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Mechanisms underpinning protection against eccentric exercise-induced muscle damage by ischemic preconditioning

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ABSTRACT

Eccentric exercise training is effective for increasing muscle mass and strength, and improving insulin sensitivity and blood lipid profiles. However, potential muscle damage symptoms such as prolonged loss of muscle function and delayed onset of muscle soreness may restrict the use of eccentric exercise, especially in clinical populations. Therefore, strategies to reduce eccentric exercise-induced muscle damage (EIMD) are necessary, and an extensive number of scientific studies have tried to identify potential intervention modalities to perform eccentric exercises without adverse effects. The present paper is based on a narrative review of current literature, and provides a novel hypothesis by which an ischemic preconditioning (IPC) of the extremities may reduce EIMD. IPC consists of an intermittent application of short-time non-lethal ischemia to an extremity (e.g. using a tourniquet) followed by reperfusion and was discovered in clinical settings in an attempt to minimize inflammatory responses induced by ischemia and ischemia-reperfusion-injury (I/R-Injury) during surgery. The present hypothesis is based on morphological and biochemical similarities in the pathophysiology of skeletal muscle damage during clinical surgery and EIMD. Even though the primary origin of stress differs between I/R-Injury and EIMD, subsequent cellular alterations characterized by an intracellular accumulation of Ca^{2+}, an increased production of reactive oxygen species or increased apoptotic signaling are essential elements for both. Moreover, the incipient immune response appears to be similar in I/R-Injury and EIMD, which is indicated by an infiltration of leukocytes into the damaged soft-tissue. Thus far, IPC is considered as a potential intervention strategy in the area of cardiovascular or orthopedic surgery and provides significant impact on soft-tissue protection and downregulation of undesired excessive inflammation induced by I/R-Injury. Based on the known major impact of IPC on skeletal muscle physiology and immunology, the present paper aims to illustrate the potential protective effects of IPC on EIMD by discussing possible underlying mechanisms.

Introduction

The significance of eccentric strength training as a method to effectively induce neuromuscular adaptations in athletic and clinical populations is widely accepted, and has been fairly well investigated [1–4]. The beneficial adaptations of prolonged eccentric strength training are typically attributed to the superior physiological and neuromuscular responses to eccentric (lengthening) muscle contractions compared to concentric (shortening) muscle actions [5–9]. It has been shown that eccentric muscle contractions can produce greater muscle force compared to concentric or isometric muscle contractions, while the amplitude of the recorded electromyographic activity is lower [5,6]. Furthermore, exercises consisting of mainly eccentric muscle contractions (e.g. descending stair walking) are less metabolically demanding compared to exercises consisting of mainly concentric muscle contractions (e.g. ascending stair walking), performed at comparable mechanical power outputs [9]. This has also been shown by lower

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oxygen consumption as well as reduced heart rate and cardiac output during eccentric cycling exercise at both low and high intensities [7,8].

Eccentric exercises induce mechanical strain to muscle fibers and their surrounding extracellular matrix [10], initiating a series of biological cascades in the loaded muscle tissue, ultimately leading to muscle damage. It has been reported that eccentric muscle contractions impair Ca^{2+}-homeostasis [11] with a minatory loss of the sarcolemmal integrity [12]. Additionally, oxidative stress [13] is produced as the result of an incipient immune response [14] and an increased activity of enzymes, such as xanthin oxidase [15]. These changes are even more pronounced when unaccustomed eccentric exercises are performed, and may result in exercise-induced muscle damage (EIMD), characterized by prolonged decreases in muscle function and delayed onset muscle soreness (DOMS) [16,17].

Since the symptoms of muscle damage may negatively affect adherence to exercise, scientific studies have attempted to provide methods that would help minimize adverse effects of eccentric exercises. For example, it has been shown that a prior bout of low intensity and/or low volume of eccentric muscle actions induce protective mechanisms for EIMD caused by maximal eccentric contractions for up to several weeks [18–20]. Furthermore, maximal voluntary isometric muscle contractions at long muscle length confer protection against EIMD induced by maximal EIMD eccentric contractions, although this effect seems to last for a much shorter period of time only [21–23]. Many previous studies have also attempted to examine the effects of dietary supplements on EIMD protection in an attempt to modulate antioxidant and/or anti-inflammatory processes [24]. Among these supplements, those that have been shown to provide favorable effects include curcumin [25,26], low-fat milk [27] and black currant nectar [28]. Furthermore, it was shown that supplementation of estradiol may blunt EIMD, possibly due to its neuro- or osteoprotective effects [29].

During medical procedures in orthopedic surgery, tourniquets are commonly applied in order to reduce blood loss [30], to obtain a clearer visualization of the surgical field [31], and to provide optimal conditions for the use of bone cement in knee replacement surgery [32]. However, this occlusion and the subsequent reperfusion are associated with substantial cellular and immunological changes in skeletal muscle, similar to those occurring in eccentric EIMD [33]. The applied pressure of the tourniquet as well as the time under ischemia with subsequent reperfusion have been shown to cause severe muscle damage, in some cases even leading to rhabdomyolyses [34].

From intervention studies it is known that preconditioning of the skeletal muscle by short-time intermittent non-lethal ischemia and subsequent reperfusion (ischemic preconditioning, IPC) may reduce this ischemia- and reperfusion-induced tissue damage [35–37]. However, to the best of our knowledge so far no study has investigated whether IPC may also protect against EIMD.

We propose a hypothetical model about the possible protective mechanisms of IPC against EIMD, by which cellular adaptations are stimulated, and the adverse effects of eccentric exercise are minimized. As IPC aims at downregulating the immune responses [38], it is possible that concomitant inhibitive effects on EIMD may sustain for much longer than those observed by nutritional supplementations. The present paper may be considered as a base for experimental study designs, confirming our hypothesis and provides practitioners with a possible method to minimize EIMD in order to facilitate the application of such training regimen.

Ischemic preconditioning (IPC)

The phenomenon of IPC is based on the observation that repeated bouts of non-lethal ischemia with subsequent reperfusion applied to the afferent vessels of several organs (e.g. myocardium, liver and/or kidney) leads to an improved tolerance of these organs to long-term ischemic periods [39,40] or ischemia – reperfusion injury (I/R-Injury) [41,42]. Przyklenk and colleagues [43] demonstrated in canine models that IPC of the circumflex branch prior to a sustained left anterior descending coronary artery occlusion led to a reduced infarct size of the myocardium at risk. Much later applications of these early findings to an occlusion of extremities (called remote ischemic preconditioning) [44], made it a potential non-invasive method for the prospective use in clinical procedures such as surgical care.

To date, several clinical studies have tried to replicate the findings obtained from animal models [44] by using IPC in surgical or conservative therapies through occlusion of the femoral- [45] or brachial artery [46]. While scientific evidence suggests that IPC applied remotely prior to and during surgeries may reduce cardiac and skeletal muscle damage [47] and protect distant organs (e.g. heart, liver and/or kidney) [48–50], thus far no official consensus about the efficacy of IPC in the clinical practice exists.

Despite some knowledge originating from animal- and human-models, the exact mechanisms underlying the protective effects of IPC are still unknown. However, previous observations suggest several systemic alterations rather than a single cellular modification as the probable cause [51]. Specifically, some studies indicate that the effects of IPC are attributed to cellular alterations induced by various circulating mediators, such as agonists for opioid-receptors [44] or exosomes [52], as well as modifications of neural pathways through autacoids, such as adenosine [53]. Furthermore, a protective genomic response may be initiated by IPC, characterized by a modified transcription of pro-inflammatory-genes as well as an increased expression of antioxidative enzymes [54] and pro-survival proteins [33]. These adaptations were previously shown both in the conditioned organ as well as in the circulating leukocytes [55], supporting the evidence for a systemic response to IPC.

Effects of IPC on ischemia- or reperfusion-induced skeletal muscle damage

Acute ischemia typically induces an initial shift in the energy metabolism towards anaerobic glycolysis, with subsequent cellular acidosis [56,57]. When maintained for a prolonged time, ischemia may also lead to a concomitant ATP-depletion by glycolytic substrate exhaustion [58]. This O_2-depletion, in turn, increases the production of reactive oxygen species (ROS) [31] by an enhanced activity of xanthine oxidase [59,60], as well as by changes in mitochondrial function [61,62]. Collectively, these alterations in muscle cell homeostasis may lead to a failure of ATP-depending systems such as Na^+/K^+-ATPases [63] and an enhanced activity of the $Na^+/Ca2^+$-Exchanger (NCX) [64], possibly contributing to an uncontrolled influx of Ca^{2+} through membrane depolarization [63,65]. Thus, long-term ischemia of extremities may lead to a large magnitude of tissue damage, characterized by inflammation, interstitial edema and myonecrosis [66,67].

In addition to prolonged ischemia, the subsequent reperfusion of blood into ischemically stressed tissue may lead to further damage (I/R-Injury). This is thought to be attributed to additional cellular alterations, such as a continued accumulation of Ca^{2+} [68] and a secondary increase in ROS-production [69], as well as systemic modifications such as an ischemia-induced leukocytosis [70]. Thus, I/R-Injury is considered as a serious medical condition with wide ranging characteristics including local tissue damage like fiber disruptions or necrosis [35,71], but also systemic lethal pathologies associated with inflammatory syndromes or rhabdomyolysis-induced renal impairment [72].

The mechanisms underlying I/R-Injury may be related to pro-inflammatory responses during reperfusion, initiated by an activation of the complement system [73] and a concomitantly