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Exercise training and experimental myocardial ischemia and reperfusion: A systematic review and meta-analysis

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ABSTRACT

Background: Despite the success of interventional coronary reperfusion strategies, morbidity and mortality from acute myocardial infarction are still substantial. Physical exercise is a well-recognized effective non-pharmacological therapy for cardiovascular diseases. Therefore, the objective of this systematic review was to analyze studies in animal models of ischemia–reperfusion in association with physical exercise protocols.
Search strategy: Articles published on the topic over a 13-year period (2010–2022) were searched in two databases (PubMed and Google Scholar) using the keywords exercise training, ischemia/reperfusion or ischemia reperfusion injury. Meta-analysis and quality assessment of the studies were performed using the Review Manager 5.3 program.
Results: From the 238 articles retrieved from PubMed and 200 from Google Scholar, after screening and eligibility assessment, 26 articles were included in the systematic review and meta-analysis. For meta-analysis comparing the group of previously exercised animals with the non-exercised animals and then submitted to ischemia–reperfusion, the infarct size was significantly decreased by exercise ($p < 0.00001$). In addition, the group exercised had increased heart-to-body weight ratio ($p < 0.00001$) and improved ejection fraction as measured by echocardiography ($p < 0.0004$) in comparison to non-exercised animals.
Conclusion: We concluded that the animal models of ischemia–reperfusion indicates that exercise reduce infarct size and preserve ejection fraction, associated with beneficial myocardial remodeling.

1. Introduction

Myocardial infarction (MI) is a major cause of mortality and morbidity in developed contries, and the most common outcome of coronary artery disease (CAD), corresponding to one third of deaths of people over 35 years of age. Depending on the infarct size resulted from the ischemic insult, the imposed overload induces pathological remodeling characterized by excentric hypertrophy, capilar rarefaction and intersticial fibrosis, with decreased ejection fraction and long-term heart failure [1].

Thus, one of the best strategy is to discontinue the ischemic state of the heart throughout the restoration of blood flow (i.e. reperfusion). Although early reperfusion can indeed reduce the infarct size and recovery myocardium function, even when lately performed, reperfusion or angioplasty has also its pathophysiological benefits. Described effects of the reperfusion include an improvement of oxidative stress, preservation of cellular respiration and energy production, controlled activation of the inflammatory process, and improvement of the contractile function by metabolic pathways including mitochondrial function and other intracellular protective effects, which support the benefits to the cardiovascular function [2,3].

Furthermore, it is well established in the literature that physical

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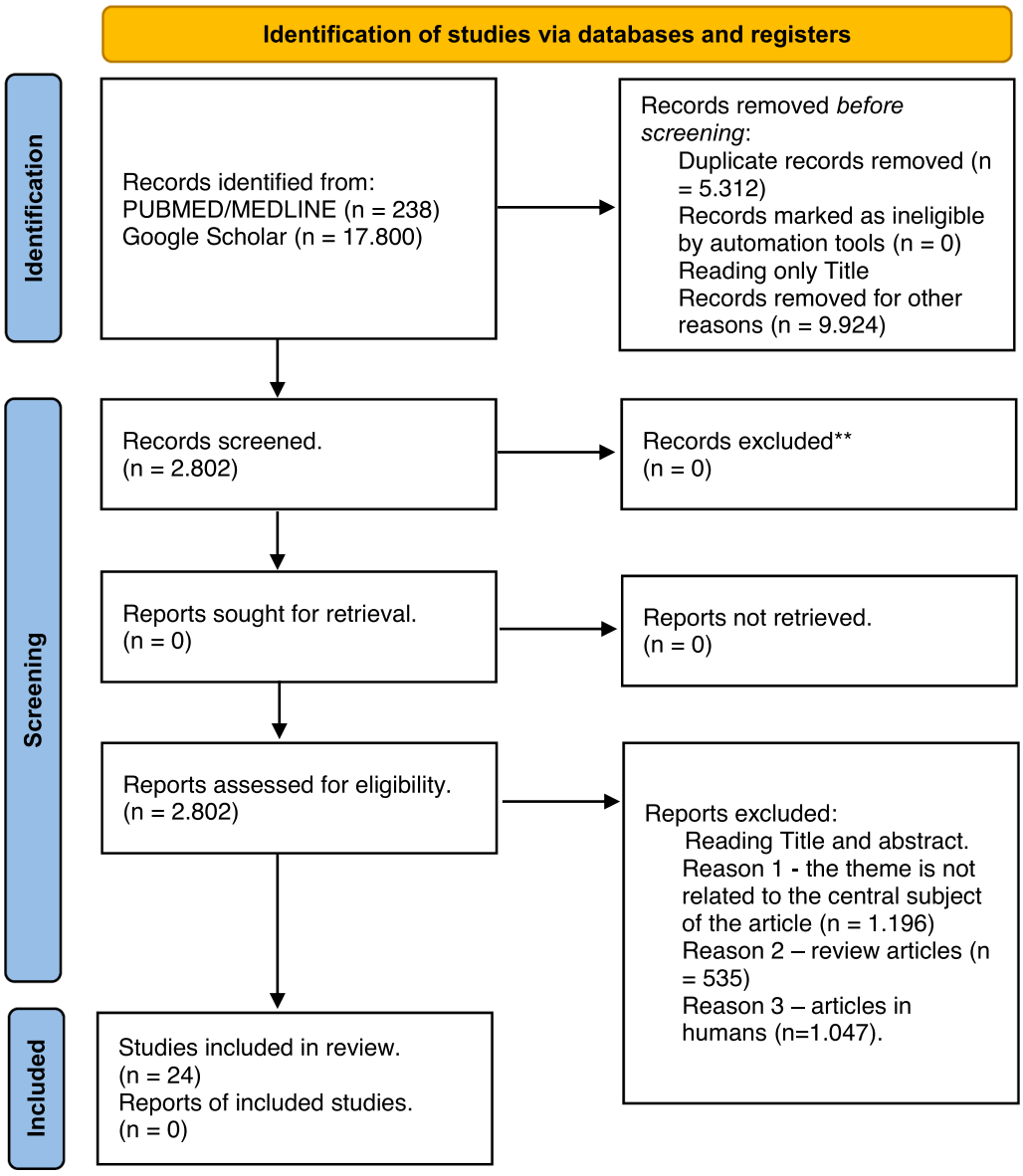

Fig. 1. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

exercise is efficient in the prevention/treatment of CAD and MI by reducing the cardiovascular damage, decreasing morbidity and mortality [4]. Therefore, it is suggested that the combined approached of exercise and reperfusion can present cumulative benefits in mitigating the acute/late damages and the impairment of heart function in rodent experimental models and in humans [5-7].

Therefore, this systematic review fills a gap on experimental models in animals that practiced physical exercise before the insult and underwent ischemia and reperfusion treatment at different times. Therefore, the objective of this study is to evaluate whether physical exercise in animals undergoing ischemia and reperfusion brings benefits to the heart.

2. Material and methods

This meta-analysis was conducted in accordance with the [8]Deeks et al, 2022 and [9]Arya et al, 2021 and for the systematic reviews we use several articles including [10]Berstock et al, 2019, [11]Hennessey et al, 2019, [12]Muka et al, 2020 and [13]Page et al, 2021.

2.1. Search strategy

For the identification of the elected studies to be included in this review, articles from January 2010 to July 2022 indexed in PUBMED and Google Scholar were considered. Firstly, we selected keywords from related articles, and MeSH international data lines were used to find more related key words with close meanings, these included: ("exercise training" [MeSH Terms] OR ("exercise" [All Fields] AND ("ischemia/reperfusion") [MeSH Terms] [All Filds] OR ("physical exercise" [MeSH Terms] "physical examination" OR "exercise training" [MeSH Terms] "exercise" AND "ischemia reperfusion injury". The search strategy was carried out on the two databases. PubMed searches including the other animals' filters resulted in 238 potential articles. Google scholar with the filter only in the title resulted in 17.800 articles. The terms used were "exercise training and ischemia reperfusion" MeSH terms: ischemia reperfusion; exercise; the search was repeated following review of the eligible papers to specifically search for methodologies, outcomes, and parameters of ischemia reperfusion. We also reviewed the retrieved articles to identify possible additional studies (Fig. 1). The search for Google Scholar was performed through advanced search with the descriptors that entered only the title of each search. This review was

Table 1
Study the characteristics of selected control experiments studies of prior exercise and experimental myocardial infarction.

Authors	Animal type	Gender	Animal race	Age (months)	Weight (g)	Induction model
Sayevand et al, 2022	Rats	Male	Wistar	6–8 weeks old	200–250	Myocardial ischemia and reperfusion model
Ranjbar et al, 2022	Rats	Male	Sprague-Dawley	7–8 weeks old	180–200	Myocardial ischemia and reperfusion model
Fatahi et al, 2022	Rats	Male	Wistar	2 months and 20 months	180–200 and 380–400	Myocardial ischemia and reperfusion model
Wang et al, 2021	C57BL/6 mice	Male	C57BL/6 mice	8 weeks old	–	Myocardial ischemia and reperfusion injury
Guo et al, 2021	Mice	Male	iNOS− /− mice C57BL/6 and eNOS− /− mice	–	–	Myocardial ischemia and reperfusion model
Hjortbak et al, 2020	Rats	Male	–	8 months old	–	Ischemia and reperfusion in an isolated perfused heart model
França et al, 2020	Rats	Male	Wistar	–	–	Ischemia and reperfusion in an isolated perfused heart model
Banaei et al, 2020	Rats	Male	Wistar	8–12 weeks old	250	Myocardial ischemia and reperfusion model
Ramez et al 2019	Rats	Male	Wistar	8–10 weeks old	250–300	Myocardial ischemia and reperfusion model
Veiga et al 2019	Rats	Female	Wistar	12 weeks old	180–220	Myocardial infarction and ischemia reperfusion
Ghahremani et al 2018	Rats	Male	Wistar	8 weeks old	–	Myocardial ischemia and reperfusion model
Parry et al 2018	Rats	Male	Sprague-Dawley	8 weeks old	–	Langendorff isolated perfused heart
Bei et al 2017	Mice	Male	C57BL/6	8 weeks old	–	Ishchemia reperfusion injury
Shi et al 2017	Mice	Male	C57BL/6	8 weeks old	–	Cardiomyocyte isolated
Alleman et al 2016	Rats	Male	Sprague-Dawley	3 mouths old	250–300	Langendorff isolated perfused heart
McGinnis et al 2016	Mice	Male	56 C57, C57BL/6J and 48 IL6^{-}/$^{-}$	–	–	Ishchemia reperfusion injury and ischemic precontining
Li et al 2014	Mice	Male	C57BL/6	4 weeks old	–	Ishchemia reperfusion injury
Wang et al 2014	Rats	Male	Wistar	3 and 18 mouths old	–	Ishchemia reperfusion injury and ischemic precontining
Nicholson et al 2013	Mice	Male	Six strain of mice	8–10 weeks old	–	Ischemia reperfusion in vivo
Doustar et al 2012	Rats	Male	Wistar	3 mouths old	220–240	Ishchemia reperfusion injury
Quindry et al 2012	Rats	Male	Sprague-Dawley	4 mouths old		Ishchemia reperfusion injury
Calvert et al 2011	Mice	Male	C57BL/6	8 to 10 weeks old		Ishchemia reperfusion injury
Frasier et al 2011	Rats	Female	Sprague-Dawley	2 to 3 mouths old	150–250	Langendorff isolated perfused heart
Farah et al 2010	Rats	Male	Wistar	–	Mean 384	Langendorff isolated perfused heart

conducted according to the recommendations established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [13].

2.2. Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: English-language, studies on animal models, theme relevance for this systematic review (exercise in ischemia and reperfusion, or ischemia reperfusion injury), articles reporting exercise performed previously or after ischemia and reperfusion. Some articles with animal and in vitro experiments were also included, but articles that presented only in vitro experiments were not selected. Exclusion criteria were: human studies, review articles and systematic reviews, studies from more than last 13 years.

2.3. Data extraction and quality assessment

Several articles were deleted because they fled the topic. For example - articles not related to the subject of exercise and experimental ischemia and reperfusion were 9.924 articles. Duplicate records removed are 5.312. What resulted in recorded screening of 2.802 articles to read the title and abstract. As explained in Fig. 1, for other reasons, another 2,776 articles were excluded from the systematic review, leaving 26 articles for final inclusion to do the systematic review and meta-analysis (Fig. 1).

The process of retrieving the papers, as well as evaluating the titles and abstracts obtained were conducted by two researchers with the ability to compile systematic reviews (E.C.V. and D.S.B.) independently and blindly, following the inclusion and exclusion criteria according to the components of P.I.C.O. [13]. The selected articles were then critically evaluated to be included or excluded in the review. Any discrepancies about the study selection were solved by consulting a third investigator (J.M.S.J.).

We also used a risk of bias analysis based on the Cocharane tool for animal intervention studies. SYRCLE's RoB tool is an adapted version of the Cochrane RoB tool. Widespread adoption and implementation of this tool facilitate and improve critical appraisal of evidence from animal studies. This tool has been adjusted for aspects of bias that play a specific role in animal intervention studies [14].

The information extracted from the studies selected were: first author, publication year, animal species and strain, gender (M/F), age (months), body weight (grams), I/R induction model (Table 1).

2.4. Statistical analysis

For descriptive statistics, the mean, standard deviations, mean difference and 95% of interval confidence were calculated. Meta-analysis was carried out with the Review Manager 5.4.1 software program (Cochrane Collaboration, Oxford, UK) by comparing the means and standard deviations of the exercise and the control groups. Heterogeneity was calculated via the I^2 statistic, where a number $\geq$ 50% was considered to indicate substantial heterogeneity between the tests (Higgins and Thompson, 2002). For the values of 95% CI and "Test for overall effect size" values of $p \leq 0.05$ were assumed the significant differences (Dettori et al, 2021). We enforced a random-effects model, considering that is a more conservative method which allows that the heterogeneity of the study may fluctuate beyond chance, providing further generalizable results [8].

3. Results

3.1. Characteristics of the included studies

The Table 1 shows that most studies used rats, although a few others

Table 2
Study of the characteristics (samples size, number of groups, number of animals/groups, dependent variables) of selected experimental studies of controlled animals on effects of exercise and experimental myocardial ischemia and reperfusion.

Authors	Sample size	Number of groups	Number of animals/ groups	Methodology of exercise	The ischemia and reperfusion proocedings	Exercise intensity	Time of Training and detraining.	Dependent variables
Sayevand et al, 2022	50	5	10	Treadmill trained 5 days/week for 10 weeks	In vivo ischemia and reperfusion – 30 min of ischemia and 5 days of reperfusion	Moderate aerobic	10 weeks of T – 6 days of DET	Infarcted size, biometric analysis, M rna expression of several molecules
Ranjbar et al, 2022	50	5	10	Treadmill trained 5 days/week for 8 weeks	In vivo ischemia and reperfusion – 30 min of ischemia and 7 days of reperfusion	High-Intensity Interval Training	8 weeks of T – 7 days of DET	Doppler Echocardiography, Myocardial Infarct Size Assay, Collecting Heart Tissues, Angiogenesis Indices, Capillary Density, Antioxidant Enzymatic Activities
Fatahi et al, 2022	40	4	10	Treadmill high intensity interval training for 5 days/ week for 8 weeks	In vivo 30 min of ischemia and 120 min of reperfusion	high intensity interval training 60–90 Vo2 max	8 weeks of T – 3 days of DET	Measurement of infarct size and area at risk, Determination of oxidative stress factors, measuments of arrhythmias
Wang et al, 2021	–	4	–	Swimming 90 min/ day, 5 days/week for 3 weeks	In vivo 45 min of ischemia and 24 h or 3 weeks of reperfusion	–	3 weeks of T – 24 h or 3 weeks of reperfusion	Primary Cardiomyocytes Isolation, Culture, and Treatment, Immunofluorescent and TUNEL Staining, Western Blotting, Immunohistochemical Staining and Histological Analysis
Guo et al, 2021	–	3	–	Treadmill moderate intensity 60 min twice per day for 2 days	In vivo 30 min of ischemia and 24 h of reperfusion	moderate intensity	2 days of T – <1 day of DET	Effect of exercise on eNOS and PKCε, effect of exercise on infarct size
Hjortbak et al, 2020	100	4	25	Treadmill running moderate intensity	In vitro perfusion 30 min of ischemia and 120 min of reperusion	moderate intensity	4 months of T – and 2 days of DET	Isolated perfused heart model, Infarct size, Glucose uptake, Western blot analyses
França et al, 2020	40	4	10	Treadmill – High intensity interval training and moderate intensity	In vitro perfusion 30 min of ischemia and 60 min of reperfusion	High intensity interval training and moderate intensity	4 days of T and 1 day of DET.	Isolated perfused heart model, Infarct size, Cardiac function following myocardial insult, Lipid profile.
Banaei et al, 2020	50	4	12	Treadmill – High intensity interval training for 8 weeks	In vivo 30 min of ischemia and 24 h of reperfusion	–	8 weeks of T and 2 days of DET	Echocardiographic Data, Caspase-3, Gene Expressions in the Border Zone Left Ventricular, infarct Size.
Ramez et al 2019	80	7	11	Treadmill – High intensity interval training versus moderate intensity continuous training for 5 consecutive days	In vivo ischemia and reperfusion model – 30 min of ischemia and 24 h of reperfusion	High intensity 50–60% and 85–90% of VO2max – moderate intensity 70% VO2 max	5 days of T – 2 days of DET	Assessment of infarct size, Measurement of plasma levels of klotho, LDH, and CK-MB, TRPC6 protein expression.
Veiga et al 2019	40	4	10	Swimming 60 min/ day, 5 days/week for 8 weeks	In vivo ischemia and reperfusion – 60 min of ischemia and 4 weeks of reperfusion	Moderate intensity about 60–65% of VO2 máx	8 weeks of T – 4 weeks of DET	Mortality, Echo, biometric analysis, hemodynamics analysis, histomorphometric analysis, apoptosis, collagen analysis and western blot.
Ghahremani et al 2018	32	4	8	Treadmill High-intensity aerobic training 60 min/day, 5 days/week, 8 weeks	In vivo ischemia and reperfusion – 30 min of ischemia and 90 min of reperfusion	High-intensity aerobic training 60, 80–85 % of Vo2max	8 weeks of T – 2 days of DET	Measurement of infarct size, Real-time polymerase chain reactions (RT-PCRs).
Parry et al 2018	49	4	26/23	Treadmill trained 5 days/week for 6 weeks	Isolated perfused hearts – 25 min of ischemia and 15 min of reperfusion	75–80% of VO2 máx	7 weeks of T and 5 h of DET	Metabolomics determination, Nitrogen metabolism, Aminoacyl-tRNA biosynthesis, Citric acid cycle, heart weight to body weight.
Bei et al 2017	–	–	–	Swimming 90 min/ day, 5 days/week for 4 weeks	In vivo ischemia and reperfusion – 30 min of ischemia and 24 h of reperfusion	–	4 weeks of T and 24 of DET.	In vivo and in vitro expermients, heart weight to body weight, Effects on cardiac cell proliferation and cell size, Infarcted size
Shi et al 2017	28	4	6	Swimming 90 min/ day, 5 days/week for 3 weeks and voluntary wheel running for 90 min/	Transverse aortic constriction, 30 min of ischemia and 4 weeks of reperfusion.	Moderate intensity about 60–65% of VO2 máx	3 weeks of T – 4 weeks of DET.	Cell proliferation assay, TUNEL assay, Quantitative reverse transcription polymerase chain reaction (RT-PCR), western blot, Echo, heart weight to body weight.

(*continued on next page*)

Table 2 (*continued*)

Authors	Sample size	Number of groups	Number of animals/ groups	Methodology of exercise	The ischemia and reperfusion proocedings	Exercise intensity	Time of Training and detraining.	Dependent variables
				day, 5 days/week for 3 weeks				
Alleman et al 2016	–	–	–	Treadmill trained 5 days/week for 10 days	Isolated heart studies, myocyte isolations or mitochondrial experiments	Moderate to hight intensity of exercise.	10 days of T and 24 h of DET.	Isolated heart preparation and assessment of arrhythmia, Two-photon microscopy whole heart imaging during ischemiareperfusion, glutation levels, cardiomyocyte cell isolation, mitochondria isolation.
McGinnis et al 2016	64/40	2/2	32/20	Treadmill training during 3 days for 60 min	In vivo IR injury – 30 min of ischemia and 120 min of reperfusion	Moderate intensity about 60–65% of VO2 máx	3 days of T and 24 h of DET.	Infarcted size measuments of area of risk by Evańs blue, PCR, western blot, Arrhythmia scoring, apoptosis.
Li et al 2014	–	–	–	Treadmill training during 8 weeks for 45 mins/day for 5 days/ week	30 min of ischemia and 24 h of reperfusion	Moderate intensity about 60–65% of VO2 máx	8 weeks of T and 24 h of DET	Infarcted size by TTC, Echo, western immunobloting analysis.
Wang et al 2014	–	–	32 young and 96 old rats	Treadmill running – old rats run for 6 weeks, 20 min/day for 5 day/week and young rat run 60 min/day for 5 days/ week for 6 weeks	30 min of ischemia and 30 or 120 min of reperfusion – in vivo, cardiac isolation and cardiomyocyte isolation	Moderate intensity about 60–65% of VO2 máx.	6 weeks of T and 24 h of DET	Infarcted size by TTC, LDH activity, hemodynamics measuments, isolation of cardiac mitochondrial, measurements of mitochondrial consumption, western blot analysis, ROS production in cardiomyocyte.
Nicholson et al 2013	–	–	–	Voluntary wheel running 4 weeks	Early and late preconditioning – 30 min and 2 h of IP and 24 h of IP.	–	4 weeks of T and 24 h of DET	Echo, NO Metabolite Measurements, Nitrite Reductase Activity Measurements, western blot and PCR.
Doustar et al 2012	40	2	20	Resistence exercise – 12 repetitions/set, 4 sets/day and 5 days/ week for 4 weeks	In vivo 40 min of ischemia and 80 min of reperfusion	–	4 weeks of T – 24 h of DET	Infarcted size by Evańs blue, left ventricule development pressure, coronary flow, apoptosis,
Quindry et al 2012	86	2	54/32	Treadmill training during 8 days for 50 min	In vivo 50 min of ischemia and 120 min of reperfusion	About 70 % of VO2 máx	8 days of T and 2 days of DET	Arrhythmia scoring, Infarcted size by TTC, western blot analysis for markers of apoptosis and autophagy, Analysis of antioxidant enzyme activity and oxidative stress
Calvert et al 2011	–	–	–	Voluntary running training during 4 weeks	In vivo IR injury – 45 min of ischemia and 24 h of reperfusion	Moderate intensity about 60–65% of VO2 máx	4 weeks of T and 24 h of DET, 1 week and 4 weeks of DET	Infarct size determination, by troponin-I measurements, western blot analysis, Analysis of Nitrite, Nitrate, and Nitrosothiols, Analysis of catecholamine levels
Frasier et al 2011	71	–	–	Treadmill training during 10 days for 50 min	Isolated perfused heart – 30 min of ischemia and 30 min of reperfusion	–	10 days of T and 24 h of DET	Arrhythmia assessment, Cardiac myocyte isolation, Cellular ROS fluorescence measurements, Myocardial glutathione, glutathione peroxidase, and glutathione reductase.
Farah et al 2010	–	–	–	Treadmill training during 4 weeks, 5 days/week for 60 min	Isolated perfused heart – 30 min of ischemia and 120 min of reperfusion	Moderate intensity about 50% of VO2 máx	4 weeks of T and 24 h of DET	CO exposure, Ca^{2++} handling in cardiomyocytes, heart antioxidant enzyme activity, LDH activity in coronary effluents, western blot analysis

T – training; DET – detraining; Echo - echocardiography measurements; Echo – echocardiogram analysis; TTC – triphenyltetrazolium chloride staining; TUNEL assay method for measuments of apoptosis; LDH activity methods for measurement of lactato deshidrogenasa; ROS reaction oxygen species; NO – nitric oxide; ECG – eletrocardiogram; CO – carbon dioxide; Ca^{2++} - Calcium.

used mice. Moreover, regarding genre, most of the selected studies used males. The I/R model included "in vitro" (Langendorff isolated heart perfusion technique) and "in vivo" models (ischemia and reperfusion injury, and ischemic preconditioning) (Table 1). Table 2 presents sample characteristics (size, number of groups and animals per group) and exercise protocol (exercise type and intensity, session duration and frequency, and training and detraining duration). The exercise protocols included forced swimming [15-18], resistance exercise [19], and running training [20-2930-38], being some few exercise protocols were voluntary [17,32,39]. Table 2 also reports the I/R procedures (ischemia and reperfusion duration until sacrifice, and dependent variables evaluated.

3.2. Exercise impacts on the I/R models

The results of the meta-analysis were very robust, indicating that infarct size as measured by tetrazolium (% risk area of the left ventricle) significantly smaller in exercised group ($p < 0.00001$) compared to sedentary (Fig. 2A). Also, the variable heart-to-body weight index (mg/g), as indicative of heart hypertrophy, was greater ($p < 0.00001$) in the

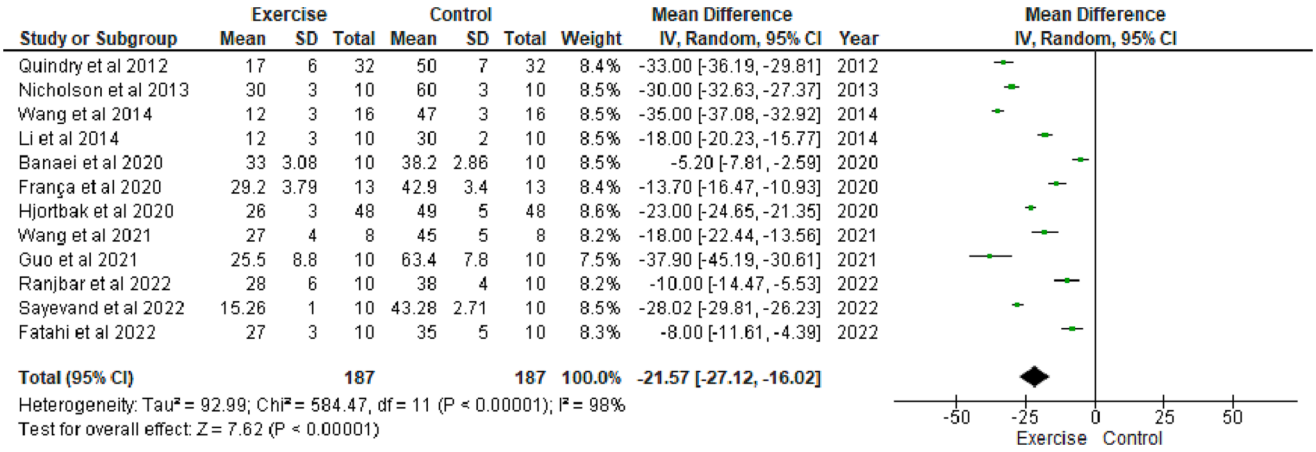

Fig. 2A. Meta-analysis comparing the group of animals that exercised and then underwent ischemia and reperfusion (Exercise) with the group of animals sedentary that only underwent ischemia and reperfusion (Control) with the variable of the infarct size measured by tetrazolium (TTC - % risk area of the left ventricle).

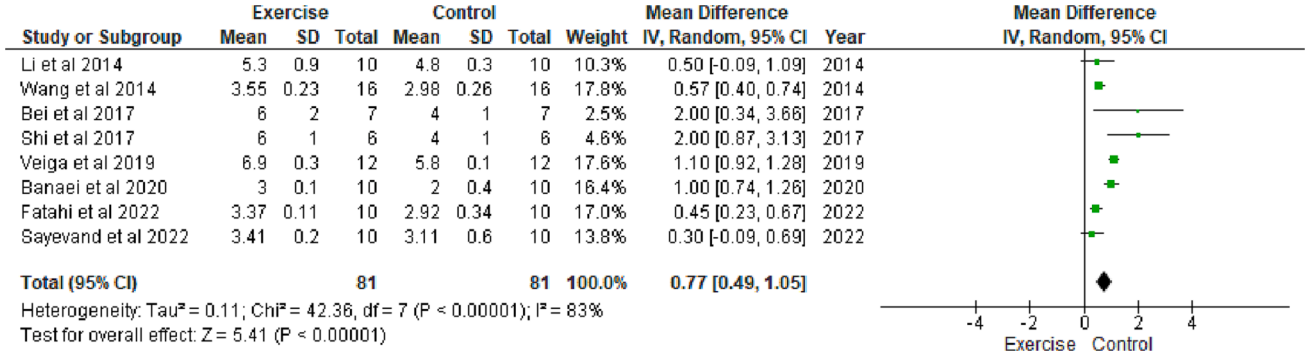

Fig. 2B. Meta-analysis comparing the group of animals that exercised and then underwent ischemia and reperfusion (Exercise) with the group of animals sedentary underwent ischemia and reperfusion (Control) with the variable of heart weight / body weight (mg / g) indicative of heart hypertrophy.

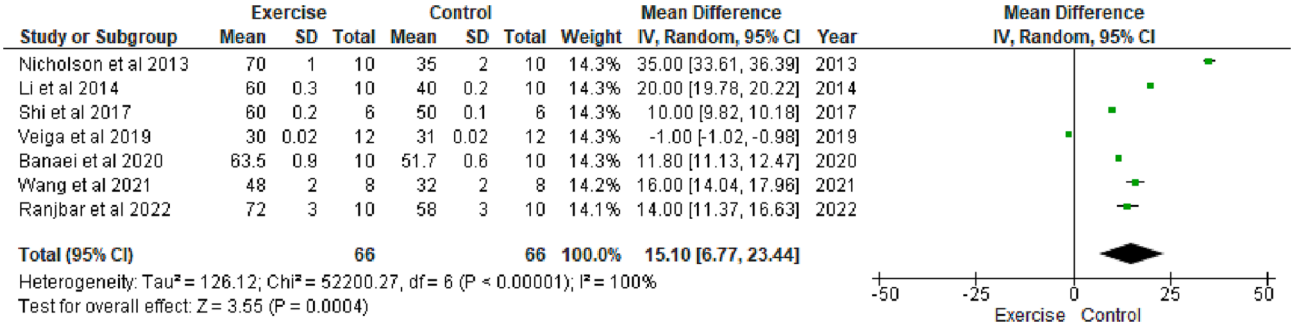

Fig. 2C. Meta-analysis comparing the group of animals that exercised and then underwent ischemia and reperfusion with the group of animals sedentary underwent ischemia and reperfusion with the variable of the ejection fraction measured by echocardiogram (% of the left ventricle).

exercised group (Fig. 2B). This hypertrophic remodeling was associated to improved ejection fraction (by echocardiography) in the exercised group (Fig. 2C).

The Table 3 shows nine variables evaluated by at least two of the selected studies indicating whether exercise was statistically significant to improve the response to I/R protocol compared to non-exercised group. Regarding the infarct size, although it has been measured in 22 studies by various techniques (i.e. echocardiogram, tetrazolium, or risk area by Evans Blue), 20 have shown that exercise led to smaller infarct sizes [15,20-27,29 28,31,32,34-38] and only two studies did not report differences between exercised versus non-exercised animals [16,19]. Heart-to-body weight index was accessed by 13 studies, of which 12 articles reported increased in this indication of cardiac hypertrophy [17,18,20,23,27,29–31,36,38]. Cardiac function parameters also were significantly improved in exercised groups reported by the selected studies. Left ventricular systolic and diastolic pressures as well as positive and negative pressure derivatives were increased by exercise in 8 of the 9 studies that evaluated ventricular hemodynamics [16,19,21,24,25,30,36]; and ejection fraction was improved in 5 of the 6 studies that performed transthoracic echocardiography [17,21,26,27,32] indicating functional benefits of physical exercise in I/R. When arrhythmias were evaluated as an outcome (6 studies), all authors reported reduction on the post-I/R arrhythmias [22,31-34,38].

Regarding the potential mechanisms involved in the benefits of exercise for I/R injury, all 12 studies that accessed oxidative stress reported reduction on this variable due to exercise[19,21-23,27,31-

Table 3
Study characteristics of selected experimental controlled animal study of positive effects- statically significant among the measures evaluated.

Authors	Measurements of infarcted size	HW/BW	Ejection fraction	Hemodynamic measuremnts	Analysis of oxidative stress	Arrhythmia assessment	Mitochondrial analysis	Apoptosis	Benefits of gene/protein expression with exercise*
Sayevand et al, 2022	X	X	–	–	–	–	–	–	X
Ranjbar et al, 2022	X	–	X	X	X	–	–	–	–
Fatahi et al, 2022	X	–	–	–	X	X	–	–	–
Wang et al, 2021	X	–	–	–	–	–	–	X	X
Guo et al, 2021	X	X	–	–	X	–	–	–	X
Hjortbak et al, 2020	X	–	–	X	–	–	–	–	X
França et al, 2020	X	–	–	X	–	–	–	–	X
Banaei et al, 2020	X	–	X	–	–	–	–	–	X
Ramez et al 2019	X	X	–	–	–	–	–	–	X
Veiga et al 2019	NS	–	NS	X	–	–	–	X	X
Ghahremani et al 2018	X	X	–	–	–	–	–	–	X
Parry et al 2018	–	X	–	X	–	–	–	X	X
Bei et al 2017	X	X	–	–	–	–	–	–	X
Shi et al 2017	–	X	X	–	–	–	–	X	X
Alleman et al 2016	–	–	–	–	X	X	X	–	–
McGinnis et al 2016	X	X	–	–	X	X	–	X	X
Li et al 2014	X	NS	–	–	–	–	–	–	X
Wang et al 2014	X	X	–	X	X	–	X	–	X
Nicholson et al 2013	X	–	X	–	X	–	–	–	X
Doustar et al 2012	NS	–	–	X	–	–	–	NS	–
Quindry et al 2012	X	–	–	–	X	X	–	X	X
Calvert et al 2011	X	–	–	–	X	–	–	–	X
Frasier et al 2011	–	X	–	NS	X	X	–	–	–
Farah et al 2010	X	–	–	–	X	X	–	–	X

X - The difference of the variable between the sedentary animal and exercise animals with ischemia reperfusion or ischemia reperfusion injury was statistically significant. NS – not signigicant. – (-) means that in this work this specific variable was not used. HW/BW – heart weight/body weight. * Western blot analysis and polymerase chain reactions analysis.

34,36,38]; 2 of the 2 studies indicated improved cardiac mitochondrial function [19,36]; and 6 of the 7 studies reported mitigation of apoptosis on the myocardium [15-17,30,34,38] while only one study showed no effect [40]. Finally, in regard of pathological changes on the gene/protein expression with I/R, all 20 studies that evaluated molecular remodeling [15-18,20,23-27,29,30,32,34,36-39] reported a beneficial profile in exercised compared with non-exercised groups.

3.3. Assessment of the quality of the included studies

The quality verification of the selected study in Fig. 3 is based on the article by Hooijmans et al, 2014[14], that proposed how to analyze the most frequent recommendations appearing in preclinical research guidelines for in vivo animal's experiments. Then, it was calculated the percentage of selected articles that followed each recommendation.

When Random sequence generation was used as criteria, 40% of the studies were classified as low risk of bias, about 15% had high risk of bias and the remaining studies were classified as unclear risk of bias. Concerning Allocation concealment, about 40% had a low risk of bias and the other 60% were classified as unclear risk of bias. The analysis of Blinding of participants and personnel classified one study as low risk of bias, and since this information was not found in the methods section of the remaining papers, they were classified as unclear risk of bias. Forty percent of the articles were classified as low risk of bias and 60% had unclear risk of bias, when incomplete outcome data judgment was evaluated.. For Selective reporting, 50% had a low risk of bias and 50% were unclear. Seventy five percent of the articles were classified as low risk of bias due to baseline characterization, and only 25% were unclear risk. Due to adequate Random housing, 5 studies were at high risk of bias, 5 articles were classified as low risk of bias, and the remaining as unclear risk of bias. Random outcome assessment classified 5 studies as high risk of bias, followed by only 3 at low risk of bias and 15 studies as unclear. If considering other nonrelated bias, 30% had a low risk and 70% was classified as unclear risk of bias. Briefly, most of selected studies was classified as unclear risk of bias, about 30% as low risk of bias, and only few studies had variables categorized as high risk of bias.

Of the total of 15 recommendations, 7 were followed by 100% of our selected studies: outcomes blind assessment, appropriated control group election, baseline characterization of the dependent variable to be analyzed, mechanistic pathway investigation, matching the evaluated

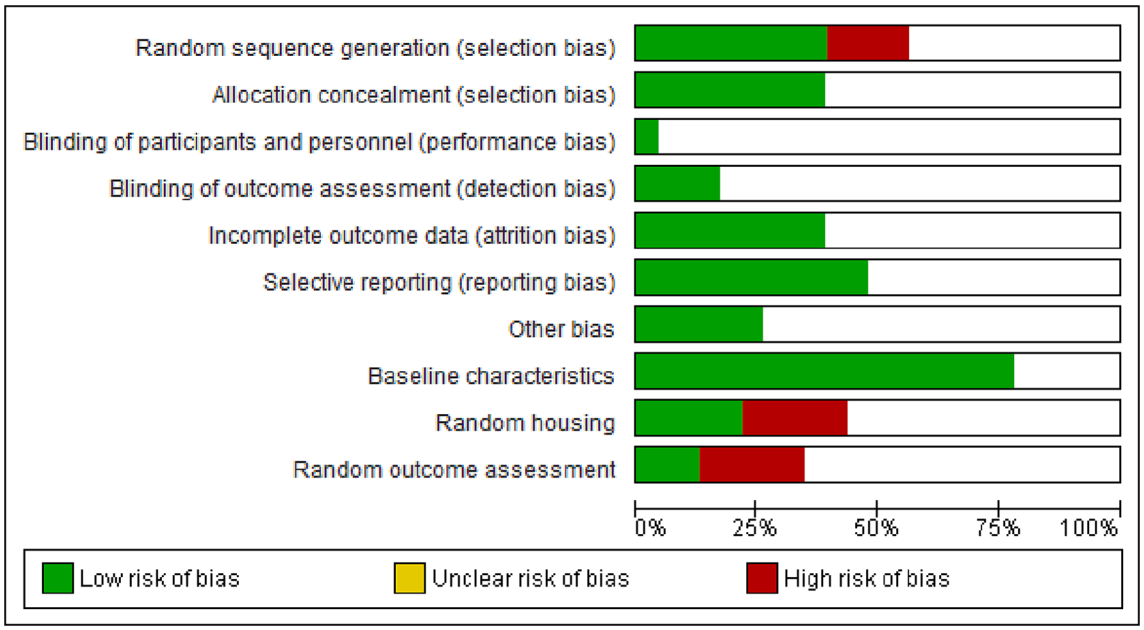

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

outcome to clinical setting, matching the age model to the patients ages in the clinical setting, and replication in different species. Other 2 recommendations were stated by more than 50%, such as randomized group allocation in 53.33%, and independent replication in 73.33% of selected studies. However, 4 recommendations were found in less than 50% of the studies: choice of sample size were detailed in 40%, clear correspondence of the experimental mode to human manifestation of the disease was found in 46.66%, replication in different models of the same disease was done in 46.66%, and an inter-study standardization of the experimental design was identified only in 33.33%. Finally, just two recommendations were not cited by the studies. Thus, according to the parameters used here, the quality of the studies can be considered very good (Fig. 3 and Fig. 4).

4. Discussion

The main finding of this study were acquired by the meta-analysis and demonstrated that physical exercise in animal models of ischemia and reperfusion had benefits such as reduced infarct size, a physiological hypertrophy profile and improvement of ejection fraction.

The deterioration of cardiac function in animal models closely depends on the extent of the myocardial damage and infarction produced by coronary occlusion [41], and decrease in the infarction size by exercise is decisive to the improvement of survival and cardiac function [7,42]. In fact, the meta-analysis indicates that the decreased infarct size in exercised group was associated with improved their survival, remodeling process, in parallel with attenuation of heart failure signs either after reperfusion or therapies [43,44]. As a result, this review reinforces that after the previous application of aerobic exercise protocols, the restriction in the size of the infarction and the remodeling certainly had a positive impact on the global cardiac function. Just as there is an improvement in cardiac function after several other strategies that are proven to reduce infarction in small rodents [45], we could credit a good part of the benefits identified by the studies analyzed in this review to this effect of physical exercise.

Physiological hypertrophy resulting from exercise training is another result that deserves to be highlighted in our study because among the benefits of physiological hypertrophy are improved cardiac function, increased cardiac output, improved contractility and exercised animals that underwent ischemia and reperfusion showed better physiological hypertrophy indices than sedentary animals undergoing ischemia and reperfusion, these data are in agreement with recent literature [4,5]. The improvement in ejection fraction measured by the echocardiogram was significantly greater in animals that exercised and underwent ischemia and reperfusion compared to sedentary animals with ischemia and reperfusion. The ejection fraction indicates the amount of blood being ejected by the heart and the improvement of this index is an important indicator of the heart's recovery. ejection fraction is an important indicator both in animals and in clinical studies[46-48].

Other benefits of exercised animals undergoing ischemia and reperfusion compared to sedentary ones in selected studies were better hemodynamic parameters, reduced oxidative stress analysis, improvement of reperfusion arrhythmia and apoptosis, and improvement of gene and protein alterations that were studied. In the literature, we found these mechanisms of improvement in cardiac function and others, such as the review by [49], which discusses how exercise improves the electrophysiology of the heart, has beneficial effects on the metabolism of hearts in the elderly, and protects against damage from the ischemia reperfusion injury. In the review by [50] the authors demonstrated how prolonged exercise acts on nitric oxide and contractility, bringing benefits to these parameters.

Among the benefits of physical training in animals are an increase in the antioxidant capacity of cardiomyocytes by the upregulation of SOD, catalase and overexpression of HSP70, in addition to an increase in the precursor of nitric oxide. Exercise also induces an increase in Mn-SOD activity that attenuates ischemia/reperfusion-induced oxidative modifications of calcium handling proteins and results in decreased cardiomyocyte death. Among other benefits of exercise are that preconditioning is an immediate protector against ischemia–reperfusion injury, regulates pro-inflammatory cytokines, improves mitochondrial performance by improving energy consumption and elevates protein C kinase, which has beneficial actions to improve contractile function and calcium handling.[3-5].

Regarding myocardial ischemia and reperfusion, it is time-dependent, that is, the earlier the reperfusion is performed, the more benefits it brings to the heart. Other benefits include decreased infarct size and coronary microvasculature damage, the molecular pathways by which these benefits are realized are complex and include activation of sarcolemma receptors and cytosolic kinases as well as reduced mitochondrial permeability transition pore opening, calcium overload and

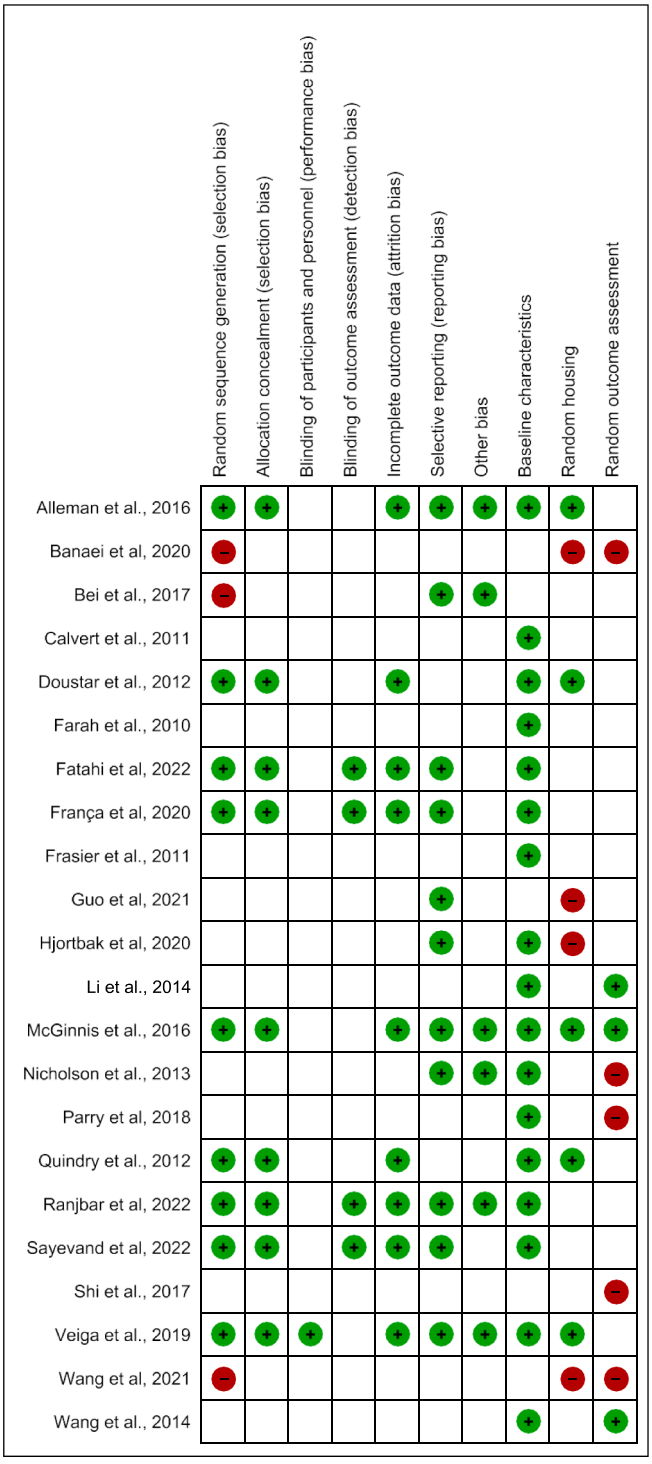

Fig. 4. Risk of bias summary: review of authors' judgment regarding each risk of bias item for each included study.

proteolysis and remote ischaemic conditioning improved clinical outcomes in patients with ST-segment elevation myocardial infarction in one phase III clinical trial [51-54].

The literature demonstrates that the basic sciences have a greater control of the variables with animals than studies in humans and in the case of the myocardium and ischemia and reperfusion, it is known, from basic studies, that the earlier the coronary artery is opened, the greater the benefits for the people undergoing reperfusion, then reperfusion is time dependent (61,62Rangel, 2021, Martin et al, 2022). Relevant data in animals have led to a greater understanding of the pathophysiology of myocardial ischemia and reperfusion injury, and knowing the intracellular pathways of signal transduction makes it more possible to seek effective therapeutic approaches for this complex comorbidity (63Bai et al, 2023).

Our current systematic review has several strengths. To our knowledge, this is the first meta-analysis assessing cardiac function and infarct size between exercised and sedentary animals submitted to the ischemia and reperfusion model. In addition, most of the included studies were of good quality based on the SYRCLE's tool for assessing risk of bias scoring system, which ensured the credibility of our results. All the studies used matched controls for age, and some studies used very detailed matching mechanisms. Well-defined criteria for ischemia/infarct determination and reliable morphofuncional tests in the included studies guaranteed the reliability of our analyses to some extent. However, some limitations should be noted. First, Few variables were chosen for comparison in the meta-analysis because the articles have very different objectives and therefore very different analyzes in each article selected for the study, according to most of the experimental studies selected for the systematic review used a 30-minute model of ischemia followed by different times of reperfusion and with this time of ischemia not all heart cells died and it is not possible to obtain an infarct size similar to the permanently occluded one, which does not reflect what happens to humans, especially in third world countries, in which most reperfusion procedures only occur days after people have had a heart attack such as a myocardial infarction or ischemia.

In conclusion, our meta-analysis revealed that exercised rats subjected to ischemia and reperfusion have a smaller infarct size, eject blood from the heart better and have greater physiological hypertrophy compared to sedentary animals subjected to ischemia and reperfusion. The connection between aerobic physical exercise should be further explored not only as a therapeutic strategy but also as a preventive approach to reduce ischemic damages to the cardiovascular system.

CRediT authorship contribution statement

Eduardo Carvalho de Arruda Veiga: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rozeli Ferreira Levy:** Data curation, Formal analysis, Writing – review & editing. **Danilo Sales Bocalini:** Data curation, Formal analysis, Writing – review & editing. **Jose Maria Soares Junior:** Writing – original draft, Visualization, Validation, Writing – review & editing. **Edmund Chada Baracat:** Writing – original draft, Visualization, Validation, Writing – review & editing. **Ricardo Carvalho Cavalli:** Writing – original draft, Visualization, Validation, Writing – review & editing. **Leonardo dos Santos:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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