players who experienced an initial concussive injury and consequently died after a minor, follow up head injury[95]. This occurs when an individual sustains an initial concussion and suffers a supplementary, often minor, head injury or concussion before the symptoms from the initial injury have alleviated[76,96]. While postmortem examination is still required in order to diagnose SIS, it is believed that the second impact results in massive brain swelling alongside a loss of cerebral autoregulation as a result of a catecholamine surge and rapid, uncontrollable increases in cerebral blood pressure[97]. The result is marked increases in intracranial pressure and eventual herniation of the brain through the foramen magnum[96,97]. Prompt deterioration in the health of the patient ensues[96–98] with devastating effects such as respiratory failure, epidural hematoma, and death[95–98].

Summary of findings. The biomechanical injury stimulates mechanical opening of the otherwise voltage-gated K^+ channels of the neuron cells. This causes a cascade of K^+ efflux, large increases in extracellular glutamate, and Ca^{2+} and Na^+ influx. These events lead to a sudden energy crisis within the neurons, neurotransmission disruption and structural degradation, which leave the patient with cognitive impairment and at risk for supplemental injury such as second-impact syndrome.

Concussion Assessment and Management

In order to prevent further injury, proper assessment and management of a concussion is necessary. Following a potential concussive injury, an athlete may present one or more of a variety of signs and symptoms. Such signs and symptoms include[4]:

1. Somatic (ex; headache), cognitive (ex; feeling in a fog), and/or emotional symptoms
2. Physical signs (ex; loss of consciousness, amnesia)
3. Behavioural changes (ex; irritability)
4. Cognitive impairment (ex; slowed reaction time); and/or
5. Sleep disturbances.

While a wide variety of signs and symptoms have been reported, Lovell et al.[99] investigated the incidence rates of reported signs and symptoms in 260 university and high school athletes using the Post-Concussion Symptom Scale. It was found that the most commonly reported symptom of concussion was headache (79%), followed by fatigue, feeling 'slowed down', drowsiness, difficult concentrating, feeling 'foggy', and then dizziness[99]. The least common symptoms included nervousness, being 'more emotional than usual', numbness or tingling, and vomiting, all of which were reported by less than 25% of the sample[99]. Guskiewicz et al.[100] conducted a similar study by surveying 888 concussed high school football players and found that headaches were the most common symptom (88% of respondents), followed by dizziness (67%), and confusion (59%), while loss of consciousness (8.9%) and amnesia (27.7%) were the lowest[100]. The presence of these symptoms have regularly been linked with a multitude of

neural and cognitive dysfunctions[101–104], indicating the increased likelihood that the individual has indeed suffered a concussion.

If it is suspected that an individual suffered a concussion, an evaluation of cognitive function is recommended to assess and assist the diagnosis of the injury[4]. At this point in time the Sideline Concussion Assessment Tool 3 (SCAT3) is the recommended method of completing such an assessment[4]. The SCAT3 incorporates components to test for attention, memory, cognition, postural control and onset symptoms[4], and uses components that have been previously shown to be valid and reliable in certain circumstances[105]. Yet this assessment protocol relies heavily on subjective reporting, as opposed to objective physiological data. This reliance has led to work by Gall et al.[106], Gaetz and Iverson[107], and Morissette et al.[108] contradicting the reliability of the tool, showing that physical exertion can change the results, and potentially cause an athlete to be unnecessarily pulled from a competition. Additionally, it is known that the symptoms associated with concussion may not appear immediately. McCrea et al.[109] showed within a subpopulation of individuals who suffered a concussion, that symptoms did not appear for a mean time of 14.4 minutes ± 15.5 minutes. Therefore, it would be possible that an individual could suffer a concussive hit, sit for the recommended 15-minute rest period before assessment, and complete the assessment before any symptoms appear, thus allowing an injured athlete to return to play. Recently another concussion assessment tool known as the King-Devick test has been used to identify concussions in a multitude of sports[110–113]. This device has been able to accurately identify concussions that older editions of the SCAT have missed[112,113], but has yet to undergo longitudinal studies to determine reliability, validity or generalizability[114]. These tools heavily rely on either a

bystander to identify that a concussion may be present, or for the athlete to be forthcoming about symptoms in order for the test to be completed, despite the aforementioned evidence of the inconsistences associated with concussion reporting practices. Other tests such as the Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) battery have shown to be an indicator of concussion[115–117]. However, a recent review by Alsalaheen et al.[118] concluded that the ImPACT composite scores do not demonstrate reliability, and that 40-80% of participants were misclassified after use. This tool also requires accessibility to a computer (thus limiting immediate utility in recreational sporting contexts), often demand payment in order to be used which limits utilization to medical institutions and to those who can afford it, and require an initial baseline assessment in order to be utilized appropriately. Ultimately these tools and tests are reliant on subjective symptom scores and are still susceptible to having results manipulated by an athlete, potentially in the form of purposely delayed reactions or deliberately incorrect responses during baseline testing, who may want to hide the presence of a concussion from a trainer, coach, or medical professional in order to get back to playing as soon as possible.

Despite the creation and commonplace usage of these assessment tools, it must be emphasized that no test or assessment protocol has been found that can replace proper evaluation from a physician[4], who will be aware of the medical history including any pre-existing conditions, and capable of making a proper referral.

After a concussion diagnosis has been made, the overwhelming recommendation for management revolves around complete physical and cognitive rest until symptoms dissipate[4,28,119]. This recommendation is likely in response to the aforementioned energy

crisis and the idea that complete rest would help expedite recovery and lessen the likelihood of secondary injury. That being said, evidence is lacking in support of this theory. Kruijk et al.[120] completed a randomized control trial comparing full cognitive and physical (bed) rest to no bed rest, and found that bed rest did not improve concussion outcomes at 2 weeks, 3 months, or 6 months post injury[120]. Additionally Majerske et al.[5] retrospectively examined neurocognitive tests in athletes who participated in various levels of activity following a concussion diagnosis. The participants took part in activity levels varying from no school or exercise activity to regular attendance at school and participation in a sports game, and the authors were unable to find any statistically significant differences in the outcomes regardless of the level of activity[5]. Prolonged rest may also lead to secondary symptoms of fatigue, depression and physiological deconditioning[5]. Regardless of these findings, a 6-step return-to-play protocol for athletes still stands as the suggested method. It appears as follows[4]:

1. No Activity
2. Light aerobic exercise
3. Sport specific exercise
4. Noncontact training drills
5. Full contact practice
6. Return to play.

Patients are instructed to progress a step forward every 24 hours, provided they remain symptom free, equating to a minimum of 1 week of time before a full return to sport participation[4]. Should any sign or symptom resurface at any point in time, the patient is to revert to the previously asymptomatic stage and 'try again' after a 24-hour wash out

period. Current recommendations for returning to work and school are much less thorough. Students are recommended to take time off from school, partake in shortened days and classes, allow time for rest, receive extra time to complete assignments, and not complete standardized testing until completely recovered[119]. The general population is recommended to avoid driving, perform no work with machinery, avoid heights, work shortened days, reduce tasks, and allow for breaks if symptoms arise[119].

The developed guidelines are based on expert opinion and there is a paucity of research supporting these methods. These protocols and recommendations once again rely heavily on subjective reporting of symptoms, and it has been shown that despite diminished symptoms, physical and cognitive homeostasis may not yet be achieved[121]. The problems outlined here are all examples of how determining when an individual should return to normal functioning is one of the hardest decisions a medical professional may have to make[122]. To assist these decisions and optimize concussion assessment protocols, an objective, physiologically based tool or marker should be a point of emphasis for researchers.

Recently there has been a push towards an individualized treatment plan for each concussion, as opposed to the current "one size fits all" approach[123,124]. Leddy et al.[123], who proposed the utilization of progressive exercise therapy to reduce symptoms and enhance recovery from concussion and post-concussion syndrome, developed one such management plan[125]. The research team took 12 subjects of both athlete and non-athlete status who had concussive symptoms for an average period of time of 19 weeks and instructed them to complete a treadmill exercise protocol, replicating the Balke protocol, until the onset of symptom exacerbation. The initial speed was set at 3.3 mph and 0.0%

incline. At the third minute the incline increased to 2.0% and every minute thereafter the incline was increased by 1.0% while maintaining a speed of 3.3 mph. The test was immediately stopped as a result of patient request, or in response to symptom exacerbation. These tests occurred at baseline and again after a 2-3 week baseline period before intervention. The following intervention phase consisted of subjects exercising for the same duration of time they achieved during the second treadmill test, at an intensity of 80% of their maximally achieved heart rate, once per day for 5-6 days of the week. This was completed every week, with follow-up exercise tests taking place every 3 weeks until symptoms were no longer brought on by the test. Any symptoms were graded before each examined exercise test or independent exercise session using a validated graded symptom checklist. The authors found this protocol to be safe, as on no occasion could a participant not resume exercising the day after testing and it was an effective method for relieving chronic subjects from their symptoms. While athletes were able to complete the program faster than non-athletes (6 weeks vs. 15 weeks), both saw reductions in symptom scores with 10 of the 12 subjects completely symptom free at rest, and total exercise time improved from 9.75 ± 6.38 minutes to 18.67 ± 2.53 minutes. This study by Leddy et al.[125] was the first such study to show the effectiveness of exercise as a treatment method for those suffering post-concussion syndrome. Further work by the research team has shown this method to be superior to a placebo stretching program for recovery[10], and to have high inter-rater reliability across individuals with various medical backgrounds, as well as retest reliability[9]. Thus, progressive exercise treatment may provide superior option for concussion management than the currently recommended guidelines.

Summary of findings. Following a concussive injury, a variety of signs and symptoms may appear, with headache being the most common. If a concussion is suspected an assessment tool should be utilized to assist the diagnosis. The SCAT3 is currently recommended. To date the assessment methods available are problematic as these tools rely heavily on the subjective reporting of symptoms, have been shown to report inconsistent results following exercise, and may not catch delayed symptom onset. Currently, no tool exists that is superior to a physician's diagnosis. Concussion management protocols have also been called into question, as recommended protocols have been shown to provide minimal benefit and have no scientific support. An objective, physiologically based tool or marker to assist with these decisions should be a focus of researchers to optimize care. One such attempt to personalize management comes from Leddy et al., who have proposed a progressive exercise treatment with positive and reliable results thus far.

Cerebral Oxygen Delivery and Concussion

The aforementioned exercise protocol developed, and research completed, by Leddy's group works upon the theory that a concussive injury results in ANS dysfunction[10,123,126,127]. The result is a perturbation of the cerebral vasoreactivity and autoregulation systems provoking a diminished response to changes in $PaCO_2$ and MAP[10,123,126,127]. Golding et al.[128] were among the first to examine these events, using a rat model to compare replicated mTBI to a sham brain injury. Through the utilization of laser Doppler, Golding and colleagues found that reactivity to changes in $PaCO_2$ in the injured rats was drastically reduced in response to both hyper- and hypocapnia conditions when compared to the sham injury group, indicating hampered cerebral vasoreactivity in

response to concussive injury[128]. Len et al.[129] more recently completed a similar study with 31 human subjects, 10 of which recently suffered a concussion, challenging each to stress their cerebral vasoreactivity via hyperventilation (to cause onset hypocapnia) and breath holding (hypercapnia). Using Transcranial Doppler ultrasound (TCD) to monitor cerebral blood flow velocity; this study revealed that while velocity appeared normal at rest, when the concussed group was physiologically challenged the vasoreactive response was abnormal in comparison to the control group[129]. The concussed subjects saw a larger drop in velocity during the trials and failed to return to resting velocities after 40 seconds of recovery, while healthy individuals all recovered within 30 seconds of cessation[129]. Moreover, Junger et al.[130] investigated cerebral autoregulation in patients with concussion and found the patients were unable to maintain constant CBF during MAP disturbance when compared to age-matched controls.

These dysfunctions following injury are problematic and result in excessive changes in perfusion pressure[131]. The consequential decreases in cerebral perfusion pressure may cause critical reductions in CBF, and therefore oxygen delivery[130], which will either limit the ability of the brain to function metabolically, or require an already damaged brain to work harder in order to retrieve the needed oxygen supply. Sudden increases in cerebral perfusion pressure may also result in secondary haemorrhages and/or edema[130,132]. The inability to maintain control of CBF, and thus adequately deliver the necessary levels of oxygen to the brain while it is already at metabolic risk, could therefore prove to be a physiological method of identifying a concussion. This theory has already become the focus of research. Chen and colleagues[127] used blood oxygen level dependent (BOLD) functional MRI (fMRI) techniques with 16 male athletes suffering from post-concussion

syndrome (PCS) and eight control subjects who were instructed to complete a variety of memory tasks. The symptomatic group displayed reduced CBF as well as diminished oxygen delivery in response to the task. Furthermore, those with symptoms displayed increased variability in activation patterns indicating a lack of control over the process[127]. More specifically the PCS subjects displayed a weaker BOLD fMRI response in the prefrontal cortex, an area of the brain critical for the active monitoring of the physiological processes associated with working memory[127]. Maugans et al.[126] examined a pediatric population of 12 concussed children aged 11 to 15 using MRI and quantitative flow software. The group reported findings of decreased CBF values of the concussed children from individually matched and group control values, lasting upwards of one month from the initial injury, indicating that these effects are present in children as well as adults[126]. Finally, Mutch et al.[16] demonstrated the effect that changes in $PaCO_2$ can have on cerebral perfusion and oxygen delivery in concussed individuals. Using a RespirAct (Thornhill Research Inc., Toronto, Canada) device, developed for the purpose of end-tidal CO_2 targeting. The research group took 12 individuals with PCS and compared their responses to a predetermined CO_2 challenge to a group of six control subjects using BOLD fMRI. The PCS group demonstrated abnormal responses to the CO_2 challenge, with diminished oxygen delivery throughout the brain[16]. It was postulated that the inability of the brain to properly respond to the changes in CO_2 and adequately deliver oxygen to the brain structures that need it most may be, "an important mediator of persistent concussion symptoms and patient outcomes"[16].

Moreover, changes in CBF and oxygen delivery have shown that cerebral physiological health could still be diminished, thus indicating continued concussive

injury, despite symptom-based tests demonstrating recovery. In the study completed by Chen et al., the concussed and control groups did not differ on working memory test scores, a vital part of symptom-based concussion testing[127]. Yet the results of the study clearly indicated that physiological injury was still present, meaning participants would still be at risk of further neurological insult. Furthermore Maugans et al.[126] measured CBF volumes and had participants complete the ImPACT test at three time points; <72 hours post-injury, 2 weeks post injury, and at a minimum of 30 days post injury. The researchers reported that CBF differences for the concussed group persisted through the final time point, thus indicating continued injury, despite the fact that ImPACT testing indicated clinical recovery[126]. This re-emphasizes the underlying risks of reliance on symptom-based testing protocols in indicating return to activity, and the potential benefits of a shift towards objective, physiology-based testing methods. As such it is possible that monitoring changes in cerebral autonomic function, CBF, or cerebral oxygenation levels could be used as a physiological marker for the persistence of concussion.

A pilot study completed by Clausen et al. recently attempted to demonstrate how monitoring CBF may be used to indicate recovery from concussion[11]. The researchers tracked the degree of CBF disturbance in patients suffering PCS via TCD, with the added benefit of monitoring progression toward recovery using the aforementioned exercise protocol developed by Leddy et al[9,10]. At the initiation of the study protocol, a group of nine female athletes suffering from prolonged concussive symptoms displayed disproportionally increased $PaCO_2$, which caused abnormal CBF readings when compared to a control group of 13 age-matched controls. These readings resulted in an onset of concussion-like symptoms while participating in light aerobic exercise, which

limited their ability to progress through Leddy's protocol. As the patients progressed through the prescribed exercise treatment over a few weeks, their ability to respond to changes in CO_2 levels normalized to those seen in control subjects, thereby displaying seemingly normal levels of CBF response as well and an ability to continue the treadmill exercise protocol to exhaustion. This suggests that monitoring CBF, autoregulation, or oxygenation values may also be utilized as a future marker to indicate when a patient has returned to normal functioning and physiological recovery from a concussion.

Summary of Findings. Following a concussive injury, autonomic nervous system function is hampered, thus affecting the vital mechanisms that it controls. Two of these mechanisms include cerebral vasoreactivity and cerebral autoregulation, which work to control cerebral perfusion, CBF and thus cerebral oxygen delivery in the presence of fluctuations in MAP and $PaCO_2$. As these processes can be measured and tracked, it is possible that changes in CBF and cerebral oxygenation could be used as objective, physiological markers for the diagnosis of concussion, superior to the subjective practice of symptom-based diagnosis. Moreover, pilot research has indicated that monitoring these mechanisms may be an effective way to physiologically indicate recovery from concussion and a safe time to return to regular activity.

Exercise Effect on Cerebral Blood Flow and Oxygenation

Before studying the use of CBF and cerebral oxygenation as indicators of concussion, recovery, or utilization as a treatment, we require an enhanced understanding of how these processes respond to a variety of relevant stressors. One such stressor that is already being used as a treatment method is exercise, which can be broken into aerobic, anaerobic and resistance types; similar to what may be experienced throughout sport participation,

or throughout daily life; while walking down the street, going for a bike ride, chasing after kids, or lifting a heavy box at work. Assuming the brain responds similarly to all types of exercise may lead to inappropriate treatment methods, or inappropriate clearance for return-to-work or school, depending on the physiological demands of the workplace or school setting. Without understanding the standard, healthy responses to each type of exercise on the brain, it would be difficult to differentiate the normative changes during recovery from one type of maximal exercise from another. Further, it would be challenging to recognize an unhealthy neural response to the challenge, such as that following a concussion, when compared to a healthy one.

A multitude of research has previously been completed investigating the cerebral vascular and oxygenation responses to various levels of aerobic exercise. Much of the research was summarized in a review and meta-analysis of 25 peer-reviewed journal articles by Rooks et al[133]. It was found that during low and moderate intensity aerobic exercise frontal lobe cerebral oxygenation progressively increases from baseline, remains stable from moderate-to-hard intensity, then suddenly drops to levels below baseline as one reaches maximal intensity[133]. Although less research has observed oxygenation through recovery, it is believed that this rapid drop is followed by a progressive recovery and return to baseline levels throughout the recovery stage[133]. More specifically, Gonzalez-Alonso et al. estimated this drop off to approach levels of approximately 30% below resting oxygenation[134], while Volianitis and Secher estimate this drop off to be equivalent to 10% below resting values[22]. Rooks et al.[133] attempted to explain the phenomenon by stating that as an individual reaches an intensity near the respiratory compensation threshold, the continuous increases in $PaCO_2$ resulting in a progressive

drop in blood pH hits a minimum, stimulating a hyperventilation response in order to reduce $PaCO_2$ and return pH to a regular homeostatic level. Further research completed by Meyer et al. has indicated that resultant increases in lactic acidosis may contribute to this response as well[135]. As a result of the close relationship between $PaCO_2$ and cerebral autoregulation, the hyperventilation causes reductions in cerebral blood volume to a degree that causes strained cerebral oxygenation[15,133,134,136–138]. Interestingly despite the decrease in overall blood volume, there is a continued increase in measured deoxygenated hemoglobin levels in the venous blood supply[133]. This indicates an attempt by the brain to maintain oxygenation despite the clear reductions in blood supply. However, this compensatory mechanism appears insufficient as the reduced supply of oxygen relative to the required metabolic demand forces a resultant drop in oxygenation. This degree of reduction will interfere with the optimal functioning level of the brain[139] and as a result, activation of the prefrontal cortex, which may ultimately play a role in the eventual cessation of exercise[133,136].

Despite Rooks et al. describing a progressive return to baseline following the drop in oxygenation, Ide et al[140]. reported different results. Ide's research group displayed increases in both glucose and lactate uptake by the brain for metabolism[140], which occurred concurrently with an increase in oxygenation of the brain. This oxygenation escalated beyond the levels observed at rest for an extended period of time throughout recovery, until a gradual decline towards baseline levels approximately 30-minutes post-exercise.

While understanding the events that occur during aerobic exercise is valuable, it is insufficient in the context of all maximal exercise. Currently, there are gaps in the

literature pertaining to the events that occur throughout the recovery phase of maximal exercise, along with the responses to anaerobic or resistance types of exercise. Understanding this would allow for comparison to an individual recovering from a concussive injury, in order to ensure physiological recovery before full clearance to return to a relevant sporting, workforce, or school environment.

Sports such as football and ice hockey, which were alluded to earlier as two sports with the highest concussion incidence rates[37,42–46], are highly anaerobic in nature. More commonly, parents who have to run after children or pets, or children running and playing throughout gym class and on the playground, may be exerting themselves anaerobically throughout their daily lives. As such, it is important to understand a healthy individual's reaction to, and recovery from, maximal anaerobic exercise. Only one previous study has attempted to investigate the cerebral response to anaerobic-type exercise. Shibuya et al.[141] took six male participants through what was termed a 'supramaximal' protocol that had each participant complete seven, 30-second intervals at a work rate equivalent to 150% of their VO_2 maximum, each separated by 15 seconds of rest. The research group found that this protocol resulted in no significant changes in cerebral oxygenation or blood volume, with only slight decreases in these values as the intervals progressed to completion[141]. The authors noted that there was no relationship between $PaCO_2$ and cerebral blood volumes or oxygenation[141]. Despite these findings, there are limitations in the methods that indicate more work needs to be completed in this area. First of which was a very small, and unjustified, sample size that limits the generalizability and validity of the results. It could also be argued that the researcher's methods were unable to push the participants to maximal exertion. It is reported that the

mean VO_2 maximum of the subjects was 43ml/kg/min. Yet in the results section the authors report that subjects achieved maximal exertion throughout testing at a VO_2 maximum of approximately 36.6 ml/kg/min, which falls short of their indicated 'supramaximal' goal. Due to these factors, further research investigating the cerebral responses to maximal anaerobic exercise are warranted.

Research is also limited in regards to studying the impact of maximal strength/resistance exercise on cerebral oxygenation. Many of the studies investigating changes in cerebral vasculature control have opted to use TCD methods to measure cerebral blood flow velocity (CBFv) as an indirect measure of CBF to detect the onset of changes resulting from resistance exercise. Edwards, Martin & Hughson[142] used such a method in their study of nine subjects. Participants completed a leg press at a targeted weight allowing for no more than 10 repetitions (approximately 75% of 1 repetition maximum [1-RM]), while CBFv data was collected among a variety of other physiological measures including MAP, heart rate, and end-tidal CO_2 ($P_{ET}CO_2$) as a surrogate for $PaCO_2$. Results indicated that while MAP gradually increased throughout exercise, mean CBFv remained statistically unchanged. CBFv rose and fell throughout the duration of the lifting, but did not reach a significant change in either direction until exhaustion was achieved. Following the point of exhaustion CBFv decreased below baseline values, concurrent with a rapid drop in MAP and $P_{ET}CO_2$[142], which may indicate a similar relationship between increases in blood pH, hyperventilation, and CBF control that was evident during aerobic exercise. Interestingly, a secondary rise in $P_{ET}CO_2$ was reported from approximately 15 to 30 seconds into the resting period which was subsequently followed by a responsive rise in CBFv, above the progressive return to

baseline[142]. This was speculated to be the result of delayed hyperventilation by the participants[142], but there is potential that this secondary rise may indicate a difference in recovery between resistance training and aerobic exercise recovery. The lack of change in CBFv throughout the duration of exercise was justified as being due to the ability of the brain to maintain consistent flow across a range of MAP between 50-140 mmHG via autoregulation[18,143,144]. That said, as exercise progressed, MAP continually increased to levels beyond the 140 mmHg limit, soon followed by a drop in both MAP and CBFv. Ultimately the authors were able to provide an outline of the changes occurring throughout a resistance exercise session, but concluded that an individual contraction may be too short in duration to initiate an effective response in the brain[142]. Therefore, prolonged strain would be required to allow for changes to occur. Koch et al. expanded on this information with 39 subjects who completed two exercise tests to exhaustion; a 'strength-endurance' protocol that was completed at 50-60% of the participants' 1-RM, and a 'maximal-strength' protocol that was completed at 80-90% of the participants' 1-RM[145]. It is important to note that the results found by Koch et al. replicated those of Edwards, Martin & Hughson. Both protocols[142] reported that CBFv and $PaCO_2$ levels remained relatively stable throughout exercise duration, followed by an event of elevation during the immediate recovery period[145]. This provides further evidence that resistance training and aerobic exercise may differ in recovery. While these studies have provided some insight to the activity of the cerebral vasculature system, there are limitations involved with the use of TCD as a data collection method. Transcranial Doppler measures CBFv as opposed to CBF, and therefore relies on the assumption that the diameter of the artery under investigation does not change. While this assumption has

been supported in the past[146], it has also been brought into question[147]. As such, the reliability of results found using TCD have been challenged, with the results found using TCD potentially being deemed invalid[147]. Additionally, maintaining a constant and strong signal for analysis via TCD can be extremely difficult. Any movement by a participant will likely change the view that the external probes can achieve, preventing the acquisition of a clear and accurate reading and resulting in the loss of data. As it simply is not feasible to prevent someone from moving while conducting intense exercise, it is fair to assume that a quantity of data gathered using TCD has been deemed invalid for use. Therefore, in a recent review by Pereira, Gomes and Bhambhani[148], it was stated that further research is needed to understand how oxygen delivery to the cerebral tissue changes throughout resistance exercise, particularly with an improved measurement tool such as near infrared spectroscopy (NIRS).

Summary of Findings. Before investigation of CBF and cerebral oxygen delivery as methods of detecting concussion onset and dissipation can be put into action, it is vital to understand how these functions respond to a variety of stressors, such as various types of maximal exercise. This will allow patients to exert themselves in a similar fashion to the requirements of the environment that they are returning to, as opposed to the current practice of assessment while in a resting state with a physician. Previous research has already established a framework for the response to aerobic exercise. Throughout mild to moderate aerobic exercise frontal lobe cerebral oxygenation progressively increases from baseline, remains stable from moderate-to-hard intensity, before suddenly dropping to levels below baseline as one surpasses the respiratory compensation threshold. Minimal research has been conducted directly observing the recovery from such exercise, but

preliminary results suggest a sudden increase in oxygenation levels, followed by a gradual, progressive return to the baseline levels. Gaps in the literature also exist in regards to determining the reaction of oxygen delivery following maximal anaerobic and resistance exercise. That being said, early research has indicated that there may be a difference in the recovery patterns of aerobic- and resistance-type exercise. Additionally, anecdotal evidence has determined that individuals participating in anaerobic and resistance exercise exhibit more concussion-like symptoms, namely dizziness, vomiting, blurred vision, balance problems, and pressure in the head, in the early recovery phases following maximal exertion compared to aerobic activity. This may insinuate contrasting recovery mechanisms during the stages following differing methods of exercise, and resultant differences in concussion symptoms. Without this knowledge, it remains difficult to adequately and safely examine the potentially hampered response concussed individuals display in response to such exercise when compared to a normally functioning healthy brain.

Purpose and Hypothesis

The purpose of this research project is to identify the differences in cerebral oxygenation recovery following bouts of maximal anaerobic, resistance and aerobic exercise in a healthy population.

It is hypothesized that aerobic, anaerobic and resistance-type exercise will differ in regards to the time it takes for cerebral oxygenation saturation to return to baseline following maximal exertion.

Chapter Two: Study Design

Methods

Subjects

All study methods received ethical approval from the Health Research Ethics Board at the University of Manitoba. In order to carry out the proposed research, 28 physically active, healthy participants aged 18 to 35 years were recruited. Recruitment took place via word of mouth, and blocked participants into two equal groups according to gender. Previous physical activity levels were established via self-report, requiring individuals to participate in at least 150 minutes of moderate-to-vigorous physical activity per week with two days of bone and muscle strengthening exercise. Participants were excluded if they had any history of concussion, asthma, recent and/or relevant musculoskeletal injury, a history of cardiovascular disease, a 'yes' response on the Physical Activity Readiness Questionnaire, were currently pregnant, or had any medical history contraindications as specified by the 2002 American College of Cardiology/American Heart Association Practice Guidelines: Contraindications to Exercise Testing. Each participant was compensated $25 for each of the two sessions they attended, for a maximum of $50.

Participation Outline

An initial orientation session was utilized to introduce each participant to all equipment in order to establish comfort. Additionally, baseline anthropometric data and general characteristics were recorded, and a leg press 1-repetition maximum (1-RM) was established, using a predictive 1-RM protocol[149], for future use as a reference point during the resistance training protocol.

At least one week following the orientation session participants engaged in a testing day. During this session, the participants completed three maximal exercise tests with 30-minutes of passive rest allotted between each test. The order of completion of the three tests were as follows; maximal anaerobic, maximal resistance training, then maximal aerobic. Participants were connected to a metabolic cart and cerebral oximeter for the duration of, and for fifteen minutes following, each test.

General Characteristics, Anthropometric Measures and 1-Repetition Maximum

At the initial orientation session, resting heart rate (RHR) and resting blood pressure (RBP) were manually measured following a 5-minute rest period using a stethoscope sphygmomanometer. Participant height and weight were measured using a calibrated stadiometer and scale (Seca, Germany). Body Mass Index (BMI) was then calculated using the equation weight (kg)/height^2 (cm^2). Waist circumference (WC) was measured utilizing the standardized Canadian Society for Exercise Physiology protocols[150]. The participant stood with their feet shoulder width apart, midriff exposed and arms crossed over the chest. Two measurements were taken with a measuring tape along the superior edge of the iliac crest. If the two readings differed, the average of the two was used for analysis. Body fat percentage (BF%) was estimated utilizing a seven-site skinfold measurement and supplementary equations as outlined by Jackson & Pollock[151,152]. A pinch of skin was taken and measured using a skin caliper (Baseline Evaluation Instruments, Fabrication Enterprises Inc., UK) at the right pectoral/chest, triceps, subscapularis, midaxillary region, iliac crest, abdomen and quadriceps. Following measurement at each site, all measurements were repeated for accuracy. If the two

readings differed, the average between the two was utilized for analysis. All anthropometric measurements were taken by the primary investigator (TH).

Participant leg press 1-RM was calculated following the completion of a predictive protocol as outlined by Brzycki[149]. Each individual was allocated a brief warm-up set at light resistance, allowing for 5 – 10 repetitions. Following a 1-minute rest, the participant then performed 1 set of 10 reps at a resistance that was postulated to equate to 60-80% of 1-RM. Finally, following a 3-5 minute rest, weight was increased to a degree that allowed the participant to complete no more than 10 repetitions. This selected weight and the number of repetitions completed in the final set were slotted into the following equation to predict 1-RM: (1-RM) = weight lifted (lbs) / [1.0278 – (reps to failure x 0.0278)].

Maximal Anaerobic Test Protocol

Participants completed the 30-second Wingate test[153] in order to achieve maximal anaerobic capacity. Following a 5-minute warm-up on a cycle ergometer (Ergomedic 894E, Monark, Sweden), the participants were instructed to start pedaling to a self-selected maximal speed. Once self-perceived maximal rotations per minute (rpm) were reached, a weight equivalent to 0.075 kg per kg of body mass was instantaneously applied. The participant then pedalled at a maximal effort for 30 seconds against the resistance. Participants were allowed to sit or stand throughout the duration of the test, and received verbal encouragement. Following test cessation, the participant was immediately moved to a seated position in a chair and sat for the 15-minutes of recorded recovery time. Monark ATS software (Monark, Sweden) was used to calculate peak power (watts), relative peak power (watts/kg), average power (watts), relative average power (watts/kg), and fatigue index (%).

Maximal Resistance Exercise Test Protocol

The maximal resistance exercise protocol was completed as explained by De Salles Painelli et al[154] using a leg press exercise. Utilizing the predicted 1-RM from the orientation session, the protocol started with an initial warm up set composed of 8 repetitions at 50% of the test load (80% of 1-RM), followed by 2 minutes of rest. A second warm up set of 3 repetitions at 70% of the test load followed, with another 2 minutes of rest. The test then 'initiated' with the participant completing four sets at 80% of 1-RM until failure. Between each set a period of 2-minutes passive rest was allotted. Participants were instructed not to utilize the Valsalva maneuver, and thus, maintain continuous breathing throughout the protocol. More specifically, participants were instructed to exhale during knee extension, and inhale during knee flexion. Moreover, during the first repetition of the warm-up set, each participant was instructed to lower the leg press platform slowly so a marker could be placed on the leg press once knee flexion was at an angle of approximately 90-degrees. Each participant was instructed to flex their knees to 90-degrees and not beyond, then exert force and push the platform away from the body. Following testing cessation, the participant was instructed to stay seated at the leg press for the 15-minutes of recorded recovery time.

Maximal Aerobic Test Protocol

The aerobic VO_2 maximum test was completed as explained by Bell et al[155]. Following a 5-minute warm up on the cycle ergometer (Ergomedic 894E, Monark, Sweden), participants were instructed to maintain a pedalling cadence of 60 rpm. This pace was clearly visible on the ergometer display and a nearby metronome was used to assist each participant in maintaining the instructed pace. Starting at a measure of 60

Watts for two minutes, the participants continued to pedal with an increase of 40 Watts occurring every two minutes. Once the respiratory exchange ratio reached a value of 1.00, the 40 Watt increase occurred every minute. This continued until VO_2 maximum was reached, as indicated by the achievement of any two or more of the following; a plateau in oxygen consumption associated with a respiratory exchange ratio higher than 1.10, achievement of the age predicted maximal heart rate, and/or a subjective feeling of exhaustion. Following test cessation the participant was immediately moved and seated in a chair for the duration of the 15-minute recorded recovery time.

Cerebral Oxygenation

Participants were connected to a cerebral oximeter (Root, Masimo, California) using NIRS technology as a non-invasive technique to assess the oxygen saturation levels in the frontal lobe via the placement of two imaging pads placed on the forehead. Each pad was placed directly above the eyebrow, lined up centrally with the pupil. Regional cerebral oximeters measure a mix of arterial, capillary, and venous blood in cerebral tissue in order to calculate tissue oxygenation. To do this, each of the imaging pads contain a sensor comprising near-infrared light, alongside near-field and far-field light detectors. Most biological tissues are transparent to light in the near infrared range of 700-1000nm[156,157]. However, oxygenated and de-oxygenated hemoglobin reflect specific wavelengths at this range[156–158]. Therefore, photons introduced at the scalp pass through most of the tissue, and are either absorbed, scattered or reflected back to the detectors in a predictable "banana shaped" path[156]. Utilizing a modified version of the "Beer-Lambert law," which states that "a portion of the light transmitted through a solution containing a colored compound is absorbed by the compound"[157], the pair of detectors are able to

measure absorbance and reflectance changes at two distinctive wavelengths, one of which is more sensitive to oxygenated hemoglobin, the other to de-oxygenated hemoglobin[156,157]. The changes in the relative concentration of these two chromophores can then be calculated in order to measure tissue oxygenation[156–158]. NIRS technology has been found to be a valid and reliable method of determining oxygen saturation via hemoglobin oxygen states comparable to fMRI measures[156,159–163] . Additionally it has been shown to provide a better signal-to-noise ratio when compared to both fMRI and PET[159], is much less restraining to an exercising individual, and is tolerant to movement[156,162].

Following an initial five minutes of passive rest for preliminary HR and BP readings, participants were left in a seated position and attached to the cerebral oximeter. Once a reading was established baseline recording began for five minutes before the initiation of each exercise protocol. Readings continued at two-second intervals throughout the duration of each exercise protocol and for fifteen minutes following the achievement of maximal exertion. Markers were noted at the immediate cessation point, and at 60-, 90-, 120-, 300-, 600-, and 900-seconds post-test for evaluation. Following data collection, the pre-exercise baseline measurement was utilized to calculate the duration of time it took for each participant to return to, and remain at, that baseline following exercise cessation for each respective test. It is known that there is large individual variability in cerebral oxygenation at rest[164]. In order to account for the natural variance within each individual, the mean oxygenation value ± the standard deviation throughout the five minutes of recorded baseline time was considered the ‘baseline range’. ‘Return to baseline’ was equated to a 30-second return to the baseline range, without the cerebral oxygen

saturation percentage leaving said range for 30-seconds or longer at a later point in time throughout the remaining recorded recovery time. The highest and lowest deviation from the calculated baseline measurement throughout the totality of exercise and recovery time was also determined for each individual throughout each of the exercise tests.

Metabolic Cart, Blood Pressure and Heart Rate

Following the 5-minute warm-up period, throughout the duration of each exercise protocol and for fifteen minutes of recovery time, participants were also connected to a metabolic cart (TrueOne 2400, Parvo Medics, Utah, USA) and heart rate monitor (Polar A300, Polar Electro Oy, Canada) to assess oxygen uptake, carbon dioxide production, respiratory rate and heart rate, based on breath-by-breath measurements. Calculation of relative VO_{2max} ($RelVO_{2max}$) and absolute VO_{2max} ($AbsVO_{2max}$) was based on 20-second averaging of the breath-by-breath measurements. Similar to the time point marked on the cerebral oximeter, exercise cessation, 60-, 90-, 120-, 300, 600, and 900-second time points were noted on the metabolic cart. Additionally, blood pressure was measured using an automated blood pressure cuff (Life Source UA-767 Plus, A & D Medical, Japan) at the 60-, 90-, 120-, 300-, 600- and 900-second time points. As mentioned previously, $PaCO_2$ appears to be a vital contributor to changes in cerebral oxygenation. As collection of $PaCO_2$ requires invasive methods that would not allow for the movements that may occur during the exercise protocols, $P_{ET}CO_2$ was collected as an aggregate measure[165].

Blood Lactate

Blood lactate concentrations were measured pre- (immediately before test initiation) and post-test (5 minutes following test termination) for each of the three exercise tests. For each measurement the participant's finger was wiped clean using a disposable

alcohol swab, with all excess alcohol and dirt wiped away using sterile gauze. The finger was then pricked with a single-use lancet (Unistick 3, Mumford, UK). The first approximate 0.5 µl of blood was cleaned away with gauze to prevent any contamination in the sampling. Following which two 0.5 µl samples were taken up and analyzed using two Lactate Pro handheld monitors (Arkray Global Business, Australia) to ensure consistency of the measurement. If the two monitors differed in their readings, the numbers were averaged with the resultant number used for analysis. Following the sampling, the participant's finger was wiped clean and the prick was sealed via temporary wrapping in the gauze with pressure applied.

Statistical Analysis

Based on a systematic review and meta-analysis completed by Rooks et al.[133] the estimated effect size when observing the cerebral oxygenation of healthy individuals throughout exercise is 0.64 (alpha error probability = .05, desired statistical power = .80). This data was used to calculate the sample size alongside an estimated twenty percent dropout rate. Descriptive statistics, means and standard deviations for continuous variables and proportions for categorical variables, were generated for all variables recorded. Normality of the distribution for all variables was tested using a Shapiro-Wilk test. Since the values associated with time to return-to-baseline, highest increase from baseline, and lowest drop from baseline are not independent measures, one-way repeated measures analysis of variance (ANOVA) was used to test for a main effect of exercise type. If sphericity could not be assumed, a Greenhouse-Geisser correction was applied. followed by a post-hoc analysis utilizing a Bonferroni correction to determine the mean differences for each pair of exercise types (aerobic vs. anaerobic, anaerobic vs. resistance,

and aerobic vs. resistance). Similar statistics were compiled to determine the differences between the three exercise groups at baseline within the male and female subgroups, as well as the lactate measures pre- and post-test. Repeated measures two-way ANOVA was conducted to compare the main effects of exercise type and time into the recovery period, as well as the interaction effect between exercise type and time into the recovery period on cerebral oxygenation, $P_{ET}CO_2$, HR, RR, and Systolic BP. If sphericity could not be assumed, a Greenhouse-Geisser correction was applied. When a significant interaction effect was found, simple effects analysis was performed. In addition, a post hoc analysis was calculated using a Bonferroni correction to determine which levels within each independent variable were significantly different. Independent t-tests were utilized to identify the difference between males and females for general characteristic and anthropometric data, exercise results, oxygenation, and physiological metabolic variables. Furthermore, paired t-tests were used to determine the difference between pre- and post-exercise lactate values for each of the exercise tests. Additionally, stepwise multiple linear regression analysis was used to determine the association of cerebral oxygenation with any individual, or combination, of age, gender, height, weight, RHR, RBP, BMI, WC, BF%, aerobic fitness and muscular strength.

Chapter Three: Results

General Characteristics and Anthropometrics

All 28 participants (14 male, 14 female) who completed the orientation session completed the exercise testing session. Average age of the sample population was 24.6 ± 3.2 years, with a RHR of 72 ± 8 beats per minute, and RBP of 114/73mmHg ± 10/7mmHg. Participant average height and weight was 173.4 ± 9.5cm and 71.6 ± 12.1kg

respectively, leading to a calculated BMI of 23.7 ± 3.0. Waist circumference was 81.3 ± 8.9cm, and calculated body fat percentage was 12.5 ± 3.9%. Differences between males and females in regards to general characteristics and anthropometry can be viewed on Table II. Seven participants (3 male, 4 female) experienced a sense of light-headedness or discomfort to the degree that they removed the metabolic cart mouthpiece before the 15-minute recovery period was completed following the anaerobic test. In such a situation, the last recorded data point was carried forward. The cerebral oximeter continued recording in every one of these instances. Each of these participants were able to continue through the remaining tests following the allocated recovery time period.

Table 2. General Characteristics

	Male	Female	t	df	p-value
Age (years)	24.8 ± 3.2	24.5 ± 3.3	.23	26	.818
Resting Heart Rate (beats per minute)	71 ± 7	73 ± 8	-.71	26	.484
Resting Blood Pressure	117(± 8) / 73(±8)	111(±11) / 73(±7)	.41/.96	26/26	.106/.882
Height (cm)	178.9 ± 7.5	167.9 ± 8.0	3.77	26	.001*
Weight (kg)	77.2 ± 10.7	66.0 ± 11.1	2.71	26	.012*
Body Mass Index	24.1 ± 2.4	23.3 ± 3.5	.65	26	.520
Waist Circumference (cm)	83.6 ± 6.9	79.2 ± 10.2	1.29	26	.208
Body Fat (%)	11.4 ± 4.6	13.5 ± 2.9	-1.46	26	.157

Data presented as mean ± standard deviation, or percentage. *denotes significantly different from male subgroup ($p < 0.05$).

Males were both taller and heavier than female participants. Participants who experienced light headedness differed from the remaining participants in regards to waist circumference (75.1 ± 5.3cm vs. 83.5 ± 8.9cm, respectively); t(26) = -2.31, p = .029.

Exercise Tests

Males and females were different in all variables from the exercise tests, with the exception of fatigue index percentage (Table III).

Table 3. Exercise Results

	Male	Female	t	df	p-value
Wingate Peak Power (watts)	762.29 ± 102.04	493.06 ± 108.65	6.37	23	.000*
Wingate Relative Peak Power (watts/kg)	9.90 ± 1.32	7.49 ± 0.99	5.19	23	.000*
Wingate Average Power (watts)	592.76 ± 74.42	382.02 ± 75.28	7.03	23	.000*
Wingate Relative Average Power (watts/kg)	7.69 ± 0.88	5.80 ± 0.56	6.46	23	.000*
Wingate Fatigue Index (%)	47.14 ± 7.47	43.68 ± 5.29	1.33	22	.149
Leg Press 1-Repetition Maximum (kg)	278.05 ± 65.13	182.99 ± 52.95	4.24	26	.000*
VO_2 Peak (L/min)	3.56 ± 0.36	2.44 ± 0.38	7.89	26	.000*
Relative VO_2 Peak (ml/kg/min)	46.43 ± 6.41	37.32 ± 5.11	4.16	26	.000*

Data presented as mean ± standard deviation, or percentage. *denotes significantly different from male subgroup ($p < 0.05$).

Males had higher peak power, relative peak power, average power, and relative average power on the Wingate test. Male participants also had a higher leg press 1-RM,

$RelVO_{2max}$, and $AbsVO_{2max}$. Participants that experienced light headedness did not differ from the remaining participants in any aspects of exercise performance.

Cerebral Oxygen Saturation

Baseline cerebral oxygen saturation percentage ($BaseO_{2SAT}$) before the anaerobic test was 66.96 ± 5.79%, before the resistance exercise was 66.89 ± 5.62%, and before the aerobic test was 66.00 ± 5.48%. A difference between exercise types was found at baseline $F(2, 52) = 3.37$, $p = .042$. Post hoc analysis identified there was a difference between anaerobic and aerobic $BaseO_{2SAT}$, as seen in Table IV.

Table 4. Cerebral Oxygenation Response

	Baseline (O_2 Saturation %)	Time to Return (s)	Highest (Δ Baseline %)	Lowest (Δ Baseline %)
Anaerobic	$66.96 \pm 5.79^{\sigma}$	637.41 ± 330.42	$6.41 \pm 3.35^{\sigma}$	-5.63 ± 4.23
Resistance	66.89 ± 5.62	$363.07 \pm 366.34^{*\sigma}$	$5.29 \pm 3.02^{\sigma}$	-5.89 ± 4.08
Aerobic	66.00 ± 5.48*	689.29 ± 311.05	9.14 ± 3.90*	-4.75 ± 3.73

Data presented as mean ± standard deviation. *denotes significantly different from Anaerobic, $^{\sigma}$denotes significantly different from Aerobic ($p < 0.05$).

It is of importance to note that following the anaerobic protocol, 15 participants did not return to their baseline value without secondary deviation within the 15-minute recovery period. Additionally, 6 participants following the resistance protocol, and 22 following the aerobic protocol did not return to baseline within the 15-minute time period. That said, at no point did the baseline measurement differ between one exercise and the protocol that immediately followed it, indicating that by 30-minutes following exercise cessation, cerebral oxygenation recovery occurred. Average time to return to $BaseO_{2SAT}$

(TTR) following the anaerobic test was 637.41 ± 330.42 seconds, following the resistance exercise was 363.07 ± 366.34 seconds, and following the aerobic test was 689.29 ± 311.05 seconds. TTR was found to differ between exercise types $F(2, 52) = 10.68$, $p = .001$. Post hoc analysis found that anaerobic and aerobic tests both had longer TTR than the resistance exercise test. The highest oxygen saturation percentage deviation ($HighO_{2SAT}$) from baseline throughout and following aerobic exercise was 9.14 ± 3.90%, which was higher than both anaerobic 6.41 ± 3.35% and resistance 5.29 ± 3.02% exercise $F(2, 52) = 19.75$, $p = .001$. No differences existed in the lowest oxygen saturation percentage deviation ($LowO_{2SAT}$) between anaerobic (-5.63 ± 4.23%), resistance (-5.89 ± 4.08%), or aerobic (-4.75 ± 3.73%) exercise. There were no differences between male and female participants in regards to TTR, $HighO_{2SAT}$ or $LowO_{2SAT}$. However, sex differences were present in regards to $BaseO_{2SAT}$, as displayed in Table V.

Table 5. Cerebral Oxygenation Baseline Sex Differences (%)

	Male	Female
Anaerobic	69.15 ± 5.01	64.93 ± 5.88
Resistance	69.57 ± 4.22	64.21 ± 5.60$^{\Delta}$
Aerobic	68.14 ± 5.26	63.86 ± 4.99$^{\Delta}$

Data presented as mean ± standard deviation. $^{\Delta}$denotes significantly different from Male subgroup ($p < 0.05$).

Females had lower $BaseO_{2SAT}$ values than males before both resistance $t(26) = 2.86$, $p = .008$ and aerobic exercise $t(26) = 2.21$, $p = .036$, but not anaerobic exercise $t(26) = 2.00$, $p = .056$. Upon this further analysis, it is evident that the differences in $BaseO_{2SAT}$ before

anaerobic and aerobic exercise were not present once the population was divided into males $F(2, 26) = 2.23$, $p = .13$ and females $F(2, 26) = 1.95$, $p = .16$. Participants who experienced light headedness displayed lower $LowO_{2SAT}$ following the anaerobic exercise test ($-8.83 \pm 6.21\%$); $t(26) = -2.27$, $p = .032$ when compared to the remaining participants (-4.71 ± 3.40).

Blood Lactate

Blood lactate levels before and after each exercise test can be viewed in Table VI. Pre-test exercise type had an effect on blood lactate levels $F(2, 48) = 28.20$, $p = .001$, with post hoc analysis showing anaerobic blood lactate was lower than pre-test measurements for both resistance and aerobic protocols. Blood lactate levels increased from pre- to post-test for each exercise type. Exercise type also influenced post-test lactate levels $F(2, 48) = 30.94$, $p = .001$, with post hoc analysis showing anaerobic exercise resulted in the highest post-test levels, with resistance exercise resulting in the lowest.

Table 6. Blood Lactate Response (mmol/L)

	Pre-Test	Post-Test
Anaerobic	$1.75 \pm 0.94^{\sigma}$	$11.95 \pm 2.42^{\Delta\sigma}$
Resistance	3.51 ± 1.31*	$6.94 \pm 2.72^{\Delta}$*$^{\sigma}$
Aerobic	3.08 ± 1.19*	$10.23 \pm 2.77^{\Delta}$*

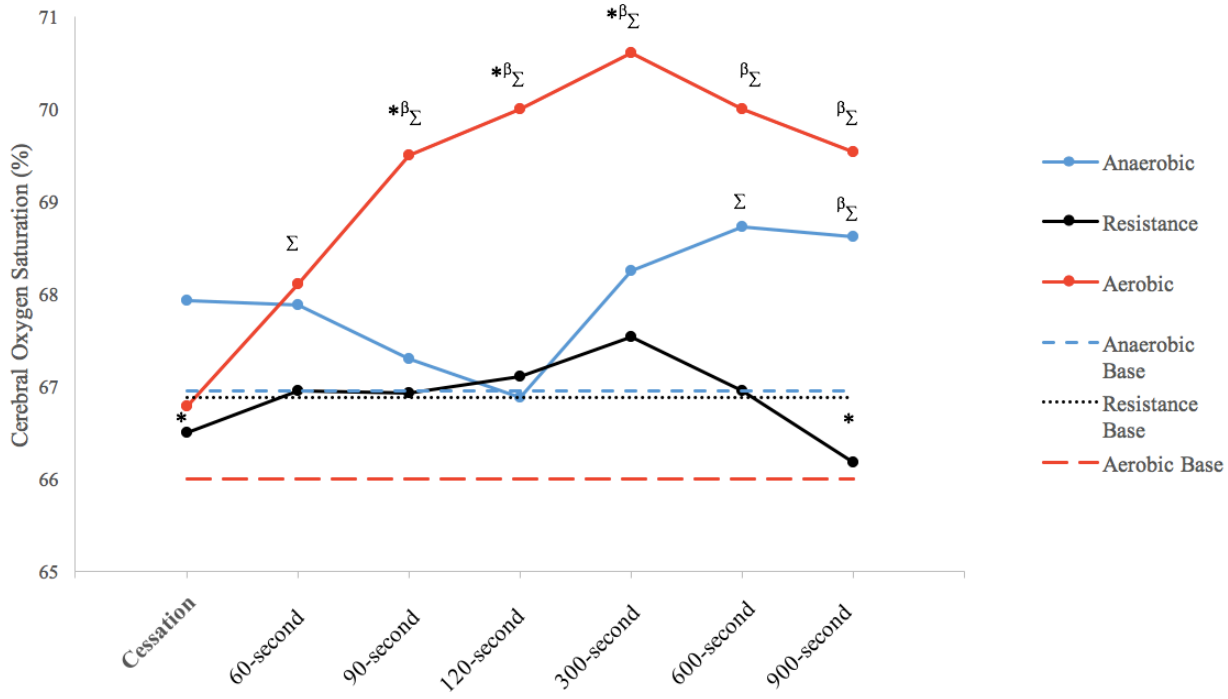
Data presented as mean ± standard deviation. $^{\Delta}$denotes significantly different from Pre-Test *denotes significantly different from Anaerobic, $^{\sigma}$denotes significantly different from Aerobic ($p < 0.05$).

Physiological Recovery from Exercise

Cerebral Oxygenation

The main effect for exercise type resulted in an F ratio of F(2, 50) = 3.68, p = .032, indicating a significant effect of exercise type. The main effect for time into the recovery period resulted in an F ratio of F(7, 80.82) = 4.04, p = .008, indicating a significant effect for time. The interaction effect was significant, F(14, 139.80) = 5.15, p = 0.01. Analysis of simple effects indicated a significant difference between time points throughout recovery following aerobic exercise F(7, 19) = 4.69, p = .003, but not anaerobic exercise F(7,19) = 1.64, p = .184 or resistance exercise F(7,19) = 1.63, p = .187. Simple effects also identified a significant different between exercises at 90 seconds F(2, 24) = 4.51, p = .022, 120 seconds F(2, 24) = 5.96, p = .008, 300 seconds F(2,24) = 4.14, p = .028, 600

Figure 1. Post-Exercise Cerebral Oxygen Saturation



*denotes significantly different from Anaerobic, $^{\beta}$denotes significantly different from Resistance, $^{\Sigma}$denotes significantly different from baseline ($p < 0.05$).

seconds F(2,24) = 3.93, p = .033, and 900 seconds F(2,24) = 5.84, p = .009, but not at exercise cessation F(2, 24) = 2.77, p = .083 or 60 seconds F(2,24) = .883, p = .427. Post hoc analysis identifying the differences at each level of the independent variables can be viewed in Figure I and Table VII.

Table 7. Post-Exercise Cerebral Oxygen Saturation (%)

	Anaerobic	Resistance	Aerobic
Baseline	66.96 ± 5.79	66.89 ± 5.62	66.00 ± 5.48
Cessation	67.93 ± 6.98	66.50 ± 7.23	66.79 ± 7.51
60s-Post	67.89 ± 6.28	66.96 ± 5.97	68.11 ± 6.56$^{¥}$
90s-Post	67.30 ± 6.57	66.93 ± 6.59	69.50 ± 6.93$^{¥*β}$
120s-Post	66.89 ± 6.99^{βØ}	67.11 ± 6.69	70.00 ± 7.09$^{¥*β}$
300s-Post	68.26 ± 7.86	67.54 ± 6.57	70.61 ± 7.41$^{¥*β}$
600s-Post	68.73 ± 7.22$^{¥}$	66.96 ± 6.42	70.00 ± 7.53$^{¥*β}$
900s-Post	68.62 ± 6.88$^{¥}$	66.18 ± 6.44^{ØΩ}	69.54 ± 7.14$^{¥*}$

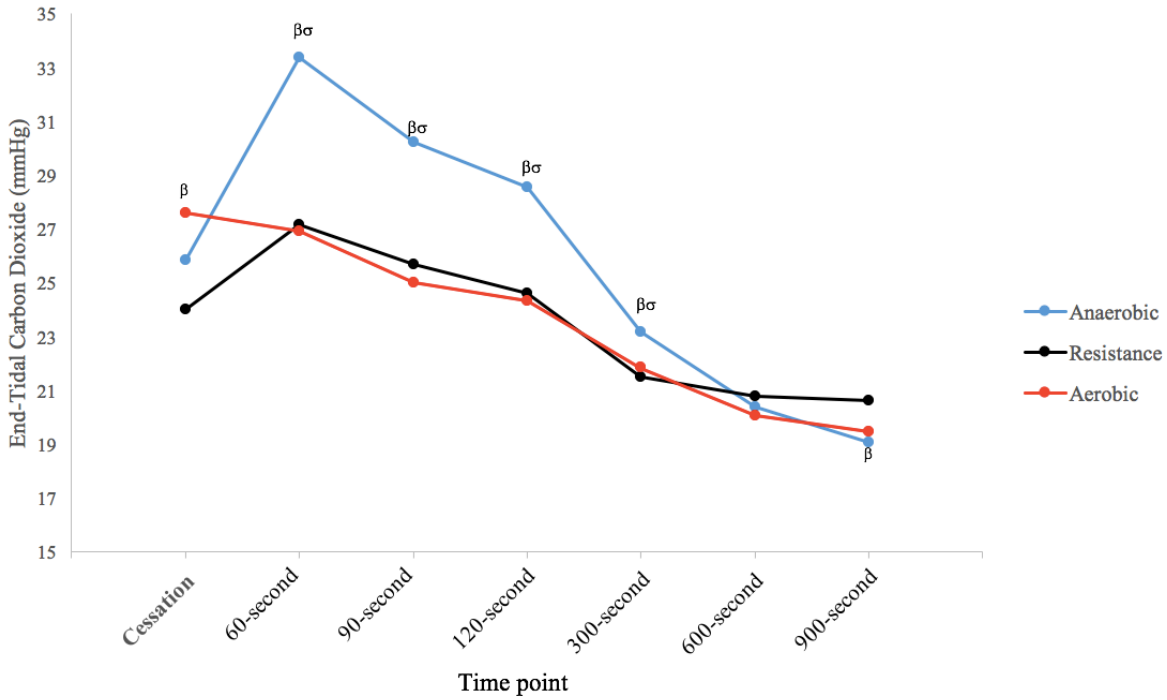
Data presented as mean ± standard deviation. $^{¥}$denotes significantly different from baseline, *denotes significantly different from Exercise Cessation, ^{β}denotes significantly different from 60s-Post, ^{Ø}denotes significantly different from 300s-Post, ^{Ω}denotes significantly different from 600s-Post ($p < 0.05$).

End-Tidal Partial Pressure of CO_2

The main effect for exercise type resulted in an F ratio of F(2, 40) = 33.88, p = .001, indicating a significant effect of exercise type. The main effect for time into the recovery period resulted in an F ratio of F(6, 53.82) = 128.16, p = .001, indicating a significant

effect for time. The interaction effect was significant, F(12, 98.16) = 23.86, p = 0.001. Analysis of simple effects indicated a significant difference between time points throughout recovery following anaerobic exercise F(6,15) = 83.49, p = .001, resistance exercise F(6,15) = 33.41, p = .001, and aerobic exercise F(6, 15) = 19.21, p = .001. Simple effects also identified a significant different between exercises at exercise cessation F(2, 19) = 8.41, p = .002, 60 seconds F(2, 19) = 73.16, p = .001, 90 seconds F(2,19) = 51.44, p = .001, 120 seconds F(2,19) = 46.69, p = .001, 300 seconds F(2,19) = 8.88, p = .002, and 900 seconds F(2,19) = 4.62, p = .023, but not at 600 seconds F(2,19) = 1.31, p = .294. Post hoc analysis identifying the differences at each level of the independent variables can be viewed in Figure II and Table VIII.

Figure 2. Post-Exercise End-Tidal Carbon Dioxide



[β]denotes significantly different from Resistance, [σ]denotes significantly different from Aerobic ($p < 0.05$).

Table 8. Post-Exercise End-Tidal Carbon Dioxide (mmHg)

	Anaerobic	Resistance	Aerobic
Cessation	$25.84 \pm 4.58^{\beta\sigma\Delta\Omega\dagger}$	$24.03 \pm 2.62^{\beta\emptyset\Omega\dagger}$	$27.62 \pm 4.23^{\sigma\Delta\emptyset\Omega\dagger}$
60s-Post	$33.37 \pm 4.18^{\S}$	$27.15 \pm 3.78^{\S}$	$26.92 \pm 4.32^{\sigma\Delta\emptyset\Omega\dagger}$
90s-Post	$30.22 \pm 4.23^{\S}$	$25.71 \pm 3.06^{\beta\Delta\emptyset\Omega\dagger}$	$25.02 \pm 3.64^{\S}$
120s-Post	$28.57 \pm 3.99^{\S}$	$24.61 \pm 3.25^{\beta\sigma\emptyset\Omega\dagger}$	$24.35 \pm 3.34^{\S}$
300s-Post	$23.19 \pm 3.42^{\beta\sigma\Delta\Omega\dagger}$	$21.52 \pm 2.60^{*\beta\sigma\Delta}$	$21.85 \pm 2.76^{\S}$
600s-Post	$20.40 \pm 2.80^{\S}$	$20.81 \pm 3.26^{\beta\sigma\Delta}$	$20.06 \pm 2.62^{\beta\sigma\Delta\emptyset}$
900s-Post	$19.09 \pm 2.69^{\S}$	$20.65 \pm 3.14^{\beta\sigma\Delta}$	$19.48 \pm 2.49^{\beta\sigma\Delta\emptyset}$

Data presented as mean ± standard deviation. §denotes significantly different from all timepoints, *denotes significantly different from Exercise Cessation, $^{\beta}$denotes significantly different from 60s-Post, $^{\sigma}$denotes significantly different from 90s-Post, $^{\Delta}$denotes significantly different from 120s-Post, $^{\emptyset}$denotes significantly different from 300s-Post, $^{\Omega}$denotes significantly different from 600s-Post, †denotes significantly different from 900s-Post ($p < 0.05$).

Respiratory Rate

The main effect for exercise type resulted in an F ratio of $F(2, 40) = 32.16$, $p = .001$, indicating a significant effect of exercise type. The main effect for time into the recovery period resulted in an F ratio of $F(6, 54.54) = 93.14$, $p = .001$, indicating a significant effect for time. The interaction effect was significant, $F(12, 85.26) = 15.86$, $p = 0.001$. Analysis of simple effects indicated a significant difference between time points throughout recovery following anaerobic exercise $F(6,15) = 24.92$, $p = .001$, resistance exercise $F(6,15) = 3.51$, $p = .023$, and aerobic exercise $F(6, 15) = 17.03$, $p = .001$. Simple effects also identified a significant different between exercises at exercise cessation

Table 9-A. Post-Exercise Respiratory Rate

	Anaerobic	Resistance	Aerobic
Exercise Cessation	$56 \pm 17^{\beta}$	$27 \pm 9^{*}$	$46 \pm 13^{*\beta}$
60s-Post	27 ± 7	24 ± 6	$31 \pm 9^{*\beta}$
90s-Post	24 ± 6	22 ± 6	$30 \pm 13^{*\beta}$
120s-Post	23 ± 8	23 ± 6	$27 \pm 7^{*\beta}$
300s-Post	20 ± 7	20 ± 6	23 ± 7
600s-Post	20 ± 6	19 ± 7	19 ± 5
900s-Post	21 ± 7	18 ± 7	19 ± 6

Data presented as mean ± standard deviation. *denotes significantly different from Anaerobic, $^{\beta}$denotes significantly different from Resistance ($p < 0.05$).

Table 9-B. Post-Exercise Respiratory Rate

	Anaerobic	Resistance	Aerobic
Cessation	$56 \pm 17^{\S}$	$27 \pm 9^{\sigma\Delta\emptyset\Omega\dagger}$	$46 \pm 13^{\S}$
60s-Post	$27 \pm 7^{*\Delta\emptyset\Omega}$	$24 \pm 6^{\sigma\emptyset\Omega\dagger}$	$31 \pm 9^{\S}$
90s-Post	$24 \pm 6^{*\emptyset\Omega}$	$22 \pm 6^{*\beta}$	$30 \pm 13^{*\beta\emptyset\Omega\dagger}$
120s-Post	$23 \pm 8^{*\beta\emptyset}$	$23 \pm 6^{*\dagger}$	$27 \pm 7^{*\beta\emptyset\Omega\dagger}$
300s-Post	$20 \pm 7^{*\beta\sigma\Delta}$	$20 \pm 6^{*\beta}$	$23 \pm 7^{\S}$
600s-Post	$20 \pm 6^{*\beta\sigma}$	$19 \pm 7^{*\beta}$	$19 \pm 5^{*\beta\sigma\Delta\emptyset}$
900s-Post	$21 \pm 7^{*\beta}$	$18 \pm 7^{*\beta\Delta}$	$19 \pm 6^{*\beta\sigma\Delta\emptyset}$

Data presented as mean ± standard deviation. §denotes significantly different from all time points, *denotes significantly different from Exercise Cessation, $^{\beta}$denotes significantly different from 60s-Post, $^{\sigma}$denotes significantly different from 90s-Post, $^{\Delta}$denotes significantly different from 120s-Post, $^{\emptyset}$denotes significantly different from 300s-Post, $^{\Omega}$denotes significantly different from 600s-Post, †denotes significantly different from 900s-Post ($p < 0.05$).

F(2, 19) = 39.67, p = .001, 60 seconds F(2, 19) = 10.79, p = .001, 90 seconds F(2,19) = 6.36, p = .008, and 120 seconds F(2,19) = 6.42, p = .007, but not at 300 seconds F(2,19) = 2.10, p = .150, 600 seconds F(2,19) = 0.04, p = .958, or 900 seconds F(2,19) = 2.63, p = .098. Post hoc analysis identifying the differences at each level of the independent variables can be viewed in Table IX-A and Table IX-B.

Heart Rate

The main effect for exercise type resulted in an F ratio of F(2, 44) = 78.39, p = .001, indicating a significant effect of exercise type. The main effect for time into the recovery period resulted in an F ratio of F(6, 64.46) = 775.05, p = .001, indicating a significant effect for time. The interaction effect was significant, F(12, 110.19) = 21.79, p = 0.001. Analysis of simple effects indicated a significant difference between time

Table 10-A. Post-Exercise Heart Rate (beats per minute)

	Anaerobic	Resistance	Aerobic
Exercise Cessation	174 ± 12$^{\sigma}$	151 ± 18*$^{\sigma}$	185 ± 8*
60s-Post	136 ± 13$^{\sigma}$	111 ± 16*$^{\sigma}$	146 ± 11*
90s-Post	128 ± 15	104 ± 16*$^{\sigma}$	133 ± 11
120s-Post	121 ± 14	102 ± 14*$^{\sigma}$	125 ± 10
300s-Post	106 ± 13	94 ± 12*$^{\sigma}$	110 ± 10
600s-Post	101 ± 14	91 ± 11*$^{\sigma}$	104 ± 9
900s-Post	97 ± 13	91 ± 10*$^{\sigma}$	101 ± 9

Data presented as mean ± standard deviation. *denotes significantly different from Anaerobic, $^{\sigma}$denotes significantly different from Aerobic ($p < 0.05$).

points throughout recovery following anaerobic exercise $F(6,17) = 122.40$, $p = .001$, resistance exercise $F(6,17) = 132.43$, $p = .001$, and aerobic exercise $F(6, 17) = 462.45$, $p = .001$. Simple effects also identified a significant different between exercises at exercise cessation $F(2, 21) = 126.51$, $p = .001$, 60 seconds $F(2, 21) = 87.21$, $p = .001$, 90 seconds $F(2,21) = 68.37$, $p = .001$, 120 seconds $F(2,21) = 50.64$, $p = .001$, 300 seconds $F(2,21) = 50.73$, $p = .001$, 600 seconds $F(2,21) = 33.35$, $p = .001$, and 900 seconds $F(2,21) = 36.70$, $p = .001$. Post hoc analysis identifying the differences at each level of the independent variables can be viewed in Table X-A and Table X-B.

Table 10-B. Post-Exercise Heart Rate (beats per minute)

	Anaerobic	Resistance	Aerobic
Exercise Cessation	$174 \pm 12^{\S}$	$151 \pm 18^{\S}$	$185 \pm 8^{\S}$
60s-Post	$136 \pm 13^{\S}$	$111 \pm 16^{\S}$	$146 \pm 11^{\S}$
90s-Post	$128 \pm 15^{\S}$	$104 \pm 16^{*\beta\emptyset\Omega\dagger}$	$133 \pm 11^{\S}$
120s-Post	$121 \pm 14^{\S}$	$102 \pm 14^{*\beta\emptyset\Omega\dagger}$	$125 \pm 10^{\S}$
300s-Post	$106 \pm 13^{\S}$	$94 \pm 12^{\S}$	$110 \pm 10^{\S}$
600s-Post	$101 \pm 14^{\S}$	$91 \pm 11^{*\beta\sigma\Delta\emptyset}$	$104 \pm 9^{\S}$
900s-Post	$97 \pm 13^{\S}$	$91 \pm 10^{*\beta\sigma\Delta\emptyset}$	$101 \pm 9^{\S}$

Data presented as mean ± standard deviation. §denotes significantly different from all time points *denotes significantly different from Exercise Cessation, $^{\beta}$denotes significantly different from 60s-Post, $^{\sigma}$denotes significantly different from 90s-Post, $^{\Delta}$denotes significantly different from 120s-Post, $^{\emptyset}$denotes significantly different from 300s-Post, $^{\Omega}$denotes significantly different from 600s-Post, †denotes significantly different from 900s-Post ($p < 0.05$).

Physiological Recovery from Exercise – Sex Differences

No differences between males and females existed in regards to RR, HR or BP at any time point throughout recovery. As significant differences between the sexes were located at sporadic time points for cerebral oxygen saturation and $P_{ET}CO_2$ throughout recovery, data pertaining to these differences at each recorded time point can be viewed in Table XII.

Predictive variables for cerebral oxygenation baseline and response

Regression analysis determined that there was no effect of age, gender, height, weight, RHR, RBP, BMI, WC, BF%, aerobic fitness or muscular strength individually, or as a combination were capable of providing any predictive ability towards $Base O_{2SAT,}$ TTR, $High O_{2SAT}$ or $Low O_{2SAT}$.

Table 11. Physiological Recovery from Exercise – Sex Differences

Post-Exercise Cerebral Oxygen Saturation (%)

Time	Anaerobic		Resistance		Aerobic	
	Male	Female	Male	Female	Male	Female
Exercise Cessation	71.08 ± 7.44	65.00 ± 5.22*	68.93 ± 6.09	64.07 ± 5.57	70.07 ± 8.08	63.50 ± 5.35*
60s	70.23 ± 7.03	65.71 ± 4.78	68.57 ± 6.25	65.36 ± 5.42	70.29 ± 6.50	65.93 ± 6.07
90s	69.69 ± 6.99	65.07 ± 5.48	68.50 ± 6.87	65.36 ± 6.13	71.29 ± 6.45	67.71 ± 7.16
120s	69.77 ± 7.17	64.21 ± 5.85	68.36 ± 7.04	65.86 ± 6.32	71.21 ± 6.55	68.79 ± 7.63
300s	71.23 ± 6.64	65.50 ± 8.11	69.36 ± 6.74	65.71 ± 6.08	71.50 ± 6.63	69.71 ± 8.26
600s	70.38 ± 6.58	67.08 ± 7.71	69.50 ± 6.35	64.43 ± 5.61	70.79 ± 7.61	69.21 ± 7.66
900s	69.69 ± 6.09	67.54 ± 7.68	68.64 ± 6.59	63.71 ± 5.47*	71.14 ± 6.21	67.93 ± 7.86
Post-Exercise End-Tidal Carbon Dioxide (mmHg)						
Exercise Cessation	26.21 ± 4.75	25.46 ± 4.55	24.80 ± 2.60	23.27 ± 2.50	29.51 ± 3.04	25.72 ± 4.50*
60s	33.96 ± 3.89	32.79 ± 4.52	28.45 ± 3.49	25.84 ± 3.70	27.51 ± 2.92	26.33 ± 5.43
90s	30.75 ± 3.57	29.70 ± 4.89	26.84 ± 2.51	24.58 ± 3.22*	25.39 ± 2.92	24.65 ± 4.33
120s	29.74 ± 3.26	27.39 ± 4.42	26.02 ± 2.38	23.21 ± 3.48*	24.65 ± 2.89	24.06 ± 3.83
300s	24.12 ± 2.91	22.34 ± 3.73	22.57 ± 1.99	20.47 ± 2.77*	22.92 ± 2.05	20.78 ± 3.02*
600s	21.27 ± 2.55	19.53 ± 2.89	21.74 ± 2.17	19.88 ± 3.94	21.39 ± 1.94	18.73 ± 2.59*
900s	19.79 ± 1.87	18.33 ± 3.31	21.27 ± 2.46	20.02 ± 2.68	20.63 ± 2.43	18.33 ± 2.04*

Data presented as mean ± standard deviation. *denotes significantly different from Male subgroup ($p < 0.05$). Specific p-values can be viewed in Appendix 1.

Chapter Four: Discussion

The novel finding of this investigation is that it takes healthy, recreationally active adults aged 18-35 longer to return to baseline cerebral oxygenation following maximal bouts of aerobic and anaerobic exercise than maximal resistance exercise. Aerobic exercise also resulted in a higher deviation from baseline than both anaerobic and resistance exercise, while all three exercises dropped below baseline similarly. While it is notable that aerobic $BaseO_{2SAT}$ was significantly lower than anaerobic $BaseO_{2SAT}$ in a statistical sense, the difference between the respective baseline values was less than one percent, bringing the clinical significance of this difference into question. Furthermore, TTR, $HighO_{2SAT}$ and $LowO_{2SAT}$ values were all determined relative to the respective exercise $BaseO_{2SAT}$, meaning the potential effect of differing baseline measures are considered.

This study demonstrated that no differences between the sexes existed in regards to TTR, $HighO_{2SAT}$, or $LowO_{2SAT}$; however male $BaseO_{2SAT}$ before resistance and aerobic exercise was higher than that of the females. While this difference is in line with the findings of Kameyama et al.[166] it differs from that of Gur et al.[167], as well as Aaneurd and colleagues[168], who identified no difference between males and females in regards to cerebral oxygen consumption at rest. The sex-based diversity that exists between males and females in regards to cerebral oxygenation is not fully elucidated. One theory behind a potential difference was outlined by Aanerud et al.[168] who pointed to an anatomical disparity in the brain for an explanation. Here it was detailed that research completed by Pakkenburg and Gundersen[169] in 1997 identified a discrepancy in the neocortical thickness between males and females. This in addition to a further investigation by

Alonso-Nanclares et al.[170], who concluded that synaptic density is higher in males than in females, led to the belief that at a resting state the male brain would require more oxygen to remain metabolically active. However, research investigating this theory and the potential sex-based differences in $Base O_{2SAT}$ values is limited, meaning additional works are necessary to provide clarification.

Physiological Recovery from Exercise

Immediately following aerobic exercise cessation, it is clear that the body and brain are still recovering; following the achievement of respiratory compensation threshold (RCT) and exhaustion. With a continuous decline in $P_{ET}CO_2$, cerebral oxygen saturation clearly rising from the previously reported drop that follows respiratory compensation threshold, and an elevated respiratory rate, the physiological response to maximal aerobic exercise is in line with the outcomes described by Gonzalez-Alonso et al.[134], Bhambhani et al.[138], and Rooks et al.[133]. As these authors have previously explained, the progression towards maximal aerobic exercise will eventually hit a point at which the buffering capabilities of the body cannot compensate for the increasing acidity causing blood pH to drop. This occurs due to the gradual accumulation of CO_2, lactate[135], and hydrogen ions (H^+), which is reflected in these findings via the large rise in lactate concentration in the post-test readings. The drop in blood pH induces a hyperventilation response as the body attempts to restore homeostasis through enhanced removal of carbon dioxide, forcing an onset of hypocapnia. This response typically occurs immediately preceding exercise cessation. It has been proposed that the hyperventilation associated reductions in $PaCO_2$ cause a resultant aftereffect of dropping CBF, which will bring about a supplementary reduction in cerebral oxygenation to levels below baseline[20–22,134,138,139]. This drop in

cerebral oxygenation is believed to be a major contributor to the perception of fatigue and the decision to stop exercising[133]. Moreover, the results here report an observed rapid 'rebound' in oxygenation in the recovery period following cessation, to a degree that surpassed the recorded baseline resting levels. This overcompensation lasted for an extended period of time, beyond what was originally described by Rooks et al.[133], Bhambhani et al.[138] and Gonzalez-Alonso et al.[134]. Rather, the response appears closer to the findings by Ide and colleagues[140], who tracked cerebral oxygen consumption throughout recovery from aerobic exercise. Oxygen levels did not return to baseline until closer to 30 minutes following cessation. This could explain the observed phenomenon of multiple participants not returning to baseline within the 15-minute tracked recovery period, yet returning to similar baseline levels for the start of the next exercise protocol after the total 30-minte allotted recovery time.

Anaerobic exercise resulted in a seemingly similar, yet delayed and diminished, response to what is typically witnessed upon the achievement of exhaustion and through the recovery of aerobic exercise. The results found here displayed similarities to those found by Shibuya et al.[141], who replicated multiple sets of anaerobic exercise via seven sets of 'supramaximal' exercise set at 150% of VO_{2max}. Shibuya et al. reported a gradual increase in $P_{ET}CO_2$ through the first two sets of the exercise protocol, which was then promptly followed by a steady decline, coinciding with increases in ventilation, and likely the achievement of the respiratory compensation threshold. As would be predicted, cerebral oxygenation values were reported as rising throughout the first three stages of their protocol, before sharply declining as repetition time increased, coinciding with declines in $P_{ET}CO_2$, and similar in response to the changes caused by alterations in carbon

dioxide that are commonly reported following aerobic exercise. These alterations in cerebral oxygenation reflect those found in the research reported here. Unfortunately, Shibuya et al. did not report the results from the exercise tests, but based on the physiological responses it is likely that maximal ability was achieved with the third set, with a drop in performance throughout the continuation of the protocol. This would be in accordance with the fatigue and cessation of exercise that occurs shortly after the observed drop in cerebral oxygenation following aerobic exercise. It is worth noting that unlike the results found by Shibuya et al. the results here displayed only a slight drop in cerebral oxygenation approximately 60-seconds following exercise cessation, and hit its lowest value around the 120-second point. This apparent delay in response is likely due to the relatively short nature of the Wingate test, in that it lasts 30-seconds, potentially not allowing the adequate time for the buildup of CO_2, lactate and H^+ to cause a noticeable drop in pH until after cessation occurs. As such, unlike maximal aerobic tests where protocols encourage participants to continue beyond the point of respiratory compensation until exhaustion, the build-up and increases in $P_{ET}CO_2$ continued until the 60-second post-test time point within this protocol. It would appear that this was the point at which clearance of the acidic by-products occurred, as $P_{ET}CO_2$ began to decline towards levels similar to aerobic and resistance-type exercise. Interestingly, the results found here displayed no coinciding alterations in RR alongside the changes in cerebral oxygenation and $P_{ET}CO_2$. This indicates that there was no compensatory hyperventilation in an attempt to restore balance in acidity, which would have resulted in a reduced impact on the CBF response when compared to aerobic exercise. Therefore, although there was an observed rise and decline in $P_{ET}CO_2$, it did not occur to the hyperventilation-inducing

degree regularly seen with aerobic exercise. As a result, the immediate impact on cerebral oxygenation was diminished when compared to aerobic exercise, despite the observed drop at 120-seconds post-test. However the timing in which the cerebral oxygenation reduction occurred was in accordance with reports by Bhambhani et al., who found that an approximate 20-40 second delay in dropping oxygenation values occurs following reductions in $P_{ET}CO_2$[138]. It is of importance to note that this observed reduction did not result in a significant change from baseline values within the population, or a significant difference from resistance-type exercise. However, similar to aerobic exercise, a gradual increase in oxygenation was observed following the noted drop; to a higher degree than both baseline and resistance-type exercise.

Similar to findings reported by Edwards, Martin and Hughson[142], a slight increase in $P_{ET}CO_2$ was detected approximately 60-seconds following cessation. Subsequently $P_{ET}CO_2$ gradually dissipated, likely resulting in a slight increase in CBF, similar to what was detected by Koch et al.[145]. That being said, when compared to aerobic and anaerobic exercise, the physiological responses were diminished and significantly lower on many accounts. This is comparable to the differences that are observed during participation in aerobic and resistance exercise, as research has detected no statistical changes in CBFv throughout resistance exercise protocols[142,145], quite unlike the drastic increases and decreases that occur throughout aerobic exercise. Furthermore, the deviation observed throughout recovery following resistance-type exercise did not differ from baseline cerebral oxygenation at any point of time, with TTR occurring almost 300-seconds sooner than either anaerobic or aerobic exercise. This was despite a protocol designed to be much more strenuous than those developed by Edwards and colleagues or Koch et al.,

which included multiple sets to failure aimed to achieve the maximal strength output of the lower body. These findings could likely be a result of the minimal anaerobic recruitment and lack of CO_2 accumulation occurring throughout resistance-type exercise. Resistance-type exercise resulted in the lowest accumulation of lactate, indicating minimal anaerobic energy-producing recruitment and thus, minimal release of the acidic H^+. Moreover, all participants were instructed to maintain consistent breathing throughout the exercise, preventing breath-holding and the repercussive hypercapnia, which helped restrict the buildup of $PaCO_2$. Without the need to re-establish homeostasis from a drop in pH via the induction of hyperventilation to force a hypocapnic state, there was no sudden drop in CBF; thereby no drastic alterations in oxygen delivery to the brain. Not only does this indicate that resistance-type exercise may not cause the same physiological 'strain' on the brain that anaerobic and aerobic exercise apparently do, but these results provide further evidence for the possible influence of $PaCO_2$ and pH balance on oxygen delivery to the brain.

As blood pH balance has been established as an important factor influencing oxygen delivery to the brain, it is important to note the potentially concerning effect that the accumulation of lactate, and thus the associated increase in H^+ may have had on the results. It was found that following the anaerobic protocol, pre-test lactate levels for both the resistance and aerobic protocols were elevated, potentially as a result of first participating in the Wingate test, indicating a preliminary reduction in blood pH. Due to the close relationship of blood pH and the onset of RCT, and the effect that RCT has on reducing $PaCO_2$, CBF, and cerebral oxygenation, it is possible that the elevated lactate levels signified a change that impacted the cerebral oxygenation results throughout the

recovery period. Reduced pH levels at the start of resistance and aerobic exercise may have resulted in an earlier achievement of RCT than would have otherwise occurred, meaning a potential reduction in accumulated CO_2, and thus, a diminished impact on CBF and oxygenation. There is a possibility that this effect played a role in the minimal fluctuation following resistance exercise, and may have even reduced the response following aerobic exercise. Alternatively, the preliminary increase in excess lactate may have influenced the early rise in oxygenation following aerobic exercise, as lactate is a known metabolite that is used in the brain[140], or influenced a stronger RCT response due to a summated impact due the large increases in both H^+ and $PaCO_2$. However, post-test lactate values following both resistance and aerobic exercise were lower than anaerobic, as one would suspect, indicating that despite the excess lactate presence pre-test, concentrations did not increase beyond expected levels throughout the duration of the resistance or aerobic protocols. As such, the effect of pre-test lactate levels may have been minimal.

Differences in Recovery Time Between Exercise Types

Important questions rising from this study are what caused the differences in TTR, as well as the rise above $Base O_{2SAT}$ so late into the recovery stage following both aerobic and anaerobic exercise when compared to resistance-type exercise? It has been well established in the past that increases in cerebral oxygenation reflect metabolic activity at the cerebral level[20,140], thereby indicating that this late flux in oxygenation following aerobic and anaerobic exercise is signalling a degree of energy-requiring activity in the brain. There are seemingly two potential explanations for this activity. First, as explained by Kinni et al.[171], based off of a review completed by Ogoh and Ainslie[20], maximal

exercise resulting in a drop in CBF (and thus, cerebral oxygenation) may create a small metabolic deficit in the brain that requires compensation. The large, prolonged increase in oxygenation seen late in the recovery following aerobic exercise could be viewed as a continued effort by the brain to re-establish the resting levels of metabolic fuel that had been previously drained. Moreover, the dampened increase seen in anaerobic exercise and the lack of change in resistance exercise could be viewed as smaller and unnecessary responses, respectively, to the metabolic deficit, displaying the potential for a dose-response relationship.

A second explanation for the increased metabolism may be related to cell generation and growth within the cerebral tissue. It has been well established that acute bouts of exercise temporarily increase the concentrations of vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) proteins, which contribute significantly to various cellular pathways and sections of neural generation that require energy to function[6–8,172–175]. When an individual regularly engages in bouts of exercise over a extended period of time, neural VEGF is known to promote angiogenesis in the brain[172–174], yet it was shown by Tang et al.[173] to substantially increase within the brain in response to acute bouts of aerobic exercise as well. Similarly, research has shown that BDNF contributes to many facets of neural growth, including synaptic plasticity[6,8], neuronal signalling[6], neural cell proliferation, and differentiation, which has a positive impact on learning, memory and long-term potentiation[6–8,172] as a result of maintained exercise training. Moreover, research by Vega et al.[175], alongside a review of the literature by Knaepen et al.[8], identified upwards of 400% increases in peripheral BDNF concentrations, lasting up to 60-mintes, following acute bouts of intense aerobic exercise.

Therein lies the possibility that the observed increases in oxygenation could be related to an increase in metabolic demand due the introduction and acute influx of VEGF and BDNF concentrations to the neural tissue. As such, chronic engagement in bouts of aerobic exercise, resulting in regular influxes of BDNF and VEGF proteins, would result in the mentioned beneficial growth and generation processes. Furthermore, Knaepen et al.[8] also reported that although minimal research has attempted to define the BDNF response to acute resistance-type exercise, the majority of results have found no response, with only one article published by Yarrow et al.[176] reporting a relatively small (32%) increase in BDNF concentrations. The aforementioned research seemingly falls in line with the results found here. Should the delayed rise in oxygenation be related to metabolic activity as a result of VEGF and BDNF introduction, the conclusions from Knaepen and Yarrow would suggest that aerobic exercise would result in the largest increase, while resistance exercise would see a greatly reduced response. As predicted the results found here indicated that aerobic exercise results in the largest increase in cerebral oxygen post-test, followed by anaerobic, with a minimal response following resistance-type exercise.

While there appears to be a connection between these two phenomena, additional research monitoring the fluctuations in VEGF and BDNF concentrations and their potential relationship with changes in cerebral oxygenation following exercise are necessary to draw further conclusions. Moreover, additional research investigating the differences in recovery times between aerobic, anaerobic and resistance-type exercise, in order to deduce the explanations behind them, remains needed.

Translation to Concussion Treatment Research

Recent research has started to push for, and show positive results in utilizing, aerobic exercise as a treatment for those with PCS[9–11,125,177]. As a result of concussion, previous research has indicated that the ability of the ANS to adequately respond to physiological stressors[16,126–130], most notably alterations in CO_2 as displayed by Len et al.[129] and Mutch et al.[16], is severely diminished. This particular response is a repercussion of the inhibited functioning of the ANS controlled cerebral vasoreactivity response, likely as the ability of central chemoreceptors to properly communicate with the ANS in response to the change in blood pH is hampered due to axonal injury[79,80,83]. Stemming from this lack of control CBF delivery is hindered, resulting in wide variability in supply relative to demand. This creates areas of hyper- and hypo-perfusion, causing a lack of oxygen delivery to areas of the brain that are in need for metabolic function, and an overabundance in areas that do not, which may be the cause of some onset symptoms following concussion. Leddy's research group has repeatedly shown that a graded exercise test, alongside a light aerobic exercise prescription can seemingly 're-establish' ANS control[11] in the brain, re-establishing function of cerebral vasoreactivity and sensitivity to fluctuations in $PaCO_2$[11]. As a result, the brain is able to better regulate CBF control, and therefore oxygen delivery, which then helps with the alleviation and ultimate recovery from PCS in a variety of populations[9,10,125,177]. The results found here demonstrate that while progressive aerobic exercise treatment may be proving to be beneficial, personalized treatment methods directing patients towards anaerobic or resistance-type exercise differ in regards to their cerebral oxygenation, and thus the stressors or the responses demanded of the ANS, and thus may not translate into similar successes. Aerobic exercise resulted in the largest variability in oxygenation from

BaseO_{2SAT} and, alongside anaerobic exercise, resulted in a longer TTR when compared to resistance-type exercise in recreationally active, healthy individuals. As such, it is likely that the neural processes underlying physiological recovery from these exercises differ to some extent.

It is clear that continued precautions should be taken when utilizing aerobic exercise as a treatment for PCS patients. Exposing an individual to such variability in their neural oxygenation, and the expected variability in CBF, metabolite availability, and metabolic activity, who may still be experiencing a metabolic state of emergency at the neural level following a concussion may prove to not only be detrimental to recovery, but also dangerous for their overall health. Interestingly, provided that the patient is not permitted to implement the Valsalva maneuver, a more conservative and potentially safer approach for exercise therapy may be to administer a progressive resistance exercise treatment. Should a patient struggle to succeed with participating in aerobic exercise, or potentially preceding an attempt at anaerobic or aerobic exercise, it may cause less metabolic stress on the brain for a patient to initially be treated with resistance exercise before progressing to more stressful treatment methods. As resistance exercise results in a lower HighO_{2SAT} than aerobic exercise with no difference in LowO_{2SAT}, a shorter TTR, and minimal deviation in $P_{ET}CO_2$, the strain placed on the brain throughout the exercise appears minimal in comparison to continuous aerobic or anaerobic exercises. This could prove to be greatly beneficial for patients attempting to return to work that requires manual labour and who would benefit more from being able to physically lift and carry object as opposed to being aerobically active. However, should the influx in oxygenation seen in the later stages of recovery following both aerobic and anaerobic exercise be reflective of

necessary increases in metabolism due to an influx of BDNF and VEGF concentrations, there is potential that the neural generation and growth that accompanies these proteins following regular engagement in exercise are providing benefits that contribute and lead to the improvement seen in PCS patients following their engagement in the aerobic training protocol. As such, patients may not observe similar benefits from resistance exercise as they have with aerobic treatment methods.

While research continues to increase demonstrating recovered ANS functioning via autoregulation and cerebral vasoreactivity following graded aerobic exercise treatment, gaps remain in regards to explaining exactly how and why this process is occurring. It is possible that it is the actions of VEGF in influencing cerebral angiogenesis[172,173], or the effect that BDNF has on neurogenesis[6–8,172,175] following regular engagement in exercise training parlays into improvements throughout the ANS that parlays into a re-establishment of CBF control and oxygenation following a concussion. Should this be the case, improvements may not occur without utilizing aerobic exercise, or potentially anaerobic exercise, for treatment. Further research is necessary to investigate the safety and potential benefits of implementing an anaerobic or resistance exercise-based method for the treatment of patients with PCS. Doing so could provide alternative treatment options based on the educational, athletic, or workplace environment that a patient is returning to, and may prove an alternative option for patients who are unable to adequately complete aerobic-based exercise treatment. Moreover, there remains a paucity of research deciphering the mechanisms behind the seemingly effective method of utilizing aerobic exercise as a tool for ‘re-establishing’ ANS functioning and its resultant ability for use as a treatment for PCS.

Translation to Concussion Identification and Diagnosis

The findings of this research could help contribute to advancing the knowledge and improving the current concussion diagnosis and RTP guidelines. Present sideline assessment protocols, a key factor in determining if an athlete can return to play after suffering a potential concussion, require that an athlete must wait 15 minutes before test administration[4]. While a plethora of evidence already exists indicating the ineffectiveness of this approach and tool[106–108], these findings provide further support for reconsideration of the SCAT3 protocols as an assessment tool, showing that in healthy individuals a 15-minute time period may not suffice for full recovery in the brain following maximal exercise. Twenty-two of the study participants had not returned to $Base O_{2SAT}$ within the monitored 15-minutes of recorded passive recovery following maximal aerobic exercise, with 15 not returning following anaerobic, and 6 not returning after resistance-type exercise. These findings are in line with those of Ide et al.[140], who found that the brain may remain metabolically active and maintain an increased level of cerebral oxygenation for upwards of 30-minutes following maximal exercise. This could affect the ability of a healthy athlete to adequately respond to the tests administered during a sideline assessment, regardless of a potential concussion, leading to a misdiagnosis and unnecessary removal from play.

Further, this research contributes to the comprehension of what healthy neural recovery from maximal aerobic, anaerobic, and resistance-type exercise, in the context of cerebral oxygenation, looks like. Research by Leddy et al.[177], Len et al.[129], Chen et al.[127] and others[11,16,126,130] has shown that a concussion will hamper not only the ability to control CBF, but also the ability of the brain to consume and utilize oxygen in a normal

manner. Therefore, by understanding how a healthy brain responds to maximal exercise, it may be possible to examine an individual who has suffered a concussion following an exercise test and compare and contrast their results to a healthy recovery. Through this method physicians or other medical professionals may be able to accurately diagnose a patient, or more precisely detect when a patient is no longer physiologically suffering from concussion symptoms. As a result, the generally inaccurate, easily manipulated, subjective nature of concussion diagnosis and RTP methods that are currently held as the gold standard could be improved upon or replaced. This becomes more appealing when the affordability, portability, and ease of use of a cerebral oximeter, in comparison to other techniques for monitoring CBF and cerebral oxygenation, such as BOLD fMRI imaging, is taken into consideration; factors that could help make such a diagnostic method available to many more family physicians, athletic trainers, nurses, or other medical professionals. Notwithstanding, before such implementation can occur, additional research much be completed to maximize the understanding of how cerebral oxygenation fluctuates following maximal bouts of exercise. Doing so would allow standardization of test results with normative values, and consideration of how they may compare to results found within someone who has suffered a concussion.

Limitations

While the findings reported here are both novel and encouraging, there were various limitations throughout this study that need to be addressed. First, while the study population was inclusive for healthy, recreationally active young adults, this does not encapsulate the entirety of the population. It remains possible that those who are inactive, sedentary, older, or who are currently diagnosed with a disease or chronic condition may

respond differently to exercise. Further research is needed to fully reflect the population and create normative data. Next, it is important to take into consideration that these results are only observing the neural oxygenation response to exercise for 15-minutes of passive rest. Multiple subjects did not see their full recovery time taken into consideration, as a deviation from the determined baseline measurements lasted longer than the allocated 15-minutes of recording. Future research should consider extending this time period to approximately 30-minutes to fully encapsulate the potential recovery, as outlined by Ide et al[140]. Moreover, recovery may differ in response to various types of recovery, particularly that which is active in nature. As such, research identifying the effects of various methods of recovery should be conducted. Additionally, therein lies the potential that completing all three exercise tests in one day may have had an underlying effect on the results. This may have been the cause for the difference in baseline lactate concentration levels between anaerobic exercise and aerobic and resistance exercise. These results seemingly differ from those of Cook et al., who found that 10 minutes following a Wingate protocol, pH levels were fully recovered to baseline[178]. The study design of completing anaerobic exercise first, followed by resistance-type and then finally aerobic with 30-minte total recovery between each, was deliberately constructed to minimize or eliminate the potential after-effects of completing the tests in a relatively short period of time, so each exercise may be treated as independent of the others. Not only has previous research, such as that completed by Cook et al., shown that by 15-minutes following a Wingate test levels of ATP, pH and creatine have all regenerated[178–180] to allow for maximal performance, but findings from Alves et al.[181], Drummond et al.[182], and Collins and Sow[183] all indicate that by having participants complete resistance

exercise before maximal aerobic, and allowing a total of 30-minutes recovery between each, should have been sufficient to allow for maximal performance throughout the testing session. An alternative option to the presently designed protocol would have been randomizing the exercise order that each participant completed the study protocol. While this would theoretically would have been able to account for the potential effect of previously completed exercise tests, the sample size selected for the completed project would have been insufficient to adequately account for each potential scenario at a power large enough to produce significant results. Further research with the adequate resources to complete this research project with a sample size large enough to account for each of the potential randomization scenarios should be completed in future. Finally, a further by-product of completing all three tests on the same day was the previously mentioned increase in pre-test lactate measures detected before the resistance and aerobic protocols. The increased lactate suggests a similar increase in H^+, which may have influenced the fluctuations of oxygenation throughout the recovery stage following resistance and aerobic exercise. The exact impact may have been minimal but remains unknown. Therefore, future research should allow for complete recovery following the anaerobic test and ensure a return back to resting lactate concentrations before progressing.

Conclusions

The findings of this research indicate that within young, healthy, recreationally active adults aged 18-35, it takes the brain longer to restore baseline cerebral oxygenation values following aerobic and anaerobic exercise when compared to resistance exercise following maximal exertion. Aerobic exercise also results in a higher deviation from baseline than both anaerobic and resistance exercise, while all three exercises dropped

below baseline similarly. These results contribute to our understanding of natural neural responses to maximal exercise, which may be used in the future to detect abnormalities in an individual who has suffered a concussion, or as a method to indicate when someone has physiologically recovered from the injury. Moreover, the results may indicate an underlying mechanism as to why aerobic exercise has shown to be a successful treatment mechanism for PCS patients, and that anaerobic exercise may prove to be an equally advantageous tool in the future.

References

1. Public Health Agency of Canada. Chronic Disease Risk Factor Analysis. (2013).
2. Wen, C. P. *et al.* Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *The Lancet* **378,** 1244–1253 (2011).
3. Das, P. & Horton, R. Rethinking our approach to physical activity. *The Lancet* **380,** 189–190 (2012).
4. McCrory, P. *et al.* Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport, Zurich, November 2012. *J. Athl. Train.* **48,** 554–575 (2013).
5. Majerske, C. W. *et al.* Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J. Athl. Train.* **43,** 265–274 (2008).
6. Ding, Q., Ying, Z. & Gómez-Pinilla, F. Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. *Neuroscience* **192,** 773–780 (2011).
7. Aguiar Jr., A. S. *et al.* Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: Involvement of hippocampal plasticity via AKT, CREB and BDNF signaling. *Mech. Ageing Dev.* **132,** 560–567 (2011).
8. Knaepen, K., Goekint, M., Heyman, E. M. & Meeusen, P. D. R. Neuroplasticity — Exercise-Induced Response of Peripheral Brain-Derived Neurotrophic Factor. *Sports Med.* **40,** 765–801 (2012).

9. Leddy, J. J., Baker, J. G., Kozlowski, K., Bisson, L. & Willer, B. Reliability of a graded exercise test for assessing recovery from concussion. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **21,** 89–94 (2011).
10. Leddy, J. J. *et al.* Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *J. Head Trauma Rehabil.* **28,** 241–249 (2013).
11. Clausen, M., Pendergast, D. R., Willer, B. & Leddy, J. Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes. *J. Head Trauma Rehabil.* (2015). doi:10.1097/HTR.0000000000000145
12. Waxman, S. G. *Clinical Neuroanatomy*. (McGraw Hill Educational, 2013).
13. Christian W. Kreipke. *Cerebral Blood Flow, Metabolism, and Head Trauma The Pathotrajectory of Traumatic Brain Injury*. (Springer, 2012).
14. Jean Tamraz. *Atlas of Regional Anatomy of the Brain Using MRI With Functional Correlations*. (Springer Berlin Heidelberg, 2006).
15. Tan, C. O., Meehan, W. P., Iverson, G. L. & Taylor, J. A. Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Neurology* **83,** 1665–1672 (2014).
16. Mutch, W. A. C. *et al.* Brain MRI CO2 stress testing: a pilot study in patients with concussion. *PloS One* **9,** e102181 (2014).
17. Hamner, J. W. & Tan, C. O. Relative Contributions of Sympathetic, Cholinergic, and Myogenic Mechanisms to Cerebral Autoregulation. *Stroke* **45,** 1771–1777 (2014).
18. Paulson, O. B., Strandgaard, S. & Edvinsson, L. Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* **2,** 161–192 (1990).

19. White, R. P., Vallance, P. & Markus, H. S. Effect of inhibition of nitric oxide synthase on dynamic cerebral autoregulation in humans. *Clin. Sci. Lond. Engl. 1979* **99,** 555–560 (2000).
20. Ogoh, S. & Ainslie, P. N. Cerebral blood flow during exercise: mechanisms of regulation. *J. Appl. Physiol.* **107,** 1370–1380 (2009).
21. Ainslie, P. N. & Duffin, J. Integration of cerebrovascular CO2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* **296,** R1473–R1495 (2009).
22. Volianitis, S. & Secher, N. H. Cardiovascular control during whole body exercise. *J. Appl. Physiol. Bethesda Md 1985* jap.00674.2015 (2016). doi:10.1152/japplphysiol.00674.2015
23. Donovan, J., Cancelliere, C. & Cassidy, J. D. Summary of the findings of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Chiropr. Man. Ther.* **22,** 38 (2014).
24. Congress of Neurological Surgeons: Proceedings of the Congress of Neurological Surgeons in 1964: Report of the Ad Hoc Committee to Study Head Injury Nomenclature. *Clin. Neurosurg.* **12,** 386–394 (1966).
25. Ommaya, A. K. & Gennarelli, T. A. Cerebral Concussion and Traumatic Unconsciousness. *Brain* **97,** 633–654 (1974).
26. Colorado Medical Society. Report of the Sports Medicine Committee: Guidelines for the Management of Concussions in Sports (revised). *Colo. Med. Soc.* (1991).

27. Kelly JP *et al.* Concussion in sports: Guidelines for the prevention of catastrophic outcome. *JAMA* **266,** 2867–2869 (1991).
28. McCrory, P. *et al.* Summary and agreement statement of the second international conference on concussion in sport, prague 2004. *Phys. Sportsmed.* **33,** 29–44 (2005).
29. The Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J Head Trauma Rehabil* **8,** 86–87 (1993).
30. Stoller, J. *et al.* Do family physicians, emergency department physicians, and pediatricians give consistent sport-related concussion management advice? *Can. Fam. Physician* **60,** 548–552 (2014).
31. Sosin, D. M., Sniezek, J. E. & Thurman, D. J. Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj.* **10,** 47–54 (1996).
32. Thurman D & Guerrero J. Trends in hospitalization associated with traumatic brain injury. *JAMA* **282,** 954–957 (1999).
33. Fu, T. S., Jing, R., McFaull, S. R. & Cusimano, M. D. Recent trends in hospitalization and in-hospital mortality associated with traumatic brain injury in Canada: A nationwide, population-based study. *J. Trauma Acute Care Surg.* (2015). doi:10.1097/TA.0000000000000733
34. Kristman, V. L. *et al.* Methodological Issues and Research Recommendations for Prognosis After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch. Phys. Med. Rehabil.* **95,** S265–S277 (2014).

35. Deb, S. ICD-10 codes detect only a proportion of all head injury admissions. *Brain Inj.* **13,** 369–373 (1999).

36. Tate, R. l., McDonald, S. & Lulham, J. m. Incidence of hospital-treated traumatic brain injury in an Australian community. *Aust. N. Z. J. Public Health* **22,** 419–423 (1998).

37. Cassidy, J. D. *et al.* Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J. Rehabil. Med. Off. J. UEMS Eur. Board Phys. Rehabil. Med.* 28–60 (2004).

38. Wrightson, P. & Gronwall, D. Mild head injury in New Zealand: incidence of injury and persisting symptoms. *N. Z. Med. J.* **111,** 99–101 (1998).

39. Peloso, P. M., von Holst, H. & Borg, J. Mild traumatic brain injuries presenting to swedish hospitals in 1987-2000. *J. Rehabil. Med. Taylor Francis Ltd* **36,** 22–27 (2004).

40. Langlois, J. A., Rutland-Brown, W. & Wald, M. M. The epidemiology and impact of traumatic brain injury: a brief overview. *J. Head Trauma Rehabil.* **21,** 375–378 (2006).

41. Cassidy, J. D., Boyle, E. & Carroll, L. J. Population-Based, Inception Cohort Study of the Incidence, Course, and Prognosis of Mild Traumatic Brain Injury After Motor Vehicle Collisions. *Arch. Phys. Med. Rehabil.* **95,** S278–S285 (2014).

42. Lincoln, A. E. *et al.* Trends in Concussion Incidence in High School Sports A Prospective 11-Year Study. *Am. J. Sports Med.* **39,** 958–963 (2011).

43. Rosenthal, J. A., Foraker, R. E., Collins, C. L. & Comstock, R. D. National High School Athlete Concussion Rates From 2005-2006 to 2011-2012. *Am. J. Sports Med.* 0363546514530091 (2014). doi:10.1177/0363546514530091

44. Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W. & Comstock, R. D. Concussions among United States high school and collegiate athletes. *J. Athl. Train.* **42,** 495–503 (2007).

45. Marar, M., McIlvain, N. M., Fields, S. K. & Comstock, R. D. Epidemiology of concussions among United States high school athletes in 20 sports. *Am. J. Sports Med.* **40,** 747–755 (2012).

46. Dompier, T. P. *et al.* Incidence of Concussion During Practice and Games in Youth, High School, and Collegiate American Football Players. *JAMA Pediatr.* (2015). doi:10.1001/jamapediatrics.2015.0210

47. Delaney, J. S., Lacroix, V. J., Leclerc, S. & Johnston, K. M. Concussions during the 1997 Canadian Football League season. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **10,** 9–14 (2000).

48. Llewellyn, T., Burdette, G. T., Joyner, A. B. & Buckley, T. A. Concussion reporting rates at the conclusion of an intercollegiate athletic career. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **24,** 76–79 (2014).

49. McCrea, M., Hammeke, T., Olsen, G., Leo, P. & Guskiewicz, K. Unreported concussion in high school football players: implications for prevention. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **14,** 13–17 (2004).

50. Register-Mihalik, J. K. *et al.* Knowledge, Attitude, and Concussion-Reporting Behaviors Among High School Athletes: A Preliminary Study. *J. Athl. Train.* **48,** 645–653 (2013).

51. Meehan, W. P. & Bachur, R. G. Sport-Related Concussion. *Pediatrics* **123,** 114–123 (2009).

52. Delaney, J. S., Lamfookon, C., Bloom, G. A., Al-Kashmiri, A. & Correa, J. A. Why University Athletes Choose Not to Reveal Their Concussion Symptoms During a Practice or Game. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* (2014). doi:10.1097/JSM.0000000000000112

53. Kaut, K. P., DePompei, R., Kerr, J. & Congeni, J. Reports of head injury and symptom knowledge among college athletes: implications for assessment and educational intervention. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **13,** 213–221 (2003).

54. Robbins, C. A. *et al.* Self-reported concussion history: impact of providing a definition of concussion. *Open Access J. Sports Med.* **5,** 99–103 (2014).

55. Martin, K., Hrubeniuk, T. J. & Leiter, J. Concussions in rugby: incidence, knowledge and attitudes. *Manuscr. Prog.*

56. Giza, C. C. *et al.* Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* **80,** 2250–2257 (2013).

57. Giza, C. C. & Hovda, D. A. The Neurometabolic Cascade of Concussion. *J. Athl. Train.* **36,** 228–235 (2001).

58. Giza, C. C. & Hovda, D. A. The new neurometabolic cascade of concussion. *Neurosurgery* **75 Suppl 4,** S24-33 (2014).

59. Barkhoudarian, G., Hovda, D. A. & Giza, C. C. The Molecular Pathophysiology of Concussive Brain Injury. *Clin. Sports Med.* **30,** 33–48 (2011).

60. Julian, F. J. & Goldman, D. E. The Effects of Mechanical Stimulation on Some Electrical Properties of Axons. *J. Gen. Physiol.* **46,** 297–313 (1962).

61. Takahashi, H., Manaka, S. & Sano, K. Changes in extracellular potassium concentration in cortex and brain stem during the acute phase of experimental closed head injury. *J. Neurosurg.* **55,** 708–717 (1981).

62. Katayama, Y., Becker, D. P., Tamura, T. & Hovda, D. A. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J. Neurosurg.* **73,** 889–900 (1990).

63. Yoshino, A., Hovda, D. A., Kawamata, T., Katayama, Y. & Becker, D. P. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res.* **561,** 106–119 (1991).

64. Xiong, Y., Gu, Q., Peterson, P. L., Muizelaar, J. P. & Lee, C. P. Mitochondrial dysfunction and calcium perturbation induced by traumatic brain injury. *J. Neurotrauma* **14,** 23–34 (1997).

65. Fineman, I., Hovda, D. A., Smith, M., Yoshino, A. & Becker, D. P. Concussive brain injury is associated with a prolonged accumulation of calcium: a45Ca autoradiographic study. *Brain Res.* **624,** 94–102 (1993).

66. Leão, A. A. P. Further Observations on the Spreading Depression of Activity in the Cerebral Cortex. *J. Neurophysiol.* **10,** 409–414 (1947).

67. Kubota, M. *et al.* Changes of local cerebral glucose utilization, DC potential and extracellular potassium concentration in experimental head injury of varying severity. *Neurosurg. Rev.* **12,** 393–399 (1989).

68. Sunami, K. *et al.* Hypermetabolic state following experimental head injury. *Neurosurg. Rev.* **12 Suppl 1,** 400–411 (1989).

69. Meyer, J. S., Kondo, A., Nomura, F., Sakamoto, K. & Teraura, T. Cerebral Hemodynamics and Metabolism Following Experimental Head Injury. *J. Neurosurg.* **32,** 304–319 (1970).

70. Nilsson, B. & Pontén, U. Experimental head injury in the rat. *J. Neurosurg.* **47,** 252–261 (1977).

71. Yang, M. S., DeWitt, D. S., Becker, D. P. & Hayes, R. L. Regional brain metabolite levels following mild experimental head injury in the cat. *J. Neurosurg.* **63,** 617–621 (1985).

72. Verweij, B. H. *et al.* Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). *Neurol. Res.* **19,** 334–339 (1997).

73. Kalimo, H., Rehncrona, S. & Söderfeldt, B. The role of lactic acidosis in the ischemic nerve cell injury. *Acta Neuropathol. Suppl.* **7,** 20–22 (1981).

74. Kalimo, H., Rehncrona, S., Söderfeldt, B., Olsson, Y. & Siesjö, B. K. Brain Lactic Acidosis and Ischemic Cell Damage: 2. Histopathology. *J. Cereb. Blood Flow Metab.* **1,** 313–327 (1981).

75. Mihalik, J. P. *et al.* Posttraumatic migraine characteristics in athletes following sports-related concussion. *J. Neurosurg.* **102,** 850–855 (2005).

76. Cobb, S. & Battin, B. Second-impact syndrome. *J. Sch. Nurs. Off. Publ. Natl. Assoc. Sch. Nurses* **20,** 262–267 (2004).

77. Prins, M. L., Alexander, D., Giza, C. C. & Hovda, D. A. Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability. *J. Neurotrauma* **30,** 30–38 (2012).

78. Pettus, E. H., Christman, C. W., Giebel, M. L. & Povlishock, J. T. Traumatically induced altered membrane permeability: its relationship to traumatically induced reactive axonal change. *J. Neurotrauma* **11,** 507–522 (1994).

79. Pettus, E. H. & Povlishock, J. T. Characterization of a distinct set of intra-axonal ultrastructural changes associated with traumatically induced alteration in axolemmal permeability. *Brain Res.* **722,** 1–11 (1996).

80. Maxwell, W. L. & Graham, D. I. Loss of axonal microtubules and neurofilaments after stretch-injury to guinea pig optic nerve fibers. *J. Neurotrauma* **14,** 603–614 (1997).

81. Maxwell, W. L., Povlishock, J. T. & Graham, D. L. A mechanistic analysis of nondisruptive axonal injury: a review. *J. Neurotrauma* **14,** 419–440 (1997).

82. Blumbergs, P. C. *et al.* Staining of amyloid precursor protein to study axonal damage in mild head injury. *Lancet Lond. Engl.* **344,** 1055–1056 (1994).

83. Povlishock, J. T. & Pettus, E. H. Traumatically induced axonal damage: evidence for enduring changes in axolemmal permeability with associated cytoskeletal change. *Acta Neurochir. Suppl.* **66,** 81–86 (1996).

84. Miller, L. P. *et al.* Excitatory amino acid receptor subtype binding following traumatic brain injury. *Brain Res.* **526,** 103–107 (1990).

85. Sihver, S. *et al.* Changes in mACh, NMDA and GABAA receptor binding after lateral fluid-percussion injury: in vitro autoradiography of rat brain frozen sections. *J. Neurochem.* **78,** 417–423 (2001).

86. Osteen, C. L., Giza, C. C. & Hovda, D. A. Injury-induced alterations in N-methyl-D-aspartate receptor subunit composition contribute to prolonged 45calcium accumulation following lateral fluid percussion. *Neuroscience* **128,** 305–322 (2004).

87. Lowenstein, D. H., Thomas, M. J., Smith, D. H. & McIntosh, T. K. Selective vulnerability of dentate hilar neurons following traumatic brain injury: a potential mechanistic link between head trauma and disorders of the hippocampus. *J. Neurosci. Off. J. Soc. Neurosci.* **12,** 4846–4853 (1992).

88. Wilde, E. A. *et al.* Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology* **70,** 948–955 (2008).

89. Lipton, M. L. *et al.* Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: a voxel-wise analysis of diffusion tensor imaging. *J. Neurotrauma* **25,** 1335–1342 (2008).

90. Spain, A. *et al.* Mild fluid percussion injury in mice produces evolving selective axonal pathology and cognitive deficits relevant to human brain injury. *J. Neurotrauma* **27,** 1429–1438 (2010).

91. Sanders, M. J., Sick, T. J., Perez-Pinzon, M. A., Dietrich, W. D. & Green, E. J. Chronic failure in the maintenance of long-term potentiation following fluid percussion injury in the rat. *Brain Res.* **861,** 69–76 (2000).

92. D'Ambrosio, R., Maris, D. O., Grady, M. S., Winn, H. R. & Janigro, D. Selective loss of hippocampal long-term potentiation, but not depression, following fluid percussion injury. *Brain Res.* **786,** 64–79 (1998).

93. Vagnozzi, R. M. D. *et al.* Hypothesis of the Postconcussive Vulnerable Brain: Experimental Evidence of Its Metabolic Occurrence. *Neurosurgery* **57,** 164–171 (2005).

94. Longhi, L. *et al.* Temporal window of vulnerability to repetitive experimental concussive brain injury. *Neurosurgery* **56,** 364-374-374 (2005).

95. Schneider, R. C. in *Head and Neck Injuries in Football: Mechanisms, Treatment, and Prevention* 77–126 (Williams & Wilkins, 1973).

96. Cantu, R. C. Second-impact syndrome. *Clin. Sports Med.* **17,** 37–44 (1998).

97. Wetjen, N. M., Pichelmann, M. A. & Atkinson, J. L. D. Second impact syndrome: concussion and second injury brain complications. *J. Am. Coll. Surg.* **211,** 553–557 (2010).

98. Saunders RL & Harbaugh RE. The second impact in catastrophic contact-sports head trauma. *JAMA* **252,** 538–539 (1984).

99. Lovell, M. R. *et al.* Measurement of Symptoms Following Sports-Related Concussion: Reliability and Normative Data for the Post-Concussion Scale. *Appl. Neuropsychol.* **13,** 166–174 (2006).

100. Guskiewicz, K. M., Weaver, N. L., Padua, D. A. & Garrett, W. E. Epidemiology of concussion in collegiate and high school football players. *Am. J. Sports Med.* **28,** 643–650 (2000).

101. Collie, A., Makdissi, M., Maruff, P., Bennell, K. & McCrory, P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J. Neurol. Neurosurg. Psychiatry* **77,** 241–245 (2006).

102. Fazio, V. C., Lovell, M. R., Pardini, J. E. & Collins, M. W. The relation between post concussion symptoms and neurocognitive performance in concussed athletes. *NeuroRehabilitation* **22,** (2007).

103. Cancelliere, C. *et al.* Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch. Phys. Med. Rehabil.* **95,** S210-229 (2014).

104. Broglio, S. P., Macciocchi, S. N. & Ferrara, M. S. Neurocognitive Performance of Concussed Athletes When Symptom Free. *J. Athl. Train.* **42,** 504 (2007).

105. Guskiewicz, K. M. *et al.* Evidence-based approach to revising the SCAT2: introducing the SCAT3. *Br. J. Sports Med.* **47,** 289–293 (2013).

106. Gall, B., Parkhouse, W. S. & Goodman, D. Exercise following a sport induced concussion. *Br. J. Sports Med.* **38,** 773–777 (2004).

107. Gaetz, M. B. & Iverson, G. L. Sex differences in self-reported symptoms after aerobic exercise in non-injured athletes: implications for concussion management programmes. *Br. J. Sports Med.* **43,** 508–513 (2009).

108. Morissette, M. P., Cordingley, D., Ellis, M. J., MacDonald, P. B. & Leiter, J. R. The effect of maximal aerobic capacity fitness testing on Sport Concussion Assessment Tool-3 scores in healthy adult subjects. *Curr. Res. Concussion* **1,** 19–21 (2014).

109. McCrea M, Guskiewicz KM, Marshall SW & et al. Acute effects and recovery time following concussion in collegiate football players: The ncaa concussion study. *JAMA* **290,** 2556–2563 (2003).

110. Galetta, K. M. *et al.* The King–Devick test and sports-related concussion: Study of a rapid visual screening tool in a collegiate cohort. *J. Neurol. Sci.* **309,** 34–39 (2011).

111. Galetta, M. S. *et al.* Saccades and memory: baseline associations of the King-Devick and SCAT2 SAC tests in professional ice hockey players. *J. Neurol. Sci.* **328,** 28–31 (2013).

112. King, D., Clark, T. & Gissane, C. Use of a rapid visual screening tool for the assessment of concussion in amateur rugby league: a pilot study. *J. Neurol. Sci.* **320,** 16–21 (2012).

113. King, D., Brughelli, M., Hume, P. & Gissane, C. Concussions in amateur rugby union identified with the use of a rapid visual screening tool. *J. Neurol. Sci.* **326,** 59–63 (2013).

114. King, D., Brughelli, M., Hume, P. & Gissane, C. Assessment, management and knowledge of sport-related concussion: systematic review. *Sports Med. Auckl. NZ* **44,** 449–471 (2014).

115. Nakayama, Y., Covassin, T., Schatz, P., Nogle, S. & Kovan, J. Examination of the Test-Retest Reliability of a Computerized Neurocognitive Test Battery. *Am. J. Sports Med.* **42,** 2000–2005 (2014).

116. Bruce, J., Echemendia, R., Meeuwisse, W., Comper, P. & Sisco, A. 1 year test–retest reliability of ImPACT in professional ice hockey players. *Clin. Neuropsychol.* **28,** 14–25 (2014).

117. Elbin, R. J., Schatz, P. & Covassin, T. One-Year Test-Retest Reliability of the Online Version of ImPACT in High School Athletes. *Am. J. Sports Med.* **39,** 2319–2324 (2011).

118. Alsalaheen, B., Stockdale, K., Pechumer, D. & Broglio, S. P. Measurement Error in the Immediate Postconcussion Assessment and Cognitive Testing (ImPACT): Systematic Review. *J. Head Trauma Rehabil.* (2015). doi:10.1097/HTR.0000000000000175

119. Centers for Disease Control and Prevention. Heads up: facts for Physicians about mild traumatic brain injury (mTBI). (2012).

120. Kruijk, J. R. de, Leffers, P., Meerhoff, S., Rutten, J. & Twijnstra, A. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. *J. Neurol. Neurosurg. Psychiatry* **73,** 167–172 (2002).

121. Lovell, M. R. *et al.* Recovery from mild concussion in high school athletes. *J. Neurosurg.* **98,** 296–301 (2003).

122. Doolan, A. W., Day, D. D., Maerlender, A. C., Goforth, M. & Brolinson, P. G. A Review of Return to Play Issues and Sports-Related Concussion. *Ann. Biomed. Eng.* **40,** 106–113 (2012).

123. Leddy, J. J., Kozlowski, K., Fung, M., Pendergast, D. R. & Willer, B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. *NeuroRehabilitation* **22,** (2007).

124. Collins, M. W., Kontos, A. P., Reynolds, E., Murawski, C. D. & Fu, F. H. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surg. Sports Traumatol. Arthrosc.* **22,** 235–246 (2013).

125. Leddy, J. J. *et al.* A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin. J. Sport Med. Off. J. Can. Acad. Sport Med.* **20,** 21–27 (2010).

126. Maugans, T. A., Farley, C., Altaye, M., Leach, J. & Cecil, K. M. Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics* **129,** 28–37 (2012).

127. Chen, J.-K. *et al.* Functional abnormalities in symptomatic concussed athletes: an fMRI study. *NeuroImage* **22,** 68–82 (2004).

128. Golding, E. M. *et al.* Cerebrovascular reactivity to CO2 and hypotension after mild cortical impact injury. *Am. J. Physiol. - Heart Circ. Physiol.* **277,** H1457–H1466 (1999).

129. Len, T. K. *et al.* Cerebrovascular reactivity impairment after sport-induced concussion. *Med. Sci. Sports Exerc.* **43,** 2241–2248 (2011).

130. Jünger, E. C. *et al.* Cerebral autoregulation following minor head injury. *J. Neurosurg.* **86,** 425–432 (1997).

131. DeWitt, D. S. & Prough, D. S. Traumatic Cerebral Vascular Injury: The Effects of Concussive Brain Injury on the Cerebral Vasculature. *J. Neurotrauma* **20,** 795–825 (2003).

132. Simard, J. M. & Bellefleur, M. Systemic arterial hypertension in head trauma. *Am. J. Cardiol.* **63,** C32–C35 (1989).

133. Rooks, C. R., Thom, N. J., McCully, K. K. & Dishman, R. K. Effects of incremental exercise on cerebral oxygenation measured by near-infrared spectroscopy: A systematic review. *Prog. Neurobiol.* **92,** 134–150 (2010).

134. Gonzalez-Alonso, J. *et al.* Brain and central haemodynamics and oxygenation during maximal exercise in humans. *J. Physiol.* **557,** 331–342 (2004).

135. Meyer, T., Faude, O., Scharhag, J., Urhausen, A. & Kindermann, W. Is lactic acidosis a cause of exercise induced hyperventilation at the respiratory compensation point? *Br. J. Sports Med.* **38,** 622–625 (2004).

136. Tempest, G. D., Eston, R. G. & Parfitt, G. Prefrontal cortex haemodynamics and affective responses during exercise: a multi-channel near infrared spectroscopy study. *PloS One* **9,** e95924 (2014).

137. Olin, J. T., Dimmen, A. C., Subudhi, A. W. & Roach, R. C. Cerebral blood flow and oxygenation at maximal exercise: the effect of clamping carbon dioxide. *Respir. Physiol. Neurobiol.* **175,** 176–180 (2011).

138. Bhambhani, Y., Malik, R. & Mookerjee, S. Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. *Respir. Physiol. Neurobiol.* **156,** 196–202 (2007).

139. Secher, N. H., Seifert, T. & Lieshout, J. J. V. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J. Appl. Physiol.* **104,** 306–314 (2008).

140. Ide, K., Schmalbruch, I. K., Quistorff, B., Horn, A. & Secher, N. H. Lactate, glucose and O2 uptake in human brain during recovery from maximal exercise. *J. Physiol.* **522,** 159–164 (2000).

141. Shibuya, K.-I., Tanaka, J., Kuboyama, N. & Ogaki, T. Cerebral oxygenation during intermittent supramaximal exercise. *Respir. Physiol. Neurobiol.* **140,** 165–172 (2004).

142. Edwards, M. R., Martin, D. H. & Hughson, R. L. Cerebral hemodynamics and resistance exercise. *Med. Sci. Sports Exerc.* **34,** 1207–1211 (2002).

143. Lassen, N. A. Cerebral Blood Flow and Oxygen Consumption in Man. *Physiol. Rev.* **39,** 183–238 (1959).

144. Brys, M., Brown, C. M., Marthol, H., Franta, R. & Hilz, M. J. Dynamic cerebral autoregulation remains stable during physical challenge in healthy persons. *Am. J. Physiol. - Heart Circ. Physiol.* **285,** H1048–H1054 (2003).

145. Koch, A. *et al.* Cerebral autoregulation is temporarily disturbed in the early recovery phase after dynamic resistance exercise. *Clin. Auton. Res. Off. J. Clin. Auton. Res. Soc.* **15,** 83–91 (2005).

146. Birch, A. A., Dirnhuber, M. J., Hartley-Davies, R., Iannotti, F. & Neil-Dwyer, G. Assessment of Autoregulation by Means of Periodic Changes in Blood Pressure. *Stroke* **26,** 834–837 (1995).

147. Giller, C. A., Giller, A. M., Cooper, C. R. & Hatab, M. R. Evaluation of the cerebral hemodynamic response to rhythmic handgrip. *J. Appl. Physiol.* **88,** 2205–2213 (2000).

148. Pereira, M. I. R., Gomes, P. S. C. & Bhambhani, Y. N. A brief review of the use of near infrared spectroscopy with particular interest in resistance exercise. *Sports Med. Auckl. NZ* **37,** 615–624 (2007).

149. Brzycki, M. Strength Testing—Predicting a One-Rep Max from Reps-to-Fatigue. *J. Phys. Educ. Recreat. Dance* **64,** 88–90 (1993).

150. Canadian Society for Exercise Physiology. *Canadian Society for Exercise Physiology - Physical Activity Training for Health (CSEP-PATH)*. (Canadian Society for Exercise Physiology, 2013).

151. Jackson, A. S. & Pollock, M. L. Generalized equations for predicting body density of men. *Br. J. Nutr.* **40,** 497 (1978).

152. Jackson, A., Pollock, M. & Ward, A. Generalized equations for predicting body density of women. *Med. Sci. Sports Exerc.* **12,** 175–181 (1979).

153. Bar-Or, O. The Wingate anaerobic test. An update on methodology, reliability and validity. *Sports Med. Auckl. NZ* **4,** 381–394 (1987).

154. de Salles Painelli, V. *et al.* Creatine supplementation prevents acute strength loss induced by concurrent exercise. *Eur. J. Appl. Physiol.* (2014). doi:10.1007/s00421-014-2903-0

155. Bell, G. J., Syrotuik, D., Martin, T. P., Burnham, R. & Quinney, H. A. Effect of concurrent strength and endurance training on skeletal muscle properties and hormone concentrations in humans. *Eur. J. Appl. Physiol.* **81,** 418–427 (2000).

156. Irani, F., Platek, S. M., Bunce, S., Ruocco, A. C. & Chute, D. Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. *Clin. Neuropsychol.* **21,** 9–37 (2007).

157. Green, M. S., Sehgal, S. & Tariq, R. Near-Infrared Spectroscopy The New Must Have Tool in the Intensive Care Unit? *Semin. Cardiothorac. Vasc. Anesth.* 1089253216644346 (2016). doi:10.1177/1089253216644346

158. Redford, D., Paidy, S. & Kashif, F. Absolute and Trend Accuracy of a New Regional Oximeter in Healthy Volunteers During Controlled Hypoxia: *Anesth. Analg.* **119,** 1315–1319 (2014).

159. Strangman, G., Culver, J. P., Thompson, J. H. & Boas, D. A. A Quantitative Comparison of Simultaneous BOLD fMRI and NIRS Recordings during Functional Brain Activation. *NeuroImage* **17,** 719–731 (2002).

160. Toronov, V. *et al.* Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Med. Phys.* **28,** 521–527 (2001).

161. Jasdzewski, G. *et al.* Differences in the hemodynamic response to event-related motor and visual paradigms as measured by near-infrared spectroscopy. *NeuroImage* **20,** 479–488 (2003).

162. Perrey, S. Non-invasive NIR spectroscopy of human brain function during exercise. *Methods San Diego Calif* **45,** 289–299 (2008).

163. Plichta, M. M. *et al.* Event-related visual versus blocked motor task: detection of specific cortical activation patterns with functional near-infrared spectroscopy. *Neuropsychobiology* **53,** 77–82 (2006).

164. Leenders, K. L. *et al.* Cerebral Blood Flow, Blood Volume and Oxygen Utilization. *Brain* **113,** 27–47 (1990).

165. Yosefy, C., Hay, E., Nasri, Y., Magen, E. & Reisin, L. End tidal carbon dioxide as a predictor of the arterial Pco2 in the emergency department setting. *Emerg. Med. J.* **21,** 557–559 (2004).

166. Kameyama, M., Fukuda, M., Uehara, T. & Mikuni, M. Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. *NeuroImage* **22,** 1715–1721 (2004).

167. Gur, R. C. *et al.* Sex Differences in Regional Cerebral Glucose Metabolism During a Resting State. *Science* **267,** 528–531 (1995).

168. Aanerud, J., Borghammer, P., Rodell, A., Jónsdottir, K. Y. & Gjedde, A. Sex differences of human cortical blood flow and energy metabolism. *J. Cereb. Blood Flow Metab.* 0271678X16668536 (2016). doi:10.1177/0271678X16668536

169. Pakkenberg, B. & Gundersen, H. J. G. Neocortical neuron number in humans: Effect of sex and age. *J. Comp. Neurol.* **384,** 312–320 (1997).

170. Alonso-Nanclares, L., Gonzalez-Soriano, J., Rodriguez, J. R. & DeFelipe, J. Gender differences in human cortical synaptic density. *Proc. Natl. Acad. Sci.* **105,** 14615–14619 (2008).

171. Kinni, H. *et al.* Cerebral metabolism after forced or voluntary physical exercise. *Brain Res.* **1388,** 48–55 (2011).

172. Dorr, A. *et al.* Effects of voluntary exercise on structure and function of cortical microvasculature. *J. Cereb. Blood Flow Metab.* 0271678X16669514 (2016). doi:10.1177/0271678X16669514

173. Tang, K., Xia, F. C., Wagner, P. D. & Breen, E. C. Exercise-induced VEGF transcriptional activation in brain, lung and skeletal muscle. *Respir. Physiol. Neurobiol.* **170,** 16–22 (2010).

174. Cechetti, F. *et al.* Forced treadmill exercise prevents oxidative stress and memory deficits following chronic cerebral hypoperfusion in the rat. *Neurobiol. Learn. Mem.* **97,** 90–96 (2012).

175. Rojas Vega, S. *et al.* Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Res.* **1121,** 59–65 (2006).

176. Yarrow, J. F., White, L. J., McCoy, S. C. & Borst, S. E. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neurosci. Lett.* **479,** 161–165 (2010).

177. Leddy, J. J., Kozlowski, K., Fung, M., Pendergast, D. R. & Willer, B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. *NeuroRehabilitation* **22,** 199–205 (2007).

178. Cooke, S. R., Petersen, S. R. & Quinney, H. A. The influence of maximal aerobic power on recovery of skeletal muscle following anaerobic exercise. *Eur. J. Appl. Physiol.* **75,** 512–519 (1997).

179. Söderlund, K. & Hultman, E. ATP and phosphocreatine changes in single human muscle fibers after intense electrical stimulation. *Am. J. Physiol.* **261,** E737-741 (1991).

180. Bogdanis, G. C., Nevill, M. E., Boobis, L. H., Lakomy, H. K. & Nevill, A. M. Recovery of power output and muscle metabolites following 30 s of maximal sprint cycling in man. *J. Physiol.* **482,** 467–480 (1995).

181. Vilacxa Alves, J. *et al.* Does aerobic and strength exercise sequence in the same session affect the oxygen uptake during and postexercise? *J. Strength Cond. Res. Natl. Strength Cond. Assoc.* **26,** 1872–1878 (2012).

182. Drummond, M. J., Vehrs, P. R., Schaalje, G. B. & Parcell, A. C. Aerobic and resistance exercise sequence affects excess postexercise oxygen consumption. *J. Strength* **19,** 332–337 (2005).

183. Collins, M. A. & Snow, T. K. Are adaptations to combined endurance and strength training affected by the sequence of training? *J. Sports Sci.* **11,** 485–491 (1993).

APPENDIX 1

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: **The exploration of cerebral oxygenation as an objective measure of cerebral autonomic function**

Principal Investigator:
Travis Hrubeniuk
[redacted], Winnipeg
[redacted]

Co-Investigators:
Jeff Leiter MSc PhD
[redacted], Winnipeg
[redacted]

Dean Cordingley MSc
[redacted], Winnipeg
[redacted]

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

This research study is being conducted to identify the effects of aerobic, resistance, and anaerobic exercise on cerebral oxygenation after maximal exertion in a healthy population. Secondary objectives are to identify the differences in cerebral oxygenation response between male and female participants, and determine potential associations of cerebral oxygenation with age, height, weight, sex and tobacco use

A total of 28 participants will participate in this study.

Study procedures

If you take part in this study, you will have the following procedures to complete. You will first come to the clinic for an orientation. At this orientation, your first task will be to complete a Physical Activity Readiness questionnaire (PAR-Q Plus) and have your resting heart rate and blood pressure measured, which will indicate if it is safe for you to partake in physical activity. If you are cleared for exercise participation, you will be introduced to a cerebral oximeter and metabolic cart, then partake in a one-repetition maximum leg press test. This orientation will last approximately 20 minutes. Following your orientation, the testing session~~s~~ will be scheduled. The testing session~~s~~ will be scheduled approximately one week from the orientation session.

Prior to the session, it is requested that you do not consume caffeine for two hours, do not drink alcohol for six hours, or engage in strenuous physical activity for 6 hours. Upon arrival, resting blood pressure and heart rate will be recorded. Following which you will complete a 30-second Wingate test, a maximal resistance exercise protocol, and a maximal bike-based aerobic test, in that order. Each test will be separated by 30 minutes of rest. During each you will be hooked up to two non-invasive tools: a metabolic cart and a cerebral oximeter. The metabolic cart will require you to have a mouth piece in, very similar to a mouth guard, which will measure how much air you are breathing out and how much of it is oxygen throughout the duration of each test. The cerebral oximeter will require two sticky pads to be placed on your forehead, and will measure the oxygen saturation levels in the frontal lobe of your brain throughout each test, and for 15-minutes post exercise. Your heart rate and blood pressure will also be measured continuously throughout each test, and for 15-minutes post exercise. Additionally, blood lactate levels will be collected and measured immediately before and following the completion of each exercise test. This will require a small finger prick using a single-use lancet device and analyzer requiring a 50-microliters sample of blood. Analysis of lactate will take a maximum of 60 seconds. Excess blood will be wiped away with sterile gauze and each prick will be treated with an alcohol swab containing 70% isopropyl alcohol and dressed with a bandage. No blood will be stored following analysis. You will be given a maximum of 30 minutes recovery between each of the exercise tests.
The testing session will take approximately three hours.

Participation in the study will be for one week, from the day of orientation to the completion of the testing session.

The researcher may decide to take you off this study if you are unable to meet the requirements of the study.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first.

Risks and Discomforts

Each test implemented requires maximal exertion in an attempt to mimic what is possible during sport participation, which may make some people feel uncomfortable and/or exhausted. These tests may cause soreness in your legs immediately after for the following days. This soreness typically goes away 48 hours after the exercise. Some also find breathing through the mouthpiece uncomfortable, and it may make your mouth feel dry.

Additionally, there is a small chance of infection as a result of the finger prick. In order to further minimize this risk, each prick will be treated with an alcohol swab and immediately dressed to reduce potential exposure.

Benefits

There may or may not be direct benefit to you from participating in this study. We hope the information learned from this study will benefit people with concussions in the future.

Costs

All the procedures, which will be performed as part of this study, are provided at no cost to you.

Payment for participation

You will be given $25.00 per completed study visit to a maximum of $50.00 upon termination of your participation in this research study. Payment will be mailed to you following the termination of your participation.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. All study documents related to you will bear only your assigned patient number and/or initials.

The University of Manitoba Health Research Ethics Board may review records related to the study for quality assurance purposes.

All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be

removed. No information revealing any personal information such as your name, address or telephone number will leave the Pan Am Clinic.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not affect your care at this center. If the study staff feels that it is in your best interest to withdraw you from the study, they will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.
You are not waiving any of your legal rights by signing this consent form, or releasing the investigator(s) from their legal and professional responsibilities.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the Study Coordinator, Travis Hrubeniuk at [redacted].

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at [redacted]

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Results of the Study

All individuals who participate in this study are eligible to receive information on the outcomes of the study, via a 1-page synopsis of the key findings of the research. If you would like to receive information on the results of this study please state your mailing address below:

Address: _____
City: _____
Postal code: _____
Email: _____

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Travis Hrubeniuk and/or his study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by The University of Manitoba Research Ethics Board for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Participant signature_____ Date _____

(day/month/year)

Participant printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____ Date _____

(day/month/year)

Signature: _____

Role in the study: _____