Etiology of Exercise-Induced Muscle Damage

Priscilla M. Clarkson and Stephen P. Sayers

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Abstract/Résumé

Muscle damage is caused by strenuous and unaccustomed exercise, especially exercise involving eccentric muscle contractions, where muscles lengthen as they exert force. Damage can be observed both directly at the cellular level and indirectly from changes in various indices of muscle function. Several mechanisms have been offered to explain the etiology of the damage/repair process, including mechanical factors such as tension and strain, disturbances in calcium homeostasis, the inflammatory response, and the synthesis of stress proteins (heat shock proteins). Changes in muscle function following eccentric exercise have been observed at the cellular level as an impairment in the amount and action of transport proteins for glucose and lactate/H+, and at the systems level as an increase in muscle stiffness and a prolonged loss in the muscle’s ability to generate force. This paper will briefly review factors involved in the damage/repair process and alterations in muscle function following eccentric exercise.

Un dommage au muscle est causé par un exercice intense et inhabituel et particulièrement un exercice fait de contractions musculaires pliométriques (contractions au cours desquelles les muscles s’allongent tout en exerçant une force). Les dommages peuvent être constatés directement au niveau cellulaire et indirectement, grâce à divers indices de la fonction musculaire. L’étiologie du processus de dommage/réparation du tissu musculaire inclut des facteurs comme la tension et la contrainte, un dérangement de l’homéostasie du calcium, une réaction inflammatoire et la synthèse de protéines du stress (protéines de stress thermique). Les variations de la fonction musculaire après un exercice pliométrique sont observables au niveau cellulaire par la modification de la quantité et de l’activité des protéines

The authors are with the Department of Exercise Science, Totman Bldg., University of Massachusetts, Amherst, MA 01003 USA.
de transport du glucose et du lactate/H⁺ et au niveau macrocellulaire, par une augmentation de la raideur de muscle et par une perte prolongée de la capacité d’exercer une force. Cet article présente une brève analyse des facteurs associés au processus de dommage/réparation et à la modification de la fonction musculaire après un exercice pliométrique.

Introduction

In 1902 Hough first suggested that exercise resulting in delayed onset muscle soreness was caused by damage to muscle fibers. Several studies have since documented that strenuous, unaccustomed exercise damages muscle cellular structures and disrupts the extracellular matrix, and this damage is accompanied by an impairment in muscle function (Bär et al., 1994; Fridén, 1984; Fridén et al., 1983; 1984; Fritz and Stauber, 1988; Jones et al., 1986; Newham et al., 1983a; Stauber et al., 1990). Eccentric muscle actions where muscles lengthen as they exert force, such as lowering a weight, result in significantly more muscle damage than concentric (muscle shortening) contractions. Because eccentric exercise is less metabolically stressful and produces less lactic acid than concentric exercise, other factors must explain why eccentric contractions are so damaging to muscle (Clarkson and Newham, 1995). This paper reviews the mechanisms involved in the muscle damage/repair processes after eccentric exercise and provides an overview of the consequences of damage on muscle function.

Muscle Damage and Repair Processes

Histological and ultrastructural examination of eccentrically exercised muscle has provided direct evidence of damage to the internal environment of the muscle fiber, the sarcolemma, T-tubules, myofibrils, and the cytoskeleton (Armstrong et al., 1983; Fridén et al., 1983; 1984). Z-disc (Z-line) streaming is a common characteristic of exercise-induced damage (see reviews by Armstrong, 1984; Ebbeling and Clarkson, 1989; Clarkson et al., 1992; Clarkson and Newham, 1995; Fridén and Lieber, 1992; MacIntyre et al., 1995). The damage appears to worsen in the days immediately following the exercise and then is gradually repaired within 2 or 3 weeks postexercise (Jones et al., 1986; Newham et al., 1983a). Not only are muscle cells damaged but there is also an increase in indices of collagen breakdown in the days after eccentric exercise, indicating damage to connective tissue (Brown et al., 1997).

Factors hypothesized to be responsible for damage following eccentric exercise are mechanical stress, disturbances in intracellular calcium homeostasis, and the inflammatory response. Mechanical factors initiate the damage while disturbances in calcium homeostasis and some of the inflammatory mediators exacerbate damage in the days following exercise. Other inflammatory mediators and synthesis of stress proteins appear to play a role in repairing the damage.

MECHANICAL FACTORS

One reason eccentric contractions cause more damage to muscle than concentric contractions is because fewer motor units are recruited during eccentric exercise, and therefore a smaller cross-sectional area of muscle is activated to handle the
same load as would be handled in a concentric contraction (Enoka, 1996). Warren et al. (1993a) found that decrements in isometric tension immediately after injury to the muscle were closely related to peak force produced during the eccentric actions, implying that tension may produce damage. However, Lieber and Fridén (1993) found that the extent of muscle injury was related more to the change in length than to the amount of force generated by the muscle. They suggested that muscle injury was associated with the magnitude of strain rather than the high forces imposed on the muscle, even though these high forces may in part contribute to injury. Studies on humans have shown that more damage is caused by eccentric actions at long muscle lengths than at short muscle lengths (Child et al., 1998; Newham et al., 1988), lending further support to the contention that strain causes damage.

Morgan (1990) hypothesized that certain sarcomeres may become overextended and "pop" due to the stress placed on them by the lengthening actions of the muscle. Because some sarcomeres may be stronger than others, weaker sarcomeres are unable to maintain tension as the fiber lengthens, thus passive structures are left to provide support. In an examination of amphibian muscle following forced lengthening, Talbot and Morgan (1996) provided direct evidence of overstretched sarcomeres that were randomly scattered in the stretched muscle. These data are consistent with the ultrastructural changes observed following eccentric exercise where some sarcomeres (the proposed weaker ones) are disrupted while most sarcomeres remain intact (Fridén et al., 1981, 1983; Newham et al., 1983a; Nurenberg et al., 1992).

In a recent study, Talbot and Morgan (1998) examined the effects of damage induced by eccentric exercise in tetanically activated toad muscle. They reported that the amount of damage was related to the amplitude of the stretches and the range of sarcomere lengths over which the stretch occurred. Damage was not significantly related to the velocity of the stretch or the tension during the stretch. These data are consistent with the finding of Lieber and Fridén (1993).

DISTURBANCES IN CALCIUM HOMEOSTASIS

Damage to the sarcoplasmic reticulum (SR) or muscle membrane can increase intracellular calcium (Ca++) and trigger calcium-sensitive degradative pathways. Duan et al. (1990) reported an increase in mitochondrial Ca++ concentration in animal muscles damaged from downhill walking. Although earlier work (Lowe et al., 1994) found that mouse muscles injured by eccentric contractions were able to buffer the increased influx of Ca++, more recent studies from the same laboratory (Warren et al., 1995) reported that mouse fibers injured by eccentric contractions had an elevated free cytosolic Ca++ concentration. Lieber et al. (1996) postulated that increased strain on the fibers from forced lengthening would trigger strain-activated calcium channels in the membrane, increasing Ca++ influx into muscle cells.

Yasuda et al. (1997) found a loss of SR membrane integrity in rats after inducing eccentric contractions by percutaneous electrical stimulation. There was a degradation of SR membranes at 12 hours posteccentric exercise and a loss of SR vesicle membrane integrity, suggesting that Ca++ may leak from the SR lumen.
However, in a study of exercise following hindlimb suspension, dantrolene sodium, a muscle relaxant that affects the flux of Ca\(^{2+}\) from the SR, had only a limited effect in preventing exercise-induced injury (Bigard et al., 1997).

Calpain, a non-lysosomal, calcium-activated neutral protease located at the I and Z regions of skeletal muscle, is suggested to play a role in the muscle damage process (Belcastro et al., 1998). In vitro, calpain was found to cleave substrates such as cytoskeletal proteins (e.g., desmin, \(\alpha\)-actinin, vimentin). Desmin serves to attach adjacent myofibrils at the Z-discs (McComas, 1996; Patel and Lieber, 1997), synemin and vimentin coexist with desmin at the Z-disc, and \(\alpha\)-actinin anchors actin to the Z-disc (Patel and Lieber, 1997). The propensity for degradation of these proteins may make the Z-disc vulnerable to exercise-induced damage.

Disruption to the fiber’s cytoskeleton and sarcolemma appears to be the initial damage induced by lengthening muscle actions. In an animal model, Lieber et al. (1996) found a significant loss of desmin labeling from muscle 15 minutes after exposure to eccentric contractions. Belcastro et al. (1998) reported a concomitant loss in Z-disc structure and a loss of two proteins that had a molecular weight consistent with desmin and \(\alpha\)-actinin. Also, an increase in calpain activity has been found after exhaustive exercise (Belcastro, 1993). The fact that actin and myosin are not substrates for calpain would explain why ultrastructural damage is noted predominantly in the Z-disc regions, with actin and myosin structure remaining relatively intact.

INFLAMMATORY RESPONSE

Damage to muscle fibers results in an inflammatory response that causes a transfer of fluid and cells to the damaged tissue. Increased fluid produces the characteristic swelling after injury. Specific chemotactic agents lead to the emigration of leukocytes through the endothelial lining to the injured area (Abrams, 1997). In a study examining the presence of 99mTc-labeled white blood cells (WBC), MacIntyre et al. (1996) took blood from subjects who had performed eccentric knee extension exercise, labeled the WBCs, then reinjected the cells. Increased labeling of the WBCs in the quadriceps muscle occurred from 4 to 20 hrs following exercise, demonstrating an invasion of WBCs in the damaged tissues.

Neutrophils are speculated to be the first cells to infiltrate damaged muscle fibers (Abrams, 1997; Smith, 1991; Tidball, 1995). Belcastro et al. (1998) suggested that peptide fragments of calpain may be associated with neutrophil chemotaxis, and Raj et al. (1998) found a relationship between calcium-stimulated cysteine protease (calpain-like) and neutrophil accumulation, also suggesting that the calpain system was involved in promoting neutrophil invasion. Although increases in both circulating neutrophils (Cannon et al., 1990; 1994; Smith et al., 1989) and accumulation of neutrophils in skeletal muscle tissue (Fielding et al., 1993) have been reported in humans following eccentric exercise, the role of neutrophils in the damage and repair process is unknown (MacIntyre et al., 1995).

Macrophages, like neutrophils, are capable of producing oxygen free radicals and cytotoxic enzymes leading to tissue degradation (MacIntyre et al., 1995). Xanthine oxidase activity and indicators of inflammation were examined in subjects who performed leg eccentric exercise (Hellsten et al., 1997). Xanthine
oxidase uses molecular oxygen as an electron acceptor and generates reactive oxygen species (ROS) which can cause muscle damage (Hellsten et al., 1996). Hellsten et al. (1997) found an increased expression of xanthine oxidase in the microvasculature endothelial cells and an invasion of leukocytes, which may contain xanthine oxidase, over 4 days postexercise. They suggested that a secondary inflammatory process that induces xanthine oxidase may contribute to the generation of ROS in the days immediately following eccentric exercise and aggravate existing damage from the mechanical insult. This would explain the increase in ultrastructural damage noted in the days following eccentric exercise.

ROS damage to capillary endothelium can also occur after reperfusion of an ischemic limb. Jones and Round (1997) hypothesized that radicals may be generated when oxygenated blood returns to the damaged tissue (a reperfusion injury), and Howell et al. (1990) showed that blood flow dramatically increases in the muscle immediately after eccentric exercise. Increased xanthine oxidase in capillary endothelium has been implicated in reperfusion injury (Jones and Round, 1997). However, it would seem that the reperfusion injury would occur immediately after exercise and not be able to explain the delayed increase in xanthine oxidase, which lends support to the involvement of inflammatory cells.

Lowe et al. (1995) examined protein metabolism after eccentric contraction-induced injury in mouse muscle. At 48 hrs postexercise the protein degradation rates were elevated, which correlated with infiltration of phagocytic macrophages. Noting there were no signs of enhanced degradation in the muscle until the phagocytic cells appeared, Lowe et al. suggested that the inflammatory response plays a key role in removal of damaged proteins before regeneration ensues. Macrophages also give rise to cytokines including interleukin-1, interleukin-6, and tumor necrosis factor. Cytokines may exacerbate damage by potentiating cytotoxic mechanisms of other inflammatory cells to enhance free radical production and release proteolytic enzymes (Evans and Cannon, 1991). Bruunsgaard et al. (1997) reported an increase in circulating cytokines (interleukin-6) and elevation of natural killer cells and CD8+ cells after eccentric cycling exercise.

Following degradative processes, some macrophages may then play a role in muscle repair (Tidball, 1995). Macrophages are the predominant type of inflammatory leukocyte at any time after the first 12 hours postexercise and are the principal removers of cellular debris (Tidball, 1995). Two subpopulations of macrophages, ED1+ and ED2+, have been observed in animal muscle (Honda et al., 1990; St. Pierre and Tidball, 1994). ED1+ macrophages act as phagocytes and function in the removal of cellular debris in necrotic tissue. ED2+ macrophages may regulate the consequent repair process since they appear when muscle necrosis is complete and muscle regeneration begins (St. Pierre and Tidball, 1994; Tidball, 1995).

As a consequence of the inflammatory response, swelling occurs in the eccentrically exercised muscle (Clarkson et al., 1992). Muscle breakdown products (e.g., protein fragments) are slowly removed from the extracellular matrix via the lymphatic system and can attract water, leading to localized edema (Mair et al., 1992). Peak swelling may not occur until 5 to 10 days postexercise (Clarkson et al., 1992). Swelling begins inside the muscle and then spreads into the subcutaneous space starting at about 5 days postexercise. Nosaka and Clarkson (1996) observed that the accumulated fluid moved toward the outside of the perimysium over 10 days posteccentric exercise.
STRESS PROTEINS

Stress proteins play an important role in maintaining cellular homeostasis. Cells can rapidly synthesize stress proteins in response to increased muscle temperature, reactive oxygen species (ROS), abnormal proteins, and alterations in Ca" in cells (Essig and Nosek, 1997; Kilgore et al., 1998; Locke, 1997). These changes are consistent with what is observed with eccentric exercise; eccentric contractions generate greater muscle temperature than concentric, Ca" accumulates in the cytoplasm, cytoskeletal proteins are damaged, and leukocyte invasion may increase ROS. Stress proteins function in the damage clean-up, and Essig and Nosek (1997) proposed that an increased synthesis of stress proteins would reduce oxidative damage to the SR proteins.

Stress proteins are usually classified and referred to by molecular weight, which is determined by migration on gels (or nucleic acid sequence analysis) (Locke, 1997). The nomenclature is somewhat confusing. Most studies refer to these as heat shock proteins (HSP) because they were first identified after heat stress in drosophila (Kilgore et al., 1998). However, because they are synthesized in response to many stresses, they are also known as stress proteins (SP). Those associated or examined in response to exercise damage are HSP 27, HSP 72/73 (generally referred to as HSP 70), and ubiquitin.

Of HSP 72/73, HSP 72 is the inducible isoform and can be rapidly transcribed because it lacks intervening sequences in HSP 73 gene (Locke, 1997). HSP 72/73 is involved in protein synthesis, folding, transport, disassembly, degradation, denaturation, and restoring function of damaged proteins. After exercise damage, they may play a role in the restoration of damaged proteins and target proteins for lysosomal import and degradation (Kilgore et al., 1998). HSP 27 is less universally conserved, has a slower response to stress, and lasts longer (Locke, 1997). The exact function is not known, but they are considered to be involved in growth, differentiation, signaling pathways, and actin polymerization at the cell membrane (Locke, 1997).

Free ubiquitin is found constitutively in nonstressed cells and can form complexes with abnormal proteins, "tagging" them for degradation. Greater amounts of ubiquitin are found in slow-twitch fibers, and a high density of conjugated ubiquitin is found at the Z-discs (Riley et al., 1992). The ubiquitin-proteasome system, of which stress proteins are an important component, is the major system in muscle for identifying and degrading damaged/denatured proteins (Attaix et al., 1998). In this system, targeted proteins are covalently attached to polyubiquitin chains; the complex is then recognized and degraded by the 26S proteasome complex (Attaix et al., 1998).

Few studies have investigated the role of stress proteins in exercise-induced muscle damage and repair. Reichsmann et al. (1991) took biopsies of human subjects 2 days after one-arm eccentric exercise with the other arm serving as a control. The exercise produced indirect evidence of muscle damage, such as soreness and decreased range of motion. Analyzing the samples on SDS gels, Reichsmann et al. found increases in several protein bands, including two at about 33 and 76 kD. They suggested these could be stress proteins which may be involved in the damage/repair process of muscle. In a follow-up study from the same laboratory, Thompson et al. (unpublished data) used antibodies for SP-72/73 and SP-27 on biopsy samples after the eccentric exercise protocol of Reichsmann et al. and found...
a 67% higher level of SP 72/73 and a 49% higher level of SP 27 in the exercised compared with the control arm at 2 days postexercise. However, the response among the 8 subjects was variable.

Using the same exercise protocol and some of the same tissue as the studies cited above, Thompson and Scordilis (1994) performed SDS gel electrophoresis and immunoblotting of whole muscle extracts to assess free and conjugated ubiquitin levels. Compared with the control arm, the average increase for ubiquitin was 64% on SDS gels. There was a 55% increase in free ubiquitin and a 62.5% increase in conjugated ubiquitin from immunoblotting. This study also observed a considerable intersubject variability in the response. The large intersubject variability in the stress protein response in humans is not unexpected, since biopsy samples yield but a small fraction of the whole muscle and are composed of mixed fiber types which differ in the amount of stress proteins and probably in their response to exercise (Hernando and Manso, 1997; Neufer et al., 1996).

In the above cited studies, no direct evidence of muscle damage was assessed, so it is difficult to know whether the response was due to the damage or to other stresses induced by exercise. However, in a controlled study of eccentrically exercised mouse muscle, Ingalls et al. (1998a) found that HSP 72 began to increase in muscle at 6 hrs postinjury, peaked 1 to 5 days postinjury, then declined over the next 9 days. The increase in HSP occurred in the same time period that the content of myosin heavy chain and actin declined. The time frame is also consistent with the results of Lowe et al. (1995), who found that the rate of protein degradation gradually increased in the same time period. Ingalls et al. (1998a) suggested that damaged proteins and/or an elevation of intracellular Ca++ may serve to induce the HSP response.

There appears to be an increase in stress proteins in the days after damage-inducing exercise. Studies that used nondamaging types of exercise have reported a more rapid and short-lived HSP response compared with eccentric exercise. Puntschat et al. (1996) found that HSP-70 protein content and mRNA increased shortly after 30 minutes of level treadmill exercise and appeared to be subsiding by 3 hours postexercise. Also, Salo et al. (1991) found that HSP-70 mRNA increased in muscles after treadmill running, with the peak increase 30 to 60 min after exercise and returning to baseline by 6 hours postexercise. These short-duration stress protein responses may be due to factors induced by exercise other than damage (e.g., temperature). Also, it is important to note that HSP mRNA typically have a shorter half-life than HSPs. Long-lasting alterations (over days) in cellular responses and muscle function are more characteristic of exercise damage.

**Effects of Damage on Muscle Function**

Several studies have reported a prolonged loss in the ability of eccentrically exercised muscle to generate force (Brown et al., 1996; Child et al., 1998; Clarkson et al., 1992; Howell et al., 1993; Jones et al., 1986; MacIntryre et al., 1996; Newham et al., 1983b). There is also an increase in stiffness of the damaged muscle (Chleboun et al., 1995; 1998; Howell et al., 1993). These changes may be due to alterations in excitation-contraction coupling and crossbridge formation/function. Other disturbances have been noted in cellular metabolism of exercise-damaged muscle such that substrates and metabolites cannot be transported effectively.
DYSFUNCTION IN TRANSPORTER PROTEINS

Sarcolemmal transport proteins and the process of transport appears to be impaired after eccentric exercise. A marked decrease in muscle content of glucose transporter proteins (GLUT-4) has been found in exercise-damaged rats (Asp et al., 1995b) and humans (Asp et al., 1995a). Kristiansen et al. (1996) investigated whether the increase in glucose transport during exercise was also affected by eccentric exercise in rats, and there appeared to be a reduction in glucose transport. Further study revealed a decrease in GLUT-4 transcription rate and a decrease in mRNA for glucose transporters at 48 hours post-eccentric exercise (Kristiansen et al., 1997).

It is possible that the dysfunction in glucose transport can explain why glycogen resynthesis is impaired after eccentric exercise (Costill et al., 1990; O’Reilly et al., 1987). Asp et al. (1995a, 1996) found a significant decrease in both muscle glycogen and GLUT-4 concentration at 24 and 48 hours after eccentric exercise in human subjects, suggesting that low glycogen concentration could be the result of an inability to transport glucose into muscle cells.

Pilgaard and Asp (1998) examined the effects of eccentric exercise on skeletal muscle lactate/H⁺ transport in rats. Lactate/H⁺ carriers are membrane transport systems that mediate lactate flux and H⁺ transport. In measures taken 2 days postexercise, it was found that eccentric exercise reduced sarcolemmal lactate/H⁺ transport capacity. This inability to buffer H⁺ ions would impair muscle pH regulation and cellular function.

MUSCLE STRENGTH

High force eccentric exercise results in a prolonged loss in muscle strength, such that immediately after exercise we find strength losses of 50 to 60% and strength is not fully restored until 10 or more days later (Clarkson et al., 1992). Soreness itself is unlikely result in a reduced ability to generate force, since strength is already markedly reduced immediately following eccentric exercise before soreness is perceived, and strength loss persists long after the soreness diminishes. Moreover, in animal models, stimulated muscle contractions also exhibit declines in ability to generate force after eccentric exercise.

Ultrastructural damage worsens in the 2 to 3 days postexercise as strength is being restored, thus ultrastructural damage is not the only factor explaining strength loss. Hesselink and colleagues (1996) reported only a weak relationship between the loss in isometric torque after forced lengthening contractions of rat muscle and damage determined from histological analysis. More recently, Ingalls et al. (1998a) found that decreased contractile protein content of muscle was not related to the initial decline in isometric tetanic force (P₀) after lengthening contractions in mice, but did account for 58% of the P₀ at 5 days postexercise and for all of the decline in P₀ from 14 to 28 days postexercise. Ingalls et al. suggested that force production immediately after muscle injury may be due to problems with force-transmitting proteins and/or the excitation-contraction coupling process, and that the long-lasting force decrements could be due to decreases in contractile proteins.

Brown et al. (1996) examined muscle contractile function for up to 9 days following electrically-induced eccentric exercise. Immediately postexercise and again 3 days later, Brown et al. observed a delay between the start of muscle stimu-
lation to the onset of contraction. Results of a study on rat muscle by Warren et al. (1993b) suggested there was a failure of excitation-contraction coupling after eccentric contractions. Warren et al. found that force loss due to eccentric contractions could be recovered by using caffeine to potentiate Ca\textsuperscript{2+} release from the SR. In a recent article from the same laboratory (Ingalls et al., 1998b), studies of mouse muscle after eccentric contractions showed that excitation-contraction failure could explain 57 to 75\% of the decrements in P\textsubscript{o}, from 0 to 5 days postexercise.

Eccentric exercise also produces long-lasting, low frequency fatigue, an impairment in the ability to generate force when stimulated at low frequencies (Jones, 1996; Newham et al., 1983b; Sargeant and Dolan, 1987). Westerblad et al. (1993) suggested that low frequency fatigue was caused by a reduction in Ca\textsuperscript{2+} release from the SR due to structural damage to proteins involved in excitation-contraction coupling. Essig and Nosek (1997) proposed that low frequency fatigue could result from increases in ROS that cause damage to proteins in the SR-Ca\textsuperscript{2+} release mechanism. Failure of tetanic Ca\textsuperscript{2+} release has been demonstrated in stretched, tetanically-stimulated single mouse muscle fibers (Balnave et al., 1997).

A change in the length-tension relationship has also been reported after eccentric exercise (Jones et al., 1997; Saxton and Donnelly, 1996) which may contribute to strength loss. Saxton and Donnelly (1996) found that the greatest decline in ability of the elbow flexors to generate force after eccentric exercise was at the shortest muscle length (most acute elbow angle) that was tested. They suggested that the disproportionate loss of strength at shorter muscle lengths may be due to an overstretching of sarcomeres from the lengthening actions. This would imply a smaller number of crossbridges formed between the contractile proteins to generate force. Morgan (1990) suggested that repeated active lengthening would overstretch weaker sarcomeres which may not fully return to their normal configuration upon relaxation, and Jones (1996) hypothesized that eccentric exercise results in damage to sarcomeres in the middle section of the fiber from overextension of the end sarcomeres.

**MUSCLE STIFFNESS**

Howell et al. (1993) examined forces required to passively extend the arm (taken as a measure of stiffness) after eccentric exercise. Stiffness increased immediately after exercise and remained elevated for about 4 days. Chleboun et al. (1995) applied intermittent pneumatic compression to subjects who had performed eccentric exercise and found that immediately after treatment, both swelling and stiffness were reduced, although the effect was only temporary. These results might suggest that stiffness and swelling were closely related. However, in a more recent study from the same laboratory, Chleboun et al. (1998) found that muscle volume continued to increase after exercise and peaked on Day 4, while stiffness increased immediately after exercise and remained at about the same level over the 4 days. Thus, swelling and stiffness are not directly related.

In studies of animal muscle, Benz et al. (1998) estimated the relative number of attached crossbridges by measuring instantaneous stiffness during an isometric contraction immediately prior to an eccentric stretch of soleus muscle. There was only a 30\% decrease in muscle stiffness, but isometric force prior to stretch decreased by 85\% over the 30-min eccentric exercise. These data indicate a dra-
matic decrease in the number of crossbridges entering the force-generating state. In other words, the crossbridges form but the myosin heads do not produce the "power stroke." Benz et al. suggested that the benefit of crossbridge formation would be that the muscle could serve a "braking" role to resist stretch and possibly prevent further injury. Whether increases in the number of formed crossbridges (without generating a power stroke) continues in the days following eccentric exercise is not known, but if so, this would explain the stiffness observed at these time points.

Summary

It is likely that no one mechanism is solely responsible for the observed muscle damage following eccentric exercise. Several processes may be acting together with damage being initiated by several factors (strain, reperfusion injury) and exacerbated by others (Ca$^{++}$ accumulation, phagocytic infiltration, increases in ROS). It is not known whether or how exacerbation of damage in the days following exercise is related to remodeling and repair of muscle. Preliminary research on the role of stress proteins in the repair process provides some insight into the removal of denatured, damaged proteins from the fiber. Further research is needed to determine how these mechanisms may interact in the damage/repair process to result in impairment and then restoration of muscle function following exercise-induced muscle damage.

References


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