Georgia State University
ScholarWorks @ Georgia State University

Respiratory Therapy Theses | Department of Respiratory Therapy

Summer 8-2020

Measuring Muscle Fatigue associated with tourniquet use using Accelerometer-Based Mechanomyography: A Pilot Study

Erica Armstrong

Follow this and additional works at: https://scholarworks.gsu.edu/rt_theses

Recommended Citation

Armstrong, Erica, "Measuring Muscle Fatigue associated with tourniquet use using Accelerometer-Based Mechanomyography: A Pilot Study." Thesis, Georgia State University, 2020.
https://scholarworks.gsu.edu/rt_theses/45

This Thesis is brought to you for free and open access by the Department of Respiratory Therapy at ScholarWorks @ Georgia State University. It has been accepted for inclusion in Respiratory Therapy Theses by an authorized administrator of ScholarWorks @ Georgia State University. For more information, please contact scholarworks@gsu.edu.

Summer 2020

Measuring Muscle Fatigue associated with tourniquet use using Accelerometer-Based Mechanomyography: A Pilot Study

Erica Armstrong
Georgia State University

ACCEPTANCE

This thesis, MEASURING MUSCLE FATIGUE WITH ACCELEROMETER-BASED MECHANOMYOGRAPHY: A PILOT STUDY, by Erica Armstrong, was prepared under the direction of the candidate's thesis committee. It is accepted by the committee members in partial fulfillment of the requirements for the degree of Master of Science in Respiratory Therapy in the Byrdine F. Lewis College of Nursing and Health Professions, Georgia State University.

_____

Douglas S. Gardenhire, EdD, RRT, RRT-NPS, FAARC
Committee Chair

_____

Kyle Brandenberger, PhD
Committee Co-Chair

_____

Rachel Culbreth, PhD, MPH, RRT
Committee Member

_____

Date

AUTHOR'S STATEMENT

In presenting this thesis as a partial fulfillment of the requirements for the advanced degree from Georgia State University, I agree that the library of Georgia State University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote, copy, or publish this thesis may be granted by the author, or in her absence, by the professor under whose direction it was written, or in his absence, by the Director for Respiratory Therapy in the Byrdine F. Lewis College of Nursing and Health Professions. Such quoting, copying, or publishing must be solely for scholarly purpose and will not involve potential financial gain. It is understood that any copying or publication of this thesis which involves potential financial gain will not be allowed without permission from the author.

_____

Erica Armstrong

NOTICE TO BORROWERS

All theses deposited in the Georgia State University Library must be used in accordance with the stipulations prescribed by the author in the preceding statement.

The author of this thesis is:

Erica Armstrong
2035 Memorial Drive, Apt #903
Atlanta, GA 30317

The director of this thesis is:

Douglas S. Gardenhire, EdD, RRT, RRT-NPS, FAARC
Chair
Department of Respiratory Therapy
Byrdine F. Lewis College of Nursing and Health Professions
Georgia State University
P.O. Box 4019
Atlanta, Georgia 30302

Users of this thesis not regularly enrolled as students of Georgia State University are required to attest acceptance of the preceding stipulation by signing below. Libraries borrowing this thesis for use of their patrons are required to see that each user records here the information requested.

NAME OF USER	ADDRESS	DATE	TYPE OF USE EXAMINATION ONLY (OR COPYING)

Curriculum Vitae

Erica Armstrong
2035 Memorial Dr, Apt #903
Atlanta, Georgia 30317

I. Education

a. Georgia State University, Atlanta, GA **2020**
Lewis College of Nursing and Health Professions
M.S. in Health Sciences, with a concentration in Respiratory Therapy
Thesis: "Measuring Muscle Fatigue with Accelerometer-based Mechanomyography: A Pilot Study"

b. **University of Utah, Salt Lake City, UT** **2015**
College of Health
B.S. in Speech and Hearing Sciences
B.S. in Psychology
Minor: Nutrition

II. Professional certifications and licensure

a. Certificate Earned, Neonatal Resuscitation Provider, 2019
b. Certificate Earned, Advanced Cardiac Life Support Provider, 2019
c. Certificate Earned, Cardiopulmonary Resuscitation Provider, 2018

III. Professional Development

a. Publications
    i. Journal articles
        1. Published: Armstrong, E.L., Bryan, C.J., Stephenson, J.A., Bryan, A.O., & Morrow, C.E. Warzone stressor exposure, unit support, and emotional distress among U.S. Air Force Pararescuemen. *Journal of Special Operations Medicine*., 14(2), 26-34.

b. Professional Presentations
    i. Armstrong, E. Measuring Muscle Fatigue with Accelerometer-Based Mechanomyography. Graduate Research Conference, Georgia State University, 2020.
    ii. Armstrong, E.L., Bryan, C.J., Stephenson, J.A., Bryan, A.O., & Morrow, C.E. Warzone stressor exposure, unit support, and emotional distress among U.S. Air Force Pararescuemen. Rocky Mountain Psychological Association, 2015.

IV. Honors, Awards, Recognitions

a. Alpha Eta Honor Society, (Georgia State University), 2020
b. Undergraduate Research Scholar (University of Utah), 2015
c. University of Utah Honors Program (University of Utah), 2011-2015

ACKNOWLEDGEMENTS

“Success is not final, failure is not fatal: it is the courage to continue that counts.”
- Winston Churchill

To my family and friends; my professors and the respiratory therapists who imparted their experience and wisdom; and all others who supported me in this venture. You believed in me when I failed to believe in myself. For that, I am truly and sincerely grateful.

MEASURING MUSCLE FATIGUE WITH ACCELEROMETER-BASED MECHANOMYOGRAPHY: A PILOT STUDY

By

Erica Armstrong, BS

A Thesis
Presented in Partial Fulfilment of Requirements for the

Degree of Master of Science
in Health Science
in the Department of Respiratory Therapy
in the College of Nursing and Health Professions
Georgia State University

Atlanta, Georgia 2020

ABSTRACT

MEASURING MUSCLE FATIGUE WITH ACCELEROMETER-BASED MECHANOMYOGRAPHY: A PILOT STUDY

By

Erica Armstrong, BS

Objectives: Patients admitted to the intensive care unit (ICU) are at a higher risk for developing muscle weakness, which is associated with prolonged recovery, poor quality of life, and greater rates of mortality. This study mimicked changes we expect to see in patients with clinical weakness by manipulating blood flow to determine whether mechanomyography is sensitive enough to detect the expected change. **Methods**: Recreationally active individuals (n = 10) were recruited for this study. Stimulating electrodes and an accelerometer were placed on the muscle belly of the extensor carpi radialis and tibialis anterior. Muscles were stimulated at a rate of 2, 4, and 6, Hz for three minutes each at 60mA. Two trials were performed for each muscle, one with and one without occluded muscle blood flow. **Results**: Accelerations (muscle twitch height) decreased in the extensor carpi radialis (0.944 ± 0.188g, $p < 0.001$) and tibialis anterior (0.515 ± 0.198g, $p = 0.018$) when blood flow was occluded compared to the normal blood flow trials. The normal blood flow trial accelerations were higher in the extensor carpi radialis compared to the tibialis anterior (1.173 ± 0.242g, $p < 0.001$). After data were normalized these differences were no longer significant. **Conclusions**: The results of this study indicate accelerometer based mechanomyography can differentiate between fatigue associated with impaired blood flow to the muscle. Future research should examine whether accelerometer based mechanomyography can distinguish muscle quality in clinically relevant populations.

TABLE OF CONTENTS

CHAPTER I

Introduction

Neuromuscular weakness often results from extended periods of critical illness or injury. This weakness, called intensive care unit acquired weakness (ICUAW), is associated with prolonged periods of recovery and a decreased quality of life (Sidiras et al., 2019). Patients with ICUAW have higher rates of functional impairments after discharge compared to those who do not have ICUAW, with as many as 80% of patients having functional impairments for up to five years after discharge (Jolley et al., 2016). These patients also have greater rates of mortality pre and post ICU discharge (Hermans et al., 2014; Wieske et al., 2015).

Early diagnosis is thought to be crucial in the treatment of ICUAW (Wieske et al., 2014; Novak et al., 2009; Latronico et al., 2009). However, the tests that are currently available have multiple drawbacks and limitations that prevent their use in patients early in the disease process. Nerve conduction studies detect muscle weakness by calculating the speed of the electrical impulse in motor nerves via electrodes placed on the skin. However, nerve conduction studies do not assess the muscle itself; instead, they provide information on the number of functioning nerve fibers, as well as nerve conduction velocity (Kane & Oware, 2012; Tavee, 2019). Research has also indicated that this test lacks standard diagnostic criteria, and is not a definitive test (Fan et al., 2014). Nerve conduction studies alone cannot determine the cause of the illness and must be used in conjunction with other diagnostic tests (Camdessanché et al., 2006). These tests also require a high level of patient cooperation, as well as medical personnel expertise (Fuller, 2005; Jolley et al., 2016; Kress & Hall, 2014). Nerve conduction studies are expensive and can be painful for the patient (Fuller, 2005). The ICU patient has an increased risk for injury due to movement during the test, as well as an increased risk for developing edema due to the needle

electrodes used (Morris & Trinder, 2002; Schweickert & Hall, 2007; Trojaborg, 2006). Subsequent attempts have been made to use surface electrodes instead of needles, but findings indicate these electrodes are not accurate, as skin resistance interferes with the calculated nerve conduction velocity (Evangelopoulos et al., 2017; Kural et al., 2016).

Another muscle function test is a clinical strength assessment. These strength assessments can be performed via one of two avenues: a manual muscle test (Medical Research Council, 1976) or dynamometry. In a manual muscle test, muscle groups of the upper and lower extremities of the patient are measured against the medical examiner's resistance. The patient's strength is rated on a zero to five scale, with zero indicating no muscle activation and five indicating full range of motion and activation against the examiner's resistance (Bohannon, 2019; Ciesla et al., 2011; Naqvi & Sherman, 2019). If patient effort is reduced, the test allows the patient to perform the test with gravity eliminated. Notwithstanding, testing outcomes vary due to subjective scoring methods and poor interobserver agreement (Hough et al., 2011). Manual muscle testing does not accommodate patients who suffer from painful musculoskeletal conditions (Naqvi & Sherman, 2019). Notably, however, is that this test does not quantify muscle strength, but suggests a strength level (Naqvi & Sherman, 2019). Dynamometry, on the other hand, quantifies muscle strength through a dynamometer – a device that records force by loading compression of a spring (Samosawala et al., 2016). Although dynamometry is more objective than manual muscle testing, it is still subject to various drawbacks. For instance, it does not pertain to all clinical conditions; reliability can vary depending on disease states (O'Shea et al., 2007). Dynamometry results also vary depending on the type of dynamometer used and the specific muscle tested (Mafi et al., 2012). Age and/or gender may play a role in dynamometry outcomes, but as to how or what extent of a role they play is unclear (Davies et al., 1984;

Wadsworth et al., 1992). Manual muscle testing and dynamometry additionally require that the patient be awake, alert, and cooperative (Hough et al., 2011; Kress & Hall, 2014; Schweickert & Hall, 2007). This is not feasible in a large number of ICU patients, as many receive sedatives during their ICU length of stay, and/or may be comatose or delirious (Ely et al., 2004; Hough & Herridge, 2012).

Other researchers have suggested that measuring muscle weakness is futile, as treatment and interventions are not being implemented despite attempts to diagnose weakness (Morris & Trinder, 2002). In cases where treatments are implemented, they are not standardized, and outcomes are varied (Koukourikos et al., 2014). While some research has suggested limiting medications that may contribute to muscle weakness and loss – such as corticosteroids, neuromuscular blockers, and aminoglycosides – other research has suggested limiting parenteral nutrition (Falagas & Kasiakou, 2006; Koukourikos et al., 2014; Nanas et al., 2008; Rich & Pinter, 2003; Yang et al., 2018). Conversely, prior research has shown by and large that early mobilization plays a major role in preventing muscle atrophy (Anekwe et al., 2019; Hashem et al., 2016; Lynch et al., 2007; Wischmeyer & San-Millan, 2015). Walking, and even small movements, such as positioning the patient in the bed or chair, are associated with positive outcomes (Jang et al., 2019; Koukourikos et al., 2014).

Failure to implement these treatments for patients with ICUAW may in part be a result of a lack of appropriate, valid, and reliable diagnostic tests. This ultimately highlights the need for a test that is objective, can be easily administered by the medical practitioner, and poses little risk and discomfort to the patient, regardless of the patient's state of consciousness.

Recent research has examined the use of accelerometer mechanomyography to measure muscle fatigue during intermittent contractions, and thereby muscle function (Willingham &

McCully, 2017). Although a muscle may contract, the force produced by said contraction varies according to the strength of the electrical signal that originates within the central nervous system (CNS); as the signal diminishes – either by reducing the firing frequency of the neurons or reducing the number of neurons that are firing – the force of the contraction decreases (Shinohara & Søgaard, 2006). However, muscle contraction and endurance of contraction is also dependent upon the structure of the muscle fiber itself (Frontera & Ochala, 2015). A muscle that is oxygen deficient will be unable to maintain the resynthesis of adenosine triphosphate (ATP), the molecular unit of energy, over an extended period of time. Lack of ATP – and a lowered ATP/ADP ratio (adenosine diphosphate, or ADP, is an organic compound created when ATP loses a phosphate group) – is associated with an inability to maintain the force of a muscle contraction. The more rapidly the blood supply (and therefore oxygen) diminishes, and the more metabolites (such as inorganic phosphate) accumulate, the faster the muscle fatigues (Bigland-Ritchie & Woods, 1984). Ultimately, a muscle that fails to sustain the force of a contraction is indicative of fatigue (Tachi et al., 2004; Tarata, 2003).

When paired with electrical stimulation, an accelerometer can detect the amount of muscle acceleration, and therefore muscle force. The force of a contraction is the result of acceleration upon a particular mass. The overall force of muscle contraction is generated by the force per cross-bridge formed (discussed in detail below) (Grazi, 2010). As the velocity and length of a muscle change, it affects the acceleration of the muscle, which in turn affects the force generated by the muscle (Roberts & Marsh, 2003). By measuring the acceleration of the muscle, it may be possible to distinguish patterns of fatigue in the muscle. Theoretically, by measuring rates of fatigue, functional impairments in the muscle can be determined.

Furthermore, accelerometer mechanomyography is preferred because it is noninvasive, inexpensive, and does not require that the patient be alert or conscious (Ibitoye et al., 2014).

In order to test accelerometer mechanomyography in a population with true ICUAW, this test must first be done on healthy individuals so the test can be validated. As such, healthy, recreationally active athletes were recruited for this study. Clinical muscle weakness was simulated in each participant by reducing the amount of oxygen (i.e., perfusion) to muscles using a tourniquet.

Purpose of Study

The purpose of this study was to determine whether accelerometer-based mechanomyography can detect functional changes in the muscle (i.e., levels of muscle fatigue) by discriminating between conditions of blood flow to the muscle. To date, most tests measuring muscle atrophy and fatigue fail to provide objective data or are unable to be conducted in patients with severe critical illness, most often due to neurocognitive impairments (Ely et al., 2004). By measuring muscle acceleration, we sought to identify a significant increase in fatigue during the occluded blood flow trial.

The following hypotheses were considered in the current project:

1. Poorly perfused muscles will have decreased muscle twitch accelerations compared to adequately perfused muscles.
2. Decreases in poorly perfused muscle twitch accelerations will appear at lower stimulation frequencies compared to adequately perfused muscles.

Significance of Study

By evaluating the use of accelerometer-based mechanomyography, this study hopes to provide evidence that this procedure could detect functional changes that mimic what we would expect in an ICU patient with clinical weakness. This study will advance clinical work in the field of respiratory care, physical therapy, and other medical practice by identifying those who are most at risk for muscle atrophy and ICUAW. According to the American Thoracic Society (Fan et al., 2014), there is no current, standard criteria for diagnosis of ICUAW, and current results are inconclusive and subjective. Consequently, there is a clear need for a new methodology used to assess muscle weakness in ICU patients.

Definition of Terms

Accelerometer: a device that records muscle acceleration (twitch) on three axes of motion (x, y, z).

Adenosine Triphosphate (ATP): the primary organic chemical responsible for providing energy to living cells. It is often referred to as the "molecular unit of currency" in regard to cellular energy.

Clinical Strength Assessment: a diagnostic test that evaluates muscle force production. See *Manual Muscle Test* and *Dynamometry*.

Dynamometry: a diagnostic test in which patient strength is measured by the force of loading via tension or compression.

Electromyography: the process of measuring electrical activity in muscle tissue via electrodes placed on the skin.

g: gravitational force equivalent, colloquially known as g-force. A measurement of the force per unit mass due to gravity at the earth's surface.

Intensive Unit Care Acquired Weakness (ICUAW): neuromuscular impairment acquired in the intensive care unit as a result of polyneuropathy, myopathy, and/or muscle atrophy. Commonly seen in patients who have bed sores, inadequate physical activity, and who are mechanically ventilated for 21 days or longer (MacIntyre et al., 2005).

Manual Muscle Test: a diagnostic test in which muscles of the upper and lower extremities are measured against a medical examiner's resistance. Patient strength is rated on a zero to five scale, with zero indicating no muscle activation and five indicating full range of motion and activation against the examiner's resistance.

Mechanomyography: the process of detecting muscle vibration, or twitch, by the summation of electrical signals generated by motor units near electrodes via a device that measures acceleration.

Motor Unit: a motor neuron and the muscle fibers it innervates. Muscle force is dependent upon both the firing rate of the motor unit and the number of motor units that are firing.

Nerve Conduction Study: a diagnostic test that evaluates nerve function and velocity. Sensory or motor nerves are stimulated by an electrical impulse via electrode patches attached to the skin.

Perfusion: the passage of blood through the cardiovascular or lymphatic system, delivered to an organ or tissue. Malperfusion (poor perfusion) can lead to ischemia.

Delimitations

This study includes a population that is involved in moderate to high levels of physical activity. Although there were attempts to mimic the clinical population, results cannot be generalized to other populations. This pilot study is the first in a series of many that will look at muscle function in different populations; tests should not be used on critically ill populations until indications are warranted. These limitations are beyond the control of the researcher.

Assumptions

1. Each participant tested meets criteria for the operational terms ‘healthy’ and ‘recreational athlete’.
2. Lack of distal pulse is a valid indicator of limited perfusion to the muscle.

CHAPTER II

Review of Literature

In the United States alone, approximately 4 million individuals are admitted to the intensive care unit (ICU) each year, with mortality rates estimated at 8-19% (Mukhopadhyay et al., 2014). Among those who survive, approximately 25% will experience some form of ICUAW (Angus et al., 1996; Fan et al., 2014). ICUAW is associated with numerous adverse outcomes, including increased length of hospital stay, prolonged mechanical ventilation, and increased rates of mortality both before and after ICU discharge (Hermans & Van den Berghe, 2015; Sharshar et al., 2009). Given these high rates, it becomes imperative that medical professionals seek ways to combat muscle weakness and therefore avoid adverse patient outcomes. In order to provide effective, adequate care, a comprehensive understanding of skeletal muscle anatomy and physiology is needed.

Skeletal Muscle Anatomy

Skeletal muscle comprises approximately 40% of body weight and is responsible for producing a variety of voluntary movements, including explosive movements such as running or jumping (Frontera & Ochala, 2015; Westerblad et al., 2010). Due to the nature of such movements, skeletal muscle has evolved in order to rapidly increase its energy expenditure compared to cardiac muscle (Mukund & Subramaniam, 2020; Westerblad et al., 2010). Yet unlike cardiac muscle, skeletal muscle is subject to fatigue, defined as any reversible decline in muscle performance due to muscle activity (Allen et al., 2008). Fatigue can be measured by a decrease in muscle force, as well as reduced velocity of muscle contraction (Allen et al., 2008). Closer examination of the cellular structure and molecular changes that occur in skeletal muscle reveal how force is produced (how fatigue occurs within the muscle is discussed later).

Like most systems within the body, muscle is organized in a hierarchical fashion. The muscle fiber, (known also as a myofiber or muscle cell), is a multinucleated cell, with nuclei evenly distributed throughout the periphery of the fiber (Roman & Gomes, 2018). Myofibers are composed of numerous myofibrils, which contain the smallest unit of contraction, known as the sarcomere (Frontera & Ochala, 2015). Within each sarcomere resides various contractile thick and thin filaments (and their associated proteins), or myosin and actin, respectively (Gash et al., 2020; Mukund & Subramaniam, 2020). These alternating filaments are what give skeletal muscle its distinctive, striated appearance (Kuo & Ehrlich, 2015). Actin is covered by a protein, tropomyosin, which blocks the myosin binding sites on actin (Kuo & Ehrlich, 2015). An additional protein, troponin, can be found along actin and adjacent to tropomyosin. Composed of three subunits (I, T, and C), troponin I is responsible for blocking the interaction of actin and myosin, troponin T is responsible for the binding of calcium, and troponin C is responsible for binding to tropomyosin (Chen et al., 2015; Gash et al., 2020).

Groups of these muscle fibers (or bundles) are referred to as fascicles, which then bundle together to form muscle tissue. Of note is that each layer is surrounded by a matrix of connective tissue (Lieber et al., 2017). Finally, the various muscle tissues give rise to the muscle itself.

Cell Organelles

Muscle fibers are surrounded by the sarcolemma, a plasma membrane. Contained within the sarcolemma are the sarcoplasmic reticulum, transverse (t) tubules, and mitochondria, all of which play a role during muscle contraction. More specifically, the sarcoplasmic reticulum stores and releases calcium while the t-tubules conduct the nerve signal along the length of the muscle fiber. The mitochondria form a network that is responsible for using oxygen, making ATP available to the cell (Frontera & Ochala, 2015).

Muscle Fibers Types

Not all skeletal muscle cells have the same properties. In fact, muscle cells differ in speed of contraction, metabolic processes (oxidative versus glycolytic), fatigue resistance, and handling of calcium ions (Ca^{2+}) (Allen et al., 2008; Westerblad et al., 2010). Early classification of muscle fibers focused primarily on histochemical staining procedures: fibers containing larger amounts of myoglobin appeared redder (versus pale) and contracted more slowly than fibers that had smaller amounts of myoglobin (Zierath & Hawley, 2004). Current classification systems group muscle fibers according to their myosin heavy chain isoforms (Talbot & Maves, 2016). Under the current system, three fiber types exist: type I, type IIA, and type IIx (a fourth fiber, type IIb, exists in other mammals but is not present in humans) (Allen et al., 2008; Frontera & Ochala, 2015). Type I fibers, known colloquially as slow-twitch fibers, are slower to contract and have greater oxidative capacities than fast type II fibers (fast-twitch fibers), due to their greater amounts of mitochondria (Westerblad et al., 2010). In contrast to type I fibers, type IIa fibers have intermediate contraction speeds, while type IIx fibers have the fastest contraction speeds (Allen et al., 2008). Fast isoforms more readily use adenosine triphosphate (ATP) (the biological currency of energy) compared to slow isoforms. Moreover, fast type II fibers fatigue more rapidly than slow type I fibers, due to the discrepancies in the mitochondrial content of the fiber (Allen et al., 2008; Frontera & Ochala, 2015; Herbison et al., 1982). Ca^{2+} pumps are also expressed differently in the sarcoplasmic reticulum of each fiber type. Type II fibers contain SERCA1, while type I fibers contain SERCAII. Of particular note is that fast fibers have a greater density of Ca^{2+} pumps compared to slow fibers (Allen et al., 2008; Westerblad et al., 2010). Consequently, there is a larger, more pronounced spike in Ca^{2+} concentration in the type II fibers, which allows for faster and stronger muscle contractions compared to the type I fibers.

Skeletal Muscle Physiology

The process of muscle contraction is referred to in literature as excitation - contraction coupling (ECC) (Calderón et al., 2014). In this model, a nerve actional potential originates in the brain (specifically the motor cortex) and travels along the spinal cord down to the motor unit, which consists of an alpha (α) motor neuron and the muscle fibers it innervates (Potvin & Fuglevand, 2017). At the neuromuscular junction – where the axon terminal of the α motor neuron synapses with the muscle cell – acetylcholine is released into the synaptic cleft, where it activates sodium (Na^+) channels along the sarcolemma (Allen et al., 2008; Kuo & Ehrlich, 2015). From here, the action potential is transmitted along the t-tubules to a protein called the dihydropyridine receptor (also known as the L-type Ca^{2+} channel) and then to another protein complex called the ryanodine receptors (also known as the SR Ca^{2+} channels), located in the sarcoplasmic reticulum (SR) (Calderón et al., 2014; Lanner et al., 2010). This causes the SR to release Ca^{2+}, whereupon it binds to troponin C, causing tropomyosin to shift, exposing the myosin binding site of the actin filament (Frontera & Ochala, 2015; Mukund & Subramaniam, 2020). ATP binds to myosin, allowing myosin to release actin (from a previous cross-bridge contraction), and subsequently hydrolyzes to form adenosine diphosphate (ADP) and inorganic phosphate (Pi) (Kuo & Ehrlich, 2015). Pi then detaches from the myosin, allowing a new cross-bridge to form and creating a power stroke, 'sliding' actin past myosin, and ultimately causing muscle contraction (Frontera & Ochala, 2015; Geeves & Holmes, 1999). With ECC complete, ADP is released, allowing myosin to detach from troponin and return to its original position (Gash et al., 2020). Finally, the increased levels of Ca^{2+} are pumped back into the SR via SERCA, thereby causing tropomyosin to block the binding site on actin once again, and relaxing the muscle (Allen et al., 2008; Lanner et al., 2010).

Skeletal Muscle Energy Systems

As described above, ATP is used during the process of muscle contraction. Indeed, it is *the* energy currency of muscle contraction, as well as other aspects of cell metabolism (e.g., protein assembly, biochemical transport, biosynthesis) (Hara & Kondo, 2015). Despite the continuous need for ATP, the body stores very little ATP within each cell (Bonora et al., 2012). Consequently, each muscle cell must constantly synthesize ATP, especially in cases of continuous contractions. This process, known as cellular respiration, can be divided into two basic pathways: aerobic (oxidative) and anaerobic (glycolytic) metabolism (Westerblad et al., 2010).

If ATP is the energy currency of the cell, then glucose is the primary fuel (fats and amino acids are also utilized but at much lower frequencies) (Frontera & Ochala, 2015; Toyoda & Saitoh, 2015). In the first step of cellular respiration, glucose and nicotinamide adenine dinucleotide (NAD^+) undergo glycolysis to form pyruvate and nicotinamide adenine dinucleotide (NADH), respectively. If oxygen is present, then the cell undergoes aerobic metabolism, and pyruvate is decarboxylated and attached to coenzyme A (CoA) to form acetyl-CoA (Toyoda & Saitoh, 2015). Acetyl-CoA subsequently enters the citric acid cycle (also known as the Krebs cycle), where it is continuously converted and reduced to produce the two cofactors NADH and flavin adenine dinucleotide (FADH2) (Bonora et al., 2012). From here, NADH and FADH2, as well as oxygen, undergo oxidative phosphorylation via the electron transport chain (ETC). Composed of a series of electron transfer complexes across the mitochondrial membrane, the ETC ultimately generates ATP (from ADP and P_i), water, and carbon dioxide (Bonora et al., 2012; Toyoda & Saitoh, 2015).

Meanwhile, if oxygen is not present, then the cell will undergo anaerobic metabolism. Once glycolysis occurs, pyruvate and NADH (from the citric acid cycle) are further reduced into lactate and NAD^+. This temporarily maintains glycolysis by transferring hydrogen ions (H^+) to pyruvate, thereby producing NAD^+ (Bonora et al., 2012; Mukund & Subramaniam, 2020; Westerblad et al., 2010).

Incidentally, and of extreme importance, is the influence of exercise intensity on metabolism. Muscle fibers will use the small, existing reserves of ATP for short, intense bursts of physical activity lasting approximately one second. In contrast, high intensity isometric exercise lasting a few minutes, such as weightlifting, uses anaerobic glycolysis to produce ATP. Meanwhile, isotonic exercises of longer duration (minutes to hour), such as walking or running, use aerobic oxidation (Frontera & Ochala, 2015; Mukund & Subramaniam, 2020). Moreover, these pathways do not occur in an "all or none" fashion, but may be employed simultaneously at various points throughout a single session of exercise (Frontera & Ochala, 2015). Likewise, different sources of fuels, such as carbohydrates, fats, and proteins, may be used to produce ATP for one session of exercise (Frontera & Ochala, 2015).

Oxygen and Carbon Dioxide Transport

In order for the body to undergo cellular respiration, oxygen needs to be transported to the cells and carbon dioxide (CO_2) removed. While the full, detailed understanding of internal and external respiration (not to be confused with cellular respiration) is beyond the scope of this paper, suffice it to say that oxygen makes its way into the body from the atmosphere through a series of concentration gradients and diffusion processes (both facilitated and unfacilitated) in the respiratory system (Law & Bukwirwa, 1999; Popel, 1989). Once in the alveoli of the lungs, oxygen diffuses across the alveolar-capillary membrane (ACM) to enter the bloodstream. The

heart then pumps this oxygenated blood to the various peripheral tissues of the body, to be used by the mitochondria for energy production (Treacher & Leach, 1998). Each muscle is supplied oxygen by a network of capillaries, the extent of which correspond to the muscle fiber's metabolic requirements (Frontera & Ochala, 2015). While oxygen diffuses into the muscle, carbon dioxide, a waste product of cellular respiration, diffuses back into the venous bloodstream. From there, the carbon dioxide travels back to the heart, through the ACM, into the alveoli, and through the lungs to be exhaled back into the atmosphere (Yang & Liu, 2016).

The rate at which the body consumes oxygen is also important: during periods of rest, oxygen delivery exceeds oxygen consumption, while during periods of exercise, oxygen consumption increases. In other words, oxygen consumption is dependent upon muscle fiber metabolic requirements (Frontera & Ochala, 2015). Equally important is that the body has no storage system for oxygen (Law & Burkwirwa, 1999; Treacher & Leach, 1998). If the body is unable to extract oxygen from the environment or cannot readily use oxygen available in the bloodstream, hypoxic hypoxia develops (as opposed to anemic or carbon monoxide hypoxia) (Popel, 1989). This lack of oxygen leads to anaerobic metabolism and production of lactate, resulting in muscular fatigue, hypoxemia, and tissue ischemia (Treacher & Leach, 1998).

Skeletal Muscle Fatigue

As stated previously, muscle fatigue is a decline in performance related to muscle activity. However, other definitions have described fatigue as a decrease in contractile function; an inability to sustain a contraction; a decline in peak power; a decrease in muscle shortening force and velocity; and a delay in the rate of muscle relaxation (Allen et al., 2008; Enoka & Duchateau, 2008; Fitts, 2008; Westerblad et al., 2010). For the purposes of this paper, fatigue is

defined and examined in relation to the decline in the acceleration of the muscle fiber contraction.

Fatigue is a result of various physiological factors and can occur throughout any step of muscle contraction. Fatigue may occur centrally or peripherally. In central fatigue, impairment occurs anywhere along the path from the motor cortex to the motor neuron. Muscles generate greater amounts of force by increasing either the number of motor neurons stimulated or the firing rate of the motor neuron; when central fatigue occurs, the nerve firing rate decreases while synaptic inhibition occurs, causing the motor neurons to become less responsive to excitation (Allen et al., 2008; Fuglevand, 1996; Martin et al., 2006). In contrast, peripheral fatigue transpires within the muscle itself (Westerblad et al., 2010). The force generated by each myosin-actin cross-bridge, as well as the number of cross-bridges formed, decreases during states of fatigue (Fitts, 2008). Failure of the SR to release Ca^{2+} also creates a reduction in the rate of ATP consumption, while myofibers have a reduction in sensitivity to Ca^{2+} (Allen et al., 2008; Westerblad et al., 2010).

Although lactic acid and H^+ due to anaerobic processes have been considered one of the primary factors of fatigue, recent research has indicated these factors play a minor role in causing skeletal muscle fatigue (Allen et al., 2008; Westerblad et al., 2010). For example, a study conducted by Lamb et al. found (1993) that a reduction in muscle force was due to the movement of water to the extracellular space, rather than by lactate. A 2005 study found that decreasing the rate of H^+ accumulation in the cytosol of a frog muscle cell did not delay the onset of fatigue (Stary & Hogan, 2005). Instead, accumulated H^+, along with an increase in P_i and ADP, appears to contribute to fatigue by inhibiting the SR Ca^{2+} pumps from binding with free floating Ca^{2+} (Kent-Braun et al., 2012; Allen et al., 2008). Other research has shown that an increase in H^+

may contribute more directly to fatigue by inhibiting the force per cross-bridge of the actin-myosin cross-bridge, rather than by directly reducing the force output of the muscle fiber (Fitts, 2008).

Fatigue is additionally mediated by the production of reactive oxygen species (ROS). Multiple studies have shown that a decrease in ROS delays the onset of muscle fatigue (McKenna et al., 2006; Moopanar & Allen, 2006; Reid, 2001; Reid, 2008). Radical and non-radical ROS are produced during oxygen reduction in the electron transport chain (Ray et al., 2012). Interestingly, ROS can contribute to normal cell function, but an imbalance in prooxidants and antioxidants (i.e., oxidative stress) can lead to inflammatory response, cellular dysfunction, and diseases such as stroke, atherosclerosis, and diabetes (Forrester et al., 2018). While the site of ROS production in the muscle cell is still unclear, research has suggested it can occur in the mitochondria, SR, t-tubules, sarcolemma, and various enzymes (Powers et al., 2011). ROS production often increases during exercise, due to increased temperatures (Moopanar & Allen, 2005). However, the exact mechanisms by which ROS cause fatigue is still under debate. Previous research has suggested production of ROS may lead to damage in actin, myosin, and tropomyosin, contribute to the decreased sensitivity of Ca^{2+} in the myofibers, and alter the structure of regulatory proteins (Fitts, 2008; Reid, 2001).

Lack of oxygen supply has also been implicated in the onset of fatigue. In studies where blood flow has been occluded, muscle fatigue has developed more rapidly (Alfonsi et al., 1999; Russ & Kent-Braun, 2003). Similarly, a study that examined postural differences in subjects found that positions that restrict blood flow – thereby inducing greater intramuscular pressures and creating lower blood volumes – resulted in increased muscle fatigue (Tachi et al., 2004). This ultimately suggests that blood flow restriction, and therefore lack of oxygen, during muscle

contraction results in a greater energy cost. More specifically, when oxygen is no longer available to synthesize ATP, the body decreases the ATP demand (Lanza et al., 2006). Furthermore, different degrees of supplemental, inspired oxygen have resulted in a delayed onset of fatigue in recreationally active individuals and athletes (Amann et al., 2006; Hogan et al., 1999). Clearly, while oxygen is not the only factor that contributes to muscle performance, there is a critical level of tissue oxygenation. If this level is not met, fatigue may be exacerbated.

Mechanomyography

Multiple methods have been used to study muscle fatigue, including electromyography, transcranial magnetic stimulation, and near infrared spectroscopy (Taelman et al., 2011; Todd & Gandevia, 2003; Schillings et al., 2003). In more recent years, however, mechanomyography has been proposed as an alternative method due to the methodological limitations (i.e., cost and technical factors) of current practices (Woodward et al., 2019).

Simply put, mechanomyography (MMG) is the study of skin surface displacement due to a contracting muscle. The mechanomyogram measures the compound mechanical signal generated by the motor units (Shinohara & Søgaard, 2006). However, the MMG measurement is a reflection of the number of motor units recruited, rather than the motor unit firing rate (Ebersole & Malek, 2008). As the number of recruited motor units increases, the muscle generates a greater force. This causes a greater displacement of the skin surface and is recorded as a change in amplitude on the MMG (Shinoara & Søgaard, 2006). On the other hand, as a muscle fatigues, twitch height and the number of firing motor units decreases. This subsequently causes both a decrease in the displacement of the skin surface and the amplitude of the MMG (Shinohara & Søgaard, 2006).

Preliminary studies have examined whether MMG is an accurate method to assess muscle endurance. For instance, Willingham & McCully (2017) found that acceleration correlated with muscle torque with the use of MMG via an accelerometer. A second study conducted by McCully et al., (2018) indicated use of MMG via an accelerometer accurately evaluated muscle endurance in the lower back erector muscles. MMG has also been found to correlate with electromyography results, as well as measurements of muscle force (Akataki et al., 2001; Ebersole & Malek, 2008; Gobbo et al., 2006; Orizio et al., 1999).

Despite these promising results, MMG has not been used to examine conditions of blood flow. As discussed previously, muscle fatigue is exacerbated when oxygen is unavailable to conduct aerobic respiration. As muscle continues to fatigue, muscle fiber acceleration decreases. Theoretically, MMG should detect the decline in acceleration as a decrease in amplitude. Given these points, the current study sought to determine whether MMG is sensitive enough to distinguish between different states of blood flow, thereby detecting functional changes within the muscle.

CHAPTER III

Methodology

The proposed research design was a quantitative, interventional study. Participants were enrolled from August 2019 to December 2019. Participants underwent a series of tests that measured the acceleration of the dominant wrist extensor (extensor carpi radialis muscle) and the dominant leg dorsiflexor (tibialis anterior muscle). Muscle acceleration was assessed with complete blood flow (i.e., no occlusion) and full occlusion of blood flow for each muscle. This study was conducted with full review and approval by the Georgia State University Institutional Review Board.

Participants

Ten participants (*female = 2, male =8*) were recruited voluntarily via word of mouth and flyers posted around Georgia State University. Each participant provided written informed consent and completed a health history form (Appendix A) before participating in the study. All participants were over the age of 18 and were recreational athletes that engaged in high levels of exercise. Participants at risk for cardiovascular and musculoskeletal injury according to the American College of Sports Medicine Guidelines (Thompson et al., 2009) were excluded from the study. Pregnant women and children were also excluded from the study.

Experimental Procedures

Each participant performed a muscle acceleration test twice each for the ankle dorsiflexor and the wrist extensor. In one trial, blood flow was occluded using a commercially available tourniquet (Combat Application Tourniquet, North American Rescue: Greer, SC). Trial order was counterbalanced with half the participants performing the tourniquet trial first and the other half of participants performing the tourniquet trial second in order to counteract any testing order

bias. Participants were allowed a ten minute break between trials in order to allow the muscle to rest and recover.

During the ankle dorsiflexor muscle test, the participant lay supine with the dominant ankle secured to a metal base place via an orthopedic brace and Velcro straps. During the wrist extensor muscle test, the participant sat upright with the dominant arm extended upon a table. The wrist was secured to a metal brace via an orthopedic brace and Velcro straps. A triaxial accelerometer (Axivity A3: Axivity, Newcastle, UK) was placed on the belly of the muscle, 1/3 of the muscle length from the origin to the insertion sites for both the ankle dorsiflexor and wrist extensor muscle. In order to avoid aliasing of the twitch signal, the accelerometer began recording at 800Hz immediately after disconnection. Uni-Patch^{TM} S series electrodes (Covidien, Mansfield, MA) were placed superior and inferior to the accelerometer. A clinical electrotherapy stimulator (Vectra Genisys, Chattanooga®, Vista CA), was programmed to stimulate the muscle at 2, 4, and 6 Hz for 3 minutes each at 60mA.

Tourniquet Procedure

Once each muscle was secured properly, a tourniquet was tightened across the brachial artery and the popliteal artery in order to fully occlude blood flow in the wrist extensor and ankle dorsiflexor, respectively. Blood flow was determined to be occluded once the researcher could no longer palpate the radial arterial pulse or the dorsalis pedis arterial pulse. Each muscle was then stimulated for 2, 4, and 6 Hz for 3 minutes each at 60millimaps.

Data Analysis

After completion of each trial, recording on the accelerometer was stopped and the data was downloaded to a secured, password protected computer. Data was deidentified before analyses. Acceleration data were stored in a .CSV time series file for analyses. A program

written in Python, Jupyterlab Version 0.35.3, was used to identify the peak and trough muscle accelerations for each participant using the following formula:

$$Total\ Acceleration = \sqrt{XAcceleration^2 + YAcceleration^2 + ZAcceleration^2}$$

These accelerations were then saved to a new .CSV file for further comparisons. Minimum twitch height was subtracted from the peak height to ascertain the individual peak to peak height. Each subject's peak to peak analysis was normalized to the peak acceleration for each blood flow trial. This was done for each stimulation frequency in order to perform a comparison between trials. A repeated measures analysis of variance (ANOVA) was performed with stimulation frequency (2Hz, 4Hz, 6Hz) used as the within factor and trial (normal blood flow and full occlusion) as the between factor. A separate ANOVA was performed using trial order as the between factor to test whether the ordering of the trials affected the outcome. If a difference was detected, a main effects test with Bonferroni correction was performed in order to determine when the differences occurred.

CHAPTER IV

Results

The purpose of this study was to determine whether accelerometer based mechanomyography could detect functional changes in the muscle (i.e., level of muscle twitch height) by simulating different conditions of blood flow to the muscle. This research study explored patterns of twitch height among different stimulation frequencies in the dominant ankle dorsiflexor and dominant wrist extensor muscles. The results are presented in this chapter. Descriptive statistical analyses are included.

Research Hypotheses

1. Poorly perfused muscles will have decreased muscle twitch accelerations compared to adequately perfused muscles.
2. Decreases in poorly perfused muscle twitch accelerations will appear at lower stimulation frequencies compared to adequately perfused muscles.

Descriptive Data

Age of participants ranged from 23 to 46 years (M = 33.6, SD = 8.42). Height, weight, and body mass index (BMI) means and standard deviations are presented in Table 1.

Table 1. Height, weight, Body Mass Index (BMI), and sex of participants (n = 10)

	Mean or %	Standard Dev
Height (cm)	178.56	11. 67
Weight (kg)	83.5	20.06
BMI	25.80	3.34
Female	20%	-
Male	80%	-

Ankle Dorsiflexor

Statistical analyses indicated muscle twitch height in the occluded blood flow trial was decreased by 0.515 ± 0.198*g* compared to the normal blood flow trial ($p = 0.018$). Specifically, the twitch height in the occluded blood flow trial was significantly lower than the twitch height in the normal blood flow trial throughout the 2Hz, 4Hz, and 6Hz stimulation frequencies (Figure 1).

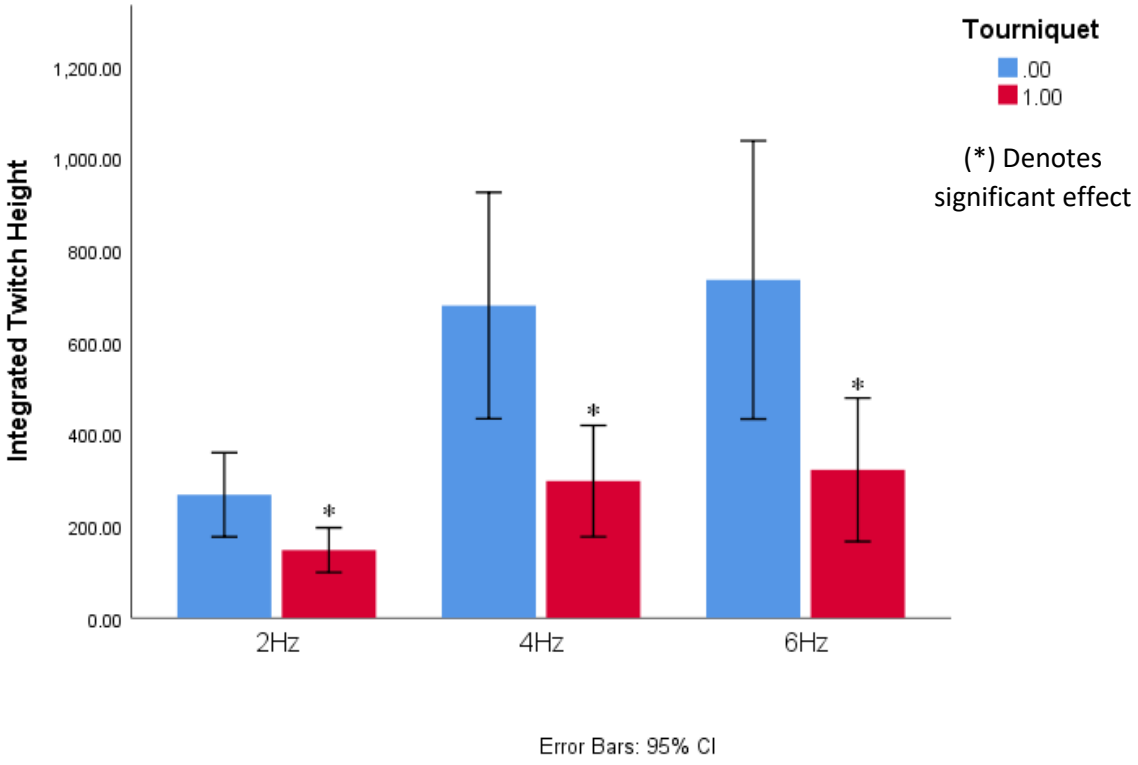

Figure 1. Comparison of Mean Muscle Twitch Accelerations in Non-Occlusion vs. Full Occlusion Trials in the Ankle Dorsiflexor.

Wrist Extensor

Statistical analyses revealed muscle twitch height in the occluded blood flow trial was decreased by 0.944 ± 0.188*g* compared to the normal blood flow trial ($p < 0.001$). Occluded

blood flow trial muscle twitch height was significantly lower than the twitch height in the normal blood flow trial throughout the 4Hz and 6Hz stimulation frequencies (Figure 2).

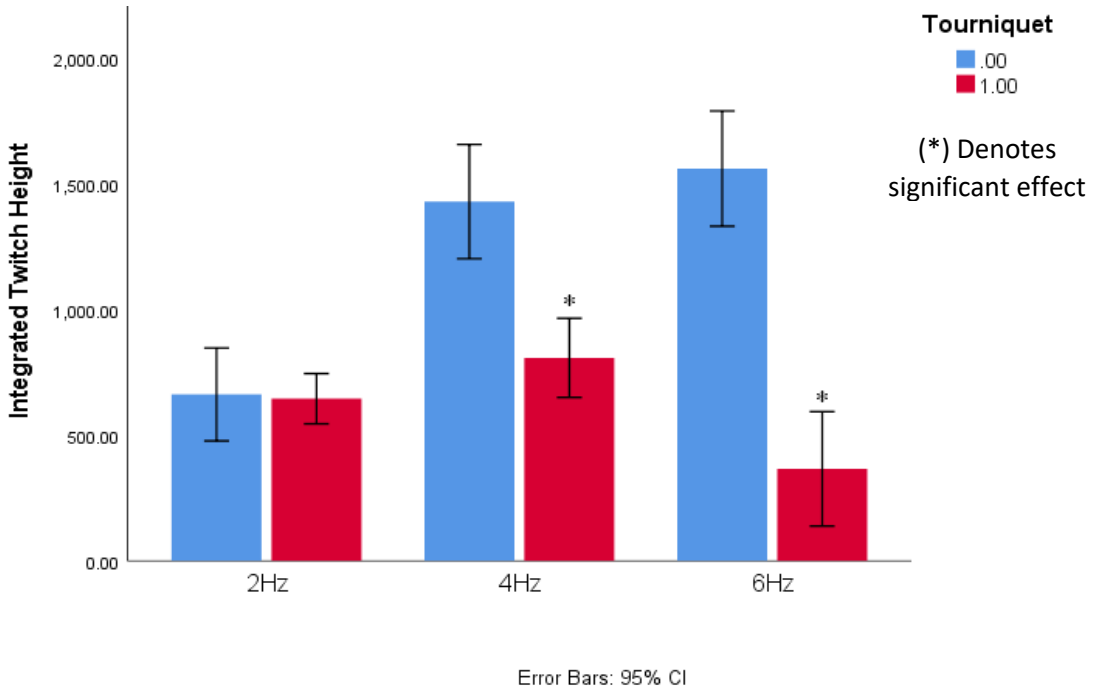

Figure 2. Comparison of Mean Muscle Twitch Accelerations in Non-Occlusion vs. Full Occlusion Trials in the Wrist Extensor.

Comparison between Muscle Groups.

Statistical analyses indicated that compared to the muscle twitch accelerations in the wrist extensor normal blood flow trial, the muscle twitch accelerations in the ankle dorsiflexor were decreased by 1.173± 0.242*g* ($p < 0.001$). However, after normalizing the data, differences were eliminated between the ankle dorsiflexor and wrist extensor muscle twitch accelerations ($p = 0.401$).

Statistical analyses indicated that compared to the muscle twitch accelerations in the wrist extensor occluded blood flow trial, the muscle twitch accelerations in the wrist extensor were decreased by $0.744 \pm 0.130g$ ($p < 0.001$). However, differences between the ankle dorsiflexor and wrist extensor muscle twitch accelerations were no longer significant after the 4Hz stimulation frequency.

CHAPTER V

Discussion

As mentioned previously, the focus of this study was to ascertain whether accelerometer based muscle mechanomyography could discriminate between different levels of muscle twitch accelerations, and therefore detect functional changes within the muscle. Overall, poorly perfused muscles (i.e., muscles with occluded blood flow) had decreased muscle twitch accelerations compared to muscles with normal perfusion (i.e., muscles with full blood flow). This indicates that accelerometer based muscle mechanomyography is sensitive enough to detect changes in blood flow.

Prior researched has found that occluding blood flow has enhanced fatigue during voluntary and stimulated contractions (Broxterman et al., 2015; Cole & Brown, 2000; Royce, 1958). In a 2000 study conducted by Cole & Brown, significant fatigue occurred after five minutes of contractions, even when the blood flow was only partially occluded. In the current study, application of a tourniquet to occlude blood flow above the elbow resulted in significantly lower muscle twitch heights compared to normal blood flow, indicating greater muscle fatigue. In contrast, application of the tourniquet to occlude blood flow above the knee resulted in overall decreases of muscle twitch heights but failed to enhance true fatigue. These discrepancies could be a result of the different levels of stimulation: in the current study, relatively low levels of stimulation were used (60mA), compared to the high levels used (200-300mA) in Cole & Brown (2000).

Previous research has also found that different patterns of muscle twitch heights occur between different muscles while using this technique. In one recent study, Willingham & McCully (2017) found significantly greater rates of fatigue in the forearm muscle when it was

compared against the calf muscle. And in two further studies, differences in muscle fatigue were found among the erector spinae, trapezius muscles, vastus lateralis, and wrist flexors, with the erector spinae and trapezius muscles having significantly greater amounts of fatigue compared to the vastus lateralis and wrist flexors (McCully et al., 2019; McCully et al., 2018). In the current study, differences in muscle twitch height were found between the ankle dorsiflexor and wrist extensor during the occluded blood flow trial. Muscle twitch height in the ankle dorsiflexor was significantly lower across all stimulation frequencies, while muscle twitch height in the wrist extensor was significantly decreased only during the 4Hz and 6Hz stimulation frequencies. Findings also indicated ankle dorsiflexor twitch height was lower than wrist extensor twitch height during the normal blood flow trial. Yet when data were normalized, these differences were no longer significant. These discrepancies may be attributed to the physiological makeup of each muscle group. The ankle dorsiflexor is composed of a greater number of type I and type IIA muscle fibers, while the wrist extensor is composed of a greater number of type IIx muscle fibers (Green et al., 2015; Hata et al., 2019; Rodrigues et al., 1994). As mentioned previously, type I and type IIA fibers have higher aerobic capacities, while type IIx fibers have higher anaerobic capacities (Herbison et al., 1982; Talbot & Maves, 2016). By occluding blood flow, the ankle dorsiflexor may have depleted its aerobic and anerobic energy stores faster than the wrist extensor.

Significant Limitations

Significant limitations were considered in the current study. First, this study used a small, limited sample size comprised of mostly males (80%). Second, because we intentionally sought to include recreationally athletic individuals, and despite our efforts to simulate clinical conditions in participants, the observed results of the study may not generalize to clinically

relevant populations. Third, occlusion of blood flow was subjectively determined by palpation; intra-rater and inter-rate reliability were not examined in this study.

Recommendations for Future Research

Future research in the area of accelerometer based mechanomyography should be conducted. Mechanomyography is cost effective and can be used on sedated or unresponsive patients. A controlled, randomized in vivo study should be conducted on clinically relevant populations. In addition, other data parameters, such as muscle contraction time frame, or time to peak muscle acceleration during stimulation, should be considered. Future studies should also consider using an objective measure, such as a doppler ultrasound, to determine when blood flow is fully occluded. Furthermore, analyses should examine whether muscle twitch height or other similar parameters differ between males and females or among different age groups.

Conclusion

Current diagnostic procedures for muscle fatigue and atrophy are limited. This study serves to highlight a new, alternative procedure for diagnosis. Outcomes of this study indicate accelerometer measured muscle fatigue is capable of detecting differences between normal and occluded blood flow states. Future research should be conducted on accelerometer based mechanomyography in order to ameliorate, treat, and prevent muscle weakness. Future research should additionally ascertain whether differences exist in morbidity, morality, and quality of life when patients receive no intervention, early intervention, and late intervention for muscle weakness.

REFERENCES

Anekwe, D., Biswas, S., Bussières, A., & Spahija, J. (2019). Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: A systematic review and meta-analysis. *Physiotherapy, 107*, 1-10.

Akataki, K., Mita, K., Watakabe, M., & Itoh, K. (2001). Mechanomyogram and force relationship during voluntary isometric ramp contractions of the biceps brachii muscle. *European Journal of Applied Physiology, 84***,** 19–25 (2001). https://doi.org/10.1007/s004210000321

Alfonsi, E., Pavesi, R., Merlo, I. M., Gelmetti, A., Zambarbieri, D., Lago, P., Arrigo, A., Reggiani, C., & Moglia, A. (1999). Hemoglobin near-infrared spectroscopy and surface EMG study in muscle ischaemia and fatiguing isometric contraction. *The Journal of sports medicine and physical fitness*, *39*(2), 83–92.

Allen, D. G., Lamb, G. D., & Westerblad, H. (2008). Skeletal muscle fatigue: cellular mechanisms. *Physiological reviews*, *88*(1), 287–332. https://doi.org/10.1152/physrev.00015.2007

Amann, M., Romer, L. M., Pegelow, D. F., Jacques, A. J., Hess, C. J., & Dempsey, J. A. (2006). Effects of arterial oxygen content on peripheral locomotor muscle fatigue. *Journal of applied physiology (Bethesda, Md. : 1985)*, *101*(1), 119–127.

Angus, D. C., Linde-Zwirble, W. T., Sirio, C. A., Rotondi, A. J., Chelluri, L., Newbold, R. C., 3rd, Lave, J. R., & Pinsky, M. R. (1996). The effect of managed care on ICU length of stay: implications for medicare. *JAMA*, *276*(13), 1075–1082.

Bigland-Ritchie, B., & Woods, J. (1984). Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle & Nerve, 7*(9), 691-699.

Bohannon, R. W. (2019). Considerations and Practical Options for Measuring Muscle Strength: A Narrative Review. *BioMed Research International, 2019*, 8194537. https://doi.org/10.1155/2019/8194537

Bonora, M., Patergnani, S., Rimessi, A., De Marchi, E., Suski, J. M., Bononi, A., Giorgi, C., Marchi, S., Missiroli, S., Poletti, F., Wieckowski, M. R., & Pinton, P. (2012). ATP synthesis and storage. *Purinergic signalling*, *8*(3), 343–357. https://doi.org/10.1007/s11302-012-9305-8

Broxterman, R., Craig, J., Smith, J., Wilcox, S., Jia, C., Warren, S., & Barstow, T. (2015). Influence of blood flow occlusion on the development of peripheral and central fatigue during small muscle mass handgrip exercise. *The Journal of Physiology, 593*(17), 4043-4054.

Calderón, J. C., Bolaños, P., & Caputo, C. (2014). The excitation-contraction coupling mechanism in skeletal muscle. *Biophysical reviews*, *6*(1), 133–160. https://doi.org/10.1007/s12551-013-0135-x

Camdessanché, J.P., Convers, P., & Antoine, J.C. (2006). Advantages and limitations of electroneuromyography for analysis of upper limb pain. *Presse medicale, 35*(4), 584-586.

Chen, Y. C., Sumandea, M. P., Larsson, L., Moss, R. L., & Ge, Y. (2015). Dissecting human skeletal muscle troponin proteoforms by top-down mass spectrometry. *Journal of muscle research and cell motility*, *36*(2), 169–181. https://doi.org/10.1007/s10974-015-9404-6

Ciesla, N., Dinglas, V., Fan, E., Kho, M., Kuramoto, J., & Needham, D. (2011). Manual muscle testing: a method of measuring extremity muscle strength applied to critically ill patients. *Journal of visualized experiments: JoVE*, (50), 2632. https://doi.org/10.3791/2632

Cole, M., & Brown, M. (2000). Response of the human triceps surae muscle to electrical stimulation during varying levels of blood flow restriction. *European Journal of Applied Physiology, 82*(1-2), 39-44.

Davies, C. W., Jones, D. M., & Shearer, J. R. (1984). Hand grip – a simple test for morbidity after fracture of the neck of femur. *Journal of the Royal Society of Medicine, 77*(10), 833–836. https://doi.org/10.1177/014107688407701006

Ebersole, K. T., & Malek, D. M. (2008). Fatigue and the electromechanical efficiency of the vastus medialis and vastus lateralis muscles. *Journal of athletic training, 43*(2), 152–156. https://doi.org/10.4085/1062-6050-43.2.152

Ely, E.W., Shintani, A., Truman, B., Speroff, T., Gordon, S.M., Harrell, F.E., Inouye, S.K., Bernard, G.R., & Dittus, R.S. (2004). Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Journal of the American Medical Association,* 291, 1753-1762.

Enoka, R. M., & Duchateau, J. (2008). Muscle fatigue: what, why and how it influences muscle function. *The Journal of physiology*, *586*(1), 11–23. https://doi.org/10.1113/jphysiol.2007.139477

Evangelopoulos, M.E., Humpert, S., & Rösler, K.M. (2017). Ultrasound-Guided Electrodes for Conduction Studies of the Saphenous Nerve. *Journal of Clinical Neurophysiology, 34*(3), 243-247.

Falagas, M. E., & Kasiakou, S. K. (2006). Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Critical care (London, England), 10*(1), R27. https://doi.org/10.1186/cc3995

Fan, E., Cheek, F., Chlan, L., Gosselink, R., Hart, N., Herridge, M.S., Hopkins, R.O., Hough, C.L., Kress, J.P., Latronico, N., Moss, M., Needham, D.M., Rich, M.M., Stevens, R.D., Wilson, K.C., Winkelman, C., Zochodne, D.W., & Ali, N.A. (2014). An official American thoracic society clinical practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *American Journal of Respiratory and Critical Care Medicine, 190*(12), 1437-1446. doi:10.1164/rccm.201411-2011ST

Fitts, R. H. (2008). The cross-bridge cycle and skeletal muscle fatigue. *Journal of applied physiology (Bethesda, Md. : 1985), 104*(2), 551–558. https://doi.org/10.1152/japplphysiol.01200.2007

Forrester, S. J., Kikuchi, D. S., Hernandes, M. S., Xu, Q., & Griendling, K. K. (2018). Reactive Oxygen Species in Metabolic and Inflammatory Signaling. *Circulation research*, *122*(6), 877–902. https://doi.org/10.1161/CIRCRESAHA.117.311401

Frontera, W.R., & Ochala, J. (2015). Skeletal muscle: a brief review of structure and function. *Calcified Tissue International, 96*, 183-195. doi: 10.1007/s00223-014-9915-y

Fuglevand, A. J. (1996). Neural Aspects of Fatigue. *The Neuroscientist*, *2*(4), 203–206. https://doi.org/10.1177/107385849600200407

Fuller, G. (2005). How to get the most out of nerve conduction studies and electromyography. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76 Suppl 2*(Suppl 2), ii41–ii46. https://doi.org/10.1136/jnnp.2005.067355

Gash, M.C., Kandle, P.F., Murray, I., & Varacallo, M. (2020). Physiology, Muscle Contraction. *StatPearls Publishing* [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK537140/

Geeves, M. A., & Holmes, K. C. (1999). Structural mechanism of muscle contraction. *Annual review of biochemistry*, *68*, 687–728. https://doi.org/10.1146/annurev.biochem.68.1.687

Gobbo, M., Cè, E., Diemont, B., Esposito, F., & Orizio, C. (2006). Torque and surface mechanomyogram parallel reduction during fatiguing stimulation in human muscles. *European journal of applied physiology*, *97*(1), 9–15. https://doi.org/10.1007/s00421-006-0134-8

Grazi E. (2010). Muscle mechanism: The acceleration of the load. *Archives of biochemistry and biophysics*, *504*(2), 204–209. https://doi.org/10.1016/j.abb.2010.09.004

Green, H., Ranney, D., Burnett, M., Iqbal, S., Kyle, N., Lounsbury, D., Ouyang, J., Tupling, R., Smith, I.C., Stewart, R., & Tick, H. (2015). Cellular properties of extensor carpi radialis brevis and trapezius muscles in healthy males and females. *Canadian Journal of Physiology and Pharmacology*, *93*(11), 953-966.

Hashem, M. D., Parker, A. M., & Needham, D. M. (2016). Early Mobilization and Rehabilitation of Patients Who Are Critically Ill. *Chest*, *150*(3), 722–731. https://doi.org/10.1016/j.chest.2016.03.003

Hara, K. Y., & Kondo, A. (2015). ATP regulation in bioproduction. *Microbial cell factories*, *14*, 198. https://doi.org/10.1186/s12934-015-0390-6

Hata, J., Nakashima, D., Tsuji, O., Fujiyoshi, K., Yasutake, K., Sera, Y., Komaki, Y., Hikishima, K., Nagura, T., Matsumoto, M., Okano, H., & Nakamura, M. (2019). Noninvasive technique to evaluate the muscle fiber characteristics using q-space imaging. *PlosONe*, *4*(14), e0214805.

Herbison, G., Jaweed, M., & Ditunno, J. (1982). Muscle fiber types. *Archives of Physical Medicine and Rehabilitation*, *63*(5), 227-230.

Hermans, G., & Van den Berghe, G. (2015). Clinical review: intensive care unit acquired weakness. *Critical care (London, England), 19*(1), 274. https://doi.org/10.1186/s13054-015-0993-7

Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., Casaer, M.P., Meersseman, P., Debaveye, Y., Van Cromphaut, S., Wouters, P.J., Gosselink, R., & Van de Berghe, G. (2014). Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *American Journal of Respiratory and Critical Care Medicine, 190*(4), 410-420.

Hogan, M. C., Richardson, R. S., & Haseler, L. J. (1999). Human muscle performance and PCr hydrolysis with varied inspired oxygen fractions: a 31P-MRS study. *Journal of applied physiology (Bethesda, Md. : 1985), 86*(4), 1367–1373. https://doi.org/10.1152/jappl.1999.86.4.1367

Hough, C.L., Lieu, B.K., & Caldwell, E.S. (2011). Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Critical Care, 15*(1), R43.

Hough, C. L., & Herridge, M. S. (2012). Long-term outcome after acute lung injury. *Current Opinion in Critical Care*, *18*(1), 8–15. https://doi.org/10.1097/MCC.0b013e32834f186d

Ibitoye, M., Hamzaid, N., Zuniga, J., & Abdul Wahab, A. (2014). Mechanomyography and muscle function assessment: A review of current state and prospects. *Clinical Biomechanics, 29*(6), 691-704.

Jang, M. H., Shin, M. J., & Shin, Y. B. (2019). Pulmonary and Physical Rehabilitation in Critically Ill Patients. *Acute and critical care*, *34*(1), 1–13. https://doi.org/10.4266/acc.2019.00444

Jolley, S.E., Bunnell, A.E., & Hough, C.L. (2016). ICU-acquired weakness. *Chest, 50*(5), 1129-1140.

Kane, N.M., & Oware, A. (2012). Nerve conduction and electromyography studies. *Journal of Neurology, 259*(7), 1502-1508.

Kent-Braun, J. A., Fitts, R. H., & Christie, A. (2012). Skeletal muscle fatigue. *Comprehensive Physiology*, *2*(2), 997–1044. https://doi.org/10.1002/cphy.c110029

Koukourikos, K., Tsaloglidou, A., & Kourkouta, L. (2014). Muscle atrophy in intensive care unit patients. *Acta informatica medica: Journal of the Society for Medical Informatics of Bosnia & Herzegovina: casopis Drustva za medicinsku informatiku BiH*, *22*(6), 406–410. https://doi.org/10.5455/aim.2014.22.406-410

Kress, J.P., & Hall, J.B. (2014). ICU-acquired weakness and recovery from critical illness. *New England Journal of Medicine, 370*, 1626-1635. doi: 10.1056/NEJMra1209390

Kural, M.A., Pugdahl, K., Fuglsang-Frederiksen, A., Andersen, H., & Tankisi, H. (2016). Near-Nerve Needle Technique Versus Surface Electrode Recordings in Electrodiagnosis of Diabetic Polyneuropathy. *Journal of Clinical Neurophysiology*, *33*(4), 346-349.

Kuo, I. Y., & Ehrlich, B. E. (2015). Signaling in muscle contraction. *Cold Spring Harbor perspectives in biology*, *7*(2), a006023. https://doi.org/10.1101/cshperspect.a006023

Lamb, G. D., Stephenson, D. G., & Stienen, G. J. (1993). Effects of osmolality and ionic strength on the mechanism of Ca2+ release in skinned skeletal muscle fibres of the toad. *The Journal of physiology*, *464*, 629–648. https://doi.org/10.1113/jphysiol.1993.sp019655

Lanner, J. T., Georgiou, D. K., Joshi, A. D., & Hamilton, S. L. (2010). Ryanodine receptors: structure, expression, molecular details, and function in calcium release. *Cold Spring*

Harbor perspectives in biology, *2*(11), a003996. https://doi.org/10.1101/cshperspect.a003996

Lanza, I. R., Wigmore, D. M., Befroy, D. E., & Kent-Braun, J. A. (2006). In vivo ATP production during free-flow and ischaemic muscle contractions in humans. *The Journal of physiology*, *577*(Pt 1), 353–367. https://doi.org/10.1113/jphysiol.2006.114249

Latronico, N., Shehu, I., & Guarneri, B. (2009). Use of electrophysiologic testing. *Critical Care Medicine*, *37*(10 Suppl), S316–S320. https://doi.org/10.1097/CCM.0b013e3181b6f9f3

Law, R., & Bukwirwa, H. (1999). The physiology of oxygen delivery. *Update in Anaesthesia, 10*, 20-25.

Lieber, R. L., Roberts, T. J., Blemker, S. S., Lee, S., & Herzog, W. (2017). Skeletal muscle mechanics, energetics and plasticity. *Journal of neuroengineering and rehabilitation*, *14*(1), 108. https://doi.org/10.1186/s12984-017-0318-y

Lynch, G.S., Schertzer, J.D., & Ryall, J.G. (2007). Therapeutic approaches for muscle wasting disorders. *Pharmacology & Therapeutics, 113*(3), 461-487.

Mafi, P., Mafi, R., Hindocha, S., Griffin, M., & Khan, W. (2012). A systematic review of dynamometry and its role in hand trauma assessment. *The Open Orthopaedics Journal*, *6*, 95–102. https://doi.org/10.2174/1874325001206010095

MacIntyre, N., Epstein, S., Carson, S., Scheinhorn, D., Christopher, K., & Muldoon, S. (2005). Management of patients requiring prolonged mechanical ventilation: Report of a NAMDRC consensus conference. *Chest, 128*(6), 3937-3954.

Martin, P. G., Smith, J. L., Butler, J. E., Gandevia, S. C., & Taylor, J. L. (2006). Fatigue-sensitive afferents inhibit extensor but not flexor motoneurons in humans. *The Journal of*

neuroscience : the official journal of the Society for Neuroscience, *26*(18), 4796–4802. https://doi.org/10.1523/JNEUROSCI.5487-05.2006

McCully, K.K, Moraes, C., Patel, S.V., Green, M., & Willingham, T.B. (2019). Muscle-Specific Endurance of the Lower Back Erectors Using Electrical Twitch Mechanomyography. *Journal of Functional Morphology and Kinesiology, 4*(1), 12.

McCully, K. K., Prins, P., Mistry, K., & Willingham, T. B. (2018). Muscle-specific endurance of the trapezius muscles using electrical twitch mechanomyography. *Shoulder & Elbow*, *10*(2), 136–143. https://doi.org/10.1177/1758573217726269

McKenna, M. J., Medved, I., Goodman, C. A., Brown, M. J., Bjorksten, A. R., Murphy, K. T., Petersen, A. C., Sostaric, S., & Gong, X. (2006). N-acetylcysteine attenuates the decline in muscle Na+,K+-pump activity and delays fatigue during prolonged exercise in humans. *The Journal of physiology*, *576*(Pt 1), 279–288. https://doi.org/10.1113/jphysiol.2006.115352

Medical Research Council. (1976). *Aids to the Investigation of the Peripheral Nervous System*. London: Her Majesty's Stationary Office.

Moopanar, T. R., & Allen, D. G. (2005). Reactive oxygen species reduce myofibrillar Ca2+ sensitivity in fatiguing mouse skeletal muscle at 37 degrees C. *The Journal of physiology*, *564*(Pt 1), 189–199. https://doi.org/10.1113/jphysiol.2005.083519

Moopanar, T. R., & Allen, D. G. (2006). The activity-induced reduction of myofibrillar Ca2+ sensitivity in mouse skeletal muscle is reversed by dithiothreitol. *The Journal of physiology*, *571*(Pt 1), 191–200. https://doi.org/10.1113/jphysiol.2005.101105

Morris, C., & Trinder, J. T. (2002). Electrophysiology adds little to clinical signs in critical illness polyneuropathy and myopathy. *Critical Care Medicine*, *30*(11), 2612. https://doi.org/10.1097/00003246-200211000-00048

Mukhopadhyay, A., Tai, B. C., See, K. C., Ng, W. Y., Lim, T. K., Onsiong, S., Ee, S., Chua, M. J., Lee, P. R., Loh, M. L., & Phua, J. (2014). Risk factors for hospital and long-term mortality of critically ill elderly patients admitted to an intensive care unit. *BioMed research international*, *2014*, 960575. https://doi.org/10.1155/2014/960575

Mukund, K., & Subramaniam, S. (2020). Skeletal muscle: A review of molecular structure and function, in health and disease. *Wiley interdisciplinary reviews. Systems biology and medicine*, *12*(1), e1462. https://doi.org/10.1002/wsbm.1462

Nanas, S., Kritikos, K., Angelopoulos, E., Siafaka, A., Tsikriki, M., Poriazi, D., Kontogeorgi, M., Pratikaki, M., Zervakis, D., Routsi, C., & Roussos, C. (2008). Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. *Acta Neurologica Scandinavica*, *118*(3), 175-181.

Naqvi, U., & Sherman, A. L. (2019). Muscle Strength Grading. In *StatPearls*. StatPearls Publishing.

Novak, K. R., Nardelli, P., Cope, T. C., Filatov, G., Glass, J. D., Khan, J., & Rich, M. M. (2009). Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. *The Journal of Clinical Investigation*, *119*(5), 1150–1158. https://doi.org/10.1172/jci36570

Orizio, C., Diemont, B., Esposito, F., Alfonsi, E., Parrinello, G., Moglia, A., & Veicsteinas, A. (1999). Surface mechanomyogram reflects the changes in the mechanical properties of

muscle at fatigue. *European Journal of Applied Physiology and Occupational Physiology*, *80*(4), 276-284. https://doi.org/10.1007/s004210050593

O'Shea, S., Taylor, N., & Paratz, J. (2007). Measuring muscle strength for people with chronic obstructive pulmonary disease: Retest reliability of hand-held dynamometry. *Archives of Physical Medicine and Rehabilitation, 88*(1), 32-36.

Popel, A. S. (1989). Theory of oxygen transport to tissue. *Critical reviews in biomedical engineering*, *17*(3), 257–321.

Potvin, J. R., & Fuglevand, A. J. (2017). A motor unit-based model of muscle fatigue. *PLoS computational biology*, *13*(6), e1005581. https://doi.org/10.1371/journal.pcbi.1005581

Powers, S. K., Ji, L. L., Kavazis, A. N., & Jackson, M. J. (2011). Reactive oxygen species: impact on skeletal muscle. *Comprehensive Physiology*, *1*(2), 941–969. https://doi.org/10.1002/cphy.c100054

Ray, P. D., Huang, B. W., & Tsuji, Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cellular signaling*, *24*(5), 981–990. https://doi.org/10.1016/j.cellsig.2012.01.008

Reid M. B. (2008). Free radicals and muscle fatigue: Of ROS, canaries, and the IOC. *Free radical biology & medicine*, *44*(2), 169–179. https://doi.org/10.1016/j.freeradbiomed.2007.03.002

Reid M. B. (2001). Invited Review: redox modulation of skeletal muscle contraction: what we know and what we don't. *Journal of applied physiology (Bethesda, Md. : 1985)*, *90*(2), 724–731. https://doi.org/10.1152/jappl.2001.90.2.724

Rich, M. M., & Pinter, M. J. (2003). Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. *The Journal of Physiology*, *547*(Pt 2), 555–566. https://doi.org/10.1113/jphysiol.2002.035188

Roberts, T. J., & Marsh, R. L. (2003). Probing the limits to muscle-powered accelerations: lessons from jumping bullfrogs. *The Journal of experimental biology*, *206*(Pt 15), 2567–2580. https://doi.org/10.1242/jeb.00452

Rodrigues, A., Silva M dal, D., & Pai, V. (1994). Distribution of different fibre types of M. extensor carpi radialis longus of the rat. *Anatomia, Histologia, Embryologia: Journal of the World Association of Veterinary Anatomists, 23*(4), 352-356.

Roman, W., & Gomes, E. R. (2018). Nuclear positioning in skeletal muscle. *Seminars in cell & developmental biology*, *82*, 51–56. https://doi.org/10.1016/j.semcdb.2017.11.005

Royce, J. (1958). Isometric fatigue curves in human muscle with normal and occluded circulation. *Research Quarterly American Association for Health, Physical Education and Recreation, 29*(2), 204-212.

Russ, D. W., & Kent-Braun, J. A. (2003). Sex differences in human skeletal muscle fatigue are eliminated under ischemic conditions. *Journal of applied physiology (Bethesda, Md. : 1985)*, *94*(6), 2414–2422. https://doi.org/10.1152/japplphysiol.01145.2002

Samosawala, N. R., Vaishali, K., & Kalyana, B. C. (2016). Measurement of muscle strength with handheld dynamometer in Intensive Care Unit. *Indian Journal of Critical Care Medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 20*(1), 21–26. https://doi.org/10.4103/0972-5229.173683

Schillings, M. L., Hoefsloot, W., Stegeman, D. F., & Zwarts, M. J. (2003). Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. *European*

journal of applied physiology, *90*(5-6), 562–568. https://doi.org/10.1007/s00421-003-0913-4

Schweickert, W. D., & Hall, J. (2007). ICU-acquired weakness. *Chest*, *131*(5), 1541–1549. https://doi.org/10.1378/chest.06-2065

Sharshar, T., Bastuji-Garin, S., Stevens, R. D., Durand, M. C., Malissin, I., Rodriguez, P., Cerf, C., Outin, H., De Jonghe, B., & Groupe de Réflexion et d'Etude des Neuromyopathies En Réanimation (2009). Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Critical care medicine*, *37*(12), 3047–3053. https://doi.org/10.1097/CCM.0b013e3181b027e9

Shinohara, M., & Søgaard, K. (2006). Mechanomyography for studying force fluctuations and muscle fatigue. *Exercise and Sport Sciences Reviews*, *34*(2), 59-64.

Sidiras, G., Patsaki, I., Karatzanos, E., Dakoutrou, M., Kouvarakos, A., Mitsiou, G., Routsi, C., Stranjalis, G., Nanas, S., & Gerovasili, V. (2019). Long term follow-up of quality of life and functional ability in patients with ICU acquired Weakness - A post hoc analysis. *Journal of Critical Care*, *53*, 223–230. https://doi.org/10.1016/j.jcrc.2019.06.022

Taelman, J., Vanderhaegen, J., Robijns, M., Naulaers, G., Spaepen, A., & Van Huffel, S. (2011). Estimation of muscle fatigue using surface electromyography and near-infrared spectroscopy. *Advances in experimental medicine and biology*, *701*, 353–359. https://doi.org/10.1007/978-1-4419-7756-4_48

Tachi, M., Kouzaki, M., Kanehisa, H., & Fukunaga, T. (2004). The influence of circulatory difference on muscle oxygenation and fatigue during intermittent static dorsiflexion. *European Journal of Applied Physiology, 91*, 682-699. Doi: 10.1007/s00421-003-1024-y

Talbot, J., & Maves, L. (2016). Skeletal muscle fiber type: using insights from muscle developmental biology to dissect targets for susceptibility and resistance to muscle disease. *Wiley interdisciplinary reviews. Developmental Biology*, *5*(4), 518–534. https://doi.org/10.1002/wdev.230

Tarata, M.T. (2003). Mechanomyography versus electromyography in monitoring the muscular fatigue. *Biomedical Engineering Online, 2*, 3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC443861/

Tavee, J. (2019). Nerve conduction studies: basic concepts. *Handbook of Clinical Neurology, 160*, 217-224.

Thompson, W.R., Gordon, N.F., & Pescatello, L.S. (2009). *ACSM's guidelines for exercise testing and prescription*. Hubsta Ltd.

Todd, G., Taylor, J. L., & Gandevia, S. C. (2003). Measurement of voluntary activation of fresh and fatigued human muscles using transcranial magnetic stimulation. *The Journal of physiology*, *551*(Pt 2), 661–671. https://doi.org/10.1113/jphysiol.2003.044099

Toyoda, Y., & Saitoh, S. (2015). Adaptive regulation of glucose transport, glycolysis and respiration for cell proliferation. *Biomolecular concepts*, *6*(5-6), 423–430. https://doi.org/10.1515/bmc-2015-0018

Treacher, D. F., & Leach, R. M. (1998). Oxygen transport-1. Basic principles. *BMJ (Clinical research ed.)*, *317*(7168), 1302–1306. https://doi.org/10.1136/bmj.317.7168.1302

Trojaborg, W. (2006). Electrophysiologic techniques in critical illness-associated weakness. *Journal of the Neurological Sciences, 242*(1-2), 83–85. https://doi.org/10.1016/j.jns.2005.11.019

Wadsworth, C., Nielsen, D., Corcoran, D., Phillips, C., & Sannes, T. (1992). Interrater reliability of hand-held dynamometry: Effects of rater gender, body weight, and grip strength. *The Journal of Orthopaedic and Sports Physical Therapy., 16*(2), 74-81.

Westerblad, H., Bruton, J., & Katz, A. (2010). Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability. *Experimental Cell Research., 316*(18), 3093-3099.

Wieske, L., Dettling-Ihnenfeldt, D. S., Verhamme, C., Nollet, F., van Schaik, I. N., Schultz, M. J., Horn, J., & van der Schaaf, M. (2015). Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. *Critical Care (London, England)*, *19*(1), 196. https://doi.org/10.1186/s13054-015-0937-2

Wieske, L., Witteveen, E., Verhamme, C., Dettling-Ihnenfeldt, D.S., van der Schaaf, M., Schultz, M.J., van Schaik, I.N., & Horn, J. (2014). Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study. *PLoS One*, *9*(10), e111259. doi:10.1371/journal.pone.0111259

Willingham, T.B., & McCully, K.K. (2017). Assessment of skeletal muscle endurance using twitch electrical stimulation and accelerometer-based mechanomyography. *Advances in Skeletal Muscle Function Assessment, 1*(2), 14-20.

Wischmeyer, P. E., & San-Millan, I. (2015). Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. *Critical Care (London, England), 19 Suppl 3*(Suppl 3), S6. https://doi.org/10.1186/cc14724

Woodward, R. B., Stokes, M. J., Shefelbine, S. J., & Vaidyanathan, R. (2019). Segmenting Mechanomyography Measures of Muscle Activity Phases Using Inertial Data. *Scientific reports*, *9*(1), 5569. https://doi.org/10.1038/s41598-019-41860-4

Yang, S. H., & Liu, R. (2016). For the pursuit of oxygen and carbon dioxide channels in mitochondria. *Medical gas research*, *6*(4), 237–238. https://doi.org/10.4103/2045-9912.196908

Yang, T., Li, Z., Jiang, L., Wang, Y., & Xi, X. (2018). Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. *Acta Neurologica Scandinavica*, *38*(2), 104-114.

Zierath, J. R., & Hawley, J. A. (2004). Skeletal muscle fiber type: influence on contractile and metabolic properties. *PLoS biology*, *2*(10), e348. https://doi.org/10.1371/journal.pbio.0020348

APPENDIX A

Applied Physiology Laboratory
Department of Respiratory Therapy
Georgia State University

Health History

All information given is personal and confidential. The information will enable us to better understand you and your health and fitness habits.

Name_____Date_____

Address_____

Home Phone_____

City/State_____

Zip Code_____

Email_____

Occupation_____

Other Phone_____

Birth
Date_____Gender_____Height_____Weight_____Ethnicity_____

****

I. Signs and Symptoms

****

Have you ever experienced any of the following:

(please circle yes or no)

yes no 1. Pain, discomfort, tightness or numbness in the chest, neck, jaw or arms.

yes no 2. Shortness of breath at rest or with mild exertion.

yes no 3. Dizziness or fainting.

yes no 4. Difficult, labored or painful breathing during the day or at night.

yes no 5. Ankle swelling.

yes no 6. Rapid pulse or heart rate.

yes no 7. Intermittent cramping.

yes no 8. Known heart murmur.

yes no 9. Unusual shortness of breath or fatigue with usual activities.

If you answered yes to any of the above—

How often do you experience the symptom?_____

Have you ever discussed the symptom with a doctor?_____

Explain the symptom in more detail:_____

_____

****

II. Major Risk Factors

****

yes no 1. Do you have a body mass index ≥ 30 or a waist girth >100 cm?

yes no 2. Have you had a fasting glucose of ≥ 110 mg/dl confirmed by measurements on at least 2 separate occasions.

yes no 3. Has your father or brother experienced a heart attack before the age of 55? Or has your mother or sister experienced a heart attack before the age of 65?

yes no 4. Do you currently smoke or quit within the past 6 months?

yes no 5. Has your doctor ever told you that you have high blood pressure?

yes no 6. Do you have high cholesterol?

Total cholesterol:_____HDL:_____Date tested:_____

yes no 7. Do you have a sedentary lifestyle? (sitting most of the day in your job with no regular physical activity)

****

III. Medical Diagnoses

****

Have you ever had any of the following? Circle all that apply:

heart attack	angioplasty	heart surgery	coronary artery disease
angina	hypertension	heart murmur	heart clicks

asthma	emphysema	bronchitis	stroke
anemia	phlebitis	emboli	cancer
osteoporosis	emotional disorders	eating disorders	

Any special problems not listed above:_____

If any of the above are circled, please give details and explain:_____

_____

_____

_____

****

IV. General

****

yes no 1. Are you pregnant?

yes no 2. Do you have arthritis or any bone or joint problem?

If yes, please explain:_____

_____

yes no 3. Do you currently exercise?

If yes, how long have you been exercising?_____

What do you do and how often?_____

yes no 4. Are you taking any medication, vitamins or supplements?

Name them and their dosage (list both prescribed and over-the-counter medications)

Drug name and dosage / purpose of drug / prescribed or over-the-counter

_____

_____

****

My signature certifies that all of the above is true, to the best of my knowledge.

Signature:_____Date:_____

****

STAFF USE ONLY

****

Comments:_____

Stratification(circle one): Low Risk Moderate Risk High Risk

Resting blood pressure:_____Resting heart rate:_____

yes no Do meds affect BP or HR?

Date:_____Initials:_____