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Indices of metabolic stress following resistance exercise

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INDICES OF METABOLIC STRESS FOLLOWING RESISTANCE EXERCISE

An Abstract of a Thesis

Submitted

in Partial Fulfillment

of the Requirements for the Degree

Master of Arts

Steven Alexander Long

University of Northern Iowa

May 2020

ABSTRACT

The purpose of this study was twofold: 1). to evaluate the metabolic responses to varying volume load (VL), manipulated through relative training intensity and 2). to evaluate the metabolic response to training via direct and indirect methods to assess the application potential of non-invasive methods. Recreationally trained male weight lifters (n = 11) volunteered to participate in this resistance training (RT) study. During three separate testing sessions, participants completed three sets of repetitions of the barbell bicep curl exercise to technical failure with short inter-set rest intervals (60 seconds). Participants were randomly assigned one of three training intensities immediately prior to each testing session: low-load (30% 1RM), moderate-load (60% 1RM), or high-load (90% 1RM). Blood lactate was measured at baseline (Pre), immediately post exercise (Post), five minutes post exercise (Post5), and at 15 minutes post exercise (Post15). Metabolic markers VO_2, VCO_2, and RER were monitored at all times during each session. Low-load training resulted in significantly greater accumulated VL compared to moderate and high-load training. However, no significant differences were observed in blood lactate, VO_2, or VCO_2. RER values significantly favored the 30% condition over the 60% and the 90% between Post1 and Post2 and favored the 30% condition over the 90% between Post2 and Post3. Observed RER values were similar during the 30% and 60% conditions at all time points other than the period between Post1 and Post2. These results indicate that blood lactate measurements may underestimate the total exercise-associated accumulation of metabolites, and that non-invasive, indirect markers may be more useful in assessing the metabolic training response. Additionally, these findings

suggest that VL may not exert significant influence over lactate accumulation. Lastly, these findings indicate that moderate intensities may induce similar metabolic responses to low intensity training when exercise is performed for multiple sets of repetitions.

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This Study by: Steven Alexander Long

Entitled: Indices of Metabolic Stress Following Resistance Exercise

has been approved as meeting the thesis requirement for the

Degree of Master of Arts

_____   _____
Date   Dr. Jacob Reed, Chair, Thesis Committee

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Date   Dr. Forest Dolgener, Thesis Committee Member

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Date   Dr. Fabio Fontana, Thesis Committee Member

_____   _____
Date   Dr. Jennifer Waldron, Dean, Graduate College

DEDICATION

The immense amount of time, effort, and sacrifices that manifested as this written work are dedicated to an idea: the relentless pursuit of knowledge. Never stop asking questions and seeking truth.

ACKNOWLEDGEMENTS

Far too many individuals have contributed to the successful completion of this project for them each to be acknowledged within these pages. Those who have given support, friendship, and mentorship have received my most sincere appreciation in person and will continue to do so. There are, however, organizations and groups of individuals which deserve acknowledgement for their contributions to this work and I would like to use the following text to do so.

I would like to extend my gratitude to the faculty and staff of the University of Northern Iowa. These individuals have created an environment which is truly conducive to the learning process and, ultimately, to student success. Their willingness to go above and beyond expectations to assist and mentor their students is deserving of the highest commendation. Deserving of special recognition are my friends and former coworkers in the University of Northern Iowa Department of Recreation Services. Your overwhelming support during my tenor as both a program and graduate assistant was appreciated more than you know. The countless hours spent in the UNI Personal Training office working on this project contributed immensely to my personal, academic, and professional development, and I sincerely appreciate that I was not charged rent for the substantial amount of time in which I occupied this working space.

The contributions of my fellow students must also be acknowledged, for without them, this project surely would not have reached its culmination. Thought provoking dialogue, an extra pair of hands during data collection, and invitations to social events to relieve stress were but a few of the countless ways in which my peers lent their support to

both myself and this project. I have garnered a great many close friendships whilst attending the University of Northern Iowa and I will cherish each and every one of them.

Next, I must acknowledge the contributions of my friends and family. Whether you directly supported me in my day-to-day academic efforts, or you supported me by respecting my dedication and understanding my distance throughout the previous years, you have my sincerest appreciation.

Lastly, I must acknowledge my extended family, the United States Marine Corps. My time in the Marine Corps played a great role in my development as an individual. The relentless pursuit of perfection that was instilled in me as an enlisted Marine has driven me to pursue more out of life than most people believe is possible. To quote the words of my last commanding officer, Lt. Phillips, "Never stop running."

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CHAPTER 1

INTRODUCTION

<u>Rationale</u>

Increased skeletal muscle cross-sectional area (CSA) is highly correlated with increased muscular strength (Haff & Triplett, 2015; Maughan, Watson, & Weir, 1983). This relationship is one of the primary reasons why increasing or maintaining lean body mass has become a common training goal amongst elite athletes and recreational weight lifters alike. The ability to generate and tolerate high level forces enhances athletic abilities and performance during training and competition (Anderson, Triplett-Mcbride, Foster, Doberstein, & Brice, 2003). In addition to its role in promoting increases in skeletal muscle CSA and muscular force production, traditional resistance training (RT) carries the added benefit of reducing the risk of sports-related injuries amongst athletes (Faigenbaum & Myer, 2010; Heidt, Sweeterman, Carlonas, Traub, & Tekulve, 2000).

As skeletal muscle hypertrophy has been identified as the primary process through which humans increase their volume and CSA of skeletal muscle tissue (, 2010, 2016), hypertrophy has become essential in developing individual health and fitness. Considering the significance that the accretion of lean body mass has in athletic, recreational, and rehabilitation settings, the immense amount of research surrounding hypertrophy is understandable. Although researchers have tirelessly investigated the hypertrophic process and its mediators, there is much about hypertrophy which remains unclear.

Currently, three primary hypertrophic mechanisms have been identified (Schoenfeld, 2010, 2016). These mechanisms include muscular damage, metabolic stress, and mechanical tension. Many studies have been conducted with the intention of providing further insight into the interrelationship between these mechanisms and training adaptations, however, the potential contribution of each mechanism towards the growth and development of skeletal muscle fibers remains unclear. Without a clear understanding of the hypertrophic role of each individual mechanism, best practice methods for maximally influencing muscular growth remain unknown.

More recently, *in vitro* and *in vivo* studies (Oishi et al., 2015; Tsukamoto et al., 2018) have demonstrated the hypertrophic potential of metabolic stress by observing the effects of lactate administration. The observations made in these studies support a strong role for metabolic stress in accelerating the differentiation of muscle precursor cells and the growth of myofibers. Although the accumulation of metabolites during exercise was believed to promote increased intramuscular protein accretion prior to the completion of these studies, the methodology employed in these contemporary investigations allowed the effects of exercise-induced metabolic stress (EIMS) to be observed in the absence of additional mechanisms of hypertrophy. As hypertrophic mechanisms generally occur in tandem with one another during RT (Schoenfeld, 2016), the process of isolating a singular hypertrophic mechanism has been a consistent methodological problem which has proven difficult to solve. However, the methodology employed in these hypertrophic investigations (Oishi et al., 2015; Tsukamoto et al., 2018) has seemingly provided a

means to isolate metabolic stress allowing observations to made which reflect the net anabolic effects of this singular mechanism of hypertrophy.

Considering the anabolic effects that the accumulation of blood lactate has demonstrated (Oishi et al., 2015; Tsukamoto et al., 2018), additional studies should be conducted to identify best practice methods for maximizing the metabolic response to RT through the manipulation of specific training variables. Many studies have been conducted which have examined the metabolic response following the manipulation of training variables including training volume (MacDougall et al., 1999; Schoenfeld, 2013; 2016), inter-set rest intervals (Abdessemed, Duche, Hautier, Poumarat, & Bedu, 1999; Henselmans & Schoenfeld, 2014; Kraemer et al., 1990; Schoenfeld, 2013; 2016), and training tempo (Martins-Costa et al., 2016; Schoenfeld, 2016; Schoenfeld, Ogborn & Krieger, 2015), however, little information is available regarding the influence of training volume load (VL) on EIMS. Future studies should consider manipulating training VL when attempting to induce metabolic stress as VL accounts for both the volume of physical work performed and the intensity at which this work is performed. This information may be highly beneficial in identifying the optimal training intensity for inducing metabolic stress.

Additionally, currently used direct methods of measuring metabolic accumulation during exercise, including blood sampling and muscle biopsies, pose potential health and methodological concerns. Due to these concerns, future investigations should examine the viability and accuracy of indirect methods of assessing the exercise-associated accumulation of metabolites. Indirect methods of measuring the metabolic response to

exercise, if found to be viable and accurate, will assist in the development of best practice methods for inducing metabolic stress by providing reliable values for metabolite accumulation reflecting the effectiveness of exercise protocols in inducing a metabolic response.

Practical Significance

Identifying individualized responses to RT carries considerable practical application potential for future researchers. Previous investigations have solidified the prominent role that exercise-induced metabolic stress (EIMS) has in the facilitation of muscular growth, primarily through processes such as cellular swelling, the enhanced release of anabolic hormones, and decreased recruitment thresholds of larger motor units (Gentil, Oliveira, & Bottaro, 2006; Green, Hughson, Orr, & Ranney, 1983; Reeves et al., 2006; Schoenfeld, 2013; 2016; Takarada, Nakamura, et al., 2000). However, there is currently a lack of knowledge regarding inducing EIMS. A direct relationship appears to exist between training volume and EIMS (MacDougall et al., 1999; Schoenfeld, 2013; 2016), however, in these studies, training volume is typically manipulated through the completion of additional sets of exercise. This methodology has neglected to take into account the differing accumulated volume load when RT is performed at varying intensities for an equal number of sets. Such information would assist researchers in determining the appropriate exercise intensity to induce varying degrees of metabolic stress.

Current methods of measuring metabolite accumulation involve invasive techniques such as blood draws, finger pricks, and muscle biopsies (Tesch, Daniels, &

Sharp, 1982; Shanely et al., 2014). These methods are potentially disruptive to experimental procedures as they require additional time to complete and may hinder exercise protocols involving short or no inter-set rest intervals. Methods of directly measuring metabolic stress also pose a potential risk to the health and comfort of participants. Thus, indirect, non-invasive methods of measuring the exercise-associated accumulation of metabolites would be beneficial to researchers who seek to observe the metabolic response to exercise. These indirect methods may include monitoring changes in VO_2, VCO_2, and RER which occurring during and immediately post exercise, as these changes may reflected alterations in metabolic activity which may influence metabolite accumulation.

Additionally, due to the known anabolic effects associated with the accumulation of metabolites (Reeves et al., 2006; Schoenfeld, 2013; 2016; Takarada, Nakamura, et al., 2000; Takarada, Takazawa, et al., 2000), a deeper understanding of the acute metabolic response to RT will be an asset to strength and conditioning, health and fitness, and rehabilitation professionals who seek to increase, maintain, or regain skeletal muscle CSA within athletes, clients, and patients. Millions of recreational weight lifters who seek to optimize the hypertrophic adaptations of their training regimens also stand to benefit from knowing the optimal working intensity at which acute metabolic stress is maximized.

<div align="center">Problem Statement</div>

Currently, there is substantial information available regarding the metabolic responses resulting from the manipulation of various training variables. However, there is

a lack of information available surrounding the relationship between metabolic accumulation and RT VL. As VL accounts for both the volume of physical work performed during a specified period of time and the intensity at which this work is performed, examining the relationship between VL and the metabolic response to training may assist researchers and practitioners in selecting appropriate working intensities to induce substantial metabolic stress which may promote hypertrophic adaptations in skeletal muscle (Oishi et al., 2015; Tsukamoto et al., 2018).

In addition to the need for an increase in the available information regarding the metabolic response to the manipulation of VL, it is also necessary to identify additional methods for accurately assessing the metabolic response to training. Currently, studies which evaluate the metabolic response to exercise use direct methods for measuring the accumulation of metabolites. The two direct methods typically utilized include the retrieval of muscle biopsy samples and blood draws. Muscle biopsies and blood draws are both invasive procedures which create a risk for infection and subject participants to a certain degree of discomfort. Additionally, these two procedures can be disruptive to experimental procedures which involve short inter-set rest intervals or the time sensitive collection of biological samples. For these reasons, identifying indirect methods of evaluating the metabolic response to exercise, such as VO_2, VCO_2, and RER, would be highly beneficial to future investigations involving metabolic stress.

This investigation will expand the current knowledge regarding the relationship between training VL and one of the known primary mechanisms of hypertrophy, exercise-induced metabolic stress (EIMS), by providing insight into the expected

accumulation of blood lactate following traditional resistance exercise performed at varying intensities. Additionally, this study will evaluate metabolic metrics (VO_2, VCO_2, and RER) with the intention of identifying a potentially less invasive, indirect marker of exercise-associated metabolic stress. The results of this study will provide a foundation from which future researchers can develop evidence-based methods for optimizing exercise-associated metabolic stress.

<div align="center">Delimitations</div>

1. Due to safety considerations, the primary investigator made the decision to include only those participants who, at the start of the study, were not currently suffering from any known musculoskeletal injuries.

2. Researchers decided to exclude all participants who indicated that they had in the past year, or were currently, supplementing with any dietary supplements in which creatine monohydrate or hydrochloride were a primary ingredient.

<div align="center">Limitations</div>

1. Limitations of any exercise-based study will include the subjective effort of participants. Without the enticement of personal gain, it is possible that participants will quit prematurely during testing procedures or during initial strength testing, in response to exercise-associated discomfort.

2. Participants of the proposed study were required to provide researchers with an estimated training history by completing a training history questionnaire. There is always an inherent risk of self-report bias associated with the use of questionnaires.

Definitions

1. Exercise-induced Muscular Damage (EMID): Exercise-induced muscular damage refers to the disruption of the ultrastructural content of skeletal muscle fibers following the execution of resistance exercises.

2. One Repetition Maximum (1RM): The greatest absolute amount of resistance that an individual can lift for a single repetition through a complete range of motion for a specified exercise.

3. Exercise-induced Metabolic Stress (EIMS): The accumulation of various metabolic byproducts, most notably lactate, following the execution of exercise which relies heavily on anaerobic metabolism.

4. Muscular or technical failure: Failure will refer to an inability to complete another repetition of a specified exercise through the complete range of motion.

5. Inter-set rest interval: The total time which elapses between successive sets of exercise during a single training session.

6. Intra-set work duration: The total time which elapses during a single set of resistance training exercise.

CHAPTER 2

LITERATURE REVIEW

<u>Skeletal Muscle Hypertrophy</u>

The addition of lean muscle mass has been a common goal for athletes, recreational weight lifters, and rehabilitation patients for centuries. The process of growing skeletal muscle involves a complex and intricate relationship between human physiology and the external environment. The exact individual factors, physiological processes, mechanisms, and pathways which facilitate the growth of myofibers are still not entirely understood after being the focus of thousands of scientific investigations. However, these investigations have revealed much about the physiological phenomenon referred to as *hypertrophy*, a term used to describe an increase in the size of muscle tissue (Schoenfeld, 2016). Skeletal muscle hypertrophy involves an increase in the diameter of each myofiber, ultimately causing an increase in whole muscle cross-sectional area (CSA) (Schoenfeld, 2010) or whole muscle volume (Haff & Triplett, 2015). In humans, it is believed that hypertrophy occurs via two distinct processes: myofibrillar hypertrophy and sarcoplasmic hypertrophy (Schoenfeld, 2010).

<u>Myofibrillar Hypertrophy</u>

When human skeletal muscle fibers experience a sufficient overloading stimulus, a series of physiological events are initiated. These events have many possible outcomes, one of which is the growth of skeletal muscle fibers (Schoenfeld, 2010). The growth of muscle fibers most often involves the enlargement and addition of new intramuscular contractile elements, specifically the contractile proteins actin and myosin. The growth of

current myofilaments; and the acquisition of new contractile proteins; ultimately forces

existing sarcomeres to expand, and eventually creates a need for the formation of

additional sarcomeres. As sarcomeres are enlarged, and new sarcomeres are established,

each affected myofiber is compelled to expand, rather than risk rupturing. Most typically,

a mechanically overloading stimulus, commonly induced via traditional RT, facilitates

the acquisition of sarcomeres in parallel, rather than in a series orientation (Haff &

Triplett, 2015; Schoenfeld, 2010; 2016; Toigo & Boutellier, 2006). The inclusion of new

sarcomeres in parallel increases the diameter of each myofiber, which ultimately results

in an increase in the overall size of the entire associated muscle belly. As fibers undergo

myocellular expansion, their enlargement creates a need for the extracellular matrix

surrounding each muscle fiber to expand as well. This physiological phenomenon is

referred to interchangeably as both *compensatory hypertrophy* and *myofibrillar*

hypertrophy, and it is a training adaptation sought by hundreds of millions of individuals

for competitive, recreational, and health benefits.

Sarcoplasmic Hypertrophy

In contrast, *sarcoplasmic hypertrophy*, a process in which myocellular expansion

is believed to result from the accumulation of non-contractile elements and fluid within

the muscle cell, has been presented as an alternative hypothesis to myofibrillar

hypertrophy (Schoenfeld, 2012; 2016; Zatsiorsky, 1992). It is speculated that muscular

growth resulting from sarcoplasmic hypertrophy is accompanied by little to no chronic

accretion of contractile elements or improvements in maximal voluntary contraction

(MVC) (Cassano et al., 2009; Fisher, Steele, & Smith, 2013; Schoenfeld, 2010; 2016;

2019; Zatsiorsky, 1992). However, sarcoplasmic hypertrophy has been shown to increase cellular swelling (Schoenfeld, 2010; 2016), a phenomenon which may have positive implications on muscle protein synthesis (MPS) rates, and may ultimately contribute to the addition of contractile elements within the muscle cell (Schoenfeld & Contreras, 2014). The phenomenon of cellular swelling will be discussed in greater detail in a subsequent section of this review.

The results of a recent RT investigation (Schoenfeld et al., 2019), appear to demonstrate the development of skeletal muscle tissue via sarcoplasmic hypertrophy. Using a sample of 45 healthy male participants (mean age 23.8 years) randomly assigned to one of three eight-week RT groups: low (1SET, n = 15), moderate (3SET, n = 15), and high volume (5SET, n = 15), researchers compared baseline and post-test muscular strength assessments and muscular thickness (MT) measurements.

Significant differences were observed in MT amongst the groups of participants. The 5SET group showed significantly greater MT than the 1SET group in the elbow flexor, rectus femoris, and vastus lateralis musculature. The significantly greater increases in MT measured in the high-volume group compared to the low-volume group validate the dose-response relationship of RT volume and hypertrophic training adaptations. Additionally, the lack of significant differences observed between groups in the post-exercise strength assessments, despite the presence of significant hypertrophic differences, alludes to the influence of sarcoplasmic hypertrophy. These findings also support the claim that hypertrophy of skeletal muscle fibers can indeed occur without concurrent increases in MVC or 1RM.

Although sarcoplasmic hypertrophy appears to have promising application in hypertrophy training programming, conflicting results suggest that additional research must be conducted to determine the precise role and implications of this physiological phenomenon in regard to increasing the size and contractile strength (MVC, 1RM) of human skeletal muscle tissue.

Hyperplasia of Skeletal Muscle

In addition to hypertrophy, another process, *hyperplasia*, has been hypothesized as a means of increasing the size of human skeletal muscle. As a process, hyperplasia differs from hypertrophy in that, hyperplasia involves increasing the number of muscle fibers within each muscle fascicle (Schoenfeld, 2012; 2016), while hypertrophy involves an increase in the size of individual muscle fibers. Evidence of muscular hyperplasia is lacking in humans, although, several studies have observed hyperplasia occurring in various animal species (Alway, Gonyea, & Davis, 1990; Gonyea, Sale, Gonyea, & Mikesky, 1986; Kelley, 1996). Hyperplasia studies focused on avian species have provided the strongest evidence to date that skeletal muscle is capable of growth via the addition of new muscle fibers. In the majority of these studies (e.g. Antonio & Gonyea, 1993a; 1993b; 1994; Sola, Christensen, & Martin, 1973), muscle tissues were subjected to an overloading stretch stimulus, rather than an overloading mechanical stimulus typically used to induce hypertrophic adaptations in humans.

In addition to insufficient human evidence, studies indicating the possibility of fiber hyperplasia have been criticized as lacking accuracy due to the difficult nature of counting the microscopic fibers present both prior to and following experimental

procedures (Paul & Rosenthal, 2002). With no established research-supported evidence to strongly postulate the process of hyperplasia in humans, individuals seeking to increase lean muscle mass have sought to promote such increases through hypertrophy of existing tissue. With few contemporary investigations focusing on hyperplasia within human subjects, it appears as though researchers have shifted their focus towards increasing our understanding of the various hypertrophic mechanisms and processes, and to understanding and manipulating individual variations in training adaptations.

<div align="center">Hypertrophic Factors</div>

Interindividual variations in training responses have been observed following both aerobic training (Mann, Lamberts, & Lambert, 2014) and RT (Erskine, Jones, Williams, Stewart & Degens, 2010; Hubal et al., 2005). Researchers have postulated that many personal factors influence an individual's physical characteristics, and that these characteristics can highly influence an individual's potential for adaptation (Schoenfeld, 2016). In regard to hypertrophy, a number of individual factors have been identified which are believed to influence individual training adaptations and adaptation potential. Amongst these factors are genetics, sex, age, and training status.

Genetics

The individual variability in training responses and variations in the maximum potential for adaptation are believed to be heavily influenced by two genetically dependent factors: genotype and phenotype (Schoenfeld, 2016). The term *genotype* is used to refer to the collective genetic makeup of an individual. In practical terms, an individual's genotype describes the blocks of hereditary information which he or she

received from their parents (genes). How our bodies interpret and mechanically execute the information encoded within our genes is referred to as the process of *gene expression*. The expression of an individual's genes, which results in the development of unique physical characteristics, is referred to as an individual's *phenotype*. An individual's phenotype influences many performance-influencing characteristics, including; muscle fiber type distribution and number (MacDougall, Sale, Alway, & Sutton, 1984), the activity of myogenic factors, and satellite cell function (Bamman, Petrella, Kim, Mayhew, & Cross, 2007; Bellamy et al., 2014; Riechman, Balasekaran, Roth, & Ferrell, 2004; Schoenfeld, 2016). The interaction between these two factors, genotype and phenotype, and environmental stimuli is believed to highly influence an individual's response to an exercise program and may account, at least in part, for the variations often observed in individual training adaptations (Hubal et al., 2005).

The considerable variation in results observed in both men and women following RT has led to the development of specific terminology which vaguely describes responsiveness. These commonly used terms are *responder* and *non-responder* (Bamman et al., 2007; Jones et al., 2016, Schoenfeld, 2016). As individual-specific genotype and phenotype are thought to greatly influence responsiveness to RT, researchers have begun to theorize that the prescription of RT might be more effective if varied based on an individual's specific genetic characteristics. This hypothesis has encouraged researchers to isolate specific genes in an effort to determine which genetic markers are most responsible for influencing training adaptations (Devaney et al., 2009; Pescatello, Devaney, Hubal, Thompson, & Hoffman, 2013).

In 2016, Jones and colleagues were the first to practically implement genotype-specific training prescriptions in two groundbreaking studies (Jones et al., 2016). Twenty-eight (n = 28) male athletes participating in varying sports completed the first study, while 39 (n = 39) male soccer players successfully completed the second. At the onset of the investigations, the genotype of all participants was determined via the DNAfit Peak Performance Algorithm, a DNA test which analyzes the genetic variants of 15 specific genes, all of which are believed to influence physical performance (Egorova et al., 2014).

All participants were randomly assigned to an eight-week RT program, focusing on either high- or low-intensity training. This random assignment resulted in "matched training" for 34 athletes, where high-intensity training was prescribed to power genotype athletes (n = 15) and low-intensity training was prescribed to endurance genotypes (n = 19). The remaining 33 athletes (13 power and 20 endurance) completed "mismatched training." In both studies, the eight-week, matched-training protocol resulted in the development of significantly greater muscular power and endurance compared to the mismatched training.

The results of genotype-specific training programs are compelling; however, much research must be conducted to fully elucidate the possible implications of such training strategies. One particular complication in gene expression research is the fact that genes do not operate singularly, rather the interaction of multiple genes and their specific locations within a genetic sequence (genetic loci) largely determine genetic influence (Schoenfeld, 2016). Due to the complexity associated with genetic research,

identifying hereditary predispositions and individual adaptation potential remains difficult and unreliable.

Sex

In addition to genetic factors, it has been shown that an individual's biological sex also heavily influences the individual response to training (Abe, DeHoyos, Pollock, & Garzarella, 2000; Bamman et al., 2003; Ivey et al., 2000; Schoenfeld, 2016). Males and females experience significantly different training responses and adaptations and have differing potential to gain and maintain skeletal muscle (Ivey et al., 2000; Schoenfeld, 2016). The average female possesses significantly less absolute and relative lean mass compared to the average male (Hansen & Kjaer, 2014; Schantz, Randall-Fox, Hutchison, Tydén, & Åstrand, 1983; Schoenfeld, 2016). These sex-based physical differences and others are often collectively referred to as *sexual dimorphism*.

Dissimilar values of relative muscle mass between sexes have largely been attributed to differing chronic concentrations of circulating hormones (Schoenfeld, 2016). On average, men tend to possess greater circulating concentrations of testosterone, which is known to promote a positive muscle protein balance. Women, however, tend to possess higher circulating levels of estrogen. While the hormone estrogen has been shown to decrease muscle protein breakdown (Pöllänen et al., 2007), the anabolic effects of estrogen are lacking in comparison to those of testosterone (Schoenfeld, 2016).

In response to a RT program designed to stimulate the growth of skeletal muscle, the average male has the potential to experience significantly greater absolute gains compared to the average female (Ivey et al., 2000; Schoenfeld, 2016). In relative terms, it

appears as though males and females experience similar rates of muscular growth

following a period of RT (Abe et al., 2000; Schoenfeld, 2016). However, as the average

female possesses significantly less relative muscle tissue at baseline values, post-training

statistics depicting relative increases in muscle tissue tend to be biased to favor female

trainees (Schoenfeld, 2016).

The sex-based variance in hypertrophic responses to RT was demonstrated in a

nine-week, unilateral strength training experiment conducted by Ivey and colleagues

(2000). Eleven young men (n = 11) and eleven young women aged 20 to 30 (n = 11)

volunteered to participate in the experiment. Following the training protocol, both groups

of participants experienced significant muscular growth of the quadriceps muscle group

of the exercised leg, however, the young males experienced significantly greater

hypertrophy compared to the group of young women. Interestingly, the young male

participants also experienced significant muscular growth in the quadriceps of the non-

exercised limb, while the females did not. This observation lends support to the

hypothesis that systemic factors, such as chronic hormonal differences, serve an essential

role in the hypertrophic process, and supports the belief that differences in lean mass

between sexes are indeed influenced, at least in part, by these systemic factors.

Age

An individual's biological age is another factor which influences the potential to

develop and maintain skeletal muscle (Buford et al., 2010; Roubenoff & Hughes, 2000;

Schoenfeld, 2016). According to a systemic review on *sarcopenia*, the age-related

atrophy of skeletal muscle, conducted by Buford et al. (2010), on average, humans reach

peak muscle mass between the ages of 20 and 40, after which they experience a consistent decline in skeletal muscle tissue. This decline generally begins after age 40 at a loss of .5% each year, until age 50 where the rate of loss increases up to 1 to 3% each year (Zacker, 2006). This decline is primarily due to the atrophy and loss of type II muscle fibers and motor neurons (Buford et al., 2010; Schoenfeld; 2016). While the effects of sarcopenia have been shown to be mitigated by a healthy, active lifestyle, the gradual decline of muscle tissue is an inevitability.

Pursuant to the growth of skeletal muscle, increased biological age beyond 40 years of age negatively affects hypertrophy via numerous physiological implications (Schoenfeld, 2016). A reduction in the quantity of type II muscle fibers and fast-twitch motor neurons reduces the total potential for fiber hypertrophy (Buford et al., 2010; Schoenfeld; 2016). Additionally, in the event that fast-twitch motor neurons die, slow-twitch neurons may undergo *motor unit remodeling*, a process which may delay the atrophy of the type II fibers previously innervated by the now dead neurons (Zacker, 2006). However, motor unit remodeling compromises the functionality of such fibers, reducing their efficiency and effectiveness. Reduced skeletal muscle function ultimately reduces the potential for fiber hypertrophy.

Advancing age has also been associated with the development of anabolic insensitivity, resulting from a milieu of factors including decreased satellite cell content and activity, decreased enzymatic activity, heightened insulin resistance, and reduced sensitivity of the muscles to amino acid stimulation (Buford et al., 2010). This desensitization contributes to a chronic negative muscle protein balance, creating a

catabolic internal environment which is counterproductive to hypertrophy. It is important

to note that older adults may still experience profound muscular growth (Ivey et al., 2000;

Roth et al., 2001); however; research suggests that greater volumes of RT may be

necessary to facilitate muscle protein accretion as one ages (Peterson, Sen, & Gordon,

2011). Additionally, it has been recommended that individuals participate in resistance

exercise earlier in life to potentially mitigate the effects of sarcopenia.

Research has determined that the decline of muscle tissue as one ages is also

influenced by one's sex (Hansen & Kjaer, 2014; Schoenfeld, 2016). On average, older

female adults experience greater muscle loss per year compared to older men. This

elevated muscle loss has been partially attributed to reduced circulating estrogen

concentrations during the postmenopausal period (Hansen & Kjaer, 2014). The acute

anabolic response to RT has also been shown to be lower in older women than in older

men (Bamman et al., 2003).

<u>Training Status</u>

While genetic characteristics, biological sex, and age are involuntarily

predetermined, an individual's training status is a controllable factor known to exert

considerable influence on training outcomes (Schoenfeld, 2016). Acute training

responses have been known to vary considerably between trained and untrained

individuals (Peterson, Rhea, & Alvar, 2005; Schoenfeld, 2016; Stone et al., 1987).

Untrained populations tend to experience an accelerated rate of adaptation early in a RT

program. In regard to muscular hypertrophy, this observation has been explained by the

ceiling effect hypothesis, which explains that the accruement and maintenance of

excessive muscle tissue can be cumbersome to the body, thus reducing physiological efficiency and burdening physiological functioning as well as human kinematics (Schoenfeld, 2016). As a result, researchers have theorized that the human body possesses a physiological limit for the addition of muscle tissue. As an individual approach their physiological limit, the rate of gains in skeletal muscle tissue are reduced via several physiological and neurological mechanisms. The mechanisms which are theorized to be responsible for the chronically-decreased rate of training adaptations include: reduced intracellular anabolic signaling (Coffey et al., 2006), decreased post-training MPS (MacDougall et al., 1995), and decreased rate of improvements in neuromuscular efficiency (Behm, 1995).

The acute, training-induced accumulation of lactate has also been observed to differ greatly when comparing trained and untrained individuals (Pierce, Rozenek & Stone, 1993; Stone et al., 1987), an observation which signifies variability in the metabolic responses to exercise. When five trained (n = 5) and five untrained (n = 5) participants were asked to perform multiple sets of barbell squats at progressive intensities, Stone and colleagues (1987) observed significantly lower blood lactate concentrations following any given exercise intensity in trained individuals. Additionally, the researchers found that trained individuals performed significantly greater work volume and exhibited significantly greater blood lactate concentrations at the point of voluntary exhaustion.

Stone and colleagues (1987) also found that the trained participants were able to reach higher exercise intensities, while untrained participants reached voluntary

exhaustion much earlier during progressive exercise. The ability to perform squats at greater exercise intensities further increased the work volume performed by the trained participants. These findings indicate that trained individuals possess greater work capacity and are capable of producing and tolerating significantly greater blood lactate concentrations during exercise performed to exhaustion.

Pierce and colleagues (1993) found similar findings in a repeated-measures study where blood lactate concentrations were compared before and after eight weeks of RT in 15 previously untrained males (n = 15). Following the eight-week, high-volume RT protocol, mean, post-test peak blood lactate significantly decreased (11.9 mmol*L^{-1} to 5.1 mmol*L^{-1}). These results are consistent with the observations of Stone and colleagues (1987), suggesting that trained individuals do indeed experience significantly lower blood lactate accumulation at submaximal exercise intensities compared to untrained individuals. These results help to confirm that the acute metabolic training responses do indeed vary significantly between trained and untrained populations.

<div align="center">Hypertrophic Mechanisms</div>

While the factors which influence hypertrophy are composed of several characteristics unique to each individual, the mechanisms which are believed to facilitate hypertrophy include many distinct physiological processes which can occur within all generally healthy individuals. Currently, three primary mechanisms have been identified which facilitate the growth of skeletal muscle tissue (Schoenfeld, 2010; 2016; Schoenfeld & Contreras, 2014). These three mechanisms include: mechanical tension, exercise-induced muscular damage (EIMD), and exercise-induced metabolic stress (EIMS).

Mechanical Tension

The majority of exercise physiology researchers agree that mechanical tension is the dominant factor for inducing muscular hypertrophy (Goldberg, Etlinger, Goldpsink, & Jablecki, 1975; Gonzalez, Hoffman, Stout, Fukuda, & Willoughby, 2016; Schoenfeld, 2010; 2011; 2012; 2016; Zanchi, Lira, Seelaender, & Lancha, 2010). Independent of all other factors, mechanical loading of muscle cells can lead to increases in total muscle volume and CSA (Drummond et al., 2009; Schoenfeld, 2010; 2016). However, it is strongly believed that when mechanical loading is employed in combination with additional mechanisms the hypertrophic response to RT will be even more significant (Schoenfeld, 2010; 2012; 2016).

By definition, mechanical tension refers to forces generated from within skeletal muscle and stretch-causing external forces (Schoenfeld, 2010; 2012; 2016). In practical terms, mechanical tension most often refers to two separate quantifiable concepts: time under tension and the total force generated by a muscle. Physiological adaptations resulting from mechanical tension have been shown to be triggered by mechanotransduction, a process by which cells experience a mechanical stimulus and initiate follow-on physiological events (Zanchi & Lancha, 2008). It is imperative that muscle cells experience an overloading-mechanical sensation for several myogenic pathways to be initiated.

Mammalian target of rapamycin (mTOR) and muscle protein balance. The rate of MPS is crucial in the pursuit of hypertrophic increases in skeletal muscle mass (Burd, Tang, Moore, & Phillips, 2008; Drummond et al., 2008; Gonzalez et al., 2016).

Intramuscular net protein balance must be positive for hypertrophy to occur (Phillips, 2014; Schoenfeld, 2012; 2016). Maintaining a positive muscle protein balance can be achieved in many ways. One can seek to enhance the rate of MPS, downregulate muscle protein breakdown (MPB), or attempt to positively influence muscle protein balance by achieving a combination of both of these factors.

The activity of the protein kinase mammalian target of rapamycin (mTOR) greatly influences MPS rates, and by extension, muscle protein balance (Schoenfeld, 2010; 2016; Zanchi & Lancha, 2008). Within human skeletal muscle tissue, mTOR is present in two distinct protein complexes: mTORC1 and mTORC2 (Drummond et al., 2009; Shoefeld, 2016). Each of these complexes carry out specific functions and are involved in different intramuscular processes. Although the critical role that mTORC1 plays in regulating MPS is well documented (Dreyer et al., 2006; Drummond et al., 2008; Drummond et al, 2009; Schoenfeld, 2016), the exact mechanisms by which mTORC1 directs the muscle remodeling process are unknown at this time.

The intramuscular protein complex mTORC1 has been shown to become activated when muscle cells are subjected to a direct overloading, mechanical stimulus, thus, resistance exercise is the most common training modality utilized to achieve hypertrophic adaptations (Dreyer et al., 2006; Drummond et al., 2008; Phillips, 2014; Schoenfeld, 2012; 2016). Currently, the consensus is that mechanical loading equal to or greater than 65% 1RM is required to induce hypertrophic adaptations, although the results of more recent investigations have brought criticism to this recommendation

(Mitchell et al., 2012; Schoenfeld, 2013; 2016; Takarada, Takazawa, et al., 2000; Tanimoto et al., 2008).

When activated, mTORC1 signals an upregulation in MPS rates, ultimately leading to a positive net muscle protein balance and facilitation of muscular growth (Gonzalez et al., 2016). This enhanced MPS rate has been observed in as little as two hours, and for up to 48 hours, post-exercise (Dreyer et al., 2006; Phillips, 2014; Schoenfeld, 2016). Additional validation of mTORC1's influence on MPS has been observed following the treatment of rapamycin, an mTORC1 inhibiting substance.

In their 2009 investigation, Drummond and colleagues assessed the hypothesized causal relationship between the post-exercise elevated rate of MPS and mTORC1 activity via an experimental study in which the treatment group was directed to take rapamycin. Analyses of blood samples collected from participants assigned to the experimental group revealed that blood rapamycin concentrations peaked immediately prior to the initiation of the RT protocol, and remained significantly elevated during the first two hours post-exercise. Treatment group blood sample analyses also revealed that mTORC1 activity was indeed inhibited post-exercise. Additionally, muscle biopsies collect from treatment group participants revealed that MPS rates were not elevated post-exercise. When interpreting these results, the authors concluded that rapamycin treatment completely inhibited the activity of the protein complex mTORC1, and that this inhibition resulted in an unchanged MPS rate following heavy bouts of RT.

Considering the role of mTORC1 in regard to MPS, established by previous researchers (Drummond et al., 2008; Zanchi & Lancha, 2008), the absence of elevated

MPS rates within the rapamycin group indicates that mTORC1 activity was inhibited due to the administration of the treatment, and provides additional evidence to support the influence that the protein kinase mTORC1 has on MPS and hypertrophy.

Satellite cells and mRNA. In addition to mTOR and MPS, satellite cells and intramuscular messenger ribonucleic acid (mRNA) also serve as potential myogenic pathways which, when activated, can enhance the hypertrophic training response. Research has identified that satellite cells play a crucial role in promoting the hypertrophy of skeletal muscle fibers in humans (Kadi et al., 2004; Schoenfeld, 2010; 2016: Toigo & Boutellier, 2006). Satellite cells, often referred to as muscle stem cells, are mono-nucleated cells which reside between the sarcolemma and basal lamina of skeletal muscle cells (Damas, Libardi, & Ugrinowitsch, 2018; Kadi et al., 2004; Schoenfeld, 2010; 2016; Toigo & Boutellier, 2006). It has been shown that satellite cells are activated in response to two distinct stimuli: mechanical loading of sufficient magnitude (Schoenfeld, 2010; 2016) and mechanical stretch (Toigo & Boutellier, 2006). Once activated, satellite cells will procreate additional cells referred to as *daughter cells* (Kadi et al., 2004; Schoenfeld, 2016). These daughter cells have three potential roles: fusion with an existing myocyte, the donation of an additional nucleus to a parent muscle cell, or daughter cells can become a new satellite cell, in which case, they will revert to an inactive state.

Unlike satellite cells, the cells which make up skeletal muscle fibers in humans are multi-nucleic (Kadi et al. 2004; Schoenfeld, 2016; Toigo & Boutellier, 2006). Each nucleus of a muscle cell exerts control over a specified intracellular space, a concept

referred to as *myonuclear domain* (Kadi et al., 2004). Each nucleus' myonuclear domain

is finite, although research has proven that the volume of each nuclear-controlled area

may be enhanced through training. In addition to intracellular space, each myonucleus

exerts control over local mRNA molecules, which reside within each specified

myonuclear domain. The mRNA molecules within a muscle cell play a critical regulatory

role in the MPS process via their role in the transcription and translation of new muscle

proteins (Kadi et al. 2004; Schoenfeld, 2016). There are currently two primary

hypotheses which attempt to explain how intramuscular mRNA may enhance the rate of

MPS: the volume increase hypothesis and the rate increase hypothesis.

The first hypothesis states that the increased rate of MPS is facilitated via an

increase in intramuscular mRNA content (Kadi et al., 2004). This increase in the total

number of mRNA molecules is a pre-translational event and is speculated to be facilitated

by the nucleic donation from satellite cells to their corresponding parent muscle fiber. As

the controllable intracellular space and mRNA volume of each myonucleus is limited, the

donation of additional nuclei from satellite cells is essential to support the continued

increase in mRNA content and cellular expansion. This hypothesis supports the claim

that satellite cells play a critical role in hypertrophy, due to the necessity of nucleic

donation to support increases in cytoplasmic and mRNA volume.

A second hypothesis states that MPS rates might be enhanced due to an increase

in the rate at which existing mRNA molecules are able to encode new amino acids (Kadi

et al., 2004). This increased rate of mRNA gene expression is a translational event, as the

myonucleus is able to translate the mRNA molecules at a faster rate, thus increasing the

rate of gene expression, and ultimately MPS. In a study of training and detraining associated modifications in the intramuscular content of satellite cells and mRNA, Kadi and colleagues (2004) established that 30 days of progressive RT is sufficient to significantly increase satellite cell and mRNA content. Analysis showed that mRNA levels were significantly increased after 30 days of training and significantly elevated at three times baseline levels immediately following the 90th day of training. During the detraining phase, mRNA returned to pre-training levels after just three days.

Researchers did not observe any significant adaptations in myonuclear domain size or myonucleic content. The findings of this investigation support the claims that intramuscular mRNA content, satellite cell volume, and myonuclear domain size can all be enhanced through prolonged (i.e. 90 days or longer) mechanical stimulation of muscle cells via progressive-resistance exercise.

The influence that mechanical stimulation can have on mTOR activity, muscle protein balance, the activity of satellite cells, and intramuscular mRNA gene expression support the claims by previous researchers (Goldberg et al., 1975; Gonzalez et al., 2016; Schoenfeld, 2010; 2011; 2012; 2016) that mechanical tension alone is a sufficient mechanism to induce hypertrophy in skeletal muscle cells. However, isolating mechanical tension from additional hypertrophic mechanisms has proven exceedingly difficult in experimental settings, thus the true role of mechanical tension in regard to the growth of myofibers remains to be fully elucidated. Future researchers should continue to study the primary mechanisms of hypertrophy, and should seek to isolate each

hypertrophic mechanism, through creative exercise programming, *in vitro* testing, and

through continued research focusing on various animal species.

Exercise-Induced Muscle Damage

In addition to mechanical tension, researchers have extensively investigated a

second mechanism, exercise-induced muscular damage (EIMD), which has been

identified as a heavy influencer of the post-exercise hypertrophic response. In 2012,

Schoenfeld evaluated the role that EIMD has on skeletal muscle hypertrophy. The

findings of Schoenfeld's review were conflicting. Although many contemporary studies

(Flann, LaStayo, McClain, Hazel, & Lindstedt, 2011; Pope, Willardson, & Schoenfeld,

2013; Reeves et al., 2006; Takarada, Nakamura, et al., 2000; Zanchi et al, 2010) have

provided evidence that muscular hypertrophy can be promoted in the absence of EIMD,

additional studies have supported the idea that EIMD has the potential to enhance

hypertrophic adaptations following exercise (Damas et al., 2018; Schoenfeld, 2012;

Schoenfeld & Contreras, 2018). EIMD increases the release of inflammatory substances,

enhances the activity of satellite cells, and upregulates the insulin-like growth factor-1

(IGF-1) system, all of which promote hypertrophy of muscle fibers (Schoenfeld, 2012).

Currently, studies focusing on EIMD have failed to provide sufficient evidence to support

a causal relationship between EIMD and muscular hypertrophy (Brentano & Martins

Kruel, 2011). The lack of evidence in support of EIMD as a substantial, or even a

necessary, factor in the mediation of muscular growth is largely due to the difficulty

involved in isolating the single hypertrophic mechanism from additional mechanisms.

This methodological problem is easily observed when reviewing studies which investigate EIMD following aerobic exercise.

Aerobic exercise and EIMD. Aerobic exercise studies evaluating training adaptations resulting from cycling (Harber et al., 2012) and running (Konopka & Harber, 2014) have found that these modes of exercise can result in significant amounts of EIMD, which may be accompanied by significant increases in skeletal muscle CSA in previously untrained individuals. However, muscular hypertrophy resulting from aerobic exercise has commonly been observed in type I muscle fibers only (Harber et al., 2009; Schoenfeld, 2016), and rarely in type IIa fibers (Harber et al., 2012). In addition, CSA of type II fibers have also been shown to decrease significantly in well-trained distance runners following high-intensity interval training (Kohn, Essén-Gustavsson, & Myburgh, 2011). The lack of hypertrophy of type II muscle fibers following aerobic training suggests that the hypertrophic potential of such training is limited, as type II fibers are well known to possess greater potential for cross-sectional growth (Schoenfeld, 2016). Aerobic training studies which intentionally induce considerable muscular damage, via downhill running, have also failed to induce significant muscular growth in well-trained individuals (Brentano & Martins Kruel, 2011; Schoenfeld, 2012). The results of hypertrophy-focused aerobic studies indicate that aerobic exercise is not an ideal mode of training to induce significant muscular growth in currently active individuals, and that EMID is not consistently concurrent with hypertrophy.

Traditional RT and EIMD. Research focusing on RT and muscle damage has led to the current consensus that resistance exercise which induces a moderate amount of

EIMD may be beneficial to a hypertrophy-focused training program (Schoenfeld, 2012; 2016). This recommendation has been made after observations in previous studies (Allen, 2001; Newham, Jones, Clarkson, 1987; Radák, Pucsok, Mecseki, Csont, & Ferdinandy, 1999; Schoenfeld, 2012) identified a maximum threshold for inducing muscular damage, after which maximal force production capabilities are decreased significantly. A significant reduction in muscular force production decreases the potential for optimizing mechanical tension, due to the obligatory lower intensity exercise during following sets. Compromising the total mechanical tension produced during a RT session inevitably compromises the potential for maximal post-exercise hypertrophic adaptations. Excessive EIMD has been observed following unaccustomed exercise and RT involving high-force eccentric muscle actions (Schoenfeld, 2012), and thus, these training protocols have been examined at length in attempts to determine the inherent effects of high-intensity training techniques.

Eccentric exercise. In his 2012 review focusing on EIMD, Schoenfeld identified eccentric exercise as one of the primary causes of EIMD. Newham et al. (1987) tested the influence that eccentric RT can have on muscular damage using the single-arm bicep curl.

Participants (n = 8, five males and three females) were instructed to perform one maximal voluntary contraction (MVC) of the single-arm bicep curl exercise, against a mechanical winch every 15 seconds for three 20-minute training sessions which were each separated by two weeks. Experimenters used the mechanical winch to slowly

overcome the MVC of each participant, forcing an eccentric muscular contraction to occur.

Newham et al. (1987) reported a significant decrease in the MVC of subjects immediately following the first bout of eccentric RT. This decrease was found to be insignificant following the second and third bouts of training, suggesting that muscle fibers can adapt to eccentric training, over time. Similarly, measured values for plasma creatine kinase (CK), a known marker for assessing muscular damage (Koch, Pereira, & Machado, 2014; Schoenfeld, 2012; 2016), were significantly elevated following the first bout of training only and decreased with each successive bout. This adaptive phenomenon is commonly referred to in the literature as the *repeated bout effect*. The repeated bout effect suggests that acute post-exercise EIMD associated with high-intensity RT programs will decrease overtime. This concept is particularly interesting as muscular hypertrophy associated with RT is observable long after the acute post-exercise muscle damage has tapered off significantly. These observations and the repeated bout hypothesis further refute the necessity of EIMD as component of a RT program which seeks to induce muscular growth.

Vascular occlusion and muscle damage. Many researchers have sought to induce muscular hypertrophy without the accompanying muscle damage which is often associated with traditional RT (Allsopp & May, 2017; Takarada, Nakamura, et al., 2000; Wilson, Lowery, Joy, Loenneke & Naimo, 2013; Zanchi, 2010). Takarada, Nakamura, et al. (2000) and Takarada, Takazawa, et al. (2000) conducted investigations which support Schoenfeld's assessment that EIMD is not essential for muscular hypertrophy to occur.

During both studies, Takarada and colleagues investigated vascular occlusion as this technique creates a hypoxic environment for skeletal muscle cells by partially obstructing major blood vessels leading to the targeted musculature, which has been shown to increase motor unit recruitment when training with lower-intensity loads (Moritani, Sherman, Shibata, Matsumoto, & Shinohara, 1992; Schoenfeld, 2013; 2016). Their first study focused on low-intensity RT performed with vascular occlusion and the resulting acute responses in plasma growth hormone (GH), creatine kinase (CK), and lactate (Takarada, Nakamura, et al., 2000).

Takarada, Nakamura, et al. (2000) recruited male athletes (n = 6), aged 20 to 22 to participate in their vascular occlusion study. The researchers utilized a repeated-measures design in which participants completed the testing procedure with occlusion devices implemented, and then without. Participants performed a seated, bilateral knee extension through a 90-degree range of motion.

Plasma GH and blood lactate levels increased significantly following the training protocol. Plasma CK concentrations did not increase significantly due to the low-intensity occlusion training procedure, indicating that EIMD did not reach significant levels. Given the well documented anabolic influence of both GH and lactate (Schoenfeld, 2012; 2016; Tsukamoto et al., 2018), the significant increases in these substances post-exercise indicates that low-intensity RT with vascular occlusion may promote increases in skeletal muscle hypertrophy.

In a second study, Takarada, Takazawa, et al. (2000) recruited older women (n = 24) aged 47 to 67 with the intention to assess the long-term (16 weeks) training

adaptations of three different RT protocols: low-intensity (30 – 50% 1RM) with occlusion (LIO), low-intensity without occlusion (LI), and high-to-moderate intensity (50 – 80%) without occlusion (HI). During each protocol, participants performed the seated, single-arm dumbbell curl exercise. The researchers compared pre- and post-exercise CSA of the elbow flexor and extensor muscles.

All three protocols resulted in significant increases in CSA or the biceps brachii and brachialis muscles. The LIO and HI protocols resulted in significantly greater increases compared to the LI protocol (6.9%, 3.8%). Increases in CSA were not significantly different between the LIO (20.3%, 17.8%) and HI (18.4%, 11.8%) protocols. Interestingly, the triceps brachii muscle only experienced significant increases in CSA following the occlusion training, although the authors offered no explanation as to the precise mechanisms responsible for this result.

The controversial results of vascular occlusion (VO) and blood flow restriction (BFR) studies such as those conducted by Takarada and colleagues have provided substantial evidence questioning the necessity of high-intensity RT techniques in the pursuit of hypertrophy. The results of studies such as these have also increased the need for future researchers to conduct additional investigations focused on these techniques and their associated exercise-induced metabolic stress (EIMS) in order to elucidate the precise mechanisms and myogenic pathways which are responsible for muscular growth in response to low-intensity RT.

Metabolic Stress

The last primary mechanism believed to heavily influence the growth of skeletal

muscle fibers is metabolic stress. In the context of exercise, metabolic stress is a term

used to refer to the accumulation of various metabolites, or by-products of metabolic

processes (Schoenfeld, 2013). These metabolites primarily include lactate, hydrogen

(H^+), and inorganic phosphate (Pi) (Gentil et al., 2006; Green et al., 1983; Reeves et al.,

2006; Schoenfeld, 2013; 2016; Takarada, Nakamura, et al., 2000; Takarada, Takazawa, et

al., 2000; Tsukamoto et al., 2018). During RT, metabolites are primarily created through

the process of anaerobic glycolysis (Green et al., 1983; Rodrigues et al., 2010), as

glycolysis is the primary process utilized to rapidly replenish stores of adenosine

triphosphate (ATP) to facilitate further muscular contractions.

Although several physiological mechanisms have been proposed to explain how

EIMS mediates the hypertrophic process, these mechanisms are not fully understood, and

thus, they have not been entirely substantiated. Additionally, best practice methods for

inducing maximal EIMS have not been determined. Future research should evaluate the

role of various training variables on intra- and post-exercise EIMS. The following

subsections will review the current literature on EIMS and will focus on the substantiated

and hypothesized processes which may influence the post-exercise accumulation of

metabolites and the growth of human skeletal muscle cells.

Cellular swelling. One process through which EIMS is believed to mediate

hypertrophy involves a training-induced increase in intra-cellular pressure (Schoenfeld,

2013; 2016; Schoenfeld & Contreras, 2014). The enhanced intra-cellular pressure

gradient which is commonly observed in conjunction with EIMS is commonly referred to as *cellular swelling,* or the *muscle pump* (Schoenfeld, 2013; 2016; Schoenfeld & Contreras, 2014). Cellular swelling is a phenomenon which is heavily dependent upon the intensity, rest duration, and type of exercise performed. Resistance exercise which is highly dependent on anaerobic glycolysis, and which is conducted with relatively short inter-set rest intervals, has been shown to illicit a significant cellular swelling response (Schoenfeld, 2013; Schoenfeld & Contreras, 2014).

When one examines the processes which ultimately contribute to cellular swelling, the connection between this physiological phenomenon and RT becomes clear. Exercise which invokes repeated intense muscular contractions has the potential to compress veins attempting to carry blood out of working tissues (Schoenfeld, 2013; 2016; Schoenfeld & Contreras, 2014). However, arteries continue to supply freshly oxygenated blood to activated musculature in an attempt to supply oxygen and other nutrients to meet the metabolic demands of exercise. Additionally, acute vasodilation of localized arteries and arterioles during exercise further enhances the delivery of blood to working tissues. This enhanced delivery of fluid to myocytes, coupled with the depressed ability of veins to remove intramuscular fluid, creates a high, intramuscular pressure gradient (Schoenfeld & Contreras, 2014). The resulting increased intramuscular plasma volume allows blood from nearby capillaries to exude into interstitial spaces surrounding each myocyte, causing extracellular pressure to be significantly increased, further increasing the accumulation of fluids within effected muscle cells. Additionally, exercise which is primarily fueled by anaerobic glycolysis produces substantial intramuscular

volumes of metabolic byproducts (lactate, H$^+$, and phosphate). This increase in intramuscular solutes also increases the intramuscular pressure gradient, causing additional fluid to enter muscle cells (Schoenfeld & Contreras, 2014). Each of these four factors, reduced venous fluid release, increased vasodilation, increased interstitial pressure, and increased intracellular solute concentration, result in a compounded increase in intracellular pressure.

The significantly elevated intramuscular pressure associated with cellular swelling is believed to mediate hypertrophy through a myriad of observed and hypothesized processes. Cellular swelling has been shown to enhance the hypertrophic training response due to the positive influence that cellular hyperhydration has demonstrated on MPS (Millar, Barber, Lomax, Travers, & Shennan, 1997). Additionally, a strong causal relationship has been identified between cellular hypohydration and increased proteolysis, suggesting that cellular hyperhydration (or at least euhydration) negatively influences rates of muscle protein breakdown (Häussinger, 1996; Haussinger, Lang, & Gerok, 1994). These combined effects create an anabolic intramuscular environment which supports the accruement of additional contractile proteins.

In addition to promoting a positive muscle protein balance, researchers have theorized that cellular swelling also promotes hypertrophy via enhanced signaling of anabolic pathways, which is initiated by integrin-associated volume osmosensors located within each muscle fiber (Schoenfeld, 2013; 2016; Schoenfeld & Contreras, 2014). These intramuscular osmosensors are stimulated in response to excessive swelling-induced stretching of the sarcolemma. This excessive intracellular pressure is perceived as a threat

to cellular integrity. In response to the threat of cellular rupturing, osmosensors initiate

signals which upregulate several myogenic pathways in an effort to reinforce the cellular

ultrastructure, thus decreasing the potential for future cellular damage and facilitating the

additional accretion of intramuscular proteins (Schoenfeld, 2013; 2016; Schoenfeld and

Contreras, 2014).

Enhanced release of anabolic hormones. In addition to facilitating the

phenomenon of cellular swelling, EIMS has been shown to positively influence

concentrations of circulation anabolic hormones. Anabolic hormones, such as

testosterone (T), GH, and IGF-1 positively influence muscle protein balance by

supporting increased rates of MPS (Buresh, Berg, & French, 2009; Schoenfeld, 2013).

Although the acute release of anabolic hormones has long been associated with the

performance of high-intensity RT (Ahtiainen, Pakarinen, Kraemer, & Häkkinen, 2003;

Schoenfeld, 2011; 2012), a growing body of evidence is immerging which has connected

increased anabolic hormonal release to low-intensity resistance exercise performed with

partial VO (Reeves et al., 2006; Takarada, Nakamura, et al., 2000). The results of such

studies offer compelling arguments in support of metabolic stress as a means of elevating

circulating anabolic hormones. In one RT study, Reeves et al. evaluated the influence that

lactic acid concentrations can exert on acute circulating hormone concentrations by

analyzing and comparing the physiological responses to three different RT protocols.

Reeves et al. (2006) recruited healthy resistance-trained, male college students (n

= 8) to participate in an investigation to a) compare the responses in GH, T, cortisol, and

lactic acid concentrations following low-volume RT performed with partial BFR to those

observed following traditional RT; and b) determine the effects of statically applied

occlusion devices on skeletal muscle fibers. Researchers observed the metabolic and

hormonal responses resulting from three RT protocols: light resistance occlusion (LRO)

protocol, moderate resistance without occlusion (MR) protocol, and the attachment of an

occlusion device without exercise (OO).

The LRO protocol alone resulted in a significant increase in plasma GH

concentrations immediately post-exercise. There were no significant changes in serum T

or cortisol concentrations observed following any of the testing procedures. These

findings indicate that GH concentrations can indeed be manipulated via alternative

methods to high-intensity RT, possibly refuting the long-standing belief that heavy RT is

essential to the hypertrophic process (Reeves et al., 2006). However, the authors noted

that the musculature targeted by their investigation (bicep brachii and gastrocnemius)

have a relatively low volume of muscle mass, and thus, this study examined the effects of

lower volume training. The investigators speculated that higher volume training, which

could be performed utilizing larger muscle groups, may illicit differing results than those

observed in this investigation.

The findings of this investigation also suggest that both the LRO and MR

protocols may be viable methods to illicit a significant metabolic response, and the

associated benefits of metabolic stress in regard to growth of muscle tissue (Gentil et al.,

2006; Green et al., 1983; Reeves et al., 2006; Schoenfeld, 2013; Takarada, Nakamura, et

al., 2000; Tanimoto, Madarame, & Ishii, 2005). Considering the previously established

role of GH in promoting increases in the rate of MPS (Buresh et al., 2009; Schoenfeld,

2013), the additional significant GH response observed post-LRO training validates the usefulness of such training in RT programs focused on the development of lean muscle mass. The combination of metabolic and hormonal factors resulting from low-intensity RT performed with partial VO indicate that training techniques of this nature may be superior to traditional RT in optimizing the hypertrophic response.

Enhanced fiber recruitment. During activities of daily living and traditional resistance exercise, skeletal muscle fibers are activated in a pattern described by *Henneman's Size Principle* (Henneman, Somjen, & Carpenter, 1965), which states that motor units are activated according to their corresponding size, from smallest to largest, only when their contribution to total force production is required. This principle dictates that larger, *high-threshold motor units*, and the muscle fibers which comprise each motor unit, will remain inactive during low-intensity RT. As larger, high-threshold motor units encompass a greater number of muscle fibers and larger, type II fibers, it's logical that larger motor units carry greater hypertrophic potential, and thus, optimizing the growth of skeletal muscle fibers can only be accomplished if these motor units are activated.

In the pursuit of maximizing the hypertrophic training response, it is vital that as many motor units as possible are activated during each training session (Kraemer & Ratamess, 2004; Schoenfeld, 2016). When muscle fibers are innervated, they will experience the training stimulus, and thus, have the potential to adapt. Heavy RT of sufficient intensity has been shown to activate the full spectrum of muscle fiber types (Schoenfeld, 2016), however, muscular fatigue, induced via substantial metabolic stress, has been shown to contradict the size principle of muscle fiber recruitment, resulting in

the activation of high-threshold motor units during low-intensity RT (Gollnick, Armstrong, Sembrowich, Shepherd, & Saltin, 1973; Sahlin, Soderlund, Tonkonogi, & Hirakoba, 1997; Schoenfeld, 2013; 2016). This abnormal pattern of fiber recruitment has been observed particularly following low-intensity RT performed to muscular failure, indicating that training to failure may be necessary when training at lower intensities to maximize fiber recruitment (Schoenfeld, 2013).

Currently, several mechanisms have been purported to explain the reduced recruitment thresholds observed during low-to-moderate intensity RT (Schoenfeld, 2013; 2016). One such mechanism is the accumulation of Pi and H+, which has been shown to inhibit the contractility of lower-threshold motor units, thus reducing their potential for force production (Debold, 2012; Schoenfeld, 2013; Smith & Reid, 2006). As a result, additional, larger motor units are recruited to generate sufficient force to complete the desired muscular action (Schoenfeld, 2016).

A second hypothesis suggests that an increased production of reactive oxygen species (ROS), initiated during exercise, accelerates the symptoms of fatigue and contributes to contractile dysfunction in the later stages of muscular fatigue (Debold, 2012; Smith & Reid, 2006). One specific ROS that has been shown to effect muscular contractility is peroxynitrite (Snook, Li, Helmke, & Guilford, 2008). Snook and colleagues found that the filament velocity of actin was reduced when inoculated with approximately 10 μM of peroxynitrite. As a result of this effect, the researchers observed a compromised actomyosin interaction, which increased the force generating capabilities of the myosin myofilament, due to a decreased detachment rate from actin (Snook et al.,

2008). Although Snook and colleagues concluded that peroxynitrite indeed contributed to contractile dysfunction, the researchers also noted that, based on their findings, the effect was minimal. Currently, the degree to which ROS production and accumulation effects muscular contraction remains unknown and requires further study.

Some researchers have also speculated that hypoxia, induced via BFR, may disrupt the contractility of low-threshold fibers. As a result, higher-threshold motor units are activated to sustain force output when training at low intensities (Moritani et al., 1992; Schoenfeld, 2013). Moritani and colleagues (1992) observed progressive increases in both the amplitude and frequency of motor unit electromyography (EMG) spikes during low intensity (20% MVC), intermittent, isometric contractions when oxygen availability was compromised (via pressure inflated cuff). These findings suggest that an increased activation of higher-threshold motor units was required to maintain isometric force production during low-intensity occlusion training.

Researchers investigating motor unit recruitment during submaximal sustained (Sahlin et al., 1997) and short-duration (Gollnick et al., 1973) exercise have also estimated the extent of fiber recruitment by examining post-exercise PCr and intramuscular glycogen depletion. Sahlin and colleagues (1997) examined muscle fiber recruitment during cycling performed to exhaustion at 75% VO_{2max}. The investigators noted that, prior to exercise, PCr levels in type II fibers were approximately 20% greater than levels measured within type I fibers. However, upon reaching fatigue, PCr levels were measured to be similar in both fiber types, suggesting that all fibers analyzed were recruited during the exercise protocol. Gollnick and colleagues (1973) also observed

abnormal recruitment of motor units during 60-second cycling sprints performed at approximately 150% of participant aerobic power. Among their findings, Gollnick et al. noted that the first muscle fibers to experience glycogen depletion were fast-twitch, type II fibers, suggesting that high-threshold motor units were activated earlier than their slow-twitch, lower-threshold counter parts during heavy exercise. These observations of abnormal recruitment patterns contradict Henneman's Size Principle, and may lend support to abnormally enhanced recruitment of larger, high-threshold units during low-intensity RT.

Additional researchers, however, have observed significantly lower fiber activation during low-intensity RT (Manini & Clark, 2009; Schoenfeld, 2016; Suga et al., 2009). Using inorganic phosphate splitting, Suga et al. (2009) compared the effects of low-intensity (20% 1RM) occlusion training and moderate-intensity (65% 1RM) traditional resistance exercise on fast-twitch fiber recruitment. The investigators found that participants experienced only 31% fast-twitch fiber recruitment during the low-intensity occlusion protocol compared to 70% recruitment observed during traditional moderate-intensity RT. Further evidence contradicting enhanced fiber recruitment during low-intensity occlusion training was observed by Manini and Clark (2009), where EMG analyses depicted significantly lower recruitment during low-intensity (20% 1RM) occlusion training compared to high-intensity (80% 1RM) traditional RT.

Considering evidence that prolonged (16 weeks) low-load occlusion training can result in similar muscular growth compared to traditional RT (Takarada, Takazawa, et al., 2000), the conflicting observations surrounding the extent of motor unit recruitment

during low-load training suggest that fiber recruitment alone cannot fully explain hypertrophic adaptations. Additionally, mixed results surrounding enhanced recruitment of high-threshold motor units and fast-twitch fibers during low-intensity RT dictates that additional research be conducted to increase our understanding of the mechanisms which mediate the innervation of high-threshold motor units during low-intensity contractions.

<div align="center">Methodological Considerations</div>

The Influence of Lactate on the Hypertrophic Process

Lactate is the primary metabolic substrate produced within myocytes and red blood cells during anaerobic exercise, or times when oxygen availability is compromised (Tsukamoto et al., 2018). Currently, the effects of lactate accumulation on training adaptations are not fully understood. However, recent *in vitro* research has provided evidence that lactate may enhance satellite cell differentiation (Willkomm et al., 2014; Tsukamoto et al., 2018) and anabolic signaling (Nalbandian & Takeda, 2016).

Willkomm et al. (2014) treated C2C12 myoblasts, myocyte precursor cells found in mice, with 10mM and 20mM of lactate for two hours a day over a five-day period. C2C12 cells were selected based on the characteristics which they have in common with skeletal muscle satellite cells in humans: they are capable of undergoing rapid differentiation and they procreate contractile myotubes. At the conclusion of the testing period, researchers concluded that lactate administration-initiated withdrawal from the cellular cycle and early differentiation in C2C12 cells, resulting in the formation of new myoblasts. However, myosin heavy chain (MHC) and myogenin, two markers reflecting the occurrence of late differentiation (myotube fusion), were decreased within

experimental cells. These results suggest that, while lactate positively influences the rapid differentiation of C2C12 cells into myoblasts, the presence of the metabolic intermediary may also hinder the differentiation of myoblasts into fused myotubes, thus delaying the development of additional myocytes.

In a similar experiment, Tsukamoto and colleagues (2018) demonstrated that cultured C2C12 cells experienced significantly accelerated myogenesis when cultured for five days with 10mM of lactate. Researchers selected 10mM as the treatment dosage as this volume of lactate is commonly observed *in vivo* during moderate-to-high intensity exercise (65% to 85% Wmax). After five days of lactate treatment, 58.5% of treated myoblasts successfully fused forming myotubes (a precursor to skeletal muscle fibers), compared to the significantly lower fusion rate of the untreated cells which was, 38.3%. These findings seem to contradict the results of Willkomm et al. (2014) and suggest that lactate indeed positively influences both early and late differentiation of C2C12 cells *in vitro* and suggests a similar relationship may exist between lactate and satellite cells.

Lactate administration has also been observed to influence rates of MPS (Oishi et al., 2015). When Oishi and colleagues (2015) treated C2C12 myotubes with 10mM of lactate for a six-hour period, the cultured samples experienced significantly elevated myogenin levels and p70S6K phosphorylation, a known primary regulator of MPS, when compared to a control culture which did not receive the lactate treatment. However, a more recent *in vitro* study (Tsukamoto et al., 2018), found that p70S6K phosphorylation was unaffected by sustained (five days) lactate treatment.

Further support of the potential myogenic relationship between lactate and satellite cells can be observed amongst the results of a recent *in vivo* study which examined the effects of direct lactate injection on muscle regeneration and hypertrophy in mice (Tsukamoto et al., 2018). Tsukamoto and colleagues (2018) demonstrated the hypertrophic potential of sustained lactate exposure within the tibialis anterior musculature of mice (n = 9) when compared to a control group (n = 9). On day one of the study, all mice were subjected to muscular damage via glycerol injection. Each mouse in the experimental group was then injected with sodium lactate at a dosage of 500mg/kg/day over a seven-day period. Three mice from the experimental group were sacrificed on day seven, 14 and 28 of the study.

Upon examination of experimental group subjects, researchers observed significantly elevated muscle tissue regeneration and fiber hypertrophy. The fact that lactate administration was induced via injection in this study, rather than through exercise, eliminates any potential influence from mechanical loading (muscular tension) on fiber growth, and thus, suggests that the presence of lactate alone initiated the significant physiological adaptations observed.

Due to semi-inconsistent findings, future research is needed to determine the full myogenic potential of lactate administration (*in vitro*) and exposure (*in vivo*). Additionally, future research should seek to identify minimal and ideal concentrations at which lactate will influence hypertrophy. Researchers should also observe the effects of short-term (less than two hours) lactate administration to ascertain potential deviations from observations made during experiments involving more chronic lactate treatment

(two hours up to 28 days). Such research would be of potential benefit to populations who are unfit to participate in higher-intensity exercise, but who are in need of myogenic stimulation, namely aging-populations and rehabilitation patients.

<u>Evaluating Metabolite Accumulation</u>

       <u>Direct measures of lactate accumulation.</u> When evaluating the exercise-induced accumulation of metabolites, researchers often proceed with one of two methods: 1) collect muscle biopsies, or 2) collect whole-blood samples (Tesch et al., 1982; Shanely et al., 2014). The former method includes invasive, potentially debilitating procedures involving the removal of irreplaceable muscle tissue. Collecting biopsy samples has also proven difficult during exercise and promptly post exercise. For these reasons, researchers often opt for the alternative method used to evaluate the accumulation of metabolites: whole-blood sampling.

       <u>Indirect measures of lactate accumulation.</u> Researchers have referred to the initial accumulation of exercise-induced lactate by a wide variety of names, including: anaerobic threshold (AT), lactate threshold (LT), onset of blood lactate accumulation (OBLA), and maximal lactate steady state (MLSS) (Plato, McNulty, Crunk, & Ergun, 2008). Regardless of the term used, this metabolic marker indicates that anaerobic pathways are predominantly responsible for ATP resynthesis, and the resulting exercise-associated lactate accumulation is a resultant of excessive lactate production beyond the ability of the body to eliminate the acidic metabolic by-product of anaerobic metabolism (Solberg, Robstad, Skjønsberg, & Borchsenius, 2005). Due to the purported negative impact that lactate accumulation is believed to exert on exercise performance

(Abdessemed et al., 1999; Myers & Ashley, 1997) researchers have long sought to

identify and delay the occurrence of the AT. Many researchers have determined the AT

by collecting venous and capillary blood samples from individual's mid-exercise

(Kraemer et al. 1990; Takarada, Nakamura, et al., 2000; Tanimoto et al., 2005). However,

the direct measuring of blood lactate involves invasive methods such as blood draws and

finger pricks. Due to the undesirable nature of these methods, many researchers have

sought to indirectly measure exercise-induced lactate accumulation (Beaver, Wasserman

& Whipp, 1986; Plato et al., 2008; Solberg et al., 2005). These researchers concluded that

an accurate estimate of AT can indeed be determined via indirect measurements.

Indirect estimates of AT have been accurately calculated based on various

ventilation metrics. Beaver and colleagues (1986) evaluated a computer simulated

regression of the volume of oxygen (VO_2) and the volume of carbon dioxide (VCO_2)

relationship and identified a crossing pattern which was indicative of excessive

intramuscular lactate accumulation. This *V-slope method* has proven as a viable method

of recognizing the OBLA as the excessive production and buffering of lactate results in a

substantial increase in the VCO_2 expired.

In addition to the V-slope method of estimating AT, other researchers have used

the *respiratory exchange ratio* (RER) when estimating the point at which lactate

production exceeds elimination rates (Myers & Ashley, 1997). It has been suggested that

a significant rise in RER indicates the occurrence of the AT. However, RER cutoff values

indicating the occurrence of the AT have varied considerable from one research team to

the next (Solberg et al., 2005). The inconsistency with the RER cutoff values used to indicate AT has led researchers to doubt the accuracy of the RER-estimated AT method.

Currently, few studies have monitored participant ventilatory exchange during the execution of resistance exercise. Researchers who have examined the metabolic effects of RT via ventilation have largely focused their investigations on individuals who had been diagnosed with chronic obstructive pulmonary disease (COPD) (Houchen-Wolloff et al., 2014; Probst, Troosters, Pitta, Decramer, & Gosselink, 2006; Sillen, Janssen, Akkermans, Wouters, & Spruit, 2008). Symptoms of COPD, such as exercise intolerance, can result in decreased peripheral muscular force production and muscle mass (Sillenet al., 2008). Symptoms such as these make it difficult, dangerous, or in some cases, impossible for individuals to perform RT exercise at high intensities. Furthermore, these symptoms compromise assessments of muscular strength, and thus, decrease the accuracy of RT intensity prescriptions based on a percentage of 1RM.

Future researchers seeking to observe the metabolic response to exercise via ventilation should focus their investigations on generally healthy and resistance-trained individuals. Additionally, future studies should include RT protocols which demand that participants work at a greater relative intensity. Such studies could prove useful in determining if ventilatory exchange can indeed serve as an accurate assessment of the exercise-induced metabolic response to RT.

Training Variables

Work volume. *Work volume*, or more simply *volume*, refers to the total quantity of exercise performed during a specified time period (Schoenfeld, 2016). In the context of

RT, volume is typically calculated by multiplying the number of exercise sets performed by the number of total repetitions completed (sets x reps). However, this equation fails to consider exercise intensity. To account for exercise intensity, *volume load* can be calculated by multiplying the training volume by the load lifted (sets x reps x load). Volume load (VL) is an important training variable to consider as it can highly influence training adaptations

A dose response relationship has clearly been identified between RT volume and hypertrophic adaptations, until a maximal threshold is reached, at which point this relationship diminishes (Burd et al., 2010; Schoenfeld, 2016; Schoenfeld, Ogborn, & Krieger, 2016; Terzis et al., 2010; Wernbom, Augustsson, & Thomeé, 2007). A common consensus amongst RT researchers is that multiple sets of exercise are recommended to achieve optimal hypertrophic training responses (Schoenfeld, 2016; Wernbom et al., 2007).

In a comprehensive review of research primarily focusing on untrained individuals, Wernbom and colleagues (2007) concluded that participants experienced greater daily increases in CSA of the elbow flexors when four-to-six sets of exercise were performed (.24%) compared to when three-to-three-and-a-half sets were completed (.17%). Wernbom et al. also concluded that, in addition to performing more total sets of exercise, performing a greater number of total repetitions per session resulted in significantly greater increases in muscle CSA (Schoenfeld, 2016; Wernbom et al., 2007). The completion of total repetitions of exercise in the range of 42 to 66 repetitions, resulted in an additional .11% of cross-sectional growth per day, compared to lower

ranges (7 to 38) (Wernbom et al., 2007). When Wernbom and colleagues evaluated the available research focusing on the hypertrophy of a larger muscle group, the quadriceps, the researchers concluded that performing 10 or more sets of exercise per training session and performing 40 to 60 repetitions per training session resulted in the greatest cross-sectional growth per day (.14 and .13%, respectively).

The dose-response relationship between RT volume and hypertrophic adaptations has also been observed within trained populations. Schoenfeld and colleagues (2019) found that five sets of repetitions per exercise elicited significantly greater increases in MT in the elbow flexors, mid-thigh, and lateral thigh when performed over an eight-week period, compared to a single set.

In addition to hypertrophic outcomes, research focusing on the accumulation of metabolites in circulation and within muscle cells suggests that exercise-associated metabolic responses increase with training volume (MacDougall et al., 1999; Schoenfeld, 2013; 2016). This observation appears to be logical as the primary source of EIMS is anaerobic metabolism, and the rate of ATP production via anaerobic energy pathways is increased significantly during, and in response to, RT conducted at moderate intensities (Schoenfeld 2013).

Macdougall and colleagues (1999) observed and measured the metabolic responses following varying volumes of resistance exercise with the intention of evaluating the effect that lactate accumulation and intramuscular phosphocreatine (PCr) depletion have on fatigue in human skeletal muscle. Researchers randomly assigned male bodybuilding competitors (n = 8) to one of two groups: Group A performed a single set

of seated, single-arm bicep curls against 80% 1RM, and Group B completed three sets of repetitions with three-minute inter-set rest intervals. All sets of exercise were performed to failure. Pre and post-test muscle biopsies and blood samples were collected.

Intramuscular and whole-blood lactate concentrations increased significantly for both groups, from pre-test to post-test measurements. However, the increase between groups was not statistically significant. Group A's (low volume) post-exercise muscle lactate was measured at 91.4 $mmol*kg^{-1}$ compared to 118 $mmol*kg^{-1}$ measured in Group B (high volume). The single set of exercise performed by Group A participants resulted in a rise in whole-blood lactate from 1.7 to 3.5 $mmol*L^{-1}$ while the three sets of exercise performed by Group B resulted in a rise from 1.7 to 4.7 $mmol*L^{-1}$.

The authors attributed the additional accumulation of intramuscular and whole-blood lactate following three sets of resistance exercise to the inadequate length of rest time given between successive bouts of muscular contractions. The three-minute rest intervals allowed between each set of repetitions were not sufficient to allow for muscle lactate to be completely cleared, and for blood lactate to fully dissipate. Although statistically insignificant, the additional accumulation of lactate experienced by Group B participants indicates that increased physical work volume and short-duration inter-set rest periods contribute to an increased metabolic response.

The insignificant differences in post-exercise lactate concentrations between groups suggests that three-minute rest periods allowed for the partial clearance of exercise-associated metabolic by-products and implicates that shorter rest periods may be beneficial for optimally inducing accumulated metabolic stress following repeated sets of

resistance exercise. Given the influence that rest periods may have on the metabolic response to training, this training variable warrants further discussion.

Inter-set rest intervals. The manipulation of inter-set rest intervals and the resulting influence on EIMS has been studied at length (Abdessemed et al., 1999; Henselmans & Schoenfeld, 2014; Kraemer et al., 1990; Schoenfeld, 2013). Abdessemed and colleagues (1999), evaluated the metabolic effect of RT conducted with varying inter-set rest intervals. Abdessemed and colleagues recruited healthy, untrained males (n = 10) and utilized a repeated-measures design in which each participant performed 10 sets of 6 repetitions of the barbell bench press exercise at approximately 70% of each individual's 1RM. Each participant repeated this exercise protocol on three separate occasions, incorporating different inter-set rest intervals during each exercise session. The rest periods tested included: one minute (Prot1), three minute (Prot3), and five-minute periods (Prot5).

Abdessemed et al. (1999) found that participants experienced a significant increase in blood lactate accumulation when comparing sets four and ten of the Prot1 exercise protocol. Although participants did experience progressive lactate accumulation with each additional set of repetitions, the inter-set lactate elevations were not statistically significant. The progressive increases in whole body lactate observed in Prot1 occurred simultaneously with degenerative effects on mean muscular power. Interestingly, Abdessemed et al. suggested that the significant decline in muscular power observed during the Prot1 protocol were not attributable to the accumulated lactate, rather

significant decreases in PCr were believed to have caused the significant decline in muscular power when 60-second inter-set rest intervals are allowed.

Kraemer et al. (1990) also conducted a RT study focusing on the EIMS resulting from varying inter-set rest intervals. Researchers assigned recreationally trained male weight lifters (n = 9) to six heavy RT protocols to be performed in a randomly selected order, with one week separating each trial. The study's experimental design was developed so that the six RT protocols were categorized into one of two series. The first series (S) of training sessions was classified as "strength workouts," and included three RT protocols, including: 5 RM performed with three-minute rest intervals (primary workout), 10 RM performed with three-minute rest intervals (load control), and 5 RM performed with one-minute rest intervals (rest control). Series two (H) RT protocols were classified as "hypertrophy workouts," which also consisted of three RT protocols, including: 10 RM performed with one-minute rest intervals (primary workout), 5 RM performed with one-minute intervals (load control), and 10 RM performed with three-minute intervals (rest control). Variations of each series' primary workout (load control and rest control) were included in the study to assist researchers in identifying the source (work, load, or rest interval) of observed deviations in post-exercise lactate values. Additionally, participants performed significantly less work volume in S training sessions compared to the workouts performed in the H series.

In both series, post-exercise whole blood lactate was observed to be greatest following the training sessions in which participants performed exercises with 60-second inter-set rest periods. This result suggests that short (e.g. 60 seconds or less) inter-set rest

durations result in optimal accumulation of metabolites, regardless of the exercise

intensity (Kraemer et al., 1990). The influence that reduced rest interval duration had on

blood lactate concentrations indicates that inter-set blood lactate clearance occurs when

three-minute inter-set rest intervals are allowed, and that if metabolic stress is to be

maximized, lower rest intervals should be prescribed (Kraemer et al., 1990; Schoenfeld,

2016). This result also suggests that longer intra-set work durations may lead to a greater

accumulation of metabolites (e.g. 10 repetitions or more per set).

     <u>Training tempo.</u> In addition to inter-set rest intervals, repetition duration, also

referred to as training tempo, has been shown to influence the accumulation of

metabolites resulting from exercise (Martins-Costa et al., 2016; Schoenfeld, 2016;

Schoenfeld et al., 2015). The term *training tempo* refers to the total time duration

required to perform the concentric, eccentric, and isometric components of each

repetition of a specified movement (Schoenfeld, 2015; 2016). Training tempo is generally

communicated in either a three- or four-digit expression (Pereira et al., 2016, Schoenfeld,

2016), where each digit represents the time duration, measured in seconds, required to

perform a portion of the specified movement. The first digit represents the concentric

duration, the second represents the isometric pause between the concentric and eccentric

actions, the third digit represents the duration of the eccentric action, and a fourth digit

can be used to refer to the isometric pause between the eccentric and concentric actions.

     Although the physiological effects of training tempo manipulation are still under

investigation, results from RT studies and the conclusions from a recent meta-analysis

(Schoenfeld, 2015) support the hypothesis that short-to-moderate (.5 to 8 seconds)

training tempos will result in optimal hypertrophy with little differences occurring (Schoenfeld et al., 2015). However, repetitions lasting 10 seconds or longer in duration may have negative effects on hypertrophic adaptations, possibly resulting from decreased muscular activation during exercise (Keogh, Wilson, & Weatherby, 1999; Schuenke et al., 2012; Schoenfeld, 2016).

In addition to hypertrophic outcomes, researchers have investigated the effects of training tempo on the accumulation of lactate during exercise (Lacerda et al., 2016; Martins-Costa et al., 2016: Mazzetti, Douglass, Yocum, & Harber, 2007; Schoenfeld, 2016). Lacerda and colleagues (2016), found that concentric and eccentric contractions lasting approximately 1.5 seconds each (1.5-0-1.5-0) resulted in greater blood lactate accumulation compared to a repetition duration of 6 seconds (3-0-3-0). An important consideration made by Lacerda and colleagues was the equalization of time under tension, and thus, work volume, between protocols. Conversely, Martins-Costa et al. (2016) observed a significantly greater blood lactate response following resistance exercise performed at a slower training tempo (2-0-4-0) compared to exercise performed at a faster tempo (2-0-2-0). Further support for longer duration repetitions was observed by Mazzetti and colleagues (2007), where slow (2-0-2-0) contractions resulted in significantly greater post-exercise blood lactate concentrations compared to repetitions which included an explosive concentric contraction (1-0-2-0).

With the recent increased interest into EIMS as an effective hypertrophic mechanism, training variables, such as training tempo, may be important considerations for researchers when creating exercise procedures designed to study the physiological

effects of metabolite accumulation. A review of the presented findings suggests that, when attempting to maximize the accumulation of metabolites during and following RT, moderate, controlled (e.g. 2-0-2-0) training tempos will elicit a superior metabolic response compared to quick, explosive repetitions (1-0-1-0).

Conclusions and Implications of Previous Research

Exercise-induced metabolic stress has been identified as a primary hypertrophic mechanism (Schoenfeld, 2010; 2013; 2016; Schoenfeld & Contreras, 2014), however, the benefits, best practices, and practical application potential of this physiological phenomenon remain unclear at this time. The observed and theorized benefits unique to the training-induced accumulation of metabolites warrants further investigation. Additionally, methods of inducing an optimal accumulation of metabolic by-products, involving the manipulation of various training variables; including work volume, rest intervals, and training tempo, should be examined and elucidated to assist future researchers seeking to investigate further the theorized benefits of EIMS (cellular swelling, elevated rate of MPS, down regulation of proteolysis, and enhanced release of anabolic hormones) (Schoenfeld, 2013; 2016; Schoenfeld & Contreras, 2014).

CHAPTER 3

METHODS

Participants

All recruitment methods and experimental procedures were approved by the

Institutional Review Board Committee of the University of Northern Iowa.

Recreationally trained males were invited to participate in a resistance training study.

Participant eligibility was contingent upon each individual being in generally good health

and fitness, allowing them to safely engage in resistance exercise. The health and fitness

status of each potential participant was assessed through the required completion of the

Physical Activity Readiness Questionnaire (PAR-Q). Due to the musculoskeletal stress

associated with RT, individuals were dismissed from the study if they indicated that they

were currently experiencing any musculoskeletal injuries which would impair their

ability to safely execute the barbell bicep curl exercise. All participating individuals were

asked to complete a brief training history questionnaire. Individuals who indicated that

they had consistently conducted RT (3 hours/wk) for at least six months prior to their

orientation session were deemed recreationally trained and were eligible to participate in

the investigation if they fulfilled all additional requirements.

Prior to the start of the study, potential participants were asked to report the use of

dietary supplements containing any form of creatine. The use of creatine supplements

was included in the eligibility criteria as this ergogenic aid has been shown to

significantly enhance an individual's work capacity (Rawson & Volek, 2003; Volek et

al., 1997). Potential subjects were dismissed if they indicated that they had supplemented

with creatine-based products within the past four weeks. Additionally, due to the demanding nature of the testing protocols, potential participants were dismissed from the proposed study if they were engaging in a calorically restricted or a carbohydrate-restricted (ketogenic) diet.

<div align="center">Instruments</div>

During all testing sessions, participants were asked to perform repetitions of the barbell bicep curl exercise utilizing a plate loaded EZ curling bar. Participants were asked if they were familiar with the exercise prior to completion of the orientation session. If a participant indicated that they were unfamiliar with the exercise, research personnel provided a demonstration. During all testing sessions, participants were fitted with an arm blaster (Celebrita MMA, USA), which was worn during the execution of all repetitions. The Parvo Medics TrueOne 2400 (Salt Lake City, UT) was used to monitor and record participant metabolic data during all trials. All whole-body blood lactate measurements were made using the Lactate Plus Meter (Nova Biomedical, Waltham, MA) using the Lactate Plus Test Strips (Nova Biomedical, Waltham, MA).

<div align="center">Procedures</div>

Orientation Session

All participants attended an initial 30-minute orientation session individually. During the orientation session, participants were first asked if they had any additional questions about the objectives, procedures, or future implications of the current study. Participants then read and signed an informed consent document.

After the informed consent was completed, participants then completed a training history questionnaire, which was used to identify that each participant had a minimum training history of six-months of consistent RT. After completing the training history questionnaire, participants were asked if they were familiar with the barbell bicep curl exercise. Individuals who indicated that they had minimal or no experience with the exercise were given a demonstration provided by research personnel. Next, each participant completed a body composition assessment using the InBody 770 bioelectrical impedance analyzer (InBodyUSA, Cerritos, CA). During the body composition assessment, the height of each participant was self-reported and documented.

Following the completion of the body composition assessment, a 1RM for the barbell bicep curl exercise was determined for each participant following guidelines established by the National Strength and Conditioning Association (NSCA) (Haff & Triplett, 2015). An attempted 1RM test for the bicep curl exercise was considered successful when a participant was able to perform a single repetition of the exercise through the full range of motion described by researchers while maintaining contact between their upper back and posterior hips with the wall located immediately behind them. Attempts began at a starting load of 38.6 kilograms and the load was increased or decreased as necessary based on participant exertion level. When attempting to establish a 1RM, participants were allowed to rest for 60 seconds between attempts.

Participants were given five minutes of rest following the 1RM testing procedure. After the five-minute recovery period, participants were asked to perform three sets of maximal repetitions of the barbell curl exercise at approximately 50% of their 1RM. The

purpose of these three sets of exercise was to allow participants to become familiarized

with the procedures and equipment which were to be used during each testing session.

Participants were allowed 60-second rest periods between each set of exercise. During

the execution of the three familiarization sets, participants were instructed to follow the

pacing of a metronome to ensure that each concentric and eccentric phase of exercise

lasted two seconds in duration.

The range of motion for the standing barbell curl exercise began with the

participant's elbow joints fully extended and ended when the barbell was returned to the

starting position. The end range of motion for the concentric phase of each repetition was

identified when the elbow joint reached maximum flexion. Throughout the duration of

each set of repetitions, each participant's upper back and posterior hips remained in

contact with the wall located immediately posterior. Each set of exercise was concluded

when each participant could no longer complete a repetition through the prescribed range

of motion, or when any part of the participant's back or hips lost contact with the surface

of the posterior wall.

Experimental Procedures

Testing sessions were conducted on three separate testing days. Seven days

passed between the completion of the orientation session and the first testing session. A

minimum recovery period of 72 hours was observed between each testing session to

allow for complete recovery of the elbow flexor muscle group. Each testing session lasted

approximately 30 minutes in duration. Participants reported to each testing session

individually. Upon arrival at the testing site, participants completed a 48-hour recall

questionnaire which was used to assess muscular soreness of the elbow flexors during the previous 48 hours, all biceps training performed during the previous 48 hours, and nutritional intake during the previous 48 hours.

Following the completion of the 48-hour recall questionnaire, participants immediately began a general warm up protocol. During the general warm up protocol, participants first biked at 70 revolutions per minute (rpm) for five minutes on a cycle ergometer working against a frictional resistance of 2 kiloponds (kp). To complete the warm up protocol, participants next performed a series of upper body dynamic exercises consisting of 20 repetitions of a chest opening exercise and 20 repetitions of both forward and backward arm circles.

After completing the general warm up protocol, participants were then fitted with the arm blaster equipment and connected to the Parvo Medics TrueOne 2400 metabolic measurement system. Participants were then instructed to stand with their back and hips in contact with the posterior wall for a three-minute baseline period. Approximately five minutes in total were allowed to elapse between the completion of the warm up protocol and the beginning of the first set of exercise.

Training intensity was randomly assigned to each participant during the three-minute baseline period immediately prior to the start of the testing procedure for each of three trials (Test1, Test2 and Test3). The three training intensities tested included 30%, 60%, and 90% 1RM. After the completion of the three-minute baseline period, participants were instructed to performed three sets of the barbell curl exercise until they reached technical failure. Researchers monitored each repetition to ensure that the

eccentric and concentric phase of each repetition followed the pacing of a metronome set at 60 bpm. Participants were instructed to allow two beats of the metronome to occur during both the eccentric and concentric phases of the movement. All repetitions completed were performed through a full range of motion, identical to the range of motion performed during the initial strength test and familiarization sets conducted during the orientation session. All inter-set rest intervals were 60 seconds in duration. All loads lifted were rounded to the nearest 2.27 kg.

Metabolic Metrics

RER, VCO_2, and VO_2 were monitored at 15 second intervals during each testing session using the Parvo Medics TrueOne 2400 metabolic measurement system. Specific time points were noted during each session, including baseline, post set 1 (Post1), post set 2 (Post2), post set 3 (Post3), five minutes post exercise (Post5), and at 15 minutes post exercise (Post15), and were used for data retrieval following the completion of all testing sessions.

Blood Lactate

All blood samples were collected via finger prick of each participant's non-dominant index finger. Pre-exercise blood samples were taken immediately prior to each trial (Pre). Following each testing procedure, blood samples were collected immediately after the completion of the third and final set of repetitions (Post). Additional samples were collected at five minutes (Post5) and 15 minutes post-exercise (Post15).

Volume Load (VL)

All repetitions performed by each participant during each set of exercise were recorded by study personnel. This data, along with the loads lifted by each participant during each respective trial were used to calculate the total VL completed by each individual during each trial. Range of motion displacement for participants was not measured as the quantity of volume load performed was not compared amongst individuals. Total VL was the product of S (number of sets performed) x R (repetitions performed) x L (load lifted).

Statistical Analysis

Participant performance during each session was recorded by study personnel in Microsoft Excel. Upon completion of all trials, participant data was entered into SPSS statistical analysis software (IBM). All data were analyzed utilizing a two-way (condition x time) ANOVA, in which each participant's biological, metabolic, and performance metrics (blood lactate, average VO_2, average VCO_2, average RER, and VL) were evaluated based on time and condition. When a significant interaction was observed, an effect size between the two variables was calculated based on criteria proposed by Rhea (2004) for adjusting effect size (ES) based on participant training status (Turner et al., 2015). Presented effect sizes for recreationally trained individuals are delineated as follows: small (.35 - .80), moderate (.8 – 1.49), and large (> 1.5). All results are presented as mean ± standard deviation.

CHAPTER 4

RESULTS

Participant Descriptive Statistics

Recreationally trained male weight lifters volunteered to participate in this RT study. Two participants withdrew from the study following the completion of the orientation session, leaving a sample size of 11. The participants ranged in age from 18 to 21 (19.5 ± 1.2) years of age. Participant mean height, weight, and body fat percent were 71.1in. ± 2.1, 80.1kg ± 9, and 13% ± 4.1, respectively. All participants successfully completed each of the three trials.

Blood Lactate

There were no significant differences observed in the blood lactate response when evaluated by time and condition, $F (6, 120) = .529$, $p = > .05$. Measured lactate values are reflected in Table 1. Blood lactate by time and condition is reflected in Figure 1.

Table 1 Blood Lactate by Time and Condition

Blood Lactate (mmol)

Condition	Pre	Post	5-min Post	15-min Post
30	3.74 ± 1.14	7.19 ± 2.7	6.05 ± 1.87	3.95 ± 1.41
60	5.35 ± 3.33	7.06 ± 2.85	6.41 ± 1.91	4.45 ± 2.09
90	4.55 ± 3.64	6.31 ± 3.98	4.42 ± 2.18	3.27 ± 2.16

Figure 1 Blood Lactate by Time and Condition

Figure 1 Blood Lactate by Time and Condition

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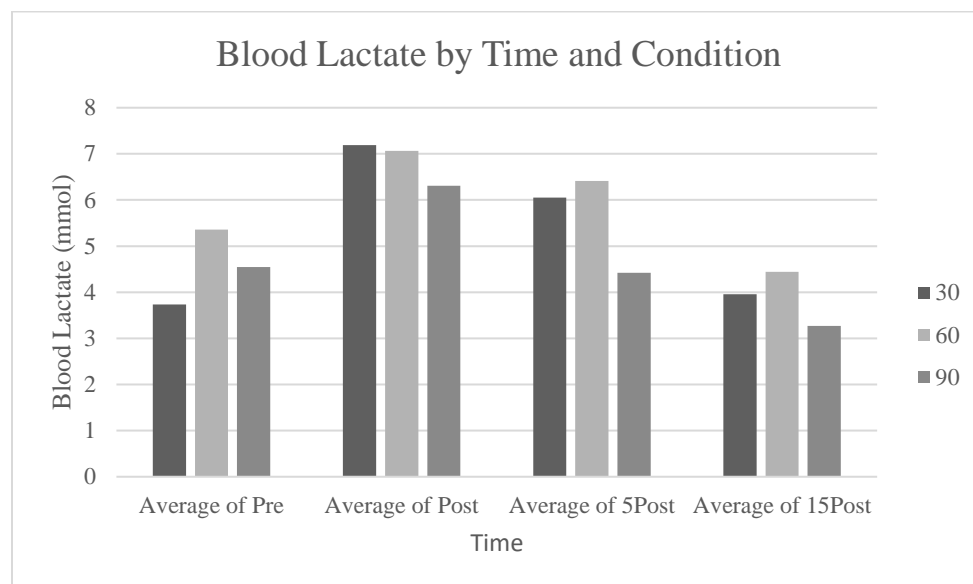
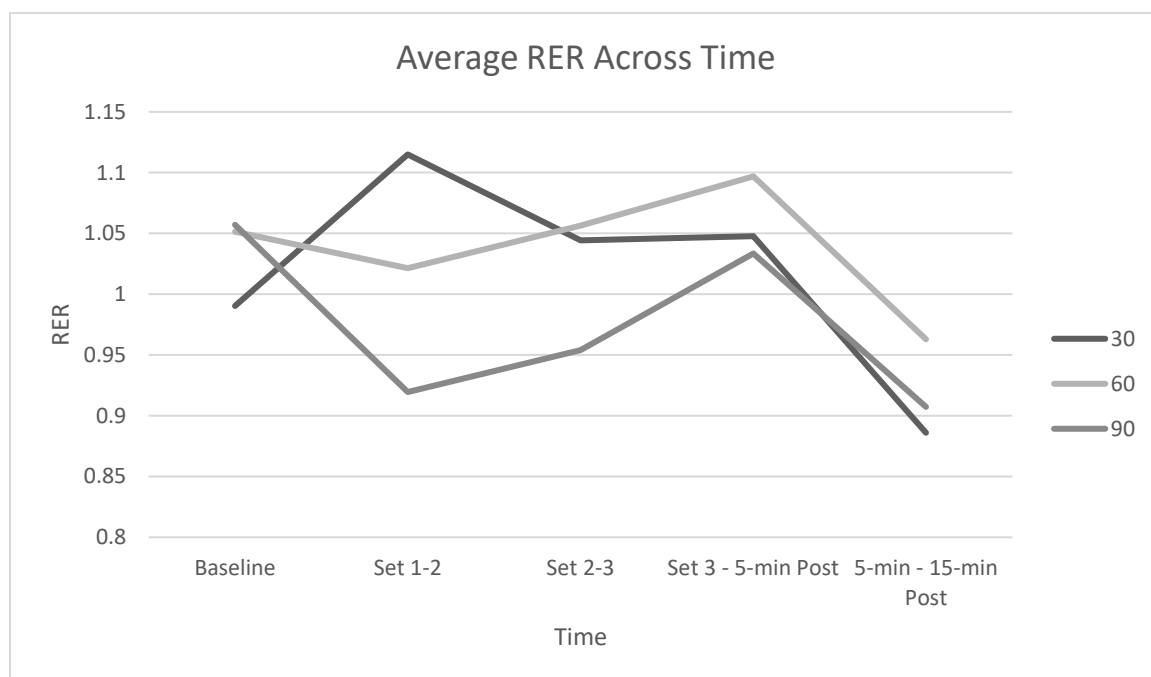<div align="center">Metabolic Metrics</div>

RER

There were statistically significant interactions between the effects of condition and time on RER, $F_{(8, 150)} = 3.314$, $p = .002$. Statistically significant differences were observed in RER between Post1 and Post2, favoring the 30% condition over the 60% (ES = 1.05, p = .026) and the 90% condition (ES = 1.79 , p < .001), and the 60% condition over the 90% condition (ES = .87, p = .016). RER values were also significant between Post2 and Post3 favoring the 30% condition over the 90% (ES = .99, p = .031) and the 60% condition over the 90% (ES = 1.11, p = .015). Observed RER values were similar during the 30% and 60% conditions at all time points other than the period between Post1 and Post2. Measured values for RER by time and condition are listed in Table 2. RER values by time and condition are presented in Figure 2.

Table 2 RER by Time and Condition

RER

Con.	Baseline	Set 1-2	Set 2-3	Set 3 - 5-min Post	5-min - 15-min Post
30	0.99 ± 0.11	$1.11 \pm 0.08^*$	$1.04 \pm 0.07^\wedge$	1.05 ± 0.08	0.89 ± 0.05
60	1.05 ± 0.13	$1.02 \pm 0.1^{*\#}$	$1.06 \pm 0.07^\#$	1.1 ± 0.07	0.96 ± 0.08
90	1.06 ± 0.14	$0.92 \pm 0.13^{*\#}$	$0.95 \pm 0.11^{\wedge\#}$	1.03 ± 0.12	0.91 ± 0.09

Note. * denotes significant difference ($p < 0.05$) between 30%, 60%, and 90% conditions, # denotes significant difference between 60% and 90% conditions, and ^ denotes significant differences between 30% and 90%

Figure 2 RER by Time and Condition

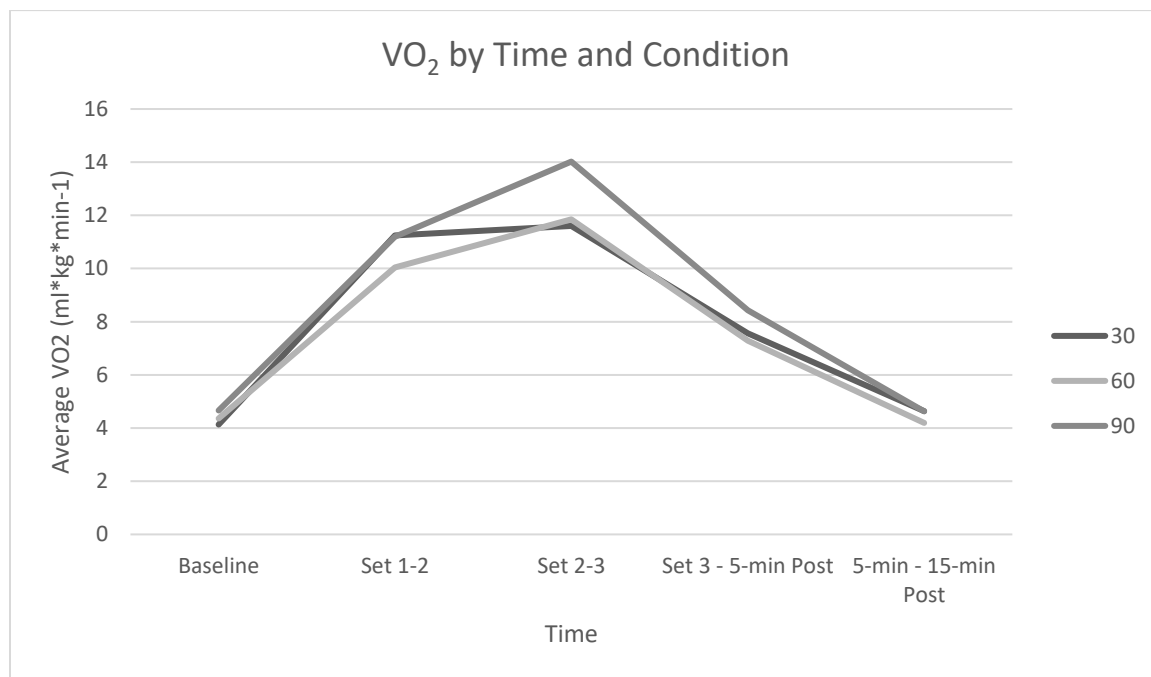VO$_2$

There were no statistically significant interactions observed between the effects of condition and time on participant VO$_2$ during any trials, $F_{(8, 150)} = .744$, $p = .653$.

Recorded values for participant VO$_2$ are listed in Table 3, and VO$_2$ is presented by time

and condition in Figure 3.

Table 3 VO$_2$ by Time and Condition

VO2 (ml*kg*min-1)					
Con.	**Baseline**	**Set 1-2**	**Set 2-3**	**Set 3 - 5-min Post**	**5-min - 15-min Post**
30	4.13 ± 1.93	11.25 ± 2.59	11.6 ± 2.54	7.56 ± 1.79	4.64 ± 1.56
60	4.35 ± 1.7	10.04 ± 3.31	11.85 ± 3	7.29 ± 2.06	4.19 ± 1.63
90	4.66 ± 1.03	11.2 ± 2.31	14.02 ± 3.22	8.42 ± 1.34	4.63 ± 0.57

Figure 3 VO$_2$ by Time and Condition

VCO$_2$

There were no statistically significant interactions observed between the effects of acute VL and time on participant VCO$_2$ during any trials, $F (8, 150) = 1.209$, $p = .298$. Measured VCO$_2$ values are presented in Table 4. VCO$_2$ values by time and condition are depicted in Figure 4.

Table 4 VCO$_2$ by Time and Condition

VCO2 (ml*kg*min-1)

Con.	Baseline	Set 1-2	Set 2-3	Set 3 - 5-min Post	5-min - 15-min Post
30	4.16 ± 2.09	12.43 ± 3.24	11.99 ± 2.8	7.69 ± 1.73	4.05 ± 1.31
60	4.61 ± 1.8	10.27 ± 3.57	12.31 ± 3.06	7.79 ± 2.21	4.02 ± 1.65
90	5 ± 1.52	10.04 ± 1.79	13.33 ± 3.41	8.5 ± 1.88	4.2 ± 0.69

Figure 4 VCO$_2$ by Time and Condition
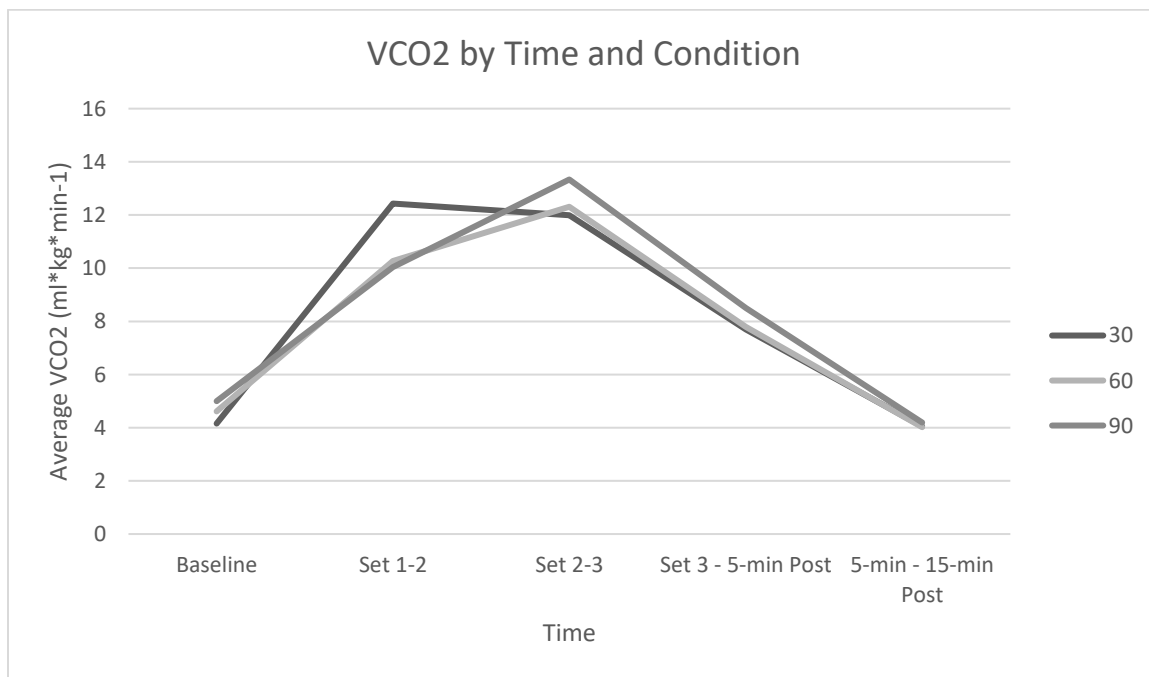
Volume Load

Statistically significant interactions were observed between the effects of condition and time on non-accumulated VL, $F(6, 120) = 10.221$, $p < .001$. VL was significantly greater Post1 during the 30% condition compared to both the 60% ($ES = 1.46$, $p < .001$) and 90% conditions ($ES = 2.61$, $p < .001$). VL was also significantly greater Post1 during the 60% condition compared to the 90% ($ES = 2.11$, $p = .004$). Significant interactions were also observed Post2 favoring the 30% condition over the 90% ($ES = 2.17$, $p = .011$). No significant effects were observed in VL between conditions Post3.

In addition to inter-set (non-accumulated) differences in VL, there were statistically significant interactions between the effects of condition and time on accumulated VL. The VL accumulated Post2 was significantly greater following the 30% condition compared to both the 60% ($ES = 1.43$, $p = < .001$) and 90% ($ES = 2.59$, $p = < .001$) conditions. The accumulated VL Post2 was also significantly greater following the 60% ($ES = 2.33$, $p < .001$) compared to the 90% condition. The total VL accumulated Post3 significantly favored the 30% condition over the 60% ($ES = 1.49$, $p < .001$) and 90% ($ES = 2.69$, $p < .001$) conditions. Additionally, the 60% condition resulted in significantly greater accumulated VL Post3 when compared to the 90% condition ($ES = 2.17$, $p < .001$). Recorded VL values by time and condition are presented in Table 5, and VL by condition and time is depicted in Figure 5.

Table 5 Volume Load by Time and Condition

Volume Load (reps x load in kg)

Con.	Post1	Post2	Post3	Total (Post2)	Total (Post3)
30	556.99 ± 214.08*	250.32 ± 87.95^	184.82 ± 58.31	807.31 ± 290.5*	992.13 ± 328.27*
60	315.45 ± 95.45*	174.55 ± 39.43#	126.06 ± 31.12	490 ± 120.78*#	616.06 ± 140.78*
90	147.34 ± 59.59*	102.06 ± 39.55#^	70.88 ± 40.17	249.39 ± 93.56*#	320.28 ± 131.39*

Note. * denotes significant difference ($p < 0.05$) between 30%, 60%, and 90% conditions, # denotes significant difference between 60% and 90% conditions, and ^ denotes significant difference between 30% and 90%

Figure 5 Volume Load by Time and Condition
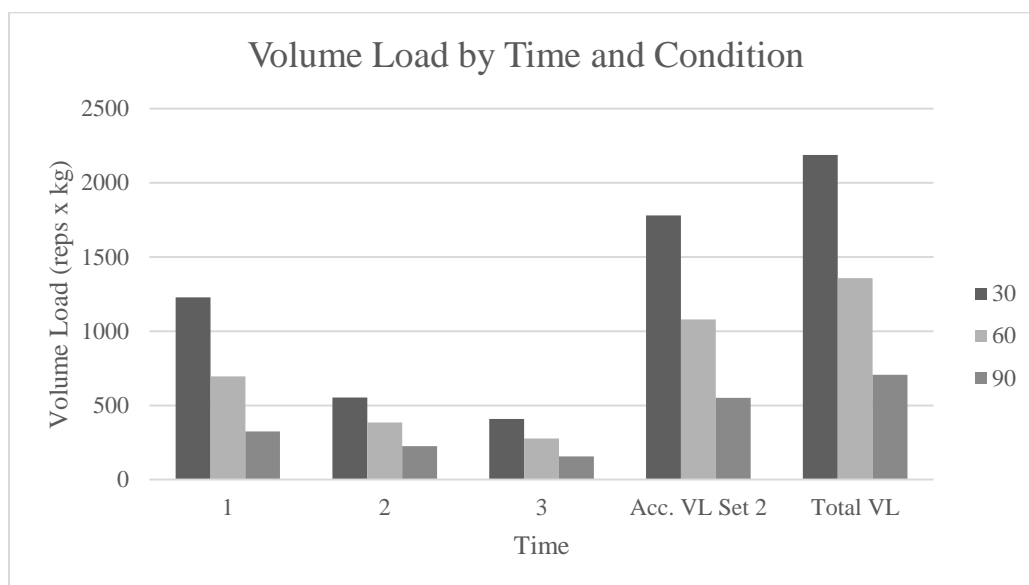
CHAPTER 5

DISCUSSION

Recent literature has presented compelling evidence supporting the prominent

roles of three primary hypertrophic mechanisms: mechanical tension, EIMD, and EIMS

(Schoenfeld, 2010; 2012; 2016). However, the extent to which each mechanism

contributes towards the pursuit of acute and chronic protein accretion remains unknown.

This is largely due to the methodological difficulties associated with isolating the

hypertrophic mechanisms from one another making it difficult to observe the singular net

anabolic effects of each mechanism.

The EIMS response is most often evaluated by assessing the extent of lactate

accumulation during and following exercise (Tesch et al., 1982; Shanely et al., 2014). *In

vitro* (Tsukamoto et al., 2018; Willkomm et al., 2014) and *in vivo* (Tsukamoto et al.,

2018) studies recently investigated the anabolic effects of lactate in the absence of both

mechanical stimulation and muscular damage. These investigations have demonstrated

that lactate accumulation alone is a viable mechanism for facilitating the hypertrophic

process and justifies an increased demand for RT studies focusing on the exercise-

associated accumulation of metabolites.

In the present study, the blood lactate response was not observed to differ

significantly between conditions at any time point. However, a possible point of

contention with these results is the fact that baseline lactate values measured considerably

higher than values expected when at rest. This observation is likely the result of the

general dynamic warm up procedure that was completed by participants approximately

five minutes prior to the baseline measurements. The elevated initial lactate measurements must be noted as they influenced the statistical analysis for this metric and all potential findings.

Although it has been well established that increased training volume is associated with increased muscular growth (Radaelli et al., 2015; Schoenfeld, 2016; Wernbom et al., 2007), the lack of significant findings in lactate accumulation between conditions and time, in the presence of significant differences in accumulated VL, suggest that lactate accumulation alone may not be a predominant factor responsible for the significantly greater hypertrophy observed following high volume training regimens. These findings also suggest that the exercise-associated accumulation of lactate may not be as closely related to training volume as previous evidence has suggested (MacDougall et al., 1999; Schoenfeld, 2013; 2016).

RT exercise performed for moderate durations significantly increases the breakdown of ATP and demands an enhanced rate of ATP resynthesis for the activity to be sustainable for any duration greater than approximately 15 seconds (Green et al., 1983; Rodrigues et al., 2010; Schoenfeld, 2016). Due to the ATP requirements of such activity, RT is heavily reliant on anaerobic glycolysis (Schoenfeld, 2013; 2016). Although ATP is resynthesized predominantly via anaerobic respiration during RT, efforts to resynthesize ATP via aerobic pathways continue in tandem with anaerobic fueling strategies (Kenney, Wilmore, & Costill, 2008). To facilitate these aerobic efforts, ventilation and oxygen consumption are increased during exercise. In addition to elevated VO_2 during RT, VCO_2 is also elevated, as CO_2 is one of the end products of aerobic

respiration (Kenney et al., 2008). However, observed values of VO_2 and VCO_2 were insignificant at all time points across all conditions. These results suggest that low-load, moderate-load, and high-load RT may be equally, insignificantly challenging on aerobic energy systems. Similarly, the insignificant lactate responses observed at all time points across all conditions suggests that each condition challenged the anaerobic energy systems to a similar, insignificant extent. However, as with observations made in baseline blood lactate measurements, VO_2 and VCO_2 baseline measurements were observed to be substantially greater than expected resting values. This observation was likely heavily influenced by the performance of a general dynamic warm up approximately five minutes prior to the collection of baseline measurements. Elevated initial measurements likely influenced the results of the statistical analyses performed for both VO_2 and VCO_2 and may have influenced any findings regarding these two metrics.

VO$_2$ and VCO_2 are used to calculate RER, a metabolic marker often used to assess the contribution of energy pathways in fueling activity (Kenney et al., 2008). RER was found to be significantly greater between Post1 and Post2 favoring the 30% condition over the 60% and the 90% conditions. Significant observations were also made between Post2 and Post3, where the 30% and 60% conditions were favored over the 90% condition. However, 30% and 60% 1RM RT resulted in similar RER values at all additional time points after Post2. The fact that RER was significant while VO_2 and VCO_2 were not suggests that the relationship between these two values changed significantly during exercise, even though the metrics themselves did not.

The significant difference in RER values observed in the absence of significant blood lactate differences across time and conditions suggests that RER may be a better indicator of total accumulated metabolic stress than blood lactate. Three primary metabolic by products are believed to accumulate with exercise, contributing to the development of metabolic stress and muscular growth via several physiological pathways (cellular swelling, elevated rate of MPS, and enhanced release of anabolic hormones) (Schoenfeld; 2013; 2016; Takarada, Nakamura, et al., 2000; Takarada, Takazawa, et al., 2000). These three metabolites include lactate, H^+, and Pi (Beaver et al., 1986: Schoenfeld, 2013; 2016). RER, a valid marker of anaerobic metabolism (Kenney et al., 2008; Myers & Ashley, 1997), may better reflect the accumulation of all three primary metabolites compared to measures of blood lactate alone.

RER was significantly greater during the 30% condition between Post1 and Post 2 compared to the 60% condition during the same period. However, RER did not differ significantly between the two conditions at any other time point. These results suggest that, during progressive sets of RT, 60% 1RM will produce a similar metabolic response compared with lower intensities (30%). This finding has important implications when evaluating the presence of each hypertrophic mechanism and in determining the total potential effectiveness of RT in promoting muscular growth.

However, similar to the other metabolic metrics observed in this study, baseline RER values were observed to be much greater than expected resting values. This is most likely a result of the general dynamic warm up procedure which was completed by participants approximately five minutes prior to the baseline measurements. Elevated

initial RER values may have influenced the results of the statistical analysis performed on this metric and may have influenced any findings regarding this metric.

Although the 30% condition resulted in significantly greater total accumulated VL, the effectiveness of this mechanical stimulation of muscle fibers may be less significant than that provided by the accumulated VL which resulted from moderate intensity RT (60%). Considering previous theory which suggests that approximately 60 to 65% 1RM is a threshold intensity for inducing muscular growth (Schoenfeld, 2010; 2013; 2016) and previous evidence which has demonstrated enhanced recruitment of type II fibers at this intensity, it is logical that greater mechanical stimulation of muscle fibers may be possible when training with moderate loads (60 - 65%), despite achieving a lower total accumulated VL when compared with low-load training. Thus, moderate intensity RT may be superior to low-load training in that similar metabolic responses are observed following multiple sets of RT and moderate intensities possess greater potential for elevated mechanical tension and fiber recruitment. The substantial presence of two hypertrophic mechanisms simultaneously indicates that moderate intensity RT may carry greater potential for muscular growth compared to low and high intensity RT.

<div align="center">Conclusions and Recommendations for Future Research</div>

The present study has demonstrated that RER may be a promising indicator of metabolic accumulation, while direct measures of whole blood lactate may underestimate the total exercise-induced accumulation of metabolic stress. A potentially accurate, non-invasive measure of metabolic stress would be highly beneficial to the research community as invasive techniques currently used to measure metabolic stress can be

disruptive to experimental procedures and pose a mild risk to participant health and comfort.

The findings of the present study support the use of moderate intensity loads ($\geq$ 60% 1RM) during RT focused on optimizing muscular growth. Moderate intensity RT has induced similar metabolic stress compared to low intensity loads when multiple sets of exercise are performed. It is believed that moderate intensities result in greater mechanical stimulation of muscle fibers, via the mTOR facilitated anabolic pathway (Schoenfeld, 2010; 2016), despite resulting in significantly less accumulated VL when compared to low load RT. Individuals capable of training at moderate intensities should do so if the addition of lean mass is a primary goal of their training program.

An important consideration with the experimental protocols used in this study is the inclusion of a general dynamic warm up protocol prior to the collection of baseline measurements. Initial VO_2, VCO_2, RER, and blood lactate measurements observed during the baseline period were substantially greater than values expected when at rest. The decision to include a general warm up protocol was made to promote participant safety during testing sessions. However, elevating metabolic markers prior to conducting each testing session may have compromised the statistical results of these metrics and may have neglected or generated erroneous findings.

Performing the warm up procedure after completing the baseline observations would have undoubtedly yielded baseline values which would have been much closer to true resting values, however, what is unknown is how much time should be allowed to pass between the completion of the warm up procedure and the start of the exercise

protocol. If participants were not given adequate recovery time between the completion of the warm up and the start of the exercise protocol being tested, then results would still be influenced by the elevated metrics which were affected by the warm up procedure. If participants were given too much recovery time between the warm up and start of the testing protocol, then the warm up would lose its effectiveness at minimizing the risk of injury during exercise as participants may cool down during this time. Although performing a warm up protocol prior to exercise is practically realistic and promotes participant safety, this practice and its timing in experimental procedures may be potential detrimental to the accuracy of statistical analyses and experiment findings.

Future RT studies should be conducted which evaluate more moderate intensities (65-75% 1RM) compared to low loads (<50% 1RM) to observe metabolic accumulation and accumulated VL. Additionally, future studies are needed to validate RER as an effective, non-invasive marker of accumulated metabolic stress. Future RT studies should also consider performing any warm up procedures after completing any baseline observations for key dependent variables. Finally, due to the well documented variation in exercise-associated lactate accumulation observed between trained and untrained individuals (Pierce et al., 1993; Stone et al., 1987), additional long-term RT studies with larger sample sizes exclusive to trained and well-trained individuals are needed to validate the proposed acute and chronic anabolic effects of the exercise-associated accumulation of metabolites, and to identify the precise myogenic pathways by which EIMS facilitates muscular growth.

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