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Factors involved in strain-induced injury in skeletal muscles and outcomes of prolonged exposures

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Abstract

Repetitive motion disorders can involve lengthening of skeletal muscles to perform braking actions to decelerate limbs under load often resulting in muscle strains and injury. Injury is a loss of isometric force (weakness) requiring days to recover. The capacity of skeletal muscle to tolerate repeated strains is dependent on multiple factors including individual variation. The most important factors producing muscle strain injury are the magnitude of the resisting force (peak-stretch force) and the number of strains. Other factors such as muscle length and fiber type contribute to the susceptibility to injury as well, but to a lesser degree. Strain injury can also lead to inflammation and pain. Chronic exposure to repeated strains can result in fibrosis that is not completely reversed after months of rest. Long rest times appear to be the only factor reported to prevent inflammation in rats following repeated strain injury. Further understanding of the mechanism for prevention of histopathologic changes by long rest times should provide a rationale for prevention of negative outcomes.

Keywords: Repetitive motion disorders; Prevention; Outcomes; Causative factors

1. Introduction

Muscle and tendon disorders are frequent in the work-place, resulting in loss of work and sometimes lead to disability [114]. Based on ergonomic assessment of the workplace and epidemiology of work-related musculoskeletal disorders, it is commonly believed that tissue intolerance to repeated loading plays a role in the etiology of cumulative trauma disorders and can actually lead to tendon pathology [65] and perhaps even tendinitis [89]. The reason for this is that the tissues involved are often in series with one another (bone to tendon to muscle to tendon to bone) or in parallel (muscle, nerve, and fascia). Therefore, additional loading of the attachments of the muscle could result if the muscle lost the ability to attenuate strains as a result of muscle pathology. Thus, the tissue initially responsible for the disorder (e.g. muscle) goes unrecognized as the source of the problem because site of pain occurs proximal or distal to the original tissue injury. Only a small part of the muscle, perhaps just one fascicle, needs to be fibrotic (stiff) for the muscle to behave as a tendon transmitting more force to the tendon of origin and to the attachment site where most of the pain receptors are found (e.g. periosteum).

Although many factors contribute to cumulative trauma disorders, this discussion will focus on how skeletal muscles lose the ability to resist externally applied forces which results in strain injury and the consequences of chronic exposure to repeated strains. Most detailed information comes from animal studies where entire muscles can be removed for functional and morphological assessments. The other advantage of animal studies is that the parameters used to produce strain injury, such as velocity, acceleration and range of motion, can be precisely controlled. However, unlike most human activities using low loads and high repetitions, the animal muscles are maximally activated by electrical stimulation so that 100% of the myofibers are active prior to the strain. The advantage of this approach is the responses seen (e.g. force deficit) are larger than would be expected for submaximal activities, while the disadvantage is that they are not typical of work-place exposure, except when high loads and high repetitions are used.

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2. Strain injury: loss of strength (weakness) and power

A prolonged loss of strength (maximal isometric force) [33] not caused by neural and metabolic factors [29] and not recovering after one hour of rest [97]—a time normally sufficient for muscles to recover from fatigue [97]—is considered to be the hallmark of muscle strain injury (Fig. 1). The loss of power has also been reported for human muscles [90] as would be expected if maximal force declined. The loss of muscle strength or power from repeated strains (stretches of active muscles) can be considered a type of material fatigue [4,107] because the force generating or force transmitting structures are disrupted over time. Unlike non-living materials which experience material fatigue, skeletal muscle can repair itself over many days [22,56] and even increase its tolerance to subsequent strains (i.e. training effect) [13,22].

3. Strain injury: histopathologic changes

Injury can also be defined by counting the number of myofibers that have lost their cellular integrity (e.g. albumin positive myofibers [37,60,103]) or suffered intracellular protein degradation (desmin negative myofibers [6,55,97]). However, histopathologic changes do not correlate well with the magnitude of the strength loss [53,63,97,110] or the time course of the force deficits [24,56]. The reason for this lack of correlation is that the loss of strength is due to sarcomere disruption [32,33,66,75], segmental lesions [31,71], and failure of excitation contraction coupling [43,75,108,121] whereas the histopathologic changes (Fig. 2) probably result from altered calcium homeostasis [27] that in turn leads to cell death and necrosis

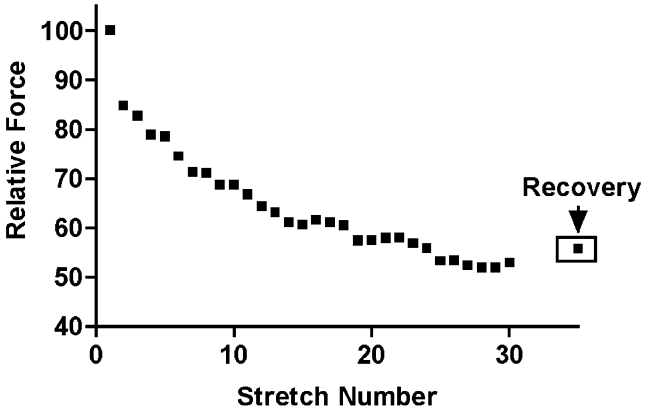

Fig. 1. Isometric force of rat plantar flexor muscles as a function of stretch (strain) number. The muscles are activated by direct nerve stimulation while the animal is under deep anesthesia. The box indicates the isometric force remaining after one hour of recovery.

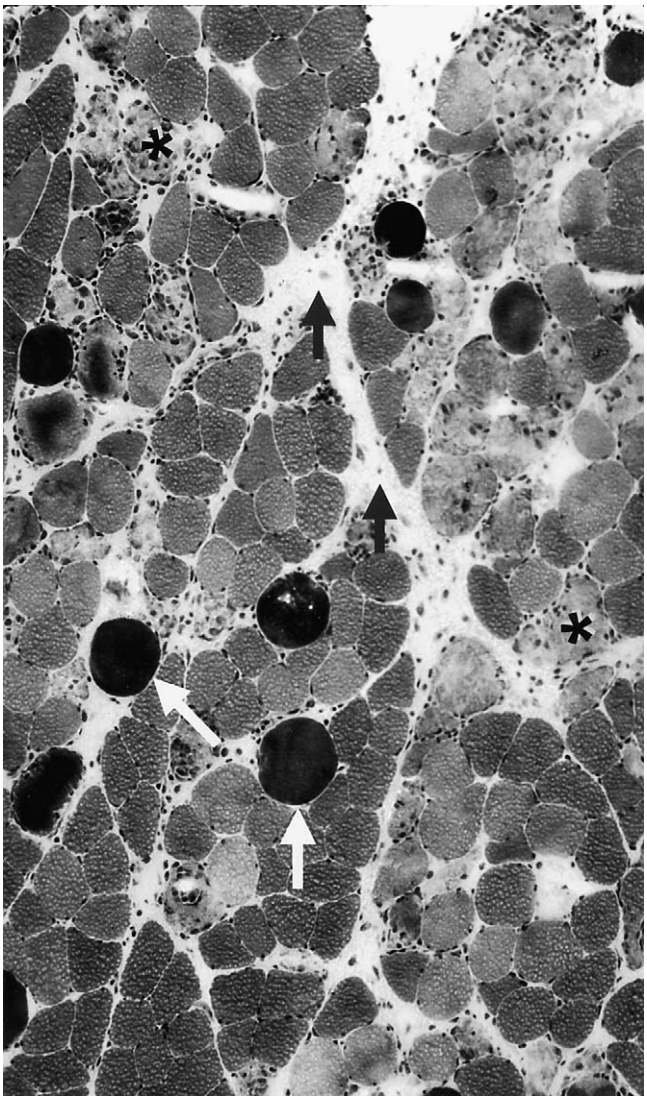

Fig. 2. Cross-section of rat medial gastrocnemius muscle 48 h after a 30 stretch protocol with 40-s inter-stretch rest times. Black arrows indicate expanded extracellar matrix indicative of muscle swelling. White arrows locate hyper-contracted myofibers. Asterisks identify necrotic myofibers that have been infiltrated by inflammatory cells. Original magnification 25×.

[120]. In our studies using rats, a 50% loss in strength can occur with only about 2% of the fibers of the medial gastrocnemius muscle injured or necrotic following a 30-stretch protocol with short inter-stretch rest times [97].

The development of histopathologic changes is accompanied by inflammation and muscle pain. The strain-injured muscles are swollen as seen by expanded extracellular space and infiltrated by inflammatory cells (Fig. 2). Hyper-contracted muscle fibers can be observed along with necrotic muscle fibers infiltrated by phagocytic cells (Fig. 2). The resolution of pain, which takes several days [22], seems to follow the reduction of inflammation after the initial exposure.

Administration of non-steroidal anti-inflammatory medication, such as naproxen, can attenuate the loss of strength and pain under certain circumstances [5], but may also be detrimental to muscle [1].

4. Risk factors for muscle strain injury

When an active muscle or myofiber is stretched to produce a muscle strain (eccentric muscle action [17], lengthening contraction [62], pliometric contraction [47]), an immediate loss of force or torque results [14]—the muscle injury. The various factors that contribute to muscle injury from muscle strains producing subsequent force deficits or weakness are discussed below.

5. Peak stretch force

Job activities requiring high forces have been associated with upper extremity injuries [84,85]. Not surprisingly then, the most important factor involved in the strength loss from muscle strain injury in animals was observed to be peak stretch force. When an active muscle is stretched, increased force or extra tension can be produced beyond the isometric maximum (Fig. 3) [46,66]. The magnitude of the peak stretch force correlates with the amount of muscle injury [63,106]. In contrast, stretching of a non-active muscle generally does not produce muscle injury [67] unless the length change exceeds the physiological length of the muscle [9,14] or is applied as a high impulse load to the tendon [104]. If strain injuries are produced over non-physiological ranges in intact rats, force deficits can be produced along with vascular disruption and micro-hemorrhage (Stauber and Willems, unpublished observations). In contrast, no bleeding occurs in single joint muscles or two joint muscles if stretches are produced within the physiologic range.

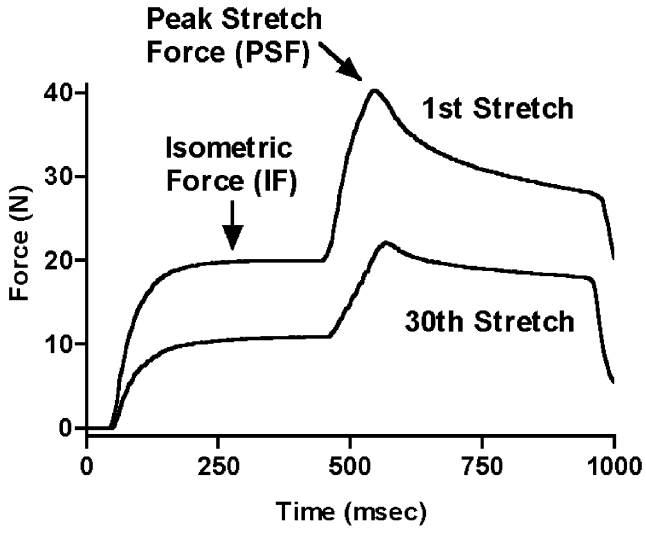

Fig. 3. Force as a function of time for the first and 30th stretch for repeated stretches with inter-stretch rest times of 40 s. Isometric force (IF) is recorded at an ankle position of 90° and precedes the stretch to an ankle position of 40°. The stretch produces additional force that peaks at the end of the stretch (peak stretch force (PSF)).

6. Number of stretches or strains

The next major factor involved in isometric force deficits from repeated strains is strain number or repetition. In a series of repeated stretches or strains, the amount of strength loss continues to increase with each subsequent strain thus providing indirect evidence of increased injury with increasing stretch number (Figs. 1 and 3) [40]. However, the majority of the loss in force occurs early [40] with less loss occurring at higher repetition number (Fig. 1) [115] perhaps due to the decline in peak stretch force (Fig. 3) [115]. The energy that is absorbed during the strain disrupts force-producing components (sarcomeres, connective tissue) and cellular membranes required for excitation–contraction coupling reducing the peak strain force of each succeeding strain. For mice, the loss of force was linear from 15 to 150 stretches [63]. Increasing the number of stretches beyond 150 did not produce further injury. For rat muscles, it appears that 240 stretches produce the maximum loss of isometric force with little additional loss after 300 stretches [40]. However, the number of injured muscle fibers, determined by morphological assessment, increased linearly throughout the entire range tested (60–300). Thus, skeletal muscle apparently undergoes material fatigue and demonstrates an endurance limit at some high repetition number [4] which may be muscle or species specific. In contrast, cell necrosis continues to increase with increasing stretch number [40].

In humans, it has been found that the combination of high forces and high repetition numbers appears to be the most damaging followed by high forces and low repetitions [84]. Even low force activities with high repetitions can produce problems [84]. In rats, strains produced by downhill running can produce muscle injury if the repetition number is large (e.g. 30 min or more of running). Chronic exposure to repeated reaching for food pellets in rats—also a low force activity—produced widespread inflammation of the forearm and painful behaviors [7]. This repeated reaching model would be useful to test whether muscles are also injured under low force reaching activities.

Other factors influencing the loss of strength with repeated muscle strains play a smaller part in the magnitude of injury produced. These factors include initial fiber length, length change, velocity and acceleration of strain, and muscle fiber type.

7. Muscle length

It is quite clear that muscles are more susceptible to injury at long muscle lengths [67] or on the descending limb of the length tension relationship [66]. For example, if humans are exposed to protocols that stretch the elbow extensor muscles at short muscle lengths or long muscle lengths, the greatest injury occurs from stretches at long muscle lengths [69]. The length of the stretch also influences the amount of damage that is produced with larger excursions producing more injury [14,51].

8. Velocity and acceleration

Wrist movements with high-accelerations (i.e. increasing velocity) have an increased risk for cumulative trauma disorder [82]. In the work-place with uncontrolled movements under load, high acceleration or high velocity movements would require high deceleration forces (high peak strain forces). The muscles resist the load by lengthening in order to slow and stop the movement of the limb. Under controlled velocity conditions in animal muscles, an absence of influence of velocity of the stretches has been reported for active muscles [63,106,116] and isolated single muscle fibers [57,98]. Similarly, acceleration of the stretch did not influence the magnitude of injury [118].

9. Fiber type and size

It has been noted that fast (type II) muscle fibers are selectively damaged by acute bouts of repeated strains in rabbits [50]. We have found similar results for the medial gastrocnemius muscle of rats [97]. Since in animals fast myofibers are larger in cross-sectional area than slow myofibers, larger muscle fibers may be more prone to strain injury. Using very large numbers of strains in rats, we found that the small fiber fast (type II) fibers were the last to be injured (Willems and Stauber, unpublished observations). Therefore, large myofibers may be at increased risk for strain injury.

In contrast, following downhill running, slow (type I) fibers in the soleus muscle were more susceptible to injury [71]. This discrepancy may be due to the fact that the larger fast fibers are not recruited during the running activity. However, in humans, the difference in fiber areas of the different fiber types is much smaller [99]. Therefore, muscle fiber area may not be a critical factor in muscle strain injury in humans.

10. Location of fibers

Few studies have looked at the distribution of injured fibers within a muscle. In our studies, it would appear that there are regions more susceptible to injury and that under certain conditions, the fibers on the outer edge of the muscle on the opposite side to the tendon plate become injured first. In humans, a higher proportion of type II fibers were observed at the boundary of a fascicle than internally [86]. Little is known about the regional differences in injured fibers except that the distal ends of the muscle are more susceptible to damage [9,19] and soreness is most common in that region as well [68].

11. Sex

No difference between men and women in muscle response to repeated strains has been reported [77], but there was a difference in the post-injury degree of soreness with women reporting less soreness than men [101]. Since soreness results from post-injury inflammation, estrogen could alter the degree of inflammatory response to injury. Likewise in rats, force deficits produced by repeated strains were not different between males and females [111,117], but in females less post-exercise inflammation was reported [88]. In another model of skeletal muscle injury (downhill running), less injury was noted in female rats using morphological criteria [3,48]. Thus, injury, as assessed by morphological criteria, may correlate with the degree of post-exercise soreness. A method of measuring muscle pain in animals is needed.

In both female and male rats, a series of 30 strains can result in a 50% reduction in muscle force (Fig. 1) [117] but, depending on the conditions, not all strain injuries are accompanied by inflammation [97]. Inflammation and histopathologic changes in skeletal muscle appear to require membrane damage and the entry of extracellular calcium into the muscle cell (Fig. 4). Calcium handling by injured muscle cells may be different in females than males so that fewer muscle cells become irreversibly injured and less necrosis and inflammation results from repeated strains. Little is known about differences in calcium handling in male and female skeletal muscles.

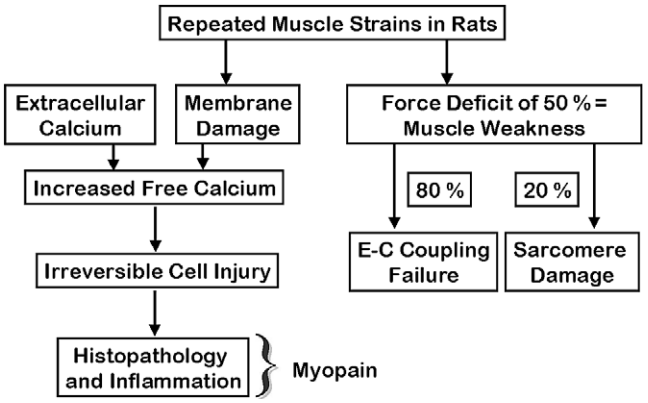

Fig. 4. Cascade of events following repeated muscle strains. The right half of the figure depicts the functional consequences of repeated strains and the elements identified in the loss of muscle force. The left side of the figure outlines the calcium overload process leading to histopathologic changes, inflammation and pain. In rats, force deficits of 50% can result with or without histopathologic changes and with or without pain.

12. Age

In humans and mice, advanced age results in weakness as measured by maximal isometric force production, but the peak stretch force is maintained [41,73]. Since peak stretch force is most important in producing muscle injury, strain-induced injury would be expected not to differ with advancing age. In old female rats, the magnitude of the force deficits of plantar flexor muscles in vivo following a series of 30 stretches was similar to that of young rats [115]. Similar force deficits were also reported for intact soleus muscles in vitro from young and old male rats after 20 stretches [36]. After 75 stretches in intact muscles of old mice, a greater isometric force deficit was reported [12]. Single permeabilzed fibers from old rats also demonstrated a greater force deficit [12] providing indirect evidence that the increased susceptibility to injury of muscles from old animals resides at the level of the sarcomere (myofilaments). However, this increase in myofiber fragility may be partially offset by changes in collagen and collagen cross-links in old muscles [2,49,78] so that testing muscles within a physiological range of motion can result in no difference in injury susceptibility with age [36,115].

In elderly humans, the risk of tendinitis may increase with advancing age [105]. Less is known about skeletal muscle. In response to resistance exercise, older individuals demonstrated equal or greater myofiber damage than younger adults [59,79,79,80]. Following a one repetition lift used to determine maximum strength, excessive injury in elderly men or women was not present, but 58% of the human volunteers complained of muscle soreness [83]. Elderly humans also did not differ in response to a maximal stretch protocol when soreness and indirect measures of muscle injury were measured (e.g. serum creatine kinase levels) [21], but other studies have reported conflicting results [59]. These indirect measures of muscle injury correlate poorly with the magnitude of the force deficit [110] and thus, conclusive statements about age as a risk factor for muscle strain injury cannot be made.

13. Inflammation

A series of 30 strains can result in a 50% reduction in muscle force (Fig. 1) but, depending on the conditions, not all injuries are accompanied by inflammation [97]. Inflammation and histopathologic changes in skeletal muscle appear to require membrane damage and the entry of extracellular calcium into the muscle cell (Fig. 4).

14. Additional issues: health status

Other factors may also influence muscle pain and weakness resulting from occupational tasks. For instance, certain medications such as the lipophilic statins [102] can produce muscle pain and loss of strength. Any disease such as hypertension [39] that reduces the capillary density of skeletal muscles could also pose additional risks. Similarly, exercise intolerance has been reported for hypothyroid patients [61]. Therefore, exposure to environmental agents such as dioxin and polychlorinated biphenyls (PCBs) [64] which interfere with thyroid hormone action and produce non-thyroidal illness, as well as some medications such as amiodarone [74], could lead to increased susceptibility to negative outcomes from repetitive motions and muscle strains. The list presented here of health issues that could pose additional risks for work-place muscle injuries is very limited serving only to illustrate the additional complexity of working with humans exposed to repeated strains or muscle over-activity.

15. Muscle repair

It is well known that skeletal muscles can recover fully from a single bout of repeated strains [23,28,33,33,56,109] even if cellular death occurred [93]. Muscle contains its own stem cell, the satellite cell, which can proliferate and participate in the regeneration of entire fibers [16], even if severely damaged by crush injury. The process requires many days but the muscles return to normal function and are often more resistant to injury (i.e. a training effect) [81,100]. Mechanisms of muscle regeneration following injury have been reviewed in detail [16].

16. Chronic exposure to repeated muscle strains

Unlike the well documented muscle responses to chronic nerve stimulation [18,42,72], less is known about muscle responses to chronic strains. However, it appears that a continuum exists where load, repetition number and rest interval interact differently to produce both positive (muscle hypertrophy) [15,119] or negative (muscle fibrosis) [92,94,96] outcomes. Such a continuum exists for other components of the musculoskeletal system such as bone where repeated microtrauma can make bones stronger or result in stress fractures. It is believed that repeated damage and inflammation lead to muscle atrophy and fibrosis similar to that seen in chronic myopathies [11,25].

Following chronic exposure to repeated strains, the number of small fibers increased dramatically in rat soleus muscles [94,96]. These small fibers returned to normal size after a long period of rest [96]. Small caliber fibers do not suffer necrosis in mouse dystrophy [45], where repeated strains occur from normal locomotion. Thus, the increased number of small fibers probably by fiber splitting [11] might be a protective adaptation.

Fibrosis is common following injury or chronic disease to skeletal muscle [92,94,96] mediated, in part, by TGF beta [87], a fibrogenic cytokine [10], acting to inhibit myoblast differentiation [38] during muscle regeneration, while stimulating connective tissue proliferation [8,54]. Muscle fibrosis, even if only limited to a single fascicle, would produce a stiffer muscle because of increased connective tissue [30]. A stiffer muscle would not attenuate strains without transmitting increased force to the attachment sites.

In our laboratory, we have demonstrated that connective tissue proliferation including both collagen content and collagen crosslinks increased dramatically following a period of daily repeated strains and did not fully return to normal even after 3 months of rest in rats [96]. Such an observation is commonly seen in muscle disease states where myofibers are repeatedly injured and regeneration is ongoing [25]. It is not known if muscle fibrosis occurs in humans exposed to repeated strains, but there is evidence for pathology and expanded non-contractile material seen in the photomicrographs for extensor carpi radialis brevis in humans with long standing lateral epicondylitis requiring surgery [55].

17. Prevention

Unlike manual lifting [112,113], there is no reported guide (equation) to serve to reduce injury from hand and upper extremity intensive tasks. The lack of a guide is due in part to the lack of knowledge of the cellular mechanisms of strain-induced muscle injury that would provide a rational basis for injury prevention [52]. However, from the limited information available, rest times may be the most important factor for reducing risk of strain injury, as well as for diminishing negative outcomes from muscle overuse. Therefore, job rotation on alternating days so that different muscles are used on different days or more frequent rest intervals for ongoing repetitive movements might prevent injuries also. In addition, reducing the speed of the activity (self-pacing) would result in decreased activation of fatiguable fibers and decreased forces required for deceleration—both would be reflected by a decrease in perceived exertion. Self-pacing has proven to be helpful in hand-intensive activities by reducing the forces required to perform the movement by 20% [70] and reducing loading of the spine during repeated lifting [26]. At present, reduced loads and decreased speed of movements with attention to deceleration of the movement would appear to be reasonable strategies to reduce muscle tissue loading.

Differences in bioenergetic capacity need to be defined for subsets of individuals at high risk for developing muscle fatigue and possible ischemia during repeated movements. Such differences may be revealed by dynamic testing [91] or exercising with 31P-magnetic resonance spectroscopy [20]. Alternative jobs that better match the physiology of the individual could prove quite beneficial.

18. Over-load and over-activity

Models of chronic overload [95] and over-activity [35,58] have been reported in animals. It appears that they can follow the same pathway from muscle cell injury to the appearance of inflammation, perhaps even leading to fibrosis as seen in the diaphragm of rats and humans with COPD [76]. In fact, the extensor carpi radialis brevis from humans with long standing lateral epicondylitis [55] resembles much of the histopathogic changes seen in our overloaded and chronic strained rat muscles.

Over-activity has been associated with an energy crisis in skeletal muscles [34], which may lead to pain and perhaps even localized ischemia [85]. Energy levels are decreased in these muscles and the morphology is similar to that seen in muscles from patients with mitochondrial myopathies (ragged red fibers) [44]. If calcium overload results from decreased energy levels, then muscle injury and necrosis will follow leading to the same pathologic changes as reported for muscles which have been injured by other methods or conditions.

19. Summary

An acute bout of repeated strains can overcome a muscle's ability to resist mechanical deformation and produce a strength loss that requires days to recover accompanied by inflammation and pain. The major factors that produce the loss of strength are within the muscle cell. The force generating structures (sarcomeres) are pulled apart by the externally applied force so that myofilament overlap does not occur without this overlap no force can be developed by that sarcomere. The other less defined region of damage, also disrupted by strain, appears to be located somewhere in the excitation–contraction coupling system—perhaps the shearing of the t-tubules. As a result, muscle action potentials do not result in the release of activator substance required for muscle force production in sarcomeres that have optimal myofilament overlap. These cellular disruptions require regenerative processes and thus the force does not recover for several days following an acute bout of strain injury.

The major factors that produce strain injury are peak-stretch force (load) and repetition number. The mechanism by which long rest times prevent or reverse the entry of extracellular calcium is not known at the present time. Understanding of the mechanism for attenuation of histopathologic changes by long inter-stretch rest times should provide a rationale or guide for prevention of negative outcomes from repeated muscle strains, such as muscle fibrosis. Without such a guide, but based on the available information, prevention of chronic muscle strain injuries and pain may result from adjusting rest times to suit individual differences (e.g. self-pacing).

20. Recommendations for prevention

Performing different jobs on consecutive days requiring different muscle groups would allow muscles a day or more to recover. Since peak stretch force and repetition number are key factors in producing strain injury, decreased loads and velocity of movements should decrease the braking forces required to decelerate loaded limbs reducing muscle strains. Decreased velocity would also decrease the repetition number. Finally, education about the importance of rest would be beneficial.

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