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Review

Injury and adaptive mechanisms in skeletal muscle

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Abstract

Work-related musculoskeletal disorders (MSD) are a major concern in the United States. Overexertion and repetitive motion injuries dominate reporting of lost-time MSD incidents. Over the past three decades, there has been much study on contraction-induced skeletal muscle injury. The effect of the biomechanical loading signature that includes velocity, range of motion, the number of repetitions, force, work-rest cycle, and exposure duration has been studied. More recently, the effect of aging on muscle injury susceptibility and regeneration has been studied. This review will focus on contraction-induced skeletal muscle injury, the effects of repetitions, range of motion, work-rest cycles, and aging on injury susceptibility and regenerative and adaptive pathways. The different physiological phenomena responsive to overt muscle injury versus adaptation will be distinguished. The inherent capability of skeletal muscle to adapt to mechanical loading, given the appropriate exposure signature will also be discussed. Finally, we will submit that repeated high-intensity mechanical loading is a desirable means to attenuate the effects of sarcopenia, and may be the most effective and appealing mode of physical activity to counteract the effects often observed with musculo-skeletal dysfunction in the workplace.
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Keywords: Aging; Skeletal muscle injury; Regeneration; Adaptation

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1. Introduction

Work-related musculoskeletal disorders (MSD) are a major concern in the United States. Overexertion and repetitive motion injuries dominate reporting of lost-time MSD incidents. Over the past three decades, there has been much study on contraction-induced skeletal muscle injury. The effect of the biomechanical loading signature that includes velocity, range of motion, the number of repetitions, force, work-rest cycle, and exposure duration has been studied. More recently, the effect of aging on muscle injury susceptibility and regeneration has been studied. This review will focus on contraction-induced skeletal muscle injury, the effects of repetitions, range of motion, work-rest cycles, and aging on injury susceptibility and regenerative and adaptive pathways. The different physiological phenomena responsive to overt muscle injury versus adaptation will also be distinguished. The inherent capability of skeletal muscle to adapt to mechanical loading, important for adequate response to repetitive mechanical exposures, will also be addressed. Finally, this review will submit that repeated high-intensity mechanical loading is a desirable means to attenuate the effects of sarcopenia, and may be the most effective and appealing mode of physical activity to counteract the effects often observed with musculo-skeletal dysfunction in the workplace.

2. Contraction-induced muscle injury

Skeletal muscle is a fascinating organ of the human body. Skeletal muscle can generate force during contraction for movement of the limbs to generate external work, as well as absorb work, and it can produce loads on other tissues such as tendons, joints, and nerves. Skeletal muscle can also generate heat, important for thermoregulation in cold temperatures. While skeletal muscle performs these important functions necessary for our everyday lives, there is also risk for injury due to repetitive motions and overexertion commonly experienced in the workplace, recreational, and athletic endeavors. In the United States, work-related musculoskeletal disorders account for approximately 38% of cases involving days away from work (Labor, 2007), 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 (Barbe and Barr, 2006; N.R.C. et al., 1999). In order to address this issue, there have been extensive studies to-date on acute contraction-induced muscle injury using both animals and humans. Single stretches as well as repetitive muscular contractions, or stretch-shortening contractions (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 mal-adaptation (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 (Ljung et al., 1999) are similar to those changes shown in chronically-loaded rat muscles (Stauber and Smith, 1998). Findings from volitional animal models of repetitive motion (Barbe and Barr, 2006; Barr and Barbe, 2004), human models of exercise overload (Carp et al., 2006; Clarkson and Hubal, 2002; Clarkson and Sayers, 1999; Ljung et al., 1999; Reid and MacGowan, 1998), and electrically stimulated rat dynamometer models (Baker et al., 2006a,b; Geronilla et al., 2003; Pizza et al., 2005) demonstrate that the cellular pathways of activation and the accompanying inflammation and histopathology are congruent. *In vivo* rat dynamometry 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 (Fig. 1). *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.

We know that eccentric muscle actions are known to cause a greater amount of muscle damage. This suggests that high load tensions in fibers may be more important than physiologic considerations in the etiology of the injury process (Armstrong, 1986; Stauber, 1989a,b). High mechanical forces produced during eccentric muscle actions have been causal in the underlying etiology of muscle strain injuries (Armstrong et al., 1983; Warren et al., 1993). This was thought to be due to high fiber stresses in the contractile apparatus due to high forces transmitted axially to the actin and myosin contractile proteins. Additionally, 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 (Armstrong, 1984; Armstrong et al., 1991). A single exposure to eccentric muscle actions results in loss of performance immediately after exposure and can last for up to 30 days (Warren et al., 1999a). Past investigations of eccentric contraction-induced muscle injury have indicated that mechanical factors such as peak force and average force (Gosselin and Burton, 2002), work during stretch (Hunter and Faulkner, 1997), fiber length (Gosselin and Burton, 2002; Hunter and Faulkner, 1997), and strain (Lieber and Friden, 1993) influence the amount of muscle

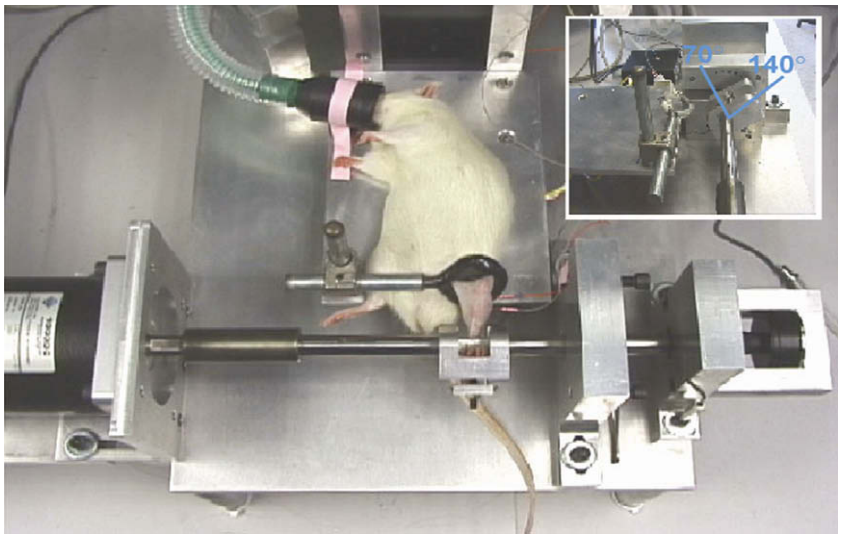

Fig. 1. In vivo rat dynamometer complete with DC servomotor, potentiometer, and load cell to measure forces of the dorsiflexor muscle group. Inset shows the ankle angle from 70° to 140°.

damage. Change in maximum isometric force after injurious exposure has been shown to be the best indicator of the degree of muscle damage (Warren et al., 1999b).

Eccentric muscle actions have been shown to result in ultrastructural damage immediately after exposure (Friden et al., 1991), and 1–3 days after exposure (Hesselink et al., 1996; McCully and Faulkner, 1986). Structural disruption occurs at the cellular level, and cellular infiltrates invade as a result of an inflammatory response (Faulkner et al., 1989; Friden et al., 1983a; Lieber et al., 1996; McCully and Faulkner, 1985). 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 (Friden and Lieber, 1998; Komulainen et al., 2000, 1998; Lieber et al., 1994). Sarcomeric lesions, disorganized actin, and Z-disc streaming also result after injury (Devor and Faulkner, 1999; Lieber et al., 1991; Stupka et al., 2001; Vijayan et al., 2001). 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 endo-sarcomeric membranes (Friden and Lieber, 1998; Lieber et al., 1994, 1996), and of the extracellular matrix (Lieber et al., 1994; Stauber and Smith, 1998) in strain-injured muscle tissue. In lengthening contraction-induced injuries, damage within the muscle is most often seen at the myotendinous junction and at specific sarcomeres (Garrett, 1996; Hasselman et al., 1995; Noonan et al., 1994; Obremsky et al., 1994). In fact, it has been hypothesized that there is a population of sarcomeres that are weaker, and tear more easily under lengthening conditions (Friden and Lieber, 1998; Morgan, 1990; Talbot and Morgan, 1996). 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 (Devor and Faulkner, 1999; Koh et al., 2003). 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 (Armstrong et al., 1983; Friden et al., 1986; Geronilla et al., 2003; Lieber et al., 1994). Chronic exposure to either high (Archambault et al., 2001; Backman et al., 1990; Stauber and Willems, 2002) or low force (Barbe and Barr, 2006; Perry et al., 2005) loading induces this inflammatory response. The inflammatory response is characterized by an infiltration of neutrophils and macrophages (Tidball, 2005; Tsivitse et al., 2003). Neutrophils infiltrate damaged muscle within 1–2 h of the initial injury (Belcastro et al., 1996; Fielding et al., 1993; Tidball, 1995) and are present for up to five days post injury (Fielding et al., 1993). These inflammatory cells 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 (Round et al., 1987; St Pierre and Tidball, 1994). These macrophages also express pro-inflammatory cytokines including tumor necrosis factor-α (TNFα)(Collins and Grounds, 2001; De Bleecker et al., 1999; Warren et al., 2002; Zador et al., 2001). During muscle adaptation, the inflammation and tissue damage are eventually resolved and normal function is restored. During this time, satellite cells (quiescent muscle precursor cells) are activated, proliferate, differentiate, and finally fuse with the existing myofiber (Charge and Rudnicki, 2004; Hawke and Garry, 2001). Further, developmental myosin heavy chain is expressed in injured fibers during this time period, and this has been suggested to comprise the developmental program (Cook and McCormick,

1994). 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 (Bigard et al., 1997; Hesselink et al., 1996).

Interestingly, exposure to concentric (shortening) or isometric muscle actions does not normally produce muscle injury (Baker et al., 2006b; Faulkner et al., 1995; Lieber et al., 1996; Warren et al., 1993). Recently, the ability to rapidly quantify both skeletal muscle degeneration and inflammation following an injurious exposure in the same tissue using a novel stereological technique has been shown to reveal further insight into the injury and repair process of skeletal muscle (Baker et al., 2006a,b, 2007; Cutlip et al., 2006b).

2.1. Repetition number

There is clear evidence that the number of lengthening contractions has an effect on the amount of resultant muscle injury and isometric force deficit (Hesselink et al., 1996). 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 (Hesselink et al., 1996). 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% L_o, typically; L_o: optimal muscle length) have not resulted in muscle damage or a pronounced force deficit (Brooks et al., 1995; Hunter and Faulkner, 1997). In other studies, it required more than one stretch within the physiological range to produce muscle injury (Geronilla et al., 2003; Gosselin and Burton, 2002; Warren et al., 1993; Willems and Stauber,2000, 2001). 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 (Brooks and Faulkner, 1990; McCully and Faulkner, 1985; Zerba and Faulkner, 1990). Recently, we have observed an increasing quantity of myofiber degeneration and inflammation with increasing SSC number (Fig. 2a), and this increase clearly exhibits a dose-response finding (this is consistent and corroborates the findings of Hesselink and Colleagues) (Hesselink et al., 1996). These results are in agreement with previous results reported by Geronilla and colleagues (Geronilla et al., 2003), and further their initial observations that myofiber necrosis and myositis increased with increasing repetition number (Fig. 2b–f) (Baker et al., 2007). Thus, we have observed an increase in the histological indices for myofiber degeneration, non-cellular interstitium (edema), and cellular interstitium (cell

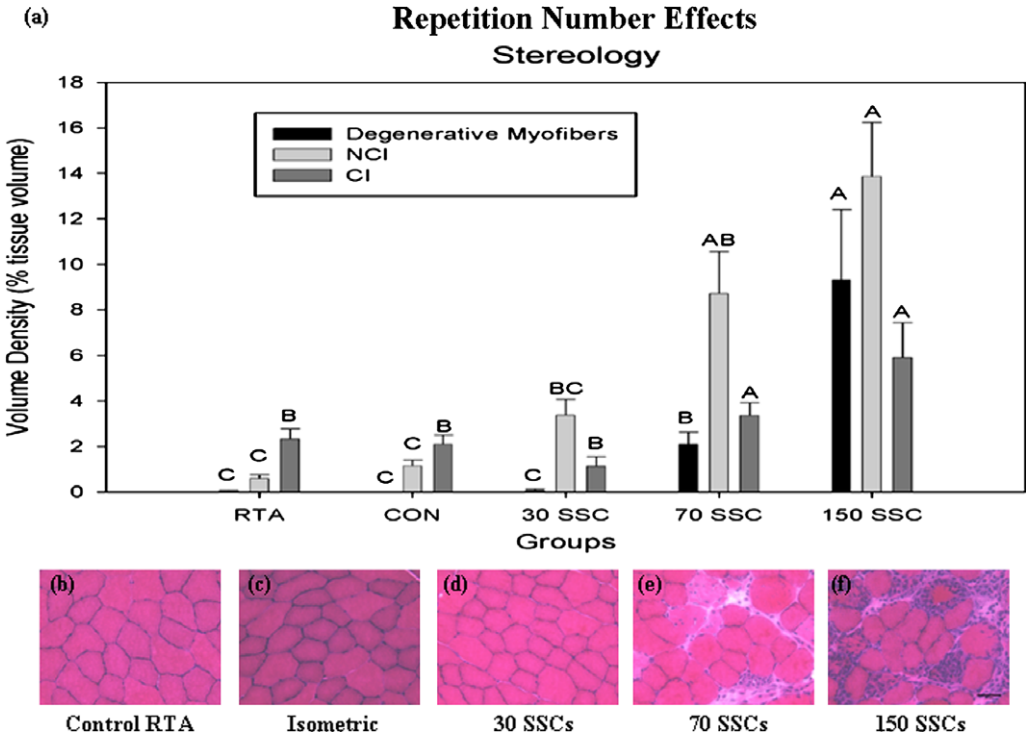

Fig. 2. (a) Stereology results that depict cellular infiltrates (CI), the change in the extracellular matrix (NCI), and change in myofiber necrosis (degenerative myofibers) for the contralateral limb (RTA), the isometric control (CON), and limbs exposed to 30 stretch-shortening cycles (30 SSC), 70 stretch-shortening cycles (70 SSC), and 150 stretch-shortening cycles (150 SSC). (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.

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.

However, previous histological studies have failed to directly quantify myofiber degeneration and its relationship to evident functional deficits following contraction-induced exposure. It was essential 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 mechanical loading. In our initial studies, we reported time-dependent changes that occurred in rodent tibialis anterior (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 (Baker et al., 2006a). Degenerative myofibers and interstitial space changes were associated with functional performance temporally (Baker et al., 2006a), and these results are in agreement with data reported previously (McCully and Faulkner, 1985).

While the ability to characterize early-phase muscle injury is essential in understanding skeletal muscle degeneration/regeneration kinetics, it is also important to understand and quantify dose-response characteristics following mechanical loading exposure. For this reason, we investigated the effect increasing numbers of SSCs had on muscle performance and morphology. Our results indicate that increasing indices of myofiber degeneration and inflammation paralleled the decrease in functional performance exhibited by the decline in isometric force production in groups exposed to increasing numbers of SSCs. 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. No myofiber degeneration or inflammatory response was observed in the control limb, animals exposed to isometric contractions, or animals exposed to 30 SSCs (Fig. 2). These measures illustrate a clear delineation for the target muscle's safety threshold (or tolerance) with increasing number of repetitions within an exposure, and that there is a level of exposure where the capacity to withstand the initial injury is compromised.

2.2. Range of motion

Past investigations of eccentric contraction-induced muscle injury utilizing single stretch models have identified key mechanical factors such as work, strain (incorporating initial and final length), and initial length as causal components in the injury process (Brooks and Faulkner, 2001; Brooks et al., 1995; Hunter and Faulkner, 1997; Lynch and Faulkner, 1998; Macpherson et al., 1996). While results from single stretch models have been informative about the causal factors in muscle injury, the target muscles were studied outside of the normal physiological range. Since fibers were typically stretched to 50% beyond optimal fiber length, muscle injury could have occurred independent of muscle activation. Indeed, passive length perturbations outside of the physiological range can result in significant strain injury (Brooks et al., 1995). Thus, it would be difficult to assess the contribution of passive versus active muscle injury in those models. In other studies, it required more than one stretch within the physiological range to produce muscle injury (Gosselin and Burton, 2002; Warren et al., 1993; Willems and Stauber, 2000; Willems and Stauber, 2001). Typically, peak force during the stretch was identified as the primary factor associated with the resultant isometric force deficit (Gosselin and Burton, 2002; Warren et al., 1993). Our observations supports those findings in that more than one repetition is required *in vivo* to produce muscle injury (Baker et al., 2006a).

In our *in vivo* rat model, we observed that muscles exposed to SSCs at longer muscle lengths did indeed result in a larger isometric force deficit 48 h after exposure as compared to those exposed only to isometric contractions (Fig. 3) (Cutlip et al., 2004). A non-recoverable isometric force deficit has been shown to be the best indicator of muscle injury (Warren et al., 1999b). This finding agrees with previous animal studies utilizing injury paradigms conducted outside of the normal physiological range (Brooks and Faulkner, 2001; Hunter and Faulkner, 1997; Wood et al., 1993), within the physiological range (Gosselin and Burton, 2002), and with human studies also conducted within the physiological range (Newham et al., 1988). Thus, SSCs conducted at longer muscle lengths (via movements of larger range of motion) resulted in a larger isometric force deficit 48 h after exposure, which is supportive of earlier studies (Gosselin and Burton, 2002; Hunter and Faulkner, 1997; McCully and Faulkner, 1986; Wood et al., 1993) (Fig. 4). We also found the dynamic function of muscle was affected after exposure to SSCs conducted at longer muscle lengths. We observed statistically significant decrements in negative work (eccentric), but not in positive work (concentric) after exposure to injurious SSCs. This finding was interesting because it suggested that the ability to perform eccentric or negative work after injury is more compromised than the ability to perform concentric or positive work.

2.3. Work-rest cycle

The isometric force deficit after exposure to multiple eccentric muscle actions commonly ranges from 40% to 60% of baseline isometric force (Faulkner et al., 1989). Generally, these findings are only specific to contractions that involve eccentric activity. These large force deficits are not seen in muscles that are exposed to isometric or

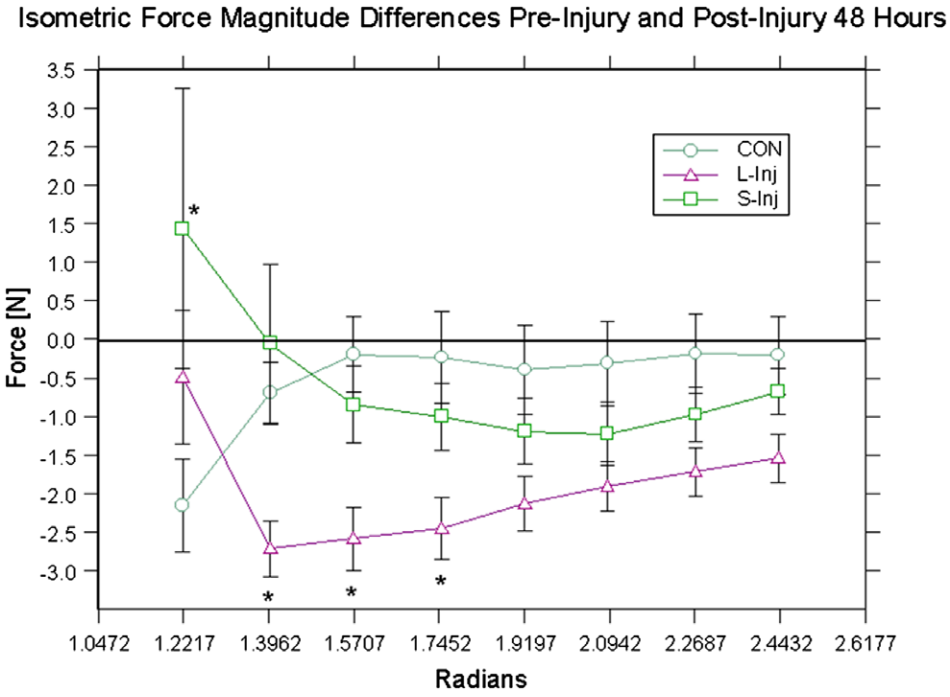

Fig. 3. Isometric force as a function of ankle angle. Isometric force was significantly depressed in animals exposed to SSCs at a long muscle length (90–140° ankle angle) versus those exposed to SSCs at shorter muscle lengths (70–120°) or isometric contractions ($p < 0.05$). Data was expressed as mean values ± standard error.

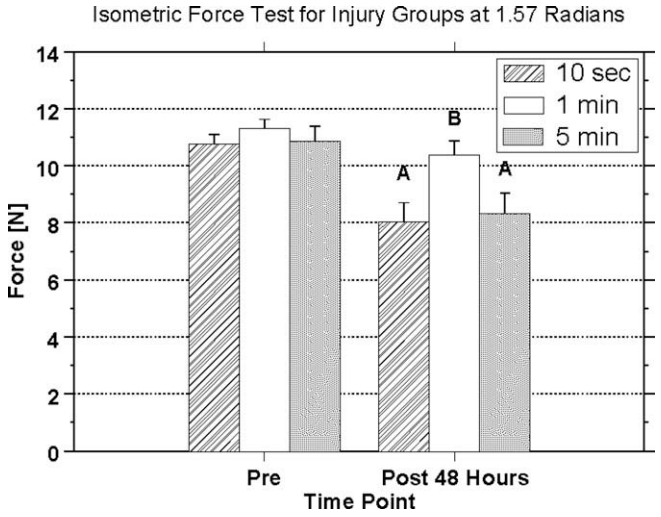

Fig. 4. Isometric force as a function of duty cycle. Animals exposed to 70 SSCs using 7 sets of 10 contractions with rest intervals of 10 s, 1 min, or 5 min between sets. Animals in the 10 s and 5 min groups had the most significant force deficit 48 h after exposure ($p < 0.05$). Data was expressed as mean values ± standard error.

concentric muscle actions (Sayers et al., 1999). Additionally, decreased force production has also been identified as part of certain enigmatic phenomena, including overload injury, delayed-onset-muscle-soreness (DOMS) and overtraining syndrome. The effect of rest intervals on muscle injury susceptibility has substantial relevance to the field of athletic and vocational performance, with specific regard to resistance exercise training programs and work practices and guidelines. Indeed, longer rest times between tasks have been shown to reduce soreness in humans (Teague and Schwane, 1995). The National Research Council and Institute for Medicine has recently recommended that the effect of work-rest cycle on muscle and other soft tissue injury be further investigated in order to elucidate the etiology of muscle injury and the sequelae of the injurious response (NRC and IM, 2001b).

Our laboratory studied the effect of work-rest cycle on muscle injury recently. Based on our prior results that 70 SSCs results in muscle injury, we used the 70 SSC exposure model that was comprised of seven sets of 10 repetitions. By varying the rest times between sets, we found that both a short rest time (10 s) and long rest time (5 min) resulted in significant isometric force deficits of the dorsi flexor muscles 48 h after exposure that were not seen in the group allowed to rest 1 min between sets. This data demonstrates that even under highly-controlled biomechanical loading conditions, short rest intervals may result in performance deficit and injury. In practical terms, for example, this could mean that even when laborers utilize appropriate technique to lift heavy objects, they still may have a significant injury exposure if sufficient rest is not taken between work bouts. Also, the longer rest period allowed the dorsi flexor muscles to generate higher forces during each subsequent set than with the short rest times, thus increasing the injury susceptibility. Translating this to the work environment, longer rest periods are beneficial and should ameliorate injury, however if coupled with high mechanical forces, muscle injury can still occur.

A larger force deficit at the short rest time can be attributed to metabolic demands placed on the muscle fibers. The influx of calcium into the cytosol via stretch-activated channels has been shown in rat skeletal muscles (Armstrong et al., 1993; McBride, 2003) and isolated mouse muscle (Yeung et al., 2003), which can be ameliorated by longer rest times via buffering of cytosolic calcium levels (Lowe et al., 1994). It has been shown that increased calcium levels in the cytosol result in increased myofiber damage (Jones et al., 1984) and apoptosis (Macho et al., 1997). Furthermore, exposure to long-term low frequency stimulation without rest has been shown to elevate cytosolic calcium levels (Gissel, 2000). Thus, shorter rest times between contractions can have a deleterious effect due to higher levels of cytosolic calcium and the inability of the muscle to buffer those levels. Thus, both high repetition rates with short rest periods and high force exertions in labor-intensive occupations, as well as prolonged high-intensity strength training practices, could be deleterious to muscle function and increase injury susceptibility (Cutlip et al., 2005). Thus, the work-rest cycle needs to be appropriate to the type of exposure, whether high-intensity or high repetition, to reduce injury susceptibility.

2.4. Influence of age

Throughout the course of one's life, there is an inevitable decline in skeletal muscle mass, and this phenomenon termed sarcopenia has been documented extensively (Brindle and Evans, 1995; Roubenoff, 2001). Coincidental with the loss of skeletal muscle mass is 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. Muscle mass decreases approximately 40% starting at the third decade with more rapid loss in the later decades of life (Brindle and Evans, 1995). There are multiple factors associated with the aging process that may be indicative of sarcopenic-like changes, which have been previously cited: contraction-induced skeletal muscle injury (Faulkner et al., 1995), increases in the inflammatory milieu as well as specific components of inflammation (Bruunsgaard et al., 1997, 2001; Sacheck et al., 2003), denervation with subsequent reinnervation of motor units principally affecting type II muscle fibers (Larsson et al., 1979; Pettigrew and Gardner, 1987), circulating and muscle-specific modifications in the "growth" hormone profile that drives both muscle growth as well as maintenance (Bross et al., 1999; Tatar et al., 2003), changes in muscle energy metabolism (Brindle and Evans, 1995), and increased reactive oxygen/nitrogen species (Bejma and Ji, 1999; Weindruch, 1995). More recently mitochondrial dysfunction (Aiken et al., 2002; Dirks and Leeuwenburgh, 2002) and the loss of specific muscle nuclei and myofibers via apoptotic events (Dirks and Leeuwenburgh, 2002; Krajnak et al., 2006; Siu and Alway, 2005) have been implicated as mechanisms contributing to sarcopenia. Irrespective of the total contribution, this multitude of variables ultimately is driving healthcare costs related with sarcopenia to new heights, especially since the population in the United States is growing considerably older. The workforce in the United States is aging too, for approximately 20% of the labor force is comprised of workers over the age of 55 (NRC and IM, 2001a). Thus, sarcopenic changes with aging are detrimental, not only with activities associated with daily living but also with more arduous labor-intensive tasks.

The best known strategy to increase skeletal muscle mass is with mechanical exposures (resistance/weight training), however, prescribing this mode of training is cautioned in aged populations due to the general condition of the older individual. Yet, our results and others (Yu et al., 2003, 2002; Yu and Thornell, 2002) indicate that not all high-intensity mechanical loading produces overt muscle damage. This is exemplified by skeletal muscle performance and morphology in both young and old rats following both acute and chronic mechanical loading that display different characteristics than those typically observed following "normal" contraction-induced muscle injury. Recently, there have been reported results in exercise/athletic populations that have investigated the ability of young and old subjects to increase muscle mass (Ivey et al., 2000; Welle et al., 1996). In addition, encouraging reports of 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 (Hartman et al., 2007).

However, as we age, skeletal muscle performance decreases, and aged muscle recovers more slowly following injury (Brooks and Faulkner, 1990, 1996; Koh et al., 2003; McBride et al., 1995; Sacco and Jones, 1992; Zerba et al., 1990; Lavender and Nosaka, 2006a,b; Manfredi et al., 1991). As the work force in the United States continues to age, it is imperative to understand the effects of aging on the susceptibility to work-related musculo-skeletal disorders (N.R.C., 2001a). It is clear that skeletal muscle's susceptibility to contraction-induced injury is increased with age in both humans (Manfredi et al., 1991) and animals (Brooks and Faulkner, 1996). This is indicated by an increased force deficit (Brooks and Faulkner, 1996; Koh et al., 2003; Zerba et al., 1990) and slower recovery of performance measures in old versus young animals following exposure (Brooks and Faulkner, 1990; Manfredi et al., 1991; McBride et al., 1995; Sacco and Jones, 1992). Thus, it is clear that aging impairs the ability of skeletal muscle to adapt to chronic mechanical loading.

In earlier studies, a single exposure to injurious eccentric exercise resulted in similar isometric force decrements regardless of age in mice (Brooks and Faulkner, 1996; Koh et al., 2003; Zerba and Faulkner, 1990) and rats (Gosselin, 2000) but older animals can exhibit larger force deficits with more severe exposures (Zerba et al., 1990).

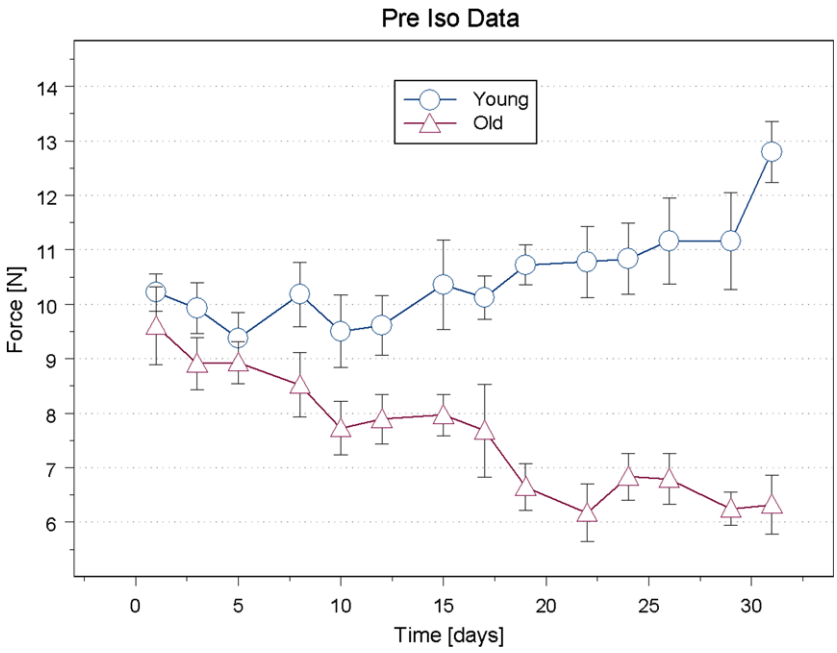

Fig. 5. Pre-test isometric force of the young and old groups at each of the fourteen exposures during the chronic exposure period. The pre-test isometric force response over the chronic exposure period was quite different for the old and young age-groups ($p = 0.0003$). The old and young groups generated very similar magnitudes of isometric force on the first day of exposure ($p = 0.455$). The isometric forces between the two groups diverged throughout the exposure period, resulting in a substantial difference in isometric force generated by the two age groups by the end of the thirty day exposure period (fourteenth exposure, $p < 0.0001$). Data are reported as mean values ± standard error.

However, McBride et al. showed that muscles from adult animals exposed to damaging eccentric muscle actions *in situ* exhibited isometric force recovery 14 days after the exposure, while muscles from old animals did not (McBride et al., 1995). Our data are consistent with these findings in that old animals appear unable to recover from repeated bouts of SSCs as evidenced by their reduced force generating capacity (Fig. 5) (Cutlip et al., 2006a).

What is quite evident is the disparity that exists in the previous literature regarding the effects of age on skeletal muscle's adaptive/mal-adaptive response following chronic mechanical loading. Moreover, some chronic exposure paradigms have focused on aerobic means of exposure to investigate the adaptive response which may not be representative of occupational exposures. For example, there is evidence that 10 weeks of treadmill training attenuated eccentric muscle damage *in vitro* in both young and older rats (Gosselin, 2000). Further, Leeuwenburgh and Ji (1995) found that exhaustive swim exercise after glutathione depletion exacerbated glutathione status, and glutathione homeostasis was critical for oxidant/antioxidant regulation following exposure (Leeuwenburgh and Ji, 1995). Exposure to resistance exercise has also been shown to provide a protective effect in both young and aged populations. In recent work, it was shown that 6 weeks of eccentric muscle actions provided a protective effect by preventing a substantial force deficit and morphological evidence of damage in muscles from both young and old animals (Brooks et al., 2001) exposed to a protocol that is injurious in an acute exposure. However, while both adult and old mice adapted successfully to the conditioning protocol (1 bout of eccentric muscle actions per week), the older mice adapted more slowly than the younger adult mice (Brooks et al., 2001). In humans, eccentric muscle actions also provided a protective effect to subsequent eccentric exposures based on muscle performance measures, although the protective effect was less in the older males (Lavender and Nosaka, 2006b). Interestingly, in this same group, biological markers of muscle injury were higher in the young males, which contradicted the performance results (Lavender and Nosaka, 2006a). While these studies showed that muscles from older animals and humans could be conditioned to be protected from eccentric contraction-induced injury, the conditioning stimulus was inadequate to promote hypertrophy of the target muscles or increase performance.

Although aging muscles have a delayed recovery from a single injurious exposure, it is encouraging that these muscles do retain some ability to adapt. For example, when damaging eccentric muscle actions are incorporated into a repetitive exposure model, there is evidence that age does not have a deleterious effect on adaptation when this eccentric protocol is administered only once per week *in vivo* (Brooks et al., 2001). In support of this, adult and old mice exhibited similar isometric and peak force deficits of the dorsiflexors after the initial exposure, and the recovery of those forces in rest periods between bouts of exposures was also similar (Brooks et al., 2001). Moreover, following 6 weeks of conditioning, the maximal isometric force was not different between age-groups. Also, a 6 week

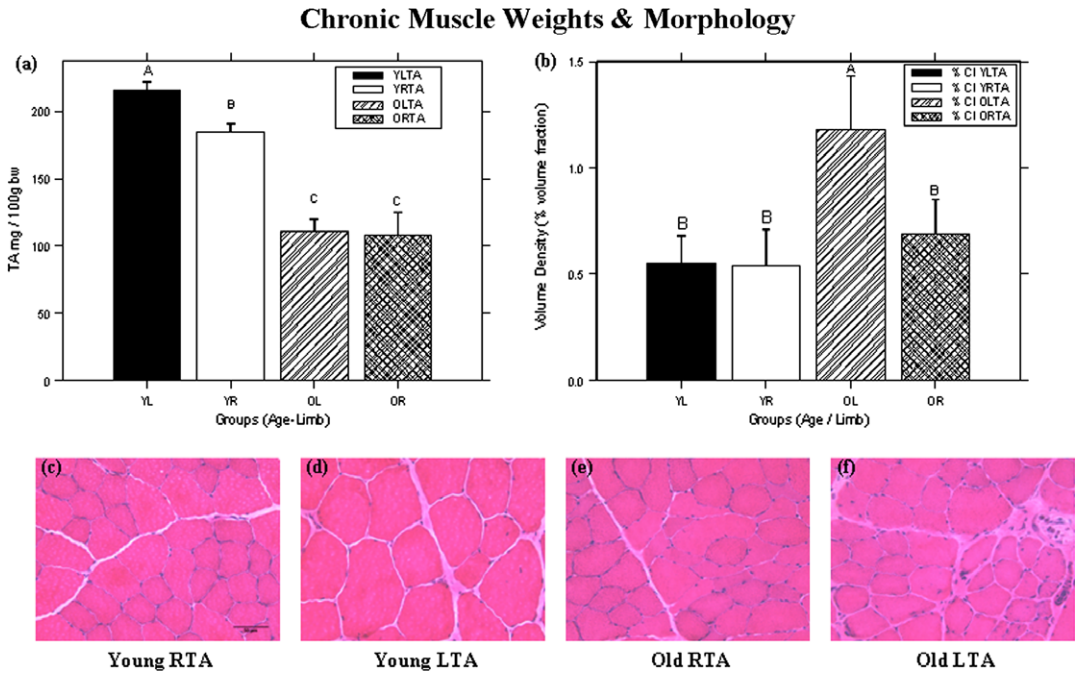

Fig. 6. (a) Tibialis anterior wet-weight normalized to body weight after fourteen exposures to the chronic SSC protocol. Groups are young treated (YL), young control (YR), old treated (OL), and old control (OR). The young treated exhibited a significant increase in muscle wet weight over its control limb ($p < 0.05$). The old animals did not exhibit an increase after exposure to the chronic protocol. (b) Volume density (% volume fraction) of the cellular interstium (CI) in the young and old animals' left (treated) and right (control) tibialis anterior. The volume density of the CI was greater in the treated limb of the old animals than all other groups. All other comparisons were not significantly different. Different letters denote significance at the 0.05 level. Data are reported as mean values ± standard error. (c) Hemotoxylin and Eosin stained cross section of tibialis anterior muscle from the young contralateral limb. (d) Hemotoxylin and Eosin stained cross section of tibialis anterior muscle from the young exposed limb. (e) Hemotoxylin and Eosin stained cross section of tibialis anterior muscle from the old contralateral limb. (f) Hemotoxylin and Eosin stained cross section of tibialis anterior muscle from the old exposed limb.

conditioning program in dorsiflexor muscles of female mice resulted in protection from contraction-induced injury in both old and young animals, despite no measurable hypertrophy. Brooks et al. (2001) hypothesized that this must be due to intrinsic strengthening of the sarcomeres within the myofibrils via regeneration of stronger sarcomeres, which are more resistant to injury. Earlier work conducted by Devor and Faulkner supports this hypothesis (Devor and Faulkner, 1999).

In spite of this, the amount of rest between exposures can affect the ability to adapt to potentially beneficial and/or injurious contractions, particularly in aged animals. The results from the repetitive loading model of Brooks et al.(2001) in mice, and Lavender et al. in humans (Lavender and Nosaka, 2006a,b) indicated that aging requires more time to adapt to injurious muscle contractions. Muscle hypertrophy and improvements in force production occur in response to constant or chronic loading in aged animals, although the extent of muscle enlargement is attenuated relative to young animals (Alway, 1995; Alway et al., 2002; Carson et al., 1995; Klitgaard et al., 1989a,b; Lowe et al., 1998). Our results are consistent with this observation, since as exposure to injurious contractions is repetitively administered, older rats were less able to adapt and the hypertrophic response was not as robust as in the young animals (Fig. 6a) (Cutlip et al., 2006a).

These findings indicate that the frequency of exposures may have profound implications on the ability to adapt to repetitive exposures of mechanical loading. In addition, we show concurrent adaptation in young animals (as evidenced by performance gains and a 17% increase in muscle wet-weight (Fig. 6a) and an increase in myofiber cross-sectional area, not shown) and mal-adaptation in old animals evidenced by loss of performance and an increase in latent inflammation (Fig. 6b) in the absence of myofiber degeneration (Fig. 6c–f). Furthermore, this strongly suggests that there is a level of exposure where the ability to adapt to mechanical exposures is severely compromised by age (Degens and Alway, 2003). Whereas muscle strength may be maintained and, in some instances, enhanced in senescence via resistive loading, the frequency of loading may play a key role in the ability of skeletal muscle to adapt in elderly populations.

2.5. Regeneration

Repeated mechanical exposures have been shown to result in adaptation, mal-adaptation, and even overt injury in both young and old age-groups (Brooks et al., 2001; Cutlip et al., 2006b; McBride et al., 1995). While muscles from old animals are able to adapt to increased loads, aging inevitably diminishes the resulting muscle

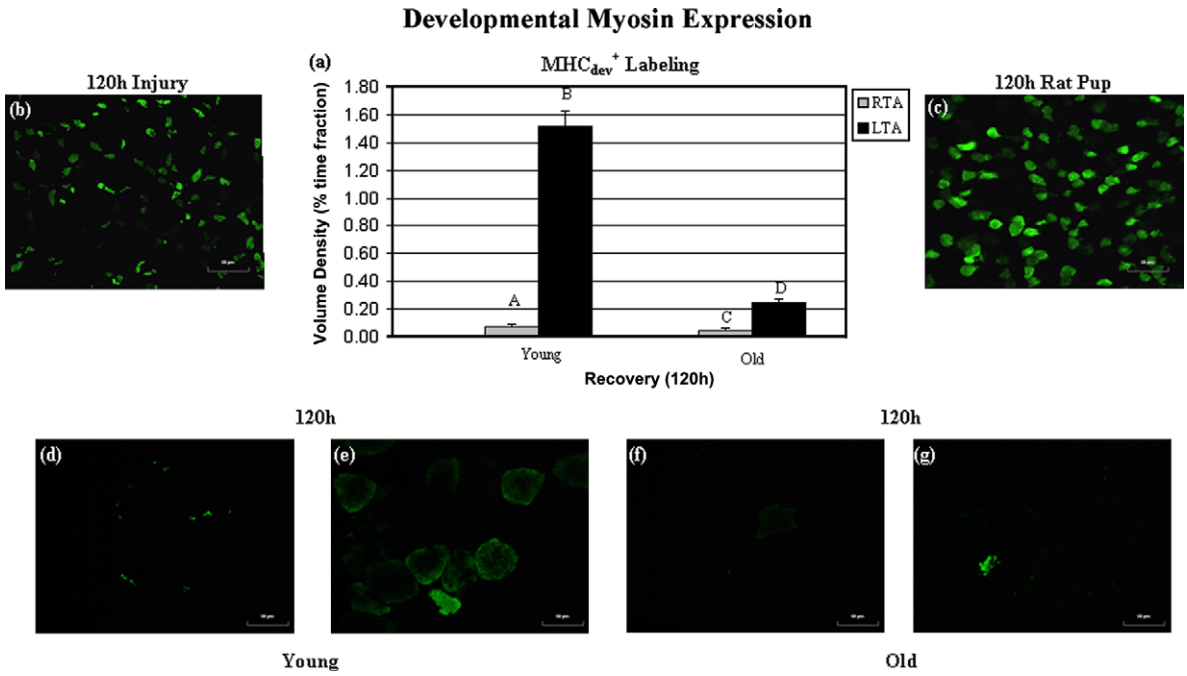

Fig. 7. Developmental myosin labeling shows in the graph that skeletal muscle from young animals exposed to a chronic protocol of SSCs has a 2000% increase MHC^{dev} versus the control limb. The old animals only have an increase of 200% vs. their control limb. The bottom panels from left to right shown expression of MHC^{dev} in young control, young exposed, old control, and old exposed, respectively. The two panels in the middle left to right show MHC^{dev} in injured tissue from young animals 120 h after exposure, and in rat pup tissue.

hypertrophy observed in old rodents (Alway et al., 2002; Degens and Alway, 2003), yet the underlying mechanisms are poorly understood. After an injurious exposure to eccentric muscle contractions, there is an increased force deficit (Zerba et al., 1990) and slower recovery of performance (McBride et al., 1995) in whole muscles (Brooks and Faulkner, 1990, 1996; Koh et al., 2003; McBride et al., 1995) and single fibers (Brooks and Faulkner, 1996) of old animals compared to young counterparts.

Recently, we have investigated various factors (i.e. recovery kinetics, repetition number, work-rest cycle, etc.) contributing to the induction of contraction-induced muscle injury (Baker et al., 2006a,b, 2007; Cutlip et al., 2004, 2005). From these studies, we have been able to optimize the exposure protocol (recovery kinetics, range of motion, work-rest cycle, number of repetitions, velocity) to produce substantial performance gains as well as muscle hypertrophy, which we have defined as adaptation, in young rodents versus old counterparts with as little as 4.5 weeks of training (Cutlip et al., 2006b). While previous data have suggested that muscle injury (myofiber degeneration) is the customary response following exposure to muscular contractions that incorporate lengthening movements (Faulkner et al., 1989; Koh et al., 2003), it is not known if this is an absolute when increased performance and muscle hypertrophy (adaptation) is the desired outcome or, moreover, if chronic mal-adaptation results from an initial injurious exposure.

The signal to respond following an acute mechanical exposure is intact in old rats (~200% increase in developmental myosin heavy chain (MHC_{dev}^{+}) labeling in exposed versus contra-lateral control limb), however this response is attenuated when compared with young rats (~2000% increase in MHC_{dev}^{+} labeling in exposed versus contra-lateral control limb) (Fig. 7); and the decrease in performance and attenuated myofiber hypertrophy exhibited in old rats indicates that they were unable to fully meet the demands after undergoing a chronic exposure (mal-adaptation without degeneration). Moreover, in both acute and chronic paradigms, developmental myosin was expressed in rodent tissue that did not exhibit signs of overt skeletal muscle injury, suggesting that developmental myosin heavy chain may be indicative of remodeling events leading to muscle hypertrophy even in the absence of myofiber degeneration. However, this diminished signal in myofibers suggests why old rodents do not have the capacity to adapt to repetitive exposures when compared with their younger counterparts. This may also explain why old rodents' performance measures were decreased compared to young rodents (young rats having increased force due to increased myofiber hypertrophy compared with old rats), since MHC_{dev} is intimately tied to the hypertrophic response of developing and mature myofibers (Alway et al., 1995; McCormick and Schultz, 1994). An alternative interpretation of the developmental myosin labeling may suggest that there was a decreased expression solely due to less damage in the old rodents; however, both young and old rodents had negligible percentages of degenerative myofibers – so this does not appear to be plausible. Furthermore, a study by Brown and colleagues (Brown et al., 1997) concluded that adaptation of skeletal muscle following eccentric muscle actions 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 (Friden et al., 1981, 1983b; Yu et al., 2002, 2003, 2004; Yu and Thornell, 2002). In a recent study, dorsiflexor muscles from young and old rodents exposed to the current protocol of 80 SSCs do not undergo the extent of myofiber degeneration (<1% degenerative myofibers present) that is typically reported for classical contraction-induced muscle injury (Baker et al., 2006a, 2007; Hesselink et al., 1996; McCully and Faulkner, 1985). Thus, corroborating our recent findings is a collection of literature that suggests that the adaptive response of muscle following mechanical loading is not dependent on myofiber degeneration (necrosis), but adaptation occurs as a result of ultrastructural changes (Brown et al., 1997; Yu et al.,2002, 2004) as well as local environmental changes in the tissue (Conboy et al., 2005; Cutlip et al., 2006b; Malm, 2001). Accordingly, the changes in the cellular and non-cellular interstitium may contribute to the collective functional and biological changes observed with aging, supporting this is our observation of increased estimates of edema at 120 h.

Muscle does have a delayed recovery from a single injurious exposure, yet the capacity to adapt remains intact (Conboy et al., 2005), as evidenced by our old rodents that displayed increased MHC^{+}_{dev} labeling in the exposed TA muscle compared with the non-exposed limb. However, this response was diminished significantly compared to exposed TA muscles from young rodents in this study (Fig. 7).

Based on the cumulative morphological changes following the 4.5 week SSC protocol, it is evident that a limited capability exists for SSC-induced adaptation to occur in aging skeletal muscle. Indeed, morphological adaptation is considerably limited and we suggest that this is due to the initial impediment of the regenerative process following a single mechanical exposure. Our results indicate that the expression of developmental MHC in individual TA muscle fibers is reduced in old rodents compared with young counterparts following a single bout of SSCs. In addition, the use of supramaximal electrical stimulation does not appear to influence the developmental MHC expression profile in myofibers, since volitional studies have reported comparable incidences of myofibers labeling positively for developmental MHC following mechanical exposure in young rodents (Smith et al., 1999). Even though aged muscle does appear to have the capacity for adaptation (as old rodents did display increased developmental MHC labeling in the exposed TA muscle compared with the non-exposed limb), this response is clearly diminished compared to exposed TA muscles from young rodents. Furthermore, this diminished signal in myofibers of old rodents that are stimulated to undergo adaptation, may suggest why old rodents do not have the capacity to adapt to chronic exposures when compared with young counterparts. When a chronic, repetitive bout of SSCs is administered over a 4.5 week period there is minimal developmental MHC expression in young and old rodents, yet young rodents exhibited marked adaptation following the exposure.

2.6. Summary

In summary, we have illustrated that there is a differentiation which clearly exists between overt skeletal muscle injury (classically defined as eccentric- or contraction-induced muscle injury) and adaptive muscle contractions (acute and chronic SSCs that incorporate eccentric movements). We suggest that initial muscle regeneration is a critical element in assuring successful adaptation, thus investigating the mechanisms involved in initiating successful muscle regeneration following exposure will be beneficial to aging populations. Again, it is essential and cannot be overstated that not all acute and chronic mechanical loading (specifically loading comprised of eccentric movements) results in overt skeletal muscle damage, which has been reported for more than twenty years. Remarkably the capacity to respond efficiently to an initial mechanical stimulus as one ages may be one of the most important factors that ultimately regulates adaptation of skeletal muscle. Optimizing the initial exposure for maximum adaptation (i.e. number of repetitions, intensity, work-rest cycle, velocity, etc.) as well as improving the muscle's host environment with age (i.e. via supplements, therapeutic agents, etc.) may improve the responsiveness of skeletal muscle to acute and chronic exposure that has currently been shown to be negatively influenced by age. Finally, as chronic exposure of skeletal muscles to high-intensity mechanical loading has been shown to be the most desirable means to attenuate the effects of sarcopenia (Brindle and Evans, 1995; Lambert and Evans, 2005), it too may be the most effective and appealing mode of physical activity to counteract the effects often observed with musculo-skeletal dysfunction in the workplace.

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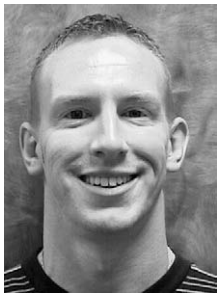

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