TITLE: Effects of Exercise Training on Heart Rate Variability in Individuals with Lower Extremity Arterial Disease and Claudication: A Systematic Review

ABSTRACT

Purpose. To perform a systematic review of studies assessing the effects of regular exercise on heart rate variability (HRV) in individuals with lower extremity arterial disease (LEAD) and symptoms of claudication.

Methods. A systematic search in the electronic databases MEDLINE, Embase, and Scielo, was conducted and updated on January 21, 2023. Randomized clinical trials investigating patients with LEAD and IC, assessing ≥ 4 wk of exercise interventions, and reporting at least one HRV measure (e.g., time or frequency domains) at baseline and follow-up were included. Two reviewers independently screened studies for inclusion, performed data extraction, and quality assessment of included studies.

Results. Data from 7 trials were included (i.e., 5 walking, 1 resistance, and 1 isometric handgrip training), totaling 327 patients (66% males; range: 61 - 68 yr; ankle brachial index: 0.4 - 0.7). Following exercise training, three studies investigating walking training reported an increase in parasympathetic modulation indices and/or a decrease in sympathetic modulation indices (n = 2) as well as an increase in non-linear indices (n = 1).

Conclusion. The current evidence is weak, and larger randomized controlled trials are needed to confirm the efficacy of exercise training in improving HRV. Additionally, the high divergence in the methodology of studies indicated the need for standard tools to improve the quality of HRV measurements in exercise trials. It is recommended to use standard procedures in future trials investigating HRV.

Key words: Autonomic Function; Peripheral Arterial Disease; Strength Training; Walking Therapy

INTRODUCTION

Lower extremity arterial disease (LEAD) is characterized by atherosclerotic lesions (i.e., accumulation of lipids and fibrous elements associated with structural disorganization) in the lower extremities, limiting blood flow to the distal muscles.[1] Claudication (i.e., leg pain during walking that resolves with resting) is a hallmark symptom of LEAD.[2] The ankle-brachial index (ABI) is the first-line noninvasive test for the diagnosis of LEAD; an ABI ≤ 0.90 should be considered the threshold for confirming the disease.[3] It can detect the presence of arterial occlusive disease in patients who are symptomatic (i.e., ABI ≤ 0.90 with pain in the legs when walking which resolves when resting) or asymptomatic (i.e., ABI ≤ 0.90 but without any symptoms).[4] LEAD has become a global 21st century problem affecting more than 202 million people worldwide.[5] The incidence of LEAD is >10% among persons aged 60-70 yr and nearly 50% in those aged 85 yr and older.[6] The presence of LEAD is strongly associated with premature cardiovascular mortality, morbidity, and other significant age-related markers of disease.[7] In this context, a further increase in LEAD prevalence rates is expected with the increased aging of the population worldwide.

Patients with LEAD often present with cardiac autonomic dysfunction,[8] characterized by an imbalance between cardiac sympathetic and parasympathetic modulations,[9] and which is directly related to the severity of the claudication symptoms.[10] It is well established that dysfunction of the autonomic nervous system is a strong and independent predictor of cardiovascular morbidity and mortality in healthy individuals and in patients with established cardiovascular disease.[11] Non-invasive methods can be used to evaluate cardiovascular autonomic function.[12] Heart rate variability (HRV) is defined as the fluctuation between intervals of consecutive heart beats and has emerged as the most valuable noninvasive tool to assess autonomic nervous system function.[13] It can be evaluated by the oscillatory patterns (e.g., cardiac rhythm) of the R-R intervals on the electrocardiogram (e.g., time elapsed between two successive R waves of the QRS signal).[12]

Exercise training has been shown to play a role in improving cardiac autonomic control by reducing cardiac sympathetic modulation and/or increasing cardiac parasympathetic modulation at

rest in the general population.[14–17] The mechanisms involved in the benefits of exercise on cardiac autonomic function are the reduction in norepinephrine levels, lowering resting heart rate, and increasing HRV by central (e.g., heart) and peripheral (e.g., vascular tone) regulations.[18,19] Improvements in HRV indexes are associated with better muscle and aerobic performance, possibly due to peripheral adaptations to metaboreflex delay, which is induced by peripheral muscle ischemia.[20] These improvements in HRV might affect both central and peripheral capacities (e.g., ABI), with possible beneficial impact on the reduction of claudication, and increase in the quality of life of patients with LEAD and claudication.

Walking training is the primary therapy recommended for improving ambulatory capacity and preventing further progression of underlying atherosclerosis in LEAD patients.[21] Supervised exercise therapy (e.g., an exercise program supervised by a health care professional both in the inpatient and outpatient setting) has been shown to be more effective than unsupervised interventions (e.g., patients who are advised to walk in the home environment without any direct supervision by a health care professional). [22] Meta-analytic research (n = 18 studies; 725 patients) by our group showed that at least 4 weeks of supervised exercise (e.g., walking, resistance, aerobic and combined training) results in significant improvements in pain-free walking distance (PFWD; +132 m; 95% confidence interval [CI], +70 - +194 m, $P < .001$) and maximum walking distance (MWD; +183 m; 95% CI +98 - +268 m, $P < .001$) in adults with LEAD and claudication.[23] Yet, it remains unclear if these exercise interventions provide a sufficient stimulus to improve cardiac autonomic balance in these patients. Hereby, to investigate whether currently prescribed exercise interventions are sufficient to improve autonomic function, we conducted a systematic review to evaluate the impact of exercise on cardiac autonomic modulation assessed by HRV in individuals with LEAD and claudication.

METHODS

Our first objective was to perform an Individual Participant Data (IPD) meta-analysis[24] which is a type of systematic review that involves collecting, verifying and re-analyzing the original data for each participant in each study following the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) for Individual Patient Data systematic reviews.[25] To achieve this, we identified eligible trials and invited via e-mail the principal investigators (n=7) to participate. Six authors provided their data via an Excel datasheet, while one trial was excluded due to lack of response. We then followed PRISMA IPD guidelines for data management, verification, data extraction, assessment of study quality, and data analysis. High inconsistencies (i.e., different assessments) and heterogeneity (i.e., variance within variables) were found among the data invalidating the execution of the IPD. Therefore, the authors carried out a systematic review of randomized clinical trials that evaluated the effects of exercise training (≥ 4 wk) on HRV in LEAD patients with claudication. In addition, the review also evaluated the quality of the studies and the quality of HRV assessment.

This systematic review was conducted and reported according to the PRISMA guidelines.[26] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in April 2021 (registration number: CRD42021206334).

SEARCH STRATEGY

A systematic search was performed in three electronic databases (MEDLINE [OvidSP], Embase [OvidSP] and SciELO) from their inception until the search date of 18 April 2021. An updated search was completed on 21 January 2023. The search strategy included a combination of free text terms for the key concepts ‘exercise training’, ‘lower extremity artery disease OR peripheral artery disease’ and ‘heart rate variability’. The full search strategy for each database search is shown in the **online Supplementary File S1**. No language restrictions were imposed on the search.

STUDY ELIGIBILITY CRITERIA

Studies were included if they: (1) were a randomized clinical trial; (2) were performed in humans (≥ 18 yr) presenting with LEAD (i.e., ABI ≤ 0.90) and claudication (typically classified as Rutherford 1-3 or Fontaine 2a or 2b); and (3) reported at least one HRV parameter prior to (baseline) and following a regular exercise intervention of at least 4 wk. There were no restrictions on the mode of delivery (e.g., virtual) or exercise (e.g., aerobic, resistance) and settings (e.g., individual sessions) of the intervention. Only data from full-text, peer-reviewed publications were considered for inclusion. Exclusion criteria included any study not meeting all the criteria above.

PRIMARY OUTCOME

The primary outcome was HRV[27] which can be accessed via time-domain or frequency-domain analyses.[11] Time-domain analysis examines the dispersion of the individual cardiac cycle lengths around the mean and includes measures such as SDNN (standard deviation of normal R-R intervals, indicator of overall HRV), SDANN (standard deviation of the average normal R-R intervals), RMSSD (root mean square of successive R-R interval differences, indicator of parasympathetic modulations), and pNN50 (percentage of normal R-R intervals that differ by ≥ 50 ms, indicator of parasympathetic modulations).[12] All time-domain HRV indices, except for pNN50, are reported in units of time (ms). Frequency-domain analysis breaks down the heart rate signal into its frequencies and measures their relative intensity (power). The two main spectral components examined are the high-frequency (HF, indicator of parasympathetic modulations) component, ranging between 0.15-0.40 Hz, and the low-frequency component (LF, indicator of indicator of combined parasympathetic and sympathetic modulations), and the ratio between LF and HF (LF/HF) is an indicator of sympathovagal balance. These components range between .04-0.15 Hz in humans and are often reported in absolute (ms^2) or normalized (nu) units.[13]

Non-linear parameters can identify complex markers of cardiac variability.[28] It is considered the complex dynamic of biological systems on RR interval series and can be analyzed using Sample Entropy (SampEn), Poincaré methods, and detrended fluctuation analysis.[29] The SampEn values near

to 0 are considered highly regular and larger values represent greater complexity.[15,30] The Poincaré method plots each RR interval against the subsequent RR interval, deriving two main measurements: the SD1 that denotes the dispersion of points perpendicular to the identity line and a measure of short-term HRV and parasympathetic modulation; and the SD2 that denotes the dispersion of points along the identity line indicating long-term HRV (i.e., correlates with LF power and baroreflex sensitivity).[31,32] The detrended fluctuation analysis consists in correlations between successive RR intervals at different time scales. This results in two main measurements including the α1 slope that consists of brief fluctuations and is related to baroreflex sensitivity, while α2 slope describes long-term fluctuations, reflecting the mechanisms that limit oscillations of the beat cycle.[12,33,34] This form of analysis complements the conventional HRV measurements, aiding in risk stratification of cardiovascular mortality.[35]

SECONDARY OUTCOMES

LEAD with claudication is characterized by impaired walking capacity, which can be assessed using various tests and is usually reported as PFWD (i.e., distance walked until pain occurs),[36] MWD (i.e., maximal distance walked until pain forces one to stop), or the maximum time walked (i.e., MWT until pain forces one to stop).[37] The MWD (obtained on a treadmill using standardized protocols and over ground using the 6 minute walk test) is recommended to assess the severity of LEAD according to Fontaine stages (i.e., from stage I: asymptomatic to stage IV: ulceration or gangrene) and Rutherford categories (i.e., from grade 0, asymptomatic, to grade IV, ulceration or gangrene, including more categories such as III, minor tissue loss).[38] The degree of difficulty in walking can be accessed via questionnaire (e.g., Walking Impairment Questionnaire) while physical activity can be objectively assessed by accelerometry using accelerometers that are worn by the patients usually for 7 days and that measure acceleration or the rate of change of velocity.[36,37,39]

STUDY SELECTION

Following the database search, citations were imported into Rayyan, a specific electronic application for systematic reviews (https://rayyan.qcri.org), and duplicates were identified and removed using the duplicate function. Then, two reviewers (I.R.M., and R.M.A) independently screened the titles and abstracts of all studies for eligibility. Subsequently, the full texts of all studies that met the inclusion criteria, or if there was uncertainty, were retrieved and reviewed by both reviewers. Any disagreements (e.g., different opinions regarding inclusion/exclusion of a study) were discussed with a third researcher (V.A.C) to reach a consensus. Reviewers were not blinded to the journal or authors. The rationale for excluding full-text articles was documented.

DATA EXTRACTION

A data extraction form was created using Microsoft Excel (Microsoft). Data extraction was performed for individual studies and included publication details (i.e., authors, country, yr of publication), patient characteristics (e.g., sex, ABI, age), and details of the exercise intervention (i.e., frequency, intensity, duration, type). Primary and secondary outcome data were also extracted. Data were extracted by the primary reviewer and verified by a second reviewer. Any disagreements between the reviewers were resolved by consensus and, if needed, discussion with a third reviewer.

METHODOLOGICAL QUALITY AND RISK OF BIAS WITHIN STUDIES

Two reviewers independently assessed the methodological quality of each study by using the "Tool for the assEssment of Study qualiTy and reporting in EXercise" (TESTEX).[40] Study quality was assessed using the following criteria: (1) eligibility criteria specified, (2) randomization specified, (3) allocation concealment, (4) groups similar at baseline; and (5) blinding of assessor for the primary outcome. Study reporting was assessed by: (6) outcome measures assessed in 85% of patients, (7) intention-to-treat analysis, (8) between-group statistical comparisons reported, (9) point measures and measures of variability for all reported outcome measures, (10) activity monitoring in control groups,

(11) relative exercise intensity remained constant, and (12) exercise volume and energy expenditure reported. Each criterion was scored as either present (1, 2 or 3 points) or absent (0), with a maximum score of 15 possible. A higher score reflected a better-quality study.[41] Each criterion was rated independently by two reviewers with agreement resolved by both reviewers. In case of disagreement, a third reviewer made the final decision. Studies were not excluded based on their quality.

QUALITY OF EVIDENCE IN TRIALS EVALUATING HRV

Catai and colleagues (2020) provided a 30-item checklist aiming to improve the conduction and reporting of interventions using HRV.[42] In this systematic review, we used this checklist as an additional tool in order to assess the quality of HRV data acquisition from the eligible studies.[42] Each criterion was scored as either present (1) or absent (0), with a maximum score of 30 possible, and a higher score reflecting better quality of HRV assessments. Any disagreements between the reviewers were resolved through discussion with the third investigator (V.A.C).

RESULTS

STUDY SELECTION

A PRISMA flow diagram is presented in **Figure 1.** The initial and updated search identified 1,465 studies, of which 15 full-text articles were assessed for eligibility. After screening, 8 studies were excluded resulting in a final sample of 7 studies that met the eligibility criteria and were included in the systematic review.

STUDY AND PARTICIPANT CHARACTERISTICS

A summary of the study characteristics is shown in **Table 1**. The trials were published between 2007[43] and 2020.[44] Three studies[45–47] were performed in Brazil, one study in Canada,[44] one study in

Australia,[48] one study in Slovenia,[49] and one study in the United Kingdom.[43] . Sample sizes of the studies ranged from 29[49] – 102,[45] totaling 327 randomized patients. Most of the patients were male (n = 217 or 66% of total sample; intervention= 124; control = 93), while females represented 34% of the patients (n = 110; intervention = 54; control = 56). The age of the patients ranged from 61[47] – 68[44] yrwhile ABI ranged from 0.4[49] – 0.7.[47] One study recruited aged-matched healthy adults, with an ABI of 1.1, as a comparator group.[48]

EXERCISE INTERVENTIONS

A detailed summary of the study characteristics of the included trials is shown in Table 1. The duration of the exercise interventions ranged from 8 wk[45] - 12 mo.[48] Most interventions were performed for 12 wk.[43,44,46,47] One study reported the duration in sessions instead of wk, totaling 36 sessions.[49] The intensity of exercise was reported as % of heart rate reserve,[44] % of maximal heart rate,[49] heart rate at pain threshold,[46] % of maximum voluntary contraction,[45] resistance exercise rating of perceived exertion scale (OMNI),[47] Claudication Pain Scale,[48] and % of peak oxygen consumption ($\dot{V}O_2$ peak).[43] The duration of the sessions ranged from 12 [48] - 60 [49] min. Most studies (n = 5) applied a walking programme (e.g., treadmill walking protocol),[43,44,46,48,49] one study investigated dynamic resistance training using machines,[47] and one study evaluated isometric handgrip training.[45] Two studies included two intervention groups (i.e., a moderate pain and pain-free walking group[49] and a supervised exercise versus home-based exercise intervention).[43] Four studies included a control group receiving no intervention,[43,44,48,49] one study provided stretching and relaxation exercises for the control group,[47] while one study instructed the control group to undertake a ball compression intervention (3 times per wk, 3 sets of 10 compressions for each hand with 1 min of rest interval between sets).[45]

HEART RATE VARIABILITY

All studies acquired short-term (5 - 10 min) electrocardiography/heart rate recordings for offline HRV analysis (**Table 1**). Data collection was performed at rest in the supine position while one study also acquired ECG data during standing and steady-state exercise conditions.[44] The effects of exercise on HRV indices are stated in **Table 2**. All studies used frequency-domain methods to quantify short-term HRV with four studies also including time-domain methods[45,47–49] . Two studies performed non-linear HRV analyses.[45,48]

Three studies did not find any significant difference in HRV indices as a result of the exercise training, regardless of the type of analysis (i.e., linear and/or non-linear approaches).[43,45,49] Moreover, linear HRV analyzes based on time-domain methods were not sensitive to identify any changes after training.[45,47–49] Considering frequency domain analyses, three studies reported an increase in parasympathetic autonomic modulations and/or a decrease in cardiac sympathetic autonomic modulations following the exercise intervention when comparing pre and post-training values.[44,46,47] However, in the study performing resistance training, the increase in cardiac parasympathetic autonomic modulations was similar to the control group (i.e., within groups), revealing no significant main effect of the resistance training intervention. [47] Additionally, one study identified an increase in SD2, a non-linear index, for the intervention group.[48]

WALKING CAPACITY

Five studies reported improvements in walking capacity after the intervention.[43,44,46,48,49] Four studies reported an increase in the MWD[44,46,48,49] and one study reported an increase in MWT[43] (**Table 2**). One study reported an improvement in PFWD.[46] One study provided PFWD at baseline only, and evaluated physical activity levels (i.e., steps per day) following the intervention, with no significant difference between groups.[45] One study investigated resistance training and did not evaluate walking capacity.[47]

RISK OF BIAS WITHIN AND ACROSS THE STUDIES

The quality of the methodologies and the study reporting were evaluated using the TESTEX scale with results presented in **Table 3**. The scores ranged from 7 to 14 points. The lowest scores (3 out of 7 points) were observed for item 5 (i.e., blinding of assessor for at least one key outcome) and item 7 (i.e., intention-to-treat analysis). The highest score was recorded for item 8, which assessed between-group statistical comparisons.

The quality of HRV recording, processing, and analysis was assessed using the 30-item scale proposed by Catai and colleagues (2020)[42] with results shown in **Table 4**. The scores ranged from a minimum of 9 points to a maximum of 18 points out of a total of 30 points. Five items were not awarded any points including the assessment of environment humidity (item 5), control of the volunteer's interactions (item 15) and distractions during the collection (item 16), occurrences (e.g., sneezed, coughed) (item 17), clinical events (e.g., dizziness, blurred vision), and recordings before, during and after the collection (item 18). The four items with the highest scores, each scoring 7 points, included: reporting on the general health of the volunteers (item 1), the baseline values (item 11), description of the device used for data collection (item 19) and reporting of the software used for data analysis (item 28).

DISCUSSION

Literature has shown that patients with LEAD report an imbalance in cardiac autonomic modulation, represented by increased cardiac sympathetic and/or reduced cardiac parasympathetic modulations.[8] It is well established that poor autonomic regulation is associated with a greater risk of premature cardiovascular morbidity and mortality.[8] Research regarding the effects of exercise training on HRV in patients with LEAD was inconclusive within this small sample size. This study systematically reviewed the available evidence on the effects of chronic exercise on HRV in patients with LEAD. Our results indicated that there was evidence that walking training[44,46,48] can increase cardiac parasympathetic modulations and/or decrease cardiac sympathetic modulations at rest in

individuals with LEAD. These cardiac autonomic changes were accompanied by a greater walking capacity for most studies included in this systematic review.[43,44,46,48,49]

Supervised walking has the strongest evidence among exercises modalities to improve ambulatory function and quality of life in patients with LEAD.[50] Three studies showed improvements in HRV together with greater walking capacity following a chronic walking intervention.[44,46,48] The positive changes in HRV associated with improved cardiovascular fitness has been reported to involve systemic adaptations such as regulation of β-adrenergic receptor expression, increased bioavailability of nitric oxide, reduction of proinflammatory cytokines, and reduction of the sympathetic autonomic contribution to heart rate control.[51] This systemic effect was further supported by Chehuen and colleagues (2017) who reported increased spontaneous baroreflex sensitivity, and reduced blood pressure, heart rate, cardiac output, and forearm vascular resistance following a walking program in patients with LEAD.[46] In contrast, two studies reported improvements in walking capacity after 12 wk of walking training with no change in HRV.[43,49] Reasons for the lack of training-induced HRV change were not clear and future trials should be encouraged to thoroughly understand the mechanisms behind these outcomes. Potentially, differences in the components of the aerobic exercise programs (e.g., frequency, intensity, duration, type) may be important for training-induced changes in HRV.[48] For instance, various strategies for exercise prescription (i.e., pain-based, or intensity-based) were implemented in the chronic exercise training protocols of the selected studies. Standardization of exercise prescription,[52] therefore, may be the first step for future research protocols to aerobic examine training-induced benefits in this population.

Systematic reviews and meta-analyses have shown that resistance training could be an effective alternative for improving walking capacity in patients with LEAD.[53,54] In the present review, the only study that investigated dynamic resistance training[47] observed a significant group effect (pre x post) with no interaction between the factors (group and time). Thus, the change in HRV (HFnu and LFnu) was not specifically attributed to the resistance training. However, the same study found

a greater reduction in blood pressure variability at 24h after the resistance training compared with the control group. In similar clinical patient populations, such as hypertension and diabetes, positive HRV changes have been observed after dynamic resistance training and have been attributed to improvements in blood pressure, glycemic control, and arterial stiffness resulting from increased vagal modulation.[55–58] However, these effects are yet to be studied extensively in patients with LEAD and claudication. Moreover, there were no improvements in HRV following an isometric training program, [45] which is further supported by a previous meta-analysis indicating that at least 4 wk of an isometric handgrip training program did not improve cardiac autonomic modulation in normotensive and hypertensive adults.[59]

Given the low number of studies published in this field, an IDP meta-analysis would provide the highest level of evidence compared to an aggregate meta-analysis (e.g., more complex analyses, moderate effect sizes with greater power, test between-study and within-study moderators) to further examine the effects of exercise training on HRV in LEAD individuals.[60] Although TESTEX demonstrated that most of the studies have good methodological quality, different HRV approaches and metrics invalidated the progress of an IDP analysis. When using a specific methodological (i.e., checklist) tool, studies revealed a poor compliance to high quality HRV data acquisition (i.e., < 20 points). To date, the Diagnostic Accuracy Studies guidelines have been adapted and used as quality assessment tool to systematically review HRV in exercise trials.[16,61] Yet, this tool is for a general appraisal of the methodology (e.g., title, abstract), and a specific tool may provide a more complex evaluation. Hereby, we recommend the use of a 30-item checklist, specific to HRV assessment [42], to improve the quality of HRV acquisition and measures in future studies.

Walking therapy is recommended to patients with LEAD to improve their ambulatory capacity.[21] Yet, it is important that each therapy offered to the patients not only increases their functionality but, where possible, also enhances their overall cardiovascular risk profile.[62] In other populations it has already been established that exercise therapy can improve autonomic

balance.[19,20,63–65] It is not known whether currently offered exercise therapy for patients with LEAD is sufficient to improve their autonomic balance and as such cardiovascular risks.[66] Given that HRV is an easy tool to measure in daily practice, [12] the effect of a walking intervention should also aim to include cardiovascular risk profile and not only ambulatory capacity.

LIMITATIONS

This systematic review presents the following limitations: (1) the number of exercise studies included, and their sample sizes were small; (2) the heterogeneity in the methodological protocols used to measure HRV was large; (3) there was substantial variability in the exercise programs (i.e., aerobic *vs* resistance *vs* isometric) utilized in each study; and (4) the divergence in the assessments of HRV. However, we emphasize the importance of this systematic review to support future studies investigating the effects of different exercise modalities and intensities on HRV, and therefore, identify which exercise modality can optimize HRV and reduce the risk of premature cardiovascular events in patients with LEAD.[67] In addition, recent guidelines have been provided for standard HRV assessments,[42,61] which should be adopted in future large randomized trials to improve the quality of evidence and allow for better tailored exercise prescriptions for patients with LEAD.

CONCLUSION

Walking training was found to have a positive effect on HRV by increasing cardiac parasympathetic and/or decreasing cardiac sympathetic modulations in patients with LEAD and IC. Additionally, our findings were based on only seven studies, revealing that the current evidence of the benefits of exercise training for HRV in patients with LEAD is weak, and indicating the need for further investigation through larger randomized controlled trials. Finally, the results also highlighted the need for improvement in the assessment of HRV in this population, supporting the

recommendation that future studies should apply a unique 30-item checklist specific for HRV assessment.

AUTHOR CONTRIBUTIONS

IRM, NC, VAC contributed to conception and design of the manuscript. IRM and RMA performed data screening, data extraction, quality of evidence analysis, drafted the manuscript and created visual data. All authors critically reviewed for important intellectual content, contributed to the writing of the manuscript as well as approved the submitted version.

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CONFLICTS OF INTEREST

No potential conflict of interest is reported by the author(s).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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551 **Figures and tables legends**

552 **Figure 1.** Flow chart of studies through the systematic review**.**

553 **Table 1.** Overview of the general characteristics of the studies and participants.

554 **Table 2.** Effects of exercise training on heart rate variability (HRV) indices and walking capacity.

555 **Table 3.** Quality and risk of bias within studies evaluated by Tool for the assEssment of Study qualiTy
556 and reporting in EXercise (TESTEX).

557 **Table 4.** Quality and risk of heart rate variability (HRV) assessment evaluated by the 30-item
558 checklist proposed by Catai et al 2020.

559

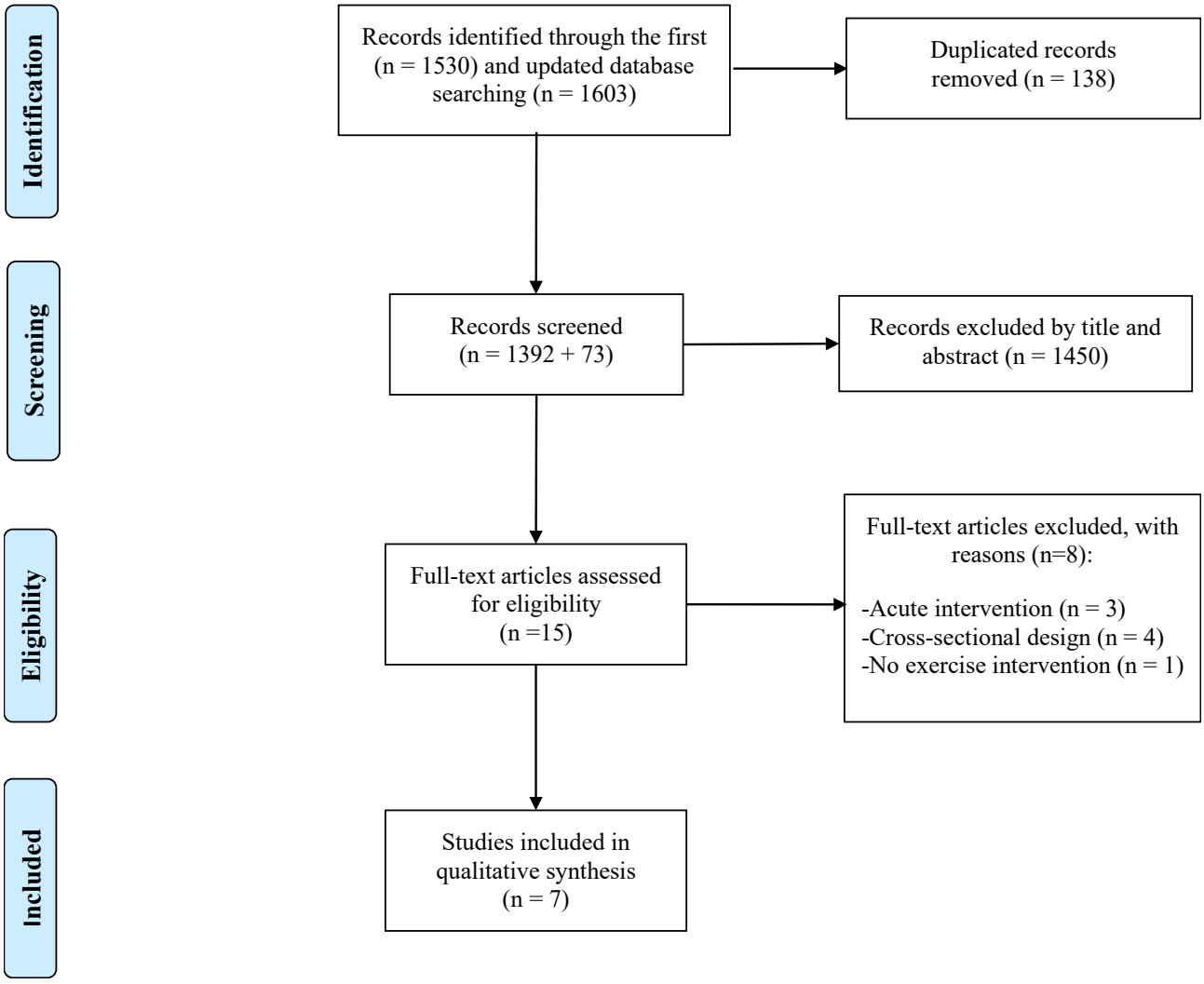
Identification
Screening
Eligibility
Included
Records identified through the first (n = 1530) and updated database searching (n = 1603)
Duplicated records removed (n = 138)
Records screened (n = 1392 + 73)
Records excluded by title and abstract (n = 1450)
Full-text articles assessed for eligibility (n =15)
Full-text articles excluded, with reasons (n=8):
-Acute intervention (n = 3)
-Cross-sectional design (n = 4)
-No exercise intervention (n = 1)
Studies included in qualitative synthesis (n = 7)

Figure 1

Table 1. Overview of the general characteristics of the studies and participants.

Study	Subjects	Age	ABI	Interventions	HRV measurements
Brenner et al., 2020, Canada	Int: 6F/12M Con: 6F/9M	Int: 68.6 ± 6.8 Con: 63.7 ± 8.4	Int: 0.6 + 0.2 Con: 0.5 + 0.2	Int: n = 18 F: 5x/ wk, 12 wk I: ≤ 40% HRR T: NA (0.4 to 3.2 km/day) M: Walking Con: n = 15, no training	Position: supine and upright standing (at rest), during steady-state exercise Duration: 10 min Device: Spacelab 514T cardiac monitor (Squibb Vitatek Inc) Software: Computer software (Yamamoto and Hughson, 1991)
Chehuen et al., 2017, Brazil	Int: 22M Con: 20M	Int: 63.0 ± 7.0 Con: 62.0 ± 8.0	Int: 0.5 ± 0.1 Con: 0.6 ± 0.1	Int: n = 22 F: 2x/wk, 12 wk I: HR of the pain threshold (±4 bpm) T: 30min M: Walking Con: n = 20, stretching exercises	Position: supine Duration: 10min Device: EMG-230, São Paulo, Brazil Software: Baroreflex Sequence Analysis
Correia et al., 2019, Brazil	Int: 17F/33M Con: 20F/32M	Int: 66.0 ± 12.0 Con: 67.0 ± 11.0	Int: 0.5 ± 0.2 Con: 0.6 ± 0.2	Int: n = 50 F: 3x/wk, 8 wk I: 30% of maximum voluntary contraction T: 4x2min (4min rest between sets) M: Isometric handgrip device Con: n = 52, 3x10 compressions ball (1min rest between sets)	Position: supine Duration: 5min Device: RS800CX; Polar Electro Software: Kubios HRV

Gomes et al., 2017, Brazil	Int: 9F/6M Con: 9F/6M	Int: 61.0 ± 3.0 Con: 66.0 ± 2.5	Int: 0.7 ± 0.0 Con: 0.7 ± 0.0	Int: n = 15 F: 2x/wk, 12 wk I: 3x10 repetitions; 5-7 OMNI scale T: 40min M: Resistance training Con: n = 15, stretching and relaxation exercises	Position: NR Duration: NR Device: 100C, EMG system Software: Kubios HRV
Leicht et al., 2011, Australia	Int: 11F/14M Con: 14F/10M	Int: 66.9 ± 8.0 Con: 65.2 ± 7.7	Int: 0.7 ± 0.2 Con: 1.1 ± 0.1	Int: n = 25 F: 3x/wk, 12 mo I: Claudication Pain Scale (≥3 or 4) T: 25-40 min M: Walking Con: n = 24, no training	Position: supine Duration: 5min Device: Chart ADInstruments Software: Kubios HRV
Novakovic et al., 2019, Slovenia	Int1 (moderate-pain group): 4F/6M Int2 (pain-free group): 2F/9M Con: 2F/6M	Int1: 65.1 ± 7.6 Int2: 65.6 ± 11.0 Con: 62.0 ± 8.3	Int1: 0.5 ± 0.1 Int2: 0.4 ± 0.1 Con: 0.5 ± 0.1	Int1: n = 10 Int2: n = 11 F: 2-3x/wk, 36 sessions I: 70% (±5%) HR_{max} T: 60min M: Walking Con: n = 8, no training	Position: supine Duration: 5min Device: Cardiax, IMED Software: Kubios HRV
Sandercock et al., 2007, United Kingdom	Int1: 4F/10M Int2: 3F/12M Con: 5F/10M	Int1: 66.0 ± 8 Int2: 62.0 ± 14.0 Con: 67.0 ± 6.0	Int1: 0.5 ± 0.0 Int2: 0.5 ±0.0 Con: 0.5 ± 0.1	Int1 (supervised): n = 14; Int2 (home-based): n = 15 F: 2x/wk, 12 wk I: Int1: 70-75% $VO2_{peak}$; Int2: 12-14 RPE T: 30min M: Walking Con: n = 15, no training	Position: supine Duration: 5min Device/Software: CardioPerfect ST 2001, Cardio Control

Data are reported as mean ± SD. ABI, ankle brachial index; Con, control group; F, frequency; HR, heart rate; HRR, heart rate reserve, HRV, heart rate variability; I, intensity; Int, exercise training group; M, mode; N, sample size; RPE, Rating of Perceived Exertion; T, time.

Table 2. Effects of exercise training on HRV indices and walking capacity.

Study	Linear HRV measures		Non-linear HRV measures	Intervention group	
	Time domain	*Frequency domains*		Outcomes	Walking capacity
Brenner et al., 2020	NA	LF (abs), HF (abs, nu), TP (abs), LF/HF ratio	NA	↑ HF (nu), ↓ LF/HF ratio	↑ MWD
Correia et al., 2019	SDNN, rMSSD, pNN50	LF (abs), HF (abs), LF; HF ratio	SD1, SD2, Shannon Entropy, Sample Entropy	-	NA
Chehuen et al., 2017	NA	LF (nu), HF (nu), LF/HF ratio	NA	↓ LF (nu), ↑ HF (nu), ↓ LF/HF ratio	↑ MWD, ↑PFWD
Gomes et al., 2018	pNN50	LF (nu), HF (nu), LF/HF ratio	NA	↓ LF (nu), ↑ HF (nu) (similar to the control group)	NA
Leicht et al., 2011	SDNN, rMSSD, pNN50, HRV triangular index	LF (abs, nu), HF (abs, nu), LF/HF ratio	SD1, SD2, SampEn, α1, α2	↑ SD2	↑ MWD
Novakovic et al., 2019	SDNN, rMSSD, pNN50%	HF (nu), LF (nu)	NA	-	↑ MWD
Sandercock et al., 2007	NA	LF (abs), HF (abs), LF/HF ratio	NA	-	↑ MWT

α1 and α2: detrended fluctuation analysis. abs: absolute units expressed in ms². HF: high frequency. HRV: heart rate variability. LF: low frequency. ln:

Natural logarithm. MWD: maximal walking distance. MWT: maximal walking time. NA: not assessed. nu: normalized units. PFWD: Pain free walking distance. PNN50: percentage of successive differences between normal adjacent intervals > 50 ms. rMSSD: root mean square of successive R-R interval differences. rMSSD. SampEn: sample entropy. SD1 and SD2: geometric parameters of the Poincare´ plot. SDNN: standard deviation of all normal RR intervals. TP: total power.

Table 3. Quality and risk of bias within studies evaluated by Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX).

	Study Quality					**Study Reporting**							
	1	**2**	**3**	**4**	**5**	**6***	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
Brenner et al., 2020	1	1	1	1	0	2	0	2	1	1	1	1	12
Chehuen et al., 2017	1	1	1	1	1	2	0	2	1	1	1	1	13
Correia et al., 2019	1	1	1	1	1	2	1	2	1	1	1	1	14
Gomes et al., 2017	1	1	0	1	1	1	1	2	1	0	1	1	11
Leicht et al., 2011	1	0	0	0	0	1	0	2	1	0	1	1	7
Novakovic et al., 2019	1	1	1	1	0	3	0	2	1	0	1	1	12
Sandercock et al., 2007	1	1	1	1	0	1	1	2	1	1	1	1	12

*Total (3 points)

Table 4. Quality and risk of heart rate variability (HRV) assessment evaluated by the 30-item checklist proposed by Catai et al 2020[42]

	Brenner et al., 2020	Chehuen et al., 2017	Correia et al., 2019	Gomes et al., 2018	Leicht et al., 2011	Novakovic et al., 2019	Sandercock et al., 2007
1. General health	1	1	1	1	1	1	1
2. Suitable place	1	1	1	0	1	1	1
3. Noise	0	0	1	0	0	0	0
4. Temperature	0	1	1	0	0	0	0
5. Humidity	0	0	0	0	0	0	0
6. Time of the day	0	1	1	1	1	1	1
7. Familirialization	0	0	0	0	0	0	1
8. Circulation of people	0	0	1	0	0	0	0
9. Substance ingestion	0	1	1	1	1	0	1
10. Physical Activity	0	1	1	1	0	0	0
11. Baseline values	1	1	1	1	1	1	1
12. Rest ≥ 15min	0	1	0	0	0	0	0
13. Body position	1	1	1	0	1	1	1
14. Dynamic/rest	1	1	1	0	1	1	1
15. Interactions	0	0	0	0	0	0	0
16. Distractions	0	0	0	0	0	0	0
17. Ocurrences	0	0	0	0	0	0	0
18. Clinical events	0	0	0	0	0	0	0
19. Device data collection	1	1	1	1	1	1	1
20. Signal acquisition rate	1	1	0	0	1	1	0
21. Software signal acquistion	1	1	0	1	1	1	0
22. Total lenght of signal	1	1	1	0	1	1	1
23. Simultaneous signals	0	1	0	0	1	0	1
24. Breathing	0	1	0	0	1	0	0
25. Signal Quality	1	0	0	0	1	0	0
26. Selected sample size	1	0	1	1	1	1	0
27. Editing/Filtering signal	1	0	0	0	1	1	1
28. Software for analysis	1	1	1	1	1	1	1
29. Number of beats	1	0	1	0	0	0	0
30. Criteria R-R interval	0	0	0	0	1	0	0
Total points	**14**	**17**	**16**	**9**	**18**	**13**	**13**