Review

Recent advances in the understanding of the repeated bout effect: the protective effect against muscle damage from a single bout of eccentric exercise

Malachy P. McHugh

The Nicholas Institute of Sports Medicine and Athletic Trauma, Lenox Hill Hospital, New York, NY, USA
Corresponding author: Malachy McHugh, Director of Research, The Nicholas Institute of Sports Medicine and Athletic Trauma,
Lenox Hill Hospital, New York, NY, USA. E-mail: mchugh@nismat.org

The repeated bout effect refers to the adaptation whereby a single bout of eccentric exercise protects against muscle damage from subsequent eccentric bouts. While the mechanism for this adaptation is poorly understood there have been significant recent advances in the understanding of this phenomenon. The purpose of this review is to provide an update on previously proposed theories and address new theories that have been advanced. The potential adaptations have been categorized as neural, mechanical and cellular. There is some evidence to suggest that the repeated bout effect is associated with a shift toward greater recruitment of slow twitch motor units. However, the repeated bout effect has been demonstrated with electrically stimulated contractions, indicating that a peripheral, non-neural adaptation predominates. With respect to mechanical adaptations there is evidence that both dynamic and passive muscle stiffness increase with eccentric training but there are no studies on passive or dynamic stiffness adaptations to a single eccentric bout. The role of the cytoskeleton in regulating dynamic stiffness is a possible area for future research. With respect to cellular adaptations there is evidence of longitudinal addition of sarcomeres and adaptations in the inflammatory response following an initial bout of eccentric exercise. Addition of sarcomeres is thought to reduce sarcomere strain during eccentric contractions thereby avoiding sarcomere disruption. Inflammatory adaptations are thought to limit the proliferation of damage that typically occurs in the days following eccentric exercise. In conclusion, there have been significant advances in the understanding of the repeated bout effect, however, a unified theory explaining the mechanism or mechanisms for this protective adaptation remains elusive.

It has been well established that a single bout of unfamiliar, predominantly eccentric exercise causes symptoms of muscle damage such as strength loss, pain and muscle tenderness. It is equally well established that a repeated bout of the same, or similar eccentrically biased exercise results in markedly reduced symptoms of damage than the initial bout (for review see McHugh, Connolly, Eston, Kremenic, Gleim, 1999b). This protective adaptation to a single bout of eccentric exercise has been referred to as the repeated bout effect (Nosaka & Clarkson, 1995). The repeated bout effect has been demonstrated in both human and animal models. It has been shown to last several weeks, and possibly up to 6 months (Nosaka, Sakamoto, Newton, Sacco, 2001a). It is apparent that the initial bout of eccentric exercise does not have to cause appreciable damage in order to confer a protective adaptation (Clarkson & Tremblay, 1988; Brown, Child, Day, Donnelly, 1997; Nosaka, Sakamoto, Newton, Sacco, 2001b). In fact, as few as 10, six, or even two maximal eccentric contractions of the elbow flexors have been shown to confer a protective adaptation for a subsequent bout of 24 (Nosaka & Sakamoto, 2001b)

or 50 (Brown et al., 1997) maximal contractions. However, it appears that the contraction intensity must be close to maximum in the initial bout in order to confer a protective effect when the repeated bout involves high intensity contractions. Eight weeks of eccentric training at submaximal levels (50% of one repetition maximum) did not confer any protection for a subsequent bout of maximal eccentric exercise (Nosaka & Newton, 2002c). The repeated bout effect is specific to the exercised muscle groups, with no evidence of a cross-transfer to contralateral muscle groups not exposed to the initial bout (Clarkson, Byrnes, Gillisson, Harper, 1987; Connolly, Reed, McHugh, 2002). However, the muscle group does not have to be exercised in the same manner in both bouts in order to see a protective effect. Eston, Finney, Baker, Baltzopoulos (1996) demonstrated that 100 maximal eccentric isokinetic quadriceps contractions provided protection against quadriceps damage following a subsequent downhill run. Of note the protection was limited to the preconditioned quadriceps.

While the conditions required to induce a protective adaptation are fairly well understood the actual

mechanism for the repeated bout effect is not well understood. Several theories have been proposed to explain the repeated bout effect (for review see McHugh et al., 1999b). Since this initial review of the potential mechanisms to explain the repeated bout effect (McHugh et al., 1999a) numerous studies have added to the understanding of this phenomenon. The purpose of this current review is to: (1) summarize the current evidence for and against previously proposed theories; (2) describe any new theories that have been proposed; and (3) identify future areas of research. The various theories explaining the repeated bout effect are divided into three broad categories: neural adaptations (fig. 1), mechanical adaptations (fig. 2) and cellular adaptations (fig. 3). Understanding the mechanism or mechanisms for the repeated bout effect is important for sports medicine and science in so far as it represents one of the most basic adaptations of skeletal muscle to use. Furthermore, eccentric contractions and/or eccentrically biased exercises have been shown to be effective in reducing muscle strains (Holmich, Uhrskou, Ulnits et al., 1999; Tyler, Campbell, Nicholas, Donellan, McHugh, 2002), reversing muscle atrophy (Hortobagyi et al., 2000) and treating tendonopathies (Silbernagel, Thomee, Thomee, Karlsson, 2001). A greater understanding of the mechanisms involved in acute and chronic adaptations to eccentric exercise is necessary for refining interventions for injury prevention, injury treatment and strength training. Since the repeated bout effect represents the first adaptation to eccentric exercise, this review focuses on adaptations to a single bout of eccentric exercise.

Neural theory
Neural theory of muscle damage

It has been proposed that "eccentric contractions require unique activation strategies by the nervous system" (Enoka, 1996). Specifically, eccentric contractions require less motor unit activation for a given muscle force (Bigland & Lippold, 1954; Komi & Buskirk, 1972; Moritani, Muramatsu, Muro, 1988) and involve preferential recruitment of fast-twitch motor units (Nardone & Schieppati, 1988; Nardone, Romano, Schieppati, 1989; Howell, Fuglevand, Walsh, Bigland-Ritchie, 1995; Enoka, 1996; McHugh et al., 2002) when compared to concentric contractions. Moritani et al. (1988) proposed that muscle damage results from a high stress on a small number of active fibers during eccentric contractions. Fast-twitch fibers have been shown to be more susceptible to disruption with eccentric contractions (Fridén, Sjøstrøm, Ekblom, 1983b; Lieber & Fridén, 1991; MacPherson, Schork, Faulkner, 1996) and this may in part be explained by the preferential recruitment of fast-twitch motor units. It follows that a change in activation that reduces high fiber stresses could limit the subsequent myofibrillar disruption. Nosaka & Clarkson (1995) suggested that a neural adaptation "would better distribute the workload among fibers.

Evidence for a neural adaptation

Changes in motor unit activation between repeated bouts have been examined using surface electromyography (EMG) in humans (Warren, Hermann, Ingalls,
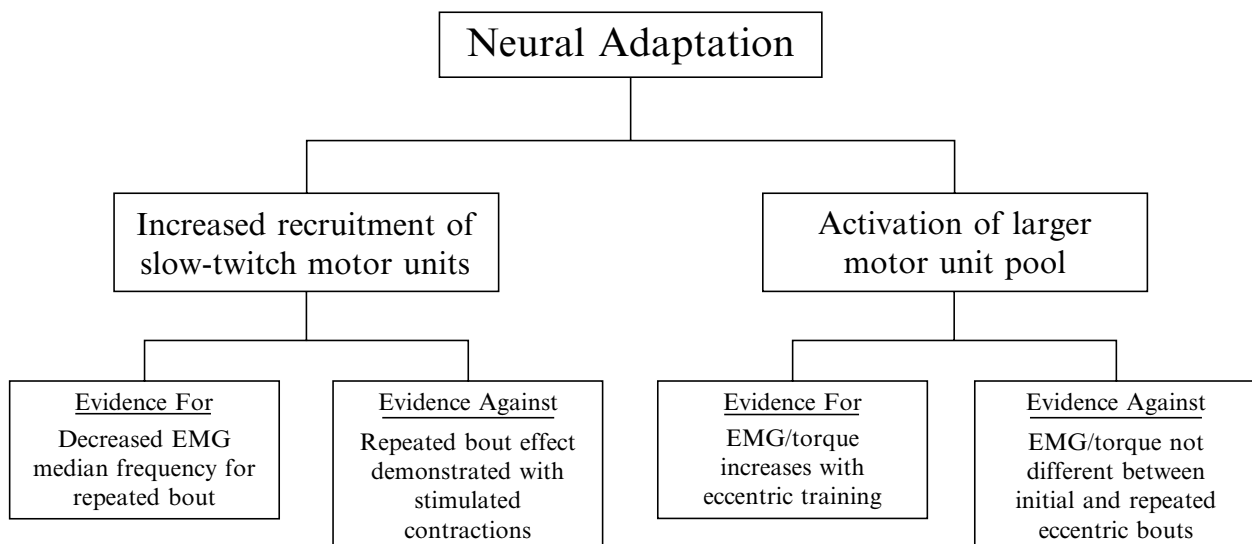

Fig. 1. Potential neural mechanisms for the repeated bout effect. EMG/torque refers to the amplitude of the EMG signal relative to torque production (See text for specific references related to evidence for and against the proposed theories).
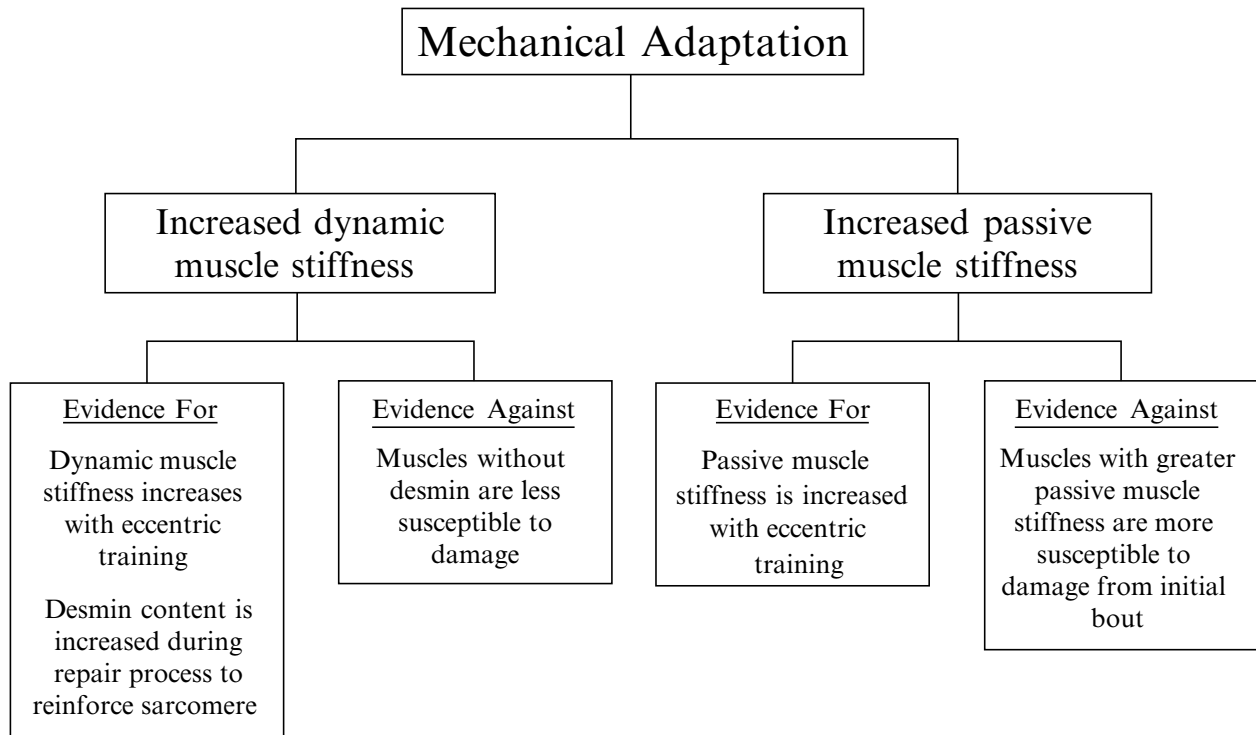
Mechanical Adaptation

Increased dynamic muscle stiffness

Evidence For

Dynamic muscle stiffness increases with eccentric training

Desmin content is increased during repair process to reinforce sarcomere

Evidence Against

Muscles without desmin are less susceptible to damage

Increased passive muscle stiffness

Evidence For

Passive muscle stiffness is increased with eccentric training

Evidence Against

Muscles with greater passive muscle stiffness are more susceptible to damage from initial bout

Fig. 2. Potential mechanical mechanisms for the repeated bout effect. Dynamic stiffness refers to the extensibility of active muscle while passive stiffness refers to the extensibility of relaxed muscle (See text for specific references related to evidence for and against the proposed theories).
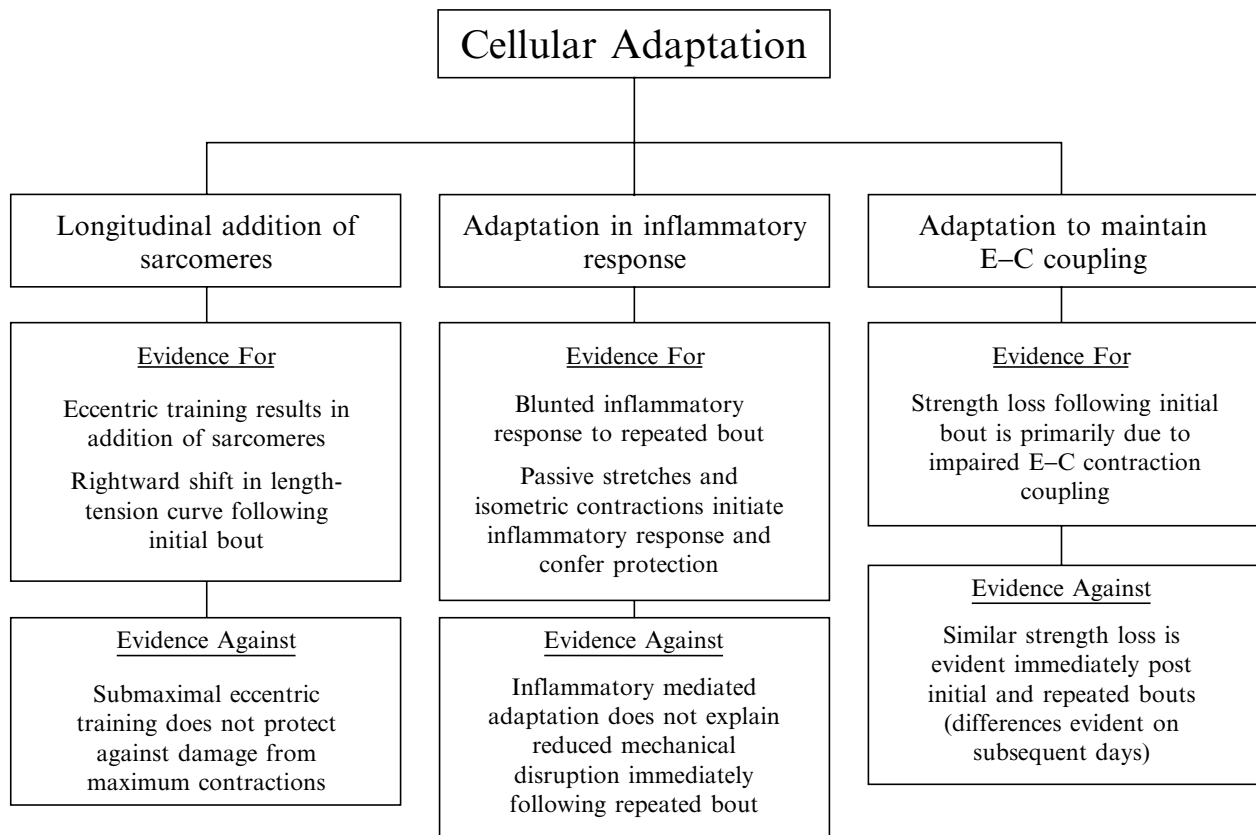
Cellular Adaptation

Longitudinal addition of sarcomeres

Evidence For

Eccentric training results in addition of sarcomeres

Rightward shift in length-tension curve following initial bout

Evidence Against

Submaximal eccentric training does not protect against damage from maximum contractions

Adaptation in inflammatory response

Evidence For

Blunted inflammatory response to repeated bout

Passive stretches and isometric contractions initiate inflammatory response and confer protection

Evidence Against

Inflammatory mediated adaptation does not explain reduced mechanical disruption immediately following repeated bout

Adaptation to maintain E–C coupling

Evidence For

Strength loss following initial bout is primarily due to impaired E–C contraction coupling

Evidence Against

Similar strength loss is evident immediately post initial and repeated bouts (differences evident on subsequent days)

Fig. 3. Potential cellular mechanisms for the repeated bout effect. E–C coupling refers to excitation–contraction coupling (See text for specific references related to evidence for and against the proposed theories).

Masselli, Armstrong, 2000; McHugh, Connolly, Eston, Gleim, 2001). Theoretically an increase in the amplitude of the EMG signal relative to torque production in the repeated bout would indicate a redistribution of contractile stresses among a greater number of fibers. Such an effect is evident with eccentric strength training (Komi & Buskirk, 1972; Hortobágyi et al., 1996a; Hortobágyi, Hill, Houmard, Fraser, Lambert, Israel, 1996b). Furthermore, a decrease in the frequency content of the EMG signal in the repeated bout would theoretically indicate a shift to the recruitment of slow-twitch motor units and/or increased motor unit synchronization. There was no evidence of a change in EMG amplitude between repeated eccentric bouts in hamstring (McHugh et al., 2001) or tibialis anterior (Warren et al., 2000) muscles. However, median frequency was decreased in the repeated bout for the tibialis anterior and this effect was attributed to increased recruitment of slow-twitch motor units (Warren et al., 2000). Alternatively, this effect could be attributed to increased motor unit synchronization. Either effect would be indicative of a neural adaptation to a single bout of eccentric exercise.

Evidence against a neural adaptation

While the results of Warren et al. (2000) are the first direct evidence of a neural adaptation to a single bout of eccentric exercise, it is apparent that the repeated bout effect can occur independent of a neural adaptation (Sacco & Jones, 1992; Nosaka, Newton, Sacco, 2002a). The repeated bout effect has been demonstrated with electrically stimulated eccentric contractions in mouse tibialis anterior muscles (Sacco & Jones, 1992) and more recently in human elbow flexors (Nosaka et al., 2002a). In humans the initial bout of electrically stimulated eccentric contractions resulted in marked strength loss, increased relaxed elbow angle, decreased flexed elbow angle, increased upper arm circumference, increased muscle thickness in ultrasound images, elevated plasma CK activity and myoglobin concentration and increased muscle soreness. Following a repeated bout of the same stimulation protocol 2 weeks later there were significantly blunted responses in all eight markers of damage. The authors concluded that "involvement of the central nervous system in the repeated bout effect is minimal, and peripheral adaptations play a more important role." However, they did not allude to any specific peripheral adaptations.

Mechanical theory
Mechanical theory of muscle damage

Muscle damage has been described as materials fatigue typical of ductile material subjected to cyclic tensile loading (Warren, Hayes, Lowe, Prior, Armstrong,

1993). The eccentric contraction-induced injury is thought to begin with a mechanical disruption of myofibrils. It follows that an adaptation serving to protect against damage might alter the mechanical properties of the musculoskeletal system. In this review mechanical adaptations refer to peripheral adaptations in the non-contractile elements of the musculoskeletal system. Included are discussions of adaptations at the whole muscle and muscle fiber level as well as adaptations at the myofibrillar level, specifically in the cytoskeleton. Much of the relevant work in this area has dealt with mechanical adaptations to chronic eccentric exercise rather than adaptations to a single bout.

Evidence for a mechanical adaptation

Adaptations to eccentric training
Increases in both passive and dynamic stiffness following eccentric training have been demonstrated in human elbow flexors (Pousson, Van Hoecke, Goubel, 1990) and rat triceps brachii muscles (Reich, Lindstedt, LaStayo, Pierotti, 2000). For these purposes dynamic stiffness refers to the elastic properties or extensibility of active muscles and passive stiffness refers to those properties in relaxed muscles. Pousson et al. (1990) demonstrated an increase in active stiffness of the elbow flexors following eccentric training. This effect was attributed to either increased tendon stiffness or increased cross-bridge stiffness. More recently, Reich et al. (2000) demonstrated increased passive and dynamic muscle stiffness following eccentric training in rat triceps brachii muscles. These effects were attributed to adaptation in the cytoskeletal proteins responsible for maintaining the alignment and structure of the sarcomere.

Cytoskeletal adaptations
Cytoskeletal proteins such as desmin and titin are responsible for the longitudinal and horizontal orientation of sarcomeres (Waterman-Storer, 1991). Electron micrographs of normal myofibrils reveal perfect parallel alignment of sarcomeres in adjacent myofibrils. Eccentric contractions disrupt this alignment between myofibrils, with sarcomeres in one myofibril no longer aligned with the sarcomeres in adjacent myofibrils. Within myofibrils disruption is primarily seen at the Z bands which appear wavy or in extreme cases are indistinguishable from the rest of the sarcomere (Patel & Lieber, 1997). Disruption of the cytoskeleton, specifically desmin, is one of the earliest events in eccentric contraction-induced damage (Lieber, Thornell, Fridén, 1996). Therefore it would seem plausible that an adaptation in the cytoskeleton may be the first line of defense in protection against repeated damage. While there is no direct evidence of an adaptation in the cytoskeleton explaining the repeated bout effect, a

recent study in a rat model demonstrated increased desmin content 3–7 days following damaging contractions (Barash, Peters, Fridén, Lutz, Lieber, 2002). This effect was thought to represent remodeling of the intermediate filament system to "provide mechanical reinforcement against excessive sarcomere strain."

Intramuscular connective tissue
Lapier, Burton, Almon, Cerny (1995) theorized that an increase in passive muscle stiffness secondary to increased intramuscular connective tissue might protect muscle from eccentric contraction-induced damage. They examined the role of intramuscular connective tissue in the susceptibility to damage in rat extensor digitorum longus muscles (Lapier et al., 1995). The ankle joints were immobilized for 3 weeks with the muscle in either a shortened or lengthened position. After 3 weeks, the muscles were subjected to an eccentric injury protocol. Muscle tissue samples were stained for collagen content as an indicator of intramuscular connective tissue. Muscles immobilized in the lengthened position had 63% more intramuscular connective tissue and 86% lower mass than contralateral control muscles. Muscles immobilized in the shortened position had 47% more intramuscular connective tissue and 21% lower mass than contralateral control muscles. Subsequent bouts of stimulated eccentric contractions resulted in 50% force loss in control muscles compared to 40% in muscles immobilized in the shortened position and 8% in muscles immobilized in the lengthened position. The protective effect was attributed to the ability of the increased connective tissue to dissipate myofibrillar stresses but changes in passive muscle stiffness were not documented. The authors suggested that tissue repair following a damaging bout of eccentric exercise is characterized by a similar increase in intramuscular connective tissue thereby protecting against damage from repeated bouts.

Evidence against a mechanical adaptation

The role of passive muscle stiffness
While increased passive muscle stiffness following eccentric training (Reich et al., 2000) and adaptations in intramuscular connective tissue following immobilization (Lapier et al., 1995) indirectly indicate that increased passive muscle stiffness may protect against muscle damage, there is contradictory evidence that passive muscle stiffness increases the susceptibility to muscle damage (McHugh, Connolly, Eston, Gleim, 1999a). Subjects categorized as having stiff hamstrings experienced greater strength loss, more pain, greater muscle tenderness and higher elevations in creatine kinase activity than subjects categorized as having compliant hamstrings (McHugh et al., 1999b). Based

on the premise that stiffer muscles are more susceptible to damage, it follows that a decrease in passive muscle stiffness might serve a protective effect. Dramatic increases in passive stiffness in the elbow flexors (Howell, Chelboun, Conaster, 1993; Chelboun et al., 1995) and plantarflexors (Whitehead, Weerakkody, Gregory, Morgan, Proske, 2001) have been demonstrated in the days following a damaging bout of eccentric exercise. These effects were thought to be due to the development of "injury contractures in the damaged muscle fibers" (Whitehead et al., 2001). However, passive stiffness was not followed to the point of full recovery in these studies and changes in passive stiffness with respect to the repeated bout effect are unknown.

The findings with respect to immobilization (Lapier et al., 1995) may be due to a sarcomere adaptation rather than a change in intramuscular connective tissue. The fact that the effect occurred primarily in the muscles immobilized in the lengthened position indicates that protection may in part have been due to longitudinal addition of sarcomeres (see section on Cellular Theory). In contrast to these results, 5 weeks of unilateral lower limb non-weight bearing has been shown to increase susceptibility to damage (Ploutz-Snyder, Tesch, Hather, Dudley, 1996).

Cytoskeletal adaptations
While increased desmin content during repair was thought to reflect a "mechanical reinforcement" to protect the sarcomere from damage (Barash et al., 2002) somewhat contradictory findings were previously reported (Sam, Shah, Fridén, Milner, Capetanaki, Lieber, 2000). In a mouse model, eccentric contraction-induced damage was compared between normal muscles and muscles lacking desmin. It was hypothesized that the muscles lacking desmin would be more susceptible to damage because desmin is partly responsible for myofibrillar alignment. Surprisingly the opposite was demonstrated, with less disruption in the muscles lacking desmin. This effect was attributed to less dynamic stiffness in the muscles lacking desmin during the eccentric contraction. Less stiffness was thought to enable greater sarcomere shortening thereby avoiding sarcomere strain. This is consistent with the finding that compliant muscles are less susceptible to damage (McHugh et al., 1999b) but is inconsistent with the findings of increased passive stiffness with eccentric training (Reich et al., 2000) and increased desmin content 3–7 days post eccentric contraction-induced damage (Barash et al., 2002).

Cellular theory

Potential adaptations discussed in this section include adaptations in the contractile machinery (longitudinal addition of sarcomeres and excitation–contraction

coupling changes) and adaptations in the inflammatory response to eccentric contractions.

Evidence for a cellular adaptation

Sarcomere strain theory

Morgan (1990) has suggested that muscle damage is due to irreversible sarcomere strain during eccentric contractions and, in particular, contractions at muscle lengths on the descending limb of the length–tension curve. In agreement with this theory data from isolated whole muscle preparations in animals (Lieber & Fridén, 1991; Brooks, Zerba, Faulkner, 1995; Hunter & Faulkner, 1997) and voluntary contractions in humans (Newham, Jones, Ghosh, Aurora, 1988; Child, Saxton, Donnelly, 1998) have clearly shown that the length of the muscle during eccentric contractions appears to be a critical factor in determining the extent of damage. Contractions performed at longer muscle lengths result in greater symptoms of damage. Based on the sarcomere strain theory of muscle damage, Morgan (1990) predicted that the repair process results in an increase in the number of sarcomeres connected in series and that this serves to reduce sarcomere strain during a repeated bout thereby limiting the myofibrillar disruption. Data from animal studies has provided evidence of addition of sarcomeres with eccentric exercise (Lynn & Morgan, 1994; Lynn, Talbot, Morgan, 1998). Additionally, indirect evidence of longitudinal addition of sarcomeres in humans was recently demonstrated following a damaging bout of eccentric hamstring contractions (Brockett, Morgan, Proske, 2001). A rightward shift in the length–tension relationship following recovery from the initial bout was attributed to longitudinal addition of sarcomeres.

Excitation–contraction coupling

Strength loss following a bout of eccentric exercise could theoretically be due to (1) an inability to voluntarily activate motor units secondary to pain or damage, (2) physical disruption of the force-generating structures (including a loss of myofibrillar contractile proteins) or (3) a failure to activate intact force-generating structures within the muscle fiber (excitation–contraction coupling). Voluntary activation of motor units is not thought to be impaired following damaging eccentric exercise (Saxton & Donnelly, 1996; McHugh, Connolly, Eston, Gleim, 2000). Strength loss is thought to be due to a combination of physical disruption and an impairment of excitation–contraction coupling (E–C coupling) (Warren, Ingalls, Lowe, Armstrong, 2001). E–C coupling refers to "the sequence of events that starts with the release of acetylcholine at the neuromuscular junction and ends with the release of Ca^2 from the sarcoplasmic reticulum" (Warren et al., 2001).

Impaired E–C coupling has been estimated to account for 50–75% of strength loss in the first 5 days following a damaging eccentric bout (Warren et al., 2001). However, this estimate is based on electrically stimulated maximal contractions in an animal model, and little is known about effects in human skeletal muscle with voluntary contractions. An adaptation in E–C coupling may explain the reduced strength loss following a repeated bout. Strengthening of the sarcoplasmic reticulum, as suggested by Clarkson & Tremblay (1988), may prevent impairment of E–C coupling with a repeated bout, however, direct evidence in support of such a theory is lacking.

Inflammatory response

With eccentric contractions the initial injury is a mechanical disruption of myofibrils. This initial injury triggers a local inflammatory response which leads to an exacerbation of the damage prior to signs of recovery (Pizza et al., 1996; Pizza, Koh, McGregor, Brooks, 2002). These events can be referred to as primary and secondary damage. Decreased neutrophil and monocyte activation have been demonstrated following a repeated bout of eccentric exercise (Pizza et al., 1996). A blunted inflammatory response to a repeated bout could reflect an adaptation to avoid proliferation of the mechanical disruption of myofibrils. Two recent studies point to the possibility that reduced damage in a repeated bout may be attributable to an adaptation mediated by the inflammatory response. At first, Koh & Brooks (2001) demonstrated in an animal model that an initial bout of passive stretches or isometric contractions provided some protection against a subsequent eccentric bout. The protective effect was not as profound as that conferred by eccentric contractions, but was notable in that the initial bout of passive stretches or isometric contractions did not result in any damage. Subsequently Pizza et al. (2002) demonstrated in the same model that both passive stretches and isometric contractions initiated an inflammatory response despite the absence of any overt injury. Neutrophils were elevated 3 days following either passive stretches, isometric contractions or eccentric contraction when compared to neutrophils from control animals. The neutrophil response to passive stretches and isometric contractions was approximately half the magnitude of the response to eccentric contractions. Then when the muscles were subjected to a subsequent eccentric bout a blunted inflammatory response was seen for the muscles that were previously exposed to passive stretches, isometric contractions or eccentric contractions. Surprisingly, the blunted inflammatory response following the eccentric bout was similar for the muscle preconditioned with eccentric contractions, passive stretches or isometric contractions. The authors proposed that the initial inflammatory response to the initial bout "may contribute to the induction of a

protective mechanism". A reduced inflammatory response to a repeated eccentric bout may simply reflect the fact that there was a reduced mechanical disruption in the repeated bout and therefore less of a stimulus for an inflammatory response. It is difficult to resolve this issue since it is not clear whether the repeated bout effect reflects (1) less myofibrillar disruption during the actual repeated exercise bout, (2) a decrease in the secondary proliferation of damage or (3) a combination of both.

Evidence against a cellular adaptation

Longitudinal addition of sarcomeres
One of the most attractive theories to explain the repeated bout effect is the longitudinal addition of sarcomeres theory. While there is experimental evidence to support such a theory (Lynn & Morgan, 1994; Lynn et al., 1998; Brockett et al., 2001) there is also some conflicting evidence. For example, the length-tension relationship has been shown to return to normal within 5 hours in toad sartorius muscles (Wood, Morgan, Proske, 1993) and within 2 days in human triceps surae muscles (Jones, Allen, Talbot, Morgan, Proske, 1997; Whitehead et al., 2001). Furthermore, while submaximal eccentric training has been shown to result in longitudinal addition of sarcomeres in rats (Lynn & Morgan, 1994; Lynn et al., 1998) submaximal training did not confer protection from subsequent maximal contractions in humans (Nosaka & Newton, 2002b). It also remains to be determined if the protective effect of the initial bout is evident if the repeated bout is performed at a longer length than the initial bout. Exercising at the longer muscle length in the repeated bout would tend to counteract any sarcomere strain reduction due to addition of sarcomeres. If the adaptation is simply due to the addition of sarcomeres then a repeated bout at a longer muscle length would be expected to result in similar damage to the initial bout.

Excitation-contraction coupling
Studies demonstrating the repeated bout effect in humans do not directly support an adaptation related to E–C coupling. Impairment of E–C coupling is greatest immediately post-eccentric exercise, accounting for 75% of the reduction in force (Ingalls, Warren, Williams, Ward, Armstrong, 1998) but strength loss immediately following eccentric exercise has been shown to be similar between initial and repeated bouts (Newham, Jones, Clarkson, 1987; Clarkson & Tremblay, 1988; Ebbeling & Clarkson, 1990; Balnave & Thompson, 1993; Brown et al., 1997). It was only on subsequent days that reduced strength loss was seen with a repeated bout in these studies. If the repeated bout effect was due to an adaptation in E–C coupling reduced strength loss should be seen immediately following the repeated bout as well as on subsequent days.

Other theories

A relatively new area of muscle damage research has focused on the role of heat shock proteins (HSPs) in protection against eccentric contraction-induced injury (Thompson, Scordilis, Clarkson, Lohrer, 2001; Koh, 2002; Thompson, Clarkson, Scordilis, 2002). HSPs play an important role in cell survival following various stressors, most notably thermal stress (hence the name). With respect to eccentric exercise HSP27 and HSP70 have been shown to be increased following damaging eccentric exercise of the elbow flexors (Thompson et al., 2001; Thompson et al., 2002). It has been postulated that this response serves to protect the tissue from damage following a repeated eccentric bout (Thompson et al., 2002). The HSP response to repeated bouts of eccentric elbow flexor exercise revealed an apparent decrease in basal levels of HSP27 and HSP70 4 weeks following the initial bout with smaller absolute increases in these HSPs following the repeated bout. However, since the relative (%) increase in HSPs was similar between the two bouts it was unclear whether the results reflected a similar HSP response between bouts or a down-regulated response. It is possible that the HSP response to the initial damaging bout resulted in an acquired stress tolerance for the repeated bout. Interpretation of these findings is difficult given the methodological problems inherent in a study requiring biopsy samples. Since the biopsy procedure involves tissue damage the authors chose not to take baseline (pre-eccentric exercise) biopsies in the arm to be exercised, as the procedure itself may have initiated a HSP response. Therefore, biopsies were taken 48 h post-exercise from both the exercised and non-exercised arms (control). This procedure was repeated following the second bout 4 weeks later. The difficulty in interpreting the results arose from the apparent decrease in HSPs in the control arm following the repeated bout. This could be interpreted as a down-regulation of HSP bilaterally or that the initial HSP measurements in the control arm reflected a systemic or bilateral increase secondary to damage in the contralateral arm. Clearly this is an important new area of research, however, it remains to be determined whether the HSPs serve a protective function in eccentric contraction-induced injury (Koh, 2002).

One of the earliest theories proposed to explain the repeated bout effect was that the initial bout resulted in damage to a pool of weak muscle fibers and that following recovery these weak fibers were replaced by stronger fibers (Armstrong, Ogilvie, Schwane, 1983). Given the apparent association between sarcomere strain and subsequent muscle damage this theory may

be more applicable to weak sarcomeres. An initial eccentric bout may result in irreversible strain in a pool of weak sarcomeres. The non-uniformity of sarcomere length during eccentric contractions indicates that some sarcomeres are more easily strained than others. During the repair process these weak sarcomeres are replaced by stronger, strain resistant sarcomeres. Based on this theory a greater uniformity of sarcomere length would be expected during eccentric contraction in the repeated bout compared to the initial bout. While a weak sarcomere theory may be difficult to prove experimentally it would be consistent with some of the experimental findings that are inconsistent with the other theories. For example, symptoms of damage are not exacerbated when a repeated bout is performed prior to full recovery from the initial bout (Mair et al., 1992; Nosaka & Clarkson, 1995). If the weak sarcomeres have already been disrupted then only the stronger sarcomeres will be contributing to force production in the repeated bout and these sarcomeres are apparently resistant to damage. It has also been shown that the initial bout does not have to result in significant symptoms of damage in order to confer a protective effect (Clarkson & Tremblay, 1988; Brown et al., 1997; Nosaka et al., 2001b). However, it appears that a high contraction intensity is needed to provide protection against damage from a subsequent bout of high intensity contractions (Nosaka & Newton, 2002c). A few high intensity eccentric contractions may be sufficient to strain the weak pool of sarcomeres without complete myofibrillar disruption. This stimulus may be sufficient for remodeling or replacement of the pool of weak sarcomeres.

Conclusions and future directions

As was previously stated, in order to understand the mechanism(s) for the repeated bout effect it is necessary to first establish whether this phenomenon reflects (1) a decrease in myofibrillar disruption during the actual exercise bout (primary damage), (2) a decrease in the secondary proliferation of damage associated with the inflammatory response (secondary damage) or (3) a combination of both. The fact that some repeated bout effect studies have shown similar strength losses immediately post-exercise in the initial and repeated bouts (Newham et al., 1987; Clarkson & Tremblay, 1988; Ebbeling & Clarkson, 1990; Balnave & Thompson, 1993; Brown et al., 1997; Nosaka et al., 2002a) supports the contention that the repeated bout reflects a protection against the secondary damage. However, it is likely that there is some reduction in primary damage with the repeated bout effect. Fridén et al. (1983b) found damage in 20% of micrographs from vastus lateralis biopsies taken 3 days following 30 min of eccentric cycling. Only 4% of micrographs showed damage following 4 weeks of eccentric cycling

training (Fridén, Seger, Sjøstrøm, Ekblom, 1983a). It is likely that more than 4% of micrographs would have shown damage immediately following the initial bout and therefore these findings may represent a protection against primary damage. Notably, this was a training study and did not examine adaptations to a single eccentric bout. Comparison of electron micrographs from muscle biopsies taken immediately following initial and repeated eccentric bouts would provide some clarification on the extent of protection against the primary damage.

Some of the discrepancies between plausible mechanisms for the repeated bout effect and actual experimental data may be explained by the distinction between primary and secondary damage. For example, the sarcomere strain theory and longitudinal addition of sarcomeres cannot explain the results of studies demonstrating a repeated bout effect where the initial bout resulted in minimal or no signs of damage (Koh & Brooks, 2001; Nosaka et al., 2001b). Two eccentric contractions (Nosaka et al., 2001b) or passive stretching (Koh & Brooks, 2001) are unlikely to be sufficient stimuli for addition of sarcomeres yet they provided some protection. In these instances the protective adaptation may be explained by an inflammatory mediated response that serves to limit secondary damage. However, other experimental data fails to fit any of the proposed theories. For example, submaximal eccentric training did not provide any protection against a subsequent bout of maximal eccentric contractions (Nosaka & Newton, 2002b). The submaximal eccentric training resulted in clear signs of damage in the early weeks of training and this should have been a sufficient stimulus to induce both a sarcomere adaptation and an inflammatory mediated adaptation. It is possible that the myofibrils damaged by the maximum contractions were in muscle fibers of motor units that were not active during the submaximal training.

In conclusion, our understanding of the repeated bout effect has improved with the increased volume of research in this area. In recent years important

Table 1. Potential questions to be addressed in future research

1. Does dynamic or passive muscle stiffness change between initial and repeated eccentric bouts?
2. What changes occur in the cytoskeleton between an initial and repeated eccentric bout?
3. Is the rightward shift in the length-tension curve a consistent finding with the repeated bout effect?
4. Does an initial bout at a short muscle length confer protection for a repeated bout at a longer muscle length?
5. What role do heat shock proteins play in the repeated bout effect?
6. Are sarcomere lengths more uniform during a repeated vs. an initial bout?
7. To what extent does the repeated bout effect reflect a decrease in myofibrillar disruption (primary damage) vs. a decrease in the proliferation of damage on subsequent days (secondary damage)?

advances have been made with respect to our understanding of neural control of eccentric contractions, eccentric sarcomere mechanics, heat shock protein expression, E-C coupling and inflammatory responses to eccentric contractions. This information can be used to stimulate additional studies to clarify conflicting findings or expand on preliminary findings (Table 1). There may be several mechanisms for the repeated bout effect and these mechanisms may compliment each other or operate independently of each other. Despite the advances in our understanding of the repeated bout effect a unified theory explaining the mechanism or mechanisms remains elusive.

Key words: muscle damage; eccentric contractions; sarcomere.

References

Armstrong RB, Ogilvie RW, Schwane JA. Eccentric exercise-induced injury to rat skeletal muscle. J Appl Physiol 1983: 54: 80–93.

Balnave CD, Thompson MW. Effect of training on eccentric-induced muscle damage. J Appl Physiol 1993: 75: 1545–1551.

Barash IA, Peters D, Fridén J, Lutz GL, Lieber RL. Desmin cytoskeletal modifications after a bout of eccentric exercise in the rat. Am J Physiol Regul Integr Comp Physiol 2002: 283: R958–R963.

Bigland B, Lippold OCJ. The relation between force velocity and integrated electrical activity in human muscles. J Physiol 1954: 123: 214–224.

Brockett CL, Morgan DL, Proske U. Human hamstring muscles adapt to eccentric exercise by changing optimum length. Med Sci Sports Exerc 2001: 33: 783–790.

Brooks SV, Zerba E, Faulkner JA. Injury to muscle fibers after single stretches of passive and maximally stimulated muscles in mice. J Physiol 1995: 488: 459–469.

Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. J Sports Sci 1997: 15: 215–222.

Chelboun GS, Howell JN, Baker HL, Ballard TN, Graham JL, Hallman HL, Perkins LE, Schauss JH, Conaster RR. Intermittent pneumatic compression effect on eccentric exercise-induced swelling, stiffness and strength loss. Arch Phys Med Rehab 1995: 76: 744–749.

Child RB, Saxton JM, Donnelly AE. Comparison of eccentric knee extensor muscle actions at two muscle lengths on indices of damage and angle-specific force production in humans. J Sports Sci 1998: 16: 301–308.

Clarkson PM, Byrnes WC, Gillisson E, Harper E. Adaptation to exercise-induced muscle damage. Clin Sci 1987: 73: 383–386.

Clarkson PM, Tremblay I. Exercise-induced muscle damage, repair, and adaptation in humans. J Appl Physiol 1988: 65: 1–6.

Connolly DAJ, Reed BR, McHugh MP. The repeated bout effect: a central or local mechanism? J Sports Sci Med 2002: 3: 80–86.

Ebbeling CB, Clarkson PM. Muscle adaptation prior to recovery following eccentric exercise. Eur J Appl Physiol 1990: 60: 26–31.

Enoka RM. Eccentric contractions require unique activation strategies by the nervous system. J Appl Physiol 1996: 81: 2339–2346.

Eston RG, Finney S, Baker S, Baltzopoulos V. Muscle soreness and strength loss changes after downhill running following a prior bout of isokinetic eccentric exercise. J Sports Sci 1996: 14: 291–299.

Fridén J, Seger J, Sjøstrøm M, Ekblom B. Adaptive response in human skeletal muscle subjected to prolonged eccentric training. Int J Sports Med 1983a: 4: 177–183.

Fridén J, Sjøstrøm M, Ekblom B. Myofibrillar damage following intense eccentric exercise in man. Int J Sports Med 1983b: 4: 170–176.

Holmich P, Uhrskou P, Ulnits L, et al. Effectiveness of active physical training as treatment for long-standing adductor-related groin pain in athletes: Randomised trial. Lancet 1999: 353: 439–443.

Hortobágyi T, Barrier J, Beard D, Braspennincx J, Koens P, Devita P, Dempsey L, Lambert J. Greater initial adaptations to submaximal muscle lengthening than maximal shortening. J Appl Physiol 1996a: 81: 1677–1682.

Hortobagyi T, Dempsey L, Fraser O, et al. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. J Physiol 2000 524: 293–304.

Hortobágyi T, Hill JP, Houmard JA, Fraser DD, Lambert NJ, Israel RG. Adaptive responses to muscle lengthening and shortening in humans. J Appl Physiol 1996b: 80: 765–772.

Howell JN, Chelboun G, Conaster R. Muscle stiffness, strength loss, swelling and soreness following exercise-induced injury in humans. J Physiol 1993: 464: 183–196.

Howell JN, Fuglevand AJ, Walsh ML, Bigland-Ritchie B. Motor unit activity during isometric and concentric-eccentric contractions of the human first dorsal interosseus muscle. J Neurophysiol 1995: 74: 901–904.

Hunter KD, Faulkner JA. Pliometric contraction-induced injury of mouse skeletal muscle: effect of initial length. J Appl Physiol 1997: 82: 278–283.

Ingalls CP, Warren GL, Williams JH, Ward CW, Armstrong RB. E–C coupling failure in mouse EDL muscle after in vivo eccentric contractions. J Appl Physiol 1998: 85: 58–67.

Jones C, Allen T, Talbot J, Morgan DL, Proske U. Changes in the mechanical properties of human and amphibian muscle after eccentric exercise. Eur J Appl Physiol 1997: 76: 21–31.

Koh TJ, Brooks SV. Lengthening contractions are not required to induce protection from contraction-induced muscle injury. Am J Physiol Regul Integr Comp Physiol 2001: 281(1): R155–R161.

Koh TJ. Do small heat shock proteins protect skeletal muscle from injury? Exerc Sport Sci Rev 2002: 30(3): 117–121.

Komi PV, Buskirk ER. Effect of eccentric and concentric muscle conditioning on tension and electrical activity of human muscle. Ergonomics 1972: 15: 417–434.

Lapier TK, Burton HW, Almon R, Cerny F. Alterations in intramuscular connective tissue after limb casting affect contraction-induced muscle injury. J Appl Physiol 1995: 78: 1065–1069.

Lieber RL, Fridén J. Muscle damage induced by eccentric contractions of 25% strain. J Appl Physiol 1991: 70: 2498–2507.

Lieber RL, Thornell LE, Fridén J. Muscle cytoskeletal disruption occurs within the first 15 min of cyclic eccentric contraction. J Appl Physiol 1996: 80: 278–284.

Lynn R, Morgan DL. Decline running produces more sarcomeres in rat vastus intermedius muscle fibers than does

incline running. J Appl Physiol 1994: 77: 1439–1444.

Lynn R, Talbot JA, Morgan DL. Differences in rat skeletal muscles after incline and decline running. J Appl Physiol 1998: 85: 98–104.

MacPherson CD, Schork AM, Faulkner JA. Contraction-induced injury to single permeabilized muscle fibers from fast and slow muscles of the rat following single stretches. Am J Physiol 1996: 271: C1438–C1446.

Mair J, Koller A, Artner-Dworzak E, Haid C, Wicke K, Judmaier W, Puschendorf B. Effects of exercise on plasma myosin heavy chain fragments and MRI of skeletal muscle. J Appl Physiol 1992: 72: 656–663.

McHugh MP, Connolly DAJ, Eston RG, Kremenic IJ, Gleim GW. The role of passive muscle stiffness in symptoms of exercise-induced muscle damage. Am J Sports Med 1999a: 27(5): 594–599.

McHugh MP, Connolly DAJ, Eston RG, Gleim GW. Exercise-induced muscle damage and potential mechanisms for the repeated bout effect. Sports Med 1999b: 27: 157–170.

McHugh MP, Connolly DAJ, Eston RG, Gleim GW. Electromyographic analysis of exercise resulting in symptoms of muscle damage. J Sport Sci 2000: 18: 163–172.

McHugh MP, Connolly DAJ, Eston RG, Gleim GW. Electromyographic analysis of repeated bouts of eccentric exercise. J Sport Sci 2001: 19: 163–170.

HcHugh MP, Tyler TF, Greenberg SC, Gleim GW. Differences in activation patterns between eccentric and concentric quadriceps contractions. Journal of Sports Sciences 2002: 20: 83–91.

Morgan DL. New insights into the behavior of muscle during active lengthening. Biophys J 1990: 57: 209–221.

Moritani T, Muramatsu S, Muro M. Activity of motor units during concentric and eccentric contractions. Am J Phys Med 1988: 66: 338–350.

Nardone A, Romano C, Schieppati M. Selective recruitment of high-threshold human motor units during voluntary isotonic lengthening of active muscles. J Physiol 1989: 409: 451–471.

Nardone A, Schieppati M. Shift of activity from slow to fast muscle during voluntary lengthening contractions of the triceps surae muscles in humans. J Physiol 1988: 395: 363–381.

Newham DJ, Jones DA, Clarkson PM. Repeated high-force eccentric exercise: effects on muscle pain and damage. J Appl Physiol 1987: 63: 1381–1386.

Newham DJ, Jones DA, Ghosh G, Aurora P. Muscle fatigue and pain after eccentric contractions at long and short length. Clin Sci 1988: 74: 553–557.

Nosaka K, Clarkson PM. Muscle damage following repeated bouts of high force eccentric exercise. Med Sci Sports Exerc 1995: 27: 1263–1269.

Nosaka K, Newton M, Sacco P. Responses of human elbow flexor muscles to electrically stimulated forced lengthening exercise. Acta Physiol Scand 2002a: 174 (2): 137–145.

Nosaka K, Newton M. Concentric or eccentric training effect on eccentric exercise-induced muscle damage. Med Sci Sports Exerc 2002b: 34(1): 63–69.

Nosaka K, Newton M. Repeated eccentric exercise bouts do not exacerbate muscle damage and repair. J Strength Cond Res 2002c: 16(1): 117–122.

Nosaka K, Sakamoto K, Newton M, Sacco P. How long does the protective effect on eccentric exercise-induced muscle damage last? Med Sci Sports Exerc 2001a: 33(9): 1490–1495.

Nosaka K, Sakamoto K, Newton M, Sacco P. The repeated bout effect of reduced-load eccentric exercise on elbow flexor muscle damage. Eur J Appl Physiol 2001b: 85(1–2): 34–40.

Nosaka K, Sakamoto K. Effect of elbow joint angle on the magnitude of muscle damage to the elbow flexors. Med Sci Sports Exerc 2001c: 33(1): 22–29.

Patel TJ, Lieber RL. Force transmission in skeletal muscle: from actomyosin to external tendons. Exercise Sport Sci Rev 1997: 25: 321–363.

Pizza FX, Davis BH, Hendrickson SD, Mitchell JB, Pace JF, Bigelow N, DiLaura P, Naglieri T. Adaptation to eccentric exercise: effect on CD64 and CD11b/CD18 expression. J Appl Physiol 1996: 80: 47–55.

Pizza FX, Koh TJ, McGregor SJ, Brooks SV. Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions. J Appl Physiol 2002: 92 (5): 1873–1878.

Ploutz-Snyder LL, Tesch PA, Hather BM, Dudley GA. Vulnerability to dysfunction and muscle injury after unloading. Arch Phys Med Rehabilitation 1996: 77: 773–777.

Pousson M, van Hoecke J, Goubel F. Changes in elastic characteristics of human muscle induced by eccentric exercise. J Biomech 1990: 23: 343–348.

Reich TE, Lindstedt SL, LaStayo PC, Pierotti DJ. Is the spring quality of muscle plastic? Am J Physiol Regul Integr Comp Physiol 2000: 278: R1661–R1666.

Sacco P, Jones DA. The protective effect of damaging eccentric exercise against repeated bouts of exercise in the mouse tibialis anterior. Exp Physiol 1992: 77: 757–760.

Sam M, Shah S, Fridén J, Milner DJ, Capetanaki Y, Lieber RL. Desmin knockout muscles generate lower stress and are less vulnerable to injury compared with wild-type muscles. Am J Physiol Cell Physiol 2000: 279(4): C1116–C1122.

Saxton JM, Donnelly AE. Length-specific impairment of skeletal muscle contractile function after eccentric muscle actions in man. Clin Sci 1996: 90: 119–125.

Silbernagel KG, Thomee R, Thomee P, Karlsson J. Eccentric overload training for patients with chronic Achilles tendon pain – a randomised controlled study with reliability testing of the evaluation methods. Scand J Med Sci Sports 2001: 11: 197–206.

Thompson HS, Clarkson PM, Scordilis SP. The repeated bout effect and heat shock proteins: intramuscular HSP27 and HSP70 expression following two bouts of eccentric exercise in humans. Acta Physiol Scand 2002: 174(1): 47–56.

Thompson HS, Scordilis SP, Clarkson PM, Lohrer WA. A single bout of eccentric exercise increases HSP27 and HSC/ HSP70 in human skeletal muscle. Acta Physiol Scand 2001: 171(2): 187–193.

Tyler TF, Campbell R, Nicholas SJ, Donellan S, McHugh MP. The effectiveness of a preseason exercise program on the prevention of groin strains in professional ice hockey players. Am J Sports Med 2002: 30: 680–683.

Warren GL, Hayes DA, Lowe DA, Prior BM, Armstrong RB. Materials fatigue initiates eccentric contraction-induced injury in rat soleus muscle. J Physiol 1993: 464: 477–489.

Warren GL, Hermann KM, Ingalls CP, Masselli MR, Armstrong RB. Decreased EMG median frequency during a second bout of eccentric contractions. Med Sci Sports Exerc 2000: 32: 820–829.

Warren GL, Ingalls CP, Lowe DA, Armstrong RB. Excitation-contraction uncoupling: major role in contraction-induced muscle injury. Exerc Sport Sci Rev 2001: 29(2): 82–87.

Waterman-Storer CM. The cytoskeleton of skeletal muscle: is it affected by exercise? A brief review. Med Sci Sports Exerc 1991: 23: 1240–1249.

Whitehead NP, Weerakkody NS, Gregory JE, Morgan DL, Proske U. Changes in passive tension of muscle in humans and animals after eccentric exercise. J Physiol 2001: 533: 593–604.

Wood SA, Morgan DL, Proske U. Effects of repeated eccentric contractions on structure and mechanical properties of toad sartorius muscle. Am J Physiol 1993: 265: C792–C800.