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Chapter 4

THE APPLICATION OF HIGH-INTENSITY MUSCULAR CONTRACTIONS FOR MAXIMAL TRAINING GAINS: THE IMPACT OF AGE ON THE CONTINUUM OF MUSCLE INJURY, MALADAPTATION AND ADAPTATION

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1. ABSTRACT

Overt skeletal muscle injury can occur following exposure to high-intensity muscular contractions implemented during mechanical loading, and this phenomenon is exacerbated with age. Yet not all muscular contractions produce injury, and evolving data supports a viewpoint that the classically reported "injury response" is not an exclusive consequence following mechanical loading. Strength gains and muscle hypertrophy are adaptive responses that result from high-intensity muscular contractions involved during mechanical loading (i.e. strength-type training); however the aging process appears to attenuate these positive training benefits, while concomitantly exhibiting a sarcopenic state that ultimately leads to senescence. The best known strategy to increase skeletal muscle mass is with resistance training, however, prescribing this mode of training has been cautioned in aged populations due to the compromised condition of the older individual – a sarcopenic state and the propensity that it will induce overt skeletal muscle injury if commenced. In spite of this, current evidence supports a model of muscle adaptation following mechanical loading, distinct from overt injury, in which myofiber degeneration and inflammation does not contribute as significantly as once reported even following muscular contractions incorporating repetitive eccentric contractions. Moreover, the inherent capability of skeletal muscle to positively adapt to repetitive

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mechanical loading is highly dependent on optimizing the biomechanical loading signature (i.e. repetition number, velocity, frequency of exposure, duty cycle, and range of motion) and the intensity of the mechanical loading exposure for any given population; this may be particularly important with aged populations. Indeed, this concept is paramount in those individuals presenting with risk factors associated with disease states, so that they too may experience the benefits of resistance training. Thus, the focus of this chapter will detail the continuum of muscle injury, mal-adaption, and adaptation based upon historical as well as current evidence of performance and biological data, and how the implementation of high-intensity muscular contractions (stretch-shortening contractions – SSCs) may offer the most effective and appealing means of physical activity to counter the deleterious effects observed with sarcopenia as we age. We will also consider and compare models of mechanical loading that use high-intensity muscular contractions to induce positive physiological responses in various populations, and suggest the applicability and modifications of these approaches when integrated into contemporary resistance training exercise prescriptions with the anticipation that they may be implemented in occupational, military, athletic, and general populations.

2. INTRODUCTION

Skeletal muscle is an exquisitely plastic tissue that has the ability to adapt to various types of stimuli. Skeletal muscle's plasticity, or capability to alter its structure-function relationship, is a hallmark that can be observed following chemical, biological, or mechanical (as well as others) exposure/s, and this plasticity is reflected in changes at the molecular and cellular level (gene expression and/or enzyme activity) as well as in gross changes in muscle appearance at the tissue level (muscle mass or size). Various types of mechanical loading (occupational work, sport/exercise training, or general physical activity) lead to a general augmentation in skeletal muscle physiology and functional capacity. For instance, there are numerous approaches to training for sport (weightlifting, powerlifting, plyometric training, and strength training – this list is not meant to be exhaustive), which will lead to positive adaptations in muscle structure-function. Specifically, as strength training (ST) has become an integral part of most training regimens (along with cardiovascular, agility, and flexibility training), it has also become much more specific in focusing on the needs of individuals or individual populations (ST in wellness centers in private and public corporations and agencies, tactical ST in the military, and sport specific ST in sport). However, as the number of ST routines and protocols are many, the exact loading signature and biologically-induced response (specific mode of ST, the number of sets and repetitions, the range of motion, the velocity of contraction, the duty-cycle or work-rest cycle along with frequency of training) for optimal performance gains is not well defined. Only recently has the extent of how these factors interact to produce positive functional and biological outcomes become elucidated. Furthermore, how these factors are affected by age in a specific population is even less well defined, and, indeed needs to be systematically addressed. In addition, recent progress in our understanding of how muscle responds to mechanical stimuli following high-intensity muscular contractions as implemented during ST regimes is suggesting that not all muscle "injury" is created equal. For the notion that all muscular contractions that incorporate a lengthening component ("eccentric movement") produce muscle injury (i.e. myofiber degeneration/necrosis) is only just being questioned [8, 33, 34, 109-111]. Whether in animals or humans, evolving data supports a viewpoint that the classically reported "injury response"

is not an exclusive consequence following mechanical loading [8, 109, 111]. Strength gains and muscle hypertrophy are adaptive responses that too result from high-intensity muscular contractions involved during mechanical loading (i.e. strength training).

Even though the best known strategy to increase skeletal muscle mass in humans is with mechanical loading or strength-type training, prescribing this mode of training has been cautioned in aged populations due to the compromised condition of the older individual – a sarcopenic state and the propensity that it will induce overt skeletal muscle injury if commenced. As this chapter will detail and, in spite of contemporary dogma, more recent evidence supports a model of muscle adaptation/remodeling following ST-type mechanical loading, distinct from overt injury, in which myofiber degeneration and inflammation does not contribute as significantly as once reported even following muscular contractions incorporating repetitive high-intensity, eccentric contractions. Moreover, the inherent capability of skeletal muscle to positively adapt to repetitive mechanical loading is highly dependent on optimizing the biomechanical loading signature (i.e. repetition number, velocity, frequency of exposure, duty cycle, and range of motion) and the intensity of the mechanical loading exposure for any given population. Since the positive health benefits resulting from ST are numerous (increased muscle mass and metabolic health with a concurrent decrease in fat mass) this may be particularly important in aged populations, which undergo conditions of muscle weakness and frailty as well as an obvious loss of skeletal muscle - sarcopenia.

3. BACKGROUND

Both acute and chronic responses following ST-type mechanical loading and the subsequent adaptations are significantly impacted by the loading signature (intensity, duration or duty cycle, frequency, number of repetitions, velocity, and range of motion). Further, the loading signature in animal models has been shown to actually determine whether muscle injury or adaptation will occur . Yet, to date, few studies in humans have been able to corroborate these findings. For this reason, the use of contraction-induced muscle injury and adaptation models in animals are useful in elucidating the etiology of occupation-, military-, and sport-related musculoskeletal disorders in humans . Our lab has focused on in vivo rat dynamometry, which has many benefits in studying muscle function and injury mechanics. This methodology allows for precise control of the biomechanical loading signature that is comprised of force, repetitions, range of motion, movement velocity, work-rest cycle, and number of exposures. In vivo dynamometry is also minimally invasive, such that the preparation does not compromise the physiological response, and allows for longitudinal study of muscle response. This model also permits the study of the limiting influence age has on muscle adaptation following mechanical loading in vivo. For these reasons, this chapter will concentrate on the various animal investigations that have utilized a number of models and paradigms, but that primarily focus on the biological/ physiological/functional response of skeletal muscle following ST-type mechanical loading.

Single stretches as well as stretch-shortening contractions (SSCs) have been shown to lead to several outcomes: overt skeletal muscle injury (inflammation, myofiber degeneration, and dysfunction), skeletal muscle adaptation (remodeling and growth with functional gains), and/or maladaptation (a sub-degenerative or sub-necrotic state that is usually associated with

low levels of persistent inflammation as well as loss of function). In most cases, muscles compensate for increased demands in a systematic fashion, yet situations do occur in which the muscle does not adequately meet those demands, thus leading to overt skeletal muscle injury or maladaptation. In recent years our lab has focused on specific factors (i.e. recovery kinetics, repetition number, duty cycle, etc.) contributing to the induction of contraction-induced muscle injury and the resulting morphology [9, 11, 12, 36, 37]. These studies provided data that helped in optimizing our loading protocol to produce substantial performance gains as well as muscle hypertrophy in a chronic model, which we have defined as adaptation. These optimized protocols allowed us to demonstrate differences in young versus old rats after as little as 4.5 weeks of resistance-type training [33]. Thus, determining and characterizing time- and dose-dependent responses for skeletal muscle injury and adaptation that follows exposure to both acute and chronic mechanical loading was essential in addressing the current voids and misconceptions. Previous studies have associated the majority of contraction-induced muscle damage into a single phenomenological event. We suggest this is not the case, since responses ranging from injury to maladaptation to adaptation may occur over a broad continuum even with high intensity mechanical loading exposure/s. The effects of age only make this task more difficult in discriminating and differentiating the time frame, capacity, and mechanisms that are associated with repair, regeneration/ remodeling, and adaptation following mechanical loading exposure/s. While previous data have suggested that muscle injury (myofiber degeneration/necrosis) is a customary response following exposure to muscular contractions that incorporate lengthening movements [42, 61], it is not known if this is absolutely obligatory when adaptation (positive training effect) is the desired outcome.

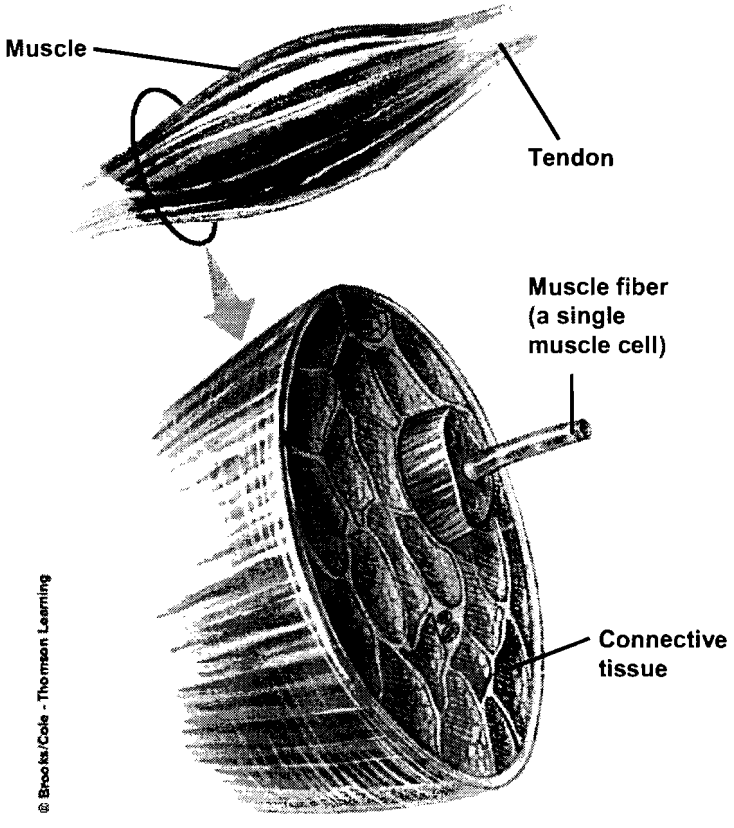
4. Skeletal Muscle Physiology

Occupational-, military-, and sport- related musculoskeletal disorders, injury, and damage have been associated with exposure to excessive physical loads, repetitive movements, awkward postures, and eccentric muscle actions [1, 17, 59, 96]. A number of different tissues, including skeletal muscles, can be injured by exposure to these various factors [16]. To understand how exposure to these factors results in muscle injury, maladaptation, and adaptation, it is necessary to understand the biological and physiological mechanisms that allow skeletal muscles to generate movement, maintain posture, and support loads. The goal of this section is to provide a brief, basic description of skeletal muscle physiology and cellular biology.

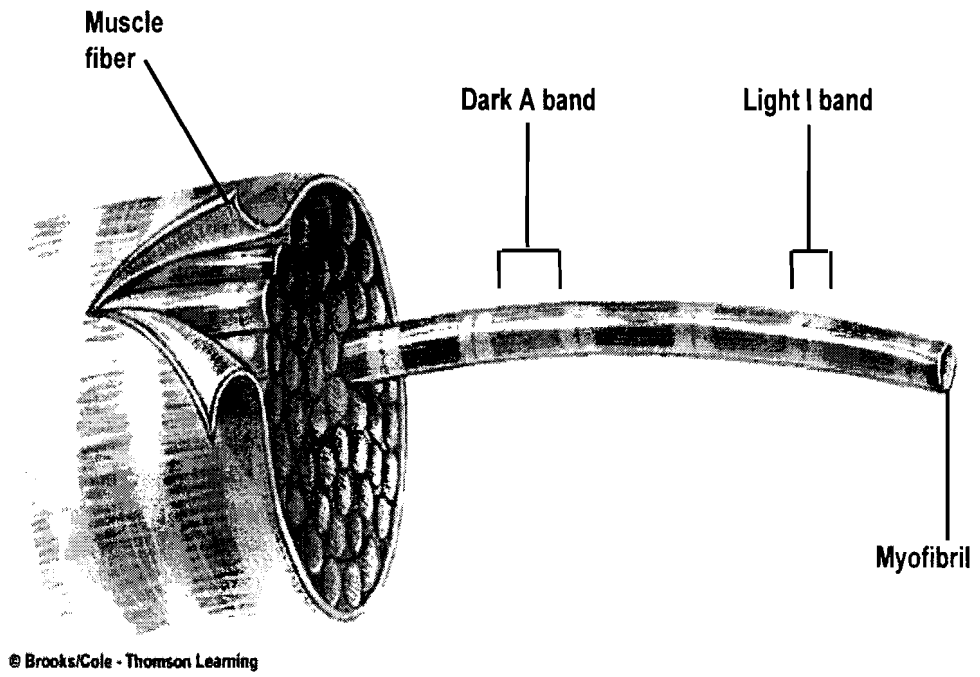
a. Muscle Physiology and Anatomy

Individual skeletal muscles are comprised of bundles of muscle cells or myofibers (Figure 1). Each myofiber is surrounded by a collagenous basement membrane (basal lamina) in addition to a cellular membrane called the sarcolemma. Myofibers are similar to other cells in the body, but they have a couple of unique features. First, myofibers contain a modified endoplasmic reticulum called a sarcoplasmic reticulum (SR). The SR functions as a protein processing and distribution organelle, and it regulates the levels of free intracellular calcium (Ca^{2+}) within the myofiber. Second, most of the intracellular space within the

myofiber is comprised of the contractile elements or myofibrils (80% of a muscle's volume) (Figure 1b). Each myofibril is comprised of thick and thin filaments. Each thick filament [12-18 nm diameter) is composed of several hundred myosin proteins. Within the thick filaments, each myosin protein has a projection or a globular head (Figure 1c). These globular heads have binding sites that can interact with and form cross bridges with the thin filaments, and an ATPase binding site. Thin filaments (5 – 8 nm diameter) are made of actin molecules that are organized in two strands twisted together to form a helix, that are covered by threadlike tropomyosin molecules and spherical troponin molecules (Figure 1d). Thin and thick filaments are organized in a specific pattern, which is repeated down the length of the muscle. It is this patterning that gives skeletal muscle its striated appearance [87]. Each repeated segment of thin and thick fibers forms a sarcomere [87]. The sarcomere is defined as the area between the Z-disk. Each sarcomere is comprised of dark areas (A bands), that contain the thick filaments, and light areas (I bands), that contain the ends of the thin filaments that do not overlap with the thick filaments. At each end of the sarcomere is a 3-dimensional structure referred to as a Z-band or Z-disk (Figure 1e). Muscle contractions are produced when cross bridges are formed between overlapping thin and thick fibers in the sarcomere, making the sarcomere the smallest contractile unit in the myofiber.



Figuer 1a. Cross-sectional view of whole muscle and the attached tendon.



Figuer 1b. Enlarged view of myofibrils within a muscle fiber.

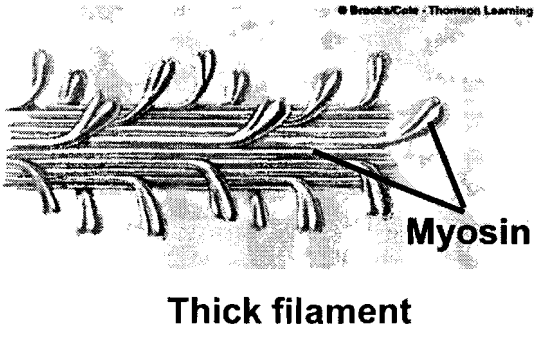


Figure 1c. View of the thick filament (Myosin).

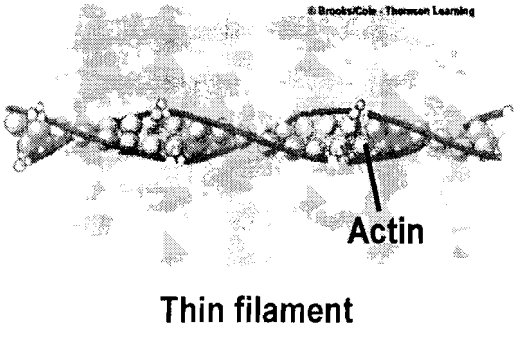


Figure 1d. View of the thin filament (Actin).

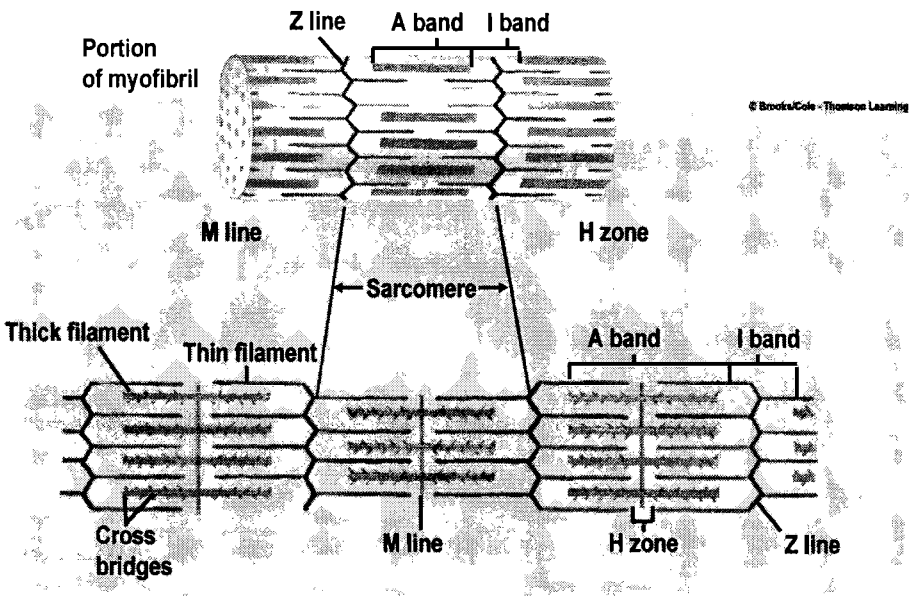


Figure 1e. Cytoskeletal components of a myofibril showing cross bridge arrangement and the smallest functional unit, the sarcomere.

b. Cellular Processes Initiating Muscle Contractions

To initiate a contraction, myofibers must receive stimulation from motor neurons located in the ventral horn of the spinal cord. Motor neurons are considered the final common pathway where skeletal muscle activity can be governed only by input from these neurons. When activated, an action potential is propagated down the nerve axon and terminates on the neuromuscular junction (NMJ). The NMJ is a space where the action potential cannot cross from the nerve axon to the muscle fibers it innervates. Thus, a chemical messenger is used to transmit the signal from the nerve axon to the muscle fibers. As the signal is transmitted down the nerve axon, voltage-gated channels open to release calcium into the terminal bouton of the NMJ. This facilitates the release of the chemical messenger Acetylcholine (ACH) that crosses the space to the motor end plate. This causes an ionic shift, which results in the propagation of the action potential down the basement membrane of the muscle fiber and then down the T-tubules of the muscle cell (Figure 2a). The action potential activates the voltage-gated dihydropyridine receptors in the T-tubule. This change in the T-tubules triggers the opening of calcium-release channels (ryanodine receptors) on the SR. Ca^{2+} leaves the SR through the ryanodine receptors, enters the cytoplasm, and binds to troponin, one of the proteins on the thin filaments. Troponin has three polypeptide units; one binds to tropomyosin, one binds to actin, and a third, which binds to Ca^{2+}. Under resting conditions, tropomyosin is bound to actin and it blocks the myosin-binding site on the actin protein, preventing the formation of cross bridges (Fig 2b). However, when free Ca^{2+} rises in the cytoplasm of a myofiber, it binds to troponin, and tropomyosin is pulled away from the myosin binding site on actin, leaving it open for cross bridge formation. Once cross bridges are formed, the ATPase located on the myosin head increases its activity and hydrolyzes ATP. This causes the cross bridge to break,

and Ca^{2+} then dissociates from its binding site on tropomyosin. When Ca^{2+} is removed, tropomyosin slides back into the blocking position and the muscle relaxes. Thus, troponin and tropomyosin are referred to as regulatory proteins in muscle contraction (Figure 2b).

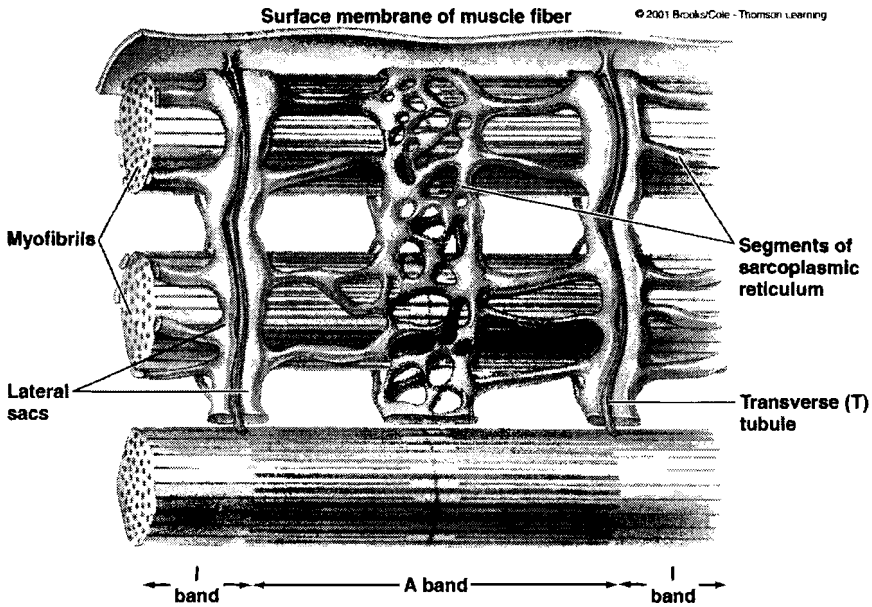


Figure 2a. The T tubules and Sarcoplasmic Reticulum in relationship to the myofibrils.

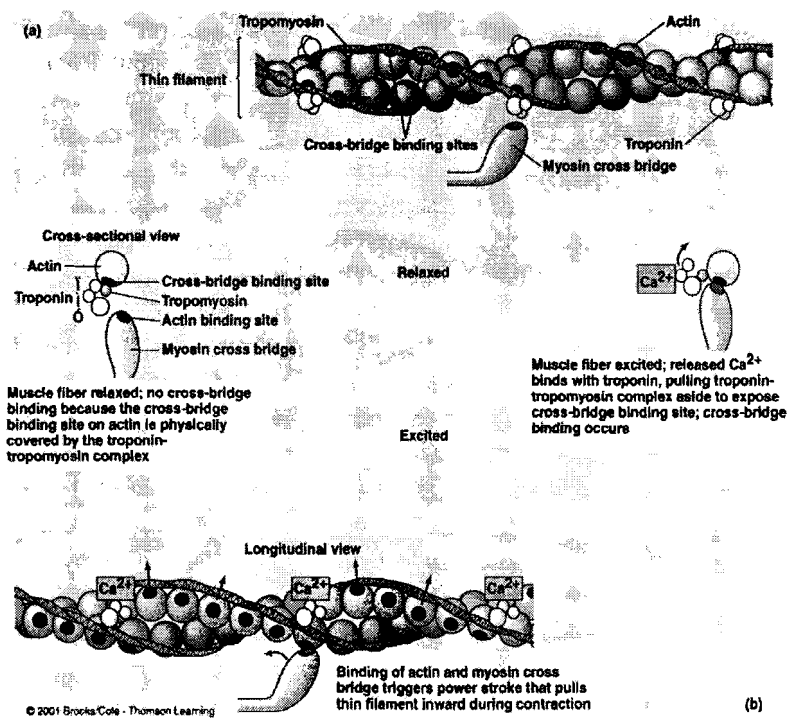


Figure 2b. The role of calcium in activating the cross bridge cycle.

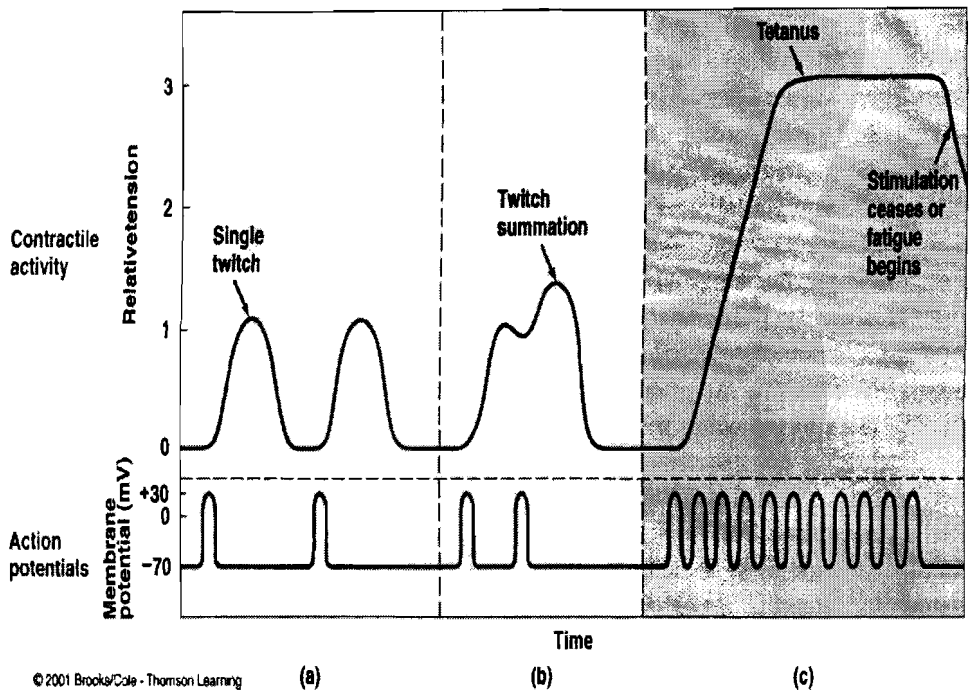


Figure 3. Muscle twitch, twitch summation, and tetanus. (A) If a muscle fiber is re-stimulated after complete relaxation, the second response is the same as the initial response. (B) If the muscle fiber is re-stimulated before complete relaxation takes place, the second twitch is added to the first twitch. (C) If the muscle fiber is stimulated rapidly such that it does not have the opportunity to relax, a maximal contraction or tetanus occurs.

c. Force Generation and Transmission in Skeletal Muscle

One of the main functions of skeletal muscle is to generate and transmit force. Force, or muscle tension, is directly related to the number of actin and myosin cross bridges that are formed and the frequency of stimulation. A single action potential results in a single muscle contraction referred to as "twitch". As the frequency of stimulation increases, the resulting twitch-tension (Figure 3, panel A) increases with increasing stimulation frequency (Figure 3, panel B) until a force plateau results (Figure 3, panel C). Force is produced at each attached cross bridge, so the total force development is proportional to the number of attached cross bridges. The number of cross bridges that can be formed depends upon the degree of overlap between the thin and thick filaments (Figure 4). When a sarcomere is overstretched or compressed, the area over which thin and thick filaments overlap is reduced, and thus there is a decrease in the number of cross bridges that can be formed resulting in a reduction in force (Figure 4). Thus, maximal force is generated when sarcomeres are at a length that produces the optimal overlap between thin and thick filaments. Force is generated at the cross bridges, but it is transmitted longitudinally and radially along myofibrils. The longitudinal transmission of force occurs down the thick myosin filament to the Z disk, and on to the next serial set of myofibrils. Two proteins, titin and nebulin, maintain length registry of the sarcomere and aid in axial transmission of contractile forces. The actions of titin and nebulin maintain registry of the A-band with the Z-disk which is important for sarcomere integrity.

Nebulin maintains length registry of the thin filaments [26, 108) by interacting with tropomyosin and troponin to form a lateral network with actin to regulate thin filament length. Titin functions as a two part spring to transmit force from the thick filaments to the corresponding Z-disk. Radial forces are transmitted via lateral stabilization of adjacent myofibrils. The protein responsible for maintaining lateral registry of adjacent myofibrils at the Z line is desmin [68]. The Z-disk structure is thought to be three dimensional in nature and comprised of the proteins desmin, actin, and α-actinin. The radial enclosure of these three proteins also extends longitudinally along the myofibrils to provide both radial and longitudinal stability [82]. These proteins are thought to be anchored to the Z-disc via intermediate filament-associated proteins (IFAP). The cytoskeletal lattice extends radially from the Z-disc to the sarcolemma via the transmembrane proteins. The transmembrane proteins are thought to anchor the myofilaments to the sarcolemma via focal adhesions [81]. These adhesions or "costameres" are made up of a variety of transmembrane proteins. The basement membrane is then attached to the sarcolemma via the dystroglycan complex [81, 82]. Radial transmission of forces occurs through structural proteins located in and outside of the sarcomeric region via the intermediate filament network, and to the sarcolemma via the transmembrane proteins [82]. Capability of radial force transmission is necessary for redundancy in case of fiber injury. Thus, force can be transmitted in any direction in relation to the axis of the muscle fibers via endosarcomeric and exosarcomeric protein lattices.

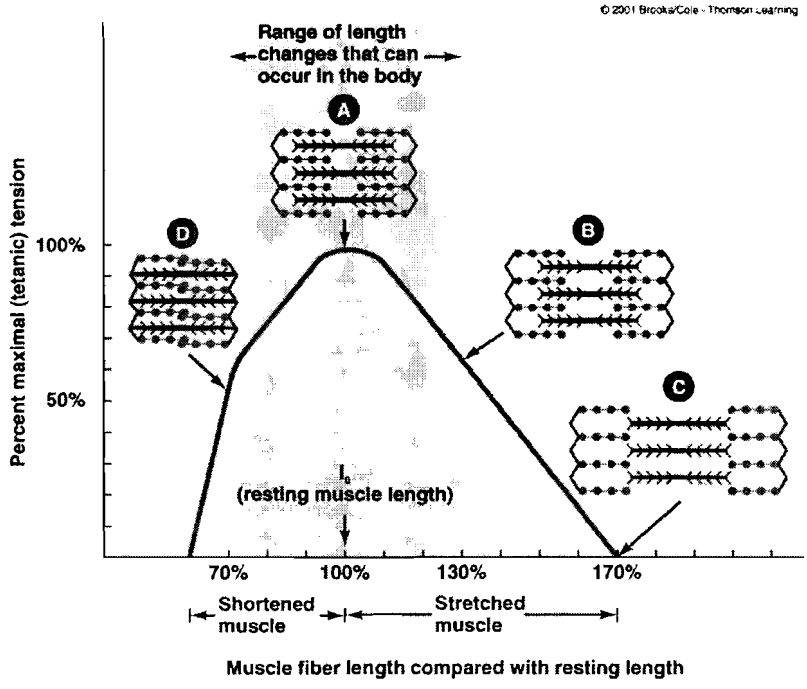


Figure 4. Length-tension relationship of muscle. At point (A) optimal overlap of thick and thin filaments results in maximal tension developed. This is referred to as the normal resting length in the body (l_o). As the muscle continues to lengthens (point B), less cross bridges are attached which results in a decrease in tension. Further increases in length correspond with less cross bridge attachment and further declines in tension (Point C). The response from point A to point C is usually referred to and the descending limb of the length-tension. relationship. If shortening occurs at less than lo, fewer filament binding sites are exposed to filament cross bridges, thus tension decreases (Point D).

d. Types of Muscle Contractions

There are three primary types of muscle contractions. These contraction types are distinguished by how the muscle length changes during the contraction [6, 24]. Isometric contractions are defined as muscle activity where tension is generated without a change in length. This is also referred to as a static contraction where muscle is generating tension but does not result in a change in length, and thus, there is no segmental (about a single joint) or whole body motion. Shortening contractions (often referred to as concentric contractions [6] are defined as the muscle generating tension while getting shorter. Concentric contractions usually generate segmental or whole body motion. Lengthening (or eccentric) muscle contractions are defined as the muscle generating tension while the muscle is lengthening. Lengthening contractions are usually used to absorb work or energy, thereby applying braking to segmental or whole body motion. During concentric muscle actions, the tension varies as a function of shortening velocity where tension decreases as shortening velocity increases. The "force-velocity" relation is hyperbolic and also depicts that maximum shortening velocity occurs at zero load and zero velocity occurs at maximum isometric force [105]. During isometric muscle contractions, it is well understood that force varies as a function of muscle length. It has been shown that muscle tension is lowest at very short and very long muscle lengths and develops higher tension in the intermediate lengths [40, 52]. This is due to the degree of sarcomere overlap in the cross bridge. Thus, the length-tension curve has an ascending and descending limb as length increases (see Figure 4). The ascending limb, defined as the increase in force with increase in length, is due to more actin binding sites being available to bind with the myosin filaments. As tension plateaus, this is thought to be due to all the actin binding sites being bound to the myosin filaments. The descending limb, defined as the decrease in muscle tension with increasing length, is due to less actin binding sites being available as the actin filaments are pulled out of register with the myosin filaments. Thus, the length-tension relationship of muscle is due to myofilament overlap in the sarcomere (as shown in Figure 4). It is now well known that muscle can generate more tension during eccentric muscle actions than during concentric or isometric contractions. This was first reported in a study involving human muscles under volitional control [88]. It is also interesting that while muscles generate more tension during eccentric muscle actions than concentric muscle actions, EMG activity is less in muscles during stretch than during shortening at the same tension. During maximal effort, the EMG signature remains constant and force varies due to the length-tension relation of that specific muscle or muscle group, however force during volitional eccentric activity never exceeded 140% of maximal shortening forces [62]. In animal studies that employ electrical stimulation to activate the muscle of interest, forces of 180% of maximum isometric force are typical [100]. High eccentric forces in humans with spastic paresis have been attained to levels similar as those seen in animal studies [60]. In addition, if muscles in humans are stimulated by external electrical stimulators, as in the case of spinal cord injured patients, the external forces generated during eccentric muscle actions are nearly 200% of the forces generated concentrically using the same electrical stimulation paradigm [97]. Thus, exogenous electrical stimulation overrides the inhibitory influences that moderate muscle output force.

e. Stretch-Shortening Contractions (SSCs)

SSCs are a type of muscle action that incorporates both eccentric and concentric muscle actions, and incorporate an important factor known as preactivation. In most sports-related activities the SSC involves an initial preactivation of the muscle prior to stretch of the muscle (eccentric or lengthening phase) followed by the contraction of the muscle (concentric or shortening phase). This preactivation and stretch has a well-defined purpose, which is enhancing the performance of the movement during the shortening phase. Activities that typically use SSCs are jumping, walking, running, and movement in and around obstacles. In occupational-related activities, it is most related to reciprocal lifting and lowering activities and repetitive lift and carry tasks. It is an excellent model to study physiological muscle function [63]. Further, it also allows for simultaneous study of the preactivation (isometric contraction), eccentric muscle function, and concentric muscle function and their synergism.

5. Differentiation between Muscle Injury & Adaptation

a. Injurious Muscular Contractions

Overt skeletal muscle injury has been well documented previously [4, 50, 76]. While the use of muscle contractions in animals to study skeletal muscle injury as well as adaptive/maladaptive mechanics is beneficial in understanding the etiology of work-related musculoskeletal disorders, they too would aid in designing better rehabilitative countermeasures to reduce the risk of further injury after return to work. In the United States, work-related musculoskeletal disorders account for approximately 38% of cases involving days away from work [67], thus making it an enormous economic and health care burden. A large component in musculoskeletal disorders is acute and chronic contraction-induced skeletal muscle injury [13]. In order to address this issue, there has been extensive studies to-date on acute contraction-induced muscle injury using both animals and humans [35]. Single stretches as well as repetitive muscular contractions, or SSCs, have been shown to lead to several outcomes: overt skeletal muscle injury (inflammation, myofiber degeneration, and dysfunction), skeletal muscle adaptation (regeneration and growth with functional gains), and/or maladaptation (a sub-degenerative or sub-necrotic state that is usually associated with low levels of persistent inflammation as well as loss of function). In most cases, muscles compensate for increased demands in a systematic fashion, yet situations do occur in which the muscle does not adequately meet those demands, thus leading to overt skeletal muscle injury. The use of muscle contractions in animals to study skeletal muscle injury mechanics is beneficial in understanding the etiology of work-related musculoskeletal disorders, and to design better rehabilitative countermeasures to reduce the risk of further injury after return to work. For example, there is evidence that histopathological changes in human extensor carpi radialis brevis muscles with long standing lateral epicondylitis [73] are similar to those changes shown in chronically-loaded rat muscles [90]. Findings from volitional animal models of repetitive motion [13, 14], human models of exercise overload [23, 27, 28, 73, 85], and electrically stimulated rat dynamometer models [9, 12, 50, 84] demonstrate that the cellular pathways of activation and the accompanying inflammation and histopathology are

congruent. We know that eccentric muscle actions are known to cause a greater amount of muscle damage than concentric or isometric muscle actions. This suggests that high load tensions in fibers may be more important than physiologic considerations in the etiology of the injury process, and that these high mechanical forces produced during muscular contractions, particularly in eccentric exercise where forces are distributed over relatively small cross sectional areas of muscles, cause disruption of contractile and intermediate filament proteins in skeletal muscle fibers and connective tissues [5]. A single exposure to eccentric muscle actions results in loss of performance immediately after exposure and can last for up to 30 days [102]. Past investigations of eccentric contraction-induced muscle injury have indicated that mechanical factors such as peak force and average force [53], work during stretch [58], fiber length [53, 58], and strain [69] influence the amount of muscle damage. Change in maximum isometric force after injurious exposure has been shown to be the best indicator of the degree of muscle damage [103]. Eccentric muscle actions have been shown to result in ultrastructural damage immediately after exposure [45], and 1-3 days after exposure [57, 77]. Structural disruption occurs at the cellular level, which is exacerbated by cellular infiltrates that physically invade the local tissue; this manifests as inflammation [42, 46, 71, 76]. Also it has been shown that exposure to injurious eccentric muscle actions results in disruption of the cellular membrane, loss of intermediate filaments and structural proteins, and the influx of extracellular proteins into the cell [44, 64, 65, 70]. Sarcomeric lesions, disorganized actin, and Z-disc streaming also result after injury [39, 72, 92, 99]. Immunostaining for structural proteins that maintain the integrity of the myofiber, such as desmin, titin, and fibronectin, have demonstrated that there are disruptions of the exo-and endosarcomeric membranes [44, 70, 71], and of the extracellular matrix [70, 90] in strain-injured muscle tissue. It has been suggested that in lengthening contraction-induced injuries, damage within the muscle is most often seen at the myotendinous junction and at specific sarcomeres [49, 55, 79, 80]. In fact, it has been hypothesized that there is a population of sarcomeres that are weaker, and tear more easily under lengthening conditions [44, 78, 93].

During the injury process, damaged cells lose apposition to neighboring cells and there is evidence of cellular infiltrates such as neutrophils and macrophages entering damaged myofibers [39, 61]. The physical disruptions of muscle fibers along with increases in intracellular calcium due to mechanical loading result in pain and inflammation that occur 1-7 days after the initial injury [4, 47, 50, 70]. Acute and chronic exposure to either high [3, 7, 91] or low force [13, 83] loading induces inflammation, and the cellular infiltrates comprising this inflammation have been reported to be neutrophils and macrophages [95, 98]. Neutrophils infiltrate damaged muscle within 1-2 hours of the initial injury [15, 43, 94] and are present for up to five days post injury [43]. These cellular infiltrates produce cytokines and chemokines which activate local pathways in damaged tissue that mediate inflammation and exacerbate damage or assist in repair during the first 5 days after muscle injury. Resident and phagocytic macrophages also invade damaged tissue in order to digest damaged tissue and promote regeneration. Macrophages can be found between 12 h and 14 days after the initial muscle injury [86, 89]. These macrophages also express pro-inflammatory cytokines including tumor necrosis factor-α [TNFα][29, 38, 101, 112]. During muscle adaptation, the inflammation and tissue damage are eventually resolved and normal function is restored. During this time, satellite cells [quiescent muscle stem cells] are activated, proliferate, differentiate, and finally fuse with the existing myofiber [25, 56]. Further, developmental myosin heavy chain is expressed in injured fibers during this time period, and this has been suggested to comprise

the developmental program [75]. At this time, the muscle demonstrates a mixture of both degenerative and regenerative processes. Finally, central nuclei appear and are present at extended time points following the initial exposure indicating resolution from previous injury [18, 57].

Interestingly, exposure to concentric (shortening) or isometric muscle actions does not normally produce muscle injury [12, 41, 71, 100]. However, a discrepancy has existed with respect to functional loss following mechanical loading, and the amount of injury quantified in the target soft-tissue. Therefore, it was our intention to devise a rapid and sensitive method that would be proficient in establishing highly reproducible results and collectively expand our understanding of contraction-induced muscle injury by determining both time- and dose-dependent responses following injurious SSC loading [9, 11]. Using our in vivo rodent dynamometry model (Figure 5) we were able to control the mechanical loading signature in a way to induce skeletal muscle injury by using a physiological paradigm that included high velocity, continuous SSCs (Figure 6) with no rest-time between repetitions and 1 minute rest between sets of contractions. From this we reported time-dependent changes that occurred in rodent TA muscle following SSC-induced muscle injury (illustrated by morphological changes occurring in TA muscle temporally following exposure, Figure 7), and the levels of myofiber degeneration, inflammation, and related changes in the interstitial space using our standardized stereological technique. Additionally, degenerative myofibers and interstitial space changes were associated with functional performance temporally [9]. These results are in agreement with data reported previously [76], yet previous histological studies have failed to directly quantify myofiber degeneration and its relationship to evident functional deficits following contraction-induced exposure. While the ability to characterize early-phase muscle injury is essential in understanding skeletal muscle degeneration/ regeneration/remodeling kinetics, it was also important to understand and quantify dose-response characteristics following an injurious mechanical loading. exposure [11]. Indeed, there is clear evidence that the number of lengthening contractions has an effect on the amount of resultant muscle injury and isometric force deficit [57]. Hesselink and colleagues have demonstrated that in rat muscle ~240 stretches may be the threshold for inducing the maximum loss in isometric force, with an insignificant additional loss in isometric force encountered following 300 repetitions [57]. Still, these results only allow us to conclude what may occur at the ceiling of contraction-induced muscle injury, while a very crucial component of contraction-induced muscle injury may be overlooked – the safety threshold. Single stretch models that have stretched muscle within the physiological range (70%-140% Lo, typically; L_o = optimal muscle length) have not resulted in muscle damage or a pronounced force deficit [21, 58]. In other studies, it required more than one stretch within the physiological range to produce muscle injury [50, 53, 100, 106, 107]. Repeated stretches that varied from 225 to 900 at a final length of 110% L_o have resulted in myofiber damage and a resultant force deficit [20, 76, 113]. Moreover, we have observed an increasing quantity of degenerative myofibers and inflammation with increasing SSC number (Figure 8), and this increase clearly exhibits a dose-response finding (this is consistent and corroborates the findings of Hesselink and Colleagues) [57]. These results are in agreement with previous results reported by Geronilla and colleagues [50], and further their initial observations that myofiber necrosis and myositis increased with increasing repetition number [10]. Thus, we have observed an increase in the histological indices for myofiber degeneration, non-cellular interstitium (edema), and cellular interstitium (cell infiltrates) with increasing SSC repetitions. These measures became

significant and continued to increase at the 70 SSC repetition number, thus suggesting a clear threshold for the target muscle safety threshold with increasing number of repetitions. These observed changes, consistent with injury, were not observed in animals exposed to isometric contractions or 30 SSCs.

Additionally, in our initial studies, we reported time-dependent changes that occurred in rodent TA muscle following SSC-induced muscle injury, and quantified the levels of myofiber degeneration, inflammation, and related changes in the interstitial space using our standardized stereological technique [9]. Degenerative myofibers and interstitial space changes were associated with functional performance temporally [9], and these results are in agreement with data reported previously [76]. Thus, our results showed that increasing indices of myofiber degeneration and inflammation paralleled the decrease in functional deficit exhibited by the decline in isometric force production in groups exposed to increasing numbers of SSCs (Isometric contractions, 30 SSCs, 70 SSCs, and 150 SSCs, respectively; see Figure 8). The results indicate an apparent division with respect to the number of SSC repetitions required to induce the subsequent inflammatory cascade and degenerative response, thus surpassing the TA's safety threshold at 70 SSC repetitions. Minimal myofiber degeneration or inflammation was observed in the contra-lateral control limb, the isometric-control group, and the 30 SSC group. These measures illustrate a clear delineation for the target muscle's safety threshold (or tolerance) with increasing number of repetitions, and that there is a level of exposure where the capacity to withstand the initial injury is compromised, and hence exceeds the muscle's safety threshold. Collectively, time- and dose-dependent factors impact the safety threshold of skeletal muscle and are critical when designing preventative strategies in vocational and recreation arenas, in rehabilitative medicine, and for understanding the etiology of acute-loading injuries. Finally, these groups of initial experiments and promising results allowed us to investigate if another paradigm existed and ask the question: is contraction-induced injury an obligatory response following all mechanical loading?

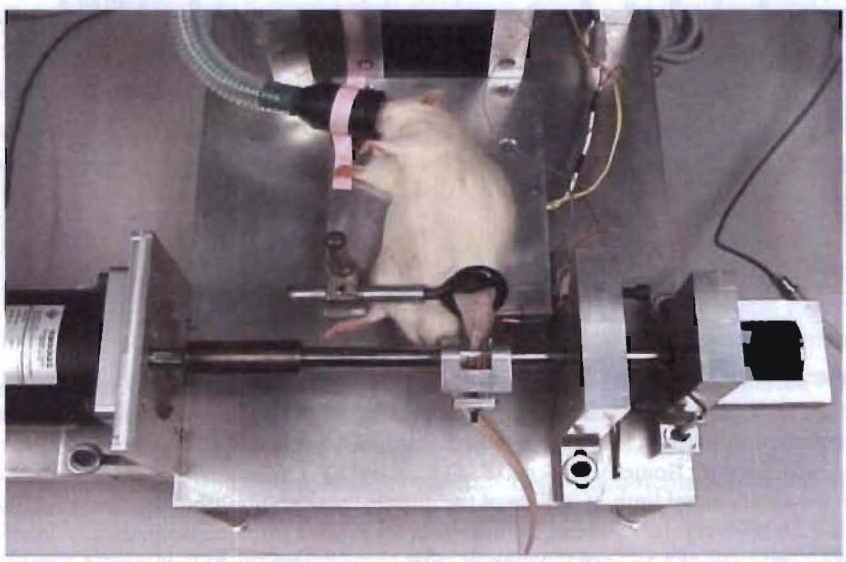


Figure 5. *In Vivo* dynamometer with an anaesthetized rat on the heated X-Y positioning table. The left foot is secured in the load cell fixture and the knee is secured in 90° flexion.

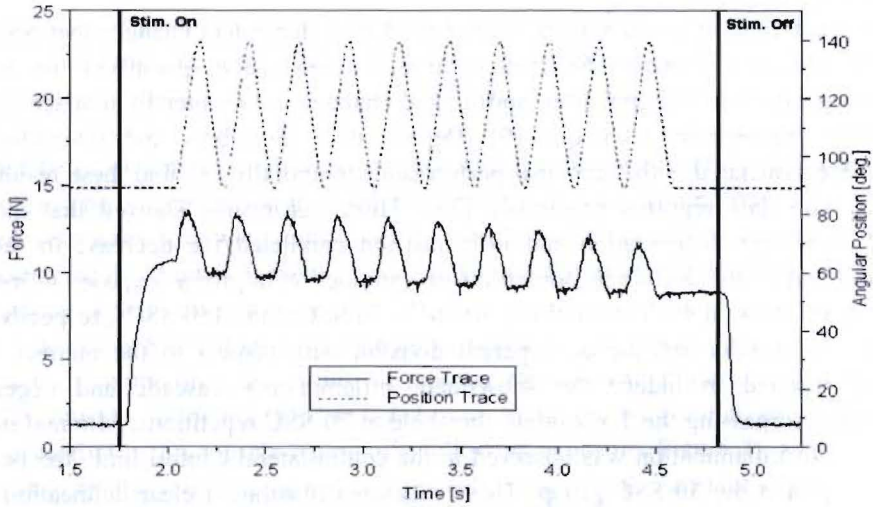


Figure 6. Typical force trace, angular position trace, and electrical stimulation timing of one set of 10 continuous, injurious SSCs.

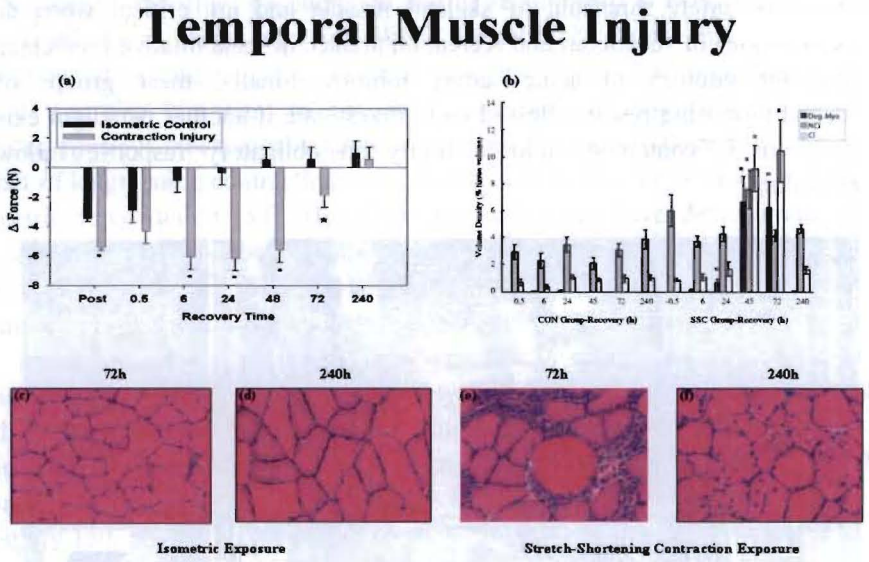


Figure 7. (A) Functional results showing the changes in isometric force temporally following Isometric or SSC loading, respectively. (B) Stereology demonstrating temporal quantitative morphological analyses of cellular infiltrates (CI), the change in the extracellular matrix (NCI), and change in degenerative myofibers for isometrically- and SSC-loaded rat TA muscle. (B) Slide of muscle cross section from the contralateral limb. (C) Slide of the muscle cross section from the isometrically-loaded TA muscle at 72 h recovery. (D) Slide of the muscle cross section from the isometrically-loaded TA muscle at 240 h recovery. (E) Slide of the muscle cross section from the SSC-injured TA muscle at 72 h recovery. (F) Slide of the muscle cross section from the SSC-injured TA muscle at 240 h recovery. Scale bar shown is 50 μm. All micrographs are captured at 40X magnification.

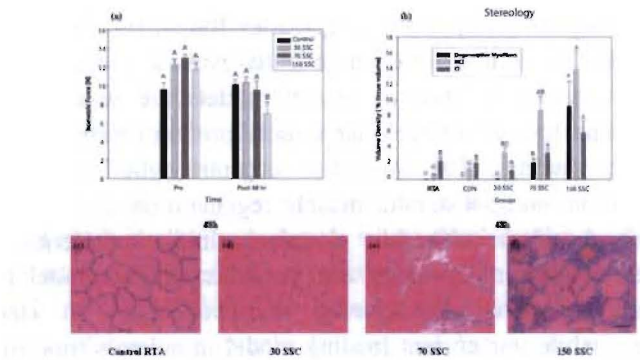


Figure 8. (A) Functional performance and change in isometric force of dorsi-flexor muscles 48h after SCC loading. (B)Stereology results that depict cellular infiltrates (CI), the change in the extracellular matrix (NCI), and change in myofiber necrosis (degenerative myofibers) for the contralateral limb (RTA), the isometric control (CON), and limbs exposed to 30 SSCs 70 SSCs and 150 SSCs (B) Slide of muscle cross section from the contralateral limb. (C) Slide of the muscle cross section from the isometric control limb. (D) Slide of the muscle cross section from the limb exposed to 30 SSCs. (E) Slide of muscle cross section from the limb exposed to 70 SSCs. (F) Slide of muscle cross section from the limb exposed to 150 SSCs. Scale bar shown is 50 μm. All micrographs are captured at 40X magnification.

b. Adaptive Muscular Contractions

To our knowledge, the functional and biological responses observed following ST in humans has not previously been reported in an animal model. Thus, it was our contention that the optimal means to accomplish this was by manipulating the biomechanical loading signature by way of the dynamometer. Therefore, we altered the velocity and duty cycle (rest time between repetitions) from our SSC-injury paradigm, so that we would produce an adaptive-SSC paradigm [33]. Indeed, by decreasing the velocity of the SSC (from 500°/s to 60°/s) and increasing the duty cycle between SSC repetitions (from no rest time to 2 seconds – now intermittent contractions (Figure 9)), we were able to provide a stimulus that still incorporated SSC lengthening movements but very importantly represented a physiological model of adaptive ST-type loading in an animal model [8, 33]. In addition the morphological data attributed to the response of skeletal muscle "injury" in humans following voluntary muscle contractions that include lengthening movements (ST-type mechanical loading) do not conform to the morphological data observed in the numerous animal models that attempt to replicate this paradigm of ST. In fact, in humans following acute ST-type mechanical loading, one sees relatively normal muscle morphology with insignificant myofiber degeneration and only mild inflammation. Furthermore, this is accompanied by focal Z-line ultrastructure disorganization and intramyocellular protein (desmin) remodeling [48, 51, 109, 111]. Currently, the magnitude of these responses has not been documented in an animal model, which incorporates lengthening contractions. In contrast, in animal models contraction-induced muscle injury is characterized by extensive myofiber fiber degeneration and a robust inflammatory response in animals [4, 9, 11, 12, 50, 66, 72]. Recently, in an impressive experiment, Crameri and colleagues [31] elegantly demonstrated in humans that skeletal

muscle's response following voluntary eccentric-type (lengthening) exercise did not result in changes described in animal models (i.e. necrosis, inflammation, loss of intracellular proteins, and extensive myofiber regeneration). Surprisingly, they found, for the first time in humans, that only when involuntary contractions (electrically-evoked contractions) of the same eccentric-type exercise previously used in animal models are used in humans is there myofiber degeneration and loss of intracellular muscle protein (desmin). Thus, in humans, following mechanical loading that includes eccentric-type movements, myofiber degeneration, inflammation, and substantial muscle regeneration does not appear to be as extensive as hypothesized, unless induced by electrical stimulation. Hence, we have shown the ability to produce muscle injury using our previous animal model [9, 11, 12, 50]; consistent with results produced by Crameri and colleagues in electrically-evoked contractions in humans, while our current loading model in animals (non-injurious) [8] has been found to mimic more closely voluntary contractions that occur in humans. The mechanism of adaptation appears to include focal myofiber and interstitial space adaptation/remodeling concomitant with increases in function.

In our chronic model of adaptive SSC loading, we sought to mimic the results of high-intensity ST that have been reported in exercise/athletic populations, which have investigated the ability of young and old subjects to increase muscle mass [104]. In order to advance these previous findings, it was our intent to illustrate possible factors involved in the adaptive phase following chronic exposure. Since the loss of skeletal muscle will directly impact skeletal muscle force production (muscle strength and power), administration of chronic mechanical loading exposures should be designed to create an adaptive environment in which muscle fiber hypertrophy would result. After exposure to a protocol of 80 low velocity SSCs administered 3 times/week for 4.5 weeks duration, the young rats increased their muscle mass in the tibialis anterior muscle by approximately 16% while increasing static and dynamic performance by over 30% [32]. In addition, there were no histological signs of myofiber injury (degeneration, necrosis) in the target muscles. Historically, studies have reported that exposure to high-intensity mechanical loading results in overt skeletal muscle damage and loss of performance. Our findings are in sharp contrast with those previous studies. Moreover, this finding is also in contrast with rodents exposed to high velocity continuous SSCs from our lab previously, which exhibited pronounced muscle degeneration following exposure (~ 10% tissue fraction)[9], similar to findings that have been reported by other investigators . The absence of an obvious degenerative effect observed following high-intensity mechanical loading in this and recent studies is very fascinating, since most published literature has showed that eccentrically-biased loading resulted in significant muscle injury and loss of performance. In our rodent model, electrodes activate the target muscle via supra-maximal electrical stimulation, an intensity that will seldom (if ever) be attained in human populations. Thus, our findings suggest that repetitive muscle contractions that include high-force eccentric contractions can be administered in a ST-type exercise regimen to promote muscle adaptation and performance gains in healthy populations. Moreover, optimizing the intensity of the exposure for an individual is paramount, especially in those individuals presenting with risk factors associated with disease states, so that they too may experience the benefits of a resistance exercise program.

c. Mechanical Loading and the Impact of Age

As we age, skeletal muscle performance decreases, and aged muscle recovers more slowly following injury [61], thus it is clear that aging impairs the ability of skeletal muscle to adapt to chronic mechanical loading. With aging, the loss of skeletal muscle mass is coincidental with the decline in function; however, whether this is causal or one of the resulting factors is less clear. More specifically, muscle strength declines approximately 15–30% in healthy populations following the seventh decade of life [2]. So it may be postulated that if mechanical loading that uses adaptive contractions does not result in customary muscle injury, then adaptive mechanical loading may be the best means to attenuate the effects of sarcopenia while also increasing function in aged populations. Indeed, the results from our animal studies indicate that not all high-intensity mechanical loading produces overt muscle damage, and that the muscle response can be much different from that typically observed following "classical" contraction-induced muscle injury [10, 32]. Our chronic loading model using low velocity intermittent muscle contractions produced a robust increase in muscle mass after a 4.5 week exposure in the young animals and approximately a 30% increase in static and dynamic muscle forces [32]. When old animals [30 months age) were exposed to this protocol, they did not increase muscle mass and lost approximately 30% in maximum static and dynamic forces. However, the tibialis anterior muscles from these animals did not display signs of injury, only low levels of cellular infiltrates. We surmised from these results that the older animals could not tolerate the 3 day/wk exposure regimen of 80 maximal SSCs/exposure, thus the muscles mal-adapted as evidenced by latent inflammatory infiltrates, lack of fiber hypertrophy, and loss of muscle performance. However, the interesting feature was these animals were exposed to 14 sessions of high-force SSCs that included eccentric contractions without resulting in muscle fiber injury [32]. Thus, titration of the exposure with either less repetitions/day or less exposures/week may allow older muscles to adapt much as those from the young animals did. Thus, the approach used in our model should be considered using a translational approach with respect to human populations, since very recent reports in older men and women exposed chronically to high-intensity resistance training concluded that this mode of exposure may be the most advantageous for improving the quality of life in aged populations [54].

d. Adaptation Following Acute ST-Type Mechanical Loading

As mentioned above, we have investigated the impact of SSCs (the most common contraction-type used in daily movement) on muscle injury and, more recently, adaptation in a chronic aging model. More recently, we investigated the effect of an acute, adaptive SSC loading exposure using the same low-velocity intermittent SSCs, and found the regenerative signal in muscle is weaker in old rats (evidenced by an ~200% increase in developmental myosin heavy chain (MHC_{dev}^{+}) labeling in exposed versus the contra-lateral control limb), when compared with young rats (~2,000% increase in MHC_{dev}^{+} labeling in exposed versus contra-lateral control limb; Figure 10) [10]. This occurs in the absence of significant myofiber degeneration (Figure 11), which is in contrast to what has been reported previously [20]. With regards to the morphological response, when 4.5 weeks of chronic, low-velocity SSCs are administered, there is a decrease in performance and myofiber hypertrophy is less in old rats compared to young rats (Figure 12). This indicates that old rats are unable to adapt to the chronic SSC loading, as indicated by maladaptation without degeneration. We have shown that older rats are less tolerant to chronic

SSC loading than their younger counterparts, and this was the first study to our knowledge that showed maladaptation in old rats (both functionally and morphologically) under controlled repetitive loading [32]. It is plausible to suggest that a decline in the regenerative/remodeling capacity in the older animals is responsible for this maladaptive response. Moreover, in our acute, low velocity loading model, developmental myosin (MHC_{dev}) was expressed in rat tissue that did not exhibit signs of overt skeletal muscle injury, suggesting that expression of developmental myosin heavy chain may be indicative of remodeling events, which ultimately lead to chronic muscle hypertrophy in the absence of myofiber degeneration [10]. This suggests one plausible mechanism as to why our old rats' performance measures were decreased at the end of the chronic exposure as compared to our young rats (young rats having increased force due to increased myofiber hypertrophy compared with old rats). Thus, MHC_{dev} may be intimately tied to the adaptive response in developing and mature myofibers [75]. Collectively, these data suggest that chronic muscle adaptation is not dependent on initial myofiber degeneration, and that myofiber degeneration does not significantly contribute to maladaptation in old rats following chronic SSC exposure. Furthermore, a study by Brown and colleagues [22] concluded that adaptation of skeletal muscle following eccentric contractions may be the result of an improved ability to repair ultrastructural changes occurring in individual myofibers (not removal of necrotic myofibers), and this suggestion is substantiated by numerous studies [48, 109, 111]. In the aforementioned studies, young and old dorsiflexor muscles exposed to an acute protocol of 80 intermittent SSCs did not undergo the extent of myofiber degeneration that is typically reported for classical contraction-induced muscle injury [9, 11, 57, 76]. Thus, our current findings and several other studies suggest that the adaptive response of muscle following mechanical loading is not dependent on myofiber degeneration, but occurs as a result of ultrastructural modifications [22, 109, 111] as well as local environmental changes (influenced by both autocrine and paracrine mechanisms) in the tissue [30, 32, 33, 74]. Together, these data indicate that the phenomena we are reporting in our current acute and chronic adaptive models more likely represent what is occurring in humans following ST-type mechanical loading when lengthening-type movements are incorporated (as reported by Crameri and colleagues) [31]. Therefore, this specific SSC loading model may represent a more physiologically representative means to investigate these adaptive/remodeling events.

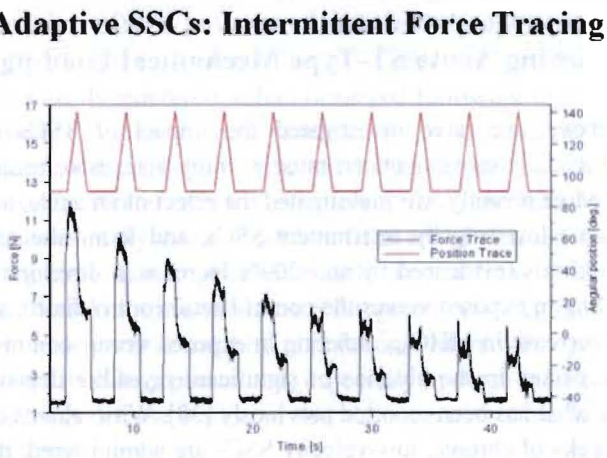


Figure 9. Typical force trace, angular position trace, and electrical stimulation timing of one set of 10 intermittent, adaptive SSCs.

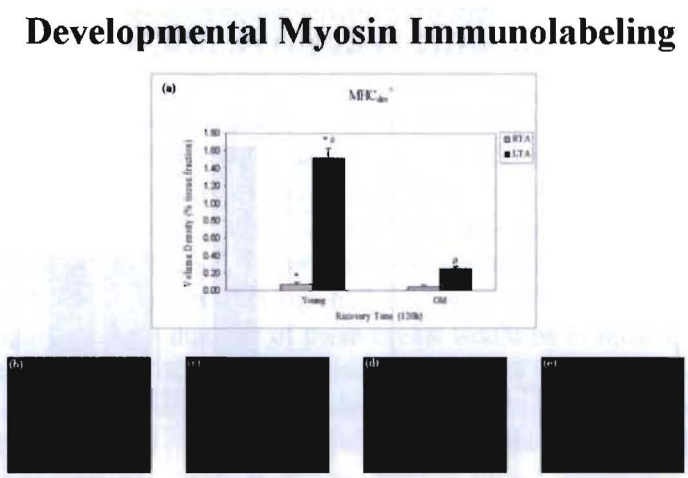


Figure 10. (A) Developmental myosin labelling analyses demonstrates that TA muscle from young rats has a 2000% increase in MHC_{dev}^{+} versus the contra-lateral control limb at 5d recovery. TA muscle form old rats have only a 200% increase versus their control limb at 5d recovery. The bottom micrographs from left to right illustrate MHC_{dev}^{+} for young (B) and old (C) SSC-loaded rat TA muscle at 5d recovery, respectively. Panel (D) and (E) illustrate positive control labelling of MHC_{dev}^{+} for SSC-injured and rat pup tissue at 5d, respectively. Scale bar shown is 50 μm. All micrographs are captured at 40X magnification.

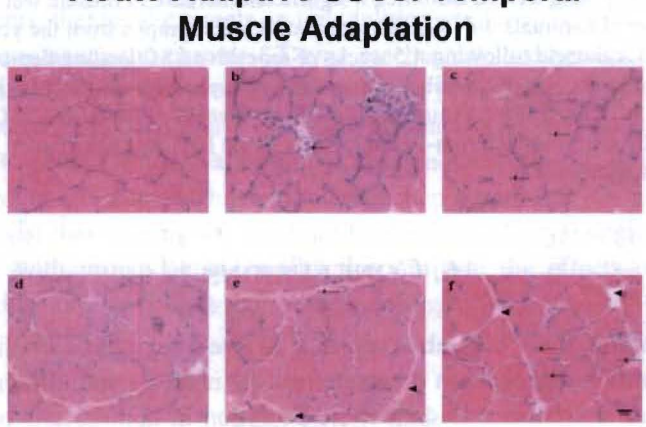


Figure 11. Morphological changes in muscle tissue from young and old rats following exposure to SSCs. No myofiber or interstitial changes were observable in contra-lateral control RTA muscle from young or old rats. (A) Micrograph representing the young exposed LTA muscle at 24h recovery (note, no myofiber or interstitial disruption present). (B) Representative micrograph from the young exposed LTA muscle at 72h recovery displaying < 1% of myofibers having a degenerative response and also an increased cellular interstitial response (increased CI, arrows). (C) Representative micrograph from the young exposed LTA muscle at 120h recovery, which exhibited few fibers with central nuclei (arrows). (D) Micrograph representing the old exposed LTA muscle at 24h recovery (note, as with young counterparts, no myofiber or interstitial disruption present). (E) Representative micrograph from the old exposed LTA muscle at 72h recovery displaying an increased cellular interstitial response (increased CI) as well as an increased swelling of the perimysium and endomysium (increased NCI, arrowheads). (F) Representative micrograph from the old exposed LTA muscle at 120h recovery, as observed with young rats few fibers exhibited central nuclei (arrows). Scale bar shown is 50 μm. All micrographs are captured at 40X magnification.

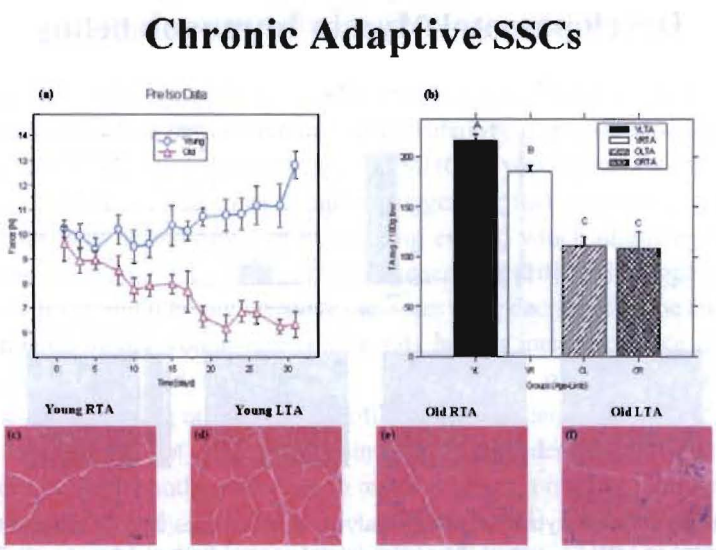


Figure 12. Functional and morphological changes in muscle tissue from young and old rats following chronic exposure to adaptive SSCs. (A) Pre-isometric force of young and old rats at each of the fourteen exposures. Even though the isometric force output was very similar in magnitude prior to SSC loading, the isometric forces between thetwo groups began to diverge starting with the seventh SSC exposure. (B) TA wet-weight normalized to body weight following 4.5 weeks of repetitive SSC loading. Groups are young treated LTA (YL), young control RTA (YR), old treated LTA (OL), and old control RTA (OR). The young treated exhibited a significant increase in muscle wet weight over its control limb, while the old animals did. (C). Representative micrographs from the young control (C) and SSC loaded (D) TA muscle following 4.5 weeks of repetitive SSC loading depicting muscle hypertrophy exhibited by increased myofiber cross-sectional area. Representative micrographs from the old control (E) and SSC loaded (F) TA muscle following 4.5 weeks of repetitive SSC loading depicting no muscle hypertrophy or change in cross-sectional area. Scale bar shown is 50 μm. All micrographs are captured at 40X magnification.

6. Conclusions

Advances resulting from our lab's research as well as other's findings suggest that "injury" or degeneration/regeneration (characterized by necrosis and inflammation) episodes may not be the main mechanism leading to a restoration in homeostasis of skeletal muscle following ST-type mechanical loading. In contrast, remodeling and adaptive events that attempt to re-establish homeostasis and growth of skeletal muscle following ST-type mechanical loading appear to be of major importance (protein synthesis, intracellular signaling events, and metabolic processes), and, collectively, these events ultimately enable one to increase performance while ST. Furthermore, the local maladaptation incurred as a result of repetitive mechanical loading as we grow older is not due to an initial degenerative insult, but appears to be limited by specific local adaptive and regenerative/remodeling events. Specifically, our model may exhibit its usefulness in elucidating what factors affect safety threshold (muscle tolerance) during repetitive mechanical loading, and thereby aide in designing exercise and rehabilitative programs that are useful for older individuals, whose number is increasing in this country. Our results indicate initial muscle remodeling is a critical element in assuring successful adaptation following ST-type mechanical loading.

Thus, investigating the distinct mechanisms involved in initiating successful muscle remodeling following exposure will be beneficial in aging populations. Again, we have demonstrated that a clear differentiation exists between overt skeletal muscle injury (classically defined as eccentric-, lengthening- or contraction-induced muscle injury) and adaptive muscular contractions (acute and/or chronic SSCs that incorporate lengthening movements). More importantly, from a clinical perspective there are various instances when an individual (i.e. an athlete) would present with muscle "damage" (i.e. myofilament disruption) resulting from high-intensity muscular contractions (i.e. ST-type mechanical loading or even throwing events as a baseball pitcher is surely to endure while pitching), however it is highly unlikely that any of these events would be evaluated or diagnosed by a clinician (i.e. athletic trainer or sports medicine physician) as a clinically-diagnosable muscle injury (i.e. first, second, or third degree muscle strain). It is to this end that we do believe that you may have myofiber "damage" (which may be compensated for by the remodeling/adaptive process) without having muscle "injury" (myofiber degeneration and inflammation). A more integrated concept is that initial myofiber remodeling/regeneration (restoration of homeostasis) are critical elements in assuring successful adaptation, regardless of age. Furthermore, it is essential that we as researchers and clinicians understand that not all acute and chronic mechanical loading (specifically loading comprised of eccentric movements) results in overt skeletal muscle injury. Since the capacity to respond efficiently to an initial mechanical stimulus may be one of the most important factors that ultimately regulate adaptation of skeletal muscle in the aging process, our best attempt at optimizing the initial exposure for maximal adaptation as well as improving the muscle's host environment (i.e. via supplements, therapeutic agents and modalities, etc.) may improve the responsiveness of skeletal muscle to acute and chronic ST-type mechanical loading. Finally, as chronic high intensity mechanical loading has been shown to be the most desirable means to attenuate the effects of sarcopenia [19], it is our belief that the most effective and appealing mode of physical activity to prescribe for healthy individuals encompassing occupation, military, and sport sectors may be ST-type mechanical loading incorporating SSCs as well. The unique possibility does exist that training for maximal functional and physiological gains may occur in parallel along with prophylactic benefits that mitigate the effects of musculo-skeletal dysfunction sustained during periods that arise as one ages.

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