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Nosaka, Kazunori; Saldanha Aoki, Marcelo
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INVITED REVIEW

REPEATED BOUT EFFECT: RESEARCH UPDATE AND FUTURE PERSPECTIVE

Kazunori Nosaka[1], Marcelo Saldanha Aoki[2]

[1] School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia
[2] School of Arts, Sciences and Humanities, University of Sao Paulo, Sao Paulo, SP, Brazil

Corresponding author:
Kazunori Nosaka, PhD
School of Exercise, Biomedical and Health Sciences
Edith Cowan University
270 Joondalup Drive, Joondalup, WA 6027, Australia
E-mail: k.nosaka@ecu.edu.au
Telephone: (+61) 8 6304 5655
Fax: (+61) 8 6304 5036

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ABSTRACT
NOSAKA, K.; AOKI, M. S. Repeated bout effect: research update and future perspective. Brazilian Journal of Biomotricity, v. 5, n. 1, p. 5-15, 2011. Responses to the same exercise are never the same, which is particularly so for eccentric exercise. Eccentric exercise results in muscle damage when performed by individuals who are unaccustomed to the exercise. However, when the same exercise is performed again within a certain period of time, it does not induce as sever muscle damage as that was induced previously. It looks as if a bout of eccentric exercise induced protective adaptation in the process of recovering from muscle damage. This adaptation is referred to as the repeated bout effect. The protective adaptation against "maximal" eccentric contractions is induced by submaximal eccentric contractions, a small number of eccentric contractions, eccentric contractions at short muscle lengths, or slow velocity eccentric contractions, which induce less muscle damage, as well as low-intensity eccentric contractions that do not induce any muscle damage, or isometric contractions at a long muscle length. The protective effect could last up to several months, but the remaining length of the effect appears to be influenced by the magnitude of muscle damage in the initial bout. It seems that adaptations of muscle fibers and/or connective tissue are responsible for the repeated bout effect, although neural adaptations are not totally discarded, and the underlying mechanisms need to be investigated further. It should be noted that the magnitude of muscle damage can be attenuated by the use of the repeated bout effect more efficiently than any other prophylactic interventions such as nutritional supplementations, and the effect should be considered when designing a study.

Key Words: eccentric exercise, muscle damage, muscle adaptation, delayed onset muscle soreness, muscle strength, recovery.

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INTRODUCTION

When the skin is exposed to strong ultraviolet for the first time or a long interval from the previous exposure, sunburn is induced. However, if the skin was previously exposed to ultraviolet that resulted in sunburn or suntan, severe sunburn is avoided for a period of time during when another exposure to ultraviolet is encountered. This kind of adaptation is also observed for the skeletal muscle when it is exposed to eccentric exercise in which contracting muscles are lengthened (eccentric contractions). If muscles involving in an exercise have been exposed to the same or similar eccentric contractions, severe muscle damage is prevented in the next eccentric exercise that is performed within a certain period of time after the previous damaging exercise. This adaptation, often referred to as the repeated bout effect, is the topic of this review. There are some review articles that explain the repeated bout effect (e.g. EBBELING & CLARKSON, 1989; CLARKSON et al., 1992; MCHUGH et al., 1999; MCHUGH, 2003), but new important information has become available in the last 5 years, which was not included in the previous review articles. This review article mainly focuses on the studies of our group and provides overview of the development of the repeated bout effect research.

What is the repeated bout effect?

We often experience muscle pain and weakness for several days after performing unaccustomed exercise or exercise with higher intensity, longer duration or larger volume than normal. Delayed onset muscle soreness (DOMS) and prolonged loss of muscle function are typical symptoms of muscle damage that is induced by eccentric contractions or isometric contractions at a long muscle length (NOSAKA, 2008). We also experience that when the same or similar exercise is repeated within several weeks, even without any exercises in between, less muscle pain or no pain is felt after exercise that previously resulted in severe DOMS. This is a typical example of the “repeated bout effect” (NOSAKA, 2008; NOSAKA, 2010).

The magnitude of muscle damage symptoms is significantly attenuated in the second bout such that the extent of DOMS is less and recovery of muscle function (e.g. maximal voluntary contraction strength) is faster following the second exercise bout compared with the initial bout (EBBELING & CLARKSON, 1989; CLARKSON et al., 1992). It should be noted that the magnitude of decrease in maximal voluntary contraction (MVC) strength immediately after exercise is generally similar between bouts, but the recovery is facilitated in the repeated bout effect (HIROSE et al., 2004; NOSAKA et al., 2005a; NOSAKA et al., 2006). The repeated bout effect is also characterised by less swelling of muscle, smaller increases in blood markers of muscle damage such as creatine kinase (CK) and myoglobin (Mb), and less abnormalities detected in magnetic resonance and/or B-mode ultrasound images following the second bout than the first bout (CLARKSON et al., 1992; HIROSE et al., 2004; NOSAKA & CLARKSON, 1996). It has been shown that the repeated bout effect could last 6-9 months, but does not last more than a year (NOSAKA et al., 2001a). We tend to think that repeated stimuli for a certain period of time (i.e. training) are necessary to induce muscle adaptations, but it is interesting that a single bout of exercise can also provide such strong and long-lasting effects.

Initially, the repeated bout effect was referred to as the adaptation in which the magnitude of muscle damage was attenuated when the same eccentric exercise was repeated (BYRNES et al., 1985; CLARKSON et al., 1992); however, such adaptation is induced even when the initial exercise bout is different from the subsequent exercise bouts. For example, eccentric exercise that induces little or no muscle damage in the initial bout still attenuates the magnitude of muscle damage in the subsequent maximal eccentric exercise (LAVENDER & NOSAKA, 2008). Thus, it is better to define the repeated bout effect as a phenomenon in which the magnitude of muscle damage is attenuated in a subsequent exercise bout after performing a single bout of exercise.

Factors influencing the repeated bout effect

The magnitude of the muscle damage attenuation in the second exercise bout is dependent on muscles, markers of muscle damage, the magnitude of muscle damage in the initial bout, and the time elapsed from the initial exercise bout. Most of the studies that have reported the repeated bout effect use the elbow flexors; however, others muscles such as the knee extensors are also reported to present the repeated bout effect (e.g. BYRNES et al., 1985; ESTON et al., 2000; KAMANDULIS et al., 2010; MIYAMA & NOSAKA, 2007).

In the case of elbow flexors when maximal eccentric exercise is repeated, Chen et al. (2007) reported that when the second maximal eccentric exercise bout was performed 2-3 weeks after the first maximal exercise bout, recovery of MVC strength at 5 days post-exercise was enhanced by 80%, increases in plasma CK activity and Mb concentration were completely abolished, and peak muscle soreness was reduced by 70%. In contrast, when a submaximal eccentric contractions were performed for the initial bout (e.g. 40% of MVC intensity), the recovery of MVC strength at 5 days post-exercise was enhanced by 11%, peak plasma CK activity were lowered by 50%, and peak muscle soreness was attenuated by 20%, which were smaller than those shown when maximal eccentric exercise was repeated. It appears that the greater the magnitude of muscle damage in the initial exercise bout, the greater the protective effect demonstrated in the second exercise bout. The magnitude of muscle damage is greater when the interval between bouts is short (e.g. 2 weeks) compared with long (e.g. 6 months) (NOSAKA, 2009), and the magnitude of the attenuation effect conferred by a single bout of maximal eccentric exercise is reduced as the time between bouts increases (NOSAKA et al., 2005a; NOSAKA et al., 2009).

Protective effect conferred by "repeated exercises"

Muscle damage is less for trained individuals compared with untrained individuals. A study (NEWTON et al., 2008) compared resistance-trained men who had trained for at least three sessions per week incorporating exercises involving the elbow flexor musculature for more than a year and untrained men who had not performed any resistance training for at least one year for changes in muscle damage markers following eccentric exercise consisting of 10 sets of 6 maximal isokinetic ($90^{o}\cdot s^{-1}$) eccentric contractions of the elbow flexors of one arm. The trained group showed significantly smaller changes in all markers except for muscle soreness and faster recovery of MVC strength compared with the untrained group such that the MVC strength of the trained group recovered to the baseline by 3 days post-exercise, where the untrained group showed approximately 40% lower strength than baseline. This suggests that resistance training makes muscles less susceptible to eccentric exercise-induced muscle damage, probably due to accumulative "repeated bout effect" from the training.

Chen et al. (2011) compared the four limb muscles; the elbow flexors (EF) and extensors (EE), knee extensors (KE) and flexors (KF) for the changes in indirect markers of muscle damage following maximal eccentric exercise. It was found that compared with KF and KE, EF and EE showed significantly greater changes in all markers without significant differences between EF and EE, and changes in all variables were significantly greater for KF than KE. The results suggest that the two arm muscles are more susceptible to muscle damage than leg muscles, but KF is more susceptible to muscle damage than KE. The difference in the susceptibility to muscle damage seems to be

Brazilian Journal of Biomotricity, v. 5, n. 1, p. 5-15, 2011 (ISSN 1981-6324)

associated with the use of muscles in daily activities. It may be that the use of muscles in daily activities confers the protective effect, which is similar to the repeated bout effect.

Chen et al. (2009b) investigated whether four bouts of submaximal eccentric exercise would confer similar protective effect to one bout maximal eccentric exercise. One group of subjects performed 30 eccentric contractions with a load of 40% MVC every 2 weeks for four times followed 2 weeks later by 30 maximal eccentric exercise of the elbow flexors of the non-dominant arm. Other group of subjects performed two bouts of the maximal eccentric exercise separated by two weeks. They found that repeating the submaximal eccentric exercise conferred the same magnitude of protective effect as one bout of maximal eccentric exercise.

Barroso et al. (2010) examined two velocity (60°·s^{-1}, 180°·s^{-1}) eccentric exercises consisting of 30 maximal eccentric contractions of the elbow flexors for changes in indirect markers of muscle damage following 3 exercise bouts that were performed every 2 weeks. No significant differences between velocities were evident for changes in any variables following exercise bouts; however, the changes were significantly smaller after the second and third bouts than after the first bout without significant differences between the second and third bouts. When 30 maximal eccentric contractions of the elbow flexors were performed every 4 weeks for 4 times by untrained subjects, changes in muscle damage markers following the second to fourth bouts became significantly smaller than those after the first bout, without significant difference between the second and third bouts (CHEN et al., 2009a). However, the decreases in MVC strength and range of motion immediately after the fourth bout were significantly smaller than other bouts. It appears that the first eccentric exercise bout confers the greatest adaptation, but further adaptation is induced when the exercise is repeated more than three times. Thus, it seems that repeating eccentric exercises consolidates the repeated bout effect; however, the greatest adaptation is produced after the first bout.

Variation of the repeated bout effect

The typical “repeated bout effect” refers to the situation that the same eccentric exercise bout is repeated; however, a similar or different type of exercise could induce the “repeated bout effect.” For example, maximal isometric contractions at a long muscle length (160°) but not at a short muscle length (90°) confer protective effect against maximal eccentric exercise performed 2 weeks later (NOSAKA, 2009). This suggests that not only eccentric contractions but also isometric contractions at a long muscle length produce protective effect against muscle damage induced by eccentric contractions.

It has been reported that performing 2 or 6 maximal eccentric contractions attenuate the magnitude of muscle damage following 24 maximal eccentric contractions performed 2 weeks later, and the magnitude of the attenuation effect conferred by the 6 contractions is the same as that induced by 24 maximal eccentric contractions, but that by the 2 contractions is smaller (NOSAKA et al., 2001b). It should be noted that only a few maximal eccentric contractions are still effective in attenuating muscle damage in subsequent exercise consisting of a larger number of eccentric contractions.

When comparing the effect of four different intensities (40%, 60%, 80% and 100%) of initial eccentric exercise on the extent of muscle damage induced by subsequent maximal eccentric exercise performed 2-3 weeks later, all submaximal intensity eccentric exercise reduced the magnitude of muscle damage following the maximal eccentric exercise, but the magnitude of repeated bout effect was significantly smaller for the 40% and 60% compared with the 80% and 100% (CHEN et al., 2007). Lavender and Nosaka (2008) found that an eccentric exercise with a light dumbbell that did not change any muscle damage markers provided some protection against a subsequent bout of a higher intensity eccentric exercise with a heavier dumbbell performed 2 days later. It appears that such effect could last 2 weeks (CHEN et al. under review).

It is known that fast velocity eccentric contractions induce greater muscle damage than slow velocity eccentric contractions (CHAPMAN et al., 2008). Chapman et al. (2011) examined whether the first bout of exercise consisting of slow velocity ($30°\cdot s^{-1}$) maximal eccentric contractions would confer protection against a subsequent bout of exercise consisting of fast velocity ($210°\cdot s^{-1}$) eccentric contractions. They found that a bout of slow velocity eccentric contractions confer protection against muscle damage induced by fast velocity eccentric contractions.

It is known that eccentric contractions at long muscle lengths induce greater muscle damage than eccentric contractions at short muscle lengths. Nosaka et al. (2005b) found that the eccentric exercise at the short muscle length (50-100°) produced a partial protective effect against muscle damage induced by the eccentric exercise of the long muscle length (130-180°, full extension: ~180°) performed 2 weeks later. The magnitude of protection varied among muscle damage markers, but this amounted to a "partial" protection of around 50% for most of markers.

Applications of the repeated bout effect to minimise muscle damage

It is likely that large number of high intensity and fast velocity lengthening contractions at long muscle lengths result in sever muscle damage. The magnitude of muscle damage can be attenuated by eliminating a factor or factors exacerbating muscle damage; that is, reducing the number of contractions, intensity, velocity, and muscle length during eccentric exercise. If eccentric exercise is preceded by isometric contractions at a long muscle length, small number of lengthening contractions, slow velocity lengthening contractions, lengthening contractions at small muscle lengths, severe muscle damage can be avoided (NOSAKA, 2009). A combination effect such as having small number and slow velocity lengthening contractions has not been investigated, and warrants further study.

It is important to note that the initial eccentric exercise bout that does not necessarily induce muscle damage still confer the repeated bout effect as mentioned above. For example, a low-intensity eccentric exercise that does not result in any changes in muscle damage markers can still attenuate the magnitude of muscle damage in the subsequent more demanding eccentric exercise (LAVENDER & NOSAKA, 2008). It should be noted that the magnitude of the attenuation in muscle damage conferred by such low-intensity eccentric exercise (e.g. 50% reduction in the peak DOMS) is greater than that induced by prophylactic interventions such as nutritional supplementation.

Because of the repeated bout effect, the recovery of muscle from eccentric exercise-induced muscle damage is not retarded by additional eccentric exercise bouts performed in early recovery days (CHEN & NOSAKA, 2006a; NOSAKA & CHEN, 2006b; NOSAKA & NEWTON, 2002a; NOSAKA & NEWTON, 2002b). Chen and Nosaka (2006a) investigated whether the second eccentric exercise performed 3 days after the initial bout would exacerbate muscle damage and retard the recovery, and showed that the elbow flexors could perform high-intensity eccentric exercise in the early stage of recovery from the initial bout and the muscles were not damaged further by performing the subsequent bout. They also reported in a separate study (CHEN & NOSAKA, 2006b) that recovery from eccentric exercise was not retarded by the second bout of eccentric exercise consisting of greater number of eccentric contractions (70 contractions) than the initial bout (30 contractions) separated by 3 days. These findings suggest that protective mechanisms are taken place soon after the first exercise bout, and further muscle damage is prevented.

Underlying mechanisms of the repeated bout effect

The mechanisms underlying the repeated bout effect are yet to be elucidated; however, neural, mechanical, and cellular adaptations are thought to be associated with the repeated bout effect (MCHUGH et al., 1999; MCHUGH, 2003). The neural adaptations include more efficient recruitment of motor units, increased synchrony of motor unit firing, better distribution of the workload among fibres, improved usage of synergist muscles, and increased slow-twitch fibre recruitment. Nosaka et al. (2002) reported that the second bout of eccentric exercise in which the elbow flexors were forcibly stretched while being stimulated by electrical stimulation resulted in smaller changes in muscle damage markers compared with the initial bout of the same exercise performed 2 weeks before. Aldayel et al. (2009) compared the first and second exercise bouts consisting of electrically evoked isometric contractions separated by 2 weeks for muscle damage profile. The knee extensors of one leg were stimulated by biphasic rectangular pulses (75 Hz, 400 µs, on-off ratio 5-15 s) at the knee joint angle of 100° (0°: full extension) to induce 40 isometric contractions. MVC decreased by 26% immediately and 1 h after both bouts, but the recovery was faster after the second bout (100% at 96 h) compared with the first bout (81% at 96 h). Development of muscle soreness and tenderness, and increases in plasma CK activity were smaller after the second than the first bout. These results suggest limited central regulations for the repeated bout effect.

Black and McCully (2008) compared the repeated bout effect on muscle damage between voluntary and electrically stimulated eccentric exercise (80 eccentric contractions) of the knee extensors. For both electrical voluntary and electrical stimulation conditions, two bouts were separated by 7 weeks. A repeated bout effect was observed in the changes in T2 relaxation time, MVC strength, and muscle soreness in both conditions similarly. They concluded that the repeated bout effect was not related to changes in muscle recruitment and was potentially related to structural changes within the muscles. Kamandulis et al. (2010) also reported that a single eccentric exercise bout was not sufficient to change the neural drive, and stated that repeated bout effect would reside primarily within the muscle not at the neural level. Muthalib et al. (under review) found that muscle activation, oxygenation and hemodynamics during eccentric exercise were not different between the first and second eccentric exercise bouts, suggesting that neural and metabolic factors are not the main mechanisms to explain the repeated bout effect.

In contrast, Howatson and van Someren (2007) reported the presence of a carry over effect from one arm to the other such that changes in MVC strength, serum CK activity, and muscle soreness were attenuated when a second bout of eccentric exercise of the elbow flexors was performed by the contralateral arm 2 weeks later. Newton et al. (under review) compared changes in markers of muscle damage between right and left arms following maximal eccentric exercise of the elbow flexors separated by 4 weeks with the order of testing between arms randomised. No significant group differences between arms were evident for any of the criterion measures, but the recovery of MVC strength was significantly faster, and increases in upper arm circumference and plasma CK activity were significantly smaller after the second bout compared with the first bout, although the magnitude of the difference between bouts was smaller when compared with the magnitude of the repeated bout effect shown in the same arm. These results suggest that the neural adaptation partially play a role in the repeated bout effect.

The repeated bout effect may be attributed more to mechanical adaptations (e.g. increases in passive or dynamic muscle stiffness, remodelling of intermediate filament system, increased intramuscular connective tissue) and/or cellular adaptations (e.g. longitudinal addition of sarcomeres, adaptation in inflammatory response, adaptation to maintain excitation-contraction coupling, strengthened plasma membrane, increased protein synthesis, increased stress proteins, removal of stress-susceptible fibers) (NOSAKA, 2010). Proske and Morgan (2001) suggested that increases in sarcomere number in series were associated with the repeated bout effect. This theory is indirectly supported by a shift of optimum angle toward a longer muscle length probably caused by increases in sarcomere number in series. However, it has been shown that the repeated bout effect is induced without a shift of optimum angle (CHEN et al., 2007). It does not appear that the repeated bout effect is explained by the increases in sarcomere number in series.

Koh and Brooks (2001) explained that upregulation of cytoskeletal proteins (desmin, talin, vinculin, dystrophin) and/or free radical scavenging pathways might be related to the repeated bout effect. McArdle et al. (2004) postulated that activation of the haemoxygenease-1 (HO-1) gene resulting from increased reactive oxygen and nitrogen species generation was related to the repeated bout effect. It has been reported that “remodelling” of cytoskeleton and/or endomysium could occur after a bout of eccentric exercise (BARASHI et al., 2002; YU et al., 2004).

It is also possible that muscle-tendon behaviour and fascicle length changes during maximal eccentric contractions are modified in the repeated bouts. If muscle fibers are lengthened less during eccentric contractions, less muscle damage may be induced. It might be that an initial eccentric exercise makes the muscle length changes in the subsequent exercise smaller, and reduced muscle strain during eccentric contractions. Further studies are necessary to delineate the mechanisms underlying the repeated bout effect.

Significance of the repeated bout effect

Regardless of the underlying mechanisms, the repeated bout effect should be used effectively to attenuate the magnitude of muscle damage when it is necessary. As shown in above, performing a light eccentric exercise or maximal isometric contractions at a long muscle length attenuates the magnitude of muscle damage and enhances the recovery following a higher intensity eccentric exercise. Peak muscle soreness is reduced 50% by performing a low-intensity eccentric exercise that does not induce any indications of muscle damage 2 weeks before maximal eccentric exercise (CHEN et al. under review). Therefore, if it is necessary to minimize potential muscle damage in exercise to be performed, it is advisable to perform a light eccentric exercise prior to the damaging exercise within two weeks, preferably within a week. When introducing eccentric exercise to individuals, it is better to start with eccentric contractions with very light load. Further studies are necessary to investigate how muscle damage is avoided completely, whether such strategy is beneficial for the outcomes of eccentric training.

It is also important to consider the repeated bout effect when designing a study. For example, if a treatment condition and control condition are compared to examine the effect of an intervention on muscle damage using a crossover design, the same muscle should not be used for the conditions. If a limb-to-limb comparison model such that one of the limbs (e.g. right arm) is used for a treatment condition, and other limb (e.g. left arm) is used for a control condition, the repeated bout effect can be minimized, if the order of the conditions is counterbalanced amongst the subjects. However, it should be noted that minor “repeated bout effect” is still evident for this model (NEWTON et al. under review).

Perspective for future research

Definitely, more research is necessary to elucidate the mechanisms of the repeated bout effect. It may be that there are several mechanisms involve in the repeated bout effect,

azilian Journal of Biomotricity, v. 5, n. 1, p. 5-15, 2011 (ISSN 1981-6324)

and the main mechanism is different among different kinds of the repeated bout effect; the repeated bout effect induced by maximal eccentric exercise; the repeated bout effect induced by submaximal eccentric exercise, and the repeated bout effect induced by non-damaging exercise. It is also possible that different mechanisms are responsible for different aspects of the repeated bout effect; faster recovery of muscle function, reduction of DOMS, and smaller or no increases in muscle proteins (e.g. CK, Mb) in the blood.

For the practical application of the repeated bout effect, it should be investigated further whether this adaptation is similar between muscles, between genders, between trained and untrained individuals, and between young and old individuals. It is interesting that isometric contractions or low-intensity eccentric contractions provide the protective effect against maximal eccentric contractions; however, it should be investigated further whether repeating the non-damaging exercise several times confers greater protective effect than a single bout. It is possible to minimize the magnitude of muscle damage using the repeated bout effect; however, it is not known whether this strategy is beneficial for maximizing muscle strength and size gain in training. If muscle damage is required to induce resistance training adaptations, minimizing the repeated bout effect is necessary. It is not known how the repeated bout effect can be eliminated. Better understanding of the repeated bout effect is necessary to clarify the mechanisms of the exercise-induced muscle damage, which have not been fully elucidated yet. Muscle damage and repeated bout effect research should be continued, although the topic is not new.

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AUTHORS BIOGRAPHY

Name: Kazunori Nosaka

Employment: Professor of School of Exercise, Biomedical and Health Sciences at Edith Cowan University, located in Joondalup, Western Australia, Australia.

Degree: PhD

Research interests: Exercise-induced muscle damage, Neuromuscular fatigue, Eccentric exercise, Resistance training, Exercise and Health.

Email: k.nosaka@ecu.edu.au

Name: Marcelo Saldanha Aoki

Employment: Assistant Professor of School of Arts, Sciences and Humanities at University of São Paulo, located in São Paulo, São Paulo, Brazil.

Degree: PhD

Research interests: Muscle plasticity, Sports nutrition, Training monitoring, Resistance exercise.

Email: saldanha.caf@usp.br

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