Task-Dependent Mechanisms Underlying Prolonged Low-Frequency Force Depression

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RICHARDS, A.J., D. WATANABE, T. YAMADA, H. WESTERBLAD, and A.J. CHENG. Task-Dependent mechanisms underlying prolonged low-frequency force depression. *Exerc. Sport Sci. Rev.*, Vol. 53, No. 1, pp. 41–47, 2025. *Prolonged low-frequency force depression (PLFFD) is an intramuscular phenomenon involving the slow recovery of submaximal muscle strength following strenuous exercise. We hypothesize that the contribution of impaired excitation-contraction coupling processes to PLFFD is task dependent, and that they will be different between metabolically and mechanically demanding exercises. We also discuss evidence of the effectiveness of interventions to mitigate PLFFD.* **Key Words:** muscle fatigue, postexercise recovery, contractile function, sarcoplasmic reticulum calcium release, myofibrillar calcium sensitivity, myofibrillar force production

KEY POINTS

- Prolonged low-frequency force depression (PLFFD) is characterized by impairments in strength that persist for hours or days following exercise cessation.
- PLFFD has implications for sport performance where the slow recovery of muscle function between competitions or training sessions hampers subsequent performance outcomes.
- The mechanisms underlying PLFFD are task dependent and differ between metabolically and mechanically demanding exercises.
- Interventions that may mitigate PLFFD include muscle heating or cooling; carbohydrate, arginine, and nitrate supplementation; and preconditioning contractions.

INTRODUCTION

Intense and prolonged exercise can result in long-lasting impairments in skeletal muscle force generation in the postexercise recovery period (1). This delay in the recovery of muscle strength likely underlies the sensation of muscle weakness during submaximal volitional efforts performed in the postexercise recovery period, or it can be exhibited in the experimental laboratory as reduced contractile force during involuntary evoked low-frequency stimulation of skeletal muscle that mimics the submaximal activation (Fig. 1A). Considering that voluntary efforts during a majority of locomotory tasks are submaximal in nature (2), the prolonged depression in strength can have marked implications on the recovery of exercise performance. This phenomenon was originally termed "low-frequency fatigue" but then rephrased as "prolonged low-frequency force depression (PLFFD)" to avoid misinterpretation that this delayed recovery of force is primarily caused by low-frequency electrically evoked contractions (1,3). Instead, PLFFD can be caused by various exercise intensities and contraction tasks, which is a focus of the current review.

Many studies in isolated single muscle fibers from humans and animals show PLFFD, suggesting that PLFFD is predominately explained by intramuscular mechanisms (3–5). Muscle contraction is evoked by the sequential intramuscular processes known as excitation-contraction (EC) coupling, which begins with action potential propagation into the transverse tubular (T)-system, where voltage sensors (dihydropyridine receptors, DHPR) are activated. DHPRs then trigger the opening of sarcoplasmic reticulum (SR) Ca^{2+} release channels (ryanodine receptors, RyR1) causing Ca^{2+} release from SR to the cytoplasm. Ca^{2+} then interacts with the actin filament regulatory troponin-tropomyosin complex, which allows myosin heads (cross-bridges) to bind to actin, and contractile force is generated. SR Ca^{2+} release and myofibrillar Ca^{2+} sensitivity predominantly cause PLFFD due to the sigmoidal relationship between force and cytoplasmic free $[Ca^{2+}]$ ($[Ca^{2+}]_i$) (see the following section; Fig. 2).

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Accepted for publication: September 26, 2024.
Editor: Chris J. McNeil, Ph.D.

0091-6331/5301/41–47
Exercise and Sport Sciences Reviews
DOI: 10.1249/JES.0000000000000352

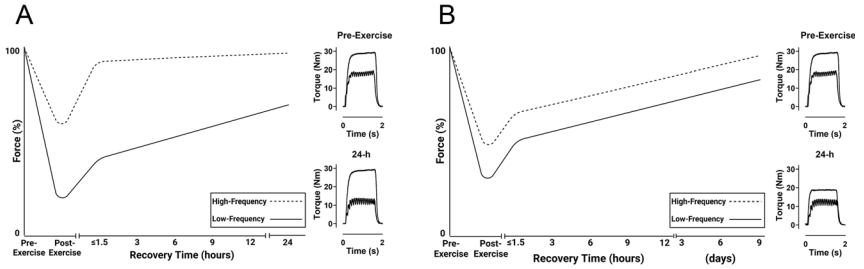

Figure 1. General schematic representing prolonged low-frequency force depression (PLFFD) following metabolically demanding (MET) and mechanically demanding (MECH) exercise in humans. A. The recovery of low- and high-frequency force following MET exercise with low-frequency force recovery displaying markedly reduced recovery compared to high-frequency force across a 24-h recovery time period. B. The recovery of low- and high-frequency force following MECH exercise with low- and high-frequency forces recovering at a slow yet similar rate across multiple days (≤9 d) following exercise. The torque traces are displaying hypothetical forces generally seen at specified recovery times during both MET and MECH exercise.

PLFFD has been observed following various exercise tasks, with these exercise types broadly classified as metabolically demanding (MET) and mechanically demanding (MECH) exercises (6). MET exercise is defined as a highly energetically demanding exercise that leads to substrate depletion or the accumulation of metabolic by-products from anaerobic and aerobic metabolism. On the contrary, MECH exercise entails mechanical stress to skeletal muscle caused by repeated eccentric (lengthening) contractions. The focus of this brief review is to provide evidence supporting the hypothesis that the intramuscular mechanisms causing PLFFD differ between MET and MECH exercise, *i.e.*, they are task dependent.

During exercise, cellular metabolic processes are highly activated in skeletal muscles to meet the energy demand of the exercise. In addition to metabolic demands, muscles are exposed to mechanical stress, especially when the exercise involves eccentric contractions, such as downhill running and drop jumps. It has been shown that PLFFD becomes more severe after MECH than after MET exercise (6,7). Furthermore, following MET exercise, PLFFD is more prolonged after interval than after continuous exercise even if the exercise volume is matched, highlighting that task dependency of PLFFD exists even between different types of MET exercise (6,8). Here, we hypothesize that i) the main contributor(s) to PLFFD are different between MET and MECH exercises, and ii) the mechanisms of PLFFD may differ depending on exercise types (*i.e.*, continuous vs interval). In particular, excessive production of reactive oxygen/nitrogen species (RONS) and glycogen depletion would be the main causes of PLFFD after MET exercise, whereas PLFFD after MECH exercise is likely to involve disruption and degradation of key proteins. In the next section, we will discuss cellular mechanisms that are proposed to underlie the task dependency of PLFFD.

PLFFD MECHANISMS

A relationship between force and $[Ca^{2+}]_i$ is dictated by the amount of Ca^{2+} released from the SR into the cytoplasm (Fig. 2A). This is demonstrated as a sigmoidal Hill curve in which the low-frequency force (*e.g.*, force evoked at 20 Hz) is on the steep portion of the curve while the high-frequency force (*e.g.*, force at 100 Hz) is on the plateau portion. When strenuous exercise causes a decrease in SR Ca^{2+} release, the same reduction in $[Ca^{2+}]_i$ will result in a greater force depression in the steep than in the plateau portion of the force-$[Ca^{2+}]_i$ relationship. Thus, decreased SR Ca^{2+} release is considered as one of the primary causes of PLFFD. Another major cause of PLFFD is that the force-$[Ca^{2+}]_i$ relationship shifts toward the right, (*i.e.*, decreased myofibrillar Ca^{2+} sensitivity) (Fig. 2B). In this case, there is a marked reduction in force on the steep but not on the plateau portion of the force-$[Ca^{2+}]_i$ relationship, even with the same $[Ca^{2+}]_i$. On the other hand, if the ability of the contractile machinery to produce force (*i.e.*, myofibrillar force) is decreased, low- and high-frequency forces are depressed to the same extent (Fig. 2C). Thus, decreases in SR Ca^{2+} release and myofibrillar Ca^{2+} sensitivity contribute to PLFFD, whereas reduced myofibrillar force causes a frequency-independent force

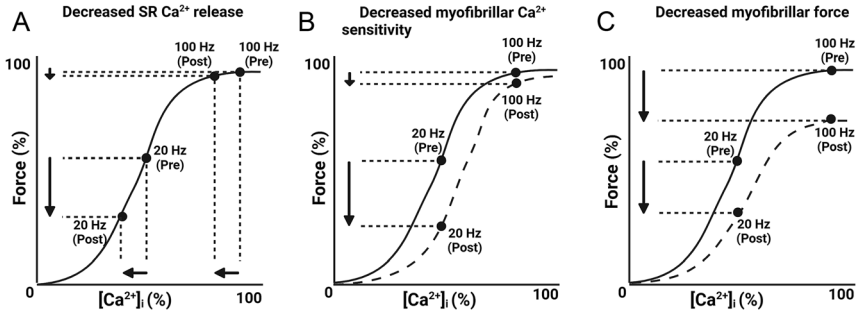

Figure 2. Schematic representing the changes typically observed in the force-$[Ca^{2+}]_i$ relationship caused by three distinct mechanisms of prolonged low-frequency force depression (PLFFD). The bold arrows depict the changes in force and $[Ca^{2+}]_i$ when stimulating at low (20 Hz) and high frequencies (100 Hz) before (Pre) and after induction of PLFFD (Post). Compared with the force-$[Ca^{2+}]_i$ relationship at Pre, (A) decreases in SR Ca^{2+} release cause a greater reduction in low versus high-frequency force, (B) decreases in myofibrillar Ca^{2+} sensitivity predominately cause a reduction in low- but not high-frequency force, and (C) decreased myofibrillar force causes a similar reduction in force at low- and high-frequencies. All three depicted mechanisms are using values typically observed based on hypothetical data.

decline. Potential task-dependent mechanisms causing PLFFD after MET exercise are an excessive production of RONS and muscle glycogen depletion, whereas PLFFD after MECH exercise involves degradation of key proteins involved in EC coupling (9,10). We will describe these intracellular mechanisms of PLFFD in further detail in the following sections.

PLFFD and RONS

RONS are free radicals that contain one or more unpaired electrons, but nonradical derivatives of oxygen (O_2) such as hydrogen peroxide (H_2O_2) or radical derivatives of nitrogen such as nitric oxide (NO) and peroxynitrite ($ONOO^{-\bullet}$) are also included as RONS. High-intensity exercise is known to increase intramuscular generation of the superoxide anion ($O_2^{-\bullet}$), which is primarily produced by NAD(P)H oxidase activity and as a byproduct of the mitochondrial electron transport chain (4). $O_2^{-\bullet}$ is moderately reactive and rapidly converted to H_2O_2 via mitochondrial superoxide dismutase. H_2O_2 is not highly reactive and is harmlessly broken down to H_2O and O_2 by the endogenous antioxidants (*i.e.*, catalase and the glutathione system). On the other hand, hydroxyl radicals ($OH^{\bullet}$), which is a highly reactive RONS, are produced when H_2O_2 reacts with free transition metals such as Fe^{2+} in the form of myoglobin. Nitric oxide synthase enzymes produce NO, and $ONOO^{-\bullet}$ is a highly reactive RONS produced when $O_2^{-\bullet}$ interacts with NO. In 1998, Andrade *et al.* were the first to show biphasic force changes depending on the cellular redox balance (11), with RONS exerting both positive and negative effects on force production (*i.e.*, brief and mild RONS exposure yields positive effects on force, whereas longer duration and excessive RONS exposure cause negative effects on force). Because oxidative modifications alter the function of the key proteins related to SR Ca^{2+} release and myofibrillar Ca^{2+} sensitivity, the excessive RONS production during and after exercise is proposed to cause PLFFD (4).

Recent studies have suggested that different RONS have distinct effects on the mechanisms causing PLFFD with MET exercise (12,13). Effects of various antioxidants on PLFFD in intact single fibers were previously investigated, and no antioxidant treatment could expedite the recovery of PLFFD (12). However, in the same study, the cellular mechanisms underlying PLFFD were different between treatments. Specifically, in nontreated control fibers, both SR Ca^{2+} release and myofibrillar Ca^{2+} sensitivity were decreased during PLFFD. On the contrary, treatment with mitochondrial $O_2^{-\bullet}$ scavenger SS-31 prevented the impairment of SR Ca^{2+} release but decreased myofibrillar Ca^{2+} sensitivity much greater than in the untreated fibers. Similar but not totally same results were observed during *in vivo* treatment of rats with Eukarion (EUK)-134, which is a potent antioxidant that converts $O_2^{-\bullet}$ to H_2O and O_2 due to its mimetic action of superoxide dismutase and catalase (13) (Fig. 3). These results suggest that mitochondrial $O_2^{-\bullet}$ is most likely to cause decreased SR Ca^{2+} release during PLFFD, whereas its downstream derivatives are likely to decrease myofibrillar Ca^{2+} sensitivity. Intriguingly, PLFFD evoked *in vivo* or *in situ* can be accompanied by increased myofibrillar Ca^{2+} sensitivity, which is then offset by a large decrease in SR Ca^{2+} release (13) (Fig. 3). RONS-induced *S*-glutathionylation of troponin I is a likely candidate for the alteration of myofibrillar Ca^{2+} sensitivity *in vivo* or *in situ* (14–16).

PLFFD and Muscle Glycogen

Muscle glycogen is a primary fuel source during exercise. From 1960s, it has been suggested that muscle glycogen depletion causes exhaustion during prolonged endurance exercise (17). Later studies showed that muscle glycogen depletion correlates with the reduction in force production during exercise, and the rate of glycogen resynthesis is positively associated with force recovery (18). Specifically, muscle glycogen depletion is a likely cause of PLFFD, which is supported by the evidence that i) force recovery at low frequencies is accelerated when muscle glycogen resynthesis is enhanced (19), and ii) severe PLFFD is observed when muscle glycogen was enzymatically removed without requiring to deplete glycogen by exercising the muscle (20). Muscle glycogen depletion has been shown to impair SR Ca^{2+} release due to functional impairments of related proteins (*e.g.*, Na^+/K^+ ATPase activity, RyR1 opening) (18,21). On the contrary, glycogen depletion would exert no or small effects on myofibrillar Ca^{2+} sensitivity and myofibrillar force (20).

Although the mechanism(s) underlying impaired SR Ca^{2+} release following glycogen depletion is not well understood, local ATP depletion in the restricted area between SR and T-tubule has been proposed. At the cellular level, it has been established that stored muscle glycogen is compartmentalized into three distinct areas: subsarcolemma (subsarcolemmal glycogen), between myofibrils (intermyofibrillar glycogen), and within myofibrils (intramyofibrillar glycogen) (22). Intra- and intermyofibrillar glycogen, but not subsarcolemmal glycogen, was decreased after repeated stimulation showing the strong correlation between $[Ca^{2+}]_i$ and glycogen in these two compartments (22). In the triads, there is a restricted space of only ~12 nm between the SR and T-tubule where key proteins involved in SR Ca^{2+} release are located. The supply of ATP in this restricted space is preferentially provided by the breakdown of glycogen, and depletion of glycogen in this region might lead to a localized reduction of [ATP] that impairs the function of key E-C coupling proteins (21). Specifically, SR Ca^{2+} release does not depend on ATP hydrolysis, but rather RyR1 opening can be inhibited by low [ATP] (19). Inhibited RyR1 opening then leads to PLFFD because a given amount of decreased SR Ca^{2+} release will cause a greater reduction in low-frequency force on the steepest portion of the force-$[Ca^{2+}]_i$ relationship than with high-frequency force on the plateau portion of the force-$[Ca^{2+}]_i$ relationship (Fig. 2A). In addition to local ATP depletion, glycogen depletion may lead to structural alterations in the triad where glycogen forms a large particle tightly attached with the SR membrane that may act as an anchor molecule (23).

PLFFD and Key Protein Degradation

Many proteins are involved in SR Ca^{2+} release, myofibrillar Ca^{2+} sensitivity, and myofibrillar force. Essential proteins for SR Ca^{2+} release are the ryanodine receptor (RyR, the SR Ca^{2+} release channel), the dihydropyridine receptor (DHPR, the T-tubular voltage sensor), junctophilin (JP, a structural protein that preserves triads), and SH3 and cysteine-rich domain 3 (STAC3, a protein interacting with DHPR). Myofibrillar Ca^{2+} sensitivity and myofibrillar force are associated with the functions of myofibrillar proteins including troponin, tropomyosin, myosin, actin, and titin. Modification of any of these proteins might be involved in PLFFD. Protein modification pathways include lysosomal proteolysis, the ubiquitin-proteasome pathway,

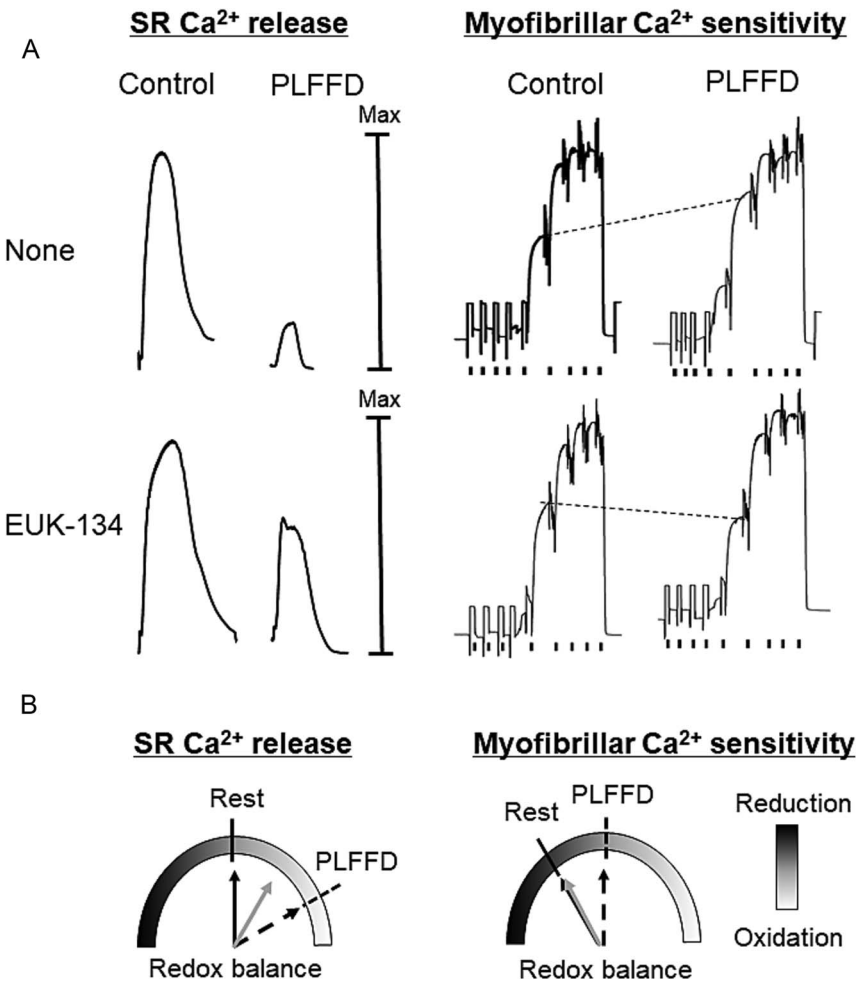

Figure 3. Injection of potent antioxidant Eukarion (EUK)-134 fails to improve prolonged low-frequency force depression (PLFFD), but cellular mechanisms underlying PLFFD are altered. A. Actual force responses in mechanically skinned fiber. Rats were treated with or without EUK-134 before metabolically demanding contractions (FC), which were then applied *in vivo*. Significant PLFFD was observed 30 min after the end of FC in both groups, with no difference in the extent of PLFFD between them. At the 30-min recovery point, mechanically skinned fibers were obtained and depolarization-induced force and myofibrillar Ca^{2+} sensitivity were measured. SR Ca^{2+} release was assessed with depolarization-induced force, which was decreased during PLFFD and EUK-134 mitigated the decline. Myofibrillar Ca^{2+} sensitivity was estimated by forces at various concentration of Ca^{2+}. Dashed lines indicate the change in force at pCa5.8 following PLFFD, which increased in no-treatment fiber but remained unchanged in EUK-134-treated fiber. B. A schematic illustration of the effect of the antioxidant on PLFFD. The antioxidant mitigates a decrease in SR Ca^{2+} release but prevents an increase in myofibrillar Ca^{2+} sensitivity, as indicated by gray arrows. [Adapted from Watanabe D, Aibara C, Wada M. Treatment with EUK-134 improves sarcoplasmic reticulum Ca^{2+} release but not myofibrillar Ca^{2+} sensitivity after fatiguing contraction of rat fast-twitch muscle. *Am J Physiol Regul Integr Comp Physiol*. 2019; 316: R543–551. Copyright © 2019 American Physiological Society. Used with permission.]

and calpains. Of these, calpains are linked to PLFFD, particularly after MECH exercise (9,10,24–27). Calpains are Ca^{2+}-activated, nonlysosomal cysteine proteases, which in skeletal muscle consist of three isoforms (*i.e.*, calpain-1, 2, and 3). Calpain-1 is thought to be a main contributor of exercise-induced protein degradation, because i) supraphysiological [Ca^{2+}] is required for the activation of calpain-2 (28), and ii) a deficiency of calpain-3 exerts no obvious effect on Ca^{2+}-induced EC uncoupling (9,29).

TASK DEPENDENCY OF PLFFD

Metabolically Demanding Exercise-Induced PLFFD

The increased energy consumption during MET exercise requires accelerated cellular energy metabolism. This metabolic stress causes muscle glycogen depletion during prolonged exercise, and it also results in increased RONS production, especially during high-intensity exercise, with both factors linked to PLFFD. Muscle glycogen can take ≥24 h to fully resynthesize after the end of exercise, and faster recovery of PLFFD has been observed when muscle glycogen synthesis was accelerated (19). Several studies show evidence for a central role of increased RONS in the development of MET-related PLFFD, although antioxidant treatment altered the underlying mechanisms rather than accelerating the early recovery of PLFFD (2,12,13). Accordingly, a recent study showed that glutathione depression delays the recovery of PLFFD induced by MET contractions in the late (6 h postexercise) but not the early (30 min postexercise) recovery phase (30).

Recovery of PLFFD after interval exercise seems to be slower than that after continuous exercise even if the exercise volume is similar. For instance, Skurvydas *et al.* (2016) showed more severe PLFFD after interval than after continuous exercise, even though the exercise times were matched (6). This suggests larger RONS production during the high-intensity intervals. Indeed, the results of a study on rodents imply that a RONS-mediated

delayed recovery of SR Ca^{2+} release underlies the slower recovery of PLFFD after interval versus continuous exercise (8). Moreover, RONS-related RyR fragmentation was observed after high-intensity interval cycling but not after a marathon race (25), which supports the link between RONS-related alterations in interval, but not continuous, exercise.

A sensation of exaggerated muscle weakness is regularly experienced after intense MET exercise; for example PLFFD becomes more noticeable several minutes after MET exercise as opposed to immediately after exercise (6,16). The further decline of the low- to high-frequency force ratio several minutes after exercise can be attributed to two factors: i) the force at high-frequency recovers more rapidly than low-frequency force (1,6,16,25), and ii) the force at low-frequency can be potentiated for a few minutes after exercise (31). For the first factor i), the removal of metabolic by-products (*e.g.*, inorganic phosphate) is thought to be a primary cause for the quick recovery of high-frequency force after high-intensity exercise (32). Regarding the second factor ii), the enhancement of submaximal force is mainly attributed to increased myofibrillar Ca^{2+} sensitivity due to myosin light chain phosphorylation (31).

Mechanically Demanding Exercise-Induced PLFFD

Mechanical stress during exercise is known to lead to a large force decline and slow force recovery. Unlike PLFFD induced by MET exercise, MECH exercise is characterized by force depression at all stimulation frequencies, which nevertheless is more marked at low than at high stimulation frequencies (6) (Fig. 1B). PLFFD after MECH exercise generally requires a longer recovery time than after MET exercise. For example, it has been demonstrated that PLFFD after drop jumps, a type of MECH exercise, appears to be more severe compared to that after MET exercises involving maximal voluntary isometric contractions or after cycling exercise (6).

Decreased SR Ca^{2+} release emerges as the main cause of PLFFD after MECH exercise (10,33,34). This decreased SR Ca^{2+} release has been shown to last for several days after MECH exercise (34). It should be acknowledged that the decreased SR Ca^{2+} release can in principle be due to impaired release function of RyR1, or to decreased SR Ca^{2+} content, and the relative importance of these can be tested in future studies by measuring the cellular Ca^{2+} content with the BAPTA lysis technique (35). Intriguingly, the relative contribution of myofibrillar dysfunction to PLFFD has been shown to increase at ~4 d after MECH exercise (36). Accordingly, actomyosin ATPase activity and the amounts of myofibrillar proteins, including myosin heavy chain and actin, were decreased >4 d after MECH exercise (37), and increased levels of fragments of myosin heavy chain in the human blood samples were observed 3 to 9 d after MECH exercise (38). Thus, decreased SR Ca^{2+} release largely contributes to PLFFD up to 3 d after MECH exercise, whereas myofibrillar dysfunction predominately causes PLFFD that persists beyond 3 d after MECH exercise. Accordingly, the time course of protein degradation after MECH exercise differs, wherein proteins regulating SR Ca^{2+} release, such as JP and STAC3, are degraded hours to a few days after MECH exercise, whereas the myofibrillar proteins are cleaved more than 4 d after MECH exercise (36,37).

PLFFD after MECH exercise most likely involves calpain-mediated protein degradation. Accordingly, calpain inhibitors reduce protein degradation and thereby mitigate PLFFD after eccentric contractions (10). The calpain activation has been attributed to an increased resting $[Ca^{2+}]_i$ due to increased influx of extracellular Ca^{2+} after MECH exercise (24,39). Moreover, increased RONS may contribute to the slow recovery of PLFFD after MECH exercise. It is well known that macrophages and neutrophils, which can produce RONS via their NADPH oxidase and myeloperoxidase, invade muscle cells days after MECH exercise (24).

The decreased myofibrillar force after MECH exercise is likely due to some structural derangements of the myofilaments. However, Kamandulis *et al.* (2017) observed no marked myofilament derangements 24 h after drop jump exercise, which caused a major decrease in myofibrillar force (7). In fact, they only observed a minor Z disc broadening, which is unlikely to be a major contributor to PLFFD after MECH exercise (24,39).

INTERVENTIONS TO MITIGATE PLFFD

Antioxidants

As discussed above, there is solid support for a central role of increased RONS production in the development of PLFFD, and antioxidant treatment can alter mechanisms underlying PLFFD. Still, it remains unclear if antioxidants can alleviate PLFFD because many studies have not observed positive effects (2,12,13). However, they may exert positive effects on the recovery from PLFFD in the late recovery phase as described above (30).

Heating

Heating muscles before exercise and during the postexercise recovery period is likely to be an effective strategy to limit PLFFD if various conditions (*e.g.*, temperature, time, and frequency) are optimized. For instance, the recovery of PLFFD was accelerated when heating was repeatedly performed once a day for 5 d before exercise (40), whereas heating only 1 d prior to MET exercise did not yield positive effects on PLFFD (41). Although the precise mechanisms responsible for the beneficial effect remain unclear, there is evidence suggesting that pretreatment with heating enhances the recovery of SR Ca^{2+} release (40). Heating during the recovery phase has been shown to accelerate the recovery from PLFFD. This positive effect has been linked to accelerated glycogen resynthesis (42), which has been observed in studies showing higher muscle glycogen levels associated with increased muscle glycogenolysis and greater lactate production after MET exercise, and faster protein resynthesis after MECH exercise (19).

Cooling

Cold water immersion has emerged as a popular postexercise recovery modality for a variety of exercise types (43), but little is known as to whether it can mitigate PLFFD following different exercise tasks. In one study, it was shown that 2 h of cooling intact single mouse muscle fibers in the postexercise recovery period after MET exercise impaired the recovery of PLFFD by depressing the recovery of SR Ca^{2+} release (19). The cause of this impaired recovery of SR Ca^{2+} release with cooling was linked to impaired glycogen resynthesis, which is suggested to occur due to a slowed metabolic rate, as well as localized cooling constricting blood flow and limiting glucose delivery to the depleted muscles (42). However, further studies are needed to

assess the task-dependent effects of cooling on PLFFD following various MET and MECH exercises.

Carbohydrates

The reversal of PLFFD can be accelerated by carbohydrate supplementation that speeds up glycogen resynthesis (44,45). However, carbohydrate supplementation did not accelerate the recovery of PLFFD at 3 h after glycogen-depleting MET exercise that was followed by six all-out, 30-s cycling sprints, although muscle glycogen recovered faster in the carbohydrate-fed versus placebo group (45). This might be taken to illustrate the dual mechanisms underlying MET-induced PLFFD: the faster glycogen restoration would speed up recovery, but the cycling sprints added glycogen-independent PLFFD caused by increased RONS production (45).

Arginine

Arginine is a substrate for nitric oxide (NO) synthase, and therefore NO production is enhanced by the ingestion of arginine. The calpain-1 activity can be inhibited by NO donor via *S*-nitrosylation of calpain-1 (34). Kanzaki *et al.* (2018) showed that arginine ingestion attenuated PLFFD 3 d after eccentric contractions concomitant with less activation of calpain-1 owing to *S*-nitrosylation (34). In line with this, soy protein that contains high amount of arginine has been shown to mitigate PLFFD after MECH exercise (46).

Nitrate

The nitrate-nitrite-NO pathway has received a lot of attention due to its potential to improve exercise performance (47). Dietary nitrate has been shown to increase SR Ca^{2+} release in mouse fast-twitch muscle fibers, indicating that it might mitigate PLFFD (48). Beetroot-based supplements in the form of beetroot juice, powder, or gel are the most common forms of nitrate supplementation, and a recent systematic review and meta-analysis show significantly increased force production after fatiguing exercise (49).

Preconditioning Contractions

Preconditioning non-damaging contractions have been shown to improve recovery rates from subsequent damaging MECH exercise (50). Accordingly, preconditioning contractions alleviate PLFFD after MECH exercise by limiting the degradation of triad and myofibrillar proteins (26,36). Furthermore, preconditioning contractions might help replace weaker muscle fibers with stronger fibers that are more resistant to MECH damage overtime with intensity of the contractions used impacting the initial damage and remodeling process. Altogether, non-damaging preconditioning contractions seem to contribute to the favorable recovery of force, range of motion, and muscle soreness compared to no preconditioning contractions (50). Future studies are needed to determine which types of exercise are most effective before a subsequent bout of damaging MECH exercise.

CONCLUSION

Most sports demand diverse skills such as agility, strength, and endurance. Therefore, athletes incorporate varied types of exercise into their training. In this review, we explored the hypothesis that the mechanism(s) underlying PLFFD differs depending on the exercise task. Interventions to limit PLFFD are crucial for athletes engaging in high-intensity training, because performing subsequent exercise without sufficient recovery may impair performance, provoke overtraining, and increase the risk of injuries (51). If athletes can choose appropriate interventions to limit PLFFD based on the exercise task, they may experience faster recovery, enabling them to train or compete more frequently without experiencing overtraining or injuries. Further basic studies are needed to increase the understanding of mechanisms underlying PLFFD after exercise with different contraction modes and intensities. Additionally, further translational studies are needed to test the effectiveness of interventions aimed at counteracting cellular PLFFD mechanisms, and in this way generate knowledge to improve athletic training regimes and performance.

Acknowledgments

This manuscript was supported by an NSERC Discovery grant awarded to A.J.C. (RGPIN-2020-06443, DGECR-2020-00136). All authors declare no conflict of interest.

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