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HIGHLIGHTED TOPIC | *Eccentric Exercise*

Eccentric exercise in aging and diseased skeletal muscle: good or bad?

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Lovering RM, Brooks SV. Eccentric exercise in aging and diseased skeletal muscle: good or bad? *J Appl Physiol* 116: 1439–1445, 2014. First published March 7, 2013; doi:10.1152/japplphysiol.00174.2013.—Evidence is accumulating regarding the benefits of exercise in people who are more susceptible to injury, such as the elderly, or those with a neuromuscular disease, for example Duchenne muscular dystrophy (DMD). There appears to be a consensus that exercise can be safely performed in aging and diseased muscles, but the role of eccentric exercise is not as clear. Eccentric (lengthening) contractions have risks and benefits. Eccentric contractions are commonly performed on a daily basis, and high-force voluntary eccentric contractions are often employed in strength training paradigms with excellent results; however, high-force eccentric contractions are also linked to muscle damage. This minireview examines the benefits and safety issues of using eccentric exercise in at-risk populations. A common recommendation for all individuals is difficult to achieve, and guidelines are still being established. Some form of exercise is generally recommended with aging and even with diseased muscles, but the prescription (frequency, intensity, and duration) and type (resistance vs. aerobic) of exercise requires personal attention, as there is great diversity in the functional level and comorbidities in the elderly and those with neuromuscular disease.

eccentric; muscular dystrophy; aging; Duchenne muscular dystrophy

WHEN THE EXTERNAL LOAD on an activated muscle exceeds the tension generated by the muscle contraction, the muscle lengthens during what is termed a lengthening ("eccentric") contraction. The difficulty of explaining the force from a lengthening contraction lies in the fact that the force produced is greater than the sum of the measured active force (from an isometric contraction) and passive force at that given muscle length. When the external load is heavy enough to exceed a maximal voluntary contraction, such maximal eccentric contractions can produce high forces, which is a goal of strength training (the overload principle). This is evident in strengthening protocols that use lengthening contractions, or "negatives," to increase strength. Not only can lengthening contractions produce more force than other types of contractions, but they can do so at a reduced oxygen requirement (47, 53). Thus the application of eccentric exercise is appealing in certain populations, where high metabolic demand is sometimes not wanted.

All of us use eccentric contractions daily without apparent detrimental effects, so why has the notion that eccentric contractions cause damage become so widely accepted? Even moderate eccentric contractions (e.g., the quadriceps while walking down stairs or transitioning from standing to sitting) that are well below maximal effort can result in damage to compromised muscles. However, the inextricable association with damage is likely due to the fact that many studies utilize maximal eccentric contractions to induce skeletal muscle injury. It is important not to confuse eccentric exercise with eccentric injury. Most studies that utilize eccentric contractions to induce skeletal muscle injury use maximal eccentric contractions without any progressive eccentric training. For humans, this is in the form of maximal voluntary contractions (MVCs) while for animals, electrical stimulation is typically used to obtain maximal stimulation of either single fibers in vitro or every fiber in a whole muscle in vivo. Supramaximal stimulation (i.e., recruitment of all motor units) is not physiological and an extreme example of eccentric contractions, but in animal studies maximal stimulation aids in obtaining reliable and reproducible injuries; it would also be difficult to assess changes in contractile function without consistency in the number of motor units recruited. Emotion, pain, or other such factors that might affect the MVC can confound results in human studies that measure contractile activity.

When activated muscles are stretched during eccentric exercise, if injury does occur, it is initiated by focal mechanical damage to sarcomeres (3, 12, 59, 74, 97). The mechanical damage triggers a more widespread injury (68, 72) that includes inflammation, disruption of the sarcolemma, and damage by reactive oxygen species (ROS) (28, 68, 82, 88). The injury culminates in degeneration of the damaged portions of fibers. Comparable protocols of damaging lengthening contractions result in more severe initial

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and secondary injury to muscle fibers of old compared with adult animals (9, 60, 100) and muscles of dystrophic compared with control animals (6, 24).

Much has been written about injury after eccentric contractions and the potential underlying mechanisms that contribute to the damage (1). Less has been written about eccentric exercise and the positive role it can play in rehabilitation (48). Whether or not eccentric exercise has a role in compromised muscle, such as with aging or disease, is still controversial.

MUSCULAR DYSTROPHY

The muscular dystrophies are a heterogeneous group of inherited disorders characterized by progressive weakness and degeneration of skeletal muscles. The development of molecular genetic mapping techniques has shown that a number of clinically similar conditions are linked to a variety of distinct single-gene disorders. So far, muscular dystrophies have been mapped to at least 29 different genetic loci that give rise to at least 34 different clinical disorders (21) and additional information is accumulating rapidly.

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy; it is an X-linked disorder that affects about 1 in 3,500 newborn males worldwide (93). DMD is characterized by progressive wasting of skeletal muscles, with the limb-girdle muscles first showing weakness by the age of 5 years, followed by an inability to walk by the age of 8 to 12 years (6, 69). Death usually occurs in the second or third decade of life due to cardiac or respiratory impairment. DMD is caused by the absence of dystrophin, a 427-kDa protein found on the cytoplasmic surface of the plasma membrane of muscle fibers (the sarcolemma) in skeletal and cardiac muscle. Dystrophin provides mechanical stability to the sarcolemma and is likely involved in force transmission between the intracellular contractile apparatus and the extracellular matrix (ECM), which envelops the fiber and is connected to the tendon (78). Without dystrophin, the sarcolemma becomes fragile and more susceptible to the stress of muscle contractions. The role of dystrophin is undoubtedly more complex than simply providing mechanical stability (30, 33, 38, 39, 43, 54, 55, 81, 96), but the consequences of its absence are clear.

The gene for dystrophin is one of the largest known in humans (~1.2 million base pairs) and its sheer size has presented one of many obstacles to gene therapy (55). Although DMD is still incurable, it is not untreatable. Several studies have pointed out the need to study exercise in patients with DMD (34, 62, 63), with a clear admonition against heavy resistance training and even eccentric exercise (34). Heavy resistance training is possible with neuromuscular diseases that are not severe (71); however, there is a risk of further muscle damage that could have catastrophic consequences in patients with DMD. Although there are very few randomized or controlled studies involving any strength training in patients with DMD, the data so far indicate little to no physical decline with exercise (26, 85). In fact, exercise appears to be beneficial to patients with DMD (23) or other muscular dystrophies (92).

So should patients with muscular dystrophy, especially the most common form (DMD), avoid eccentric exercise? Much of what is known about muscle lacking dystrophin is derived from studies of dystrophin-deficient animals, with the most common model being the mdx mouse. The DMD and the mdx conditions are similar in that dystrophin is missing from all muscle tissues. Both DMD muscle and mdx muscle show clear changes when examined with MRI (Fig. 1). In DMD patients, pathological changes at the cell level include increased adipose and connective tissue between muscle fibers, increased variability in muscle fiber size, infiltration of inflammatory cells, alterations in myofiber shape and neuromuscular junction morphology, and centrally located nuclei, indicative of ongoing necrosis and regeneration (5, 43, 55). Except for the increase in adipose tissue (98), these same changes (Fig. 2) are found in the mdx mouse model (13, 27, 38, 54). Despite the many similarities, the absence of dystrophin is not equally damaging to patients with DMD and mdx mice. A "critical period" has been described for the mdx mouse (19), whereby there is a peak in muscle weakness and degeneration/regeneration between the 2nd and 5th weeks of life. Beyond this critical period, mdx mice still show marked susceptibility to contraction-induced injury, but not the progressive weakness observed in DMD. For this reason, some investigators have used forced exercise after the described critical period for mdx mice to continue the pathogenic process of the disease (24, 31).

Although forced maximal lengthening contractions are associated with injury, a subsequent bout of the same activity performed days or even weeks after an initial bout results in significantly less damage and protection against future injury (44); this is known as the "repeated bout effect" (RBE). Several aspects of muscle damage are ameliorated due to the RBE, including the drop in force that is used as a measure for injury (76). The factors responsible for the RBE are still being studied, both in animal models and in humans. In an effort to compare responses to injury, high-energy forced eccentric contractions have been used to cause damage in healthy (32, 40, 51, 94) and dystrophic (7, 25, 58, 70, 77, 81) mouse muscle and it is clear that dystrophic muscle is more susceptible to damage than healthy muscle (13, 19, 25, 77). Nonetheless, some animal studies now show that recovery of muscle contractile function after eccentric injury is enhanced in mdx mice (7, 14), suggesting the RBE is possible with dystrophic muscle. Interestingly, repeated bouts of eccentric exercise in mdx

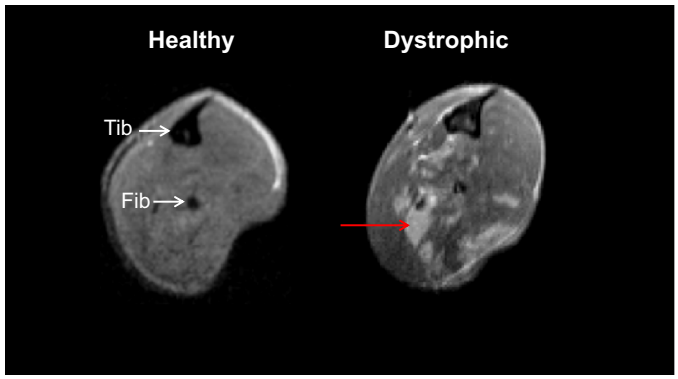

Fig. 1. Magnetic resonance imaging (MRI) of healthy and dystrophic muscle. Representative axial MRI of hindlimb leg muscles from a healthy (wild type) and a dystrophic (mdx) mouse, both at 9 wk of age. The signal in healthy muscles is homogeneously dark, but dystrophic muscles, even without exercise, show heterogeneity, identified by unevenly distributed focal hyperintensities (red arrow) that contrast the dark signal characteristic of healthy muscle. This heterogeneity reflects muscle damage and inflammation; the amount of heterogeneity varies from muscle to muscle and limb to limb. Tib, tibia; Fib, fibula.

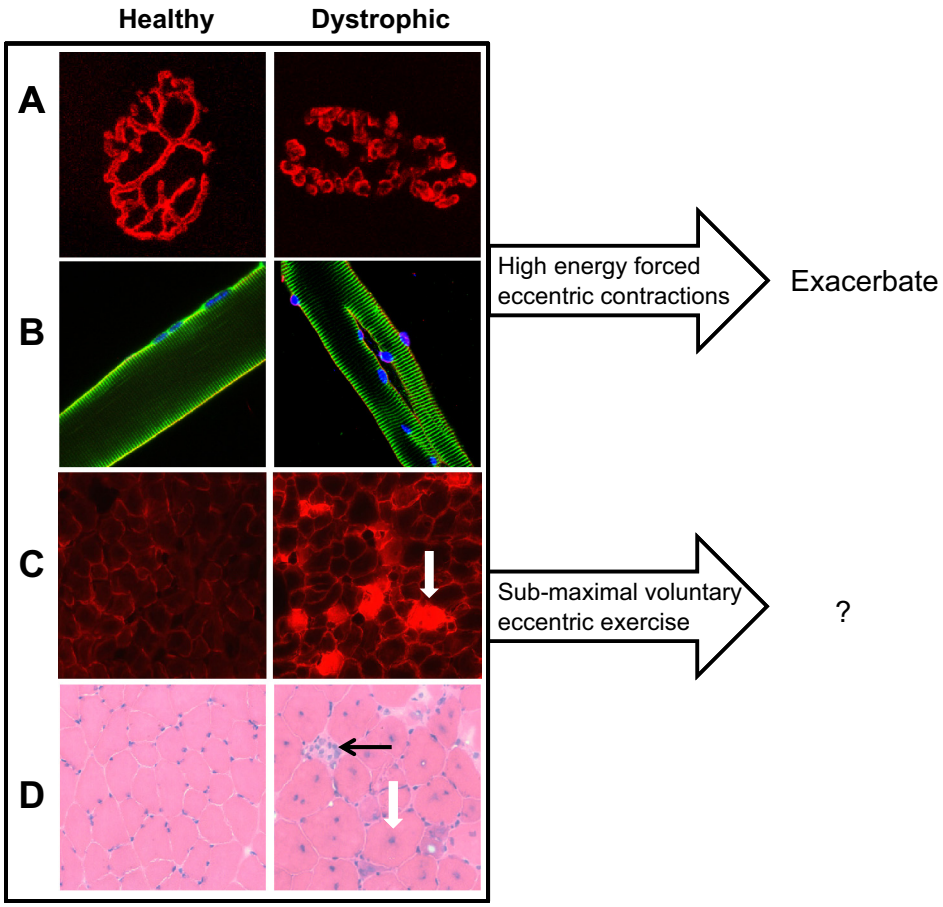

Fig. 2. Findings at the cellular level in dystrophic muscle. Shown are typical differences in unexercised healthy (wild type) and dystrophic (mdx) mice. *A*: rhodamine-conjugated α-bungarotoxin staining of the neuromuscular junction (NMJ). NMJ morphology is often abnormal (fragmented and dispersed) in dystrophic muscle. *B*: immunolabeling of isolated muscle cells. Healthy skeletal myofibers are elongated tubelike structures with no branching patterns. However, a significant portion of dystrophic myofibers display altered morphology, as shown in this typical bifurcated (split) fiber. Presence of these malformed myofibers is thought to contribute to the decreased muscle specific tension and increased susceptibility to injury seen in dystrophic muscle. *C*: cross-sections of muscle from Evans blue dye (EBD)-injected mice. The cell membranes (sarcolemma) of dystrophic fibers often show damage, seen by cells containing EBD in the cytoplasm (white arrow), indicating lack of sarcolemmal integrity. *D*: cross-sections of mouse muscle stained with HE. Pathological changes such as centrally nucleated fibers (white arrow) and necrotic fibers (black arrow), both indicative of ongoing degeneration and regeneration, are found in dystrophic muscle. All of the above changes are further exacerbated by high-force eccentric contractions, but there is far less information available about changes, good or bad, occurring with progressive submaximal voluntary exercise.

muscles not only lack a cumulative damaging effect, but instead they actually improved muscle strength (14).

Thus far, the role of exercise in neuromuscular disease, especially severe forms such as DMD, is still controversial; many believe that eccentric exercise should be performed with minimal resistance or avoided altogether (2, 42, 52). Some recent animal studies are challenging this doctrine. Many studies indicate a beneficial adaptation to moderate exercise in dystrophic animals (15, 18, 22, 56, 57, 89), but there is still a glaring gap in our knowledge regarding the use of exercise on populations with neuromuscular diseases. It is difficult to compare animal studies that use different species of animals, different protocols, and sometimes different outcome measures, but it can be misguided to take the findings from an animal model of a disease (e.g., the mdx mouse) and simply translate them to the human population (86). Thus there is a real need for further studies in patients with DMD and other muscular dystrophies (34, 55, 62, 63).

AGING

The age-associated condition of "frailty" (37, 91) is largely caused by loss of muscle mass and strength and increasing fatigability and susceptibility to injury (29, 61). Physical frailty, with its associated immobility and disability (17), is a major factor limiting an elderly person's chance of living independently (61). Muscle mass and strength decrease ~10% per decade after the age of 50 (36, 73, 80, 87). Such deficits profoundly impact quality of life, even for healthy older people (99). The decrease in muscle mass results from a loss in the total number of fibers per muscle as well as a decrease in the cross-sectional area (CSA) of the remaining fibers (36, 50). The loss of muscle fibers with aging is largely irreversible, but conditioning programs that maintain, or even increase, CSA of the remaining fibers can slow the atrophy (35, 90). Eccentric exercise is generally considered a highly effective mode of conditioning for hypertrophy (75), although this is not a universal finding (64), and increased susceptibility to exercise-induced injuries and impaired or delayed recovery from injury (8, 65) raise the critical issue of the necessity to keep elderly people safe if participation in life-long physical activity is encouraged.

The effect of age on the susceptibility to the initial mechanical damage associated with lengthening contractions has been studied in mice, rats, and humans. The deficit in isometric force following single stretches of maximally activated muscles of mice was well predicted by the work input during the stretch, with the work-force deficit relationship ~40% steeper for muscles of old compared with young or adult mice (12). In addition, when single permeabilized fibers from muscles of young and old rats were exposed to single stretches, average force deficits were ~2-fold larger for fibers from muscles of old compared with adult rats (9). In human studies, biopsies of vastus lateralis muscles obtained immediately following a bout of exercise in which subjects resisted the backward motion of a motor-driven cycle ergometer showed at least some focal damage to sarcomeres in nearly all of the fibers examined from

older subjects, compared with only 5–10% reported for young subjects (60). Similarly, biopsies of vastus lateralis muscles following the final bout of a 9-wk program of high-load resistance exercise showed ultrastructural damage in nearly 17% of fibers in older women compared with 2–5% of fibers in untrained control muscles of both young and older women and in the young subjects exposed to the exercise (83). However, when the same investigators performed this experiment in men, no difference was found between age groups (84). Although there are disparate findings, in total, the data support a greater susceptibility of muscles in old animals to injury that is due, at least in part, to a mechanically compromised sarcomeric structure that is less able to withstand stretch. One group has compared muscles of animals of different ages for damage to the sarcolemma induced by lengthening contractions (67). Resting membrane potentials were measured, with the amount of depolarization that remains in the presence of blockers of stretch-activated ion channels taken as an indicator of physical damage to the membrane (67). Despite no difference between control muscles of young and old rats for resting membrane potential, muscles of old rats showed close to 30% greater depolarization than muscles of young rats immediately following lengthening contractions (67). In addition, the portion of the depolarization that was restored through blockade of stretch-activated ion channels was less than 20% for the muscles of the old rats, compared with greater than 50% for the young rats (67), leading the authors to conclude that muscles of old animals suffer more extensive membrane damage during lengthening contractions.

Isolating the effects of age on the secondary injury is an experiment that has not been done definitively. For example, the observation by Zerba et al. (100) of a 40% greater force deficit for muscles of old compared with young or adult mice 3 days after a protocol of 75 lengthening contractions could be the result of similar secondary responses to initial mechanical injuries that varied in severity. Similarly, the threefold greater percent reduction in strength reported for older compared with young women one day following a bout of unaccustomed eccentric exercise (79) could be due to a greater susceptibility to the initial mechanical injury with a similar secondary injury response, to a more severe secondary injury in response to a given initial injury, or some combination of the two possibilities. Support for greater secondary injury in muscles of old compared with adult animals is provided by the observation that three days following a protocol of lengthening contractions that resulted in similar force deficits in adult and old mice, the number of neutrophils and macrophages, a key element of the secondary injury, was 1.5- to 2-fold greater in the muscles of the old mice (4). Inflammatory cells release reactive oxygen species (ROS). Although ROS likely play an important role in maintaining muscle health (41, 95), ROS have been proposed to promote the secondary injury, as treatment of young mice with a free radical scavenger virtually eliminated the force deficit 3 days following lengthening contractions. The same treatment in old mice only reduced the force deficit from 56% for muscles of untreated animals to 30% (100), suggesting that higher numbers of inflammatory cells in the muscles of old compared with adult mice (46) may result in greater oxygen free radical injury in old animals that was incompletely blocked by the treatment.

Recovery from injury is delayed or impaired for muscles of old animals. Following severe protocols of lengthening contractions, muscles in old mice show sustained, perhaps even irreversible force deficits and morphological evidence of damage to fibers (8, 65). For muscles of rats, force deficits following 24 lengthening contractions were eliminated in adult animals within 5 days, whereas in old animals a delay in recovery to 14 days was observed (66) and recovery of the resting membrane potential took twice as long in old compared with young animals (67). For humans, following exposure of the knee extensors to an exercise protocol with lengthening contractions, young subjects regained control levels of strength within 3–4 days, compared with 7–9 days for older subjects (79). The decreased capacity for recovery of muscles in old

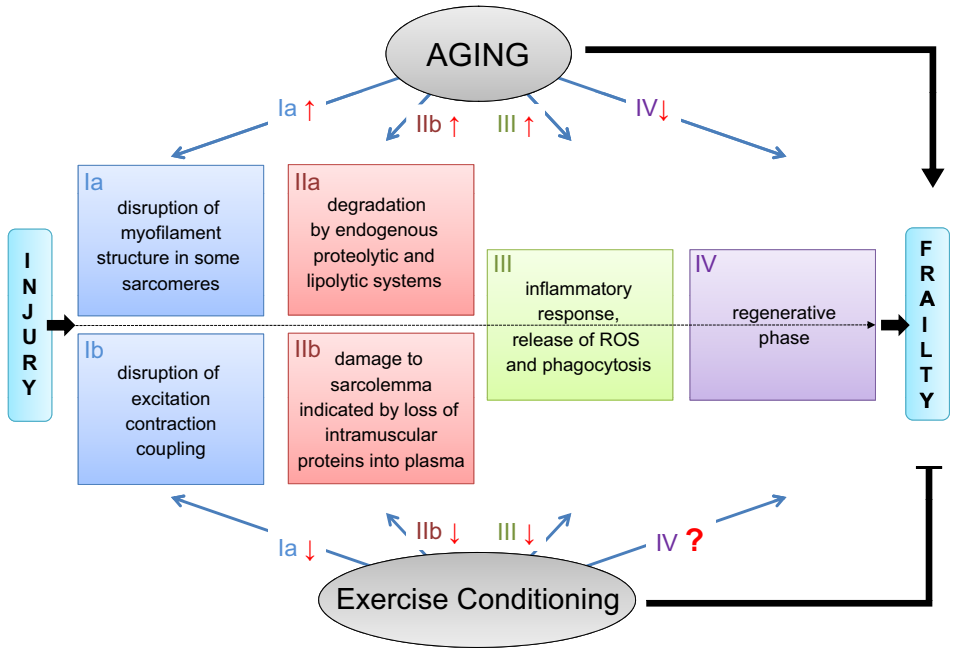

Fig. 3. Phases of lengthening contraction-induced injury and the effects of aging and exercise conditioning. Lengthening (eccentric) contractions can injure skeletal muscle. The injury process involves multiple phases. The sequence of the phases of injury is indicated by numerals I–IV, with events that happen more or less simultaneously designated by the same numeral. With aging, muscle structure and function deteriorates, contributing to physical frailty. Aging also results in an increased susceptibility to injury coupled with impaired regeneration, effects that may exacerbate frailty. Despite age-associated declines in muscle structure and function and increases in the likelihood of injury, exercise conditioning can provide protection from contraction-induced injury and potentially slow or delay the progression of frailty. Red arrows indicate the effects of aging or exercise conditioning on each phase of the injury process. In cases where there is no arrow, the effect has not been studied.

animals following contraction-induced injury is consistent with previous reports of impaired regeneration after whole muscle transplantation in old animals (16).

Despite the high susceptibility of muscles in old animals to injury and the decreased ability to recover, the RBE has been observed (11, 20, 66, 67, 79). After 6 wk of exposure of muscles in mice to a once per week protocol of lengthening contractions that initially resulted in a 30% force deficit and morphological evidence of injury in ~10% of fibers in a cross section, injury was no longer observed in either adult or old animals (10). Similarly, in humans force deficits one day following an unaccustomed bout of exercise with lengthening contractions of the knee extensors was reduced from 26% to 8% following 12 wk of twice per week resistance exercise that involved both lengthening and shortening contractions (79). Even a single bout of eccentric exercise by elderly subjects reduced subsequent lengthening contraction-induced muscle soreness and serum levels of creatine kinase (20), and exposure of muscles of old rats to a single protocol of lengthening contractions reduced the force deficit and number of damaged fibers after a second protocol (66). Although damaging lengthening contractions effectively induce protective adaptations in old animals, a significant fraction of the elderly population may be unable or unwilling to engage in this form of exercise due to both perceived and real risks of severe injury. Based on this concern, Koh and his colleagues (44, 46) tested whether overt damage, degeneration, and regeneration is required to elicit protection. Muscles of mice were exposed to stretches without activation (passive stretches) prior to administering a damaging lengthening contraction protocol. Passive stretches produced no evidence of overt damage to the muscle, yet exposure to conditioning with passive stretches prior to administration of a lengthening contraction resulted in a reduction, compared with nonconditioned muscles, in the magnitude of the injury (44). For old animals, passive-stretch conditioning prior to lengthening contractions improved force production, reduced the number of damaged fibers, and reduced neutrophil and macrophage infiltration following lengthening contractions compared with nonconditioned muscles (46). Although the experiments by Koh et al. were performed in mice, the potential for conditioning with passive stretches provides an exciting alternative to lengthening contractions for a safe and effective method of protecting elderly people from injury.

While muscles can be conditioned for increased resistance to injury at all ages, the protective adaptations associated with eccentric exercise appear to be impaired somewhat in old age. For young men, repeated bouts of eccentric exercise of the elbow flexors resulted in significant reductions in strength, range of motion, upper arm circumference, plasma creatine kinase and myoglobin levels, and soreness, but only in range of motion, myoglobin, and soreness for old men, and the effects were smaller in the old compared with young subjects (49). Similarly, exposure to lengthening contractions provided complete protection in adult rats against the force deficit induced by an identical subsequent contraction protocol 2 wk later, whereas only partial protection was observed for muscles of old rats (66). Finally, dorsiflexor muscles of adult mice exposed to weekly bouts of lengthening contractions showed progressive reductions in the force deficit until *week 4* when the force deficit was eliminated, whereas in old mice a similar level of protection was not demonstrated until *week 5* (11).

DISCUSSION

It is indisputable that repeated high-force eccentric contractions are associated with muscle damage, regardless of the initial health or age of the muscle. However, the risks and benefits of eccentric exercise involving submaximal contractions are still under investigation with regard to the elderly and those with neuromuscular disease. In a recent paper studying eccentric exercise in dystrophic animals, Call et al. state "…the dystrophic phenotype in mdx mice is not worsened when eccentric contractions are performed on a regular basis. In fact, muscle torque and force improved after multiple bouts of eccentric contractions, showing that substantial strength gains are possible without the presence of dystrophin" (14). This is one of a cadre of animal studies proclaiming the benefits of exercise in dystrophic muscle (7, 14, 15). However, there are far fewer human studies regarding the effects of eccentric exercise on muscular dystrophy, in particular DMD. Well-controlled rigorous studies are needed to determine not only the dose (frequency, intensity, and duration) of exercise appropriate for those with a neuromuscular disease, but also the type of exercise. For healthy elderly people, exercise conditioning can clearly protect muscles from injury, despite their high susceptibility to injury and an impaired ability to recover (Fig. 3). Moreover, although the adaptations are less robust than those observed following repeated bouts of damaging contractions, the exercise conditioning need not induce injury, degeneration, and/or regeneration to invoke the protective adaptations. Thus the maintenance of "conditioned" fibers in the muscles of old people has the potential to decrease the likelihood of injury, which along with skeletal muscle atrophy, weakness, and fatigability contribute to physical frailty and may actually contribute to its development and progression. Physical frailty impairs performance of the activities of daily living, increases the incidence of falls, and impacts negatively on the quality of life of old people. Despite the lack of definitive answers to many questions regarding the development of frailty and the progression of neuromuscular diseases, the longer people can be motivated to maintain a physically active life style, including both endurance and strength training, the higher will be the quality of their life.

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AUTHOR CONTRIBUTIONS

Author contributions: R.M.L. and S.V.B. prepared figures; R.M.L. and S.V.B. drafted manuscript; R.M.L. and S.V.B. edited and revised manuscript; R.M.L. and S.V.B. approved final version of manuscript.

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