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Acute Metabolic and Neuroendocrine Responses to Maximal Treadmill Exercise in Patients Recovering from Traumatic Brain Injury (TBI)

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Acute Metabolic and Neuroendocrine Responses to Maximal Treadmill Exercise in Patients Recovering from Traumatic Brain Injury (TBI)

by

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Dedication

This dissertation is dedicated to my unborn child and beautiful wife, Jenny Amonette. Thanks for the sense of urgency that compelled me to complete this project. I can't wait to meet you in November (± a few weeks) and love you so much already.

Acknowledgements

As I sit to write the acknowledgements section of this dissertation, I've reflected for the past few days on the academic journey that will presumably end in the next few months. A famous African Proverb reads: "It takes a village to raise a child." The same can be said of a doctoral student – successful completion of any terminal degree is the sum result of a large group of committed teachers and scientists who are often without credit. I want to take a moment to thank some of the key individuals who have steered me on my academic journey. Their dedication and encouragement have compelled me to "finish the race." Although many of them may never read this dissertation, I am forever indebted to them for their time and effort. First, and most importantly, I want to thank my mentor Dr. Kurt Mossberg. Thank you for believing in me as a student, giving me the freedom to choose my own project, dealing with my inconsistencies in writing, and generally taking the time to help me grow as a scientist - I now understand the effort it takes to guide a student through the doctoral process. I could not have asked for a better mentor, teacher, and friend. Second, I want to thank my dissertation committee (Drs. Masel, Moore, Paddon-Jones, Peres, and Urban) for the work you have put into this project. Your guidance, suggestions, and leadership are exceptional and I am so thankful for your willingness to help with this project. I want to extend a special thanks to Dr. Brent Masel, for allowing us to be a part of the team at the Transitional Learning Center (TLC). I also want to express my gratitude to Dr. Paddon-Jones, who in my

first two years at UTMB taught me that science could be fun and spent a great deal of time correcting abstracts and posters. Thanks for including me in your work! Gratitude is due to Paula Skinkis and Pat Lea for their assistance in data collection. Thanks for the early mornings in the lab and always being there when needed. To Shanon Casperson, Dr. Micah Drummond, Dr. Jared Dickerson, Dr. Chris Fry, and Dr. Kyle Timmerman, thank you for teaching me how to function in the biochemistry lab.

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of the late Dr. Don Hagan. So many times though the dissertation process I've remembered days sitting in Dr. Hagan's office editing the twentieth version of a paper. I wish dearly that he could read this dissertation (although I know he would find many errors). I am also thankful for the influence of Dr. Marty Hinman, who mentored me through a couple of projects and introduced me to Dr. Mossberg. Thanks for the friendship and mentorship throughout my career. Finally, thanks to Dr. Gene Coleman and Dr. Terry Dupler. It has been so much fun learning from and teaching with you guys. I am excited to be fully committed finally to the FHP program in a couple of months.

Most importantly, I am thankful to my family who has now dealt with me though 10+ years of college education and the final three months of school where I have been distant from everyone. Mom and Dad, thanks for instilling within me a work ethic and determination that has been essential to the completion of this degree. Also, thanks to my extended immediate family, Robin, Brice, and Logan Phillips. Thanks for bearing with me through all of this. Logan, I miss you more than I could ever express in writing and can't believe you are gone. Also, a special debt of gratitude is owed to Martin and Karen English— thank you for the encouraging words though the years and for letting me marry your beautiful daughter. Jenny, I love you; thanks for being there though the entire process and being the last person to read the countless abstracts, posters, and papers over this past five years. Whether you want me or not, you get your husband back in a couple of months.

A few years ago, I was speaking with my uncle, explaining to him what I was studying in my doctorate. He jokingly asked: "Why didn't you go to school to be the kind of doctor our family can use?" I thought that was a humorous statement and an interesting reflection on public perception of science. R.H. Riffenburgh, a noted clinical researcher stated "When you treat a patient, you have treated a patent. When you do research, you have

treated ten thousand patients."[a] I am not licensed to treat a patient and never will be. However, my sincere hope is that the data contained in this project will be used to make a small difference in the lives of many recovering from a traumatic brain injury.

[a] Quote obtained from Riffenburgh, RH. *Statistics in Medicine* 2nd ed. Burlington, MA: Elsevier Academic Press, 2006, p 1.

Acute Metabolic and Neuroendocrine Responses to Maximal Treadmill Exercise in Patients Recovering from Traumatic Brain Injury (TBI)

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Abstract: Public awareness of the incidence of traumatic brain injury (TBI) increased significantly throughout the past decade. The increased awareness is primarily the result of a heightened understanding of the impact of blast-related TBI in the wars in Iraq and Afghanistan and a renewed interest in sport-related concussion. A TBI can have devastating effects on an individual, yet many of the symptoms are subtle and may not be visibly evident. Impairments caused by TBI can lead to increased morbidity, decreased functional independence, and an increased reliance on the public health-care system. TBI can cause cognitive and behavioral impairments, reduced peak physical and metabolic work capacity, and endocrine irregularities. Chronic fatigue is one of the most common complaints in patients recovering from TBI and affects many facets of life, including the ability to return and contribute to the workforce. It has been documented that patients with a TBI have reduced peak aerobic capacities compared to sedentary controls and that growth hormone (GH) deficiency is associated with lower peak aerobic capacity. Moreover, research suggests

that GH deficiency may be related to perceived fatigue. The hormonal response to exercise is predictable and well documented in apparently healthy controls (CON), but to date few if any studies have quantified the endocrine response to exercise in TBI. The series of studies in this dissertation demonstrate that (1) peak metabolic, ventilatory, and cardiovascular responses are lower than predicted in patients with a TBI, irrespective of gender; (2) peak metabolic and ventilatory anaerobic threshold (V_{AT}) responses to exercise are lower in patients with a TBI compared to healthy, sedentary CON; (3) the GH/insulin-like growth factor-1 response to exercise is similar in patients with a TBI and sedentary CON, but there are marked differences in the responses of prolactin (PRO) and cortisol (COR); and finally (4) perceived fatigue is associated with lower resting insulin-like growth factor-I (IGF-1) levels and V_{AT} responses, but not the exercising response of hormones. Together, the results strongly support the use of intense physical exercise in rehabilitation of patients recovering from a TBI.

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PROJECT BACKGROUND

Chapter 1: Project Overview and Specific Aims

The Centers for Disease Control (CDC) National Hospital and Ambulatory Medical Care Survey (NHAMCS) data set suggests an estimated 1.3 million Americans experience a traumatic brain injury (TBI) each year (Centers for Disease Control and Prevention, 2001). TBI may result in numerous functional impairments including chronic fatigue, cognitive and behavioral dysfunction, reduced aerobic capacity, and hormonal irregularities among others. As a result of these impairments, it is estimated that approximately 90,000 patients experience long-term disability as a consequence of TBI (Centers for Disease Control and Prevention, 2001; Thurman *et al.,* 1999a). From a national health-care perspective, the CDC estimated that the cost of TBI was approximately $60 billion in 2000 (Centers for Disease Control and Prevention, 2001). Patients with a TBI are often physically impaired and unable to return to their occupation, further exaggerating the economic burden on society and the personal/social disabilities of the individual. Chronic fatigue is a near universal complain of patients recovering from a TBI, and research indicates it may be a primary cause of their inability to tolerate work (Englander *et al.,* 2010; Hillier *et al.,* 1997; Kempf *et al.,* 2010).

A frequent co-morbidity associated with TBI is hypopituitarism (Berg *et al.,* 2010; Herrmann *et al.,* 2006; Ives *et al.,* 2007; Landau *et al.,* 1978; Lieberman *et al.,* 2001). Largely underreported in the past, it is now estimated that 10–25% of patients with a TBI suffer a deficiency in growth hormone (GH) alone (Lieberman *et al.,* 2001; Popovic, 2005;

Urban, 2006; Urban *et al,.* 2005). Moreover, research indicates that patients with a TBI may also experience dysfunction in other hormonal axes (Rothman *et al.,* 2007; Wachter *et al.,* 2009; Webster and Bell, 1997). This is of profound importance because hormones, such as GH, modulate homeostasis in essential human processes associated with increased physical work (e.g. protein synthesis, lipolysis, glycogen synthesis, glucose utilization, metabolic functions, and increased cardiac output among others). It has also been reported that peak oxygen consumption (VO_2 peak), heart rate, and ventilation are lower in patients with a TBI compared to matched controls. Mossberg and colleagues reported that the VO_2 peak of patients with a TBI was 25% lower than age-matched controls (Mossberg *et al.,* 2007). Moreover, there is evidence that patients with a TBI, insufficient in GH levels possess lower aerobic capacities (Mossberg *et al.,* 2008) and also report greater fatigue. This suggests hormonal mechanisms may be partially related to a reduced aerobic capacity and chronic fatigue in TBI (Bushnik *et al.,* 2007).

In apparently healthy individuals, the obvious treatment for fatigue resulting from reduced aerobic capacity is physical activity - specifically vigorous exercise. However, this treatment recommendation assumes the chronic and acute physiological mechanisms that mediate metabolic function are intact and actively respond to facilitate adaptation (e.g. endocrine responses). The endocrine responses to physical exertion are well documented in healthy individuals, but to date, few data exist describing the hormonal response to exertion in patients who have experienced a TBI. Because of the now well-documented incidence of hypopituitarism, patients with a TBI may experience an altered or blunted hormonal response to physical exertion. This altered response could be related to perceived fatigue and might limit the physical exertion capabilities of patients with a TBI. Furthermore, a blunted

hormonal response to exercise could influence parameters of exercise prescription or necessitate hormone replacement to facilitate exercise adaptation.

SPECIFIC AIMS

Specific Aim One

In patients with a TBI, it was determined if peak metabolic, ventilatory, and cardiovascular responses to maximal graded exercise are lower than age-predicted normative values and if the potential differences vary by gender.

1. Hypothesis - Peak aerobic capacity, ventilation, and heart rate would be significantly lower than age-predicted normative values in patients with a TBI, irrespective of gender.

To test hypothesis one, 32 patients with a TBI (16 male; 16 female) were matched by age, ambulatory speed, and years since injury. Patients performed a peak graded treadmill test to volitional failure while exercising metabolic, ventilatory, and cardiovascular responses were measured continuously. The peak exercise responses of VO_2, volume of carbon dioxide production (VCO_2), minute ventilation (V_E), and heart rate (HR) were compared to predicted peak values within gender.

Specific Aim Two

In patients with a TBI, it was determined if ventilatory anaerobic threshold (V_{AT}) or peak aerobic, ventilatory, or cardiovascular responses differ from age- and gender-matched healthy controls with similar BMI's.

2. Hypothesis - When compared to age- and gender-matched controls, metabolic, ventilatory, and cardiovascular responses at peak exercise and V_{AT} would be significantly lower in patients with a TBI.

Hypothesis two was tested by matching 19 patients with a TBI and 19 apparently healthy controls (CON) by age and gender. After each participant performed a peak graded treadmill test, V_{AT} was calculated using a previously established method (Beaver *et al.,* 1986). Briefly, the (1) change in the relationship between VO_2 to VCO_2, (2) the nadir point of ventilatory equivalent of VO_2, (3) the nadir point of end-tidal partial pressure of O_2 ($P_{ET}O_2$), and (4) the point where an abrupt increase occurs in RER were used to determine V_{AT}. Then, VO_2, VCO_2, V_E, and HR at peak exercise and at V_{AT} were compared between groups to determine if the responses differ between patients with a TBI and healthy controls.

Specific Aim Three

In patients with a TBI, it was determined if the exercise response of the growth hormone–insulin-like growth factor-1 axis (GH/IGF-1 axis), prolactin (PRO), cortisol (COR), blood lactate or glucose differed from age- and gender- matched healthy CON.

3a. Hypothesis - There would be a blunted response of GH, insulin-like growth factor-1 (IGF-1), PRO, and COR to an acute bout of maximal exercise in patients with a TBI.

3b. Hypothesis – It is also hypothesized that there would be no difference in the responses of blood lactate and glucose to exercise between groups.

Hypotheses three (a and b) were tested in eight patients with a TBI and eight CON matched by age and gender with similar BMI. After inserting a venous catheter into a forearm vein distal to the elbow, blood was sampled every 10 minutes for an hour. At the end of the one-hour baseline-sampling period, subjects performed a maximal graded exercise test

to volitional failure. Metabolic, ventilatory, and cardiovascular responses were measured continuously during the maximal test. Immediately after reaching peak exercise, blood was again sampled every 10 minutes for one hour. From venous blood samples GH, PRO, COR, IGF-1, blood lactate and glucose were compared before and after peak exercise.

Specific Aim Four

It was determined if subject anthropometrics, aerobic fitness, resting hormone levels, or hormonal responses to exercise were associated with perceived fatigue as measured using a fatigue severity scale (FSS).

4. Hypothesis - Subject anthropometrics (i.e. body fat and BMI), aerobic fitness, baseline IGF-1 (as a surrogate measure of GH deficiency), and exercise-stimulated responses of GH would be significantly associated with fatigue.

Using the same subjects and experimental design in Specific Aim Three, hypothesis four was assessed by administering the fatigue severity scale (FSS) to all subjects prior to exercise (Krupp *et al.,* 1989). Additionally, a visual analogue scale for fatigue was completed at baseline, immediately post-, 30 minutes post-, and 60 minutes post-exercise. Associations between FSS, aerobic fitness (peak VO_2 and VO_2 at V_{AT}), resting endocrine responses (IGF-1), and post exercise responses of GH, PRO, COR, and IGF-1 were determined using Pearson's *r* correlation coefficients.

SIGNIFICANCE OF RESEARCH

Patients with a TBI undergoing physical therapy are routinely provided an array of basic strength, endurance, balance, and neuromuscular coordination training interventions. Because of the metabolic deficiencies that manifest as decreased cardiorespiratory endurance

and fatigue, it is reasonable that therapists consider vigorous aerobic exercise as an approach to improve functional work capacities and reduce fatigue. However, the prescription of vigorous exercise assumes that the physiological mechanisms used to recover from these stimuli (e.g. hormonal response) are intact as in healthy individuals. It is not known if these mechanisms, particularly the hormonal response to acute exercise, are altered in patients recovering from a TBI. If the exercise response of key hormones of the GH/IGF-1 axis are altered or blunted, intense physical exercise may be contraindicated until normal hormonal function is restored. Moreover, understanding the association between fatigue, aerobic fitness, and response of hormones to intense exercise in patients with a TBI could provide evidence supporting targeted interventions to assist in recovery of metabolic capacity. Ultimately, these data may lead to more precise exercise therapies to improve rehabilitation outcomes of patients recovering from a TBI.

Chapter 2: Epidemiology of a Traumatic Brain Injury (TBI)

Brain injuries (BI) are a primary cause of disability in the United States (Thurman *et al.,* 1999a; Thurman *et al.,* 1999b). A BI may result from numerous external and internal mechanisms and the functional consequences differ depending on the severity of injury and the site of lesion. Even if the severity of injury and lesion site are known, the resultant impairments are often unique and unpredictable. The Brain Injury Association of America (BIAA), a leading advocate for BI research and rehabilitation, operationally classifies BI according to injury mechanism. Broadly categorized, an acquired brain injury (ABI) is a term used to indicate any post-birth brain damage not hereditary, congenital, or degenerative (Ficker-Terrill *et al.,* 2009). ABI is further divided into six categories: tumor, blood clot, stroke, seizure, toxic exposure, and TBI (Ficker-Terrill *et al.*, 2009). When pooled together, ABI is the second leading cause of death in the United States.

TRAUMATIC BRAIN INJURY

TBI is a subcategory of ABI, resulting from an external force applied to the head. It is defined by the National Head Injury Foundation as:

> "… an insult to the brain, not of degenerative or congenital nature but caused by an external physical force, that may produce a diminished or altered state of consciousness, which results in an impairment of cognitive abilities or physical functioning. It can also result in the disturbance of behavioral emotional functioning. These impairments may be either temporary or permanent and cause partial or total functional or psychological disabilities" (Ficker-Terrill *et al.,* 2009).

Perhaps the most comprehensive national analysis of TBI occurred between 1995–2001 and 2002–2006 (Faul *et al.,* 2010; Langlois *et al.,* 2006) when the National Center for Injury Prevention and Control, CDC, U.S. Department of Health and Human Services tracked the number of incident cases of TBI resulting in emergency room visits, hospitalizations, or deaths. The report found that approximately 1.3 million Americans visited the emergency room for a TBI each year (Faul *et al.,* 2010). Eighty percent were treated and sent home; 15-20% were hospitalized due to injury. Approximately 4%, or 52,000 incident cases, resulted in death per year (Faul *et al.*, 2010). For perspective, there are more incident cases per year of TBI than all forms of cancer in the United States (**Figure 1**).

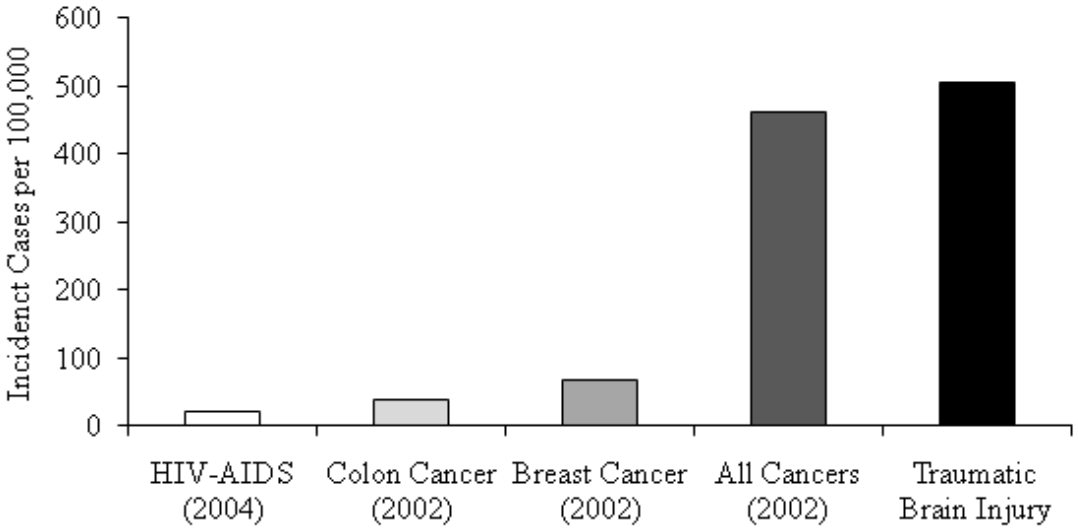

Figure 1. Estimated incident cases of TBI and compared to other prominent diseases (Ficker-Terrill *et al.,* 2009).[b]

Important to rehabilitation professionals is the disability that results from TBI. It is reported that 9% of patients suffering a TBI are permanently disabled and may be in need of life-long support to function in their daily lives (Centers for Disease Control and Prevention,

[b] Figure modified from *The Essentials of Brain Injury Guide, 4th ed*. with permission of the Brain Injury Association of America (BIAA).

2001). Since TBI occurs often in individuals under the age of 25, this may have a tremendous long-term impact on the family caring for a permanently disabled loved one (Faul *et al.,* 2010). It may also affect society in that potentially productive laborers are functionally limited and unable to work for extended time periods.

SEVERITY OF INJURY AND TRAUMATIC BRAIN INJURY

Severity of injury with respect to TBI is typically classified as mild, moderate, or severe and is defined using quantitative scales such as the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) or Loss of Consciousness Scale (LOC) (Gotschall *et al.,* 1995; McDonald *et al.,* 1994; Sternbach 2000; Teasdale and Jennett, 1974). When using GCS, patients are scored on motor response, verbal response, and eye opening. Composite scores determine severity of injury, which is classified as mild (13-15), moderate (9-12), or severe (3-8). **Table 1** provides the objective rating scale.

Table 1. Glasgow Comma Scale (GCS) rating system (Sternbach, 2000).

Score	Motor Response	Verbal Response	Eye Opening
1	None	None	None
2	Decorticate posturing	Mutters unintelligibly	Opens to pain
3	Decerebrate posturing	Inappropriate speech	Opens to command
4	Withdraws to pain	Confused	Opens spontaneously
5	Localized pain response	Alert and oriented	NA
6	Obeys commands	NA	NA
Total	1-6	1-5	1-4

The LOC is a second scale used to determine severity of injury in TBI. As implied in the name, the LOC uses a quantitative time of disorientation or unconsciousness to categorize injuries. Using LOC, a patient's TBI is termed mild, moderate, or severe if the patient is unconscious for <30 minutes, 30 minutes to 6 hours, or >6 hours, respectively. Although other scales have been proposed, these are most often used in the literature and by clinicians.

Mild TBIs (mTBI) are most common and comprise approximately 75-80% of all reported injuries. Because TBI is only documented if the patient seeks medical attention, the total number of reported TBIs undoubtedly underestimates the true incidence of injury and subsequently the magnitude of the problem. Although classified as mild, the severity of mTBI should not be underrated. It has been reported that mTBI results in significant lost work time and people who are hospitalized after mTBI miss, on average, four weeks of work because of impairments resulting from the injury (Binder *et al*., 1997; Rohling *et al.,* 2011).

AGE AND TRAUMATIC BRAIN INJURY

TBIs occur in individuals of all ages but incidence peaks in early childhood or adolescence (Bruns and Hauser 2003). The increased incidence of TBI in early childhood is likely due to unawareness of dangerous situations leading to head injury whereas the increase in late adolescence reflects individuals of legal age to operate motor vehicles. TBIs are also common in the elderly mainly because of an increased incidence of falls (Faul *et al.,* 2010).

Emergency room (ER) visits resulting from TBI are most common in infants and toddlers (0-4 years old) (Faul *et al.,* 2010). There is also a high incidence of ER visits for TBI in adults between the ages of 25-34 and the elderly. The greatest number of hospitalizations due to TBI occurs in individuals over the age of 75 years (Faul *et al.,* 2010). In fact, individuals over 65 years comprise 67% of all hospitalizations from TBI. Male and females over 75 years also have greatest death rates from TBI (Faul *et al.,* 2010).

GENDER AND TRAUMATIC BRAIN INJURY

Males encompass 59% of the total reported TBI's (**Figure 2**; **Figure 3**) (Faul *et al.,* 2010). Males also comprise of 58% of ER visits, 61% of hospitalizations (Faul *et al.,* 2010)

and 73% of deaths due to TBI are in males (Faul *et al.,* 2010). In nearly all age groups, males are hospitalized more often than females because of TBI.

CAUSES OF TRAUMATIC BRAIN INJURY

TBI results from a variety of mechanisms and the primary cause of injury differs by age.[c] The CDC reports suggest that falls were the leading known cause of ER visits and hospitalizations between the years 2002 and 2006 among all patients (Faul *et al.,* 2010). However, TBIs resulting from motor vehicle accidents (MVA) resulted in a greater number of deaths. Falls were the leading cause of TBI in elderly individuals; MVAs contributed to a greater extent to ER visits, hospitalizations, and deaths in younger patients (Thurman *et al.,* 1999).

Sport and recreational related activities are a major cause of TBI in the United States, especially in younger individuals. Between 2001 and 2005 an estimated 207,830 recreation-related TBIs were treated in the ER; 21,311 resulted in hospitalization (Gilchrist *et al.,* 2007). Activities such as cycling, American football, playground accidents, basketball, and all-terrain vehicle accidents were the leading causes of TBIs among children and young adults, ages 5-18 between the years 2001 and 2005 (Gilchrist *et al.,* 2007). Cycling and all-terrain vehicle accidents were by far the leading cause of recreational-related TBIs resulting in hospitalization among children and young adults between 2001 and 2005 (Gilchrist *et al.,* 2007).

An extensive number of combat veterans have experienced mild to moderate TBIs as a result of the concussive forces of improvised explosive devices (IED), mortars shells,

[c] The CDC categorizes mechanism of injury with respect to TBI according to the following 6 categories: falls, struck by or against an object, motor vehicle accidents, assault, other, and unknown. Faul M, Xu L, Wald M, and Coronado V. Traumatic Brain Injury In The United States: Emergency Department Visits, Hospitalizations and Deaths 2002 – 2006. *Centers for Disease Control.* Atlanta, GA, 2010.

rockets, bombs and other explosive devices detonated by enemy soldiers or used routinely in war (Sayer *et al.,* 2008). When an explosive device is detonated, it creates a pressure differential in ambient air. Upon detonation, a wave of positive energy rapidly passes over objects near the explosion. As the wave of energy passes beyond an object there is a rapid negative shift in pressure (i.e. vacuum). If an individual is near the explosion, the head and brain may be accelerated quickly in multiple directions resulting in a myriad of injuries. Injuries resulting from initial positive pressure change are termed primary injuries (Taber et al., 2006). A primary injury may occur from a direct acceleration or potentially a cephalic shift in pressure as the abdominal and thoracic cavities are rapidly decompressed. Secondary injuries occur from the negative pressure change (Taber *et al.*, 2006). At times, the positive pressure may accelerate the soldier into other objects, forcing the head into a collision. Injuries from collisions with objects are termed tertiary injuries (Taber *et al*., 2006).

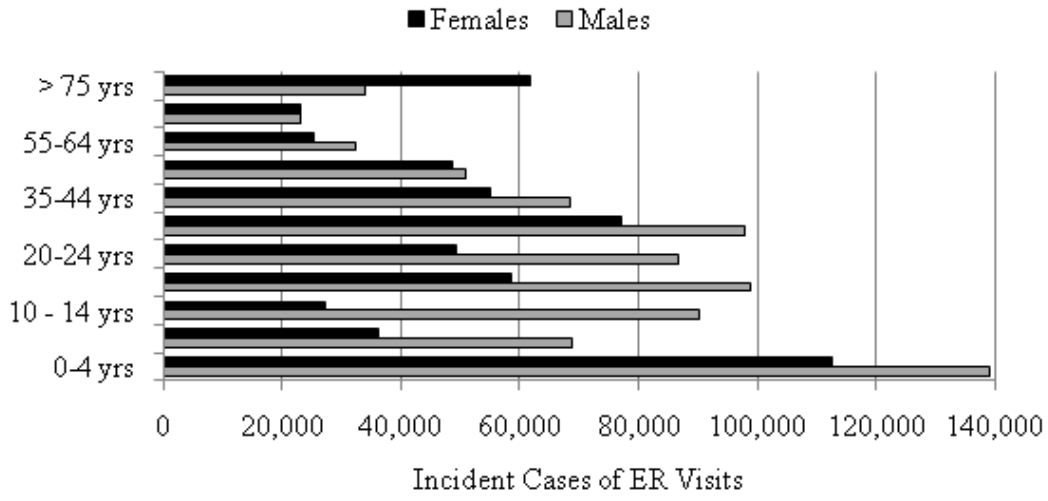

Figure 2. Difference in incident cases of males and females of various age groups who visited the ER for a TBI between 2002-2006 (Faul *et al.,* 2010). [d]

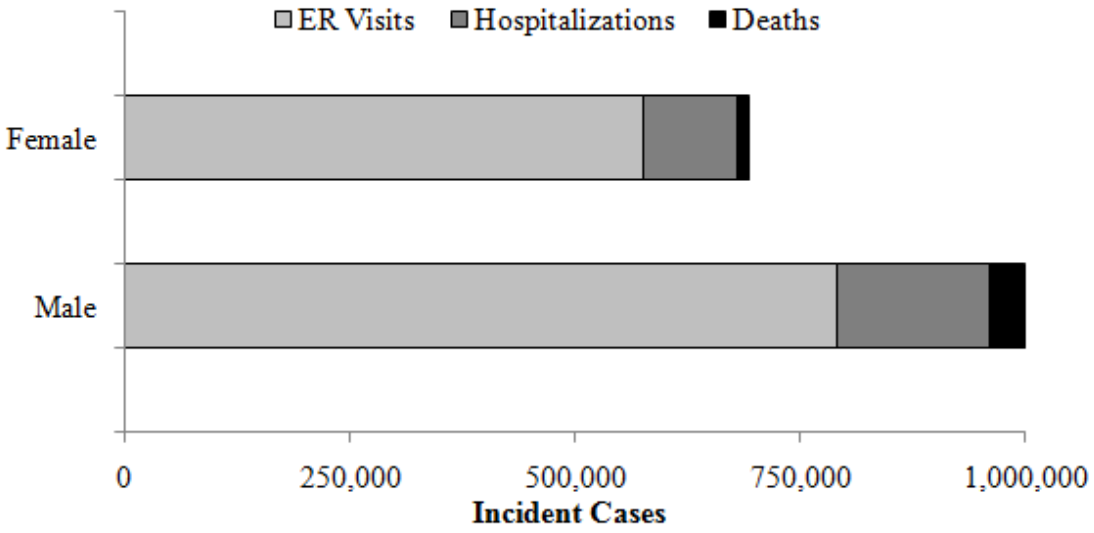

Figure 3. Incident cases of TBI resulting in emergency room visits, hospitalizations or deaths between 2002–2006 (Faul *et al.,* 2010).[d]

[d] Figures 2-5 were generated using publicly available data included in reports published by the CDC, Washington, D.C. In accordance to the Freedom of Information Act (Public Law 89-554, 80 Stat. 383; Amended 1996, 2002, 2007), permission is not needed to reproduce these data.

TIME TRENDS IN TRAUMATIC BRAIN INJURY

Realistically, it is difficult to interpret incident time trends of TBI, because significant progress has occurred in tracking systems associated with injury. Additionally, the technology used to assess TBI changed over time; therefore, long-term differences in incidence are difficult or impossible to determine. What is not in question, however, is the considerable progress in preventing death after TBI in the past century. In a comprehensive systematic review, Stein and colleagues found significant progress in the treatment and resultant survival after injury (Stein *et al.,* 2010). Their data suggest that survival rate over the past century has changed in a non-linear pattern. In fact, there were periods of remarkable progress but some periods where no apparent progress was made. They found that since 1885, mortality rates due to TBI have decreased by 50%. From 1885-1930, there was a 3% decrease in mortality due to TBI, but no change between from 1930-1970. The authors suggest that the lack of improvement in treatment between 1930-1970 is likely because of an increase in severity of injury (Stein *et al.,* 2010). More specifically, they argue that motor vehicle accidents became prominent during that period, leading to non-survivable TBI. In 1970, likely due to enhancement of standard safety features in motor vehicles, and improvements in emergency medicine and scanning, there was a 20-year period of noteworthy progress in which TBI-related deaths dropped by approximately 20%. No change is evident in the mortality rate from TBI over the past 20 years.

Although there has been no measurable change in death rates from TBI since 1975, hospitalizations have decreased. Population data in 1975 suggested that the annual incidence of TBI was 234 per 100,000 (Thurman *et al.,* 1999a). This number decreased from 99 per 100,000 between 1990-1995 (Thurman *et al.,* 1999a). It is not clear from the data whether

this suggests an improvement in the acute treatment of TBI or possibly changes in hospital funding for TBI.

A more recent time trend can be observed comparing the CDC reports for ER visits, hospitalizations, and deaths from the 1995-2001 and 2003-2007 reports (Faul *et al.,* 2010; Langlois et al., 2006). Visual inspection of these data show a slight increase in ER visits, hospitalizations, and deaths in both males and females from 2003-2007 (**Figure 4**; **Figure 5**).

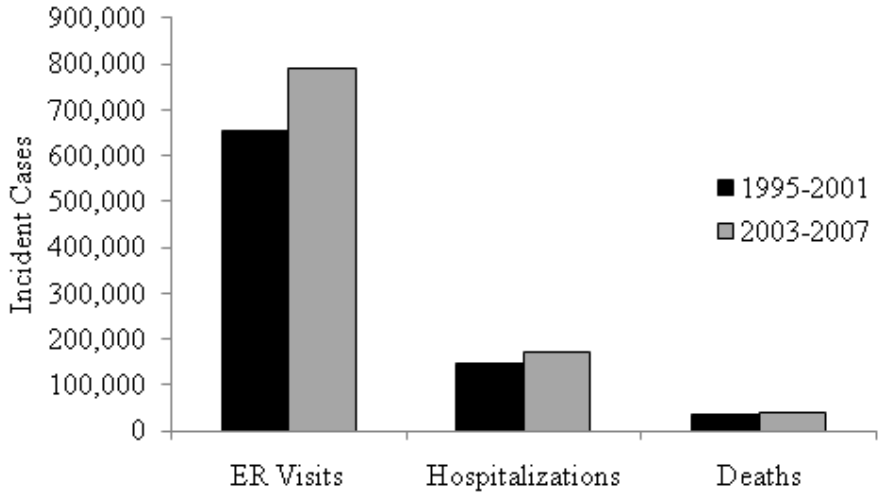

Figure 4. Time trends for average incident cases of ER visits, hospitalizations, and deaths in males with TBI (Faul *et al.,* 2010; Langlois *et al.,*2006).[d]

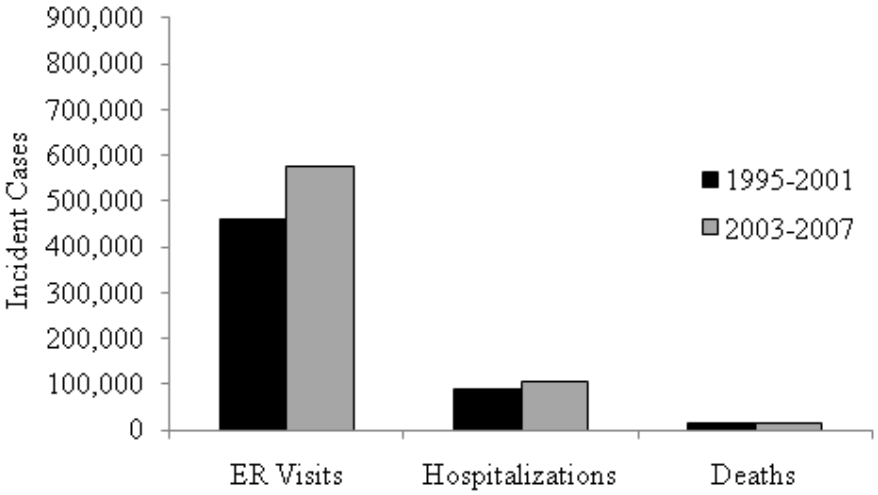

Figure 5. Time trends for average incident cases of ER visits, hospitalizations, and deaths in females with TBI (Faul *et al.,* 2010; Keller *et al.,* 2003; Langlois et al.,2006).[d]

Although only slight increases in the incident of injury are observed in the CDC data, a profound increase in TBI awareness has occurred in the past decade. This is due primarily to evidence showing deleterious effects of blast-related TBI and sport-related head injuries. TBI has received intense public attention because of blast-related head injuries in the ongoing middle-east wars. In a 2006 memo addressed to the Assistant Secretary of Defense for Health Affairs, the Armed Forces Epidemiological Board recognized the impact and substantial increase in the incidence of TBI in the American armed forces. The memo recommended that the Department of Defense increase preventive equipment, field-based assessments, return-to-duty guidelines, and education related to TBI.[e] From this initial memo and several follow up reports, blast-related TBI was coined the "signature wound" of Operation Iraqi Freedom. Wojcik studied the incidence of TBI in soldiers deployed in Iraq and Afghanistan between

[e] Memorandum addressed to William Winkenwerder, Jr. M.D. titled *Traumatic Brain Injury in Military Service Members – 2006-2002.* The memorandum was originally obtained by *USA Today* under the Freedom of Information Act (Public Law 89-554, 80 Stat. 383; Amended 1996, 2002, 2007).

2001–2007 (Wojcik *et al.,* 2010). Over the seven-year period, 2,898 soldiers were treated for TBI. They found that the injury rates were 41.8 and 24.6 per 10,000 soldier years for Iraq and Afghanistan, respectively. Over 50% of the TBIs suffered during that time were from battlefield explosions (Wojcik *et al.,* 2010). Hoge and coworkers performed an epidemiological analysis of 2,714 soldiers who experienced a TBI. They found that explosions, vehicle accidents, and falls were the leading causes of TBI in the Iraq war (Hoge *et al.,* 2008). Interestingly, the number of TBIs from blasts was more than double that of any other type of TBI (Wojcik *et al.,* 2010). Further, they found a high incidence of post-traumatic stress disorder (PTSD) in the patients that suffered TBI, suggesting that the consequences of blast-related injuries are potentially long-term (Wojcik *et al.,* 2010). Others have suggested a plethora of impairments resulting from blast injuries that cross the domains of neuropsychological and physical function (Sayer *et al.,* 2008).

Although underestimated in the past, collision sport athletes are prone to mTBI (i.e. concussion). Dementia pugilistica ("Punch Drunk Syndrome") is a neurological condition first described in boxers in the 1920s (Martland, 1928; Millspaugh, 1937). Resulting from multiple subconcussive forces to the head, dementia pugilistica is a "progressively worsening condition" whereby patients experience memory loss, dementia, slowing of speech, vertigo, and a myriad of other physical and psychological conditions (Millspaugh, 1937). In severe cases, dementia pugilistica may result in Parkinson-like syndrome, the most notable case being the former heavyweight champion Muhammad Ali.

Dementia pugilistica, now termed chronic traumatic encephalopathy (CTE) (Corsellis *et al.*, 1973), has been described in a number of collision sport athletes (McKee *et al.,* 2009). In 2005, an autopsy of a former, retired National Football League (NFL) player showed

evidence of severe CTE (Omalu *et al.,* 2005). Subsequently, several other autopsies of former NFL players were positive for CTE (Omalu *et al.,* 2006). Of notable interest, each died prematurely and their families reported cognitive, behavioral, and depressive conditions in each (McKee *et al.,* 2009). The reports of CTE initiated a firestorm public reaction to mTBI, specifically in American football. CTEs have led to a public awareness program by the NFL and increased standardization of screening for mTBI in American football players at all levels.

ECONOMIC BURDEN OF TRAUMATIC BRAIN INJURY

TBI is a major public health concern and the CDC suggested the annual monetary costs associated with these injuries were estimated at $60 billion in 2000 (Centers for Disease Control and Prevention, 2001). Eighty to ninety thousand patients with TBI are disabled, (Thurman *et al.,* 1999) many permanently, with a variety of impairments. High percentages of individuals with TBI are known to have decreased cognitive and psychological functioning 10 to 20 years after injury (Hoofien *et al.,* 2001). Although psychological impairments resulting from TBI are the best described, the physical impairments are linked with an inability to return to work or perform activities of daily living (ADL) (Mazaux and Richer, 1998). Approximately $20.6 billion are lost each year from disability; this is more than four times the estimated direct medical costs of treating a patient with TBI (Thurman and Guerrero, 1999). A study of 67 adults five years post-TBI in Australia showed that 50% of the patients tested were reliant on welfare for financial assistance (Hillier *et al.*, 1997).

Disability is not only evident in moderate to severe TBI; mTBI may have a devastating personal and economic impact. For example, in 1985 mTBI accounted for 44% of the economic cost for TBI that year (Gerberding and Binder, 2003). Not considered in this

estimate are the unreported cases of TBI that may result in loss of work time or lack of productivity and performance at work and/or school.

TRAUMATIC BRAIN INJURY: ACUTE INJURY BUT PRECURSOR TO DISEASE?[f]

The level of resultant disability from TBI is complex and difficult to define. In the framework of the Institute of Medicine (IOM) enabling-disabling model, TBI leads to pathological changes in brain structure and function (**Figure 6**). The pathological change may lead to impairment; depending on the site of lesion, the impairment may result in numerous functional limitations. For example, if the lesion is near the motor cortex, ambulatory ability may be compromised leading to mobility impairments and potentially immobility (Bell, 2007; Sullivan, 2007). Depending on the occupational, social, and recreational demands of the individual, this could lead to disability and ultimately reduced quality of life (QOL).

TBI occurs as a result of a single, acute event (i.e. injury). Unlike most injuries (e.g. knee ligament sprain, bone fracture), recovery rates are not predictable. In fact, brain injury may lead to a gradually worsening condition (Masel and DeWitt, 2010), thus increasing the impact of TBI. Many of the impairments associated with TBI may result in physical inactivity and potentially obesity. As such, patients with TBI may be at increased risk for hypokinetic diseases such as coronary artery disease (CAD), diabetes, and some forms of cancer (Colditz, 1999). Moreover, strong evidence shows that patients with a TBI are at greater risk for circulatory and respiratory diseases (Shavelle *et al.,* 2001). Although causal mechanisms are unknown, evidence also suggests that TBI may be related to Alzheimer's,

[f] The concept of TBI as a chronic disease is championed by Dr. Brent Masel. It was introduced in a 2010 publication (Masel and DeWitt, 2010), but lectured in several venues prior to publication.

dementia, amyotrophic lateral sclerosis (ALS), and Parkinson's disease in later-life (Goldman *et al.,* 2006; McMurtray *et al.,* 2006; Institute of Medicine, 2009; Schmidt *et al.,* 2010).

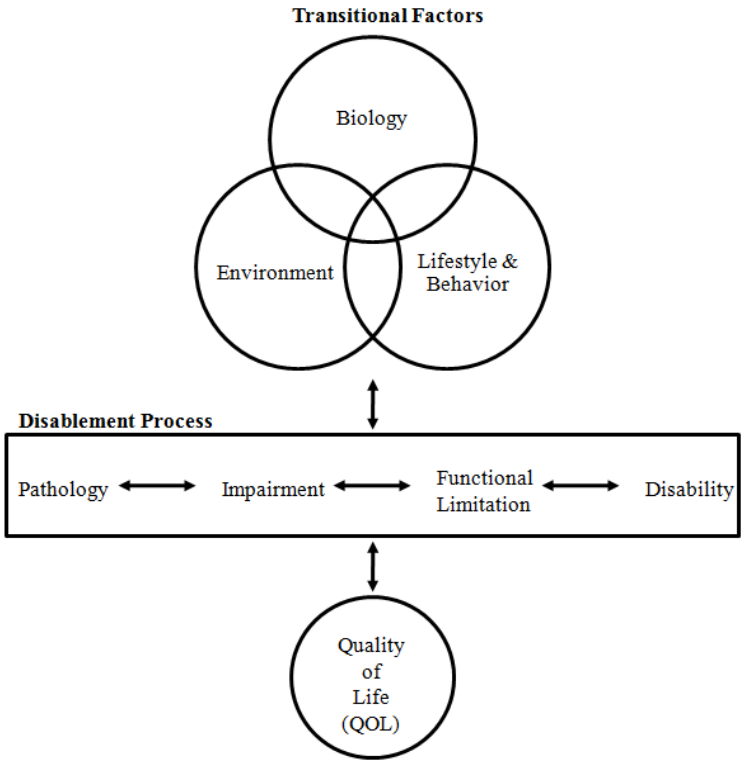

Figure 6. Institute of Medicine's enabling-disabling model (Brandt and Pope, 1997; Pope and Tarlov, 1991).[g]

Numerous functional limitations are associated with or caused by TBI; each may lead to disability. Although cognitive (i.e. memory loss, attention, problem solving) and behavioral problems (i.e. aggression, personality changes) are the most often cited in literature, large numbers of patients with a TBI also suffer from substance abuse problems, sleep disorders, and chronic fatigue (Bushnik *et al.*, 2008; Corrigan *et al.,* 2003; Hibbard *et*

[g] **Figure 6** redrawn with the permission of the Institute of Medicine (IOM)

al., 1998; Jha *et al.,* 2008; Leddy *et al.,* 2007). Moreover, literature suggests that impairments in peak metabolic and physical work capacities may be caused by or associated with TBI.

Cognitive and Behavioral Impairments

Cognitive and behavioral deficits resulting from TBI are well described and have been noted even after mTBI. Sosnoff and coworkers (Sosnoff, Broglio and Ferrara 2008) studied the effects of a mTBI on neurocognition and postural control. They prescreened 618 high school students using a cognitive test and 36 sustained an mTBI within the timeframe of the study. The concussed subjects were tested within 24-hours of injury. They found mTBI was associated with a decrease in reaction time and verbal memory. In fact, impaired cognitive performance is the primary clinical indicator of mTBI in athletes and a variety of occupations (Iverson *et al.*, 2002; Iverson *et al.,* 2006; Maerlender *et al.,* 2010; Schatz and Putz, 2006).

Continuing cognitive deficits are present in some patients when they are asymptomatic (Broglio *et al*., 2007) and lasting effects appear to be associated with mTBI. Malojcic showed overall deficits in visual attention and short-term memory in subjects tested, on average, 45 days after an mTBI (Malojcic *et al.,* 2008). Cognitive deficits in attention and verbal memory have also been described in older (>55 years) community dwelling adults who sustained a TBI compared to age-matched controls (Ashman *et al.,* 2008). Severe TBI can have profound cognitive effects, resulting in cognitive impairment 10 to 20 years post injury (Hoofien *et al.,* 2001). Leon-Carrion and colleagues reported that patients with severe TBI suffer from attention disorders (90% of patients), executive disorders (80% of patients), anterograde amnesia (70% of patients), post-concussive syndrome (50% of patients), time-space disorientation (50% of patients), post-traumatic depression (50% of patients),

retrograde amnesia (40% of patients), personality changes (30% of patients, excitability or aggressiveness (30% of patients), and language disorders (30% of patients) (Leon-Carrion 2002; Leon-Carrion *et al.,* 2001).[h]

Fatigue

Fatigue is a common complaint and symptom following a TBI that may be associated with decreased physical performance. Using three separate self-reported measures, LaChapelle and Finlayson compared fatigue levels of patients with a TBI to healthy controls (LaChapelle and Finlayson, 1998). Furthermore, the investigators determined the relationship between self-reported fatigue and objective score on a tiring task. Subjects were required to press a microswitch with their thumbs as fast as possible for 40 seconds. This procedure was repeated four times with a fifteen-second rest interval between trials (LaChapelle and Finlayson, 1998). At the conclusion, a composite, objective score was determined. In most subjective measures, patients with a TBI rated general fatigue levels higher than controls. The composite, objective fatigue score was moderately correlated with most subjective score ratings (LaChapelle and Finlayson, 1998).

Although fatigue and pain apparently decrease over the first year post-TBI, the reductions plateau substantially after the first year (Bushnik *et al.,* 2008). A subset of persons with TBI report worsening fatigue, pain, and decreased quality of sleep which is correlated with poorer physical function (Bushnik *et al.*, 2008) and QOL (Cantor *et al.,* 2008). Self-reported complaints of fatigue are documented up to five years post-TBI (Olver et al., 1996).

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[h] List of common impairments associated with a TBI derived from a chart in: Leon-Carrion J, Machuca Murga F, Murga Sierra M, and Domanguez Morales R. Outcome after an intensive, holistic and multidisciplinary rehabilitation program after traumatic brain injury. Medico legal values. *Revista De Neurologia;* 33: 377-383, 2001. The chart was orginally published in Spanish, but republished in English: Leon-Carrion J. Dementia Due to Head Trauma: An obscure name for a clear neurocognitive syndrome. *Neurorehabilitation*; 17: 115, 2002.

Although the mechanisms are not completely understood, some attribute fatigue to a greater cognitive demand for activities (Ziino and Ponsford, 2006). Fatigue is also associated with greater levels of sleep disturbance, self-reported pain, motor dysfunction, and depression (Englander *et al.,* 2010).

Metabolic and Physical Work Capacity

While psychological demands are likely a contributor to fatigue, there is also a documented decline in peak aerobic capacity. Mossberg and colleagues studied the aerobic capacity of thirteen patients with TBI vs. thirteen sedentary, age-matched controls (Mossberg *et al.,* 2007). Using a graded treadmill exercise test and metabolic measurements, they found peak aerobic capacity of patients with TBI was 25% lower compared to the uninjured cohort. The patients' body weight normalized peak VO_2 was 27.0 $\pm$ 4.6 $mL \cdot kg^{-1} \cdot min^{-1}$, which is below the 10^{th} percentile for this age group (Franklin, 2000). Peak ventilation and heart rate responses were also significantly lower in the patients with TBI compared to sedentary controls. Typically, heart rate at peak exercise is higher for deconditioned individuals because of lower cardiac stroke volume. Both the decrease in ventilation and heart rate at peak exercise suggest there could be central mechanisms (e.g. brain stem) that do not respond adequately to a physical work stress such as exercise.

Endocrine Dysfunction in TBI

Neuroendocrine dysfunction is a recognized consequence of TBI, although testing is not routine. Therefore, the true magnitude of the problem is likely unknown. It has been suggested that pituitary function testing in patients with TBI should be standard clinical practice and each axis must be tested individually (Urban *et al.*, 2005). Depending on the injury sight and type, hormones of any axis could be affected.

Anterior hypopituitarism, specifically GH deficiency, is the most studied and recognized neuroendocrine deficiency in TBI (Popovic 2005). The anterior pituitary secretes GH, a 191 amino acid polypeptide hormone, that affects virtually all tissues in the human body (Nindl *et al.,* 2003). It is responsible for signaling release of IGF-1 from the liver, and directly stimulates protein synthesis, bone growth, lipolysis, and other metabolic functions (Borer, 2003).

Other hormones tested and identified as dysfunctional in patients with TBI include adrenocorticotropic hormone (ACTH), COR, thyroxine (T_4), testosterone, and estradiol. At rest, dysfunction in one or more of the pituitary axes has been reported at 10% to 25% (Agha *et al.,* 2004; Bondanelli *et al.,* 2004; Cohan *et al.,* 2005; Klose *et al.,* 2007; Lieberman *et al.,* 2001; Schneider *et al.,* 2006). Some have suggested the severity of the TBI may be a primary determinant of hormonal dysfunction (Tanriverdi *et al.,* 2007). However, others have demonstrated delayed onset of pituitary dysfunction, which indicates the response may be highly individualized and is not fully understood (Schneider *et al.,* 2006).

FATIGUE, AEROBIC FITNESS, AND NEUROENDOCRINE FUNCTION – ARE THEY RELATED?

Altered aerobic capacities of patients with TBI could significantly contribute to symptoms of fatigue and poor tolerance of exertion after injury. Behavioral choices leading to a sedentary lifestyle post-TBI or physical impairments are likely factors leading to decreased aerobic capacity. However, evidence suggests other factors may limit aerobic capacity and result in fatigue. Bushnik and colleagues (Bushnik *et al*., 2007) studied fatigue and neuroendocrine function in patients with TBI. In a cohort of 64 subjects who were one-year post TBI, they found a significant relationship between lower stimulated GH levels and

higher scores of fatigue. Although not statistically significant, they also noticed trends towards lower basal cortisol levels and higher indices of fatigue.

Recently, Mossberg and colleagues investigated the relationship between metabolic capacity and GH deficiency in patients with a TBI. Dividing patients into three categories (GH deficient, GH insufficient, or GH sufficient), they found that patients categorized as GH deficient and GH insufficient had lower peak aerobic capacities than those patients with TBI who had normal GH levels (Mossberg *et al.,* 2008). GH deficiency has also been linked to poor or altered maximal and submaximal aerobic exercise responses in GH deficient patients without TBI (Thomas *et al.,* 2002; Woodhouse *et al.,* 1999). Together, these data seem to suggest associations between the constructs of fatigue, fitness, and neuroendocrine function.

CONCLUSION

BI is a leading cause of death in the United States. TBI, a sub-category of BI, occurs because of external head acceleration and may lead to death or significant disability. TBI is often referred to as a "silent epidemic" because many of the impairments are not visible. However, the literature suggests that even an mTBI may result in significant cognitive and physical impairments leading to long-term disability. Many patients with a TBI are young, with many potential productive years of life lost. Therefore, rehabilitation of impairment, when possible, is profoundly important for patients and society. Fatigue is one of the most common complaints after TBI and may lead to intolerance of daily activities. Metabolic capacity is also compromised in TBI, and patients with lower metabolic capacities also tend to have poor endocrine function.

ORIGINAL RESEARCH

Chapter 3: Acute Metabolic Ventilatory and Cardiovascular Responses to Exercise in Patients with a Traumatic Brain Injury

ABSTRACT

Background and Objective: It has been reported that patients with a TBI possess lower peak aerobic capacities than apparently healthy controls. The studies reporting such differences utilize a relatively small number of female subjects and potential gender differences in peak aerobic capacities have not yet been quantified. Moreover, anaerobic thresholds have not been reported in the TBI population. The purposes of the studies contained in this chapter were to (1) determine if peak metabolic, ventilatory, and cardiovascular responses to acute exercise differ from age predictive normative values and if they were similar between genders; and (2) compare the peak aerobic capacities and ventilatory anaerobic thresholds (V_{AT}) of patients with a TBI to age- and gender-matched controls.

Experimental Designs: Two separate studies were completed. First, a retrospective cohort study was completed where the measured (MEAS) peak metabolic, ventilatory, and cardiovascular responses of 16 male and 16 female patients were compared to predicted (PRED) peak responses. Comparisons were made within and between genders. Then, a case-control design was completed where peak and ventilatory anaerobic thresholds (V_{AT}) responses of 19 patients who previously suffered a mild to moderate injury (TBI) and 19

apparently healthy controls (CON) were compared. TBI and CON were matched for age and gender and had similar BMIs.

Measurements: Each volunteer performed a peak graded treadmill test to volitional failure where VO_2, VCO_2, and V_E, and HR were measured continuously.

Results: Peak measured VO_2, VCO_2, V_E were all significantly lower than PRED in males and females. The VO_2 and VCO_2 at V_{AT} and peak were lower for patients with a TBI compared to CON. V_E was also lower for TBI compared to CON at V_{AT} and peak exercise. After a Bonferroni correction of alpha, heart rate at V_{AT} and peak were not significantly lower than CON.

Conclusions: Peak metabolic, ventilatory, and cardiovascular responses of patients with a TBI are lower than calculated predicted values, irrespective of gender. Moreover, the peak and V_{AT} responses of patients with a TBI are lower than CON (except for heart rate). Functionally, the oxygen consumption at V_{AT} and peak exercise in patients with a TBI occurred below the reported metabolic demands for many routine daily activities; this may partially explain higher levels of fatigue commonly reported in this clinical population. The data suggest that physical therapy interventions for patients with a TBI should include targeted exercise prescriptions to improve cardiorespiratory fitness. These exercise prescriptions are imperative in both males and females.

INTRODUCTION[i]

In response to an acute bout of physical exertion, the metabolic, ventilatory, and cardiovascular systems respond in a predictable pattern (McArdle *et al*., 2010). Immediately after the initiation of exertion, cardiac output is increased (i.e. heart rate and stroke volume) due, in part, to an increase in sympathetic stimulation (Mazzeo 1991; Whaley *et al*., 2006). Pulmonary ventilation increases (i.e. tidal volume an respiratory rate) in a linear manner relative to physical work (Whaley *et al*., 2006). The systemic cardiovascular and ventilatory responses are required to increase oxygen (O_2) delivery to working skeletal muscle for adenosine triphosphate (ATP) generation via oxidative phosphorylation. Oxygen consumption increases as a result of increased cardiac output and arteriovenous blood difference (a-VO_2 difference) (Whaley *et al*., 2006). Carbon dioxide production is elevated depending upon the intensity of metabolic work and is removed from the blood through pulmonary ventilation.

Heart rate, cardiac stroke volume, and VO_2 increase linearly in relation to physical work demands. Minute ventilation increases linearly in response to work, but exponential elevations in V_E and VCO_2 are observed near anaerobic threshold (AT) which occurs between 60-70% of peak VO_2 in apparently healthy individuals (Gaskill *et al.*, 2001; Malek *et al.*, 2007). There is a concomitant decrease of pH in skeletal muscle and a significant increase in blood lactate (Robergs *et al*., 2004). Additionally, the ratio of carbon dioxide production to oxygen consumption (RER) exceeds 1.0 indicating a significant increase in anaerobic metabolism for ATP generation and predominant usage of glucose for substrate

[i] Portions of the Introduction were rewritten from: Mossberg K, Amonette W, and Masel B. Endurance training and cardiorespiratory conditioning after traumatic brain injury. *J Head Trauma Rehab;* 25: 173-183, 2010. Permission granted by Lippincott, Williams and Wilkens.

metabolism. At maximum work capacity, VO_2 plateaus and RER is near or exceeds 1.15 (Thompson, 2010). Heart rate and V_E reach maximum values at peak capacity (McArdle *et al*., 2010). With the cessation of work, heart rate, VO_2, and V_E decrease, but RER continues to rise for several minutes after exercise is stopped (McArdle *et al*., 2010).

Peak Exercise Responses are Lower in Patients with a TBI Compared to Matched CON

Previous data has suggested that peak aerobic capacity is compromised in TBI (Mossberg *et al.*, 2007). Although VO_2 peak is an essential variable to describe the overall metabolic capacity of a patient, daily activities are rarely performed near peak aerobic capacity. Instead, most daily activities require sustained submaximal efforts for prolonged periods. In addition, maximal exercise testing is dependent upon the effort of the patient and may vary significantly depending on motivation. Thus, quantification of submaximal exercise responses may be more functionally relevant and provide quantifiable measurements of aerobic fitness devoid of the variability resulting from peak effort based testing. AT is the point in the exercise continuum where there is a rapid decrease in cellular pH (Robergs *et al*., 2004). It can be directly determined by measuring muscle pH or indirectly determined analyzing blood lactate (Chwalbinska-Moneta *et al.,* 1989). The least invasive method of estimating anaerobic threshold is to assess systemic metabolic and ventilatory parameters (Amann *et al.,* 2004; Beaver *et al*., 1986; Gaskill *et al.,* 2001; Malek *et al.,* 2007). Estimation of anaerobic threshold using metabolic and ventilatory measurements can be termed ventilatory anaerobic threshold (V_{AT}). V_{AT} determination may be particularly relevant in patients with a TBI because it does not require a maximal motivational effort, is non-invasive, and has been used in other clinical populations (Gitt *et al.,* 2000; Gitt *et al.,* 2002; Hagberg *et al.,* 1981; Valim *et al.,* 2002).

Because of difficulties in matching and availability of subjects, most exercise studies utilizing patients with a TBI include few women. For example, the case-control evaluation published by Mossberg and colleagues utilized only one female subject (Mossberg *et al.,* 2007). With the limited published data, determining if decrements in peak VO_2 are uniform across gender is difficult. Although there is no physiologic rationale to suspect differences in peak exercise as a result of TBI, healthy males and females are motivated differently to exercise (Pierce *et al*., 1997; Troped and Saunders, 1998). Evidence also supports that male and female patient populations may adopt different therapeutic strategies post disease (Ferrand *et al*., 2008; Leung *et al.,* 2008). Moreover, few if any studies have quantified the point at which V_{AT} occurs in patients with a TBI. Therefore, the purposes of these studies were to (1) determine if peak aerobic capacity differed from predicted values and if the differences were uniform across gender; and (2) compare the peak aerobic capacities and V_{AT} of patients with a TBI with uninjured, apparently healthy controls. It was hypothesized that peak aerobic capacity, ventilation, and heart rate would be significantly lower than age-predicted normative values in patients with a TBI, irrespective of gender. Additionally, it was hypothesized that peak and V_{AT} metabolic, ventilatory, and cardiovascular response would be lower in patients with a TBI compared to matched sedentary CON.

METHODS

Study One

Participants

Data were obtained from 32 patients recovering from a TBI (**Table 2**). The sample included 16 males (179.2 ± 2.2 cm; 89.2 ± 4.9 kg; 34.7 ± 2.8 yrs) and 16 females

(164.5 ±1.5 cm; 72.2 ± 4.1 kg; 35.3 ± 2.9 yrs). Each patient read and signed an informed consent agreeing to participate. If the patient was not able to provide consent, the patient's legal guardian read and signed the form. The patients were residents in a post-acute rehabilitation center and were 5.4 ± 8.2 yrs post brain injury. The average GCS score was 7.0 ± 1.0, but Glasgow Comma Scale (GCS; see Chapter 2) data were only available on 12 of 32 subjects. Specific subject characteristics including cause of injury can be seen in

Table 2.[j] The study procedures were approved by the Institutional Review Board (IRB) at the University of Texas Medical Branch (UTMB) and the Transitional Learning Center (TLC).

Experimental Approach

A retrospective cohort analysis was performed to determine if measured (MEAS) peak metabolic, ventilatory, or cardiovascular parameters of patients with a TBI differed significantly from predicted calculated normative values (PRED). Data analyses were performed on the peak treadmill exercise tests of 32 patients with a TBI and the MEAS oxygen consumption, ventilation, and heart rate obtained from each patient was compared to a PRED value. Moreover, comparisons were made within and between genders.

[j] For the remainder of the text, the following acronyms are used to describe subject and injury characteristics: F = Female; M = male; MVA = motor vehicle accident; BHT = blunt head trauma; IED = improvised explosive device, GS = Gunshot wound, and NA = not available.

Table 2. Subject characteristics from study one.[j]

	ID	Ethnicity	GCS	Cause of Injury	Age at Test	HT (cm)	WT (kg)	BMI
Male	1	Caucasian	7	MVA	19	165.1	55.5	20.3
	2	African American		MVA	20	167.6	65.5	23.2
	3	Caucasian		Arrow	23	167.6	75.9	27.0
	4	Caucasian		Assault	23	170.2	62.7	21.6
	5	Caucasian		MVA	24	162.6	52.7	19.9
	6	African American		Assault	29	163.3	83.2	31.1
	7	Caucasian	6	MVA	29	175.3	86.4	28.1
	8	Caucasian	4	MVA	36	167.6	97.3	34.6
	9	Caucasian	6	Fall	38	154.9	51.4	21.4
	10	Caucasian		Fall	40	165.1	55.9	20.5
	11	Hispanic		Fall	40	157.5	63.6	25.6
	12	Hispanic	3	Assault	41	157.5	81.8	33.0
	13	Caucasian	15	MVA	44	170.2	83.2	28.7
	14	Caucasian	15	MVA	47	154.9	51.8	21.5
	15	Caucasian		MVA	51	172.7	101.8	34.1
	16	Caucasian		Assault	60	160.0	86.8	33.8
Female	17	Caucasian		GS	19	170.2	66.8	23.0
	18	Unspecified		GS	20	172.7	71.8	24.0
	19	Hispanic		MVA	23	167.6	102.7	36.5
	20	Caucasian		MVA	23	180.3	75.0	23.0
	21	Caucasian		MVA	24	190.5	61.8	17.0
	22	Caucasian	6	MVA	28	182.9	97.7	29.2
	23	Caucasian	3	MVA	30	195.6	111.4	29.1
	24	Caucasian		MVA	35	172.7	102.3	34.1
	25	Hispanic		Fall	37	188.0	109.5	30.9
	26	Hispanic	6	MVA	39	177.8	106.8	33.7
	27	Caucasian	4	MVA	38	175.3	64.5	21.0
	28	Caucasian		Assault	42	190.5	93.6	25.8
	29	Unspecified		Fall	43	170.2	70.0	24.1
	30	Caucasian	9	MVA	45	188.0	128.2	36.2
	31	Hispanic		BHT	50	167.6	76.8	27.3
	32	Caucasian		MVA	59	177.8	87.7	27.7

Study Two

Participants

A total of 38 subjects volunteered to participate in this study (28 male, 10 female). Nineteen subjects were matched for gender and age (± 5 yrs) to the TBI patients. The average age at injury for the TBI patients was 24.4 ± 2.2 yrs. The average time post-injury was 4.2 ± 1.0 yrs and ranged from 4 months to 19 yrs. A complete listing of subject injury characteristics and pairings are provided in

Table 3.[k] All subjects were considered healthy by American College of Sports Medicine (ACSM) guidelines for exercise testing, or were medically cleared for maximum exercise by a physician (Thompson, 2010). Additionally, all patients with a TBI had high levels of motor functioning and could ambulate without assistance, follow a minimum of two-step commands, and tolerate the testing equipment. Prior to beginning the study, subjects provided written and verbal consent to all study procedures. The study procedures were approved by the Institutional Review Board (IRB) at UTMB and the TLC.

Experimental Approach

A case-control design was used to complete the study objectives. TBI patients were matched for gender and age to apparently healthy control subjects with no known history of head injury as assessed by a medical screening questionnaire administered prior to testing.

[k] All patient and CON subject groupings are provided in Table 3. Subjects with common letters in the ID column were matched for gender and age. Note that subjects 1-19 were patients with a TBI and subjects 20-38 were CON subjects.

Table 3. TBI and CON volunteer physical and injury characteristics.

ID	Gender	GCS	Cause of Injury	Age at Test	HT (cm)	WT (kg)	BMI
1a	F	7	MVA	19.0	165.1	55.5	20.3
20a	F			24.0	160.0	59.1	23.0
2b	F	NA	MVA	24.0	162.6	52.7	19.9
21b	F			29.0	154.9	59.1	23.0
3c	F	6	MVA	29.0	175.3	86.4	28.1
22c	F			29.0	165.1	79.5	29.1
4d	F	NA	MVA	29.0	163.3	83.2	31.1
23d	F			30.0	167.6	62.3	22.1
5e	F	4	MVA	29.0	175.3	114.5	37.3
24e	F			30.0	158.8	50.6	20.1
6f	M	NA	Assault	30.0	177.8	101.0	31.2
25f	M			26.0	182.9	90.9	27.1
7g	M	9	Assault	21.0	177.8	60.9	19.2
26g	M			25.0	177.8	75.0	23.7
8h	M	NA	MVA	21.0	172.7	96.4	32.2
27h	M			24.0	185.4	89.0	25.7
9i	M	NA	AP	21.0	167.6	61.4	21.8
28i	M			26.0	182.9	84.1	25.1
10j	M	4	MVA	21.0	167.6	76.4	27.1
29j	M			24.0	170.1	81.8	28.3
11k	M	6	MVA	28.0	182.9	97.7	29.2
30k	M			27.0	180.3	97.7	29.9
12l	M	6	Fall	53.0	190.5	100.0	27.5
31l	M			53.0	175.3	72.7	23.7
13m	M	NA	MVA	21.0	174.0	84.1	27.8
32m	M			20.0	167.6	65.9	23.5
14n	M	NA	BHT	22.0	185.4	104.5	30.4
33n	M			26.0	182.9	77.3	23.1
15o	M	NA	Fall	30.0	172.7	75.9	25.4
34o	M			30.0	177.8	99.1	31.3
16p	M	4	MVA	30.0	182.9	91.8	27.4
35p	M			33.0	172.7	95.5	32.0
17q	M	NA	IED	40.0	170.2	106.8	36.9
36q	M			39.0	182.8	92.7	27.7
18r	M	NA	IED	38.0	190.5	102.7	28.3
37r	M			34.0	176.5	109.1	35.0
19s	M	NA	IED	29.0	160.0	70.0	27.3
38s	M			32.0	177.8	89.5	28.3

Combined Testing Procedures

All subjects arrived at the TLC or UTMB Exercise Testing Laboratory before 1000 hrs. The metabolic cart was calibrated prior to subject arrival using gasses of known concentrations and the pneumotach was calibrated using a 3L syringe according to the manufacturer's specifications (MedGraphics Corp., St. Paul, MN 55127). Four skin sites on the anterior thorax were prepped for three lead electrocardiogram (ECG) measurements (Cardio Perfect Inc., Atlanta, GA 30339). The ECG signals were used to obtain resting and exercising heart rates and to monitor medical safety. Additionally, blood pressure was measured before, during, and after exercise to monitor cardiovascular response and safety of the subjects. While standing on the treadmill, subjects were fitted with a neoprene facemask which connected to the automated metabolic gas analyzer and pneumotach. Baseline heart rate, metabolic, and ventilatory data were collected for three minutes before exercise commenced.

After collection of baseline data, subjects stood on the treadmill holding the handrails as the treadmill belt velocity was slowly increased in the first two minutes until the subjects were walking at a comfortable but brisk pace. The final selected treadmill testing speed was the fastest speed a subject could safely walk, but did not exceed 5.3 km $\cdot$ h^{-1} (3.3 mph). After the first two minutes at 1% grade, treadmill incline was increased by 2% each minute (**Figure 7**). Subjects were encouraged to walk without holding the handrails, using the handrails only as needed to correct balance. The test termination criteria suggested by the American College of Sports Medicine (ACSM) used in this investigation included the following: (1) volitional fatigue, (2) a respiratory exchange ratio (RER) greater than 1.1, and (3) a visible plateau in VO_2 with increased workload (Howley *et al*., 1995; Thompson, 2010). The reliability of this

testing protocol to measure peak VO_2 in patients with a TBI has been reported at 0.92 (Mossberg and Greene, 2005).

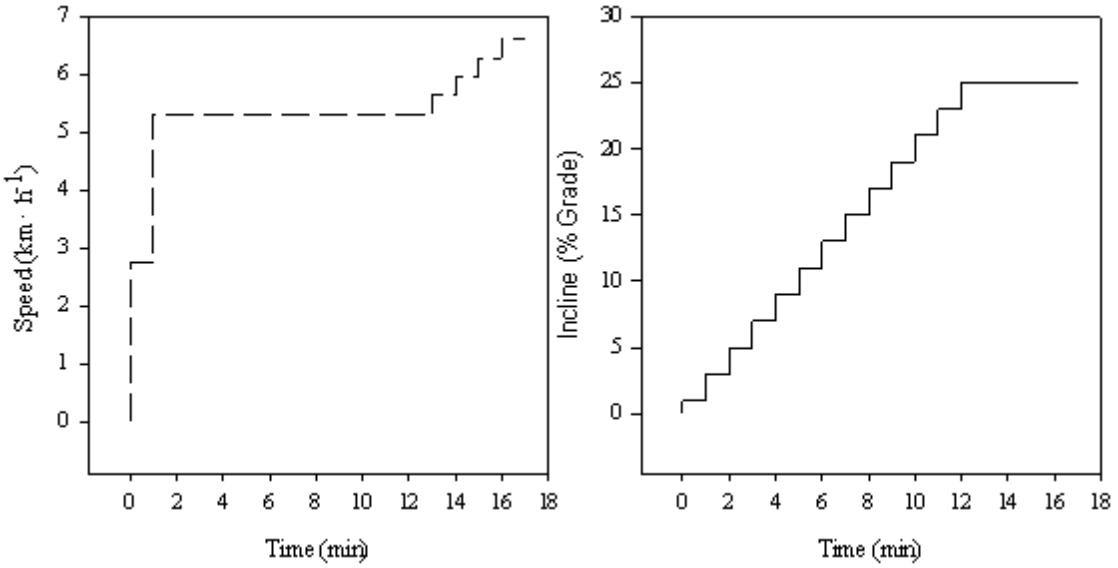

Figure 7. Graphical depiction of the modified Balke-Ware treadmill protocol (Balke and Ware, 1959). Note that some volunteers with ambulatory deficiencies achieved steady-state speed lower than 5.3 km · h-1.

Data Analysis:

During the testing protocol, VO_2 (mL · min^{-1}), VCO_2 (mL · min^{-1}), V_E (L · min^{-1}) and HR (beats · min^{-1}) were collected continuously. From these data, respiratory exchange ratio (RER) was calculated. Data used for statistical analyses were 20-second averages of the breath-by-breath data. The values of each variable at V_{AT} and peak effort were determined and used for statistical analyses.

Calculation of Predicted Normative Values

Predicted peak ventilatory, metabolic, and cardiovascular parameters were estimated using previously reported equations (Wasserman *et al.,* 1987). Although originally developed for healthy populations, the metabolic equations have been used previously to establish risk stratifications in clinical populations other than TBI (Stelken *et al.,* 1996). Specific equations

used to predict (PRED) VO_2 (**Equation 1**; **Equation 2**), VCO_2 (**Equation 3**), forced expiratory volume in one second (FEV_1; **Equation 4**; **Equation 5**), V_E (**Equation 6**), and HR (**Equation 7**) are listed below. Predicted FEV_1 was calculated because it is a needed variable in the equation to predict V_E.

$$PRED\ \mathrm{VO_2} = \mathrm{BM}\ (56.36 - (0.413\ \times Age)$$

Equation 1. Predicted oxygen consumption in male subjects. Note that BM = body mass in kg (Wasserman *et al.,* 1987)

$$PRED\ \mathrm{VO_2} = \mathrm{BM}\ (44.37 - (0.413\ \times Age)$$

Equation 2. Predicted oxygen consumption in female subjects (Wasserman *et al.,* 1987)

$$\mathrm{PRED\ VCO_2} = 1.21\ \times PRED\ \mathrm{VO_2}$$

Equation 3. Predicted CO_2 production in males and females (Thompson, 2010)

$$PRED\ \mathrm{FEV_1} = 0.5536 - (0.01303\ \times \mathrm{Age}) - (0.000172\ \times \mathrm{Age^2}) + (0.00014098\ \times \mathrm{Ht^2})$$

Equation 4. Predicted forced expiratory volume in one second in males (Carter *et al.,* 1987; Chatburn and Mireles-Cabodevila 2011). Note that Ht = height

$$PRED\ \mathrm{FEV_1} = 0.4333 - (0.00361 \times \mathrm{Age}) - (0.000194 \times \mathrm{Age^2}) + (0.0001496\ \times \mathrm{Ht^2})$$

Equation 5. Predicted forced expiratory volume in one second in females (Carter *et al.,* 1987; Chatburn and Mireles-Cabodevila 2011)

$$PRED\ \mathrm{V_E} = PRED\ \mathrm{FEV_1}\ \times 40.0$$

Equation 6. Predicted peak ventilation in males and females (Carter *et al.,* 1987; Chatburn and Mireles-Cabodevila, 2011)

$$PRED\ \mathrm{HR}\ = 220 - \mathrm{Age}$$

Equation 7. Age predicted maximum heart rate in males and females (Thompson, 2010)

Ventilatory Anaerobic Threshold (V_{AT}) Determination

V_{AT} was determined using the method described previously by Beaver and colleagues (Beaver *et al*., 1986) (**Figure 8**). Briefly, V_{AT} was determined using the following criteria: (1) a change in the relationship between VCO_2 to $VO_{2;}$ (2) the nadir point of V_{EQ} $VO_{2;}$ (3) the nadir point of $P_{ET}O_2$; and (4) an abrupt increase in RER. An example of the V_{AT} determination for a single subject is presented in Figure 11.

Statistical Analysis

All data were exported into a Microsoft Excel spreadsheet and visually inspected for anomalous points. For study one, the maximum measured (MEAS) values for body weight normalized VO_2, VCO_2, V_E, and HR were compared to age predicted (PRED) normative values. Furthermore, comparisons were made between genders. As such, 2-factor ANOVAs (ACT vs. PRED x Gender) were used to determine statistically significant main effects and an interaction between genders. If the F-ratio was significant, pair-wise comparisons were completed using Tukey's HSD post-hoc test. Alpha was set at $p \leq 0.05$ for all comparisons in study one.

In study two, statistical comparisons of the VO_2, $VCO_{2,}$ $V_{E,}$ and HR at V_{AT} and at peak exercise were accomplished using paired t-tests. A Bonferroni adjustment of alpha was computed to account for error caused by multiple comparisons. A resulting critical value of $p \leq 0.01$ (0.05 / 4) was used for all comparison. RER values were tested between groups simply to ensure subjects achieved a similar metabolic level at peak between groups.

All statistical calculations were completed using a commercial software program. (SPSS 18.0; SPSS Inc., Chicago, IL). All data are expressed as mean ± standard error of the mean unless otherwise indicated.

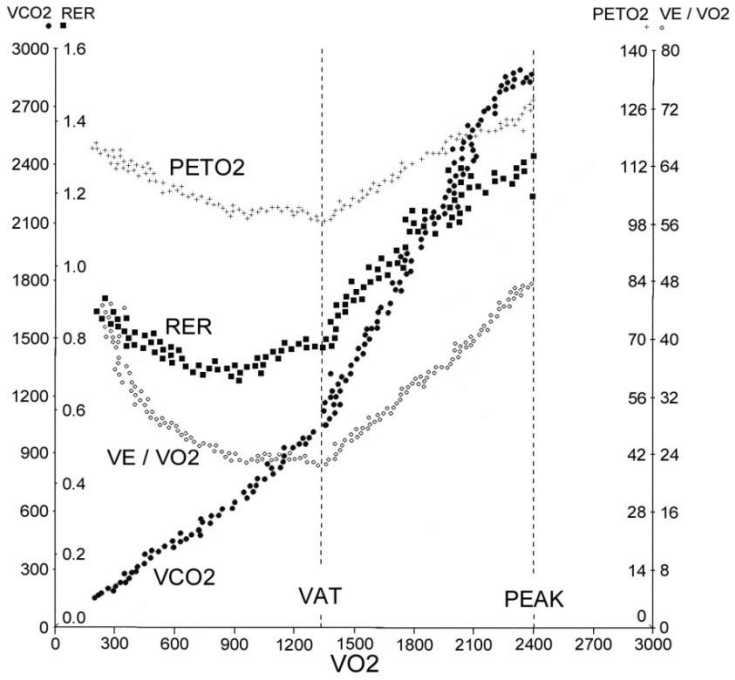

Figure 8. Graphical example of technique used to calculate V_{AT}.

RESULTS

Study One

Age, injury, and treadmill performance characteristics are provided by group in **Table 4**. There were no gender differences in age at TBI ($p = 0.76$), years since TBI ($p = 0.65$), or treadmill speed ($p = 0.16$).

Table 4: Group injury and physical characteristics for female and male participants in study 1. Data are presented as mean ± standard error of the mean.

	Females	Males
Age (yrs)	35.2 ± 2.9	34.7 ± 2.8
Age at TBI (yrs)	29.5 ± 3.5	30.4 ± 2.8
Years Since TBI (yrs)	4.7 ± 1.4	6.0 ± 2.5
Ambulatory Speed (mph)	2.7 ± 0.2	2.8 ± 0.2

Peak body mass normalized VO_2 data revealed significant main effects in gender ($F = 28.5$; $p < 0.01$) and outcome ($F = 27.3$; $p < 0.001$) (**Figure 9**). As expected, measured peak body mass normalized VO_2 was greater in males than females ($p < 0.001$). Within males, the measured peak VO_2 was less than predicted ($p < 0.001$); measured peak VO_2 was also lower than predicted in females ($p = 0.002$). ANOVA statistics revealed significant main effects in gender ($F = 125.8$; $p < 0.001$) and outcome ($F = 33.2$; $p < 0.001$) for VCO_2. VCO_2 was higher in males than females ($p < 0.001$). Measured VCO_2 was lower than predicted in males ($p < 0.001$) and females ($p = 0.002$). Significant main effects were evident in gender ($F = 81.3$; $p < 0.001$) and outcome ($F = 304.6$; $p < 0.001$) for V_E (**Figure 10**). As expected, males had higher measured V_E than females ($p < 0.001$). For males, measured V_E was lower than predicted ($p < 0.001$). Measured V_E was also lower than predicted in females ($p < 0.001$). HR main effects were detected in outcome ($F = 37.9$; $p < 0.001$), but not gender ($F = 1.2$; $p = 0.28$) (**Figure 11**). Within males, the actual peak HR was less than predicted ($p < 0.001$). Females also displayed lower actual peak HR than predicted ($p < 0.001$). Means and standard errors of the mean for measured and predicted values are provided in **Table 5**.

Table 5. Measured versus predicted peak metabolic, ventilatory, and cardiovascular variables for study 1.

	Females		Males	
	Measured	Predicted	Measured	Predicted
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	22.8 ± 1.7[!]	29.3 ± 1.4[!]	29.5 ± 1.9[!]	38.9 ± 1.5[!]
VCO_2 ($mL \cdot min^{-1}$)	1880.5 ± 154.3[!]	2464.8 ± 71.9[!]	3054.5 ± 150.5[!]	4068.1 ± 114.1[!]
V_E ($L \cdot min^{-1}$)	54.2 ± 5.1[!]	123.8 ± 3.5[!]	86.4 ± 5.7[!]	175.8 ± 5.5[!]
HR ($beat \cdot min^{-1}$)	159.7 ± 5.7[!]	184.6 ± 2.9[!]	165.1 ± 5.8[!]	185.6 ± 2.8[!]

Statistical difference between MEAS and PRED is indicated by[!].

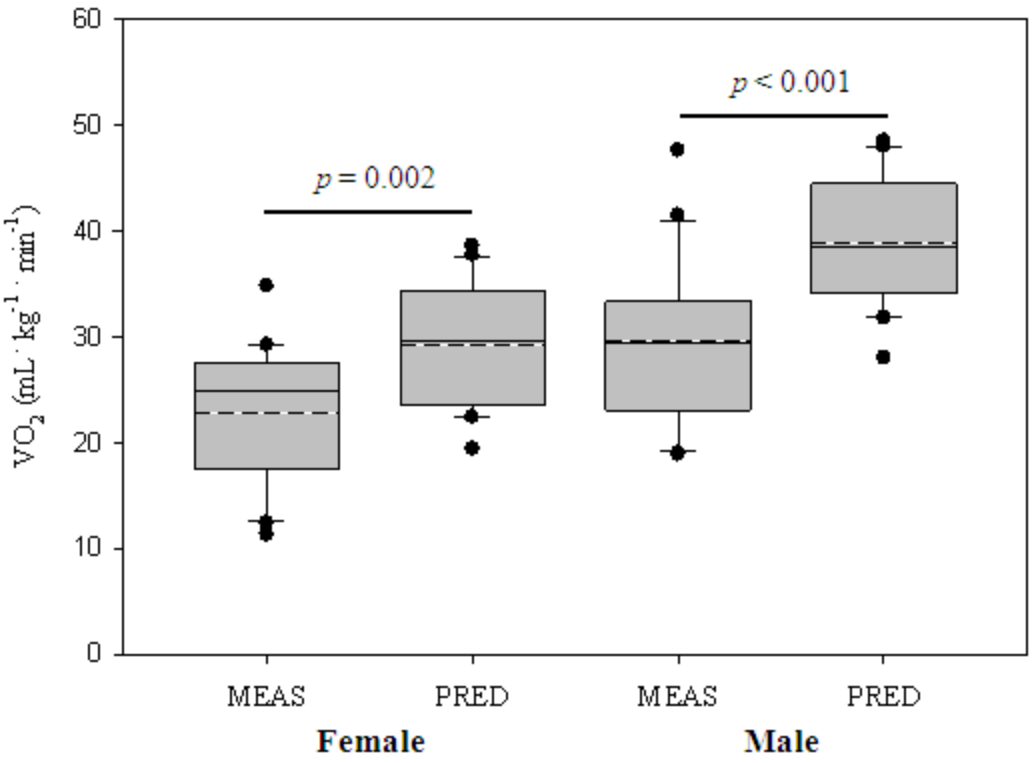

Figure 9. Box plot depicting the data distribution for measured versus predicted bodyweight normalized VO_2. Significant differences were observed within males ($p < 0.001$) and females ($p = 0.002$).[l]

[l] For all box plots contained in the dissertation, box center line and two box end caps denote the 50th, 25th, and 95th percentile scores. Whisker ends represent the 5th and 95th percentile scores and dots are data scores that fall outside of the 5th and 95th percentile. Mean line is represented by the black and white dashed line near the center of the box.

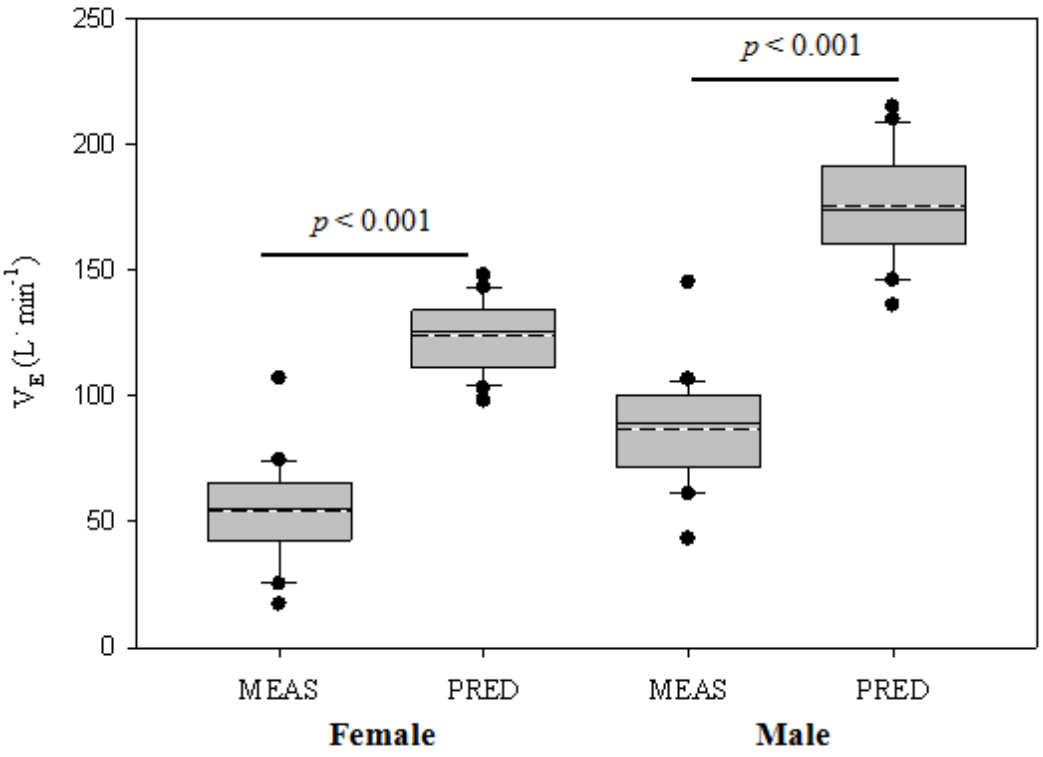

Figure 10. Box plot depicting the data distribution for measured versus predicted V_E between and within genders. Significant differences were observed within males ($p < 0.001$) and females ($p < 0.001$).

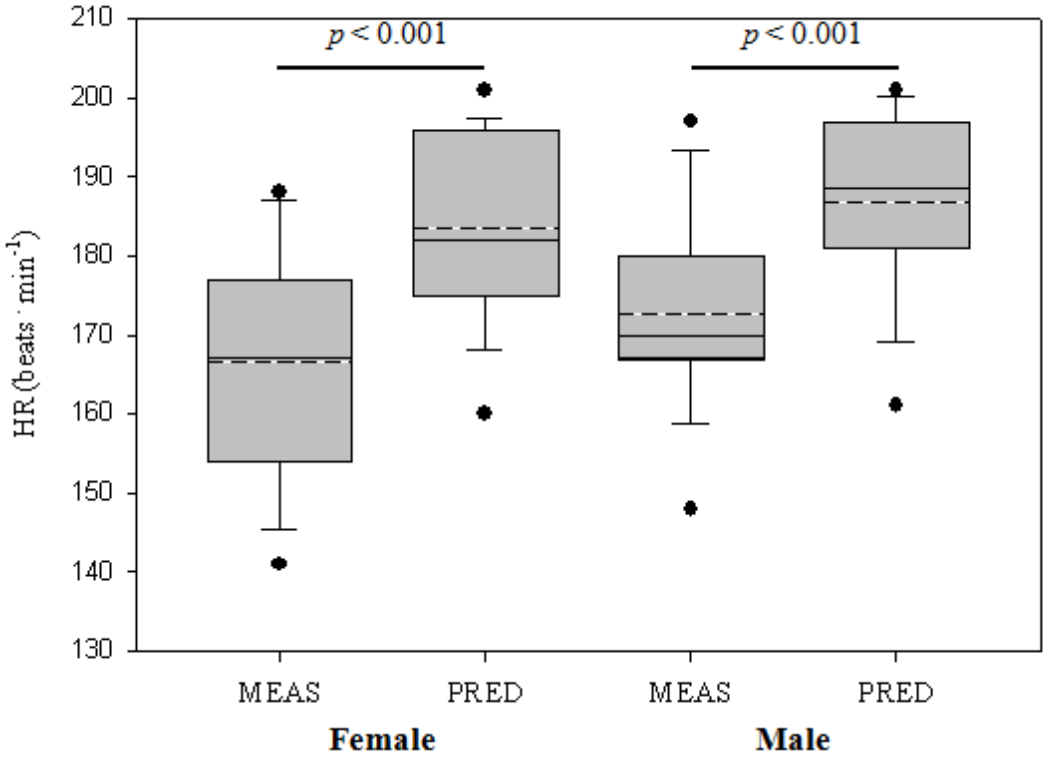

Figure 11. Box plot depicting the data distribution for measured versus predicted HR. Significant differences were observed in MEAS versus PRED peak HR within females ($p < 0.001$) and males ($p < 0.001$).

Study Two

Patients with a TBI ranged in age from 19-54 yrs and control subjects from 20-53 yrs. There were no statistical differences in age (p = 0.59), height (p = 0.79), body mass (p = 0.41), or body mass index (p = 0.34). The average peak ambulatory speed for the TBI patients was 4.5 (1.3) km · h^{-1}. All CON subjects achieved a peak ambulatory speed of 5.3 km · h^{-1}.

Ventilatory Anaerobic Threshold (V_{AT})

A summary of metabolic, cardiovascular, and ventilatory variables at V_{AT} is provided in **Table 6**. RER at V_{AT} was similar between TBI and CON (p = 0.54). Body weight normalized VO_2 was significantly greater in CON at V_{AT} compared to TBI (p < 0.001). Additionally, absolute VCO_2 (p < 0.001) at V_{AT} were significantly greater in CON than TBI. CON had significantly greater V_E at V_{AT} (p < 0.001). Heart rates at V_{AT} were not significantly different between groups with the adjusted alpha (p = 0.05).

Peak Exercise

Group means and confidence intervals for metabolic, ventilatory, and cardiovascular variables can be seen in Significant between group differences are indicated by*.

Table 7Table 7 Similar to V_{AT}, no significant between group differences were observed in RER at peak exercise (p = 0.32). However, CON subjects had a greater (p < 0.001) peak body weight normalized VO_2 (**Figure 12**) and VCO_2 (p = 0.001) compared to TBI. Likewise, V_E at peak exercises was significantly greater in CON compared to TBI (p < 0.001; **Figure 13**). With the adjusted alpha, peak exercising HR was similar between CON and TBI (p = 0.02; **Figure 14**). V_{AT} occurred at 53.1 ± 2.0% and 60.6 ± 2.3% of peak VO_2 for the TBI and CON groups, respectively. The difference was statistically significant (p = 0.02).

Table 6. Mean and standard errors for measured metabolic, ventilatory, and cardiovascular variables at $V_{AT.}$[m]

Dependent Variable	Group	Mean ± SD	95% CI Lower	95% CI Upper	*p*-value
VO_2 (mL · kg^{-1} · min^{-1})	TBI	14.6 ± 2.2	13.1	16.1	$p < 0.001^*$
	CON	22.3 ± 4.0	20.8	23.8	
VCO_2 (mL · min^{-1})	TBI	1080.2 ± 324.4	896.2	1264.4	$p < 0.001^*$
	CON	1639.3 ± 455.8	1455.4	1823.3	
RER	TBI	0.9 ± 0.1	0.9	1.0	$p = 0.44$
	CON	0.9 ± 0.1	0.9	1.0	
V_E (L · min^{-1})	TBI	29.4 ± 8.1	24.5	33.8	$p = 0.001^*$
	CON	40.3 ± 10.6	35.9	44.7	
HR (beat · min^{-1})	TBI	115.5 ± 18.7	108.0	122.9	$p = 0.05$
	CON	132.9 ± 12.9	125.5	140.4	

Significant between group differences are indicated by*.

Table 7. Mean and standard deviations for measured metabolic, ventilatory, and cardiovascular variables at peak VO_2.[m]

Dependent Variable	Group	Mean ± SD	95% CI Lower	95% CI Upper	*p*-value
VO_2 (mL · kg^{-1} · min^{-1})	TBI	28.2 ± 6.2	25.3	31.1	$p < 0.001$*
	CON	37.2 ± 6.3	34.3	40.1	
VCO_2 (mL · min^{-1})	TBI	2727.2 ± 794.0	3261.4	4007.9	$p = 0.001$*
	CON	3634.8 ± 809.9	2354.1	3100.4	
RER	TBI	1.2 ± 0.1	1.2	1.2	$p = 0.32$
	CON	1.2 ± 0.1	1.2	1.3	
V_E (L · min^{-1})	TBI	81.6 ± 24.3	68.9	93.4	$p = 0.001$*
	CON	106.2 ± 26.3	94.4	118.0	
HR (beat · min^{-1})	TBI	166.7 ± 19.8	158.1	175.3	$p = 0.02$
	CON	176.4 ± 17.2	167.8	185.1	

Significant between group differences are indicated by*.

[m] Alpha adjustment of $p \leq 0.01$ used for all statistical comparison in study 2.

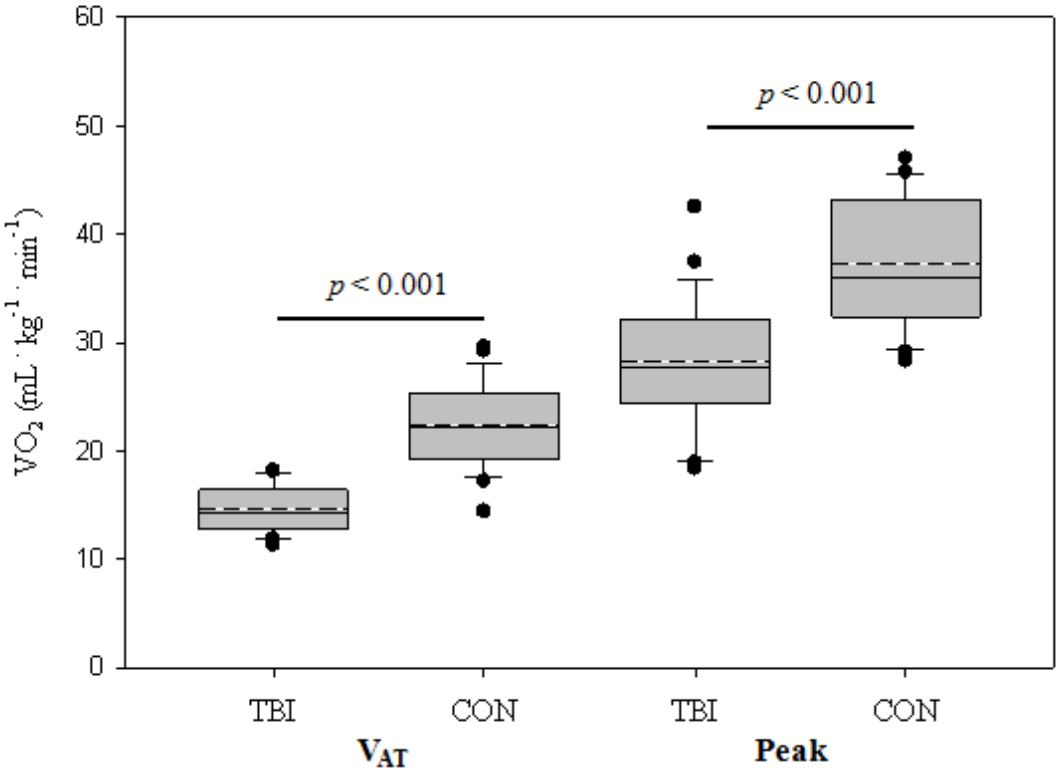

Figure 12. Box plot depicting the data distribution for bodyweight normalized VO_2 at V_{AT} and peak exercise for TBI and CON. Differences in normalized VO_2 at V_{AT} ($p < 0.001$) and at peak exercise ($p < 0.001$) were evident between groups.

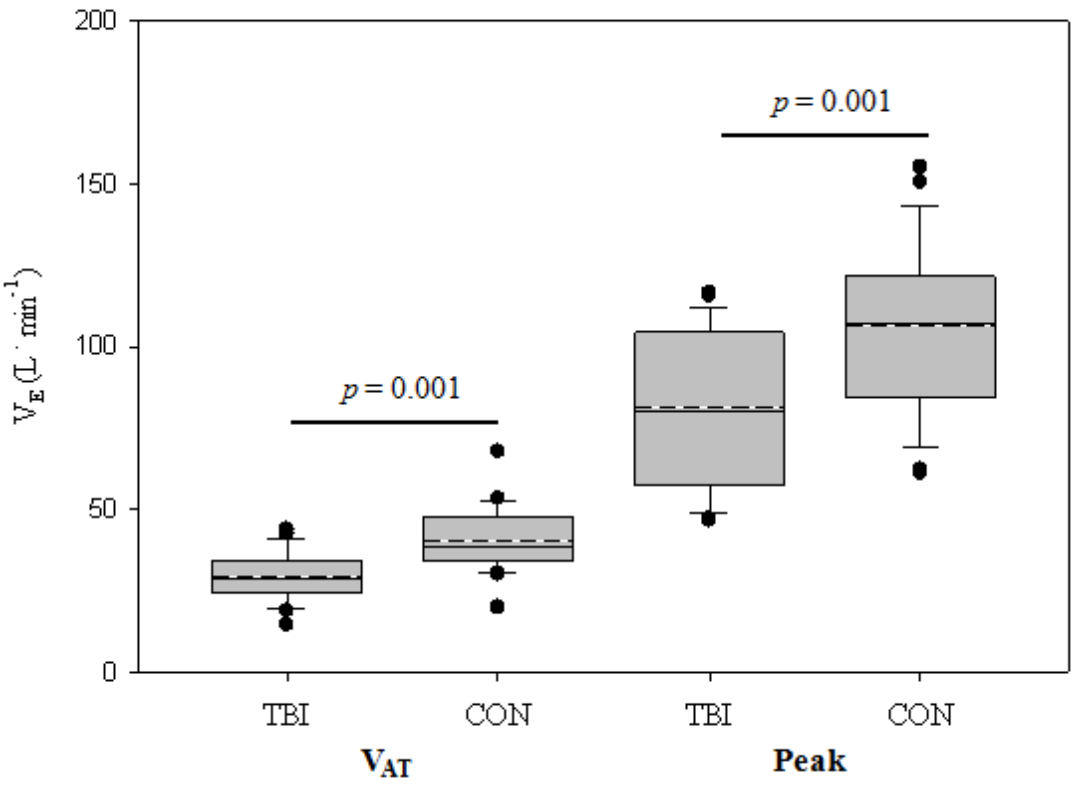

Figure 13. Box plot depicting the data distribution for V_E at V_{AT} and peak exercise for TBI and CON. Differences in V_E at V_{AT} (p = 0.001) and at peak exercise (p = 0.001) were evident between groups.

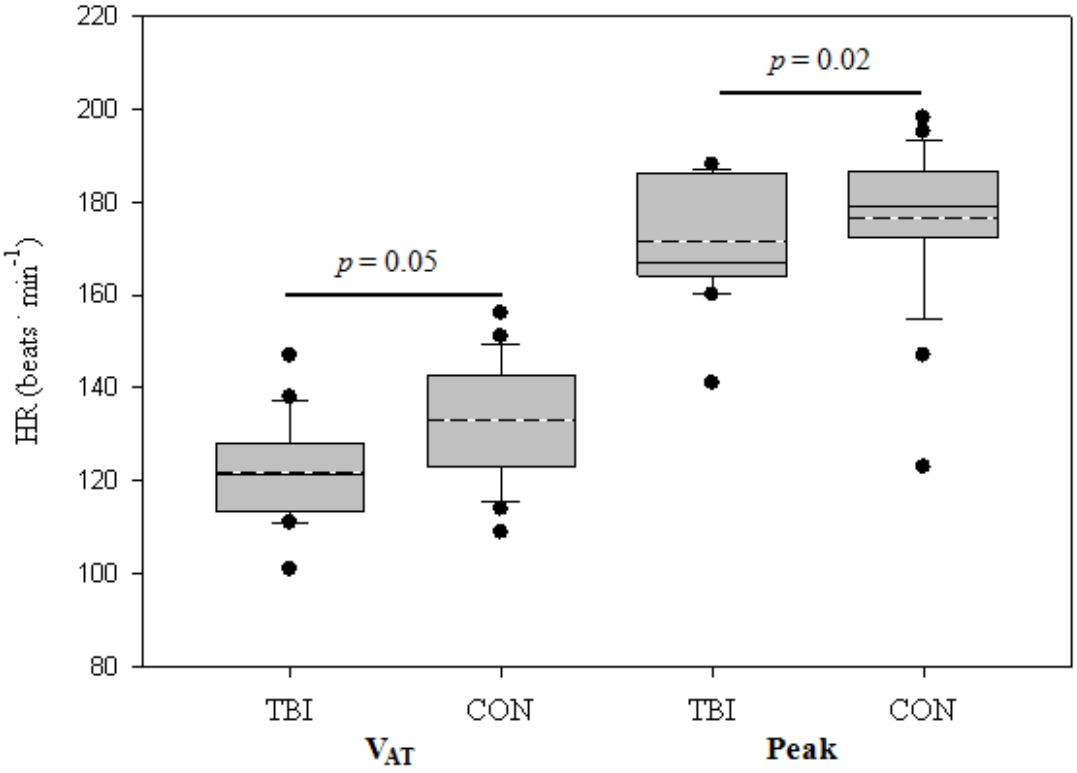

Figure 14. Box plot depicting the data distribution for HR at V_{AT} and peak exercise for TBI and CON. Differences in HR at V_{AT} (p = 0.05) and at peak exercise (p = 0.02) were not significantly different with Bonferroni adjustment.

DISCUSSION

The first purpose of these studies was to determine if the measured peak aerobic capacity of patients with a TBI differed from predicted normative values and if the difference varied by gender. The second purpose was to determine if the anaerobic thresholds, calculated using ventilatory measurements (V_{AT}), and peak exercise responses of patients with a TBI were different than apparently healthy age and gender matched CON that were similar in BMI. It was hypothesized that peak metabolic, ventilatory, and cardiovascular responses to a graded treadmill exercise would be lower than predicted, irrespective of gender - this hypothesis was confirmed. It was also hypothesized that patients with a TBI would have lower V_{AT} and peak exercise responses than matched sedentary controls. This hypothesis was also confirmed for VO_2, VCO_2, and V_E. However, with Bonferroni adjustments, HR did not differ between groups. It is clear from these data that high level motor functioning TBI patients have lower peak aerobic capacities than predicted regardless of gender and lower aerobic capacities than matched, sedentary controls (10^{th} vs. 30 -40^{th} percentile, respectively) (Pollock and Wilmore, 1990). A second novel finding of this study and perhaps the most functionally significant finding was that patients with a TBI have marked reductions in the percentage of peak VO_2 at which V_{AT} occurs. This has important implications for functional activities of daily living and could be a significant contributor to reported levels of fatigue in this patient population.

Peak and V_{AT} Exercise Responses Are Lower in Patients with a TBI and This May Be Related to Fatigue

Fatigue is a common and near universal complaint of persons with a TBI. The construct of fatigue is complex, multidimensional and involves events occurring both centrally and peripherally. From a metabolic perspective, during physical work at low

intensities, the rate of anaerobic glycolysis is low and the capacity of the mitochondria to produce energy for muscle contraction is adequate. Consequently, lactate production and hydrogen ion accumulation is minimal, resulting in relatively stable cellular pH values. However, when skeletal muscle energy demands exceed the aerobic capabilities of the patient, there is a significant shift towards anaerobic metabolism resulting in a concomitant decrease in cellular pH. The increase in hydrogen ion concentration requires buffering by bicarbonate ion and results in disproportionate increases in CO_2 levels in the blood. This is reflected in the change in the relationship between CO_2 production and O_2 consumption and an increase in RER to levels greater than 1.0. Work rates at or below V_{AT} can be sustained for relatively long periods. When the hydrogen ion concentration reaches a certain threshold, muscular contractions are disrupted and work levels become unsustainable; the subjective sensation is fatigue.

The difference in peak metabolic capacity confirms previously established data (Mossberg *et al.,* 2007). Because of these differences, it is not surprising that the level at which V_{AT} occurs differs between groups. However, the absolute VO_2 and percentage of peak VO_2 at which V_{AT} occurs is alarmingly low and suggests that the shift towards predominant anaerobic metabolism occurs earlier than expected in patients recovering from a TBI.

From a practical perspective, in most healthy individuals, the physical exertion required for routine activities of daily living are well below V_{AT}. Thus, routine activity results in minimal fatigue. However, these data indicate that patients with a TBI may reach or exceed V_{AT} performing even low-level activities of daily living (Ainsworth *et al.,* 2011; Crouter *et al*., 2006). Crouter and colleagues used a portable metabolic system and accelerometer to quantify the metabolic equivalents for oxygen (METs) of routine activities

of daily living (e.g., sweeping, yard mowing, heavy sawing) (Crouter *et al*., 2006). The metabolic costs of many of these activities are above the V_{AT} of most of the patients; some metabolic costs exceed their peak working capacity (see **Table 8**). The V_{AT} levels of our subject with TBI ranged from 3.2 – 5.2 METS. Peak VO_2 in the TBI group ranged from 5.3–12.1 METS. For three patients, sweeping, mopping, or vacuuming would be a supra-threshold activity. For all 19 patients with a TBI, lawn mowing or stair ascent was a supra-threshold activity and for four patients these activities were at or above their VO_2 peak. Finally, the reported metabolic demand of heavy sawing exceeds the V_{AT} of all patients with a TBI and exceeds the peak VO_2 of 10 of the 19 tested patients. These data indicate that patients with a TBI may not possess the metabolic capacity to perform and complete daily activities considered routine for healthy individuals. Again, this metabolic insufficiency may contribute substantially to the chronic fatigue reported in the literature (**Table 8**).

Table 8. Percentage of peak aerobic capacity for each patient compared to the metabolic demands of common daily tasks.

Patient	Standing	Filing Papers	Washing Dishes	Washing Windows	Sweeping/ Mopping	Vacuum	Raking Leaves	Fast Walk	Lawn Mowing	Ascending Stairs
1	15%	20%	25%	37%	43%	43%	47%	*57%	*78%	*88%
2	14%	19%	24%	34%	40%	40%	44%	53%	*73%	*82%
3	15%	20%	25%	36%	42%	*43%	47%	56%	*77%	*87%
4	16%	21%	27%	39%	45%	46%	50%	*60%	*83%	*93%
5	23%	30%	38%	54%	63%	*64%	*70%	*84%		
6	17%	23%	29%	42%	*48%	*49%	*54%	*64%	*88%	
7	14%	18%	23%	33%	38%	38%	42%	50%	*69%	*78%
8	10%	13%	16%	24%	27%	28%	30%	36%	*50%	*56%
9	21%	28%	36%	51%	60%	60%	*66%	79%		
10	13%	16%	21%	30%	35%	36%	39%	46%	*64%	*72%
11	13%	17%	21%	31%	36%	36%	40%	*48%	*65%	*74%
12	15%	20%	26%	37%	43%	44%	48%	*57%	78%	*88%
13	13%	17%	21%	31%	36%	36%	40%	48%	*65%	*74%
14	22%	29%	37%	53%	61%	62%	68%	*82%		
15	14%	19%	24%	34%	40%	41%	*44%	*53%	*73%	*82%
16	19%	25%	32%	46%	53%	54%	*59%	*70%	*97%	
17	15%	20%	25%	36%	42%	43%	*47%	*56%	*77%	*86%
18	13%	17%	22%	32%	37%	37%	41%	*49%	*67%	*76%
19	11%	15%	19%	27%	31%	32%	35%	41%	*57%	*64%

Note that a * indicates that the activity would likely be a supra-anaerobic threshold activity (Crouter *et al*., 2006). Blank columns indicate that the metabolic demands of an activity are above VO_2 peak.

Compromised Aerobic Fitness Could Contribute to Poor Health Outcomes in Patients with a TBI

Along with affecting physical work tolerance, the low aerobic capacities in TBI may contribute to poor overall health outcomes. Physical inactivity and poor aerobic capacity are independent risk factors for CVD and coronary artery disease (CAD) (Williams, 2001). Williams demonstrated a general linear trend between fitness level and risk for CVD. Moreover, the risk for these diseases increases exponentially for individuals with peak aerobic fitness below the 25th percentile. In both of the studies in this chapter, the fitness level of nearly all patients was below the 10th percentile suggesting that patients with a TBI may be at increased risk for CVD and CAD. Given this result, it is not surprising that patients with a TBI are three times more likely to die of cardiovascular disease (Shavelle *et al.,* 2001). This suggests that therapists should prioritize cardiorespiratory fitness training in patients with a TBI who have only minor or no motor impairments. The CDC and the ACSM currently recommend that all individuals engage in moderate exercise daily (<50% of maximal aerobic capacity) (Haskell *et al.,* 2007). Further, they suggest individuals should perform exercise at sufficient intensity to improve cardiovascular health (vigorous; 70% of maximal aerobic capacity) three days per week for at least 20 minutes per day. These minimal recommendations are likely an appropriate initial recommendation until population specific parameters are developed.[n]

STUDY LIMITATIONS

The data in this investigation are retrospective in nature and exercise recommendations are speculative. Future prospective or experimental studies are needed to

[n] Discussions of current evidence supporting exercise recommendations in patients with a TBI are included in Chapter 5.

define precise exercise prescriptions aimed to improve aerobic capacities in TBI patients. Furthermore, these data suggest that research should be targeted towards interventions that increase V_{AT} in this population. A second limitation of this study is the wide range of years since injury for the patients tested. Although the heterogeneity of the group could be viewed as a limitation, it also strengthens the argument that a TBI may result in lifelong impairment of metabolic capacity. What is not clear from these data is if the impaired V_{AT} and peak exercise responses are mechanistically related to injury or are associated with an adopted sedentary lifestyle post injury. Finally, subjects in study two were matched only by age and gender. Although the height, weight, and BMI of both groups were similar, each subject pair was not perfectly matched for each characteristic.

CONCLUSIONS

The peak aerobic capacities of patients with a TBI are lower than predicted regardless of gender. Further, the V_{AT} of individuals with a TBI was found to be lower than matched healthy sedentary controls. In most cases, it was below the metabolic work demands of many routine activities of daily living. This is likely a significant contributor to fatigue after TBI. Although physical therapy for patients with TBI generally involves basic locomotor training, results suggest that specific exercise interventions targeted at improving cardiorespiratory fitness may be necessary for successful rehabilitation outcomes regarding activities of daily living. When feasible, therapists should consider implementing more vigorous exercise strategies to improve V_{AT} (e.g., high intensity interval training). Furthermore, the entire rehabilitation team should be aware of the deficits in endurance capacity that exist in patients who have few, if any, overt physical impairments and for whom cognitive and behavioral therapies are the rehabilitation emphasis. These data also suggest that targeted health

promotion strategies may be needed to improve V_{AT} and overall fitness levels to decrease risk for CVD and CAD. Although precise exercise recommendations have not been studied adequately in TBI patients, prescriptions based on evidence derived from apparently healthy individuals may be used as a baseline to develop individual prescriptions. Exercise interventions designed to improve overall aerobic work capacity and improve anaerobic threshold are indicated and may be necessary for optimal functional outcomes in the rehabilitation of patients with TBI.

Chapter 4: The Endocrine Response to Exercise in Patients Recovering from a Traumatic Brain Injury (TBI).

ABSTRACT

Background and Objective: Hormonal dysfunction is common in patients with a TBI, with GH deficiency alone reported in 10-25% of patients. Recent evidence suggests that GH deficiency is associated with reduced aerobic capacity in TBI. Moreover, previous data suggest that GH deficiency may be related to perceived fatigue in patients with a TBI. To date, no investigations have described the hormonal response to exercise in TBI and no studies have investigated the hormonal response to exercise and its relationship with perceived fatigue in patients with a TBI. Therefore, the purposes of this study were to determine in patients with a TBI if (1) the hormonal response to exercise (GH, PRO, COR, or IGF-1) differed from CON, (2) the blood lactate or glucose responses to peak exercise differed from CON, and (3) physical characteristics, aerobic fitness, resting hormone levels, or exercise stimulated response of hormones were associated with perceived fatigue measured using a fatigue severity scale (FSS).

Experimental Design: A case-control study design was utilized to accomplish study objectives.

Measurements: Eight patients with a TBI and 8 age- and gender-matched apparently healthy controls (CON), similar in height, weight, and BMI completed a single maximal exercise test to volitional failure where VO_2, VCO_2, V_E, and HR were measured

continuously. Blood was sampled seven times prior to and after exercise and analyzed for GH, PRO, COR, IGF-1, (IGFBP-3), blood lactate, and blood glucose. Additionally, patients completed an FSS questionnaire prior to exercise and a visual analogue scale for fatigue before, immediately post-, 30 minutes post-, and 60 minutes post-exercise.

Results: GH, IGF-1, and IGFBP-3 were elevated post exercise in TBI and CON, but no significant differences between groups were evident. PRO and COR were significantly elevated in CON post-exercise, but not in TBI. Blood lactate was elevated in both groups post exercise, but was significantly higher in CON compared to TBI 10 minutes post exercise. A significant decrease was observed in blood glucose post-exercise in the CON, but an increase was seen in TBI. FSS scores were significantly correlated to VO_2 at V_{AT} ($r = -0.80$), VO_2 peak ($r = -0.54$), and resting IGF-1 ($r = -0.60$), resting FSH ($r = -0.44$), and exercise stimulated PRO ($r = -0.58$) levels.

Conclusions: TBI and CON subjects displayed similar GH responses to exercise, but distinct differences in the PRO and COR responses were noted. Fatigue was most significantly associated with VO_2 at V_{AT} and moderately associated with resting IGF-1 levels (a surrogate measure of GH deficiency). The response of GH to peak exercise was not associated with perceived fatigue. These data strongly support the use of exercise regimens designed to delay the onset of V_{AT} to reduce perceived fatigue.

INTRODUCTION

Data from the previous chapter demonstrated differences in the peak exercise responses in male and female patients with a TBI. The data in Chapter 3 also confirm that there are differences between peak exercise responses of patients with a TBI and apparently healthy controls. Moreover, there are distinct differences in the metabolic, ventilatory, and cardiovascular responses at V_{AT}. In apparently healthy individuals, many of these responses are partially modulated via hormonal mechanisms. Therefore, the conventional responses of hormones to exertion are necessary to control the acute and chronic metabolic, cardiovascular, and ventilatory responses to exercise.

Concomitant with physical exertion, circulating levels of certain hormones (e.g. GH, Thyroid Stimulating Hormone, etc.) increase. These hormones help to upregulate the physiological processes necessary to fuel the increased metabolic demands associated with physical work. Key hormones also help to facilitate recovery and immunological responses to exertional stress. As such, a normal response is essential to tolerate exertion and a blunted or altered response may reduce exercise capacity or the ability to recover after exercise.

Anterior Pituitary and the Growth Hormone/Insulin-Like Growth Factor-I Axis

The pituitary, a small endocrine gland located inferior to the hypothalamus, secretes hormones essential to regulation of homeostasis in many metabolic processes. GH is a peptide hormone released from the anterior pituitary regulated by growth hormone releasing hormone (GHRH), a peptide hormone secreted by the hypothalamus (Porterfield and White, 2007). Somatostatin, another hypothalamic hormone, inhibits GH secretion from the anterior pituitary (Porterfield and White, 2007). There are over 100 described variants of GH; the most prevalent isoform is a 22 kDa protein thought to be the most active variant in humans

(Nindl *et al.,* 2003). Circulating levels of GH are strongly influenced by circadian rhythms. (Kronenberg *et al.,* 2008). Devoid of stimulation, GH levels are highest during sleep but are increased by an array of stimuli including physical exertion (Stokes *et al.,* 2010), hypoxia (Takarada *et al.,* 2000), hypoglycemia (Sutton and Lazarus, 1976), increased body temperature (Vigas *et al*., 2000), among others (Borer, 2003; Kronenberg *et al.,* 2008).

GH is most known for its growth promoting properties. Persistently low levels of GH before puberty result in a clinical manifestation known as dwarfism (Kronenberg *et al.,* 2008). Adult onset hypopituitarism, specifically low levels of GH, may result in reduction of skeletal muscle mass and increased body fat (Van Beek *et al.,* 2010). Abnormally high levels of GH before puberty result in a condition known as gigantism; whereas high levels later in life result in acromegaly (Kronenberg *et al.,* 2008).

Along with directly affecting muscle protein synthesis, GH also indirectly increases protein accretion by stimulating IGF-1 release from the liver (i.e. GH/IGF-1 axis). IGF-1 is a polypeptide hormone that acts as both an endocrine (released by the liver) and autocrine (directly synthesized in skeletal muscle) hormone. It is responsible for an array of physiological functions, but a post-exercise response of IGF-1 is believed to assist in recovery from intense exercise (for review see (Gibney *et al*., 2007).

With respect to physical exertion and exercise, the lypolytic properties of GH may be most significant. Both aerobic and resistive exercises are known to acutely increase GH levels (Wideman *et al.,* 2002). Circulating GH levels are elevated with exercise intensities as low as 40% of peak VO_2 (de Vries *et al.,* 2000; Godfrey *et al*., 2003; Wideman *et al.,* 2002) and the elevated response of GH increases FFA oxidation. It is generally thought that blood levels of GH respond in proportion to intensity (Wideman *et al.,* 2002). Near V_{AT}, there is a

disproportional rise in GH relative to workload (Godfrey, 2008). Circulating GH levels continue to increase with intensity until cessation of exercise. When exercise ceases, GH levels begin to decrease, but may remain elevated above baseline for a short period after exercise.

The exact signaling mechanism of GH response to exercise is unknown, but some postulate lactic acidosis may be partially responsible (Godfrey, 2008). Others believe that body temperature (Vigas *et al*., 2000) or cellular pH may signal GH release. Although it is difficult to determine if cellular pH or lactic acidosis cause an increase in GH following exercise, acidosis is at least partially responsible. Wahl and colleagues measured the GH response to high intensity interval exercise performed with or without consumption of a supplement (bicarbonate) designed to buffer acid (Wahl *et al.,* 2010). They found that exercise with placebo supplement consumption resulted in a greater pH, lactate, and GH response compared to exercise with bicarbonate (Wahl *et al.,* 2010).

Prolactin (PRO), another anterior pituitary hormone regulated by the hypothalamus via dopamine secretion, is released in a diurnal pattern similar to GH (Porterfield and White, 2007). PRO release in response to exercise is also similar to GH - it is intensity dependent (de Vries *et al.,* 2000). In response to exercise, PRO is thought to influence immune function. It has been suggested that increased PRO levels may increase proliferation of human lymphocytes, enhance macrophage function, and increase natural killer cell activity (Ortega, 2003; Woods, 2000). Moreover, research suggests that PRO levels are increased in blood after graded exercise and there is an increased expression of PRO receptors in human lymphocytes following peak graded exercise (Dohi *et al*., 2003). Lower levels of PRO are uncommon and may result in problems with lactation in women (Porterfield and White,

2007). Infertility may be caused by hyperprolactinemia in both men and women (Porterfield and White, 2007). Similar to GH, PRO levels are at least partially stimulated by blood lactate (Luger *et al.,* 1992; Rojas-Vega *et al.,* 2006) and the PRO patterned release in response to exercise is similar to GH but slightly delayed. There is a substantial increase in PRO levels near V_{AT}; PRO continues to rise for a short time after maximal exercise and remains elevated slightly longer than GH. The intensity dependent release of both GH and PRO can be seen in **Figure 15** (de Vries *et al.,* 2000).

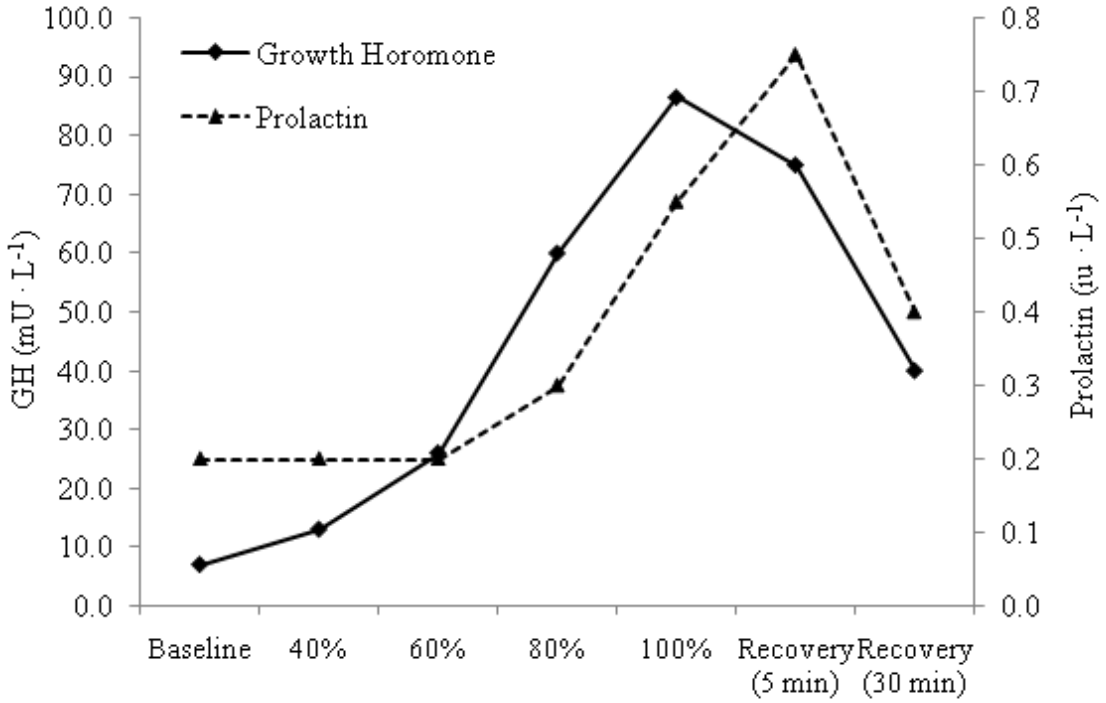

Figure 15. Relationship between GH and PRO to an acute bout of graded exercise (de Vries *et al.,* 2000).[o]

[o] **Figure 15** was generated from data published in *Psychosomatic Medicine.* Licensed permission for use of data to generate the figure was obtained from the publisher: Wolters Kluwer - Lippincott, Williams, and Wilkins.

Hypothalamic – Pituitary – Adrenal Axis

Adrenocorticotropic hormone (ACTH) is an anterior pituitary hormone that acts as a primary mediator of COR synthesis and secretion from the adrenal cortex (Borer, 2003). Classically described as a stress hormone by Hans Selye in 1956 (Selye,1956), COR levels are affected by a number of conditions (Borer, 2003) including exercise (de Vries *et al.,* 2000), hypoglycemia (Stempien, 1969), hypothermia or hyperthermia (Collins and Few 1979; Frank *et al.,* 1995), injury (Hobson *et al.,* 2004), and psychological stress (Dugue *et al.,* 1993). Hypercortisolemia, a condition known as Cushing's disease or syndrome, may result in increased body fat, decreased muscle mass or muscle weakness, and a host of other physiological changes (Kronenberg *et al.,* 2008). Non-pathological increases in COR may have similar but less dramatic catabolic clinical manifestations (Paddon-Jones *et al.,* 2003). It has been suggested that COR may compete for androgen binding sites and the ratio of cortisol to testosterone is used as an indicator of training status in athletes (Urhausen and Kindermann, 2002). A rise in COR levels relative to testosterone is an indicator of overreaching or overtraining and may result in functional decreases in performance. Interestingly, evidence suggests that overtraining syndrome may be associated with suppression of exercise stimulated pituitary hormones including ACTH and GH (Meeusen *et al.,* 2004; Urhausen *et al*., 1998). Moreover, overtrained athletes experience an array of psychological disorders similar to TBI (Anglem *et al.,* 2008; Nicholls *et al.,* 2009; Purvis, Gonsalves and Deuster, 2010; Vetter and Symonds, 2010).

ACTH and COR respond in an intensity dependent manner with increasing exercise. De Vries *et al*. reported a 35% increase in levels of ACTH compared to baseline resting levels at 80% of maximum power output (de Vries *et al.,* 2000). They also reported a 410% increase in levels of ACTH at maximum cycle ergometry exercise compared to rest. COR

responds similar to ACTH, but in a delayed manner. In the same study, COR was not significantly elevated with 40, 60, 80, or 100% of maximum power output compared to baseline, but it was elevated 5 and 30 minutes after cessation of exercise (15 and 23%, respectively) (de Vries *et al.,* 2000).

Endocrine Function and TBI

Evidence suggests that acute brain trauma results in altered function of the hypothalamus-pituitary axis and the hypothalamus-pituitary-adrenal axis (Chiolero and Berger, 1994). Chiolero and colleagues observed pituitary hormone function immediately after head injury. Comparing head injured patients to patients suffering traumatic, non-head related injuries, they measured ACTH, GH, PRO, and thyroid stimulating hormone (TSH) levels for five days post injury. Their data show that PRO and TSH levels were suppressed in head injured patients (Chiolero *et al.,* 1988). GH was elevated in both head and non-head injured subjects. Others have shown variable responses of GH and other pituitary hormones suggesting that the alterations in neuroendocrine function may be highly individualized (Woolf 1992; Yuan and Wade, 1991).

Long-term hormonal dysfunction after a TBI is common and some have suggested that endocrine testing should be routine practice (Berg *et al.,* 2010; Gauna *et al*., 2005; Herrmann *et al.,* 2006). GH deficiency is likely the most common chronic pituitary abnormality, but there is evidence for alterations in other hormones post-TBI (Agha *et al.,* 2004; Carlson *et al.,* 2009; Jackson and Mysiw, 1989; Popovic, 2005). GH deficiency may also be associated with chronic fatigue (e.g. fibromyalgia), but this is debated (Jones *et al.,* 2007). From a rehabilitation perspective, what is not debated is that normal hormonal function is important to exercise prescription. Suppression of key anterior pituitary and

adrenal hormones may negatively impact the acute responses to exercise and the ability to recover post-exercise. The general recommendation for exercise prescription in individuals with low aerobic capacities is intense exercise, but this may be contraindicated for individuals with suppressed hormonal responses to exercise.

Although deficiencies in hormones have been described in response to clinical stimulation tests, few if any studies have described the hormonal response to exercise in patients with a TBI. Since hormonal mechanisms are responsible for mediating many of the acute and chronic responses to exercise, they could partially explain the abnormal exercise responses in TBI highlighted in the previous chapter. Furthermore, these hormones play essential roles in substrate metabolism providing energy to complete tasks; therefore, a blunted response might also increase fatigue. The purposes of this study were to determine if, in patients with a TBI, (1) the hormonal response to exercise (GH, PRO, COR, or IGF-1) differed from CON, (2) the blood lactate or glucose responses to peak exercise differed from CON, and (3) if the physical characteristics, aerobic fitness, resting hormone levels, or exercise stimulated response of hormones were associated with perceived fatigue measured using a fatigue severity scale (FSS). It was hypothesized there would be a blunted response of GH, IGF-1, PRO, and COR to an acute bout of maximal exercise in patients with a TBI, but no difference in the responses of blood lactate and glucose to exercise between groups. It was also hypothesized that subject physical characteristics (i.e. body fat, BMI, etc.), aerobic fitness, resting IGF-1 (a surrogate measure of GH deficiency), and the exercise stimulated GH response to exercise would be significantly associated with fatigue as measured using an FSS.

METHODS

Participants

Sixteen subjects volunteered for this study. The sample consisted of 8 patients with a TBI (TBI; 31.3 ± 1.6 yrs, 177.8 ± 3.6 cm, 96.1 ± 5.5 kg) and 8 controls (CON; 30.6 ± 2.1 yrs, 173.2 ± 2.7 cm, 85.6 ± 6.8 kg) that were matched for gender and age (±5 yrs). The physical and injury characteristics for patients with a TBI and physical characteristics of CON are provided in **Table 9**. Patients with a TBI were recruited from the TLC in Galveston, TX, The Institute for Rehabilitation and Research (TIRR) outpatient clinic in Houston, TX, and the local community. All patients with a TBI had few, if any motor impairments and could ambulate at 5.3 km · h^{-1} without assistance.

Experimental Design

A case-control study design was used to test the hypotheses in specific aims three and four. After written and oral consent were obtained, baseline anthropometric data were collected on the eight patients with a TBI and the eight age- and gender-matched CON. Additionally, each subject completed a FSS at baseline. Subjects were seated in a chair and an indwelling venous catheter was inserted into an arm vein distal to the elbow and held patent with a saline solution. Baseline samples were drawn every ten minutes for one hour while subjects were seated in a chair. After one hour of seated rest, the subjects performed a maximal graded treadmill exercise test to volitional failure. Exercising metabolic, ventilatory, and cardiovascular responses were recorded. Additionally, a rating of perceived fatigue using a visual analogue scale (V_{FAS}) was determined prior to, immediately post, 30-minutes post, and 60-minutes post exercise. After reaching peak exercise, subjects were permitted to walk for approximately 5 minutes during recovery at a slow, self-selected pace. The subjects were

seated in a chair after recovery and blood was drawn every 10 minutes for one hour during recovery. During the final 10 minutes of the rest period, 10 minutes of recovery metabolism were measured with the metabolic cart. A diagram of the overall study protocol and timing is provided in **Figure 16**.

Table 9. Physical and injury characteristics of patients with a TBI and CON.

ID	Gender	GCS	Cause of Injury	Age at Test	HT (cm)	WT (kg)	BMI
1a	F	NA	BHT	29	175.3	114.5	37.3
9a	F			30	158.8	50.6	20.1
2b	M	9	IED	22	185.4	104.5	30.4
10b	M			20	167.6	65.9	23.5
3c	M	4	MVA	30	172.7	75.9	25.4
11c	M			32	177.8	89.5	28.3
4d	M	NA	Fall	30	182.9	91.8	27.4
12d	M			33	179.1	100.0	31.2
5e#	M	4	MVA	40	170.2	106.8	36.9
13e	M			39	182.8	92.7	27.7
6f	M	NA	IED	32	185.4	102.7	29.9
14f	M			33	172.7	95.5	32.0
7g	M	NA	IED	38	190.5	102.7	28.3
15g	M			34	176.5	109.1	35.0
8h	M	NA	IED	29	160.5	70.0	27.3
16h	M			24	170.1	81.8	28.3

Note that ID notes the matched pair for each TBI group. They were matched only for gender and age within 5 years.[jp]

[p] For the remainder of this chapter, # symbol indicates patient who screened positive for GH deficiency for a separate study.

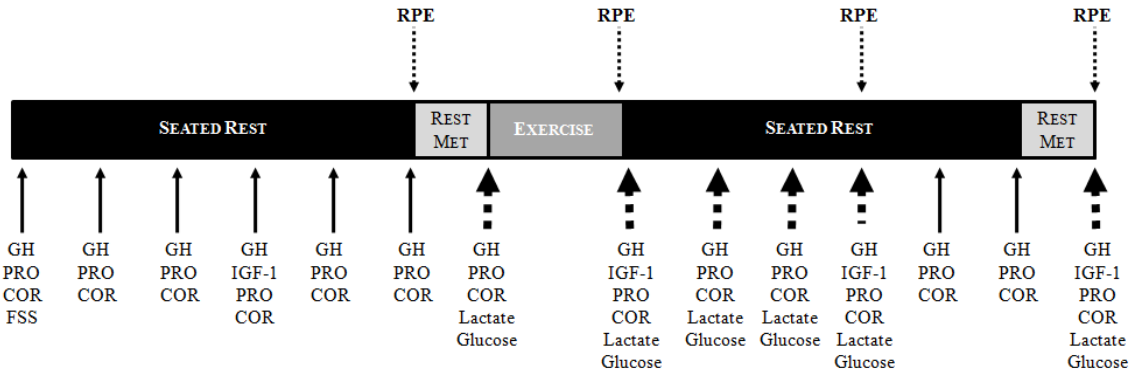

Figure 16. Overall study protocol including dependent measures at each time point.

Anthropometric Data Collection

Subject height was collected using a wall mounted stadiometer and weight using a digital scale (Befour *Inc*, Saukville, WI). Body composition data were obtained by a skilled technician using Lange skinfold calipers (Beta Technology *Inc.*, Cambridge, MA). Skinfold (SF) measurements were obtained from the following sites: pectoralis, triceps, sub scapulae, abdomen (AB), supra-iliac, mid-axillary line, and thigh. From the skinfold measurements, body density was determined using **Equation 8** and **Equation 9**. Percent fat was determined using Siri's equation (**Equation 10**).

$$BD = 1.112 - 0.00043499 + \left(\sum SF + 0.0000055\right) \times \left(\sum SF^2\right) - 0.00028826 \times AGE$$

Equation 8. Body density (BD) equation for men (Jackson and Pollock 1985; Pollock, Schmidt and Jackson 1980).

$$BD = 1.097 - 0.00046971 + \left(\sum SF + 0.00000055\right) \times \left(\sum SF^2\right) - 0.00012828 \times AGE$$

Equation 9. Body density equation for women (Jackson and Pollock 1985; Pollock, Schmidt and Jackson 1980).

$$\% \, Fat = \frac{4.95}{BD} - \ 4.5$$

Equation 10. Equation used to calculate percent fat from body density (Siri 1961).

Peak Treadmill Testing

A detailed description of the treadmill testing procedures can be found in Chapter 3. Briefly, a Balke-Ware treadmill protocol (Balke and Ware, 1959) was employed to test peak aerobic capacity using the test termination criteria of the ACSM (Thompson, 2010). Prior to exercise testing, 10 minutes of seated metabolic, ventilatory, and cardiovascular data were obtained; 10 minutes of seated metabolic data were also obtained from minutes 50-60 after exercise.

Blood Sampling Procedures

Baseline blood samples were collected upon arrival at the laboratory. Initial draws were completed between 0830-0900 hrs to minimize effects of diurnal changes in hormones. Blood was then drawn every 10-minutes for one-hour prior to exercise, and collected every 10-minutes for one-hour post exercise. An overall total of 14 draws were completed during the study. At each time point, 5mL of blood were drawn into a syringe and transferred into a sterile gold top vacutainer collection tube containing a clot activator for serum separation. Immediately prior to, immediately-post, 30-minutes post, and 60-minutes post exercise, an extra 15mL of blood was drawn and transferred in 5mL volumes into a second gold top tube, a purple top vacutainer tube containing 7.2mg of ethylene diamine acetic acid (EDTA), and a green top vacutainer tube containing lithium heparin. Immediately after collection, the tubes were inverted to allow mixing of chemicals and placed in a tube rack for 15 minutes at room temperature. Then, they were placed on ice until completion of the testing session.

After all samples were drawn, the tubes were centrifuged (Beckman Coulter Inc., Allegra 222, Fullerton, CA) at 3,000 rpm for 20-minutes at 4^{o}C to separate serum and plasma. Serum and plasma were then transferred into a labeled cryotube in 1mL volumes. Cryotubes were stored in a -80^{o}C freezer (Thermoelectron Corp, Watham, MA) until all samples were analyzed at the conclusion of the study.

Hormonal Analysis

Serum hormone levels were determined in batch at the completion of data collection using enzyme-linked immunosorbent assay (ELISA) techniques. Follicle stimulating hormone (FSH; L2KFSH2; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL), luteinizing hormone (LH; L2KLH2; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL), non-protein bound thyroxine (Free T_4; L2KFT42; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL), and IGF-1 (L2KGH2; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) were assessed at rest in duplicate using an automated chemiluminescent assay system (IMMULITE® 2000, Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL). These data were used to test for normalcy in pituitary, gonadal, and thyroid function.

Growth Hormone (GH)

Serum GH levels were measured seven times before and seven times after exercise in duplicate using a commercially available kit (L2KGRH6; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) and the IMMULITE® 2000 chemiluminescent assay system. Prior to analyses, the machine was calibrated and the sample was high and low adjusted (lyophilized GH in a non-human serum). The low and high adjustors were reconstituted in 3.0mL of deionized water, inverted, and allowed to dissolve for 30 minutes. Then, the low and high adjustors were measured four times with a coefficient of variation (CV) in measurement of

4.0 and 4.8, respectively. The analytic sensitivity of the assay is reported by the manufacturer at ± 0.01 ng · mL^{-1}.

Prolactin (PRO)

Serum PRO levels were measured seven times before and seven times after exercise in duplicate using a commercially available kit (L2KPRH6; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) and the IMMULITE® 2000 chemiluminescent assay system. Prior to analyses, the machine was calibrated and the sample was high and low adjusted with a lyophilized human PRO serum matrix. The low and high adjustors were reconstituted in 2.0mL of deionized water, inverted, and allowed to dissolve for 30 minutes. Then, the low and high adjustors were measured four times with a coefficient of variation (CV) in measurement of 4.26 and 2.63 respectively. The analytic sensitivity of the assay is reported by the manufacturer at ± 0.5 ng · mL^{-1}.

Cortisol (COR)

Serum COR levels were measured seven times before and seven times after exercise in duplicate using a commercially available solid phase, competitive immunoassay kit (L2KCOH6; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) and the IMMULITE® 2000 chemiluminescent assay system. Prior to analyses, the machine was calibrated and the sample was low and high adjusted with premixed COR, human serum solution. Then, the low and high adjustors were measured four times with a coefficient of variation (CV) in measurement of 3.9 and 6.0 respectively. The analytic sensitivity of the assay is reported by the manufacturer at ± 0.20 µg · dL^{-1}.

Insulin-Like Growth Factor-I (IGF-1)

Serum IGF-1 levels were measured prior to and three times after exercise in duplicate using a commercially available solid phase, competitive immunoassay kit (L2KPRH6; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) and the IMMULITE® 2000 chemiluminescent assay system. Prior to analyses, the machine was calibrated and the sample was high and low adjusted with a premixed IGF-1 and protein-buffer matrix. Low and high adjustors were measured four times with a coefficient of variation (CV) in measurement of 4.3 and 1.8 respectively. Prior to testing, the serum samples were diluted using an IGF-1 free buffer matrix (L2GFZ; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL). The analytic sensitivity of the assay is reported by the manufacturer at ± 20 $ng \cdot mL^{-1}$.

Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3)

Serum IGFBP-3 levels were measured prior to and three times after exercise in duplicate using a commercially available kit (L2KPRH6; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL) and the IMMULITE® 2000 chemiluminescent assay system. Prior to analyses, the machine was calibrated and the sample was high and low adjusted with a premixed IGFBP-3 and protein-buffer matrix. Low and high adjustors were measured four times with a coefficient of variation (CV) in measurement of 4.9 and 0.9 respectively. Prior to testing, the serum samples were diluted using an IGF-1 free buffer matrix (L2GFZ; Siemens Healthcare Diagnostics *Ltd*., Deerfield, IL). The analytic sensitivity of the assay is reported by the manufacturer at ± 0.1 $\mu g \cdot mL^{-1}$.

Lactate

Serum lactate determinations were completed in duplicate at baseline (BASE) and minute +0, +10, +20, +30, and +60 after exercise. The measurements were completed using

spectrophotometric analysis (YSI 2300, Yellow Spring, OH). The precision of the lactate assay using the YSI analyzer is ± 0.1 mmol · L^{-1}.

Glucose

Serum glucose measurements were also determined in duplicate at baseline (BASE) and minute +0, +10, +20, +30, and +60 after exercise. The measurements were completed using spectrophotometric analysis (YSI 2300, Yellow Spring, OH). The precision of the glucose assay using the YSI analyzer is ± 2.5 mg · dL^{-1}.

Fatigue Severity Scale (FSS)

The FSS (**Table 10**) was administered prior to exercise to assess baseline levels of fatigue during activities of daily living. The FSS is a nine-item questionnaire originally developed for multiple sclerosis and has been previously validated in patients with a TBI (Ziino and Ponsford 2005). The FSS assesses how the perception of fatigue has affected the individual during the preceding week. In each of the nine items included in the questionnaire, the subjects answered on a scale of 1-7 how appropriate the statement was to them over the previous week. A high score (i.e. 7) indicates that statement was very appropriate; a low score (i.e. 1) indicates that the statement was not very appropriate. For purpose of these analyses, only the composite score (i.e. sum of nine items) of each individual was calculated and used.

Table 10. Fatigue severity scale (FSS) routinely used in clinical populations (Krupp *et al.,* 1989). For each item, a higher score indicates a greater level of applicability.

During the past week, I found that:	**Score**						
1. My motivation is lower when I am fatigued.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
2. Exercise brings on my fatigue.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
3. I am easily fatigued.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
4. Fatigue interferes with my physical functioning.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
5. Fatigue causes frequent problems for me.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
6. My fatigue prevents sustained physical functioning.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
7. Fatigue interferes with carrying out certain duties and responsibilities.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
8. Fatigue is among my three most disabling symptoms.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
9. Fatigue interferes with my work, family, or social life.	**1**	**2**	**3**	**4**	**5**	**6**	**7**

Perceived Exercise Fatigue

Perceived exercise fatigue was measured using a V_{FAS}. The V_{FAS} was administered at baseline (BASE) and at minute +0, +30, and +60. The words "not fatigued at all" and "very, very fatigued" were written on opposing ends of a 10 cm line (**Figure 17**). Using a pen, subjects placed a mark on the scale indicating their current level of fatigue. The distance from the beginning of the scale to the marked line was used as an indication of fatigue. Similar scales have been used and validated against the rating of perceived exertion (RPE) scale developed by Borg (Borg, 1970) and routinely used in exercise studies (Capodaglio, 2001; Grant *et al.,* 1999).

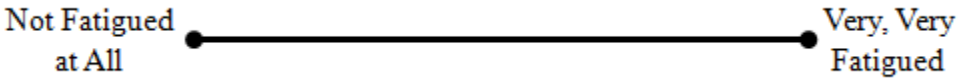

Figure 17. Visual fatigue analogue scale that will be used to determine fatigue associated with exercise.

STATISTICAL ANALYSIS

Statistical analyses were completed using SPSS 18.0 (SPSS Inc., Chicago, IL). Integral approximation values for GH, PRO, and COR were calculated using the trapezoid rule (**Figure 18**) (Kanaley *et al.,* 2001; Kline 1998). Integral values for 30 minutes prior to exercise (BASE), minutes 0-30 after exercise (Post 0-30m), and minutes 30-60 after exercise (Post 30-60m) are reported in the Results section. Assessment of between and within group differences for GH, PRO, COR, IGF-1, IGFBP-3, lactate, and glucose were accomplished using 2-Factor ANOVAs (group x time) with repeated measures. If F-ratios were significant for ANOVA comparisons, Dunett's test were used for pair-wise comparisons.[q]

Statistical associations between FSS and subject characteristics, aerobic fitness, baseline hormonal levels, and exercise stimulated hormone levels were determined by calculating Pearson's *r* values for each comparison. Although not central to the hypotheses, a complete correlation matrix was calculated between all tested variables. The critical value for significance was set at $p \leq 0.05$. A critical correlation threshold for $p \leq 0.05$ was $r = 0.44$ (df =17). All data are expressed as mean ± standard error of the mean (SEM) unless otherwise noted.

[q] Dunett's post-hoc test was selected because it allows for multiple comparisons to a defined control condition (i.e. baseline).

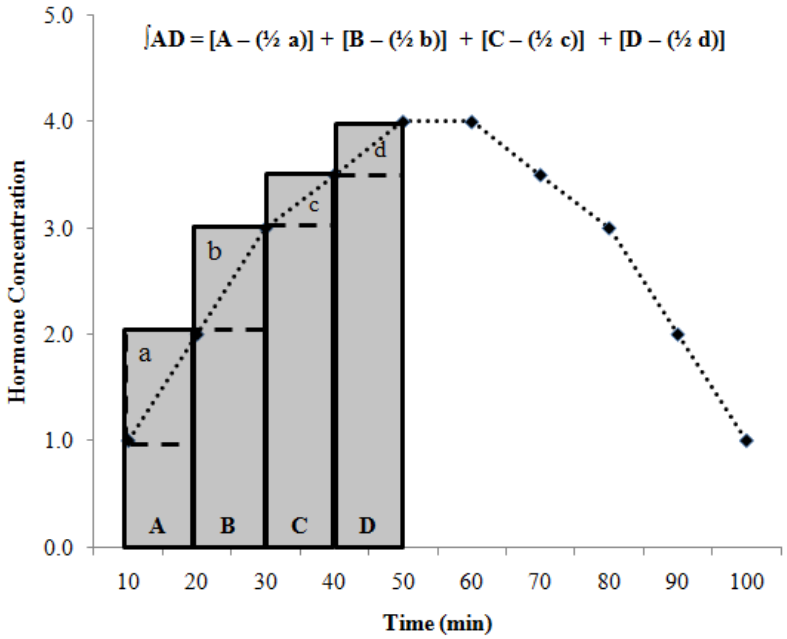

Figure 18. Integral approximation method used for GH, PRO, and COR using a hypothetical example curve (Kline, 1998).

RESULTS

A summary of anthropometric data is provided in **Table 11**. TBI and CON subjects were similar in age (p = 0.86), height (p = 0.30), weight (p = 0.28), and BMI (p = 0.42). Additionally, no significant differences were observed in calculated percent fat (p = 0.15) or lean body mass (p = 0.48) between groups. Subject baseline hormone values for FSH, LH, free T_4, and IGF-1 are provided in **Table 12**. Resting FSH was significantly lower (p = 0.04) in TBI (2.6 ± 0.4 mlU · mL^{-1}) compared to CON (4.1 ± 0.8 mlU · mL^{-1}). However, LH levels were similar (p = 0.31). Resting non-protein bound T_4 was also similar between TBI and CON (p = 0.17). Although a trend for lower IGF-1 levels in TBI compared to CON was apparent, there were no statistical differences (p = 0.06)

Table 11. Subject characteristics (TBI and CON) for data used in Chapter 4.

	TBI	CON	Difference	*p*-value
Age (yrs)	31.3 ± 2.0	30.6 ± 2.1	0.7 ± 3.5	0.86
Height (cm)	177.8 ± 3.6	173.2 ± 2.7	4.6 ± 4.1	0.30
Mass (kg)	96.1 ± 5.5	85.6 ± 6.8	10.5 ± 8.9	0.28
BMI	30.4 ± 1.6	28.6 ± 1.7	1.8 ± 2.4	0.42
% Fat	27.7 ± 1.9%	23.0 ± 2.8%	4.7 ± 2.9%	0.15
Lean Mass (kg)	65.0 ± 4.1	68.8 ± 2.6	3.8 ± 5.1	0.48

Table 12. Individual baseline hormone data for subjects tested.

		FSH $mlU \cdot mL^{-1}$	LH $mlU \cdot mL^{-1}$	Free T_4 $ng \cdot dL^{-1}$	IGF-1 $\mu g \cdot mL^{-1}$
TBI	1	4.35	3.54	0.80$	90.20$
	2	2.39	5.52	0.89	148.00$
	3	2.41	4.87	0.82$	110.00$
	4	4.05	2.35	0.86$	140.00$
	5#	2.24	2.49	0.92	118.00$
	6	1.98	4.24	0.96	191.00
	7	1.77	1.46	0.96	87.00$
	8	1.73	7.68	0.90	160.00$
CON	9	4.24	3.19	0.91	173.00$
	10	5.27	3.26	2.97	193.00
	11	3.51	1.66	0.99	226.00
	12	8.75	4.56	1.11	163.00$
	13	1.89	0.88	0.99	102.00$
	14	3.99	6.39	1.08	130.00$
	15	2.05	1.68	1.05	118.00$
	16	3.12	2.72	0.99	252.00

Note that $ indicates that the value was outside of expected ranges.

Metabolic, Ventilatory, and Cardiovascular Responses

Peak and V_{AT} metabolic, ventilatory, and cardiovascular responses for the 16 subjects tested are provided in **Table 13**. Statistical analyses should be interpreted with caution.[r] No significant differences were evident between groups ($F = 2.8$; $p = 0.12$) in resting or recovery

VO_2 (F = 0.45; p = 0.51). Resting and recovery V_E were also similar between (F = 0.06; p = 0.81) and within (F = 0.03; p = 0.87) groups. HR was significantly elevated during recovery (F = 22.1; p < 0.001). However, there were no between group differences (F = 0.01; p = 0.91).

Table 13. Exercising metabolic data for TBI and CON subjects.

Dependent Variable	Group	V_{AT}	Peak
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	TBI	15.0 ± 1.2	26.8 ± 2.1
	CON	23.1 ± 0.9^	33.5 ± 2.3
VCO_2 ($mL \cdot min^{-1}$)	TBI	1309.5 ± 139.0	3206.3 ± 236.5
	CON	1946.2 ± 144.5^	36313.2± 294.5
RER	TBI	0.9 ± 0.1	1.2 ± 0.1
	CON	1.0 ± 0.1	1.2 ± 0.1
V_E ($L \cdot min^{-1}$)	TBI	34.4 ± 3.6	92.2 ± 5.9
	CON	50.2 ± 4.0^	113.6 ± 9.2
HR ($beat \cdot min^{-1}$)	TBI	141.7 ± 6.6	159.8 ± 5.8
	CON	106.3 ± 3.6^	169.0 ± 4.4

^ Indicates that there was a significant difference between groups.[r]

Hormonal Response to Exercise

Growth Hormone

There was no significant difference (p = 0.76) in the difference score between the peak GH and baseline GH scores in CON (3.1 ± 1.2 $ng \cdot dL^{-1}$) and TBI (2.8 ± 1.3 $ng \cdot dL^{-1}$) subjects. A significant main effect was detected for time with respect to GH (F = 5.9; p < 0.001) but not group (F = 0.005; p < 0.94). GH was elevated at minute +10 (p = 0.002), +20

[r] Statistical comparisons were completed on the metabolic data, but they should be interpreted with caution due to low statistical power. All sixteen subjects were included in analyses in Chapter 3.

($p < 0.001$), +30 ($p = 0.002$), and +40 ($p = 0.05$) compared to BASE. GH responses were similar between groups at all time points (**Figure 19**).

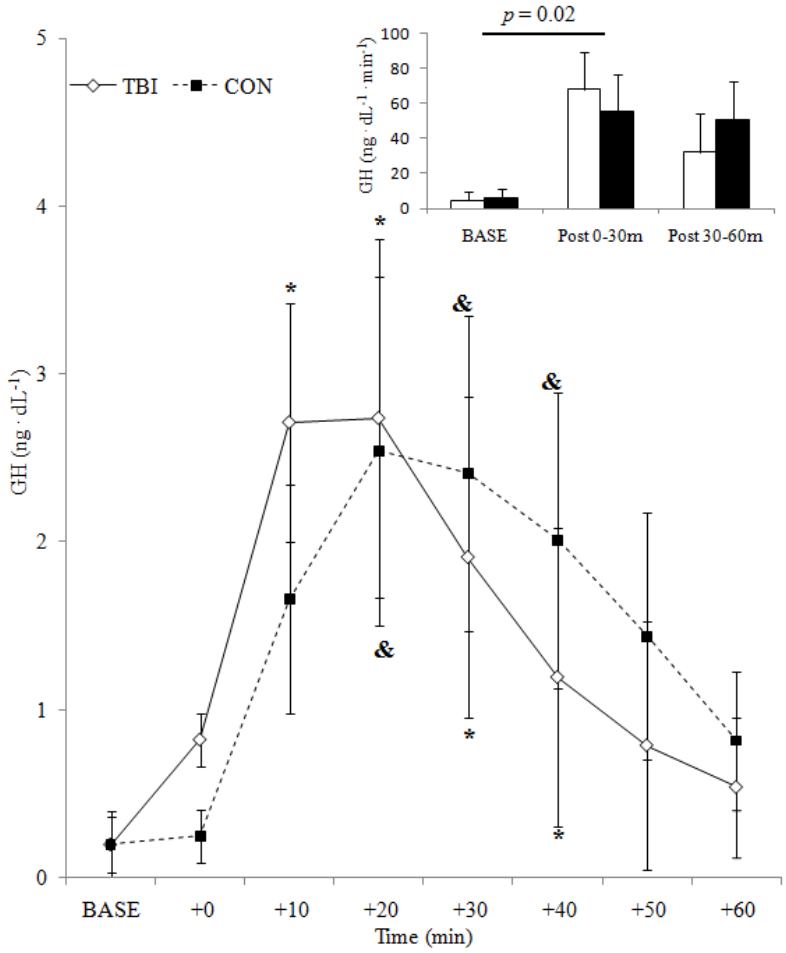

Figure 19. Time course response of GH between TBI and CON subjects. GH was elevated at time +10 ($p = 0.002$), +20 ($p < 0.001$), +30 ($p = 0.002$), and +40 ($p = 0.05$) compared to baseline. No significant between group differences were observed. [s] Integral approximation data are provided in the upper right corner of the figure. [s]

[s] Within group differences compared to baseline for patients with a TBI indicated by*. Within group differences for CON patients indicated by &.

Insulin-Like Growth Factor-1 (IGF-1) and Insulin-Like Growth Factor Binding Protein-3(IGHBP-3)

IGF-1 and IGFBP-3 data are presented in **Table 14**. There was a significant main effect for time (F = 3.0; $p = 0.006$), but not group (F = 3.0; p = 0.10). IGF-1 was elevated at minute +0 compared to +60 (p = 0.004). Additional pair-wise comparisons were not significant. Similar to IGF-1, a significant main effect for time (F = 3.1; p = 0.04), but not group differences (F = 4.2; $p = 0.06$) were observed in IGFBP-3. IGFBP-3 levels at minute +0 were greater than +60 (p = 0.03).

Table 14. IGF-1 and IGFBP-3 at BASE and after exercise. IGF-1 was elevated compared to minute + 60 ($p = 0.004$). Although there was a clear pattern for group differences, they were not statistically different. ($p > 0.05$).

	IGF-1 ($\mu g \cdot mL^{-1}$)		IGFBP3 ($\mu g \cdot mL^{-1}$)	
	TBI	CON	TBI	CON
BASE	130.5 ± 12.7	163.6 ± 18.6	3.2 ± 0.3	3.8 ± 0.2
Minute +0	147.2 ± 15.2	191.4 ± 18.3	3.4 ± 0.3	4.1 ± 0.2
Minute +30	130.4 ± 13.2	169.9 ± 17.4	3.2 ± 0.2	3.7 ± 0.2
Minute +60	131.5 ± 17.4	153.2 ± 14.2	3.1 ± 0.2	3.6 ± 0.2

Prolactin (PRO)

Comparisons of the difference score between the peak PRO and baseline PRO scores in CON (8.7 ± 4.5 ng $\cdot$ dL^{-1}) and TBI (1.6 ± 1.5 ng $\cdot$ dL^{-1}) subjects were not significant ($p = 0.15$). Baseline PRO levels were similar between groups ($p > 0.05$). A main effect for time (F = 3.4; p = 0.003) and a group x time interaction (F = 2.4; $p = 0.05$) were detected. Within CON subjects, PRO was significantly elevated compared to BASE at time minute +20 ($p < 0.001$) and +30 ($p = 0.005$). PRO was not elevated at any time compared to BASE in the patients with a TBI (**Figure 20**).

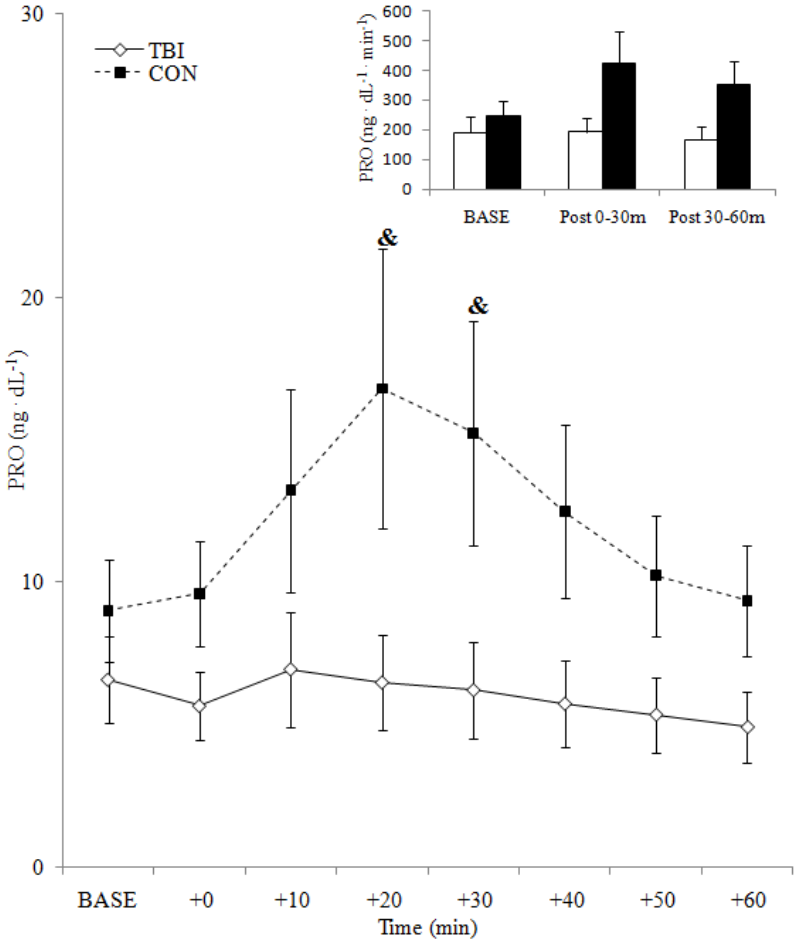

Figure 20. Time course response of PRO between TBI and CON subjects. PRO was elevated at time +20 ($p < 0.001$) and +30 ($p = 0.005$) compared to baseline in the CON but not the TBI patients. Integral approximation data are provided in the upper right corner of the figure.[s]

Cortisol (COR)

Comparison of the difference scores between the peak COR and baseline COR scores in CON (7.9 ± 2.6 µg · dL^{-1}) and TBI (5.8 ± 1.4 µg · dL^{-1}) subjects were not significant (p = 0.21). However, a main effect for time (F = 6.7; p < 0.001) and a group x time interaction (F = 3.1; p = 0.005) was detected. Within CON subjects, COR was significantly elevated compared to BASE at minutes +20 (p = 0.003), +30 (p = 0.006), +40 (p = 0.002), and +50 (p

= 0.05). COR was not elevated at any time compared to BASE within the patients with a TBI (**Figure 21**).

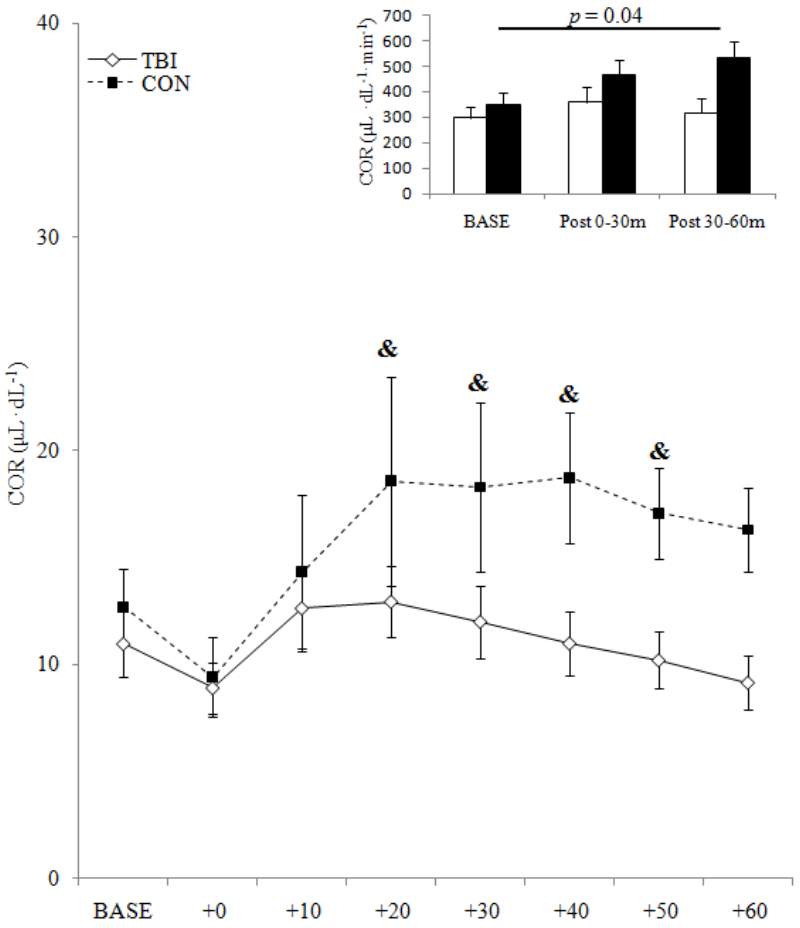

Figure 21. Time course response of COR between TBI and CON subjects. COR was elevated at minutes +20 ($p < 0.003$), +30 ($p = 0.006$), +40 (p = 0.002), and +50 ($p = 0.005$) compared to baseline in the CON but not the TBI patients. Integral approximation data are provided in the upper right corner of the figure. [s]

Blood Lactate

Serum lactate data are provided in **Figure 22**. Two-factor ANOVA (group and time) revealed a significant main effect for group ($F = 50.6$; $p < 0.001$) and a group x time interaction ($F = 50.6$; $p = 0.004$). Within CON and TBI, serum lactate was significantly elevated compared to baseline at minutes +0, +10, +20, and +30. However, there was no difference between baseline and serum lactate 60 minutes after exercise in either group. Blood lactate was similar in both groups, except at minute +10. At minute +10, serum lactate was greater ($p = 0.03$) in CON (11.9 ± 1.4 mmol · L) compared to TBI (8.9 ± 1.4 mmol · L).

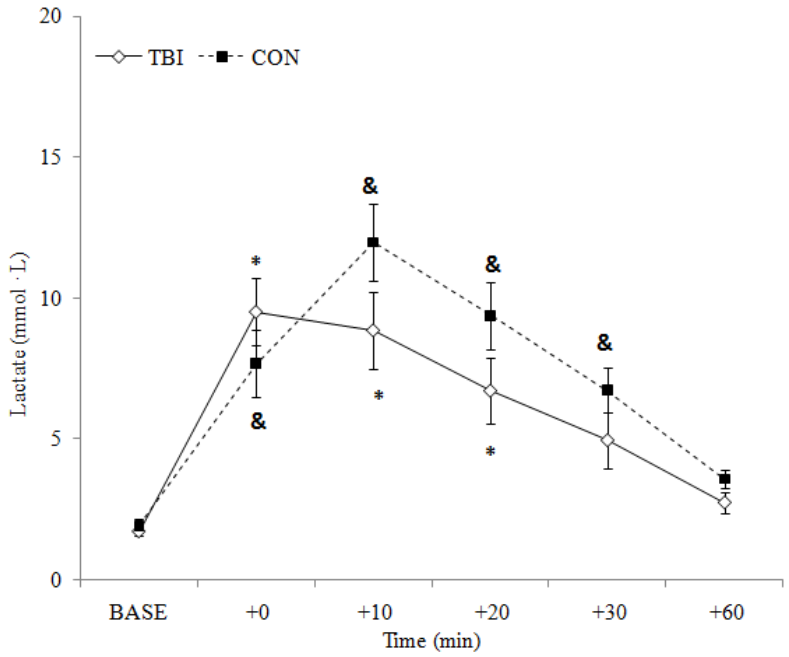

Figure 22. Serum lactate was significantly elevated compared to BASE at time +0, +10, +20, and +30. Serum lactate was greater in CON compared to TBI at time +10 ($p = 0.03$).[s]

Blood Glucose

Serum glucose data showed a significant group x time interaction (F = 6.0; $p < 0.001$), but no main effect differences (**Figure 23**). Within CON, serum glucose was significantly lower than BASE at minute +0, but at no other time point. Interestingly, serum glucose was significantly elevated in TBI at minutes +0, +10, +20, and +30. There were no differences between the baseline and serum glucose 60 minutes after exercise within TBI. Baseline blood glucose was similar between TBI (86.4 ± 3.3) and CON (89.6 ± 3.1). However, serum glucose was significantly lower (p = 0.009) in the CON (76.7 ± 4.8) compared to TBI (98.9 ± 7.2) immediately post exercise. Serum glucose was also lower (p = 0.02) within CON (86.5 ± 4.2) at minute +10 compared to TBI (105.3 ± 8.3).

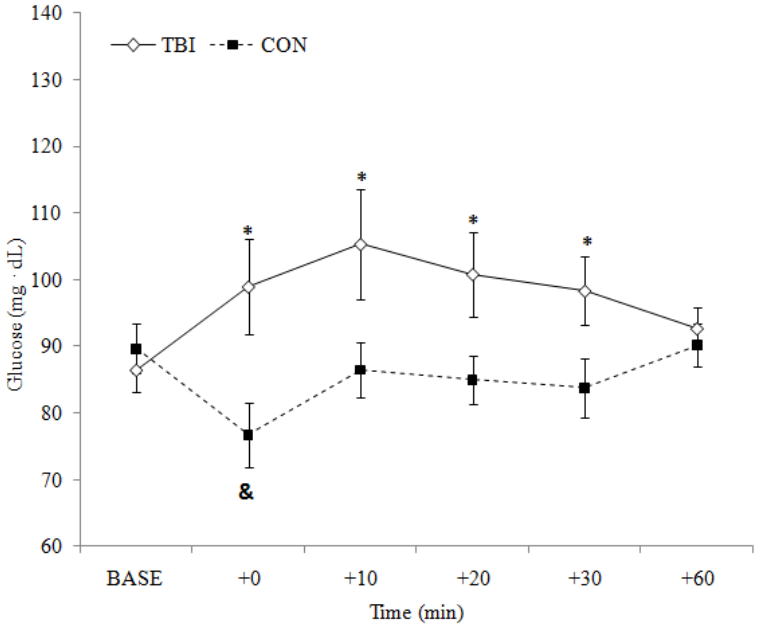

Figure 23. Serum glucose was significantly lower in CON compared to TBI at minute +0 ($p = 0.009$) and +10 ($p = 0.02$). [s,t]

[t] One CON and his matched control were eliminated from glucose analysis because they were given 8 oz. of a liquid beverage containing glucose after a rapid drop in blood pressure at minute +20.

Fatigue Severity Scale

The composite score on FSS was 44.0 ± 7.2 and 20.8 ± 13.6 for the TBI and CON subjects, respectively (**Figure 24**). The mean difference was statistically significant (p = 0.003). FSS scores were significantly correlated with resting IGF-1 (r = -0.60; $p < 0.001$), FSH (r = -0.44; $p < 0.05$), and TSH (r = -0.50; $p < 0.001$) levels (**Table 15**). VO_2 at V_{AT} (r = -0.80; $p < 0.001$), peak VO_2 (r = -0.54; $p < 0.02$) were also associated with FSS. Exercise stimulated peak PRO (r = -0.58; $p < 0.01$) was the only exercising hormonal value associated with FSS. Scatter plots of key anthropometric, metabolic, resting hormone, and exercising hormone by FSS for both groups are displayed in **Figure 26**, **Figure 27**, **Figure 28**, and **Figure 29**, respectively.

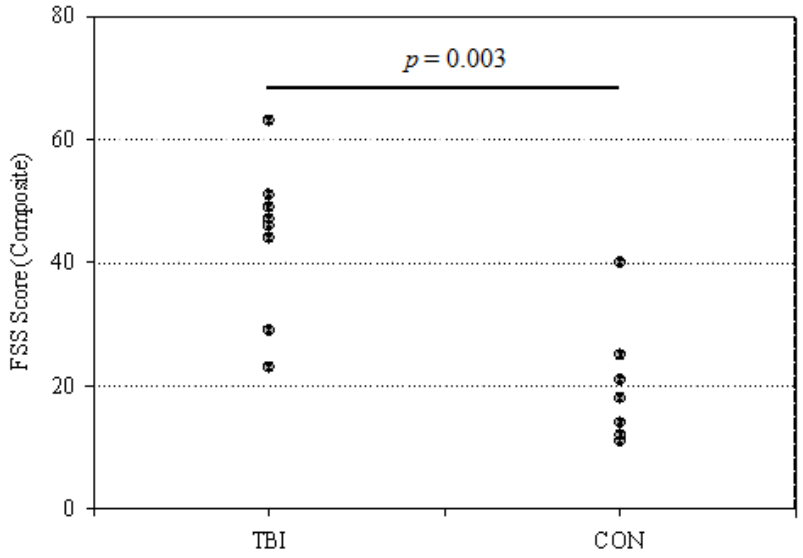

Figure 24. FSS scores were significantly lower in CON compared to TBI ($p = 0.003$).

Perceived Exercise Fatigue

Perceived exercise fatigue measured using a fatigue visual analogue scale data are provided in **Figure 25**. There was a significant main effect for time (F= 28.1; $p < 0.001$) and an interaction between group and time (F = 2.9; $p = 0.05$). Compared to BASE, perceived fatigue was elevated at minute +0 ($p < 0.001$) and +30 ($p < 0.001$). BASE scores were higher in TBI compared to CON ($p = 0.008$).

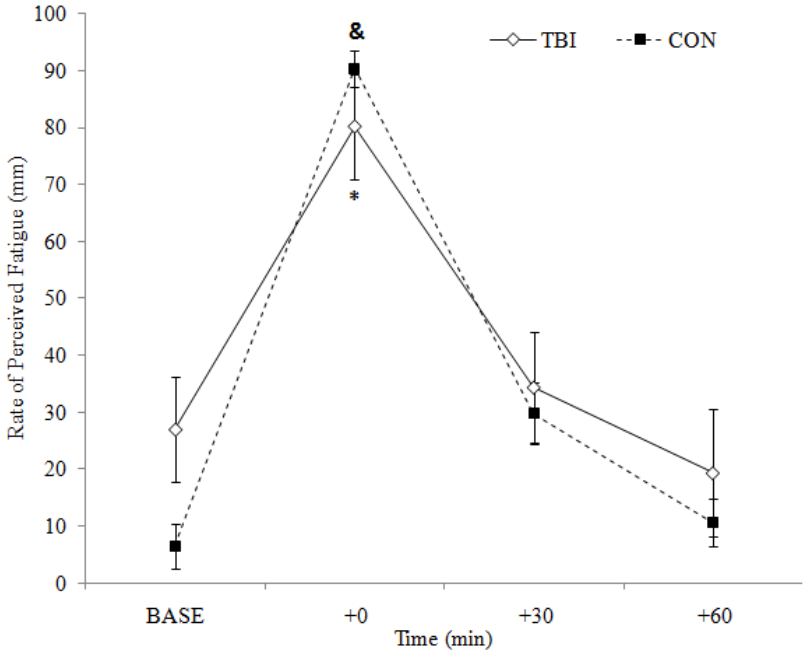

Figure 25. Rating of perceived fatigue using a visual analogue scale. Baseline perceived fatigue was higher in TBI compared to CON (p =0.008). Perceived fatigue was elevated in both groups at minute +0 ($p < 0.001$) and +30 ($p < 0.001$) compared to BASE.[n]

Table 15. Correlation matrix for key study variables. The following new abbreviations are used the table: lean mass (LM), abdominal skinfold (AB), peak lactate (LA).

	Subject Characteristics						Metabolic			Resting Hormone				Stimulated Hormone		
	FSS	Age	BMI	%Fat	LM	AB	V_{AT}	VO_2	LA	IGF1	FSH	LH	T4	PRO	COR	GH
FSS	1.00	0.06	0.09	0.40	0.17	-0.07	**-0.80**	**-0.54**	-0.42	**-0.60**	**-0.44**	0.05	-0.30	**-0.58**	-0.43	-0.07
Age	0.06	1.00	0.36	**0.53**	0.25	0.34	-0.34	-0.42	-0.22	**-0.53**	-0.24	**-0.43**	**-0.46**	-0.29	**0.56**	-0.04
BMI	0.09	0.36	1.00	**0.70**	**0.79**	**0.67**	-0.25	-0.34	-0.39	-0.38	-0.06	-0.08	-0.32	-0.36	0.06	-0.45
%Fat	0.40	**0.53**	**0.70**	1.00	**0.47**	**0.77**	**-0.49**	**-0.64**	**-0.56**	**-0.50**	-0.35	-0.26	-0.42	**-0.64**	-0.10	-0.52
LM	0.17	0.25	**0.79**	**0.47**	1.00	0.32	-0.24	-0.14	-0.22	-0.28	0.09	-0.13	-0.24	**-0.45**	0.11	-0.32
AB	-0.07	0.34	**0.67**	**0.77**	0.32	1.00	0.08	-0.28	-0.37	-0.17	-0.10	-0.19	-0.13	-0.30	0.13	-0.56
VAT	**-0.80**	-0.34	-0.25	**-0.49**	-0.24	0.08	1.00	**0.73**	0.37	**0.57**	0.33	0.19	**0.47**	0.49	0.35	0.05
VO_2	**-0.54**	-0.42	-0.34	**-0.64**	-0.14	-0.28	**0.73**	1.00	**0.73**	**0.66**	-0.03	0.22	**0.44**	**0.53**	0.33	0.43
LA	-0.42	-0.22	-0.39	**-0.56**	-0.22	-0.37	0.37	0.73	**1.00**	**0.44**	-0.12	-0.19	0.34	**0.53**	0.17	0.52
IGF1	**-0.60**	**-0.53**	-0.38	**-0.50**	-0.28	-0.17	**0.57**	**0.66**	**0.44**	**1.00**	0.23	0.08	0.28	**0.63**	0.10	0.27
FSH	**-0.44**	-0.24	-0.06	-0.35	0.09	-0.10	0.33	-0.03	-0.12	0.23	**1.00**	0.12	0.33	0.03	0.00	-0.31
LH	0.05	-0.43	-0.08	-0.26	-0.13	-0.19	0.19	0.22	-0.19	0.08	0.12	**1.00**	-0.04	-0.08	-0.15	0.00
T4	-0.30	**-0.46**	-0.32	-0.42	-0.24	-0.13	**0.47**	**0.44**	0.34	0.28	0.33	-0.04	**1.00**	0.03	-0.22	-0.18
TSH	**-0.50**	-0.10	0.05	-0.24	-0.29	-0.03	0.36	0.12	0.05	0.00	0.11	0.30	0.17	0.27	0.05	0.09
PRO	**-0.58**	-0.29	-0.36	**-0.64**	**-0.45**	-0.30	**0.49**	**0.53**	**0.53**	**0.63**	0.03	-0.08	0.03	**1.00**	0.30	0.59
COR	-0.43	**0.56**	0.06	-0.10	0.11	0.13	0.35	0.33	0.17	0.10	0.00	-0.15	-0.22	0.30	1.00	0.39
GH	-0.07	-0.04	**-0.45**	**-0.52**	-0.32	**-0.56**	0.05	0.43	**0.52**	0.27	-0.31	0.00	-0.18	**0.59**	0.39	1.00

Statistically significant associations are in **bold font.**

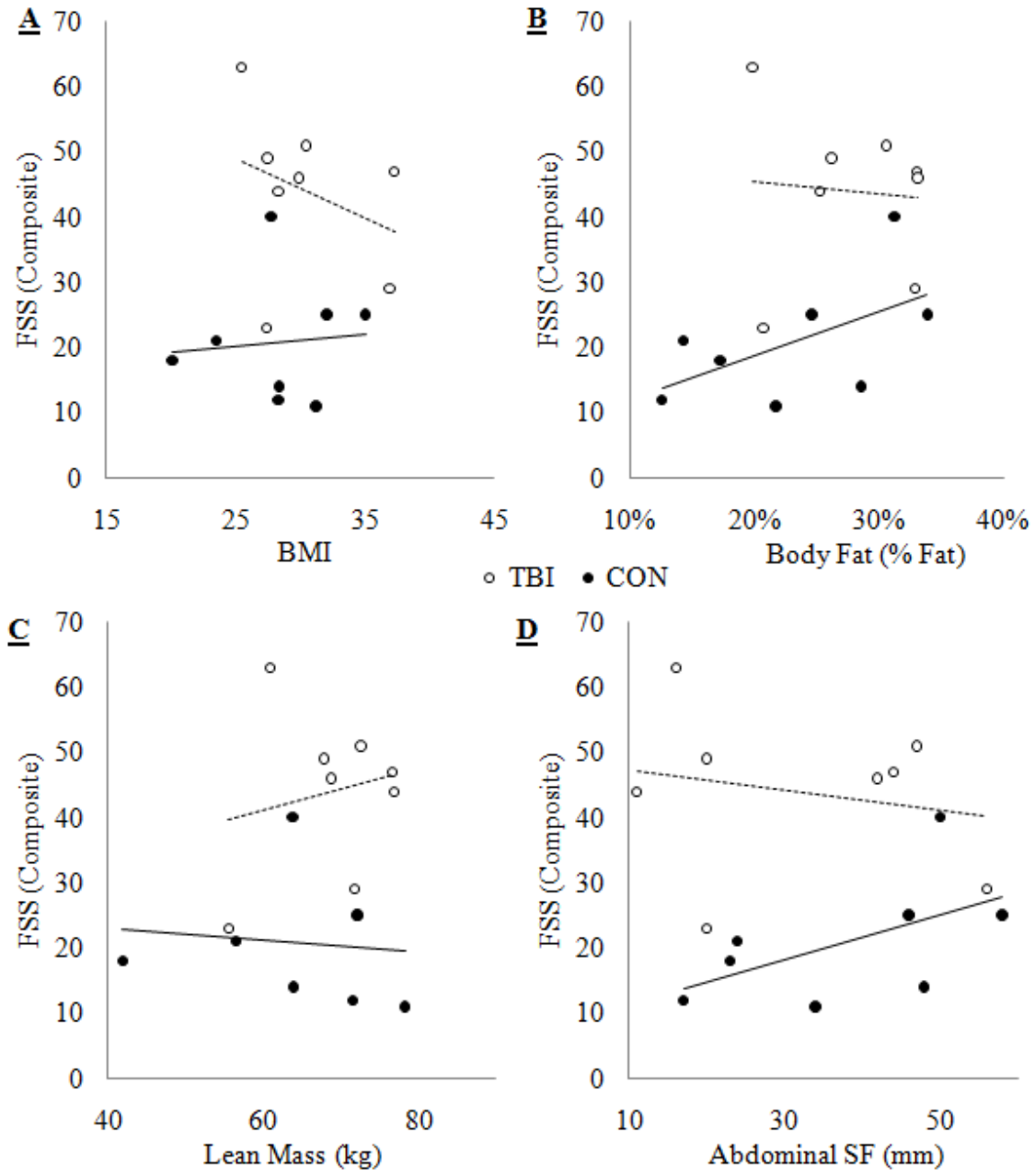

Figure 26. Relationship between composite fatigue severity scale (FSS) scores and subject (A) BMI, (B) body fat (% fat), (C) lean mass (kg), and (D) abdominal skinfold thickness (mm).

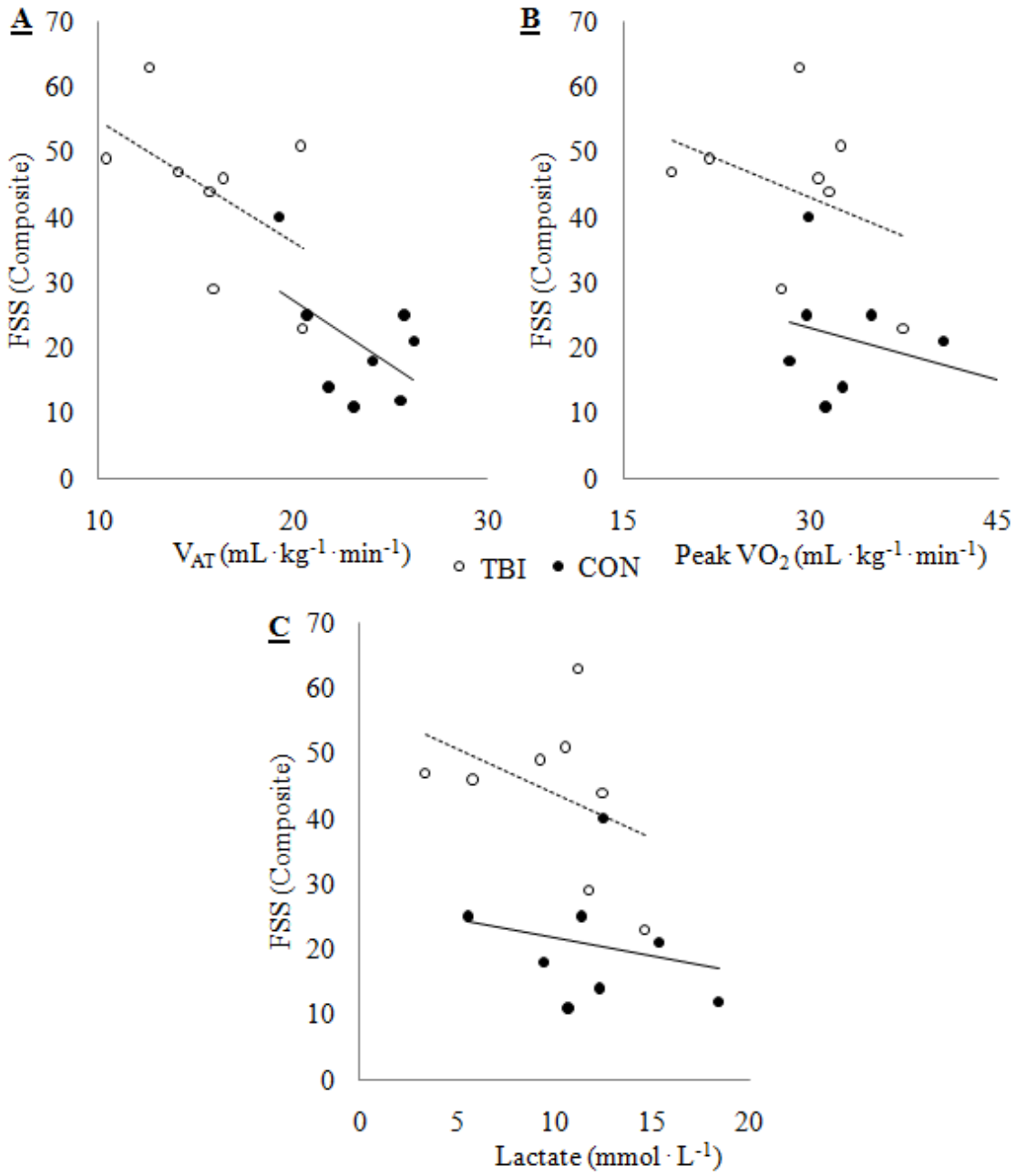

Figure 27. Relationship between composite fatigue severity scale (FSS) scores and subject (A) VO_2 at V_{AT} (mL · kg^{-1} · min^{-1}), (B) peak VO_2 (mL · kg^{-1} · min^{-1}), (C) and peak blood lactate (mmol . L^{-1}).

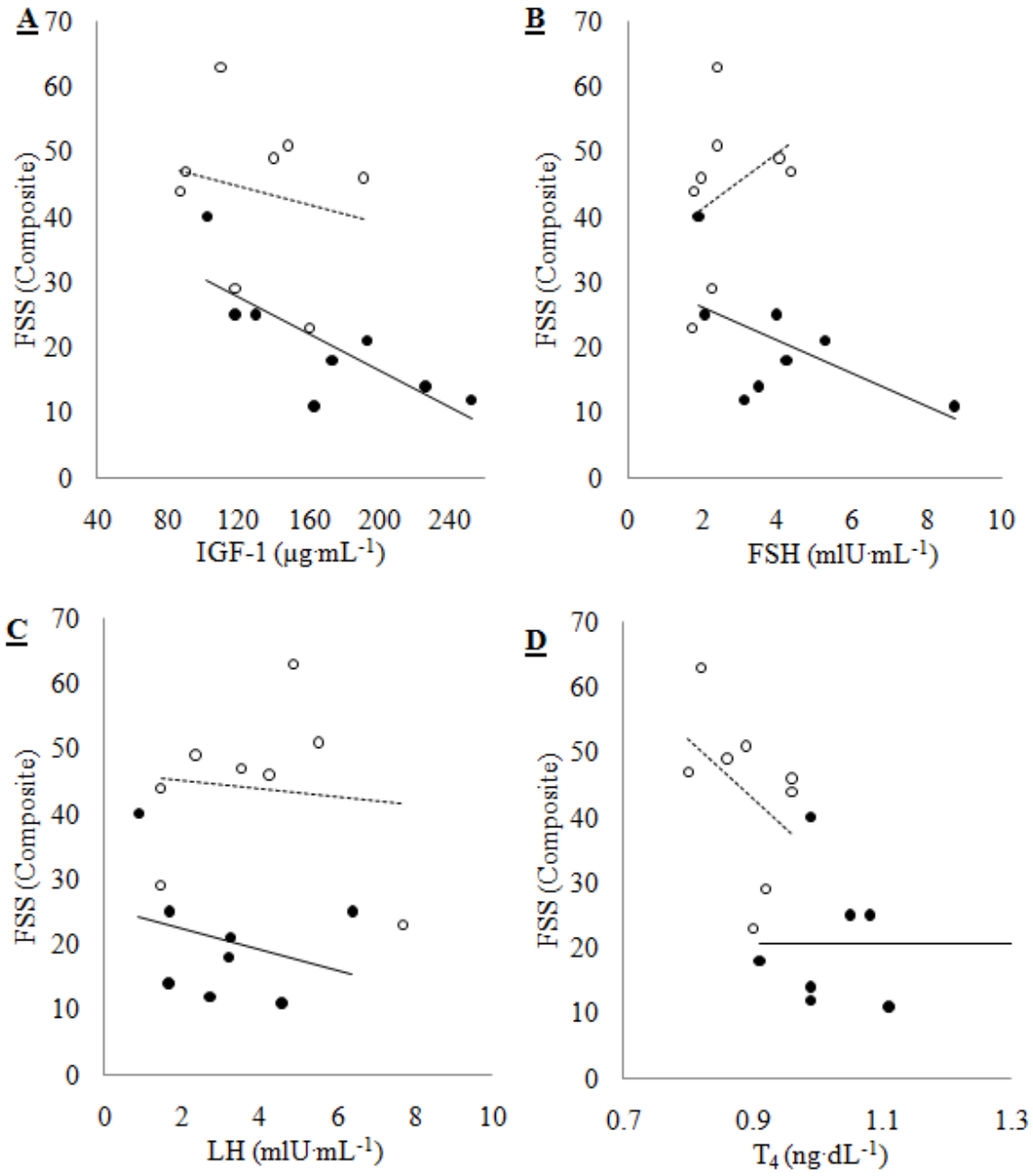

Figure 28. Relationship between composite fatigue severity scale (FSS) scores and subject (A) baseline IGF-1 ($mL \cdot kg^{-1} \cdot min^{-1}$), (B) baseline FSH ($mlU \cdot mL^{-1}$), (C) baseline LH ($mmol \cdot L^{-1}$), and (D) baseline T_4 ($ng \cdot dL^{-1}$).

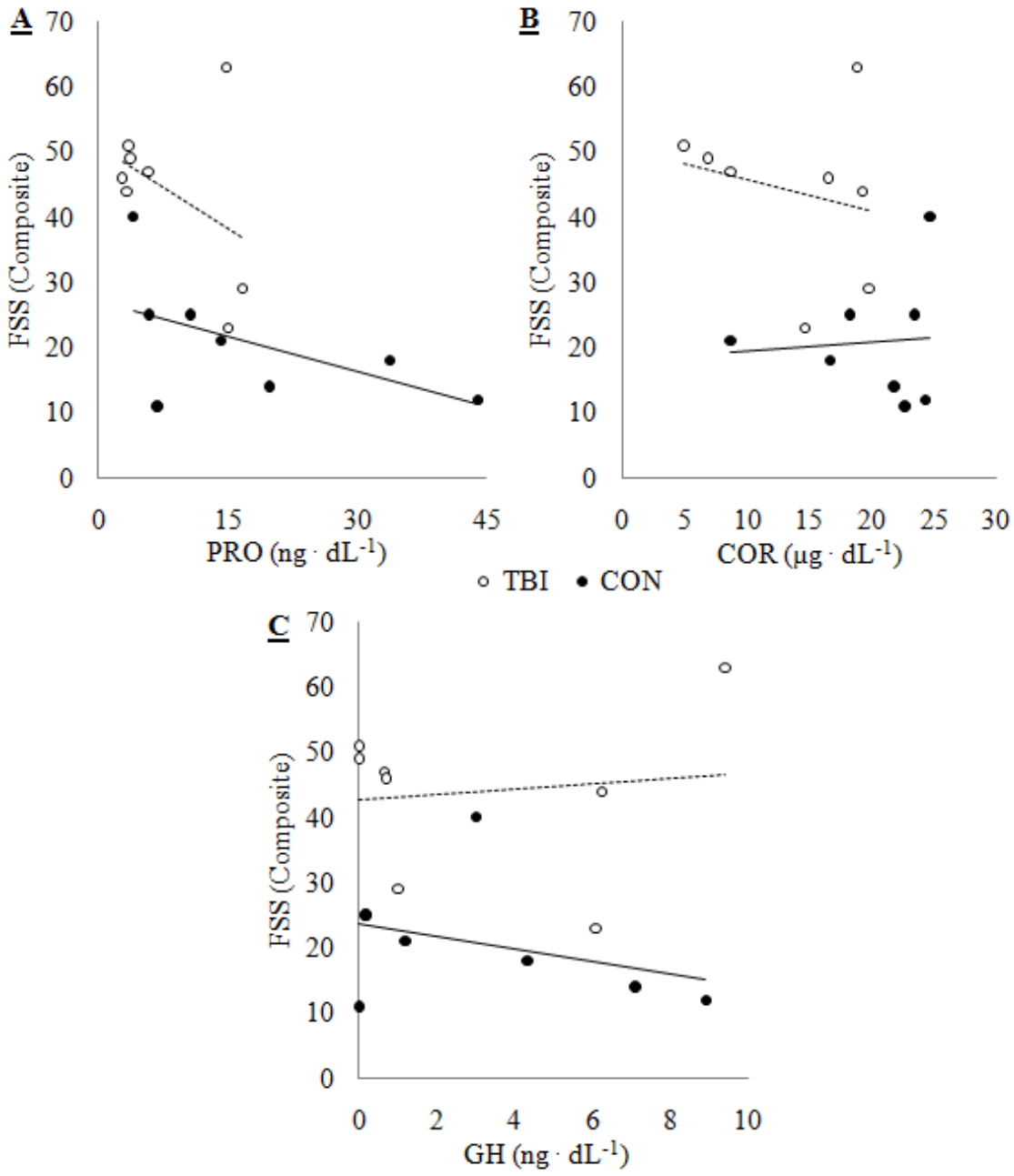

Figure 29. Relationship between composite fatigue severity scale (FSS) scores and subject (A) peak PRO (ng · dL^{-1}), (B) peak COR (µg · dL^{-1}), and (C) peak GH (ng · dL^{-1}).

DISCUSSION

The purposes of this study were to determine, in patients with a TBI, if (1) the hormonal response to exercise (GH, PRO, COR, or IGF-1) differed from CON, (2) the blood lactate or glucose responses to peak exercise differed from CON, and (3) if subject physical characteristics, aerobic fitness, resting hormone levels, or exercise stimulated response of hormones were associated with perceived fatigue measured using a fatigue severity scale (FSS). The data suggest that the hormonal responses of the GH/IGF-1 axis are similar between TBI and CON. However, there were distinct differences in the timed response of PRO and COR. Blood lactate and glucose were also different between groups. FSS scores were higher in TBI compared to CON and from these data, it is apparent that VO_2 at V_{AT} and resting IGF-1 levels are the strongest associative factors of FSS scores.

PRO and COR Response to Exercise Differed Between Groups, But the GH Responses Were Similar

It was hypothesized that there would be a blunted response of the GH/IGF-1 axis to an acute bout of graded exercise. The rationale for this hypothesis was primarily due to reports suggesting that hormonal dysfunction, and specifically GH deficiency, is common after a TBI. Despite previous findings, these data show that the GH response to exercise was similar between groups. It should be noted that the patients and control subjects in this study were not screened for pituitary sufficiency. Although screening for GH deficiency generally requires complicated medical stimulation tests, recent evidence suggests that fasting IGF-1 scores are good indicators of potential deficiency (Zgaljardic *et al.,* 2011). Zgaljardic and colleagues observed the relationship between resting IGF-1 levels and stimulated GH (Zgaljardic *et al.,* 2011). Using a stimulated GH response of $< 3.0\ \mu g \cdot L^{-1}$ as the cut point to define GH deficiency, they determined that fasting IGF-1 level of $175\ \mu g \cdot L^{-1}$ was suggestive

of GH deficiency (Positive Predictive Value = 28%; Negative Predictive Value = 90%). According to these data, seven of the eight patients with a TBI tested were below the cut-point for suspected GH deficiency, and should be referred for screening. Interestingly, five of the eight control subjects were below the cut-point for suspected GH deficiency. In addition, one patient with a TBI screened positive for GH deficiency using a stimulation test for a separate study.

The individual GH response to exercise in CON and patients with a TBI are provided in **Figure 30**. Visual inspection of the data show a significant response in some subjects, yet little or no response in others. It is feasible that a significant number of patients in both groups were GH deficient and thus had little or no response to exercise. In **Figure 30**, the response of the known GH deficient patient with a TBI is displayed using a bold black line (#). Visual observation of these data suggests that all but three patients with a TBI had smaller GH responses than the known patient with GH deficiency. Interestingly, three of eight CON subjects had a similar or smaller GH response. This supports the notion that the hormonal responses observed in this study could have been confounded by random selection of a large group of GH deficient subjects in both groups. However, this is only speculative (based on IGF-1 data) given subjects were not tested for GH deficiency prior to the study.

Previous evidence suggests that obese patients have a reduced GH response to exercise. Kanaley and colleagues studied the acute response of GH to exercise in obese and non-obese women (Kanaley *et al.,* 1999). Sampling blood every five minutes, they measured GH concentrations for 1 hour prior to and 4.5 hours after a 30-minute bout of treadmill exercise at 70% of VO_2 peak. They found that the GH response to exercise was significantly reduced in obese women (Kanaley *et al.,* 1999). Similar blunted responses to exercise in

obese subjects have been reported by others (Salvadori *et al.,* 2010). In this study, six patients had a BMI of over 30. Furthermore, 14 had a BMI of over 25. According to the percentage body fat data, five of the CON and six of the TBI patients were considered overweight or obese (Thompson, 2010). Although not tied to the hypotheses, correlation coefficients were calculated for peak GH response with selected variables (**Table 15**). BMI (r = -0.45), % fat (r = -0.52), and abdominal skinfold thickness (r = -0.56) all showed moderate negative associations with the peak GH response to exercise.

It should be noted that the response of GH and PRO, both secreted from the anterior pituitary, were moderately, but significantly correlated (r = 0.59). A surprising finding of this investigation was that the PRO response to exercise differed significantly between groups. Specifically, these data show CON had a significant elevation in PRO after exercise; patients with a TBI had little or no response. Although GH deficiency is more common, PRO insufficiency has been noted in patients recovering from TBI (Bondanelli *et al.,* 2004). PRO does not significantly affect exercise metabolic function, but as noted in the Introduction, it does contribute to the exercise immunological response (Ortega, 2003; Woods, 2000). The functional significance of PRO deficiency on exercise (or recovery) is beyond the scope of these data and is not clear from existing literature.

It is possible that the between-group differences in PRO were caused by prescription medications taken by patients with a TBI. Seven of the eight patients with a TBI reported routine consumption of at least one anti-depressant drug that was a -serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRI). In the Introduction, it was noted that dopamine inhibits PRO secretion from the anterior pituitary. The difference in acute PRO response to exercise was possibly an effect of the SNDRI drugs and not the TBI. Regardless,

future research is indicated to determine if the differential response of PRO to exercise affects the overall immune response or recovery in patients with a TBI, even if the reduction is due to prescription medicine use.

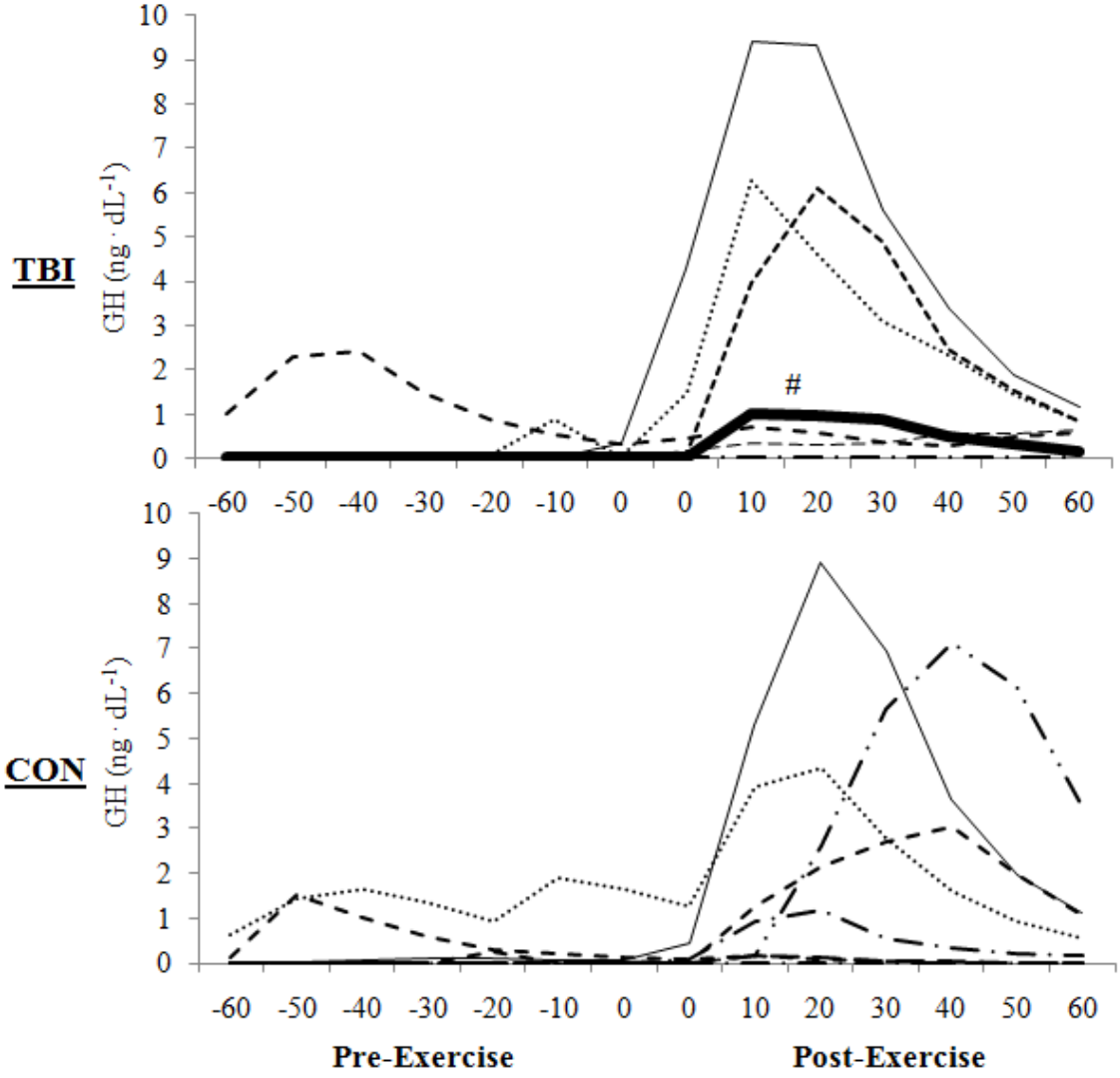

Figure 30. Individual responses to exercise in patients with a TBI (n=8) and CON (n=8).

Similar to PRO, COR responses to exercise were also suppressed in patients with a TBI. Although the deleterious and catabolic effects of COR are most often discussed, COR contributes significantly to exercise metabolism by increasing lipolysis (Borer, 2003) and

sparing glucose (Porterfield and White, 2007); therefore a blunted acute COR response may be detrimental to exercise bioenergetics. Research demonstrated that COR levels may be affected by TBI, and one study showed a trend toward lower COR levels and higher FSS scores (Bushnik *et al*., 2007). Although COR is secreted by the adrenal medulla, it is regulated by ACTH, an anterior pituitary hormone. If upstream secretion of ACTH were reduced, it may lend credence to the hypothesis that a reduced COR response is caused by TBI. However, from these data such statements are speculative and not directly supported by the data. COR response to exercise was not associated with FSS scores ($r = 0.43$) in this investigation and therefore do not support the work of Bushnik and colleagues (Bushnik *et al*., 2007).

The Pattern of Blood Glucose and Lactate Response Differed Between CON and Patients with a TBI

During low intensity exercise, fatty acid metabolism for ATP generation is advantageous because of the energy density of these molecules. However, as exercise intensity increases and the rate of ATP generation accelerates, there is a consequential shift towards ATP generation via glycolytic pathways. Characteristically, intense exercise results in an immediate decrease in blood glucose (Ahlborg and Felig, 1982; Henderson *et al.,* 2008) due to an increased uptake into skeletal muscle for ATP synthesis, but hepatic glucose production by the liver quickly equalizes blood glucose during or soon after exercise (Wahren *et al.,* 1971). When the need for ATP production exceeds the rate at which it can be produced by oxidative phosphorylation, ATP is generated in increasing percentages via anaerobic pathways. The systemic result of the shift to anaerobic metabolism is a decrease in cellular pH and an increase in blood lactate (Robergs *et al*., 2004). The amount of blood lactate is dependent upon the exercise intensity and the aerobic and anaerobic fitness of the

individual (Barstow *et al.,* 2000). A more aerobically fit individual may clear blood lactate quicker than an unfit individual (Gmada *et al.,* 2005). However, anaerobic fitness may result in an increased capacity to generate lactate (Korhonen *et al*., 2005).

Individual subject glucose responses from this study are shown in **Figure 31**. Glucose was significantly lower immediately post-exercise in CON and elevated at minute +10 for patients with a TBI (**Figure 23**). It is apparent from the individual subject responses that one subject in the TBI group experienced an abnormally large increase in blood glucose immediately post-exercise and one CON subject had an abnormally large decrease in blood glucose. These two subjects contribute largely to the variability in the data. However, it is evident that blood glucose generally increased in patients with a TBI post-exercise and generally decreased in CON, before quickly returning to normal.

It is not clear why glucose was markedly elevated in TBI after exercise and it could suggest differential responses of hormones not tested in this study (e.g. glucagon, insulin, catecholamines) (Cryer, 1991; Hoelzer *et al.,* 1986; Tuttle *et al.,* 1988). Similar to PRO, the glucose response could be partially a result of SNDRI use. Blood glucose levels are the sum result of glucose production and uptake, or glucose consumption via feeding. Hepatic glucose production is stimulated in part by norepinephrine, a catecholamine hormone (Marliss *et al.,* 2000). Therefore, it is possible that SNDRI use prevented the reuptake of norepinephrine, increasing hepatic glucose production.

A second possible reason for the elevated blood glucose in patients with a TBI is that they might have deficiencies in glucose uptake mechanisms. At rest, glucose uptake is regulated primarily by insulin. During exercise, glucose uptake is regulated by both insulin and insulin independent mechanisms (DeFronzo *et al.,* 1981; Kjaer *et al.,* 1990). Although

not measured in this study, poor glucose uptake could be due to a blunted insulin response to exercise, poor insulin-receptor sensitivity (insulin resistance) (Wilcox 2005), or a reduction in the effectiveness of the insulin independent mechanisms of glucose uptake resulting from exercise (White *et al*., 1978a; White *et al*., 1978b). Chronic disease resulting in physical inactivity is a known precursor to insulin resistance and type II diabetes (Knowler and Narayan, 1994). Because of the numerous physical impairments associated with a TBI, physical inactivity is common and it may increase the risk of insulin resistance. Although the direct effects of TBI on long-term insulin responses have not been studied, diabetic patients with TBI have been shown to be at increased risk for mortality (Ley *et al.,* 2011). This suggests that future research investigating the long-term effects of TBI on glucose metabolism, and glucose metabolism in response to exercise may be profoundly important to improve clinical outcomes.

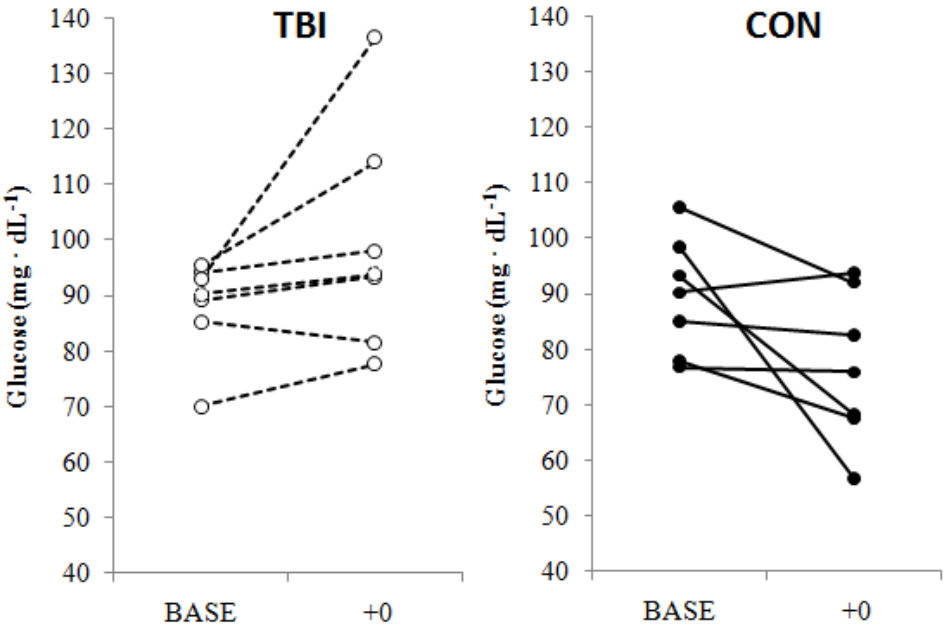

Figure 31. Individual glucose response of patients with a TBI and CON subjects at baseline and immediately post exercise.

Peak blood lactate was greater in CON compared to TBI. It could be argued that the CON group achieved higher relative exercise intensities at peak. However, this is unlikely since respiratory exchange ratios (RER) were similar between groups at peak. It is also possible that patients with a TBI had greater lactate clearance rates than CON. Again, this is likely not a sufficient explanation since the group peak VO_2 of patients with a TBI was lower than CON. It is possible that the CON subjects had greater anaerobic fitness than the TBI group and could generate greater amounts of lactate. The anaerobic fitness of patients with a TBI has not been reported. It could be that mechanisms driving anaerobic or glucose metabolism are blunted in patients with a TBI. Although these mechanisms are beyond the scope of this dissertation, it certainly warrants future investigation.

Fatigue Is Strongly Associated with V_{AT} and Moderately Associated with Resting IGF-1 and Peak VO_2

Not surprisingly, the data from this investigation show that FSS scores were higher in TBI than CON. However, exercising-related fatigue measured using a V_{FAS} did not differ between groups. Perhaps the most important and functionally relevant data were the associations between fatigue (measured with FSS) and $V_{AT.}$ Notably, VO_2 peak was also associated with FSS but not to the same extent. Post-hoc analysis not tied to the primary hypothesis suggested that VO_2 and V_{AT} were independent predictors of FSS.[u] V_{AT} alone accounted for 64% of the variance in FSS scores. The possible contribution of V_{AT} to fatigue in daily activities was discussed in Chapter 3. V_{AT} occurs below or near the metabolic costs of many ordinary activities of daily living for patients with a TBI. The strong association supports the assertion that low V_{AT} may lead to early onset of fatigue and suggests that

[u] Follow up multiple regression was performed with FSS as the dependent variable and V_{AT} and VO_2 peak as independent variables. The model showed co-linearity between the two variables.

therapy interventions designed to improve V_{AT} should be included in a comprehensive rehabilitation program.

The moderate relationship between IGF-1 and FSS is also an interesting and important finding. As discussed earlier, fasting IGF-1 levels suggest possible GH deficiency (Zgaljardic *et al.,* 2011). Previous research suggested a moderate relationship between GH deficiency and perceived fatigue (Bushnik *et al*., 2007; Bushnik *et al*., 2008). Although the current sample was relatively small, it supports these previous findings and suggests that adding fatigue screening tools to ongoing GH deficiency studies may help to better solidify this relationship.

STUDY LIMITATIONS

The key limitation of this study was the lack of differences seen in the GH response to exercise which may have been confounded by obesity (in both groups). This cannot be confirmed since neither CON nor TBI were screened for pituitary dysfunction. Patients with a TBI volunteered and were accepted regardless of their BMI and CON subjects were matched. Experience suggests that many patients with a TBI might have high BMIs due to their physical impairments or behavioral choices and this was certainly indicative of the patients selected in this study. It would be interesting to compare patients with a TBI with high and low BMIs to determine if there are differences within groups. Moreover, it may be important to screen for GH deficiency in both TBI and CON in future investigations.

Second, it is possible that the duration of the stimulation test (i.e. exercise bout) was insufficient to invoke a response in all subjects. However, the large responses seen in some subjects does not support this limitation. The stimulation protocol utilized in this study was selected for several practical reasons: (1) it was validated as a reliable test in TBI, (2) it was

maximal in nature, and (3) if it sufficiently stimulated hormonal responses, it could be used to measure peak aerobic capacity and hormonal responses in future clinical testing scenarios. Indeed, the intensity was sufficient to stimulate GH in some subjects, but a longer duration (i.e. sustained intensity) test may be more advantageous (i.e. five minute stages). Future research should investigate hormonal responses to alternative exercise stimulation tests to determine if differences arise from altered protocols.

Finally, anti-depressant medications could have affected the PRO and glucose responses to exercise in patients with a TBI. This limitation is difficult to avoid due to the high usage of anti-depressant drugs in TBI. It could be important for future research to investigate potential negative adaptive responses to exercise with altered PRO responses or poor glucose regulation with prescription drug use.

CONCLUSION

The primary hypothesis of this study, that there is a blunted GH response to exercise in patients with a TBI, was rejected. This positive finding might potentially influence the exercise prescriptions of patients with a TBI. It has been suggested previously that patients recovering from a TBI should engage in similar exercise regimens to that of apparently healthy CON (Mossberg *et al*., 2010). Of course, these recommendations assume that the physiological response mechanisms to physical exertion, particularly the metabolic hormonal response, were similar to apparently healthy individuals. The GH findings from this study support this assertion and suggest that in this small sample, there were no significant differences between hormonal responses to exercise in TBI. Finally, these data suggest that perceived fatigue is highly associated with V_{AT}. Therefore, physical therapists may consider

implementing exercise regimens designed to delay the onset of significant anaerobic metabolism to better improve functional outcomes.

Chapter 5: Clinical and Practical Recommendations for Exercise and Traumatic Brain Injury.[v]

Routine stress of the metabolic, ventilatory, and cardiovascular systems (i.e. cardiorespiratory exercise training) is an important component of an overall wellness program. Regular rhythmic exercise is associated with improved lipid profiles (Haskell 1986), improved glucose regulation (Potteiger *et al.,* 2003), lower resting blood pressure and heart rate (Wilmore *et al.,* 2001), improved blood pressure and heart rate control during exercise (Wilmore *et al.,* 2001), increased cardiac stroke volume (Daussin *et al.,* 2007), increased metabolic and physical work capacity (Klausen *et al*., 1981), among numerous other positive physiologic adaptations (Carter *et al*., 2003; Norton *et al*., 1995; Thompson 2010; Winsley *et al*., 2005). These adaptations are associated with reduced incidence of cardiovascular disease (Pescatello *et al.,* 2004; Thompson, 2010), improved health, and reduced mortality (Colditz, 1999). Appropriate exercise training may also reduce stress and depression (Raglin, 1990) and is associated with increased quality of life (Partonen *et al.,* 1998). Moreover, it has been suggested that people who routinely exercise normally "live longer than those that do not" (Department of Health and Human Services, 2000).

[v] Portions of this section were rewritten from Mossberg K, Amonette W, and Masel B. Endurance training and cardiorespiratory conditioning after traumatic brain injury. *J Head Trauma Rehab;* 25: 173-183, 2010. Permission granted by Lippincott, Williams and Wilkens.

Although often peripheral to rehabilitation, the data from these investigations suggest that regular rhythmic exercise should be central to therapy. In the context of previously published literature and the data from Chapters 3 and 4, the purpose of this chapter is to discuss practical exercise and therapeutic regimens for patients with a TBI.

EXERCISE TRAINING RESEARCH AND TBI

Few studies have investigated the effects of regular exercise in patients with a TBI. Nevertheless, the studies that have investigated the impact of exercise on TBI show positive results. Perhaps the first exercise intervention study reported in the TBI literature investigated the effects of a 16-week circuit training program on muscular strength and endurance, body composition, and peak aerobic capacity (Jankowski and Sullivan, 1990). They found that the 16-week training regimen improved muscle endurance and peak aerobic capacity. However, they also showed that circuit training alone did not reduce the O_2 cost of walking, suggesting that this type of approach may not improve mechanical efficiency of gait after a TBI (Jankowski and Sullivan, 1990).

Circuit training appears to be a popular research intervention in TBI, likely due to the time saving advantages of the modality. Bhambhani and colleagues studied metabolic adaptations arising from 18 weeks of circuit training in patients with a TBI (Bhambhani et al., 2005). Exercising subjects completed thrice per week upper body resistance exercise with steady-state aerobic exercise between sets. Subjects were monitored to ensure that they maintained a heart rate above 60% of reserve. It was determined that 12 weeks of aerobic training resulted in significant improvements of peak VO_2. Moreover, peak power output at maximum exercise was increased. Interestingly, despite this rigorous training program, improvements in peak lactate, heart rate, or reductions in body fat were not seen.

Steady state rhythmic exercise has been shown to effectively improve aerobic capacity in patients with a TBI but the data are limited. Wolman and colleagues demonstrated improvements in patients with an acquired brain injury (ABI; including TBI) after a 12-week steady state training program (Wolman *et al.,* 1994). The training regimen consisted of similar protocols as those recommended for apparently healthy individuals (thrice per week vigorous exercise). Patients completing the protocols significantly increased time to failure during exercise and increased peak power output at maximum exercise.

One of the largest and best controlled BI training investigations utilized 157 ABI patients from four different treatment centers, studying the effects of circuit resistance training on exercise tolerance, performance, and functional outcome measures (Bateman *et al.,* 2001). The 142 patients (100 TBI patients with a TBI) who completed the study were randomized into one of two groups: Exercise or Relaxation training. The Exercise group completed 12 weeks of sustained cycle ergometry exercise whereas the Relaxation group completed therapeutic techniques that did not stress physiologic or metabolic systems. After 12 weeks, it was determined that cycle ergometry exercise improved cardiovascular fitness but these changes did not necessarily improve physical functioning as determined using a variety of functional assessment scales (i.e. Barthel Index, FIM, Nottingham Extended Activity of Daily Living).

It can be concluded from previous research that exercise is effective in improving aerobic capacity in patients with a TBI. However, much of the research lacks control and there are few, if any, studies that compare the effects of regular exercise training to healthy controls. Nevertheless, exercise training improves aerobic capacity and should be included in a comprehensive TBI rehabilitation program.

POPULATION AND INDIVIDUALIZED EXERCISE EDUCATION PROGRAMS

The data from this investigation confirm the measured aerobic capacities of patients with a TBI are lower than predicted and lower than age and gender matched sedentary CON. Moreover, it was demonstrated that V_{AT} in patients with a TBI occurs at alarming low levels. There are few, if any, data that describe the exercise habits of patients with a TBI. The data from this study suggest that the hormonal responses between TBI and CON are similar. If this finding is supported by additional studies, it suggests that the poor aerobic capacities in patients with a TBI may primarily result from physical inactivity initiated by acute injury, bed rest and subtle physical impairments that prevent vigorous physical exertion. It could also be due to the neuropsychological challenges that include lack of motivation and initiation commonly seen after TBI. More importantly, it could be a lack of appreciation of the consequences of a sedentary lifestyle on the part of rehabilitation professionals.

Individuals not engaging in regular exercise are prone to hypokinetic diseases. Physical inactivity and obesity independently increase risk for diseases such as CAD, CVD, diabetes, and some forms of cancer (Colditz, 1999). Therefore, it is imperative that patients with a TBI are educated during treatment on the potential consequences of a sedentary lifestyle.

TBI is often accompanied by cognitive impairments that may reduce memory capabilities or potentially the ability to comprehend the consequences of actions or in this case lack of action. Often times, the physical or mental impairments lead to dependence on a family member or caregiver for life-long support. It may be important to educate the person responsible for the patient about the benefits of physical activity and to provide recommendations for exercise regimens appropriate for metabolic conditioning. Of course,

all of these recommendations should be individualized and consider the individual impairments of the patient.

REGULAR EXERCISE SHOULD BE A PRIORITY IN TBI REHABILITATION

Post-injury therapy for patients with a TBI is comprehensive and often includes a complex integration of cognitive, speech, occupational, and physical therapy. In many cases, time left for physical therapy is limited; thus, therapists must prioritize treatment. Due to ambulatory impairments common in TBI, much rehabilitation time is devoted to gait-specific training. The level of gait impairment often reduces the peak velocity a patient can safely ambulate and the gait training may not be sufficiently intense to stress the appropriate metabolic systems. In such cases, it may be necessary to provide alternate modes of training that safely stress the aerobic system. If lower extremity impairments, poor coordination, and balance do not allow for high intensity metabolic treadmill exercise, the therapists may choose to use a lower or upper body cycle ergometer for safe metabolic conditioning. High intensity treadmill ambulation is certainly a more functional mode of exercise. However, it is evident from the data that poor metabolic capacity, independent of gait, may lead to disability. As demonstrated in Chapter 3 of this work, the V_{AT} of many of the patients tested in these studies was below the metabolic demands of common activities. In fact, the peak aerobic capacities of some patients were insufficient to complete many routine activities. Therefore, concurrent with gait training, specific metabolic conditioning exercises should be implemented so that when the gait impairment is minimized the patient will possess the metabolic capacity to operate in a chosen physical and social environment.

EXERCISE TESTING MAY BE IMPORTANT DURING REHABILITATION

Another important finding of this investigation is that exercise testing may be important during the rehabilitation process. The ventilatory, metabolic, and cardiovascular responses of the patients tested in these studies were highly individualized and often unpredictable (see Chapter 3). Many of the measured parameters, including those typically used to prescribe exercise (e.g. HR and V_{AT}) were well below the normal predicted levels. These findings, among others, suggest that testing could be useful in targeting precise training intensities in patients with a TBI.

Although the testing performed in this study used expensive and sophisticated equipment, field-based exercise tests may be appropriate to a physical therapy environment. VO_2 max can be estimated using common gym-based equipment 2-lead HR monitors. Implementation of such testing may help therapists establish estimated baseline metabolic capacities for patients, identify weaknesses, target HR for optimal prescription, and ultimately provide more precise exercise prescriptions that lead to better functional outcomes in rehabilitation.

EXERCISE INTERVENTIONS SHOULD IMPROVE BOTH PEAK VO_2 AND V_{AT}

Exercise interventions for patients with a TBI should include target intensities that improve peak VO_2 and V_{AT}. Interestingly, the findings from this study suggest that the improvement of V_{AT} may be more important because of its association with perceived fatigue. It was established at the beginning of this chapter that exercise is effective for improving peak aerobic capacity in patients with a TBI. Few data exist showing the benefits of exercise on V_{AT}. The minimal guidelines provided by the ACSM and Centers for Disease Control suggest that all individuals should engage in moderate daily activity for 60 minutes and three times weekly sustained vigorous activity for 20-30 minutes.

Evidence from healthy individuals suggest that the incorporation of higher intensity training (e.g. interval training) may be beneficial for delaying anaerobic metabolism. Daussin and coworkers compared eight weeks of high intensity interval training to steady state aerobic training in eleven healthy subjects (Daussin *et al.,* 2007). Interval training and steady state aerobic exercise increased peak VO_2 by 15% and 9%, respectively. However, interval training was more effective at increasing mitochondrial capacity compared to steady state aerobic training (Daussin *et al.,* 2007). This research suggests that interval training may have a greater impact on overall fitness levels.

Interval training has also been shown to improve aerobic fitness in clinical populations, including patients with chronic heart failure (Nilsson *et al*., 2008). It has been suggested that interval training may be a more effective strategy than continuous steady state aerobic exercise for improving peak aerobic capacity in some patient populations, including those with chronic heart failure (Wislaff *et al.,* 2007). In addition, interval training has been shown to improve V_{AT} (Acevedo and Goldfarb, 1989; Laursen *et al*., 2002). Research is needed to determine if similar positive adaptations can be seen in patients with a TBI utilizing interval training.

EXERCISE THAT IMPROVES BOTH MECHANICAL EFFICIENCY AND METABOLIC CAPACITY SHOULD BE IMPLEMENTED.

When possible, therapists should implement exercises that concurrently improve mechanical efficiency and metabolic conditioning. Previous research demonstrates that certain training programs result in improvements in mechanical efficiency devoid of improvements in metabolic capacity (Jankowski and Sullivan, 1990). Theoretically, metabolic capacity could be improved independent of gait training through non-gait specific cardiovascular exercise. Each component could be improved independently, but for time

economical purposes therapists should investigate techniques that simultaneously improve both. Body weight support treadmill training (BWSTT) is a unique intervention that has shown potential to improve metabolic capacity. Moreover, mechanical efficiency can be improved through gait training during the conditioning. Mossberg Oleander, and Norcross implemented a 2-3 time per week BWS treadmill protocol (Mossberg et al., 2008). Measuring peak metabolic, ventilatory, and cardiovascular and work output prior to exercise, the patients exercised at a threshold intensity of 60-80% of their predicted maximum heart rates. The intensity was strictly monitored using a Polar chest strap HR monitor. The investigators found improvements in mechanical work output, power, and peak VO_2 after training. Moreover, there was a reduction in submaximal heart rate and an increase in O_2 pulse suggesting a positive cardiovascular adaptation and potentially a change in mechanical efficiency at any given workload.

NEUROENDOCRINE SCREENING SHOULD BE ROUTINE, BUT NOT AFFECT EXERCISE PRESCRIPTION.

The incidence of GH deficiency, among other hormonal deficiencies, is well established. Given the low IGF-1 levels in all but one patient with a TBI tested in this investigation, it is suspected that seven of the eight patients tested could have been GH deficient. Despite these potential deficiencies, the GH response in patients with a TBI was not different from apparently healthy CON. Therefore, with this exercise stimulation test, there appears to be no short-term difference in GH response that would inhibit performance more than sedentary, deconditioned controls. From the initial data it appears that exercise prescriptions similar to those used in apparently healthy CON would be indicated although testing using other exercise stimulation tests is warranted. Furthermore, it may be important

to assess the functional consequences of the altered PRO and COR responses and to clinically screen for abnormal function of these hormones.

GH REPLACEMENT MAY BE BENEFICIAL TO TBI REHABILITATION

Although exercising hormonal responses in this investigation, including GH, were similar between groups, it is not clear what caused the potential GH deficiencies (i.e. obesity results in GH deficiency or vice versa). GH deficiency is associated with obesity and this likely caused the potential deficiencies seen in the CON group. However, experience suggests that GH deficiency is apparent in some non-obese patients with a TBI and it is likely that the deficiency was caused by trauma {for review of potential causes of hormonal dysfunction in TBI see (Urban *et al*., 2005)}. It is unclear from the exercise literature if deficiency due to trauma to the hypothalamus or pituitary is affected either positively or negatively by exercise. Thus, clinical replacement of GH may be indicated.

GH replacement has been shown to improve body composition in deficient adults (Boguszewski *et al.,* 2005). Furthermore, studies indicate that GH replacement may improve peak VO_2 independent of exercise dose and others have demonstrated a positive shift in V_{AT} (Hartman *et al.,* 2008; Woodhouse *et al.,* 1999). GH is involved in cognition, although its mechanisms are not well understood. Receptors for growth hormone are present in the central nervous system (Kramer *et al.,* 1999; Myers 2008; Nyberg 2000) and the number of these binding sites appears to decrease with age. Aging is also associated with declines in cognitive function (Kramer *et al*., 2006; McAuley *et al.,* 2004; Myers, 2008). It has been shown that GH deficient subjects with TBI have greater declines in memory, attention and executive functioning compared to subjects with normal levels of GH (Leon-Carrion *et al.,* 2007). GH deficient patients with a TBI may be prone to emotional problems (Leon-Carrion *et al.,* 2007)

and others have shown that sufficient GH levels are associated with positive cognitive outcomes in patients with TBI (Bondanelli *et al.,* 2007). Therefore, GH replacement may target a number of factors that exercise simply cannot.

The potential benefits of GH replacement in patients with a TBI were confirmed in a recent case-report. A 43-year old GH-deficient female with a TBI underwent one year of GH replacement. Significant improvements were observed in peak VO_2, lower extremity strength, and body composition (Bhagia *et al.,* 2010). Although there were no cognitive improvements observed in this patient, the positive physical performance changes are encouraging. In addition, High and colleagues found that GH replacement may improve cognitive performance in a patient with a TBI (High *et al.,* 2010). In combination, these two studies suggest that GH replacement is beneficial in patients with a TBI who are found to be GH-deficient. Further research is needed to confirm these results in larger patient populations.

CONCLUSION

Research indicates that patients with a TBI who engage in routine, rigorous physical exercise improve metabolic capacities. In any population, lack of physical exercise increases risk for a number of diseases. Given the profound metabolic deficiencies in patients with a TBI, education on the need for exercise and potential risks of sedentary lifestyles are indicated. Moreover, it may be important to educate primary caregivers on the importance of encouraging patients to exercise. Physical therapists should make metabolic conditioning a principal component of a comprehensive treatment plan. When a patient lacks the ambulatory efficiency to sufficiently stimulate aerobic metabolism, the therapist should consider other modes where the patient can safely stimulate a training response. Abnormal cardiovascular responses to exercise are common in TBI and therapists should consider testing to define

peak and threshold intensities. Such tests may help quantify precise training intensities. When possible, therapists should implement exercises to concurrently improve mechanical efficiency while providing a metabolic training stimulus. Given the magnitude of hormonal deficiencies, endocrine testing should be routine and replacement could facilitate recovery and evidence suggests it may be especially beneficial in improving body composition. The abnormal PRO and COR responses reported in Chapter 4 suggest some hormonal responses to exercise in patients with a TBI could be altered, and physical therapists and exercise physiologists should closely monitor the recovery of patients during intense training. Regardless, the GH response to a peak exercise stress was similar between TBI and CON and the potential GH deficiency should not alter exercise plans. However, it may be important to monitor training and recovery, allowing greater recovery time between training bouts.

Chapter 6: Conclusions and Future Research

TBI is a tremendous public health concern. Although time-trend data suggest no significant change in the incidence of TBI, recently there has been a substantial increase in public awareness. This is driven primarily by blast-related head injuries in the ongoing wars and a renewed awareness of the dangers of sport-related concussions. Over the past five years, reports of suicide, reckless behaviors, depression, and substance abuse by retired athletes and "wounded warriors" have flooded the media. As this chapter is authored, it was recently reported that a professional hockey player overdosed on drugs, accidently killing himself. At the time of death, the player was on the disabled list and unable to compete in sport for the final portion of the season because of post-concussion symptoms. The family of the deceased player agreed to allow analysis of their son's brain by investigators Boston University funded to study CTE. It is likely that in the coming weeks it will be reported that the athlete suffered from early brain damage and early onset dementia from mTBI.

This year 80,000–90,000 Americans will sustain a documented TBI. Countless others will sustain mTBI and it will not be reported. Although it will not make the headlines, these patients may suffer from psychological and behavioral impairments, depression, chronic fatigue, hormonal dysfunction, and impaired metabolic capacities. Many of the impairments will be severe enough to affect their QOL.

This dissertation project highlighted the significance of the metabolic impairments in patients recovering from a TBI and provided evidence that their GH responses to exercise

may be similar to apparently healthy individuals with similar BMI. The work provides evidence that although GH deficiency is common, it likely should not affect exercise patterns in patients rehabilitating after injury. The differences in PRO and COR response to exercise are interesting and warrant future investigation.

Like any scientific work, this dissertation raises some interesting questions that hopefully will steer future investigations. Chapter 3 highlighted that peak metabolic, ventilatory, and cardiovascular responses were lower than predicted regardless of gender and confirmed that peak responses were lower than age and gender matched CON. Moreover, the data indicate that the V_{AT} responses of patients with a TBI are lower than CON. It is not known why these differences are present. It is possible that the lower responses are simply a result of physical inactivity or an inability to exercise at a sufficient intensity to simulate metabolic adaptations. In such cases, behavioral research is needed to determine why patients with a TBI choose not to engage in routine exercise so that population strategies can be developed to improve exercise compliance. Furthermore, therapists should find unique ways to implement intense exercise and study the resultant effects.

Although Chapter 5 highlighted studies demonstrating exercise improves metabolic, ventilatory, and cardiovascular fitness, most samples are relatively small, often lack a control group, and the heterogeneity of the patient population is a confounding factor. Well-controlled studies are needed to quantify rates of improvements in many physical abilities in TBI. For example, it would be interesting to compare the rate of change in metabolic, ventilatory, and cardiovascular improvements in TBI compared to sedentary CON to help establish realistic goals for training related improvements. Moreover, it may be important for future studies to quantify potential changes in exercise capacity resulting from non-steady

state training program (e.g. interval training) and determine if such programs are more beneficial for improving V_{AT} or peak VO_2 in TBI.

It was demonstrated that the GH responses to an acute maximal graded exercise test were similar between patients with a TBI and CON. However, graded exercise to failure is specific to testing and may not reflect hormonal responses resulting from the volumes and intensities of routine training bouts. It would be interesting to quantify differences in hormonal responses to steady-state, longer duration exercise (e.g. 60-80% of VO2 max for 30 minutes) and determine if hormonal responses differ from such training. Furthermore, it may be important to quantify hormonal responses to interval training or even intense physical resistive exercise to see if differences exist from such stimulation.

PRO and COR were blunted in response to exercise in patients with a TBI compared to CON. If this finding is confirmed by future research, it may be important to investigate the systemic immunological response to exercise in TBI. Immune function particularly in response to exercise was disrupted in TBI and this could have functional consequences on exercise recovery.

As discussed in Chapter 5, it is possible that the majority of patients tested, TBI and CON, were GH-deficient. Research is needed to determine if exercise related hormonal responses are different within TBI patients that are GH deficient and GH sufficient (Abdel and Baki., 2009). Therefore, screening patients for GH deficiency for such categorization in future studies may be helpful. Moreover, it may be important to track exercise related improvement in metabolic, ventilatory, and cardiovascular capacity in patients with a TBI who are GH sufficient and GH deficient. It has been demonstrated previously that non-TBI patients that are GH deficient can recover exercise capacity; however, it is possible that GH

deficient patients might recover metabolic capacity at a slower rate and GH replacement could improve recovery rates (Thomas *et al*., 2003). Alternatively, routine stimulation with exercise may help to reinitiate the GH response and return patients to GH sufficiency. These hypotheses are speculative, yet warrant a series of investigations to provide answers.

Perhaps the most interesting finding of this work is the strong relationship between VO_2 at V_{AT} and FSS scores. The lingering question from this finding is whether an improvement in VO_2 at V_{AT} would reduce perceived fatigue. Such investigations may be of greatest clinical importance and could provide potential evidence to further support the value of exercise to improve function in TBI and potentially reduce disability.

In a 1965 address, A Bradford Hill stated, "All scientific work is incomplete – whether it is observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."(Hill 1965)[w] Despite the numerous remaining questions, these data and others published previously provide evidence for clinicians to act. The data contained in this dissertation and previously published data support the notion that patients with a TBI should exercise routinely and vigorously. The altered PRO, COR, and glucose responses suggest that exercise programs may need to be more rigorously monitored to ensure safety and adaptation. If patients with a TBI choose not to exercise, an impaired metabolic capacity alone may result in disability. There are frequently impairments accompanying TBI that physical therapists and exercise physiologists must manage in order to sufficiently stimulate exercise metabolism. Nonetheless, the impairments do not "confer on us the freedom to ignore."

[w] A. Bradford Hill delivered this quote in a President's address to the Royal Society of London. The address was later published in a 1965 article in *Proc R. Soc Med.*

Instead, the impairments should compel clinicians to creatively work to implement regimens uniquely suited to TBI with the goal of improving the quality of life of patients and facilitating attainment of the copious benefits of routine exercise.

APPENDIX

ABBREVIATIONS AND ACRONYMS

1. Acquired Brain Injury (ABI)
2. Activities of Daily Living (ADL)
3. Adrenocorticotropic hormone (ACTH)
4. American College of Sports Medicine (ACSM)
5. Anaerobic Threshold (AT)
6. Analysis of Variance (ANOVA)
7. Area Under the Curve (AUC)
8. Baseline (BASE)
9. Blunt Head Trauma (BHT)
10. Body Mass Index (BMI)
11. Body Weight Support Treadmill Training (BWSTT)
12. Brain Injury (BI)
13. Carbon Dioxide (CO_2)
14. Cardiovascular Disease (CVD)
15. Centers for Disease Control (CDC)
16. Chronic Traumatic Encephalopathy (CTE)
17. Coefficient of Variation (CV)
18. Control (CON)
19. Coronary Artery Disease (CAD)
20. Cortisol (COR)
21. Electrocardiogram (ECG)
22. Emergency Room (ER)

23. End-Tidal Partial Pressure of O_2 ($P_{ET}O_2$)
24. Enzyme-Linked Immunosorbent Assay (ELISA)
25. Ethylene Diamine Acetic Acid (EDTA)
26. Fatigue Severity Scale (FSS)
27. Follicle Stimulating Hormone (FSH)
28. Force Expiratory Volume in 1 second (FEV1)
29. Glasgow Comma Scale (GCS)
30. Growth Hormone (GH)
31. Gunshot (GS)
32. Heart Rate (HR)
33. High Intensity Interval Training
34. Improvised Explosive Devices (IED)
35. Institute of Medicine (IOM)
36. Insulin Growth Factor Binding Protein 3 (IGFBP3)
37. Insulin Growth Factor I (IGF-1)
38. Kilogram (kg)
39. Kilometer (km)
40. Liter (L)
41. Loss of Consciousness (LOC)
42. Lutenizing hormone (LH)
43. Measured Value (MEAS)
44. Metabolic Equivalents (MET)
45. Mild Traumatic Brain Injury (mTBI)

46. Milliliter (mL)
47. Minute (min)
48. Minute Ventilation (V_E)
49. Motor Vehicle Accident (MVA)
50. National Football League (NFL)
51. Norepinephrine (NE)
52. Oxygen (O_2)
53. Post Traumatic Stress Disorder (PTSD)
54. Predicted Value (PRED)
55. Prolactin (PRO)
56. Quality of Life (QOL)
57. Rate of Perceived Exertion (RPE)
58. Respiratory Exchange Ratio (RER)
59. Serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRI)
60. The Institute for Rehabilitation and Research (TIRR)
61. Thyroid Stimulating Hormone (TSH)
62. Thyroxine (T_4)
63. Traumatic Brain Injury (TBI)
64. Ventilatory Anaerobic Threshold (V_{AT})
65. Ventilatory Equivalents of Carbon Dioxide Production ($\dot{V}_E / \dot{V}CO_2$)
66. Ventilatory Equivalents of Oxygen Consumption ($\dot{V}_E / \dot{V}O_2$)
67. Visual Fatigue Analogue Scale (VFAS)
68. Volume of Carbon Dioxide Production ($\dot{V}CO_2$)

69. Volume of Oxygen Consumption ($\dot{V}O_2$)

70. Years (yrs)

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Vita

BIOGRAPHY

William Emil Amonette was born on April 15, 1977, in Houston, TX. He is the first son of Billy and Judy Amonette and older brother of Rebecca Kenney who all reside in Houston, TX. Amonette graduated from Sam Rayburn High School in 1995. His bachelor's (1999) and master's (2001) degrees are from the University of Houston-Clear Lake (UHCL) in Fitness and Human Performance. Amonette has previous experience in academia as an Adjunct Instructor and Lecturer at the UHCL in the Fitness and Human Performance; he is also currently an Adjunct Instructor at UTMB in the Physical Therapy Department. Prior to beginning the Ph.D. program at UTMB, Amonette was contracted by the Chinese Basketball Association (CBA) as a strength and conditioning coach for the National Basketball Team of China at the Beijing Olympic Training Center. Amonette has worked previously as the Assistant Strength and Conditioning Coach/ Rehabilitation Coordinator for the Houston Rockets, an Astronaut Strength, Conditioning, and Rehabilitation Specialist at NASA-JSC (Wyle Laboratories), an Exercise Physiologist at NASA-JSC (Wyle Laboratories) and interned at the United States Olympic Training Center in Chula Vista, CA, as a Strength and Conditioning Coach. He has worked as a personal strength and conditioning coach for many collegiate, professional, and world-class athletes who live and train in Houston, TX, area. These athletes include basketball, baseball, American football, soccer, track & field and Olympic weightlifters. Amonette also served as a sports science-strength and conditioning consultant to the Guatemalan National Baseball Federation, Memorial Hermann Sports Medicine Institute, and Legend Healthcare. Amonette is married to Jenny Amonette, a graduate of UTMB and Physical Therapist at Progressive Physical Therapy in Webster, TX. They are expecting their first child in November of 2011 and currently reside in Houston, TX.

EDUCATION

Master's of Art (MA), Fitness and Human Performance, University of Houston–Clear Lake, December 2001.

Bachelor's of Science (BS), Fitness and Human Performance, University of Houston–Clear Lake, August 1999.

CERTIFICATIONS

- Certified Strength and Conditioning Specialist (CSCS) through the National Strength and Conditioning Association (NSCA), 1999.
- USA Weightlifting Level I Coach, 2000.
- USA Track and Field Level I Coach, 2003.

PUBLICATIONS

Journal Articles

Stroud L, Amonette WE, Dupler TD. Metabolic responses to accelerometer controlled video games. *Appl Physiol Nurt Metab*. 2010, 35: 1-7. PMID 20962920

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Book Chapters

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Government Reports

Amonette, W.E., Schaffner, G., J.R. Bentley, J.A. Loehr, S.MC. Lee, A.D. Moore, J. Norcross, F. Moore, & S.M. Schneider Evaluation of Horizontal Exercise Fixture in conjunction with the Interim Resistive Exercise Device (iRED) for use in bed rest research. Washington, DC: National Aeronautics and Space Administration, Technical Report (2009-0039503), 2009.

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Amonette WE, Bentley JR, Lee SMC, Loehr JA, Schneider SM. Differences in ground reaction forces and mechanics between the Interim Resistive Exercise Device (iRED) and Smith machine during a squat. Washington, DC: National Aeronautics and Space Administration, Technical Report (2004–212063), 2004.

Moore AD, Amonette WE, Bentley JR, Blazine KL, Loehr JA, Rapley MG, Lundquist C, Schneider SM. International Space Station Interim Resistance Exercise Device Man in the Loop Test Results. Washington, DC: National Aeronautics and Space Administration, Technical Report (2004–212062), 2004.

Amonette WE, Bentley JR, Blazine K, DeWitt JK, Laughlin M, Loehr JA, Chauvin J, Guilliams M, Moore AD, Rapley MG, Hagan DH. Man in the Loop Testing of the Schwinn Resistive Exercise Device (SCHRED). Washington, DC: National Aeronautics and Space Administration, Technical Report (2004-21207), 2003.

Intellectual Properties

W.E. Amonette (45%), K.L. English (30%), W. Buford (20%), & B.W. Amonette (5%). An apparatus to facilitate upright posture and improved gait velocity in the elderly and methods for making the same. US PSN: 61/184942. United States utility patent application filed – June 08, 2010 (patent pending).

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