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Literature Review

Effect of remote ischemic pre-conditioning on maximum oxygen consumption and maximum power in runners and cyclists: systematic review and metanalysis

Efeito do pré-condicionamento isquêmico remoto no consumo máximo de oxigênio e potência máxima em corredores e ciclistas: revisão sistemática e metanálise

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ABSTRACT | INTRODUCTION: Remote ischemic preconditioning (PIRC) is a non-invasive cardioprotective intervention that attenuates cell damage suffered by prolonged ischemia. Its protective effects on the heart, when applied to sport, can improve exercise performance. **OBJECTIVE:** To investigate the effect of remote ischemic preconditioning on maximum oxygen consumption (VO2max) and maximum power (Wmax) in runners and cyclists. **METHODOLOGY:** Systematic review and meta-analysis, with randomized clinical trials. Based on PRISMA and evaluated by the PROSPERO systematic review project repository; however, it did not obtain registration because it is an outcome of sports performance. The searches were carried out in the Medline / PubMed, SciELO, Capes Periodicals databases. The selection of studies was carried out in two stages: reading the title and summary and reading the articles in full. Data extraction was performed by transcribing the information. Methodological quality was assessed by the risk of bias scale using the Cochrane tool. Studies that investigated variables other than the outcomes selected for this review were excluded. **RESULTS:** Eight clinical trials were included. In the generation of the item of random sequence, concealment of allocation and blinding of outcome evaluators in almost all studies had a high risk of bias. The analysis of the risk of bias was high risk. The meta-analysis results revealed VO2max ($p < 0.01$), the PCIR proved to be effective; Wmax there was no significant difference. **CONCLUSION:** Remote ischemic preconditioning may be able to increase VO2max in runners and cyclists. Wmax demonstrates that the PCIR does not influence it.

KEYWORDS: Cardiorespiratory Fitness. Exercise. Ischemic Preconditioning.

RESUMO | INTRODUÇÃO: O pré-condicionamento isquêmico remoto (PCIR) é uma intervenção cardioprotetora não invasiva que atenua a lesão celular sofrida por uma isquemia prolongada. Seus efeitos de proteção sobre o coração, quando aplicado ao esporte, pode melhorar o desempenho do exercício. **OBJETIVO:** Investigar o efeito do pré-condicionamento isquêmico remoto no consumo máximo de oxigênio (VO2máx) e potência máxima (Wmáx) em corredores e ciclistas. **METODOLOGIA:** Revisão sistemática e metanálise, com ensaios clínicos randomizados. Baseado no PRISMA e avaliado pelo repositório de projetos de revisões sistemática PROSPERO; entretanto, não obteve o registro por se tratar de um desfecho de performance esportiva. As buscas foram realizadas nas bases de dados Medline/PubMed, SciELO, Periódicos CAPES. A seleção dos estudos foi realizada em duas etapas: leitura do título e resumo, e leitura completa dos artigos. A extração dos dados foi realizada pela transcrição das informações. A qualidade metodológica foi avaliada pela escala risco de viés através da ferramenta Cochrane. Excluíram-se estudos que investigaram variáveis diferentes dos desfechos selecionados para esta revisão. **RESULTADOS:** Foram incluídos oito ensaios clínicos. Verificou-se que nos itens geração de sequência aleatória, ocultação de alocação e cegamento de avaliadores de desfecho em quase todos os estudos tiveram alto risco de viés. Os resultados da metanálise revelou VO2máx ($p < 0,01$), o PCIR mostrou ser eficaz; Wmáx não houve diferença significativa. **CONCLUSÃO:** O pré-condicionamento isquêmico remoto pode ser capaz de aumentar o VO2máx em corredores e ciclistas. A Wmáx demonstra não ser influenciada pelo PCIR.

PALAVRAS-CHAVE: Aptidão Cardiorrespiratória. Exercício Físico. Pré-condicionamento Isquêmico.

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Introduction

Remote Ischemic PreConditioning (RIPC) is a non-invasive cardioprotective intervention that involves short cycles of ischemia, interspersed by reperfusion, that attenuate cell damage suffered by prolonged ischemia of the same organ.[1] It was first described in a study of Murry et al.[3], in 1986, in which dog hearts were preconditioned with four cycles of occlusion and reperfusion. It was found that the area of myocardial infarction in preconditioned hearts reduced by 75% compared to those who did not receive ischemic preconditioning.[2,3]

The ischemic stimulus provided by the RIPC leads to the production of substances that enter circulation, reach the myocardium and other tissues, and, consequently, exert a protective effect. This protection seems to involve activating protein kinase C (PKC), through the signaling cascade of protein G agonists, with subsequent opening of ATP-dependent potassium channels (KATP).[4] The protective effects of CRP on the heart and being beneficial in the clinical setting can also be applied in sport to improve exercise performance[5–8]; these effects have been analyzed in endurance athletes. In a 5 km running test, subjects were able to complete the race 34 seconds faster, and the increase in lactate was attenuated by 1.07 ± 0.11 mmol during an incremental running test after the CPIR.[9] In trained swimmers, the RIPC was associated with the gain of maximum performance, with a reduction in the swimming time of 100 m and a better swimming time concerning the personal time.[10]

Sports performance is the object of study in the most diverse areas of knowledge and desired by athletes, coaches, and physiologists. In recent years, many techniques have been studied to optimize the performance and results of athletes of all modalities. Among these techniques, the RIPC stands out, which favors the process of angiogenesis and greater resistance to tissue ischemia.[11] Sports modalities such as running and cycling that have aerobic predominance promote adaptations capable of generating increases in VO2máx and the physiological adjustments that promote functional changes in response to endurance training, they are only possible through the manipulation of aerobic capacity variables, regardless of the modality practiced.[12]

The PIRC is a non-invasive and easy-to-apply strategy that can promote improvement in exercise performance.[13,14] Thus, this study aims to investigate the effect of remote ischemic preconditioning on maximum oxygen consumption (VO2max) maximum power (Wmax) in runners and cyclists.

Methodology

This is a systematic review and meta-analysis. It was based on "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews"[15] and evaluated by the PROSPERO systematic review project repository; however, it did not obtain the record because it is a sports performance outcome. Randomized clinical trials investigating the effect of remote ischemic preconditioning on VO2max and Wmax of runners and cyclists were included. Studies that did not evaluate outcomes of interest in this review were excluded.

The selection of the studies was carried out by two independent researchers, with the same search strategy; in case of disagreement, a third researcher was called. No software was used to assist in the selection process. Subsequently, the selected articles were assessed for the risk of bias using the Cochrane tool.[16] The search was carried out through the PICOS strategy in the Medline / PubMed, SciELO, Journals Capes databases, and manual search, without the restriction of the year of publication, available in Portuguese, English, and Spanish. No filters were used in the databases. The last search was carried out on a single date, November 18, 2020, in all databases. MeSH and DeCS were used to find the descriptors and their synonyms. The keywords included in the search strategy for the Medline / PubMed database were: (((((((Ischemic Preconditioning) OR (remote ischemic preconditioning)) AND (exercise)) OR (Cardiorespiratory Fitness)) OR (exercise training)) AND (Clinical Trial). For the SciELO and Journals Capes databases, Ischemic preconditioning and exercise were used. This strategy was used to conduct a more sensitive search than it specifies, considering that these databases still have a relatively low scientific production on the subject studied.

The selection of studies was carried out in two stages. The first stage was based on titles and abstracts; the second stage the analysis of the full text. Data extraction was performed through the transcription of information, and a file was built containing authors and year of publication, participants, intervention, outcomes, and study design. The updated PRISMA guidelines were followed to present the flowchart.[15] The quality of the studies was assessed using the risk of bias scale using the Cochrane collaboration tool.[16]

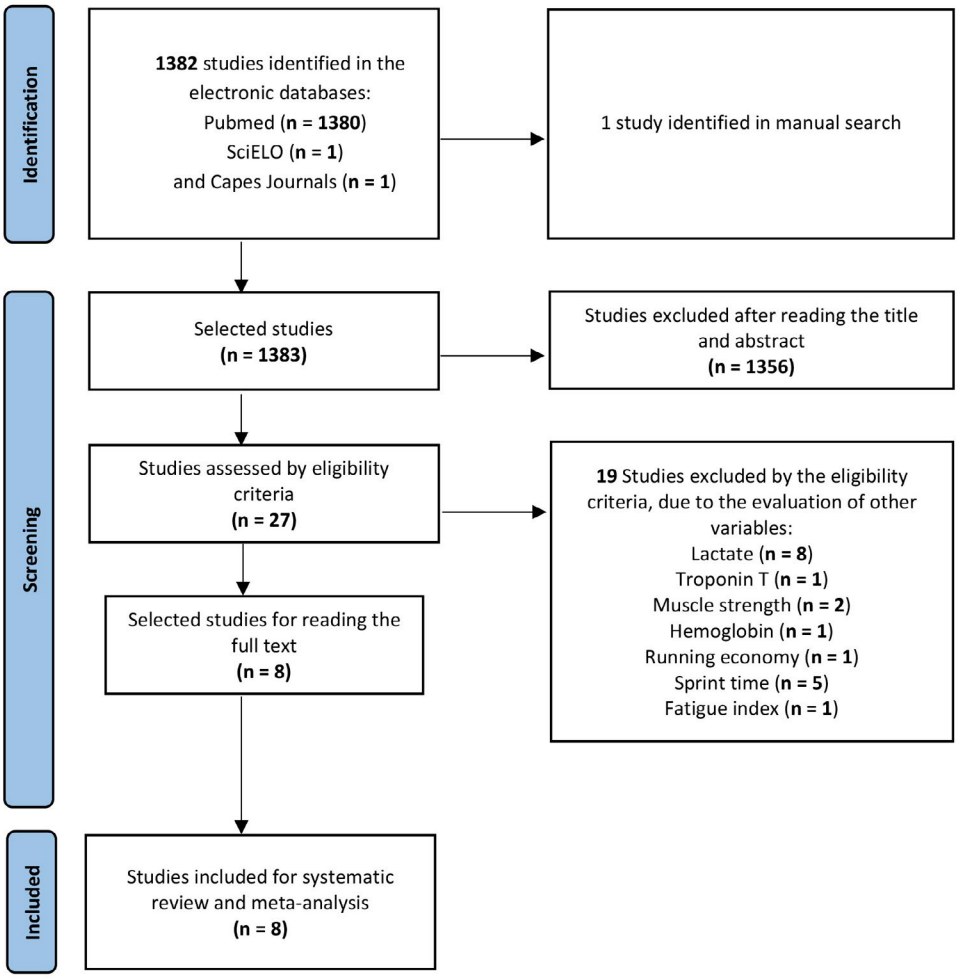
Revman 5.3 software was used for elaboration, data analysis, and construction of the Forest Plot graph. Statistical heterogeneity was assessed by visual inspection of the confidence interval, the Q-Cochran test, and the chi-square test (X2). After this evaluation, the data were analyzed using the random effect model to expect clinical and methodological heterogeneity between the studies. All data were analyzed with the same measure, milliliters per minute, studies that presented VO2max in liters per minute, the transformation was made to milliliters per minute.

Results

Selection of studies

The search and identification process of the studies included in the review are summarized in Figure 1. A total of 1383 studies were identified. After reading the title and abstract, 1356 were excluded and another 27 were selected for reading the full text. After analysis, 8 studies met the eligibility criteria, remaining in the systematic review for analysis.

Figure 1. Flowchart of the search and study identification process



Characteristics of the studies

Table 1 summarizes the descriptive characteristics of the clinical trials included in the systematic review, comprising a total of 109 male and female individuals, with an average age ranging between 18 and 35 years. Publication dates ranged from 2010 to 2019. Six studies involved cyclists[1,5,6,17–19] and two runners.[7,8] Each study used different types of protocols in the evaluation of VO2max and Wmax. The RIPC protocol was similar between studies; however, there was a variation in the number of ischemia-reperfusion cycles.

Table 1. Characteristics of clinical trials included in the systematic review. Effect of remote ischemic preconditioning on VO2max and Wmax of runners and cyclists, 2019/2020. N = 8 (to be continued)

Study	Participants	Intervention	Comparation	Outcomes	Study Design
Authors and year of publication	Control Group Number **(nGC);** Number in the Ischemic preconditioning group **(nPCI)**	Sports modality (Sport); Exercise type (Exercise)	Control group protocol (CT); Ischemic preconditioning group protocol (PCI)	Maximum oxygen consumption (VO2max) and Maximum power in watts (Wmax)	ECR Type
Patterson et al., 2015[6]	**nGC:** 14; **nPCI**: 14; **I:** 22,9 ± 3,7; **H**: 14	**Sport: Cycling** **Exercise: 12 6 "sprints with 30" rest between each sprint.**	**PCI: 4 x 5 'occlusion / 5' reperfusion - 220 mmHg.** **CT: 4 x 5 'occlusion / 5' reperfusion - 20mmHg.**	**VO2máx PCI:** 2,7 ± 0,4 L.min **VO2máx CT:** 2,6 ± 0,3 L.min	**Randomized, double-blind, crossed**
Crisafulli et al., 2011[1]	**nGC:** 17; **nPCI:** 17; **I:** 35,2 ± 9,1 **H:** 17	**Sport: Cycling** **Exercise:** Incremental test on cycle ergometer with linear increase in workload of 25 W / min.	**CT**: Without intervention **PCI**: 3 x 5 'occlusion / 5' reperfusion - 220 mmHg.	**VO2máx CT**: 2963,8 ± 256,6 (ml/min) **VO2máx PCI**: 3068,3 ± 396,1 (ml/min) **Wmáx CT**: 277,9 ± 44 W **Wmáx PCI**: 288,2 ± 47,6 W	**Randomized, crossover**

Table 1. Characteristics of clinical trials included in the systematic review. Effect of remote ischemic preconditioning on VO2max and Wmax of runners and cyclists, 2019/2020. N = 8 (conclusion)

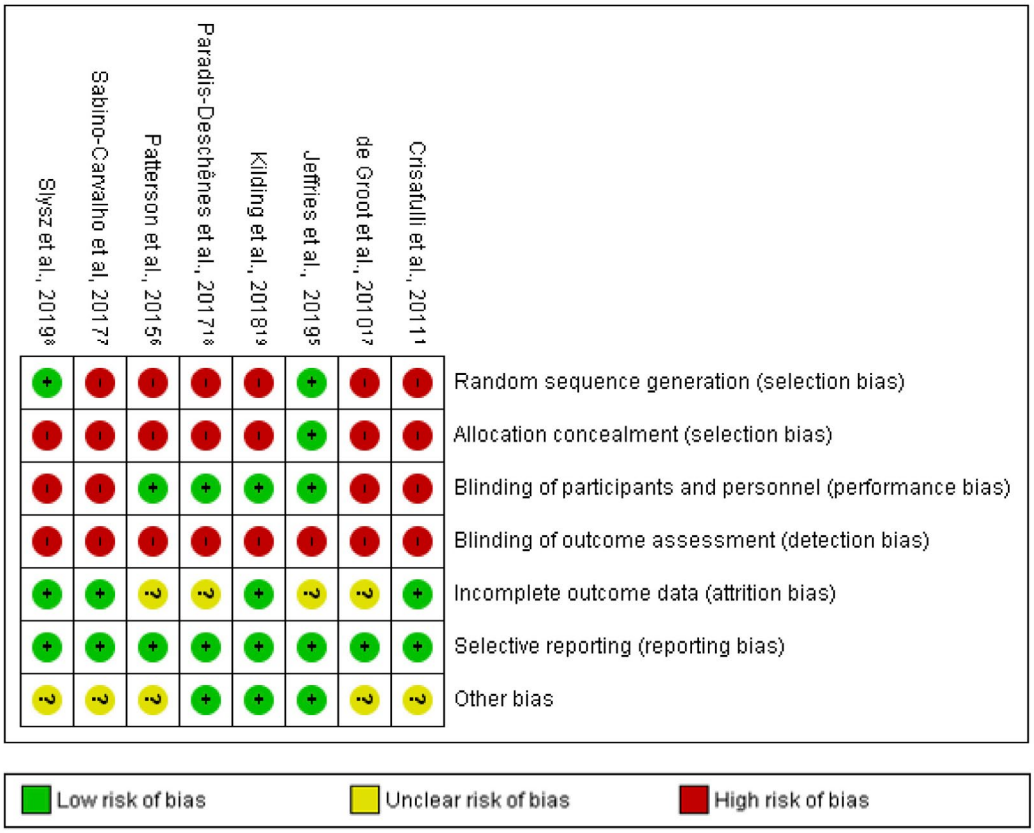
Study	Participants	Intervention	Comparation	Outocomes	Study Design
Authors and year of publication	Control Group Number **(nGC);** Number in the Ischemic preconditioning group **(nPCI)**	Sports modality (Sport); Exercise type (Exercise)	Control group protocol (CT); Ischemic preconditioning group protocol (PCI)	Maximum oxygen consumption (VO2max) and Maximum power in watts (Wmax)	**ECR Type**
de Groot et al., 2010[17]	**nGC:** 15 **nPCI:** 15 **I:** 27,2 ± 5,6 **H:** 12 **M:** 3	**Sport: Cycling** **Exercise: Test maximum incremental ergometer cycle with increased load until exhaustion.**	**CT: Without intervention** **PCI: 3 x 5 'occlusion / 5' reperfusion - 220 mmHg.**	**VO2máx CT**: 56,8 ± 6,8 (ml/min / kg) **VO2máx PCI**: 58,4 ± 6,2 (ml/min / kg) **Wmáx CT**: 366 ± 62 W **Wmáx PCI:** 372 ± 59 W	**Randomized, crossover**
Paradis-Deschênes et al., 2017[18]	**nGC:** 13 **nPCI:** 13 **I:** 27,5 ± 1,6 **H:** 13	**CT: Without intervention** **PCI: 3 x 5 'occlusion / 5' reperfusion - 220 mmHg.**	**CT: Cuff inflated to 20 mmHg.** **PCI: 3 x 5 'occlusion / 5' reperfusion - 220 mmHg.**	**Wmáx CT:** 284,6 ± 12,7 W **Wmáx PCI:** 291,3 ± 9,8 W	**Randomized, crossover**
Slysz et al., 2019[8]	**nGC:** 7; **nPCI:** 7 **I GC:** 19 ± 2; **I PCI:** 18 ± 1 **H:** 11; **M:** 3	**Sport: Running** **Exercise: Continuous incremental test and 1 km time test**	**CT: Without PCIR; PCI: 3 x 5 'occlusion / 5' reperfusion - above systolic blood pressure until complete arterial occlusion.**	**VO2máx CT:** 54,2 ± 4 (ml/min /kg) **VO2máx PCI:** 55,5 ± 2 (ml/min /kg)	**Randomized**
Kilding et al., 2018[19]	**nGC:** 8 **nPCI:** 8 **I:** 27,0 ± 7,0 **H:** 8	**Sport: Cycling** **Exercise: 4 km individual time test and ramp stress test.**	**CT: 4 x 5 'occlusion / 5' reperfusion - 50 mmHg.** **PCI: 4 x 5 'occlusion / 5' reperfusion - 200 mmHg.**	**VO2máx CT:** 4,4 ± 0,6 (L. min) **VO2máx PCI:** 4,4 ± 0,5 (L. min) **Wmáx CT:** 383 ± 46 W **Wmáx PCI:** 385 ± 42 W	**Randomized, crossover**
Sabino-Carvalho et al, 2017[7]	**nGC:** 18; **nPCI:** 18 **I:** 22,3 ± 0,9; **H:** 14; **M:** 4	**Sport: Running** **Exercise: Incremental treadmill test with increased load at each 3 'stage until exhaustion.**	**CT: Without intervention** **PCI: 4 x 5 'occlusion / 5' reperfusion - 220 mmHg.**	**VO2máx CT:** 63,4± 1,3 (ml/min /kg) **VO2máx PCI:** 64,8 ± 1,6 (ml/min /kg)	**Randomized, crossover**
Jeffries et al., 2019[5]	**nGC:** 10; **nPCI:** 10 **I GC:** 21 ± 2; **I PCI**: 22 ± 3 **H:** 20	**Sport: Cycling** **Exercise: Incremental test with increment of 30 W min until exhaustion**.	**CT: 4 x 5 'occlusion / 5' reperfusion - 20 mmHg.** **PCI: 4 x 5 'occlusion / 5' reperfusion - 220 mmHg.**	**VO2máx CT:** 40,6 ± 8,1 (ml/min /kg) **VO2máx PCI:** 45 ± 5,6 (ml/min /kg) **Wmáx CT:** 292 ± 35 W **Wmáx PCI:** 323 ± 51 W	**Randomized, simple blind**

I: Mean age and standard deviation; I CG: mean age of the control group and standard deviation; I PCI: mean age ischemic preconditioning group and standard deviation; H: male participants; M: female participants
Km: kilometers; W: watts; W.min: watts per minute; mmHg: millimeters of mercury; CT: control group; PCI: ischemic preconditioning group; ml / min / kg: milliliters per minute per kilo; L.min: liters per minute; ml.min: milliliters per minute; W: watts; RCT: Randomized clinical trial.

Analysis of the risk of bias

In the generation of the random item sequence, concealment of allocation and blinding of outcome evaluators in almost all studies had a high risk of bias; this happened because the authors did not present or performed these steps in the studies. For the blinding items of participants and professionals, incomplete outcomes, and other sources of bias, about half of the studies had high risk or uncertain risk. Only the item reporting a selective outcome was the one with the lowest risk of bias since the study protocols and their primary outcomes were reported in detail, Figure 2.

Figure 2. Bias risk assessment of the 8 studies included in the review, using the risk of bias scale using the Cochrane collaboration tool. N = 8

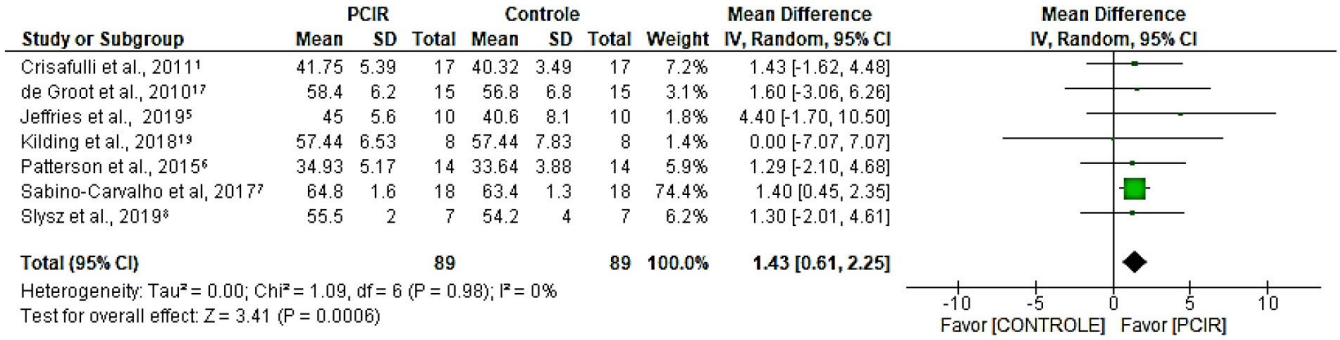


Outcome results

Maximum oxygen consumption (VO2max)

Studies that assessed the effect of remote ischemic preconditioning on VO2max1.5–8.17-19 contained a total of 89 participants. There was a significant increase in VO2max of 1.43 ml/kg.min (95% CI: 0.61-2.25) for the groups that used the PIRC protocol compared to the control groups, shown in Figure 3.

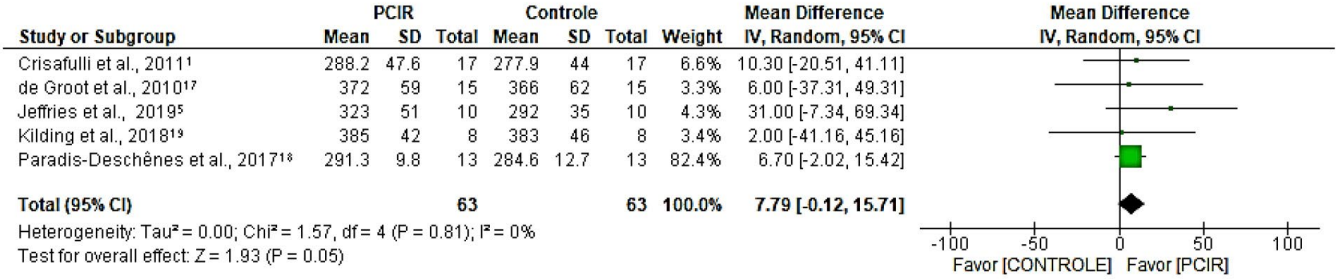
Figure 3. Forest Plot of the comparison of VO2máx between the control group and RIPC



Maximum power (Wmax)

Five studies 1,5,17–19 with a total of 63 participants, evaluated the effect of remote ischemic preconditioning on Wmax. There was no significant difference when comparing the control group with the RIPC: 7.79 (95% CI -0.12; 15.71), shown in Figure 4.

Figure 4. Forest Plot of Wmax comparison between the control group and RIPC



Discussion

This meta-analysis is original in testing the effects of remote ischemic preconditioning on performance indicators in runners and cyclists. The results indicate that a RIPC session was efficient in inducing an acute increase in VO2max. However, there was no increase in Wmax.

The increase in VO2máx is desired by athletes, a predictor of performance in time trials, and the best index for assessing cardiorespiratory fitness.[20,21] The findings of this meta-analysis corroborate the results reported by other researchers who observed an increase in the VO2max when using the RIPC before the maximum performance test in cyclists and runners.[17,22] Thus, the use of the RIPC can be a strategy used by athletes and coaches minutes before a competition.

A point to be highlighted in this study, the RIPC protocol used by all researchers was similar, with little variation in the number of ischemia-reperfusion cycles.[1,5-8,17-19] The maneuver consisted of periods of limb ischemia by insufflating a cuff up to 220 mmHg for 5 minutes, followed by 5 minutes of reperfusion with cuff deflation. However, the intervention methods were heterogeneous in terms of training variables; these differences in protocols are essential in practical applicability since the manipulation of variables can improve endurance athletes' performance.

In this review, two sports were included, runners and cyclists; this inclusion was based on the evidence that endurance athletes have similar VO2max. It is generally described that aerobic exercise with the same intensity induces greater oxygen absorption and, probably, a similar energy expenditure between these two modalities. Another justification is the pattern of recruitment of motor units related to the tasks performed, with an impact on VO2max.[23]

It is essential to point out the studies[1,5-8,17,19] that evaluated the VO2max were composed of small samples of athletes with high functional capacity, being able to skew, in this way, the results found. Thus, the analysis of the results may show low confidence, being susceptible to low external validity. However, when the studies are analyzed together, it was observed that the RIPC could increase VO2max by up to 3.41ml / kg.min. The authors consider the study by Sabino-Carvalho et al.[7] that in the original study, the data did not favor the use of VO2máx. However, when the data were included in the meta-analysis and analyzed together, it became favorable and great weight (74.4%). It was verified in the scale of the methodological evaluation that the negative items to this study were related both to the allocation of the participants in the investigated groups and to the blinding of the intervention, thus characterizing systematic errors.

Remote ischemic preconditioning causes the release of various substances by the ischemic tissue, although the substances are not well defined.[4] These can influence the opening of ATP-dependent potassium (K +) channels and local adenosine release, in addition to regulation of the nitric oxide pathway, which are potent vasodilators.[24,25] It is speculated that the vasodilator action of these mechanisms participate in the effects of the RIPC and consequently in the increase in the physical performance of athletes.[17,25]

The studies that evaluated Wmax performed a maximum incremental test on a cycle ergometer. In the meta-analysis results, the RIPC did not have a significant effect on the increase in Wmax. The findings of this research are in line with other authors who evaluated the effects of the PIR on Wmax in athletes.[18,19] These results can be explained by the low Wmax variability in high-performance athletes, which is a mechanical variable with low sensitivity to detect acute physiological changes, enhanced by the wide confidence interval in all analyzes.

From perspectives on the results of this meta-analysis, the applicability of remote ischemic preconditioning is applicable as a strategy to optimize results in endurance sports. The limitations of this systematic review refer to the diversity of intervention protocols applied in the studies; probably, this characteristic may have influenced the findings.

Conclusion

It is suggested that remote ischemic preconditioning may be able to increase VO2max in cycling and running practitioners. Wmax demonstrates that it is not influenced by remote ischemic preconditioning.

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Authors contributions

Oliveira FTO participated in the conception, design of the work and acquisition, analysis or interpretation of the work's data, and critical review. Dias CMCC contributed to the design of the work and acquisition and critical review. Queiroz C participated in reviewing the analysis/interpretation of the work's data, a critical review. Freitas ME participated in the search for data and writing of the manuscript. Santana RS and Nascimento C participated in the data collection.

Competing interests

No financial, legal, or political conflicts involving third parties (government, companies and private foundations, among others) have been declared for any aspect of the submitted work (including, but not limited to, grants and funding, participation in advisory council, study design, preparation manuscript, statistical analysis).

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