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Review Article

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Effect of Prior Muscle Contraction or Passive Stretching on Eccentric-Induced Muscle Damage

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| Abstract |

Purpose: This tutorial review investigated the effect of prior fatigue and passive stretches on eccentric contraction-induced muscle injuries, as well as the underlying mechanisms of eccentric contraction-related injuries.

Methods: Contraction-induced muscle damage is the most common disabling problem in sports and routines. The mechanisms underlying the pathology and prevention of muscle damage lessened by prior fatigue or stretches are critical in assessing musculoskeletal injuries. Even though there are treatments to reduce eccentric contraction-induced muscle injuries, fatigue negatively influences them. Therefore, we reviewed previous studies on eccentric contraction-induced muscle injuries with prior treatments using the MEDLINE and PubMed databases.

Results: Prior passive stretching had a preventative and therapeutic effect, but prior lengthening contractions did not. On the other hand, prior isometric contractions involving relatively small forces may not provide a sufficient stimulus to induce protection. As a result, high force isometric contractions may be necessary. The studies supported the positive effects of prior fatigue, concluding that it was a factor in determining the amount of damage caused by eccentric exercise. This was due to a reduction in force and increased temperature. Studies that did not support the positive effects of prior fatigue concluded that a shift in optimal length to a longer length and reduced energy absorption during lengthening are evidence that fatigue is not related to muscle injuries induced by lengthening.

Conclusion: The variability of the experiment models, conditions, muscles, and treatment methods make it necessary to interpret the conditions of previous studies carefully and draw conclusions without making direct comparisons. Thus, additional studies should be carefully conducted to investigate the positive effect of fatigue on lengthening.

Key Words: Muscle injury, Eccentric contraction, Muscle fatigue, Passive stretch

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Ⅰ. Introduction

Activities such as lowering heavy objects, downhill running, and landing from a jump, all require skeletal muscle to act as brakes or shock absorbers. Under these conditions, the active muscle must absorb work as it is lengthened, instead of performing work by shortening (Morgan & Proske, 2004). These, lengthening, eccentric, or plyometric contractions result in greater muscle injury than isometric and shortening contractions (Golden & Dudley, 1992; Jones et al., 1989; Komi & Viitasalo, 1977; McCully & Faulkner, 1985; Newham et al., 1983a, 1983b). Eccentric-induced muscle injuries are the most common disabling problems seen in sports. Therefore, numerous studies have examined the mechanisms underlying the pathology and prevention of muscle damage induced by eccentric contractions. However, the exact mechanisms of eccentric induced muscle injury are still beyond our knowledge.

Several applicable methods to reduce injury have been proposed, such as previous lengthening exercise, passive stretching, muscle fatigue, and isometric contraction. Among proposed methods, prior lengthening contraction showed a solid prevention and a long lasting adaptation even after several months, so it has been referred to as the repeated bout effect (Newham et al., 1987; Nosaka & Clarkson, 1995). Prior passive stretching also showed a protective effect on eccentric-induced muscle injury (Johansson et al., 1999; McHugh & Nesse, 2008). Although a protection effect has been shown with prior isometric contractions (Clarkson et al., 1986), it appears to be less effective than the other methods described. Lastly, current data on the effect of prior fatigue on eccentric-induced muscle damage is still contradictory in terms of the protective effect, even though sports medicine personnel widely agree that fatigue may lessen damage (Choi & Widrick, 2009; Evans et al., 2002; Gleeson et al., 2003; Woods et al., 2007). Therefore, the purpose of this review is to provide informative insight into the effect of prior fatigue on eccentric-induced muscle injury, as well as the underlying mechanisms of eccentric related injury.

Ⅱ. Prior contraction following contraction-induced muscle damage

1. Mechanisms of eccentric-induced muscle injury

1) Impaired excitation-contraction coupling

Reduced Ca^{2+} release from sarcoplasmic reticulum (SR) is an obvious phenomenon following the initial event of eccentric-induced injury (Warren et al., 2001). Impaired excitation-contraction (EC) coupling can be bypassed by using an *in vitro* single-fiber experiment. Under this condition, maximal Ca^{2+}-activated force in injured muscle fibers reduced by 34%, while maximal isometric force of the whole intact muscle was reduced by 69%. Therefore, under the assumption that there are two major factors of eccentric related injury; disrupted muscle ultrastructure and EC coupling failure, physical disruption of muscle ultrastructure may explain half of the strength loss of the whole intact muscle. However, another study showed Ca^{2+}-activated force was not significantly affected after 10 eccentric contractions with 25% strain (Balnave & Allen, 1995). Thus, physical disruption of muscle ultrastructure regards as an unreliable mechanism to explain eccentric-induced muscle injury, because Ca^{2+}-activated force after standardized eccentric contractions showed wide ranges of variance with limited data. Also, Ca^{2+}-activated forces is underestimated because single fiber preparation removes the potential for

lateral force transmission to neighboring fibers, and eliminates a mean for bypassing lesions within a fiber. Accordingly, Warren et al. (2001) suggested an impaired EC coupling as a major role in contraction-induced muscle injury system. The failure of EC coupling has been demonstrated after eccentric exercise, and it results in the loss of maximal Ca^{2+} activated force. It suggests that less calcium is released per action potential because of a damaged EC coupling system. Furthermore, the caffeine-elicited force of the eccentric contraction in injured mouse soleus muscles was not different from the normal muscle, even though injured muscle maximal isometric tetanic force was reduced by 43%. Since caffeine acts to increase free cytosolic Ca^{2+} concentration by promoting directly release of Ca^{2+} from SR (Endo, 1977; Martonosi, 1984), EC coupling failure is thought to account for about 60～75% of force drop, and disrupted muscle ultrastructure is thought to account for about 25～40% of force drop during first 5 days after injury.

2) Physical disruption of muscle ultrastructure

However, impaired EC coupling system could not readily explain two significant characteristics of eccentric-induced muscle injury, a shift in the length-tension relationship of the muscle, and increased passive tension after eccentric induced muscle damage. As a main mechanism of eccentric-induce muscle, "popping sarcomere hypothesis" proposed in term of the disruption or alteration of the force-generating and transmitting structures in muscle ultrastructure (Morgan & Proske, 2004).

The popping sarcomere theory starts with the presence of an irregular sarcomere length within single muscle fiber, which results in eccentric-induced muscle damage, because the longest sarcomere and/or weakest sarcomere is beyond the optimal length or on the descending limb of the length-tension relationship. It is supposed to stretch more rapidly and widely than other sarcomeres which are within their optimal length, due to length-tension relationship. As a consequence, weaker sarcomeres absorb most of the stretch, and if stretch occurs continually, more and more sarcomeres will become overstretched. This overstretched sarcomere may not re-interdigitate when the muscle relaxes. Thus, once one or more sarcomere have become disrupted, the damage may spread longitudinally to adjacent sarcomeres in the myofibril and transversely to adjacent myofibrils. This disrupted sarcomere will cause the structural distortions which involve membrane damage, including membranes of the sarcoplasmic reticulum, transverse tubules and sarcolemma (Morgan & Proske, 2004). This is accompanied by the uncontrolled movement of Ca^{2+} into the sarcoplasm, triggering the next stage in the damage process. Therefore, the disruption of muscle ultrastructure precedes EC coupling failure, and it is the main factor leading to reduced functional properties after eccentric contraction. In detail, disrupted sarcomeres result in tearing of the t-tubule first, this stage of damage can be reversible with caffeine exposure, and then followed by damage of sarcoplasmic reticulum which result in uncontrolled release and uptake of Ca^{2+}. This uncontrolled Ca^{2+} released into the sarcoplasm, may activate the contractile filaments to develop an injury contraction, thus it causes rising passive tension.

The proposed mechanism for a shift in muscle optimal length is due to the disrupted sarcomeres, which lie scattered at random along the myofibril. The presence of these non-contracting sarcomeres with still contracting sarcomeres increases the series compliance of the fiber, and the increased series compliance leads to a shift of the muscle's optimal length for maximal isometric force(Po) in the direction of longer muscle lengths (Morgan & Proske, 2006)..

2. Mechanism of muscle fatigue

Eccentric-induced muscle injury resembles muscle fatigue in several characteristics, such as a decline in force, shortening velocity, and muscle power (Fitts, 1994). The difference between muscle fatigue and damage is whether muscle function is able to recover within a short period of time. In other words, muscle fatigue is a generally short-lived dysfunction, whereas muscle damage is a prolonged dysfunction that needs several days for complete recovery (Hough, 1900). Although the exact mechanism of fatigue is not totally understood, there are several possible mechanisms; impaired excitation-contraction coupling, malfunction of cross-bridge, central fatigue, and metabolic energy supply.

Generally, fatigue refers to a decline in muscle performance related with muscle activity (Allen et al., 2008). Muscle fatigue is thought to be related to phosphocreatine (PCr) depletion, and the accumulation of metabolic end products. In detail, intense exercise induces high rates of adenosine tri-phosphate (ATP) hydrolysis and glycolysis and corresponding increases in cell H^+, inorganic phosphate (Pi), and adenosine di-phosphate (ADP). The increased H^+ lead to lower pH (7.0, 6.2) and it reduces the number of high-force cross-bridges in fast twitch fibers, and the force per cross-bridge in both fast and slow fibers. The former is thought to involve a direct inhibition of the forward rate constant for transition to the strong cross-bridge state. This depressive effect of low pH on peak force is due to not only H^+ inhibition of Ca^{2+} binding to troponin, but also the direct effect of H^+ on the actomyosin cross-bridge. Increased inorganic phosphate (30mM) is thought to reduce Po by accelerating the reversal step from a strong binding stage to a weak binding stage in maximally activated skinned fibers. Both pH and Pi decrease myofibrillar Ca^{2+} sensitivity. This effect is particularly important as the amplitude of the Ca^{2+} transient falls with fatigue. Increased ADP would increase force but slow velocity because with ADP rich condition, ATP can be regenerated by myokinase; $2ADP \leftrightarrow ATP + AMP$.

Another mechanism of muscle fatigue is that impairment of calcium release from the sarcoplasmic reticulum (SR) leads to a decline in muscle performance (Eberstein & Sandow, 1963). This is based on caffeine and high extracellular K^+ and they are promoting agents of Ca^{2+} from the SR. It could partly overcome the reduced force after fatigued. The application of caffeine to a fatigued muscle overcomes much of the force decline and it is associated with a substantial increase in the tetanic Ca^{2+} signal. This provides strong evidence that the impairment of SR Ca^{2+} release is the main factor of the final phase of fatigue.

3. Effect of prior passive stretches and isometric contraction following eccentric-induced muscle injury

Even though prior passive stretches and isometric contractions differ from muscle fatigue, there are some common factors, thus it may reinforce our insight by taking a different view of muscle damage mechanism. To examine not only the effect of prior passive stretches and isometric contraction, and also whether muscle degradation and regeneration induced by lengthening contractions are required for a protective effect against eccentric-induced muscle damage, 51 mice were divided into three groups which performed 75 lengthening contractions, isometric contractions, or passive stretches as a pre-interventions, respectively. After 2 weeks of pre-intervention, 75 lengthening contractions were treated as an main-intervention for induce muscle damage to all three groups (Koh & Brooks, 2001). All intervention and treatment protocols involved 75 repetitions performed at

0.25Hz for total exercise duration of 5 min (every 4 seconds). Lengthening contractions and passive stretches were initiated at optimal muscle length (Lo) and were stretched 20% at a velocity of 1 Lf/s. Also, histological evaluation was used to analyze injured fiber area.

Three day after the pre-intervention (75 lengthening contractions group), it resulted in a force deficit of about 55%, whereas isometric contractions group and passive stretch group resulted in no difference from initial values. Two weeks later after the applied treatment protocol (main-intervention), previously lengthened muscle resulted in a force deficit of about 19% and an injured fiber area of 5% which was smaller than the initial bout of lengthening contractions. Whereas the muscles which previously stimulated by 75 isometric contraction, resulted in a force deficit of 35% and an injured fiber area of 12% and passively stretched muscle resulted in force deficit of 36% and an injured fiber area of 10%. In other word, previous isometric and passive stretch provides a protective effect on eccentric-induced muscle damage, even though the protection was less than by lengthening contractions. Consequently, muscle degradation and regeneration induced by lengthening contractions is not required to induce protective effect on eccentric-induced muscle damage. As a potential mechanism, they proposed the up-regulated cytoskeletal protein network, such as desmin, talin, vinculin, and dystrophin could help to stabilize sarcomeres during lengthening contractions and thus protect muscle fibers from injury. However, it is revealed that the inflammatory cells, especially neutrophil are somewhat related to lengthening-induced muscle damage, thus neutrophil concentrations may be one factor to examine the mechanism of prior fatigue on lengthening related muscle damage (Pizza et al., 2001).

In summary, prior passive stretch has a preventative and therapeutic effect, but prior lengthening contractions did not. On the other hand, prior isometric contractions involving relatively small forces may not provide a sufficient stimulus to induce protection, high force isometric contractions may be necessary. Proposed mechanisms included increased strength of the cytoskeletal protein networks, such as desmin, talin, vinculin, dystrophin, that surrounds sarcomeres and transmits tension through the membrane. Also, inflammatory cells may be able to potential dependent variable, even though inflammatory cell was not perfectly consisted with damage evidence.

4. Effect of Prior Fatigue on Eccentric related Muscle Injury

Since muscle fatigue is a factor determining the amount of damage from eccentric exercise (McCully & Faulkner, 1986), there was several study to examine the effect of prior fatigue. However, consensus were not consistent, and still contradictory. For example, a number of studies report that fatigued muscle is more susceptible, and does not have any effect, (Friden & Lieber, 1992; Mair et al., 1996; Morgan et al., 2004) and reversely a few studies report fatigued muscle (McCully & Faulkner, 1986; Nosaka & Clarkson, 1997) is more resistible to eccentric-induced muscle damage.

1) Protection effect of prior muscle fatigue following eccentric-induced muscle damage

To define the extent of injury following eccentric contractions, various conditions were experimented, such as different duration of lengthening contraction, different force development by using fatiguing, lower frequency, and decreased lengthening of optimal length (McCully & Faulkner, 1986). In detail, mouse EDL muscles were stimulated *in situ* at 150Hz and lengthened up to 20% of optimal fiber length with different lengthening velocity;

0.2, 0.5, and 1.0 Lf/s (optimal length per second) and different stimulation duration; 0.5, 1, 2.5, 5 or 15 minute. Also, peak force during eccentric contraction with 1.0 Lf/s was decreased by 3 different methods; fatiguing by 3 minute isometric contractions with 150Hz and 500 ms at every 2 second, lower frequency between 70~100Hz, and less lengthening about 10% of Lo instead of 20%. The injury was assessed 3 days after lengthening contractions by histochemistry and maximal isometric force (Po). The left mouse EDL muscle was used for the experimental intervention and the right EDL muscle was used for the normal control or passive eccentric control. Each protocol of lengthening contraction resulted in a significant decrease in Po, and it tended to be increased with duration up to 5 min. After 5 min there was no significant decrease in force between three different velocities up to 15 min and 3 day after. However, at 1.0 Lf/s velocity with 0.5 or 1 min stimulus duration, Po was significantly decreased at 3 days after. Also muscle lengthened at 0.5 and 1.0 Lf/s showed histological injured area, but muscle lengthened at 0.2 Lf/s did not show histological injured area. The effect of force development on eccentric induced injury revealed that previous fatigue caused only 1.3% injured muscle sectioning area, whereas muscle, stimulated by lower frequency and less lengthened muscle showed about 15% and 14% respectively. Therefore, the extent of muscle injury induced by lengthening contraction was related to the peak force during the eccentric contractions. Thus, previous fatigue, which results in a decrease of the peak force during eccentric contraction, has a protective effect against eccentric-induced injury.

Another study agree with the protection effect of prior muscle fatigue on eccentric related muscle damage (Nosaka & Clarkson, 1997). To test whether prior concentric exercise exacerbated eccentric-induced muscle damage, 9 female students who had no experience of any resistance training were performed 12 maximal eccentric contractions of the elbow flexors with one arm (ECC). Two weeks later, subject performed 100 repetitions of isokinetic concentric contractions of the elbow flexors at an angular velocity of 1.05 rad/s-1 between every 10 sec to fatigue the muscle (CON-ECC). Maximal isometric force, range of motion, upper arm circumference, muscle soreness, and plasma creatinekinase were measured up to 5 days after to evaluate the degree of eccentric induced muscle damage. The average torque was decreased 60% through 100 repetitions of isokinetic concentric contractions. The decline in isometric force, from pre to post, showed similar patterns for the two groups, which was decreased 36% for ECC and 43% for CON-ECC group respectively. However, the recovery pattern from day1 to day5 was significantly faster for the CON-ECC group than the ECC only group. Especially, at day 1, and at day 5 the ECC group recovered about 78% whereas CON-ECC group recovered about 93%. Also, a lower level of muscle soreness, a smaller decrease in ROM and a smaller increase in upper arm circumference and CK level were found in CON-ECC group. Therefore, the previous concentric exercise seems to attenuate the eccentric induced muscle damage. Additionally, 5 subject (N=5) exercised their elbow from extended to a flexed position by generating minimal force to move the lever arm of the isokinetic machine as a 'warm-up'. As a result, there was no indication of fatigue during the 'warm-up' exercise, and Po between pre and post was not diff. Thus, even light warm-up exercise before the eccentric exercise also attenuated eccentric induced muscle damage and as a mechanism, the increased muscle temperature was suggested by passive warm-up.

We need to note that the assumption "CK activity level is somehow related to the magnitude of muscle injury" has not been explicitly tested. The study (Friden & Liber, 2001) revealed that there is no significant correlation

between CK activity and torque with the regression relationship (only 8% explained). So, it is relatively poor because a muscle fiber's permeability to intramuscular enzymes may or may not be correlated with cellular contractile function. Furthermore, the comparison between right arm and left arm could be a potential problem because, everyone has a preferred arm, and thus each arm may have a different response.

2) No protection effect of prior muscle fatigue following eccentric-induced muscle damage

It was proved that prior muscle fatigue did not affect to the eccentric-induced muscle injury by a handful of studies (Mair et al., 1996; Morgan et al., 2004). Before go through the study, it need to be defined the relationship between muscle's energy absorption and muscle damage. Absorbed energy was defined as the force to failure, which is the peak force achieved by the muscle when it is stretched (Mair et al., 1996). In other words, if the muscle force is higher when the muscle is stretched, more energy is absorbed. Therefore, it can withstand a higher load with less stretch than when muscle produces lower forces under stretch. Thus, the higher absorbed energy can reduce eccentric-induced muscle damage (Mair et al., 1996). Based on the assumption, the role of prior fatigue on acute muscle strain *in situ* was tested by using a rabbit model. The EDL muscle was assigned to one of three strain protocols; 1, 10 or 50cm/s, and all muscle were fatigue by two different protocols, control and fatigue. Muscle fatigue was induced by isometric contraction which consisted of 5sec stimulation and 1 sec rest, drop up to a predetermined level of Po (25% of 50% of Po). The control protocol was also fatigued in the same manner, but allowed to recover until the Po had been restored. Fatigued muscle showed significantly lower energy absorption when the muscle was pulled at a lower rate of stretch. Also, it revealed the different ability to absorb energy in the early part of muscle stretching. Fatigued muscle absorbed 42% more energy during the first 70% of the stretch, and only 6% more during the last 30% of the stretch. Therefore, fatigued muscle was more susceptible to eccentric contraction, because fatigue decreased the ability of muscle to absorb energy before force failure. However, the comparison between fatigued muscle and control muscle recovered from fatigue, could not answer what the role of prior fatigue on eccentric contraction is. That is, there was no true control group which should be treated by only eccentric contraction without fatigue and recovery.

Optimal length of muscle refer to optimal resting length for producing the maximal force, generally about 2.1～2.2μm long per each sarcomere (Chang et al., 1999). To investigate whether a shift of optimal length (Lo) followed by eccentric contraction was exclusively induced by eccentric contraction or if it can be induced by concentric contraction because the shift in Lo indicates muscle damage marker (Morgan et al., 2004). In addition, it was examined whether prior fatigue, induced by concentric contraction, can reduce the susceptibility of the eccentric-induced muscle damage. Therefore, if fatigue does not increase Lo and eccentric contractions with prior fatigue protocol does increase Lo, it can be interpreted that prior fatigue does not affect eccentric-induced damage. Four male and female cats were sacrificed, and each of their gastrocnemius muscles were subdivided into three portions. For each part of the muscle, the length-tension relation, rate of rise of tension, and force during shortening contraction were measured before and after 3 different treatment; 10 eccentric contractions only (damage group), 200 concentric contractions only (fatigue group), and both 200 concentric and 10 eccentric contractions (FD group). The fatigue group resulted in a decline of 37% of isometric force without significant

Lo change. The FD group resulted in the decline in about 50% of Po with a significantly increased Lo of 11%, which not significantly different from damage group. Therefore, eccentric-induced muscle damage is not affected by muscle fatigue, because the shift of Lo occurs in both groups. The force during shortening contraction was measured to test hypothesis that the damage and FD group would be able to sustain less force during shortening than the control group. As predicted, it resulted in the force was decreased more in the damage and FD groups than control group. Also the rising rate of isometric force was significantly lower in the damage and FD groups compared to the control and fatigue groups. Interestingly, these two papers, which do not agree with the fatigue effect on lengthening related to muscle injury, did not directly measure typical muscle functions, such as Po, Vmax or Power, and also did not give an enough recovery time.

Ⅲ. Conclusion

Lengthening contraction is closely connected with our life not only in sports situations but also in our routine life, because people tend to prefer a lengthening movement, such as downhill walking or running or lowering object, instead of shortening movement, uphill, raising object. Therefore, lengthening-induced muscle injury is also closely connected with our life quality. Typical functional consequences of lengthening contractions are reduction in peak power, loss in peak force, slowing of shortening velocity, and shift in optimal length to a longer length. The main possible mechanisms of lengthening-induce muscle damage could be divided into two factors; one factor is structural disruption of muscle ultrastructure, for example, Z-dick and sarcolemma membrane, and another factor is EC coupling impairment related with Ca^{2+} release and uptake. These two factors seem to be main sources of lengthening related muscle injury and these two factors seems to be complimentary interact each other.

As a preventive and therapeutic intervention, prior lengthening, isometric contractions, and passive stretches were tested. When an identical lengthening contraction was given before muscle injury, it is commonly observed that muscle damage are relieved. The proposed mechanisms of a protective effect by prior lengthening contraction are the increased in the number of sarcomeres in series in muscle fibers, because increases in sarcomere number would decrease sarcomere extension during lengthening contraction.

Even though it is widely accepted that prior muscle fatigue relive the muscle injury by lengthening contraction, the mechanism of prior muscle fatigue is not consistent (Friden & Lieber, 1992; Mair et al., 1996; McCully & Faulkner, 1986; Morgan et al., 2004; Nosaka & Clarkson, 1997). The studies support the protective effect of prior fatigue, concluding that muscle fatigue is a factor determining the amount of damage due to reduction in force, and increased temperature. The studies, which do not support the protective effect of prior fatigue, concluded that a stretched optimal length, and reduced energy absorption during lengthening are evidence that fatigue is not related to lengthen-induced muscle injury. The pro studies do not have strong mechanisms, and the con studies do not directly measure muscle functional properties. Furthermore, there was not an adequate recovery period followed by lengthening contraction. It is because of variability of following; experiment models (cat, rabbit, mouse, rat, human); experiment conditions (*in vivo, in vitro, in situ*); experiment muscles (gastrocnemius, soleus, extensor digitorum longus, and/or muscle group); experiment treatments (lengthening amount, velocity, method). Because these factors are

complexly tangled up, it is necessary to interpret the conditions of previous studies carefully, and draw conclusions, rather than draw conclusions through direct comparison. Therefore, further studies should be conducted to investigate the mechanism underlying the protective effect with precisely controlled and accurately designed experimental design which involved recovery periods.

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