ARTICLE

Skeletal Muscle Injury Versus Adaptation with Aging: Novel Insights on Perplexing Paradigms

Brent A. Baker and Robert G. Cutlip

National Institute for Occupational Safety and Health, Health Effects Laboratory Division, Morgantown, WV, United States

BAKER, B.A. and R.G. CUTLIP. Skeletal muscle injury versus adaptation with aging: novel insights on perplexing paradigms. *Exerc. Sport Sci. Rev.*, Vol. 38, No. 1, pp. 10–16, 2010. *A growing body of data supports a view that skeletal muscle's response after mechanical loading does not always result in the classically reported "injury response." Furthermore, current evidence supports a model of muscle adaptation and/or maladaptation, distinct from overt injury, in which myofiber degeneration and inflammation do not contribute as significantly as once reported even in aged populations.* **Key Words:** mechanical loading, stretch shortening contractions, high-intensity resistance training, muscle adaptation, myofiber degeneration, myofiber regeneration, inflammation

INTRODUCTION

Key elements of the adaptive response that result from high-intensity muscular contractions involved during mechanical loading (*i.e.*, resistance training) are strength gains and muscle hypertrophy; however, the aging process seems to attenuate these positive training benefits, although concomitantly exhibiting a sarcopenic state that ultimately leads to senescence. Not unexpectedly, 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 because of the compromised condition of the older individual — a sarcopenic state and the propensity that it will induce overt skeletal muscle injury if commenced. Despite this, current evidence supports a model of muscle adaptation after mechanical loading, distinct from overt injury, in which myofiber degeneration and inflammation do not contribute as significantly as once reported even after muscular contractions incorporating repetitive eccentric contractions.

Contraction-induced muscle injury models in animals are useful in elucidating the etiology of occupation-, military-, and sport-related musculoskeletal disorders in humans (14). Our laboratory 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 composed of force, repetitions, range of motion, movement velocity, work-rest cycle, and number of exposures. *In vivo* dynamometry also is minimally invasive, such that the preparation does not compromise the physiological response, and allows for longitudinal study of muscle performance. This model also permits the study of the limiting influence age has on muscle adaptation after mechanical loading *in vivo*.

Single stretches (eccentric contractions) as well as reciprocal eccentric/concentric contractions, or stretch-shortening contractions (SSC), have been shown to lead to overt skeletal muscle injury (inflammation, myofiber degeneration, and dysfunction) (17,20). Skeletal muscle adaptation (remodeling and growth with functional gains), and/or maladaptation (a subdegenerative or subnecrotic state that is usually associated with low levels of persistent inflammation as well as loss of function) results from a chronic administration of SSC (13). 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 (defined as a loss of function without evidence of myofiber necrosis). Previously, our laboratory has investigated various factors such as recovery after acute injury (20), the effect of repetition number on acute injury, the effect of work-rest cycles (15), range of motion (16), and isometric contraction times (19) on muscle performance, and how those factors contribute to the induction of contraction-induced muscle injury and the resulting morphology (Fig. 1A, B) (5–7,15,16). These studies provided data that helped in optimizing our loading protocol to produce substantial performance gains as well as muscle

Address for correspondence: Robert G. Cutlip, Ph.D., National Institute for Occupational Safety and Health, Health Effects Laboratory Division, 1095 Don Nehlen Drive, M/S 2027, Morgantown, WV 26505 (E-mail: rgc8@cdc.gov).
Accepted for publication: June 25, 2009.
Associate Editor: Mary P. Miles, Ph.D., FACSM

0091-6331/3801/10–16
Exercise and Sport Sciences Reviews

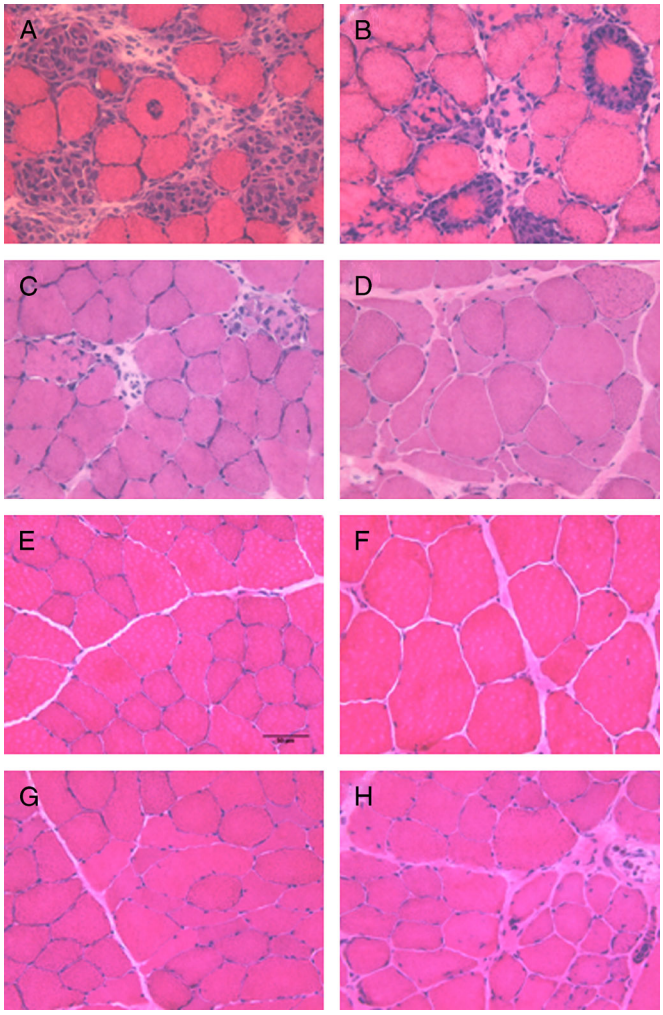

Figure 1. Morphological changes in muscle tissue from young and old rats after acute and chronic stretch-shortening contractions (SSC) loading. Representative hematoxylin and eosin micrographs from acutely exposed young (A) and old (B) left tibialis anterior muscle (LTA) at 72 h after injurious SSC displaying myofibers undergoing a significant degenerative response and increased cellular infiltrates along with increased swelling of the perimysium and endomysium. Micrograph from acutely exposed young LTA muscle at 72 h after adaptive SSC displaying less than 1% of myofibers having a degenerative response (C). Micrograph from acutely exposed old LTA muscle at 72 h after adaptive SSC displaying an increased cellular interstitial response as well as an increased swelling of the perimysium and endomysium (D). Micrograph from a young contralateral control right tibialis anterior muscle (RTA) displaying normal myofiber morphology (E). Micrograph from chronically exposed young LTA muscle at 4.5 wk after adaptive SSC displaying normal myofiber morphology and increased myofiber cross-sectional area (F). Micrograph from an old contralateral control RTA displaying normal myofiber morphology (G). Micrograph from chronically exposed old LTA muscle at 4.5 wk after adaptive SSC displaying increased cellular infiltrates with no increased myofiber cross-sectional area (H).

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 wk of resistance-type training (12,13).

Characterizing time- and dose-dependent responses for both skeletal muscle injury and adaptation, two disparate responses that can result from exposure to both acute and chronic mechanical loading, is essential in addressing the current voids and misconceptions about skeletal muscle injury. Previous studies have suggested that contraction-induced muscle damage results from a single phenomenological event with eccentrically biased loading of the target muscle (14). We suggest this is not the case because responses ranging from injury to maladaptation to adaptation may occur over a broad continuum even when exposed to high-intensity mechanical loading exposure that contains eccentric contractions. 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 after mechanical loading exposure/s. Although previous data have suggested that muscle injury (myofiber degeneration/necrosis) is a customary response after exposure to muscular contractions that incorporate lengthening movements or eccentric contractions (23), it is not known if this is absolutely obligatory when adaptation (positive training effect) is the desired outcome.

Thus, it is our hypothesis that muscle adaptation/maladaptation occurs with remodeling of the local environment (via cell-cell and/or cell-matrix modifications) in both young and old populations in the absence of myofiber degeneration and that this phenomenon is distinctly different from overt muscle injury.

CONTRACTION-INDUCED MUSCLE INJURY

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. This would aid in designing better rehabilitative countermeasures to reduce the risk of further injury after return to work. We know from previous studies that eccentric muscle actions are known to cause a greater amount of muscle damage than concentric or isometric muscle action injuries (2,32). This suggests that high load tensions in fibers may be more important than other physiological considerations in the etiology of the injury process (30). The high mechanical forces produced during muscular contractions, particularly in eccentric exercise, cause disruption of contractile and intermediate filament proteins in skeletal muscle fibers and connective tissues (3).

Eccentric contractions have been shown to result in ultrastructural damage after exposure (18), and 1–3 d after exposure (22,27). The isometric force deficit, a functional measure defined as the difference in isometric force before and after a mechanical loading protocol, may be the best indicator of the magnitude of contraction-induced injury (17). However, a discrepancy has existed with respect to functional loss after 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. In our initial studies, we reported time-dependent changes that occurred in rodent tibialis anterior (TA) muscle after SSC-induced muscle injury and the resultant levels of myofiber degeneration, inflammation, and related changes in the interstitial space using our standardized stereological technique (6). Additionally, we showed that degenerative myofibers

and interstitial space changes were temporally associated with functional performance (6). These results are in agreement with data reported previously (28), yet previous histological studies have failed to directly quantify myofiber degeneration and its relationship to evident functional deficits after contraction-induced exposure (6).

Whereas the ability to characterize early-phase muscle injury is essential in understanding skeletal muscle degeneration/regeneration/remodeling (acute phase) kinetics, it also is important to understand and quantify how changing the number of repetitions or dose affects the acute phase response kinetics (5). For this reason, we investigated the effect increasing numbers of SSC had on muscle performance and morphology (5). 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 SSC (isometric contractions, 30 SSC, 70 SSC, and 150 SSC, respectively). 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 (only a few fibers exhibit degeneration and necrosis) or an inflammatory response was observed in the contralateral 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. This effect has also been shown in eccentric-only loading models where increasing the number of repetitions produces increases in indices of muscle damage (20,22).

Depending on the magnitude of the initial contraction-induced injury, full recovery of normal structure and function requires 7–30 d (5,8,17,27,28). 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 d after the initial injury (2,20). The inflammatory response is typically characterized by an infiltration of neutrophils and macrophages (31). Neutrophils infiltrate damaged muscle within 1–2 h of the initial injury and are present for up to 5 d after injury (31). These inflammatory cells produce cytokines and chemokines that activate local pathways in damaged tissue that mediate inflammation and exacerbate damage or assist in repair during the first 5 d after muscle injury. Resident and phagocytic macrophages also invade and digest damaged tissue to promote regeneration. This response is induced by muscle loading in animals (24) and humans (29). Macrophages can be found between 12 h and 14 d after the initial muscle injury (29). Days after injury, the regenerative process is initiated, and central nuclei seem present (22). At this time, the muscle demonstrates a mixture of both degenerative and regenerative processes. During muscle adaptation, the inflammation and tissue damage are eventually resolved and normal function is restored. However, if the tissue is not able to adapt, persistent inflammation may occur, and this inflammation can result in additional tissue damage (31).

Collectively, time- and dose-dependent factors impact the safety threshold of skeletal muscle and are critical when designing preventative strategies in vocational and recreational arenas, in rehabilitative medicine, and for understanding the etiology of acute-loading injuries. As a group, these results set the stage for us to investigate and ask the question: is contraction-induced injury and resultant inflammation an obligatory response after all eccentrically biased mechanical loading?

EVOLVING RESEARCH

The morphological data ascribing the response of skeletal muscle injury in humans after voluntary muscle contractions that include lengthening movements do not conform to the morphological data observed in the numerous animal models. In fact, in humans undergoing voluntary contractions after acute mechanical loading, one observes relatively normal gross muscle morphology; skeletal muscle presenting with minimal myofiber degeneration and inflammation (inflammatory cells). This is further accompanied by focal Z-line ultrastructure disorganization and intramyocellular protein (desmin) remodeling (34,35). To date, the magnitude of these responses has not been documented in an animal model, which incorporates lengthening contractions. In contrast, contraction-induced muscle injury is characterized by extensive myofiber degeneration and a robust inflammatory response in animals (2,6,7,20). Importantly, in a recent investigation, Crameri and colleagues (11) eloquently demonstrated in humans that skeletal muscle's response after 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 the same eccentric-type exercise is electrically augmented (involuntary contractions) is there myofiber degeneration, loss of intracellular muscle protein (desmin), and subsequent muscle regeneration.

Thus, in humans, after mechanical loading that includes eccentric-type movements, myofiber degeneration, inflammation, and substantial muscle regeneration does not seem to be as extensive as hypothesized, unless augmented by electrical stimulation. Hence, we have shown the ability to produce muscle injury using our previous animal model ((5–7, 20); consistent with results produced by Crameri and colleagues (11) in electrically augmented contractions in humans) whereas our current loading model in animals (noninjurious) (4) has been found to mimic more closely voluntary contractions that occur in humans. The mechanism of adaptation seems to include focal myofiber and interstitial space adaptation/remodeling concomitant with increases in function.

Chronic, Adaptive Mechanical Loading Model

In our chronic model of SSC loading, we sought to mimic the results of high-intensity resistance training that have been reported in exercise/athletic populations, which have investigated the ability of young and old subjects to increase muscle mass (33). To advance these previous findings, it was

our intent to illustrate possible factors involved in the adaptive phase after chronic exposure. Because 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 SSC administered 3 times/wk for 4.5-wk duration, the young rats increased their muscle mass in the TA muscle by approximately 16% while increasing static and dynamic performance by more than 30% (13). 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 also is in contrast with rodents exposed to high velocity continuous SSC from our laboratory previously, which exhibited pronounced muscle degeneration after exposure (~10% tissue fraction) (6), similar to findings that have been reported by other investigators.

The absence of an obvious degenerative effect observed after high-intensity mechanical loading in this and recent studies (4) is very fascinating because most published literature has shown that eccentrically biased loading resulted in significant muscle injury and loss of performance. In our rodent model, electrodes activate the target muscle via supramaximal 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 resistance 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 also may experience the benefits of a resistance exercise program.

Mechanical Loading and the Impact of Age

As we age, skeletal muscle performance decreases, and aged muscle recovers more slowly after injury (23); 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 after the seventh decade of life (1). 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 after "classical" contraction-induced muscle injury (4,13). Our chronic loading model using low-velocity intermittent muscle contractions produced a robust increase in muscle mass after a 4.5-wk exposure in the young animals and approximately a 30% increase in static and dynamic muscle forces (13). When old animals (aged 30 months) were exposed to this protocol, they did not increase muscle mass and lost approximately 30% in maximum static and dynamic forces. However, the TA 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 $d \cdot wk^{-1}$ exposure regimen of 80 maximal SSC/exposure, thus the muscles maladapted 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 SSC that included eccentric contractions without resulting in muscle fiber injury (13). Thus, titrating the exposure with either less repetitions per day or less exposures per week may allow older muscles to adapt much as those from the young animals did. Accordingly, the approach used in our model should be considered using a translational approach with respect to human populations because 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 (21).

Acute, Adaptive Mechanical Loading Model

As previously mentioned, we have investigated the impact of SSC (the most common contraction type used in daily movement) on muscle injury and 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 SSC and found that 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 vs the contralateral control limb), when compared with young rats (~2000% increase in MHC_{dev}^{+} labeling in exposed vs contralateral control limb; Fig. 2) (4). This occurs in the absence of significant myofiber degeneration (Fig. 1C, D), which is in contrast to what has been reported previously (8). With regard to the morphological response, when 4.5 wk of chronic, low-velocity SSC are administered, there is a decrease in performance and myofiber hypertrophy is less in old rats compared with young rats (Fig. 1E–H). 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 (13). 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 (4). This suggests one plausible mechanism as to why performance in our old rats was

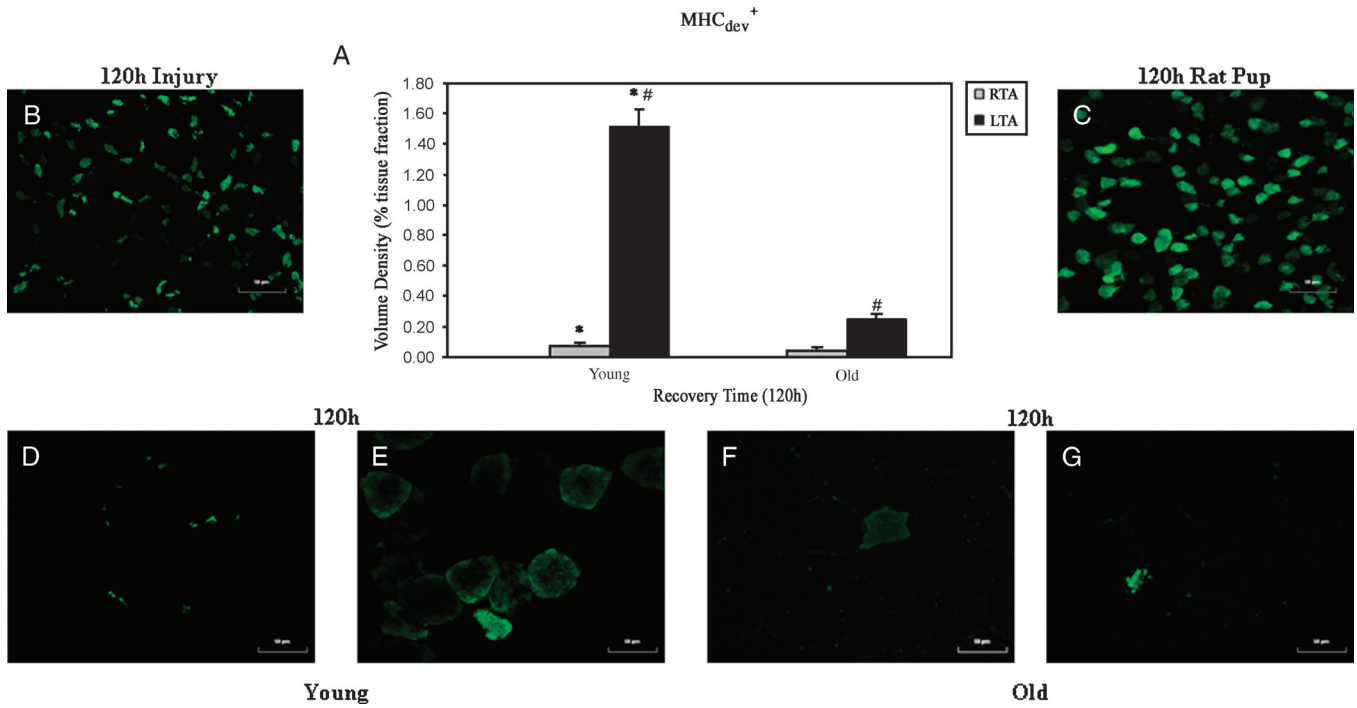

Figure 2. Developmental myosin heavy chain (MHC_{dev}^{+}) immunohistochemistry and stereology. The graph shows that skeletal muscle from young rats exposed to an acute, adaptive protocol of SSC had an approximately 2000% increase MHC_{dev}^{+} versus the control limb (A). The old rats had an increase of approximately 200% versus their control limb. The two panels in the middle (B) left to (C) right show MHC_{dev}^{+} in injured tissue from young rats 120 h after injurious SSC exposure and in rat pup tissue. The bottom panels from left to right depict MHC_{dev}^{+} expression in various myofibers from young SSC loaded rats (D and E) and old SSC loaded rats (F and G), respectively.

decreased at the end of the chronic exposure as compared with 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 (26). Collectively, these data suggest that chronic muscle adaptation is not dependent on an initial injurious event that produces a resulting myofiber degeneration/regeneration phenomenon and, notably, that a maladaptive state does not manifest because of myofiber degeneration — even in old rats after high-intensity mechanical loading.

Furthermore, a study by Brown and colleagues (9) concluded that adaptation of skeletal muscle after 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 (18,34,35). In the aforementioned studies, young and old dorsiflexor muscles exposed to an acute protocol of 80 low-velocity SSC did not undergo the extent of myofiber degeneration that is typically reported for classical contraction-induced muscle injury (Fig. 1A, B vs Fig. 1C, D) (6,22,28). Thus, our current findings and several other studies suggest that the adaptive response of muscle after mechanical loading is not dependent on myofiber degeneration but occurs as a result of ultrastructural modifications (9,34,35) as well as local environmental changes (influenced by both autocrine and paracrine mechanisms) in the tissue (10,13,25).

Together, these data indicate that the phenomena we are reporting in our current adaptive acute and chronic models more likely represent what is occurring in humans after mechanical loading when lengthening-type movements are incorporated (as reported by Crameri and colleagues) (11). Therefore, this specific SSC loading model may represent a more physiologically representative means to investigate these adaptive/remodeling events.

MODEL APPLICABILITY AND ADAPTABILITY

Our animal model demonstrates that the maladaptation incurred as a result of repetitive mechanical loading as we grow older is not due to an initial degenerative insult but seems to be limited by specific local adaptive and regenerative/remodeling events. Specifically, our model may exhibit its usefulness in elucidating what factors affect the safety threshold (muscle tolerance) when exposed to repetitive mechanical loading and thereby aide in designing exercise and rehabilitative programs that are useful for older individuals, whose number is increasing in the United States.

CONCLUSIONS AND FUTURE RECOMMENDATIONS

In summary, we have previously quantified and characterized both time- and dose-dependent effects of skeletal muscle

after acute, injurious SSC in young rodents; investigated the influence of age on the adaptive response after acute mechanical loading; examined and quantified the influence age has on chronic SSC loading; investigated the acute events that are involved in skeletal muscle regeneration/remodeling after adaptive SSC loading and considered the role aging has on this process; and finally suggested that muscle injury and muscle adaption/maladaptation resulting from mechanical loading are two distinctly different phenomena (Fig. 3). Our results from this final objective indicate that initial muscle remodeling is a critical element in assuring successful adaptation, thus investigating the distinct mechanisms involved in initiating successful muscle remodeling after 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 SSC that incorporate lengthening movements). We suggest that initial myofiber remodeling/regeneration (recapitulation of the developmental program) is a critical element in assuring successful adaptation. Furthermore, it is essential and cannot be overstated that not all acute and chronic mechanical loading (specifically loading composed of eccentric movements) results in overt skeletal muscle injury, as has been reported for more than 20 yr.

Because 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 local environment (*i.e.*, via supplements, therapeutic agents) may improve the responsiveness of skeletal muscle to acute and chronic mechanical loading. 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, it also may be the most effective and appealing mode of physical activity to prescribe for individuals encompassing occupation, military, and sport sectors to help mitigate the effects involved in musculoskeletal dysfunction.

Acknowledgments

The authors thank Drs. Frank Buczek and Murali Rao of the National Institute for Occupational Safety and Health (NIOSH) for critical review and comments regarding this article. This study was supported by Internal NIOSH funds.

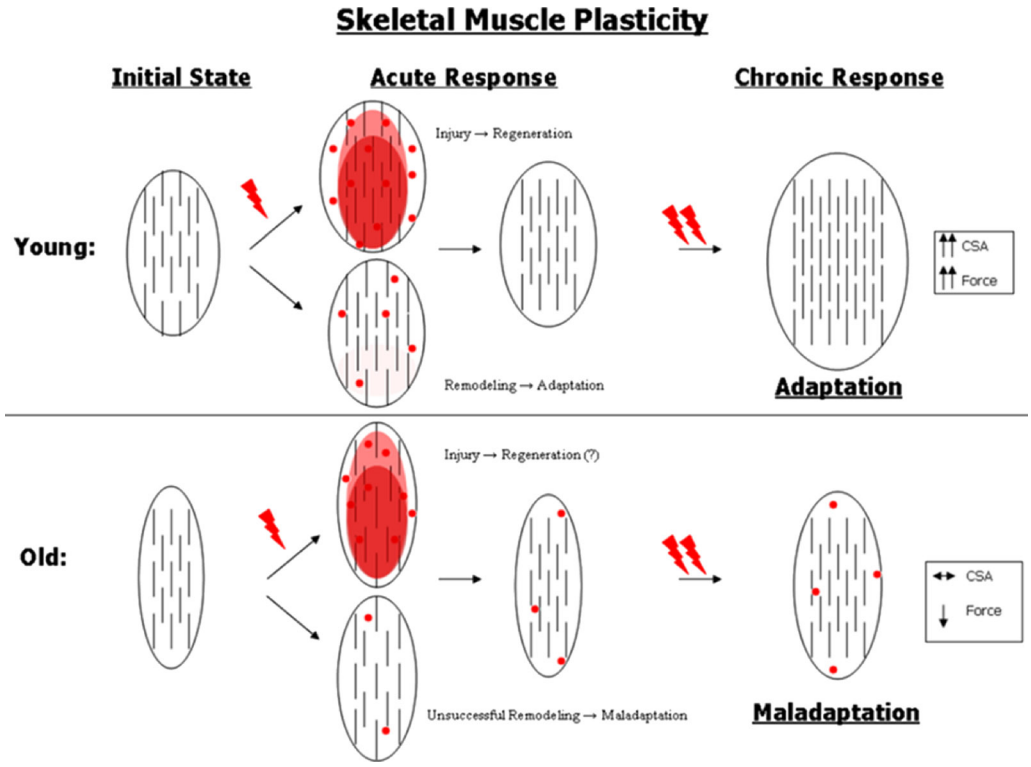

Figure 3. Overview of skeletal muscle response continuum demonstrating the differences observed in young and old rodents in response to overt skeletal muscle injury, maladaptation, and adaptation after mechanical loading. In young and old rodent skeletal muscle after an acute stretch-shortening contractions (SSC) injury exposure (), there is a significant decrease in isometric and dynamic performance and an increase in myofiber degeneration, infiltrating inflammatory cells (), and edema. Recovery of performance and resolution of degeneration, inflammation, and edema measures are resolved over a period of 7–10 d. Following an acute bout of adaptive (noninjurious) SSC, old rodents display a significant loss of performance but no myofiber degeneration, and this is accompanied by minimal inflammatory cells and edema. However, young rodents respond with a transient decrease in performance and minimal myofiber degeneration, inflammatory cells, and edema. The indices observed for myofiber degeneration and inflammation after acute, adaptive SSC are significantly decreased compared with acute, injurious SSC. When we extend our adaptive SSC paradigm out to 4.5 wk of repetitive loading (), young rodents adapt by increasing skeletal muscle mass, myofiber cross-sectional area (CSA), and performance measures, whereas old rodents maladapt by responding with no change or a decrease in muscle mass and myofiber cross-sectional area, and they have a decrease in performance measures. Importantly, the maladaptation observed in old rodents occurs in the absence of myofiber degeneration with minimal inflammation and edema. Red shading signifies the area of muscle damage.

References

1. Alway SE, Siu PM, Murlasits Z, Butler DC. Muscle hypertrophy models: applications for research on aging. *Can. J. Appl. Physiol.* 2005; 30(5): 591–624.
2. Armstrong RB, Ogilvie RW, Schwane JA. Eccentric exercise-induced injury to rat skeletal muscle. *J. Appl. Physiol.* 1983; 54(1):80–93.
3. Armstrong RB, Warren GL, Warren JA. Mechanisms of exercise-induced muscle fibre injury. *Sports Med.* 1991; 12(3):184–207.
4. Baker BA, Hollander MS, Mercer RR, Kashon ML, Cutlip RG. Adaptive stretch-shortening contractions: diminished regenerative capacity with aging. *Appl. Physiol. Nutr. Metab.* 2008; 33(6):1181–91.
5. Baker BA, Mercer RR, Geronilla KB, Kashon ML, Miller GR, Cutlip RG. Impact of repetition number on muscle performance and histological response. *Med. Sci. Sports Exerc.* 2007; 39(8):1275–81.
6. Baker BA, Mercer RR, Geronilla KB, Kashon ML, Miller GR, Cutlip RG. Stereological analysis of muscle morphology following exposure to repetitive stretch-shortening cycles in a rat model. *Appl. Physiol. Nutr. Metab.* 2006; 31(2):167–79.
7. Baker BA, Rao KM, Mercer RR, *et al.* Quantitative histology and MGF gene expression in rats following SSC exercise in vivo. *Med. Sci. Sports Exerc.* 2006; 38(3):463–71.
8. Brooks SV, Faulkner JA. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am. J. Physiol.* 1990; 258(3 Pt 1): C436–42.
9. Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *J. Sports Sci.* 1997; 15(2):215–22.
10. Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 2005; 433(7027):760–4.
11. Crameri RM, Aagaard P, Qvortrup K, Langberg H, Olesen J, Kjaer M. Myofibre damage in human skeletal muscle: effects of electrical stimulation versus voluntary contraction. *J. Physiol.* 2007; 583:365–80.
12. Cutlip RG, Baker BA, Geronilla KB, Kashon ML, Wu JZ. The influence of velocity of stretch-shortening contractions on muscle performance during chronic exposure: age effects. *Appl. Physiol. Nutr. Metab.* 2007; 32(3):443–53.
13. Cutlip RG, Baker BA, Geronilla KB, *et al.* Chronic exposure to stretch-shortening contractions results in skeletal muscle adaptation in young rats and maladaptation in old rats. *Appl. Physiol. Nutr. Metab.* 2006; 31(5):573–87.
14. Cutlip RG, Baker BA, Hollander M, Ensey J. Injury and adaptive mechanisms in skeletal muscle. *J. Electromyogr. Kinesiol.* 2009; 19(3): 358–72.
15. Cutlip RG, Geronilla KB, Baker BA, *et al.* Impact of stretch-shortening cycle rest interval on *in vivo* muscle performance. *Med. Sci. Sports Exerc.* 2005; 37(8):1345–55.
16. Cutlip RG, Geronilla KB, Baker BA, Kashon ML, Miller GR, Schopper AW. Impact of muscle length during stretch-shortening contractions on real-time and temporal muscle performance measures in rats in vivo. *J. Appl. Physiol.* 2004; 96(2):507–16.
17. Faulkner JA, Jones DA, Round JM. Injury to skeletal muscles of mice by forced lengthening during contractions. *Q. J. Exp. Physiol.* 1989; 74(5):66–70.
18. Friden J, Sjostrom M, Ekblom B. A morphological study of delayed muscle soreness. *Experientia* 1981; 37(5):506–7.
19. Geronilla K, Wu JZ, Baker BA, Cutlip RG. Characterization of isometric contractions of rat skeletal muscle in vivo: Duty cycle effects. *Biomed. Mater. Eng.* 2006; 16(6):369–80.
20. Geronilla KB, Miller GR, Mowrey KF, *et al.* Dynamic force responses of skeletal muscle during stretch-shortening cycles. *Eur. J. Appl. Physiol.* 2003; 90(1-2):144–53.
21. Hartman MJ, Fields DA, Byrne NM, Hunter GR. Resistance training improves metabolic economy during functional tasks in older adults. *J. Strength Cond. Res.* 2007; 21(1):91–5.
22. Hesselink MK, Kuipers H, Geurten P, Van Straaten H. Structural muscle damage and muscle strength after incremental number of isometric and forced lengthening contractions. *J. Muscle Res. Cell. Motil.* 1996; 17(3):335–41.
23. Koh TJ, Peterson JM, Pizza FX, Brooks SV. Passive stretches protect skeletal muscle of adult and old mice from lengthening contraction-induced injury. *J. Gerontol. A. Biol. Sci. Med. Sci.* 2003; 58(7):592–7.
24. Lapointe BM, Frenette J, Cote CH. Lengthening contraction-induced inflammation is linked to secondary damage but devoid of neutrophil invasion. *J. Appl. Physiol.* 2002; 92(5):1995–2004.
25. Malm C. Exercise-induced muscle damage and inflammation: fact or fiction? *Acta. Physiol. Scand.* 2001; 171(3):233–9.
26. McCormick K, Schultz E. Role of satellite cells in altering myosin expression during avian skeletal muscle hypertrophy. *Dev. Dynamics* 1994; 199:52–63.
27. McCully KK, Faulkner JA. Characteristics of lengthening contractions associated with injury to skeletal muscle fibers. *J. Appl. Physiol.* 1986; 61(1):293–9.
28. McCully KK, Faulkner JA. Injury to skeletal muscle fibers of mice following lengthening contractions. *J. Appl. Physiol.* 1985; 59(1): 119–26.
29. Round JM, Jones DA, Cambridge G. Cellular infiltrates in human skeletal muscle: exercise induced damage as a model for inflammatory muscle disease? *J. Neurol. Sci.* 1987; 82(1–3):1–11.
30. Stauber WT. Eccentric action of muscles: physiology, injury, and adaptation. *Exerc. Sport Sci. Rev.* 1989; 17:157–85.
31. Tidball JG. Inflammatory processes in muscle injury and repair. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2005; 288(2):R345–53.
32. Warren GL, Hayes DA, Lowe DA, Guo W, Armstrong RB. Mechanical factors in exercise-induced muscle injury. *FASEB J.* 1991; 5:A1036.
33. Welle S, Totterman S, Thornton C. Effect of age on muscle hypertrophy induced by resistance training. *J. Gerontol. A. Biol. Sci. Med. Sci.* 1996; 51:270–5.
34. Yu JG, Carlsson L, Thornell LE. Evidence for myofibril remodeling as opposed to myofibril damage in human muscles with DOMS: an ultrastructural and immunoelectron microscopic study. *Histochem. Cell. Biol.* 2004; 1421:219–27.
35. Yu JG, Malm C, Thornell LE. Eccentric contractions leading to DOMS do not cause loss of desmin nor fibre necrosis in human muscle. *Histochem. Cell. Biol.* 2002; 118:29–34.