REVIEW

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Effects of Ischemic Pre and Postconditioning on Indirect Markers of muscle damage: A Systematic Review and Meta-Analysis

Ingrid Martins de França[1], Mikhail Santos Cerqueira[2], Yves Matheus Barros de Sousa Oliveira[1], Stephen D. Patterson[3], Wouber Hérickson de Brito Vieira[1]

[1] *Neuromuscular Performance Analysis Laboratory, Department of Physical Therapy, Federal University of Rio Grande do Norte (UFRN), Natal (RN), Brazil*

[2] *State University of Southwest Bahia, Postgraduate Program in Physical Education, Jequié (BA), Brazil*

[3] *Centre for Applied Performance Sciences, Faculty of Sport, Allied Health and Performance Science, St. Mary's University, Waldegrave Road, Twickenham, London, TW1 4SX, U.K.*

CORRESPONDING AUTHOR:
Wouber Hérickson de Brito Vieira
Neuromuscular Performance Analysis Laboratory
Department of Physical Therapy
Universidade Federal do Rio Grande do Norte
Avenida Senador Salgado Filho 3000
Lagoa Nova, Natal, Rio Grande do Norte
59072-970, Brazil
E-mail: hericksonfisio@yahoo.com.br

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SUMMARY

Introduction. Exercise-induced muscle damage (EIMD) occurs following unaccustomed or eccentric exercise. Ischemic conditioning applied passively before (IPCb) or after (IPCa) exercise may mitigate EIMD. However, IPC effects on indirect markers of EIMD are not fully understood.

Objective. To evaluate IPCb and IPCa effects on indirect markers of EIMD.

Methods. We screened randomized clinical trials on PubMed, Scopus, Web of Science, SPORTDiscus, CENTRAL, CINAHL, and PEDro databases. We performed meta-analyses of mean differences (MD), standardized mean differences (SMD), and 95% confidence intervals (95% CI) using a random-effects model. To be included, studies had to evaluate at least one indirect marker related to EIMD, use some exercise modality to induce muscle damage, and use sham IPC or no intervention as a control group.

Results. Nine studies reporting data from 178 individuals (174 males) were considered eligible. The outcomes included delayed-onset muscle soreness (DOMS), creatine kinase (CK) activity, limb circumference, maximum voluntary isometric contraction (MVIC), and jump height. IPCb reduced DOMS compared with control/sham (SMD: -2.8; 95% CI -3.67 to -1.92). IPCa had a positive effect on DOMS (SMD: -2.16; 95%CI - 3.94 to -2.03), CK activity (SMD: -1.39; 95%CI -2.26 to -0.51) and countermovement jump height (MD: 1.72; 95%CI 1.13-2.30) compared with control/sham.

Conclusions. Our findings suggest that IPCb and IPCa mitigate DOMS. IPCa appeared to accelerate recovery for countermovement jump and attenuate the rise in CK activity compared with control/sham.

Study registration. International Prospective Register of Systematic Review (PROSPERO, CRD42020197822).

KEY WORDS

Ischemic preconditioning; blood occlusion; exercise; muscle damage; recovery.

INTRODUCTION

Exercise-induced muscle damage (EIMD) results from following unaccustomed or eccentric exercise and is characterized by reduced strength and range of motion, delayed-onset muscle soreness (DOMS), swelling, increased creatine kinase (CK) activity and may lead to temporary functional impairments (1-3). EIMD generally leaves to transient ultrastructural myofibrillar disruption,

could generate mechanical alterations and metabolic stress (4). This kind of muscle damage stimulate the inflammatory system, that's activate various cell types, like satellite cells, inflammatory cells (*e.g.*, neutrophils, macrophages, T lymphocytes, mast cells), vascular cells and stromal cells (*e.g.*, fibroblasts) (4). This inflammatory process is necessary to initiate tissue repair and remodeling, restoring the functional homeostasis of the damaged cell (5, 6). EIMD impairs muscle function, negatively affecting adherence to physical exercise programs (1-3).

Therapeutic methods including cryotherapy, massage, and photobiomodulation may accelerate the recovery from EIMD and help maintain the intensity and frequency of training (7-9). In addition, ischemic preconditioning (IPC) has also been used to mitigate EIMD consequences (10, 11). Ischemic conditioning consists of short periods (2 to 5 minutes) of intermittent vascular limb occlusion, followed by blood reperfusion cycles (10, 11). Ischemic conditioning may be applied before (ischemic preconditioning, IPCb) or after exercises (ischemic postconditioning, IPCa) (10, 11).

Recently, IPCb has been used to protect cardiac and skeletal muscles against ischemia-reperfusion (I/R) injury (12), defined as metabolic and contractile damage that occurs when blood supply returns to the tissue after a period of prolonged ischemia (13). Similarities, including increased intracellular calcium concentrations (14), blood muscle proteins (CK or lactate dehydrogenase (LDH)), and cytokine markers (interleukin-1, interleukin-2, interleukin-6, interleukin-7, tumor necrosis factor) and other factors, such as reactive oxygen species and c-reactive protein (12, 13, 15) have been observed between I/R injury and EIMD. IPCa could attenuates I/R injury and accelerate recovery after EIMD, because the technique mechanism involves the increase in post-ischemic blood flow (10), causing vasodilation (16, 17). Increased blood flow promotes changes in the sensitivity of ATP-sensitive K^+ channels (KATP) (16), elevating adenosine levels (17) and reducing inflammatory process (18). Inflammation reduction is followed by decreased muscle swelling and intramuscular pressure, leading to reduced nociceptive stimulation and, consequently, attenuated DOMS (10, 19). Therefore, during the reperfusion period, vasodilation increases oxygen and nutrients supply to the muscles by improving substrate resynthesis, thus enhancing muscle function (17, 20).

IPCb could also be a helpful strategy in mitigating EIMD (21, 22). IPCb and eccentric exercise have similar effects regarding tissue damage (21, 22). For example, both lead to intramuscular acidosis, increased reactive oxygen species, and excessive immune response (21, 22). Franz *et al.* (21) verified that IPCb performed in eccentric exercise sessions of elbow flexors can attenuate EIMD and DOMS. According to this study, IPCb could attenuate EIMD through a down-regulation of pro-inflammatory signaling, reducing DOMS and CK activity (22).

Although some studies showed that IPCa effectively attenuates EIMD consequences and accelerate muscle recovery (10, 11, 21), others did not find differences between IPC and sham or control groups (20). Two recent systematic reviews investigated IPC effects on indirect markers of EIMD (23, 24). However, Ma *et al.* (23) did not perform meta-analysis in their review and included only one study about IPCb, limiting the analysis of this specific technique. In contrast, the results of a meta-analysis conducted by Arriel *et al.* (24) indicate that IPCa mitigates the increase in CK activity and DOMS. However, this meta-analysis grouped data extracted at 24, 48, and 72h after EIMD in a single time and omitted IPCb in their analyses.

The conduction of meta-analyses including IPCb and IPCa, considering subgroups analyses, would be essential to understand IPC effects on EIMD at different time points (*i.e.*, 24, 48, and 72 h). Subgroup analyzes are especially relevant for DOMS and CK activity outcomes because they tend to increase at 24h after EIMD and may last up to 72h (25, 26). Therefore, this systematic review and meta-analysis aimed to investigate the effects of IPCb and IPCa on indirect markers of EIMD. We hypothesize that IPCb and IPCa attenuate muscle damage and accelerate recovery. The attenuation of EIMD would occur by mitigating the DOMS response and CK activity, and a smaller reduction in performance in the IPC group than in the control.

METHODS

This systematic review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (27).

Eligibility criteria

We considered randomized clinical trials published until June 2023 and evaluated the effects of IPCa or IPCb on indirect markers of EIMD. To be included, studies had to evaluate at least one indirect marker related to muscle damage, use some exercise modality to induce muscle damage (resistance or aerobic), and use sham IPC or no intervention as a control group. We did not include studies that used protocols without exercise, studies conducted on animals, pilots, protocols, expert opinion, book chapters, studies without a complete version or studies combining IPC with exercise.

Search strategy

We performed the searches in the National Library of Medicine (PubMed), Scopus, Web of Science, SPORTDiscus, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PEDro, and Clinicaltrials.gov. Search terms derived from "ischemic preconditioning", "muscle damage", "blood occlusion", "ischemic preconditioning", "vascular occlusion", and "recovery". Searches occurred in two moments: one for IPCb and another for IPCa. The strategy used for IPCb was: ("Ischemic Preconditioning" AND "Muscle Damage") and for BRFa was: ("Blood occlusion" OR "Ischemic preconditioning" OR "Vascular occlusion" AND "Recovery"). As filters we used complete studies, clinical trials, and human studies to guide the study selection process. We performed the last search in June 2023.

Screening of the studies

Two independent reviewers were responsible for screening the studies and a third reviewer resolved any disagreement regarding eligibility. Studies were stored on Mendeley® Desktop, and duplicates were removed. Subsequently, the studies were transferred to Rayyan QCRI® program (http://rayyan.qcri.org) (28). Titles and abstracts were read in Rayyan QCRI®, and only those meeting the inclusion criteria proceeded to the full-text screening. In case of unavailable full text or data or data that were not in mean and standard deviation, the corresponding authors were contacted via e-mail. A period of eight weeks was established for sending the information. If there was no response, the paper was excluded from the analysis.

Data extraction

We extracted the following data of the included studies: 1) characteristics of participants (sample size, training status, gender and age with mean and standard deviation); 2) indirect markers of EIMD (DOMS, CK, functional tests, muscle voluntary contraction, limb circumference); 3) intervention characteristics including cuff properties (cuff width, occlusion pressure, occlusion and reperfusion time, continuous or intermittent occlusion) and prescription mode (arbitrary or individualized); 4) comparison group including control (controlled time and conditions) or sham; 5) damaging protocol (segments involved, exercise modality, number of sets and repetitions, rest period, exercise load); 6) study design: randomized clinical trial (randomization between subjects, crossover, parallel); 7) time point measures (pre-exercise or post-exercise).

Assessment of risk of bias in included studies

Two independent reviewers assessed the risk of bias in included studies and a third reviewer was consulted in case of disagreement. We used the software RoB2 to assess risk of bias (29). Assessment was done using a series of signaling questions comprising five domains: randomization process, deviation from the intended interventions, absence of outcome data, outcome evaluation, and selection of reported results. Judgment was derived from algorithms based on the responses and is presented as "low risk", "some concerns", or "high risk".

Data analysis

We used the Review Manager 5.4.1 software to conduct the statistical analyses and generate the forest plots. For included studies with data available in graph form only, the Image J (NIH, Maryland, USA) was used to calculate mean and standard deviation values. The random-effects model was used for analyses (30). To estimate heterogeneity between studies, the I^2 statistic was used, where $I^2 = 25\%$ was considered low, $I^2 = 50\%$ moderate, and $I^2 = 75\%$ high (26). For variables with the same measurement units and similar measurement methods, an analysis by Mean Difference (MD) was conducted. However, the Standardized Mean Difference (SMD) was used for discrepant measurements or those with distinct assessment methods. Subgroup analyses were conducted to assess different intervention time points (before, 24, 48, and 72h after EIMD). A delta (after - before) of the variables was used to calculate differences. For standard deviation, the formula used was: $SD = \sqrt{[(SDpre^2 / Npre) + (SDpost^2 / Npost)]}$ (30).

RESULTS

Description of included studies

A total of 1055 scientific studies were retrieved in the databases (**figure 1**). After the removal of duplicates, 584 studies remained for title screening. Thirty-three studies proceeded to abstract screening, and the full-text version of 20 studies were screened for eligibility. Nine studies reporting data from 178 healthy participants (174 men and 4 women) were eligible for the systematic review (10, 11, 20, 21, 32-36). Studies were published between 2012 and 2021. The sample size of the included studies ranged from 12 to 30 participants, and participants were predominantly young adults, with a mean age ranging from 21.8 to 32 years. Four studies used a crossover/inter-subject design (10, 20, 33, 34), and five studies used a parallel design (11, 21, 32, 35, 36).

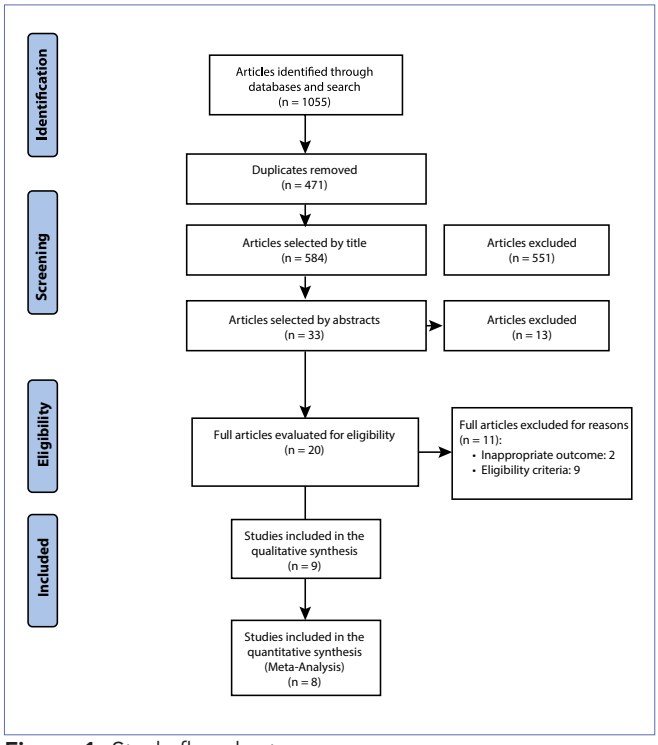


Figure 1. Study flowchart.

Risk of bias

Only three studies detailed the randomization process (32, 34, 35), whereas six studies mentioned randomization but did not explain how it occurred (10, 11, 20, 21, 33, 36). Only one study detailed allocation concealment procedures and blinding (32). Three studies mentioned blinding the evaluators for some outcomes but not for others (32, 34, 35). Only one study reported adherence to a published protocol (32). All studies included appropriate measures for assessing the proposed outcomes, and eight performed statistical analyses consistent with the research objectives and registered measures (10, 20, 21, 32-36). The risk of bias of each study is represented in **figure 2**.

Moment of IPC application

Characteristics of the included studies are reported in two tables stratified by the moment of IPC application. **Table I** shows the summary of the three IPCb studies (21, 32, 36), and **table II** shows the summary of the six IPCa studies (10, 11, 20, 33-35).

Training status

Included studies reported data from healthy or recreationally active individuals (n = 4) (10, 11, 21, 23); individuals engaged in strength training programs (n = 2) (33, 36), or athletes including soccer players (n = 1) (34), rugby players (n = 1) (20), and trained cyclists (n = 1) (35).

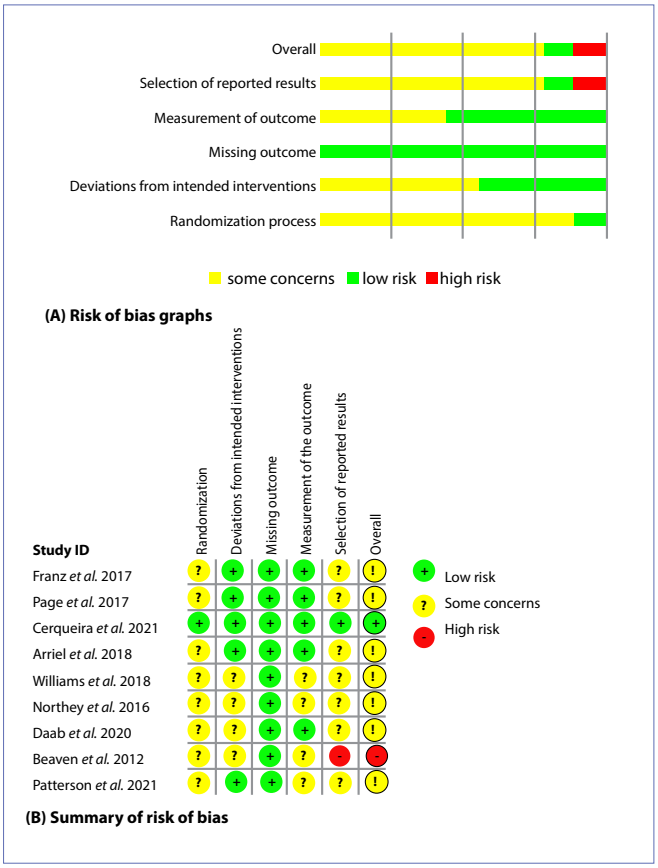


Figure 2. Risk of bias graphs.

Muscle-damaging protocol

Five studies used resistance exercise as the damaging protocol. Franz *et al.* (21) used maximum eccentric actions on the isokinetic dynamometer; while Northey *et al.* (33) used back squat and Page *et al.* (11) and Patterson *et al.* (36) used drop jumps. Three studies used aerobic exercise as the damaging protocol. Williams *et al.* (20) used 50 meters maximum sprint, Arriel *et al.* (35) used Maximal Incremental cycling test and Daab *et al.* (34) used the Loughborough Intermittent Shuttle Test. In turn, Beaven *et al.* (10) used resistance (squat jumps, countermovement jump, leg press) and aerobic exercises (maximal sprints of 40 meters) as muscle-damaging protocol.

Ischemic preconditioning before exercise (IPCb)

Three studies evaluated CK activity at baseline, 24, 48, and 72h post-EIMD (21, 32, 36). They also used a visual analog scale (VAS) to verify DOMS level and limb circumference as a parameter to measure muscle swelling at 24, 48, and 72h post-EIMD (21, 32, 36). Franz *et al.* (21) also measured tensiomyography to verify contraction speed and muscle stiffness.

Table I. Summary of studies comparing the effects of IPCb on indirect markers of EIMD.

Author (Years)	Subjects and age; (M ± SD)	Markers	Damage protocol	Intervention	Control group	Results
Franz *et al.* (2017)	19 (24.4 ± 4.2) healthy men without regular strength training	CK, Arm circumference, Muscle soreness (VAS) Tensiomyography	Eccentric exercise of bilateral elbow flexion with bar 3 × 10 of 80% of 1RM Rest: 1 min	3 × 5 min of I/R Width of cuff: 8 cm The proximal portion of the D and E arm RP: 200 mmHg	No intervention	CK is higher in control (24, 48 and 72 h); VAS is increased in control group (24 and 72 h). Tensiomyography was reduced in the control at all time intervals but did not change in IPCb. There was no intergroup difference for arm circumference
Cerqueira *et al.*(2021)	30 (21.9 ± 3.1) healthy men without regular strength training	CKR FD Muscle soreness (VAS) pressureàpain threshold (Algometry) Knee flexion ROM Thigh circumference	120 maximal eccentric actions on isokinetic dynamometer 10 × 12 repetitions Rest: 30 s	I/R: 4 × 5 min Width of cuff: 20 cm Non-dominant lower limb Thigh proximal part Dorsal decubitus Individualized Doppler PRT	I/R: 4 × 5 min Width of cuff: 20 cm Non-dominant lower limb Thigh proximal part Dorsal decubitus RP: 20 mmHg	Muscle soreness reduced in the IPCb group in 48 h. The other variables had no significant difference between groups.
Patterson *et al.*, (2021)	16 healthy trained men (23 ± 3)	CK Muscle soreness (VAS) MICV Thigh edema Countermovement jump	Drops jumps from a 0.6 m high box 5 × 20 reps with Rest: 2 min	3 × 5 min of I/R Width of cuff: 14.5 cm Thigh proximal part Bilateral RP: 220 mmHg	3 × 5 min of I/R Width of cuff: 14.5 cm Thigh proximal part Bilateral RP: 20 mmHg	IPCb group accelerated recovery in MICV and muscle swelling compared to sham. There was no difference between groups for countermovement jumping, muscle soreness, and CK.

CK: creatine kinase; RFD: rate of force development; VAS: visual analog scale; ROM: range of motion; IPCb: Ischemic preconditioning before exercise; TRP: total restriction pressure; RP: restriction pressure; MIVC:maximal isometric voluntary contraction; M: mean; SD: standard deviation.

Table II. Summary of studies comparing IPCa effects on indirect markers of induced muscle damage.

Author (Year)	Subjects and age (M ± SD)	Markers	Damage protocol	Intervention	Control group	Results
Beaven *et al.* (2012)	14 (32 ± 7) healthy subjects 10 men 4 women	3 squats jumps (90°) 3 countermovement jumps 6 repetitions on leg press 6 maximum sprints (40 m)	3 squats jumps (90°) 3 countermovement jumps 6 repetitions on leg press 6 maximum sprints of 40 m	I/R: 2 × 3 min Lower limb bilaterally Thigh proximal part RP: 220 mmHg	I/R: 2 × 3 min Lower limb unilaterally Thigh proximal part RP: 15 mmHg	IPCa showed beneficial effects in eccentric power and acceleration, squat jump, countermovement jump and jump height. There were small beneficial effects in sprint times (10 and 40 m).
Page *et al.*, (2017)	16 (22.6 ± 2.8) recreationally active men	Pain (VAS) MICV Countermovement jump CK Recovery rate	Drops jumps from a 0.6 m high box 5 × 20 reps with 2 min rest between sets	3 × 5 min I/R CW: 14,5 cm Lower limbs bilaterally Thigh proximal part Dorsal decubitus RP: 220 mmHg	Sham: 3 × 5 min I/R CW: 14,5 cm Lower limbs bilaterally Thigh proximal part Dorsal decubitus RP: 220 mmHg	CK and pain reduced in the IPCa compared to sham. There was no effect for thigh circumference and countermovement jump
Northey *et al.* (2016)	12 (24 ± 6,3) Men who perform strength Training	Recovery perception Muscle soreness PT quadriceps Squat jump Countermovement jump	10 ×10 back squats at 70% of 1 RM With 3 min rest between sets	I/R: 2 × 3 min Lower limbs unilaterally, alternating Thigh proximal part Dorsal decubitu RP: 220 mmHg 33 min lying in dorsal decubitus after BRFa	Control: Lie in dorsal decubitus for 45 min	There were no significant differences between conditions for any post-exercise measures
Williams *et al.* (2018)	24 (21.8 ± 3) Rugby players	Muscle soreness Recovery Perception Countermovement jumping CK	6 maximum sprints of 50 m 5 min rest between sprints	I/R: 2 × 3 min CW: 11 cm Lower limbs bilaterally Thigh proximal part RP: 60% of BP and thigh circumference	I/R: 2 × 3 min CW: 11 cm Lower limbs bilaterally Thigh proximal part RP: 15 mmHg	IPCa did not affect recovery in any of the variables
Arriel *et al.*, (2018)	28 (27.1±1.4) trained cyclists	CK Muscle soreness Power output	Maximal Incremental cycling Test (MICT) Starting at 40 W, increasing by 20 W/min to exhaustion	I1: 2x 5 min I2:5x2 min CW: 21,5 cm Lower limbs bilaterally and alternately Thigh proximal part Dorsal decubitus RP: 50 mmHg above SBP	Sham1: 2 × 5 min Sham2: 5×2 min CW: 21,5 cm Lower limbs Bilaterally and alternately Thigh proximal part Dorsal decubitus RP: 20 mmHg	There was no significant difference in power output or muscle soreness in 24 h compared with baseline values.
Daab *et al.* (2020)	12 (23.1±1) semi-professional soccer players	Squat jump Countermovement jump MIVC Sprint 20 m CK Muscle soreness	Loughborough Intermittent Shuttle Test (LIST) 6 sets of 15 min (55 to 95% of estimated VO_{2max}) Rest: 3 min	I/R: 3 x 5 min CW: 21.5 cm Lower limbs bilaterally Thigh proximal part Dorsal decubitus RP: 50 mmHg above SBP	I/R: 3 × 5 min CW: 21.5 cm Lower limbs bilaterally Thigh proximal part Dorsal decubitus RP: 20 mmHg	IPCa attenuated the decrease in Squat Jump, countermovement jump, MIVC and sprint. CK and LDH levels increased 24h after in both conditions, but with a lower level in the IPC. Pain was significantly less in the IPCa 24 hours

CK: creatine kinase; VAS: visual analog scale; TRP: total restriction pressure; RP: restriction pressure; MVIC: maximum voluntary isometric contraction; PT: peak torque; CK: creatine kinase; IPCa:ischemic preconditioning after exercise. M: mean; SD: standard deviation; LDH: lactate dehydrogenase; CW: cuff width.

In contrast, Cerqueira *et al.* (32) measured pressure pain threshold using algometry and knee range of motion using a goniometer (**table I**). Patterson *et al.* (36) evaluated DOMS, CK, swelling, countermovement jump, and maximal isometric voluntary contraction (MIVC). All studies showed beneficial effects in reducing DOMS in IPCb group compared with the control (21, 32, 36). Franz *et al.* (21) observed increased CK in control group compared with IPCb group. This study (17) also found that muscle stiffness measured by tensiomyography was reduced in control group despite the time point and did not show any changes in the IPCb group. Cerqueira *et al.* (32) found no statistically significant difference in CK, rate of force development, pressure pain threshold, and MIVC between sham and IPCb groups. Franz *et al.* (21) and Cerqueira *et al.* (32) showed no difference between groups regarding limb circumference. Patterson *et al.* (36) observed an attenuation of the loss of maximum voluntary contraction and muscle swelling in the IPCb group compared to sham group. Countermovement jump, DOMS, and CK activity were not different between groups (36).

Ischemic preconditioning after exercise (IPCa)

Five studies evaluated DOMS (11, 20, 33-35). Page *et al.* (11) and Williams *et al.* (20) evaluated thigh circumference to verify swelling. Five studies evaluated functional performance (10, 11, 20, 33, 34); Beaven *et al.* (10), Page *et al.* (11), Williams *et al.* (20), Northey *et al.* (33) and Daab *et al.* (34) evaluated countermovement jump, three evaluated squat jump (6, 29, 30), and two evaluated sprints (10, 34); four studies evaluated CK activity (11, 20, 34, 35); one study performed a neuromuscular evaluation measuring the knee extensors peak torque (33), and two used the maximum voluntary isometric contraction (MVIC) (11, 34).

According to Page *et al.* (11) and Daab *et al.* (34), IPCa group showed decreased CK activity after EIMD (11, 34) and a significantly lower DOMS (11, 34). Similarly, IPCa group showed a faster recovery for MVIC (7), countermovement jump and squat jump (10, 34) than sham group. There were also beneficial effects on eccentric power and acceleration for the squat jump (10).

For sprinting, two studies showed a beneficial effect in IPCa group illustrated by less pronounced performance reduction (10, 34). Arriel *et al.* (35) showed that IPCa protocols maintained their performance in the maximum incremental test, performed 24h after EIMD.

Three studies reported no differences between IPCa and control groups concerning countermovement jump (11, 20, 33). The two studies evaluating thigh circumference did not notice differences between IPC and sham groups (11, 20). Concerning DOMS, three studies reported no significant difference between IPC and control group (20, 33, 35). Northey *et al.* (33) reported no difference between IPCa and control group for squat jump height and peak torque of knee extensors (33). Another study reported no difference between IPCa and sham groups for CK and LDH concentration (20). One study showed that IPC group demonstrated more fatigue than sham group (35) (**table II**).

According to Page *et al.* (11) and Daab *et al.* (34), IPCa group showed decreased CK activity after EIMD (11, 34) and a significantly lower DOMS (7, 30). Similarly, IPCa group showed a faster recovery for MVIC (7), countermovement jump and squat jump (10, 34) than sham group. There were also beneficial effects on eccentric power and acceleration for the squat jump (10).

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Summary of meta-analysis results

Descriptive results of IPCb studies

Three studies evaluating IPCb were included in the meta-analysis. Forest plots were created using the variables: DOMS, CK activity, limb circumference and MIVC. Subgroup analyses were performed considering 24, 48, and 72h time points. The meta-analysis of MIVC was performed with data from Cerqueira *et al.* (32) and Patterson *et al.* (36), because these were the only studies analyzing MIVC. Results are reported in MD or SMD (95%CI) based on the methodological differences of each outcome.

Delayed-onset muscle soreness (DOMS)

IPCb showed a decrease in DOMS compared with the control group in 24h (SMD: -2.13; 95%CI -3.83 to -0.43; overall effect: $p = 0.01$), 48h (SMD: -3.62; 95%CI -4.47 to -2.77; overall effect: $p < 0.00001$) and 72h (SMD: -2.66; 95%CI -3.76 to -1.55; overall effect: $p < 0.00001$). The same is reflected for the overall effect meta-analysis (SMD: -2.8; 95%CI -3.67 to -1.92; overall effect: $p < 0.00001$). Howev-

er, heterogeneity was shown to be moderate to high (I^2_{24h} = 83%; I^2_{48h} = 0%; I^2_{72h} = 54%; $I^2_{overalleffect}$ = 77%) (**figure 3**).

Creatine Kinase (CK)

IPCb showed no significant effects on CK activity compared with control in 24h (SMD: -1.17; 95%CI -3.06 to 0.71; overall effect: p = 0.22), 48h (SMD: -0.9; 95%CI -2.7 to 0.9; overall effect: p = 0.33) and 72h (SMD: -1.98; 95%CI -4.39 to 0.43; overall effect: p = 0.11). However, the overall effect meta-analysis favors the IPCb group (SMD: -1.27; 95%CI: -2.22 to -0.31; overall effect: p = < 0.00001). Heterogeneity was high (I^2_{24h} = 90%; I^2_{48h} = 90%; I^2_{72h} = 92%; $I^2_{overalleffect}$ = 88%) (**figure 4**).

Limb circumference

Limb circumference was not different between groups in 24h (SMD: -0.37; 95%CI -0.86 to 0.13; overall effect: p = 0.15), 48h (SMD: -0.44; 95%CI -1.37 to 0.48; overall effect: p = 0.35), and 72h (SMD: -0.77; 95%CI -1.83 to 0.28; overall effect: p = 0.15). However, the overall effect meta-analysis showed that the IPCb group had circumference values of the lower limb compatible with less muscle swelling (SMD: -0.51; 95%CI -0.93 to -0.08; overall effect: p = 0.08). Heterogeneity was low to moderate (I^2_{24h} = 0%; I^2_{48h} = 68%; I^2_{72h} = 73%; $I^2_{overalleffect}$ = 51%) (**figure 5**).

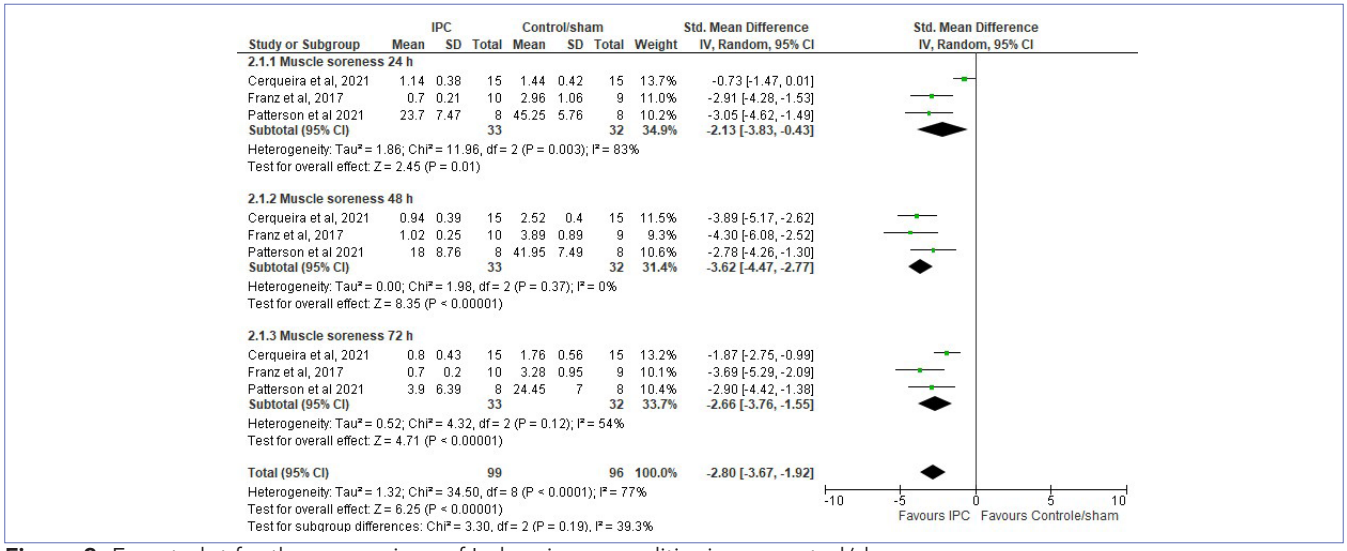


Figure 3. Forest plot for the comparison of Ischemic preconditioning × control/sham.
Outcome: muscle soreness (VAS cm); IPC: ischemic preconditioning; Mean: mean; SD: standard deviation; CI: Confidence Interval. I^2: heterogeneity.

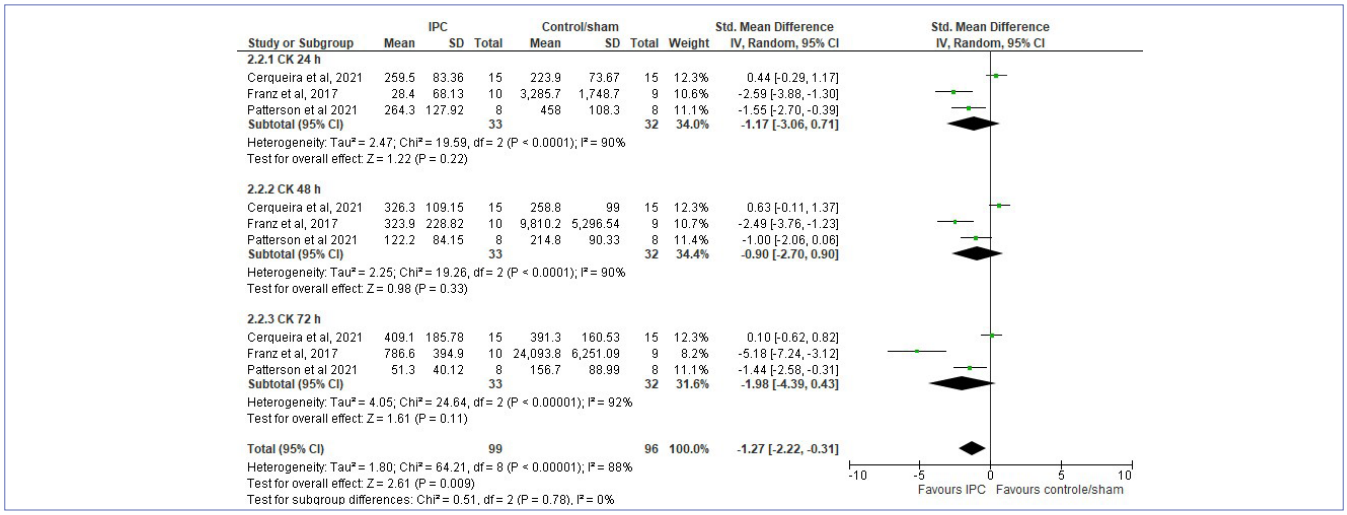


Figure 4. Forest plot for the comparison of ischemic preconditioning × control/sham.
Outcome: CK (U.L-1); IPC: ischemic preconditioning; SD: standard deviation; Std. Mean difference: standardized mean difference; CI: Confidence Interval. I^2: heterogeneity.

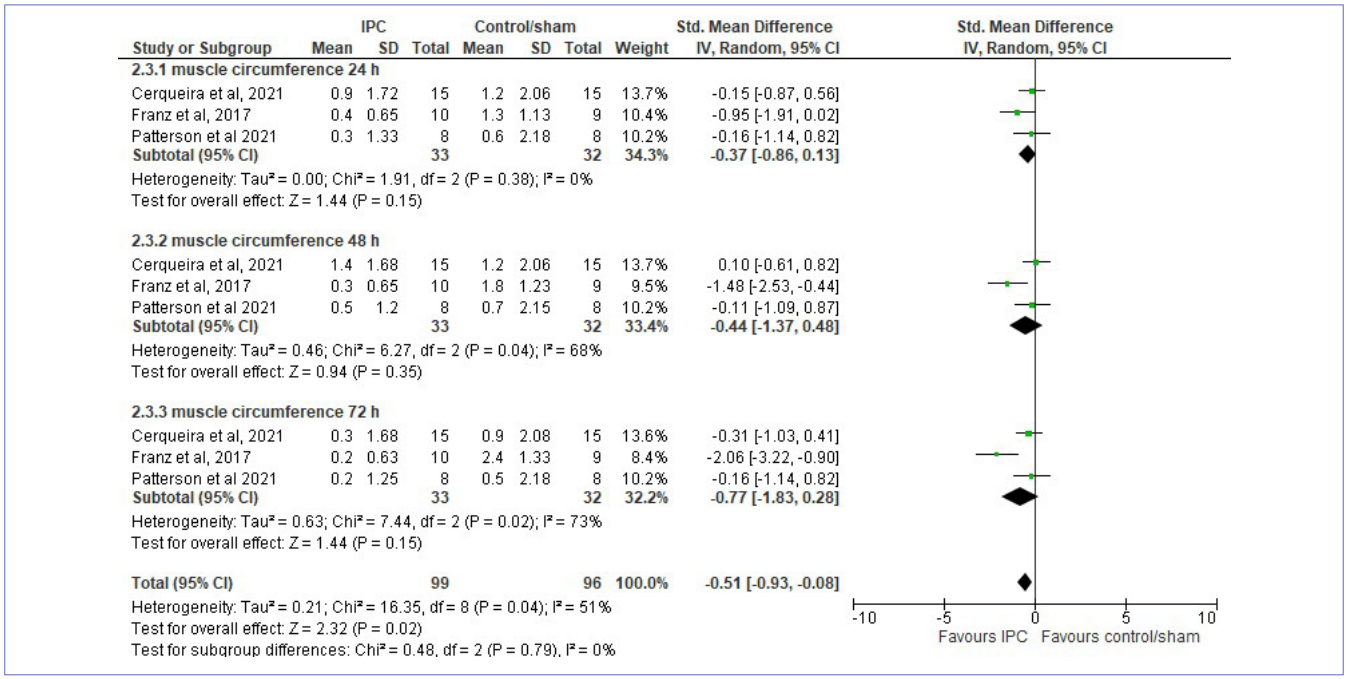


Figure 5. Forest plot for the comparison of Ischemic preconditioning × control/sham.
Outcome: segment circumference (cm); IPC: ischemic preconditioning; Mean: mean; SD: standard deviation; Std. Mean difference: standardized mean difference; CI: Confidence Interval. I^2: heterogeneity.

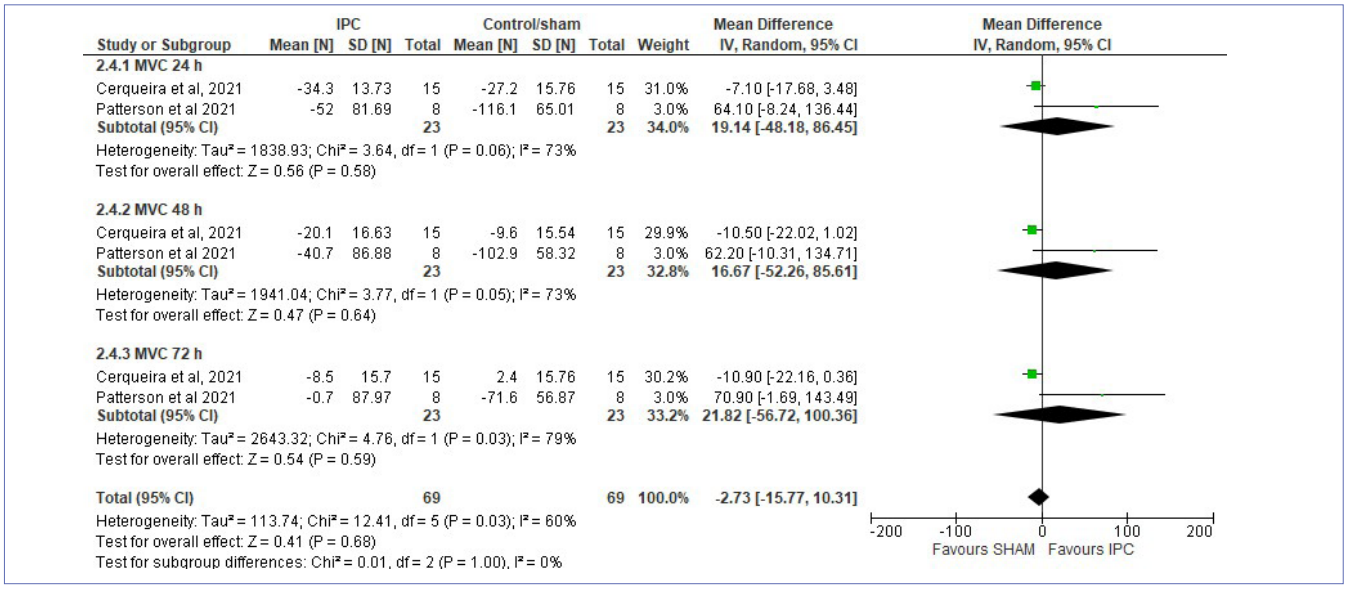


Figure 6. Forest plot for the comparison of Ischemic preconditioning × control/sham.
Outcome: maximal voluntary isometric contraction (N); IPC: ischemic preconditioning; SD: standard deviation; Std. Mean difference: standardized mean difference; CI: Confidence Interval. I2: heterogeneity.

Maximal Isometric Voluntary Contraction (MIVC)

There was no difference between groups at any time point: 24h (SMD: 19.4; 95%CI -48.18 to 86.45; overall effect: p = 0.58), 48h (SMD: 16.57; 95%CI -52.26 to 85.61; overall effect: p = 0.64), 72h (SMD: 21.82; 95%CI -56.72 to 100.36; overall effect: p = 0.59), and neither in the overall effect meta-analysis (SMD: -2.73; 95%CI -15.77 to 100.36; overall effect: p = 0.59). Heterogeneity was moderate to high ($I^2_{24h} = 73\%$; $I^2_{48h} = 73\%$; $I^2_{72h} = 79\%$; $I^2_{overalleffect} = 60\%$) (**figure 6**).

Ischemic preconditioning after exercise

Five studies evaluating IPCa were included in the meta-analysis. One study was excluded due to lack of data on mean and standard deviation. Analyses including DOMS, CK activity, squat, and countermovement jump were done separately. DOMS and countermovement jump were analyzed in three subgroups (24, 48, and 72h). The MVIC was not included in the meta-analysis due to the high heterogeneity among studies, and sprint could not be analyzed quantitatively due to data absence from one study (10). The study by Arriel *et al.* (35) was duplicated in the meta-analyses by using two different IPCa protocols. Outcomes including DOMS and CK were analyzed using SMD due to methodological differences (level of physical activity, instruments) and high heterogeneity among studies.

Delayed-onset muscle soreness (DOMS)

IPCa showed favorable results in time points of 24h (SMD: -1.96; 95%CI -3.56 to -0.36; overall effect: p = 0.02), 48h (SMD: -1.97; 95%CI -3.63 to -0.36; overall effect: p = 0.02), 72h (SMD: -2.99; 95%CI -3.94 to -2.03; overall effect: p < 0.00001) and in overall effect meta-analysis (SMD: -2.99; 95%CI -3.94 to -2.03; overall effect: p < 0.00001) (**figure 7**).

Creatine Kinase (CK)

IPCa group showed less CK concentration when compared to SHAM (SMD: -1.39; 95% CI; -2.26 to -0.51; overall effect: p = 0.002). Heterogeneity was moderate (I^2 = 63%) (**figure 8**).

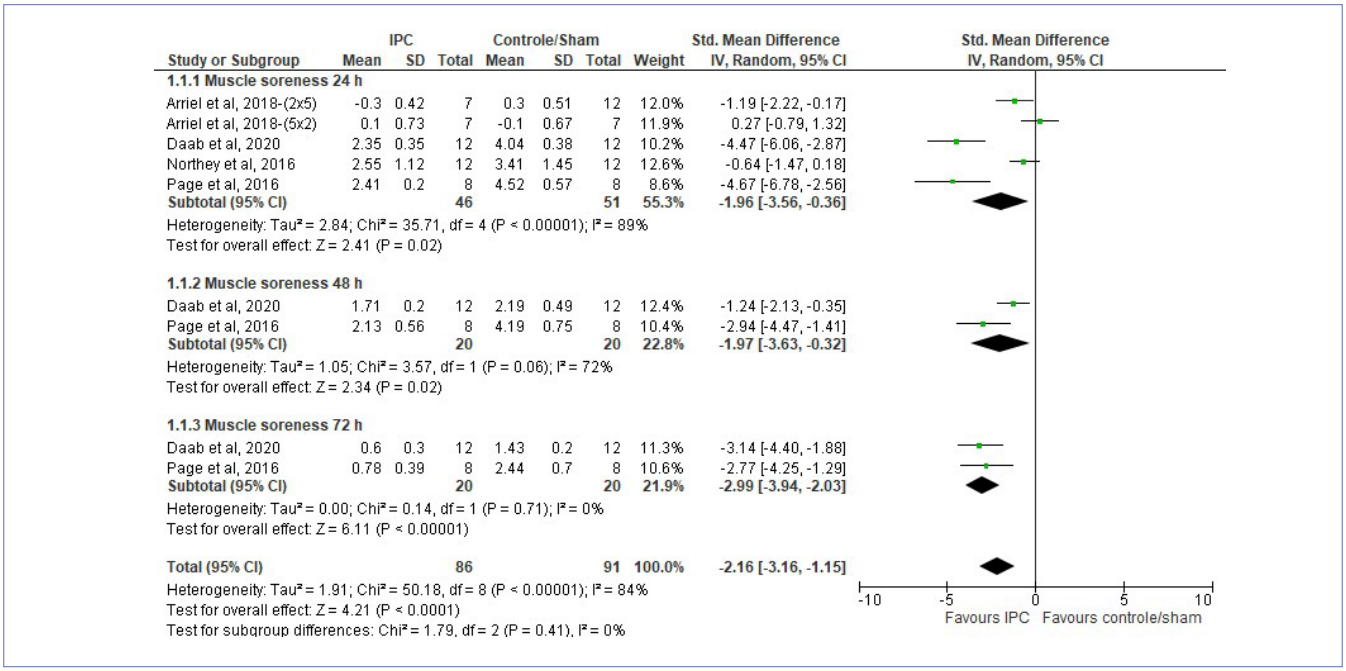


Figure 7. Forest plot for the comparison ischemic postconditioning × control/sham.
Outcome: muscle soreness (VAS cm); IPC: ischemic postconditioning; I^2: heterogeneity; Mean: mean; SD: standard deviation; std. Mean difference: standardized mean difference; CI: Confidence Interval. I^2: heterogeneity; VAS: visual analogic scale.

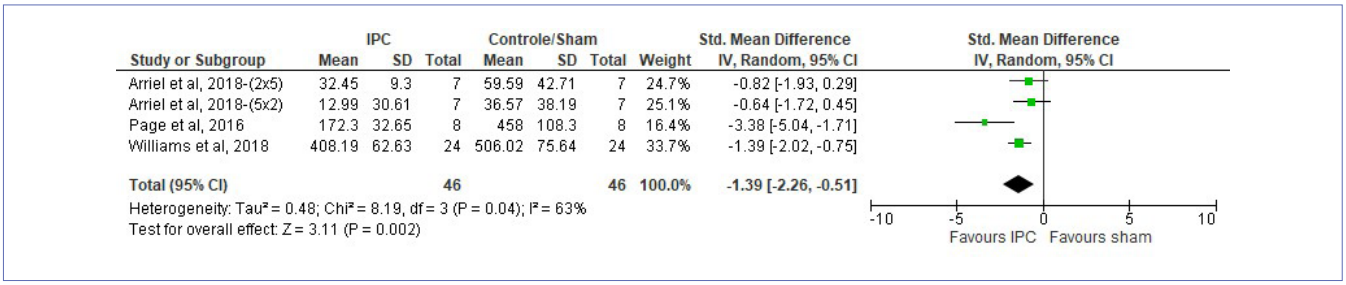


Figure 8. Forest plot for the comparison of ischemic postconditioning × control/sham.
Outcome: CK (U. L-1); IPC: ischemic postconditioning; I^2: heterogeneity; SD: standard deviation; std. Mean difference: standard mean difference; CI: Confidence Interval.

Squat jump height

IPCa group was not different from the comparison group ((MD: 1.49; 95% CI; -1.38 to 4.38; overall effect: p = 0.31). Heterogeneity was moderate (I^2 = 55%) (**figure 9**).

Countermovement jump

The meta-analysis showed favorable results for IPCa at 24h (MD: 1.49; 95%CI 0.24 to 2.74; overall effect: p = 0.02), 48h (MD: 2.13; 95%CI 1.32 to 2.95; overall effect: p < 0.00001), 72h (MD: 1.55; 95%CI 0.59 to 2.52; overall effect: p = 0.002), and in the overall effect meta-analysis (MD: 1.72; 95%CI 1.13 to 2.30; overall effect: p < 0.00001). Heterogeneity remained moderate at 24h (I^2 = 56%), and low in consecutive subgroups (I^2_{48h} = 0%; I^2_{72h} = 11%). Overall effect had a low heterogeneity (I^2 = 33%) (**figure 10**).

DISCUSSION

This systematic review aimed to analyze the evidence on IPC applied before (IPCb) or after (IPCa) exercise on indirect markers of EIMD. Our meta-analysis indicates that IPCb attenuates muscle soreness from EIMD. In addition, the reduction in countermovement jump height appeared to be less pronounced with IPCa, alongside its positive effects on reducing DOMS and CK activity compared with sham/control groups.

Effects of IPCb on indirect markers of EIMD

We observed that IPCb attenuated DOMS compared with controls. There was no difference in limb circumference, CK activity, and MVIC for the 24, 48, and 72h. The positive effect of IPCb on muscle soreness may be related to the isch-

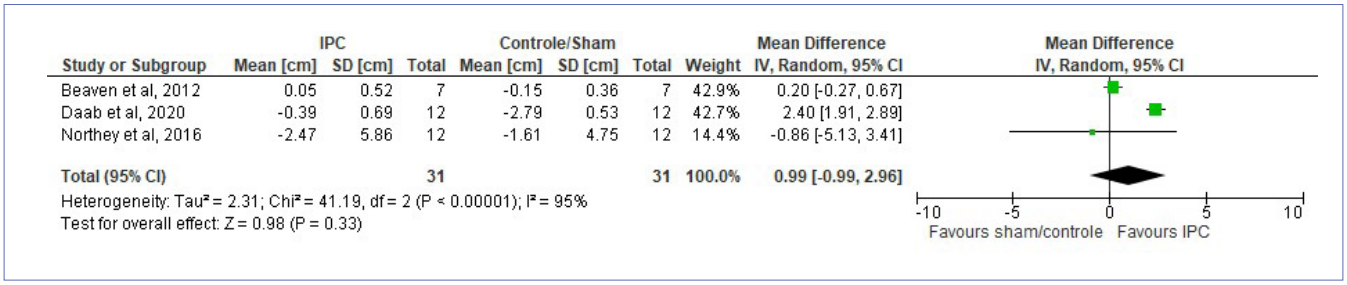


Figure 9. Forest plot for the comparison of ischemic postconditioning × control/sham.
Outcome: squat jump height (cm); IPC: ischemic postconditioning; I^2: heterogeneity; Mean: mean; SD: standard deviation; Mean difference: mean difference; CI: Confidence Interval.

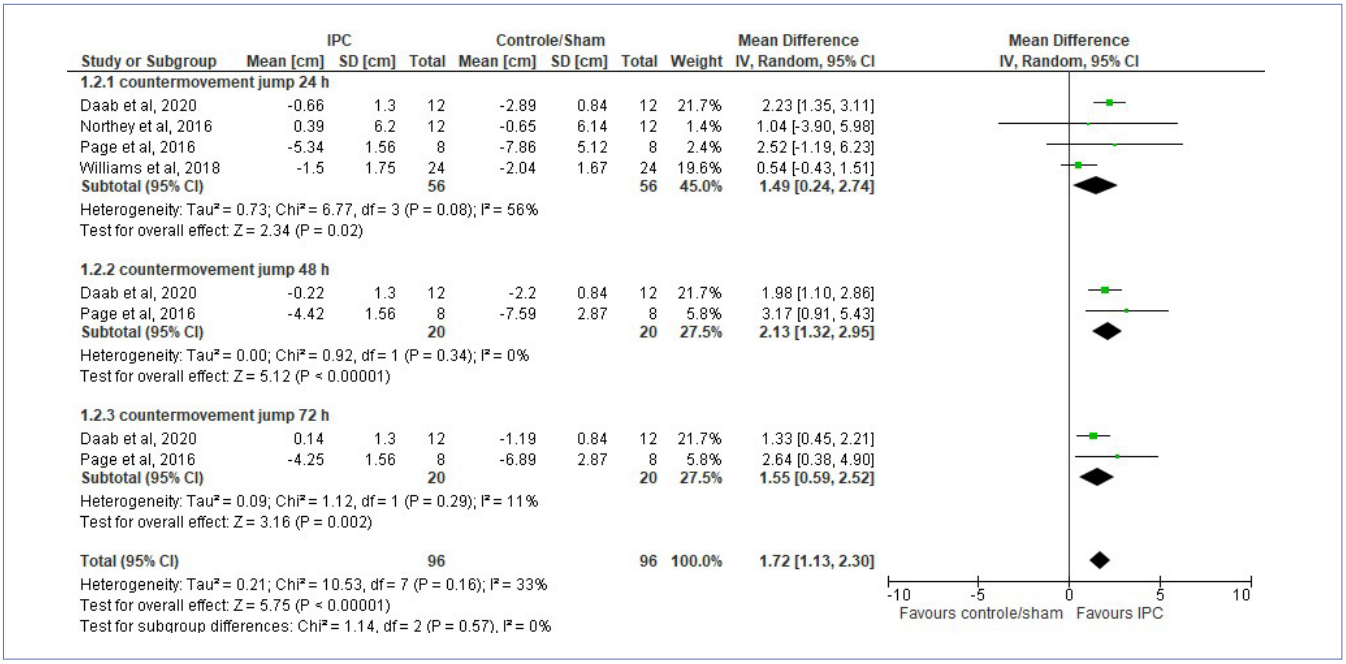


Figure 10. Forest plot for the comparison of ischemic postconditioning × control/sham.
Outcome: jump height with countermovement (cm); IPC: ischemic postconditioning; I^2: heterogeneity; SD: standard deviation; CI: Confidence Interval.

emia-reperfusion (I/R) injury (37, 38). A recent study by Hong *et al.* (39) indicated that IPCb protects the skeletal muscle from I/R injury by lowering the magnitude of necrosis, apoptosis, and alterations in the morphological structures of the cells. The authors describe the physiological adaptations as early and late (38). Early adaptations reflect significant increases in the antioxidant defense capacity (39), Ca^{2+} metabolism, and neural pathways regulation (40). Late adaptations lead to changes in gene expression and peripheral immune responses (18), which would cause a negative regulation of pro-inflammatory signaling with an associated decline in leukocyte-endothelial cell interaction via IPCb (41). Thus, IPCb may modify signaling pathways involved with DOMS and appear to attenuate muscle soreness that generally occurs following eccentric exercise (38, 40, 41).

Concerning CK activity and limb circumference, studies employed different methodologies, mainly differing in which limb served as a reference for measurement and comparison group (sham/control). Cerqueira *et al.* (32) and Patterson *et al.* (36) measured the lower limb circumference compared to a sham group. Franz *et al.* (22) performed EIMD in the upper limb and used no intervention as the control group. Furthermore, regarding MVIC, studies did not observe differences between groups at any time.

Although CK activity is a valuable biomarker, it presents high variability among individuals (42), especially in athletes (43), and its measurement may not be sensitive for functional and eccentric activities (44). Furthermore, training level, muscle groups involved, and gender may influence CK activity more than differences in the volume of performed exercise (43). Due to the constant use of the eccentric action of knee extensors in daily living activities, generating significant damage in this region may be challenging (2). This challenge is demonstrated by Chen *et al.* (2) after inducing eccentric muscle damage in knee flexors and extensors. The authors observed reduced damage signs in knee extensors for the variables of strength (isometric and concentric isokinetic) and DOMS. In contrast, signs were much more evident in the upper limbs.

There was no difference between groups for MVIC despite the time point assessed. This finding corroborates with the study conducted by Souza *et al.* (45), which did not observe differences in the number of repetitions performed or the MVIC between IPCb and sham groups followed by a knee extension protocol. Thus, IPCb acutely seems to have few local ergogenic effects on training volume variables, generalized peripheral fatigue or neuromuscular function for resistance exercise (45).

Effects of IPCa on indirect markers of EIMD

We observed that IPCa has positive effects in accelerating recovery for countermovement jump, DOMS, and CK. The squat jump height was not different from the comparison group. Due to data absence from one study, the sprint and power output variables could not be included in the meta-analysis (10). However, the two studies evaluating sprint demonstrated that IPCa positively affects recovery time, indicating accelerated muscular recovery (10, 34).

Cunniffe *et al.* (46) compared different pressures (140, 160, and 180 mmHg) for ischemia in upper and lower limbs. They showed an increase in oxyhemoglobin and muscle oxygenation index above baseline with cuff deflation, which lasted up to 15 minutes in lower limb recovery, regardless of occlusion pressure. Thus, IPCa appears to increase muscle oxygenation in the reperfusion period following technique completion. In addition, IPCa may be related to the negative regulation of leukocyte circulation and increased nitric oxide (NO) (44), responsible for regulating intracellular and intercellular inflammation and muscle remodeling (47). NO also plays an essential role in reducing inflammation and promoting muscle repair (46, 47), further contributing with DOMS reduction.

EIMD could also be attenuated by IPCa application through reactive vasodilation caused by cycles of blood restriction (17, 20). Increased blood flow would lead to more efficient and faster local responses, with increased oxygen and nutrient supply to the muscle (17, 20). Thus, it could reduce the inflammatory response and decrease CK activity and muscle swelling (17, 20). In turn, less pressure on involved tissues could reduce muscle-free nociceptor stimulation, reducing soreness (19).

Cellular effects might also be observed in IPCa, including changes in the sensitivity of KATP (16) and the elevation of adenosine levels (17). The increase in ADP/ATP ratio (*i.e.*, conditions where the oxygen supply is reduced and insufficient to meet the demands of metabolic tissues) leads to KATP channels opening and membrane hyperpolarization. Subsequently, vasodilation is a consequence of muscle cells relaxation in blood vessels (17). Moreover, when adenosine A3 receptors (17) are stimulated, serum concentrations of CK may decrease after an eccentric exercise protocol (23). In this way, a better activation of ATP in potassium channels and increased blood muscle volume (which would increase the availability and delivery of oxygen to the muscle) (17, 20). In turn, the reduction in height in countermovement jump could be less pronounced because the decreased serum concentration of CK, helping to create a favorable environment for muscle contraction.

No difference between IPCa and control groups was observed. The absence of differences between groups could be partially explained by differences between the studies, in which heterogeneity was moderate ($I^2 = 55\%$), especially concerning the type of damage protocol and participants characteristics. Daab *et al.* (34) used an aerobic protocol in a sample of soccer players, contrasting with Northey *et al.* (33) that used a resistance exercise protocol (back squat) in a sample of men practicing resistance training.

Another important aspect that may have interfered in results is the level of physical activity and the type of exercise used. According to Caru *et al.* (48) healthy and recreationally active individuals seem to benefit more from the effects of IPC. Due to mechanical and metabolic causes of EIMD, IPCa appears to have significant action on muscle metabolism and some activity on mechanical aspects (48). Meanwhile, aerobic exercises are similar to IPC in terms of having greater metabolic predominance (48). In this sense, aerobic exercises appear to be more beneficial to IPC than resistance exercise, which has a predominance of mechanical aspects (48). Therefore, individuals submitted to resistance training or to a high level of physical activity could benefit less from IPC (48).

Due to the similarities between the physiological aspects of the IPCb and the IPCa, information from the review by Caru *et al.* (48) can be used to try to explain the outcome for the squat jump. Because the difference in the sample and in the muscle damage protocol used between Northey *et al.* (33) (protocol: back squat, sample: trained men) and Daab *et al.* (34) (protocol: Loughborough Intermittent Shuttle Test, sample: football players), results may be contradictory, requiring attention to data interpretation.

In contrast with the qualitative analyses performed in the review conducted by Ma *et al.* (23) or the focus on IPCa presented in the review by Arriel *et al.* (24), our review adopted a quantitative approach with meta-analysis and stratified IPCb and IPCa effects. Our data analysis was divided into subgroups (24, 48, 72h) for DOMS and countermovement jump. Therefore, this review filled some existing gaps in literature by comparing IPCb and IPCa quantitatively.

Limitations

Differences were identified in intervention characteristics, damage protocols, and outcomes. Each author used a different muscle damage protocol with varied metabolic characteristics, intensity, duration, and rest time. The differences between the sample could explain the moderate to high heterogeneity found in most meta-analyses ($I^2 > 50\%$) (26). Due to the variation in our results and the fact that some studies evaluated up to 24h after the EIMD, some meta-analyses were conducted with only two studies, which compromises its robustness.

Although this review included only clinical trials, the quality of the evidence was affected by the small sample sizes of included studies, absence of allocation concealment strategies, lack of explanation on randomization process, and a lack of description concerning blinding of participants and evaluators. Sample size calculation was absent in most studies (10, 11, 20, 21, 33, 35, 36). In addition, interventions were heterogeneous, especially regarding the restriction pressure, which was not individualized in most studies (10, 11, 21, 33, 36). I/R cycles ranged from 12 to 30 minutes in the IPCa studies and 30 to 40 minutes in the IPCb. Therefore, results should be interpreted with caution.

CONCLUSIONS

Current evidence supports that IPCb can attenuate DOMS. In turn, IPCa could contribute to recovery in countermovement jump and to attenuate CK activity.

This systematic review emphasizes the need for clinical trials with adequate sample size, allocation concealment, and blinding of evaluators and participants. Future clinical trials should consider choosing specific and validated outcomes for assessing EIMD such as indirect markers (CK, DOMS, functional tests, neuromuscular evaluations), employing validated methods to find IPC restriction pressure, individualizing restriction pressures, using tables to display the results, and improving control over selection bias when adopting sampling strategies.

Practical applications

Ischemic preconditioning before (IPCb) or after (IPCa) exercise would be promising strategy to mitigate delayed-onset muscle soreness. Besides, IPCa appeared to accelerate recovery for countermovement jump and attenuate the rise in CK activity compared with control/sham. This technique could be more interesting for athletes, especially during competition periods, as they need to maintain performance and accelerate recovery. In addition, it is important to verify the most appropriate protocols for users and the modalities practiced, thus being able to use the IPC in the most suitable and specific way.

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DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

IMF, MSC: conceptualization. IMF, MSC, YMB: design, coordination. IMF: writing – original draft. SDP, WHBV: writing – review & editing.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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