Ischemia–Reperfusion Intervention

Subjects: Biology
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It has been demonstrated that brief cycles of ischemia followed by reperfusion (IR) applied before exercise can improve performance and, IR intervention, applied immediately after exercise (post-exercise ischemic conditioning—PEIC) exerts a potential ergogenic effect to accelerate recovery. Thus, the purpose of this systematic review with meta-analysis was to identify the effects of PEIC on exercise performance, recovery and the responses of associated physiological parameters, such as creatine kinase, perceived recovery and muscle soreness, over 24 h after its application. From 3281 studies, six involving 106 subjects fulfilled the inclusion criteria. Compared to sham (cuff administration with low pressure) and control interventions (no cuff administration), PEIC led to faster performance recovery ($p = 0.004$; ES = −0.49) and lower increase in creatine kinase ($p < 0.001$; effect size (ES) = −0.74) and muscle soreness ($p < 0.001$; ES = −0.88) over 24 h. The effectiveness of this intervention is more pronounced in subjects with low/moderate fitness level and at least a total time of 10 min of ischemia (e.g., two cycles of 5 min) is necessary to promote positive effects.

Keywords: intermittent occlusion ; blood flow occlusion ; sports ; ergogenic ; ischemic postconditioning

1. Introduction

High-level sports performance is dependent on several factors that require high mechanical [1], psychological [2] and physiological [3] demands. Elite competitors are usually submitted to successive high volume and intensity training sessions and/or to multi-days competitions, with short intervals of recovery. These events can lead to physiological [3] and psychological [4] alterations, impairing sports performance. Thus, to increase the resistance to fatigue and to improve performance, many athletes and coaches search post-exercise recovery strategies [5].

In this context, cycles of ischemia–reperfusion (IR) performed immediately after exercise (post-exercise ischemic conditioning—PEIC) are an interesting ergogenic aid to accelerate recovery during high intensity exercise sessions [6][7]. This intervention is actually low cost, non-invasive, easy and quick-to-apply compared to other methods, such as cold-water immersion [8][9]. The IR requires the use of a cuff (tourniquet) on the proximal regions of the lower or upper limbs and the execution of repeated bouts of ischemia interspersed with reperfusion periods [10]. Analyzing the studies with IR and exercise performance, it is possible to verify that the most common applied IR protocols encompass three or four bouts of 5 min of ischemia followed by 5 min of reperfusion among bouts [11][12].

IR interventions were initially used before a prolonged ischemic insult that causes myocardial necrosis. This type of intervention, termed ischemic preconditioning, was able to confer cardiac protection against myocardial infarct [13] and it was associated with low increases in tissue necrosis biomarkers (i.e., creatine kinase (CK)) [14] and improved cardiac performance during exercise [15][16]. Afterwards, the use of IR interventions after prolonged ischemic insult, termed ischemic postconditioning, also promoted protection to heart tissue [14] and reduced oxidative stress [17]. When IR interventions were applied to improve exercise performance, the history was similar: firstly, performance before physical exercise promoted a better skeletal muscle capacity [18], improved performance of swimmers [19], runners [20], and cyclists [21]. Then, application immediately during recovery phase from exercise prevented the drops in performance 24 h, 48 h, and 72 h after an exercise-induced muscle damage, mitigating increases in CK [7]. It is important to note that both the mentioned tissue biomarkers and oxidative stress are associated with drop in sports performance [22][23]. Therefore, during recovery, PEIC application could attenuate tissue and oxidative injury caused by exercise.

The first study that evaluated the PEIC effect during recovery phase [24] employed the intervention immediately after an exercise protocol that involved jumps and repeated sprints. After PEIC, the participants repeated the exercise protocol, and again 24 h later. Beneficial effects were observed both immediately and 24 h post intervention. Specifically, recovery of power production and sprint performance were improved. Compared with other IR studies [25][26], the authors used a short protocol (two bouts of 3 min of ischemia followed by 3 min of reperfusion; 2 cycles × 3 min). Based on this protocol, Northey et al. [27] evaluated the velocity of recovery applying the PEIC immediately after a fatiguing resistance exercise protocol. PEIC was not able to attenuate the loss in muscle force during jumps and the torque during concentric isokinetic contractions 1 h and 24 h later. Similar lack of beneficial results using the same IR protocol were observed in academy rugby players 2 h and 24 h after PEIC application [28] but longer protocols (e.g., three cycles × 5 min) were also efficient to prevent decrements in maximal voluntary contraction, jumps and sprints performance [7][29].

Beyond a limited amount of investigations and controversial results, it is important to describe the heterogeneity of PEIC and exercise protocols to induce fatigue (specific and non-specific), as well as the fitness level of evaluated volunteers. Therefore, it would be appropriate to evaluate the current status and the future perspective of PEIC on physical performance recovery including their possible mechanisms. To this aim, we conducted this review and meta-analysis.

2. Quality of the Papers

Although a high-quality score has been achieved by studies, some limitations were found. Most of the studies did not clearly describe the characteristics of the subjects included in the investigation (criterion 3) [7][27][28]. This can make it difficult to interpret results and to reapply the protocols used. Only two studies reported the exact *p*-value (criterion 10) for main results [28][29]. The latter one provided information about the strength of the evidence against the null hypothesis, avoiding doubts for the reader to make a decision. We have also concern about the appropriate use of statistical analysis (criterion 12) [7][24][28], as authors did not perform normality tests of data nor parametric tests for categorical variables (e.g., perceived exertion and pain perception). In addition, they utilized the independent test for paired sample. However, this inappropriate statistical did not influence our meta-analysis, since we have worked with raw data.

Finally, only one study included confidence intervals (CIs) for the main results (criterion 14) [24]. The CI is employed to show the dispersion or variability/reliability of an estimate, which likely includes the estimate of the average of populations. This is influenced by the sample size and the homogeneity of the data sample and it can be used to describe how reliable the results of a research study are. In addition, only two studies estimated the sample size and statistic power [6][29].

3. Participants Involved

Of 106 participants, only four were female, which reduces the possibility of suggesting the PEIC effects in women. The studies that demonstrated favorable effects of PEIC on performance recovery [6][7][24][29] involved healthy participants, semi-professional soccer players and recreationally trained or active subjects, while other studies involved well trained and college level participants [27][28]. There is no study with elite or high-trained athletes. This fact is comprehensible due to the difficulty in recruiting athletes available for this kind of research. Therefore, the positive effects of PEIC have not been investigated in this type of population because their physiological and performance responses are different from those found in non-athletes in several aspects. In addition, the responsiveness of IR intervention, when applied before exercise or test to improve performance, has been associated with the training level of the subjects. Specifically, it was demonstrated that participants with low fitness level presented large [30] while high training level small [19] or no response to this intervention [31]. In this context, since PEIC responses have the same pattern, it could be speculated that its responses are also dependent on the fitness level of subjects. However, it is important to highlight that, following the quality scores of studies, most of them did not clearly describe the characteristics of the enrolled subjects.

4. Exercise Protocols to Induce Fatigue and Assess Performance

The PEIC effects were primarily tested in exercise types that involved vertical jumps, sprints, and resistance exercise [24]. Although one study investigated used an incremental cycling test [6], the most common tests were jumps and maximal voluntary contraction [7][27][28][29]. Although these tests were largely used to evaluate changes in performance [32], they may not be sensitive enough to identify these changes 24 h after exercise [27]. Among studies selected for this review, some did not identify significant declines in exercise performance 24 h after the execution of fatiguing protocols in the sham/control, or PEIC groups when compared to pre-intervention. For example, in the Northey et al. [27] study, the performance of the countermovement jump and the concentric isokinetic peak torque measured in the pre-fatiguing protocol were not different after 24 h among and within groups. The same result was obtained by Williams et al. [28], who investigated peak power output and jump height. They found no difference 24 h after fatiguing protocol for both sham/control and PEIC groups when compared to pre-intervention. On the other hand, in the Arriel et al. [6] study, the sham group presented a drop of performance during incremental cycling 24 h after fatiguing protocol, but after PEIC this phenomenon was not observed. The same happened in the study by Page et al. [7] and by Daab et al. [29] but on the maximal isometric voluntary contraction. Alternatively, this fact may also mean that the physical exercise dose to induce fatigue was not able to cause a drop in performance 24 h after physical exercise. Therefore, these procedures may lead to misleading conclusions on the potential effects of PEIC 24 h post physical exercise.

5. PEIC Effects on Performance Recovery, CK and MS

Oxidative stress, muscular damage, increased inflammation, and MS associated with a decreased performance have all been reported after exhaustive exercise performed by different athletes involved in different sports [3][33][34], especially those over the course of the multi-day races (i.e., 2 to 7 consecutive days of competition) [3][34] and with high training volumes [35]. This phenomenon may be useful for athletes and coaches searching strategies that minimize decrements in performance or to accelerate the recovery from fatiguing efforts. As exposed in **Figure 1**, our statistical analysis showed a favorable PEIC effect on performance recovery, CK (muscle damage markers), and MS. Although there is not enough evidence to support a remarkable use of the PEIC immediately after exercise to reduce these biomarkers and to speed recovery, this intervention could lead to an improvement in recovery in these individuals.

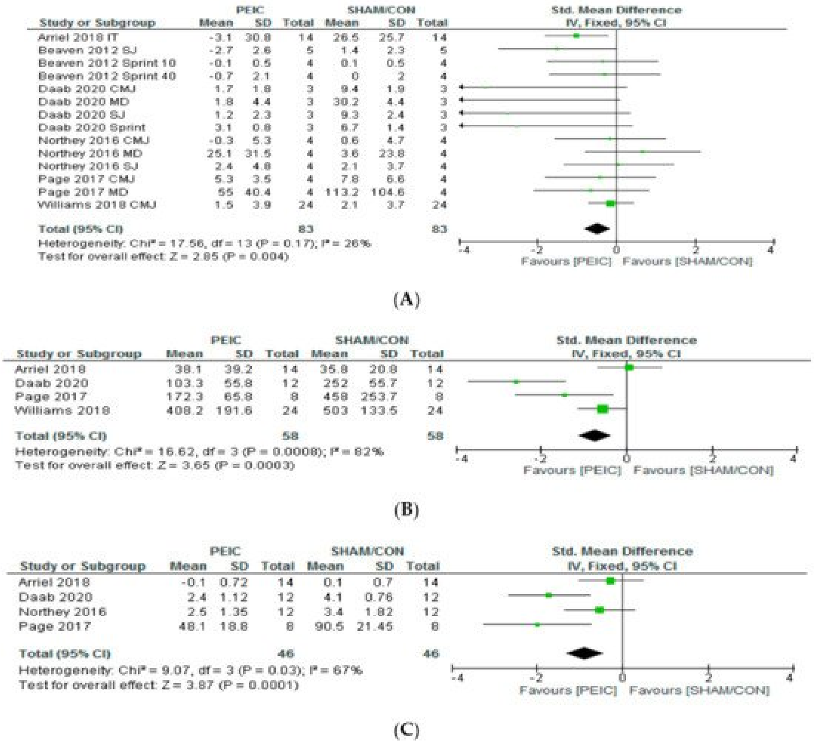

Figure 1. Forest plot of performance recovery (A) creatine kinase (B) and muscle soreness (C) variables between post-exercise ischemic conditioning (PEIC) and a cuff administration with low pressure (SHAM) or control (CON; no cuff) interventions. The square is the weight for a given study and is proportional to the weight of the study in the meta-analysis. The horizontal line indicates the 95% confidence interval (CI) for an effect. The diamond at the bottom represents the overall effect calculated using a fixed-effects model. IT = incremental test; SJ = squat jump; sprint 10 = 10 m sprint times over the 6 repeated sprints; sprint 40 = 40 m sprint times over the 6 repeated sprints; CMJ = countermovement jump; MD = muscle dynamometry; sprint = 20 m sprint.

It is important to note that all studies analyzed by the present review evaluated only the acute effect of PEIC application. Although there is no study that investigated the repeated effect of PEIC application (i.e., several days of application), recent study showed that several days of application of blood flow restriction (just one cycle, and lower pressure than PEIC intervention) after resistance exercise was associated with an impaired muscle adaptation [36], and this fact may be due to magnitude of oxidative stress. The oxidative stress, when moderate, plays multiple regulatory roles in cells, such as regulation of cell signaling pathways. However, it was speculated that low-to-none levels are not beneficial [37]. Therefore, as cycles of IR were associated with the attenuated stress oxidative level [38][39], we suggest that PEIC application should be performed before main competitions or when athletes incorporate a high training volume session. However, further studies are necessary to investigate the PEIC contribution when applied repeatedly on different exercise modes and kinds of sport activities.

6. PEIC Protocols and Possible Mechanism

At first glance, there is no consensus among researchers about the number and duration of IR cycles during PEIC. Furthermore, no consensus exists on the period between PEIC application and the return to exercise and whether participants involved were informed about the possible effects of PEIC.

The cycles of ischemia presented a total time ranging from 6 to 15 min and the complete PEIC protocol (occlusion and reperfusion periods) from 12 to 30 min (**Table 1**). Only one study analyzed two different protocols [6]. While some authors using a total time of ischemia above 10 min described positive effects on recovery [7][29][30], others using shorter time did not [27][28]. Although Beaven et al. [24] found positive results for PEIC using total time of 6 min, in this investigation subjects were recreational athletes. Only one study verified two different PEIC protocols with the same total time of ischemia (10 min), but authors did not find significant difference between protocols [6]. A clinical study [40] that demonstrated cardiac injury protection applying intermittent vascular occlusion before prolonged ischemic insult, reported that 4 to 6 ischemic cycles lasting 2 to 5 min yielded significant cardioprotection. Therefore, in addition to training level, it is conceivable that a minimal dose of ischemia is necessary to generate a PEIC response and that highly trained subjects would need a higher dose of PEIC than trained and untrained individuals.

Table 1. Characteristics of the PEIC protocols.

	PEIC Sets	Total PEIC and SHAM Time (min)	Ischemia Pressure (mm Hg) PEIC/SHAM/Limb	Time to Test	Groups	Were Subjects Informed about Effects of PEIC?
Beaven et al. (2012) [24]	2 × 3 min	6	220/15/thigh	5 min–24 h	PEIC/SHAM	No
Northey et al. (2016) [27]	2 × 3 min	6	220/#/thigh	1–24 h	PEIC/CON	It was not exposed by authors
Page et al. (2017) [7]	3 × 5 min	15	220/20/thigh	24–48–72 h	PEIC/SHAM	No
Williams et al. (2018) [28]	2 × 3 min	6	171–266/15/thigh	2–24 h	PEIC/SHAM	Yes
Arriel et al. (2018) [6]	2 × 5 min and 5 × 2 min	10 and 10	50 > SAP/20/thigh	24 h	PEIC/SHAM	Yes
Daab et al. (2020) [29]	3 × 5 min	15	50 > SAP/20/thigh	0–24–48–72 h	PEIC/SHAM	It was not exposed by authors

PEIC, post-exercise ischemic conditioning; SHAM, cuff administration with low pressure; CON, control (no cuff); SAP, systolic arterial pressure; #, no SHAM application.

The time between PEIC application and the return to exercise was usually 24 h. However, PEIC effects were also evaluated at 5 min, 1 h, 2 h, 48 h and 72 h. While no positive effects were found between 1 and 2 h after PEIC application [27][28], 24 h has revealed significant changes [6][7][24][29]. Among the few established IR intervention mechanisms, the early (active immediately after reperfusion and lasts 2–3 h) and late (begins 12–24 h after reperfusion) phases of protection, commonly known as the first and second window of protection [16], should be considered. Looking at our results, the second phase appears to be more pronounced. However, some variables (e.g., CK and MS) used to assess the effects of PEIC on recovery have their peak 24 h post exercise. Therefore, it remains unclear whether the first, the second or both phases are effective on performance recovery.

Finally, we can hypothesize that on the early phase, the PEIC could increase nitric oxide and modulate mitochondrial oxygen consumption leading to a decrease in mitochondrial reactive oxygen species (ROS) generation [38] and consequently limit oxidative injury on muscle cell. During the late phase, PEIC could increases iNOS expression (an isoform that synthesizes nitric oxide) [41], and consequently increases nitric oxide production, leading to a possible improvement in exercise performance by diminishing the level of ROS [38]. These occurrences are also associated with reduced muscle fatigue and damage [42]. In addition, it was speculated that PEIC could lead to an attenuated inflammatory response after physical exercise due to a downregulation of circulating leukocytes [7]. This could be, at least in part, responsible for the beneficial effects of PEIC on recovery.

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