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Exercise-based training programs for patients with chronic Chagas cardiomyopathy: A systematic review and *meta*-analysis

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ABSTRACT

Background: We assessed the effects of exercise-based training programs (EBTP) in patients with chronic Chagas cardiomyopathy (CCC) through a systematic review and *meta*-analysis.
Methods: We conducted a search in Pubmed/Medline, Embase, Scopus, Web of Science, Cochrane Library, Virtual Health Library, and SciELO until January 2023. Randomized controlled trials (RCTs) and non-randomized intervention studies (NRIS) investigating the effects of EBTP in CCC patients were included. The primary outcomes were all-cause mortality, cardiovascular mortality, and health-related quality of life (HRQoL), and the secondary outcomes were exercise capacity by peak VO2, heart failure-related hospital admissions (HFRHA), and left ventricular ejection fraction (LVEF).
Results: The search strategy yielded 3617 studies. After removing duplicates and screening, eight studies (3 RCTs and 5 NRIS) involving 222 patients were included. Seven studies were conducted in Brazil. The age range was from 30 to 71 years, and 47.1% were male. Data on mortality, HRQoL, LVEF, and HFRHA were scarcely reported. The *meta*-analysis pooling four studies showed that the peak VO2 was significantly higher (mean difference 4.45, 95% confidence interval 3.50 to 5.39 mL/kg/min, I2 = 0%) in the EBTP group compared to the control group.
Conclusion: The evidence available was limited and heterogeneous. While EBTP has shown to improve HRQoL and exercise capacity, there is no conclusive information about the other proposed outcomes. These positive effects present an opportunity to provide treatment to CCC patients in low- and middle-income countries. Further studies are needed to ascertain the effects of EBTP on hard outcomes in this population.
Registration number: CRD42022334060.

1. Introduction

Chagas disease, also known as American trypanosomiasis, is an anthropozoonosis caused by the hemoflagellate protozoan *Trypanosoma cruzi* [1]. It is endemic in 21 Latin American regions [2]. Nevertheless, it has spread beyond its original boundaries to non-endemic areas, such as North America, Europe (mainly Spain), and the Western Pacific region (Japan, Australia, and New Zealand), due to new migration patterns and forms of dissemination [1–3].

Patients with chronic infection may remain asymptomatic for years or decades, but around 30% may progress to cardiac and/or gastrointestinal damage [4]. Chronic Chagas cardiomyopathy (CCC) comprises any case of Chagas disease with cardiac involvement, defined by the presence of at least a typical electrocardiographic pattern in patients with positive serological tests [5]. CCC has several presentations that can be categorized as abnormalities of electrical conduction, heart failure (HF), ventricular aneurysm formation, and thromboembolism [6]. Consequently, patients with CCC have lower survival rates than other forms of cardiomyopathy of similar severity [6].

It is well known that most patients with cardiac diseases benefit clinically and prognostically from regular exercise-based training programs (EBTP) [7]. These programs decrease all-cause mortality, overall hospital admissions, and HF-specific hospitalization in patients with HF [8]. In addition, it is considered one of the most effective interventions

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to improve health-related quality of life (HRQoL) and cardiopulmonary functional capacity [9]. However, Chagas disease is considered a neglected disease, and these patients are underrepresented in clinical trials. In particular, the impact of EBTP is uncertain in this group of patients [10,11]. Therefore, our objective was to assess the effects of EBTP (aerobic exercises alone or the combination of aerobic and resistance muscle exercises) compared to not undergoing EBTP or receiving standard care (when applicable according to the study design) in patients with CCC through a systematic review, as well as conducting *meta*-analysis when data are available for it. We aimed to investigate primary outcomes such as all-cause mortality, cardiovascular mortality, and HRQoL. Additionally, we examined secondary outcomes including exercise capacity (measured by peak VO2), heart failure-related hospital admissions (HFRHA), and left ventricular ejection fraction (LVEF).

2. Methods

This systematic review was conducted according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in the PROSPERO database (CRD42022334060).

2.1. Information sources

We searched for studies published in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/Medline, Embase, Scopus, Web of Science Core Collection, Virtual Health Library, and Scientific Electronic Library Online (SciELO) without restrictions on language or period.

2.2. Search strategy

We elaborated a search strategy for PubMed, which was used as the basis for search strategies for the other databases listed (**Supplementary Table S1**). We used the following search terms with their combinations, including but not limited to: exercise, cardiac rehabilitation, and Chagas cardiomyopathy. We re-ran the search strategy just before the final analysis in January 2023, and any further studies identified were retrieved for inclusion. We conducted a backward and forward citation search of included studies to identify further eligible studies. In addition, any relevant systematic review was searched. Moreover, we searched ClinicalTrials.gov (www.clinicaltrials.gov) and the International Clinical Trials Registry Platform (https://trialsearch.who.int/) for unpublished trials.

2.3. Eligibility criteria

Studies were included if they met the following criteria: (a) adult patients (≥18 years) with CCC confirmed by serological or molecular tests and with HF, regardless of their LVEF, and at any New York Heart Association (NYHA) stage at baseline evaluation; (b) EBTP either alone (without cointerventions) or as part of exercise-based cardiac rehabilitation (plus nutritional and pharmaceutical counseling), which could comprise aerobic exercises alone or the combination of aerobic and resistance muscle exercises, monitored by health care professionals during the exercise sessions, with any length of time or intensity training of the sessions, and any follow-up length; (c) when there was a comparator, which could be a non-EBTP or standard of care; (d) at least one of the following outcomes was reported: all-cause mortality, cardiovascular mortality, HRQoL, exercise capacity (measured by peak VO2), HFRHA, and LVEF; and (e) randomized controlled trial (RCT) or non-randomized intervention studies (NRIS) including studies with one or more arms, and had a prospective protocol for the specific evaluation of the intervention's effect. We excluded retrospective studies, cross-sectional studies, case-control studies, conference abstracts, narrative or systematic reviews, case series, and case reports.

2.4. Selection process

Search results were downloaded and exported to Rayyan (https://www.rayyan.ai/). One author (PMCR) removed duplicate records. Three authors (PMCR, DFG, and BCC) independently screened the titles and abstracts and removed irrelevant reports. The full text of potentially relevant reports was retrieved. Multiple reports of the same study were linked together, and three authors (PMCR, DFG and BCC) assessed for full-text eligibility criteria. Each author's decision was blinded to the other authors. Any disagreement was resolved through consensus with a fourth author (CDA).

2.5. Data collection process

Two groups of authors (PMCR / CSMG and DFG / BCC) independently collected information using a standardized data extraction form (**Supplementary Table S2**). We performed a pilot data collection to ensure its usability. Any disagreements over collected data were recorded and resolved through consensus with a fifth author (CDA).

2.6. Data items

All the data extracted is detailed in **(Supplementary Table S2)** and includes the first author's name, year of publication, study design, country, eligibility criteria, sample size, age, sex, description of intervention and control groups, primary and secondary outcomes, length of follow-up, attrition rate and adverse effects during EBTP sessions.

2.7. Risk of bias assessment

Three authors (PMCR, DFG, and BCC) independently assessed the risk of bias using the Risk of Bias 2.0 (RoB 2) tool for RCTs and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool for NRIS. We produced graphics representing the risk of bias judgments for each study and domain. RCTs were categorized as having low, some concerns, or high risk of bias, while NRSI were categorized as having low, moderate, serious, critical, or no information on risk of bias. Any discrepancies were resolved through consensus with a fourth author (CDA).

2.8. Outcomes and effect measures

Primary outcomes defined *a priori* were all-cause mortality, cardiovascular mortality, and HRQoL while the secondary outcomes were exercise capacity (measured by peak VO2), HFRHA, and LVEF. Desirable effect measures for all-cause mortality, cardiovascular mortality, and HFRHA were risk ratios (RR) or hazard ratios (HR). However, when these measures were not available, these outcomes were reported as frequencies for all-cause mortality, cardiovascular mortality, and HFRHA. Exercise capacity, measured by peak VO2 in mL/kg/min as a numerical variable, was reported as means, medians, and mean differences. HRQoL was measured using validated scales as a numerical variable and reported as means, medians, and mean differences. Finally, changes in LVEF is measured in percentages as a numerical variable and reported as means and mean differences.

2.9. Statistical analysis

Due to the limited reporting of information and the presence of clinical/methodological heterogeneity among studies, we considered that conducting a *meta*-analysis for the primary outcomes and two secondary outcomes was not appropriate. Therefore, we present our findings as a narrative synthesis. However, a *meta*-analysis was conducted for exercise capacity changes. This decision was based on the availability of a considerable number of studies with a control group (4 studies) that evaluated this outcome, and the data were found to be

homogeneous across these studies. We used a random-effects model. The between-study variance was estimated using the Paule-Mandel method. Continuous data on exercise capacity (peak VO2), measured as the difference between the final and basal values, were pooled using the mean difference (MD) with its 95% confidence interval (CI) for studies with both experimental and control groups. We assessed statistical heterogeneity using the chi-squared test (threshold $p < 0.10$) and the I2 statistic (threshold < 60%). The *meta*-analysis was performed using the "meta" package from R 4.2.0 software (www.r-project.org).

2.10. Assessment of the certainty of evidence

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach when there was no single estimate of effect [13], and the following aspects were considered: methodological limitations, indirectness, imprecision, inconsistency, and publication bias.

3. Results

3.1. Selection of studies

Our initial search identified a total of 3617 records in seven databases, out of which 1861 duplicates were removed. After screening by title and abstract, 21 records remained eligible for full-text assessment, and 12 records were excluded. Finally, 9 records for 8 studies were included for qualitative analyses according to our criteria eligibility [12–20]. This implies that there were two published articles for one study [15,16]. For practical reasons, we refer to this study only as the first article published, "Mediano MFF, 2016″ (Fig. 1).

3.2. Characteristics of the studies included

The eight studies included were published between 2008 and 2023 and consisted of three RCTs [13,14,19] and five NRIS (one with a control group and four single-arm studies) [12,20,16–18]. Seven studies were conducted in Brazil [12–14,16–19] and one in Argentina [20]. A total of 222 patients participated in the studies, of which 169 subjects were assigned to different EBTP and the rest to control groups, when appropriate. The follow-up time ranged from 6 weeks to one year. The age range was from 30 to 71 years and 47.1% were male. The severity of Chagas heart disease was assessed based on the stages defined in the Brazilian consensus and the NYHA Functional Classification. According to the Brazilian consensus, the majority of patients (n = 61) were classified as stage C, indicating severe cardiac involvement. Additionally, 15 patients were categorized as stage B2, reflecting moderate cardiac involvement without heart failure, and 2 patients were classified as stage D, representing end-stage heart failure. In terms of the NYHA

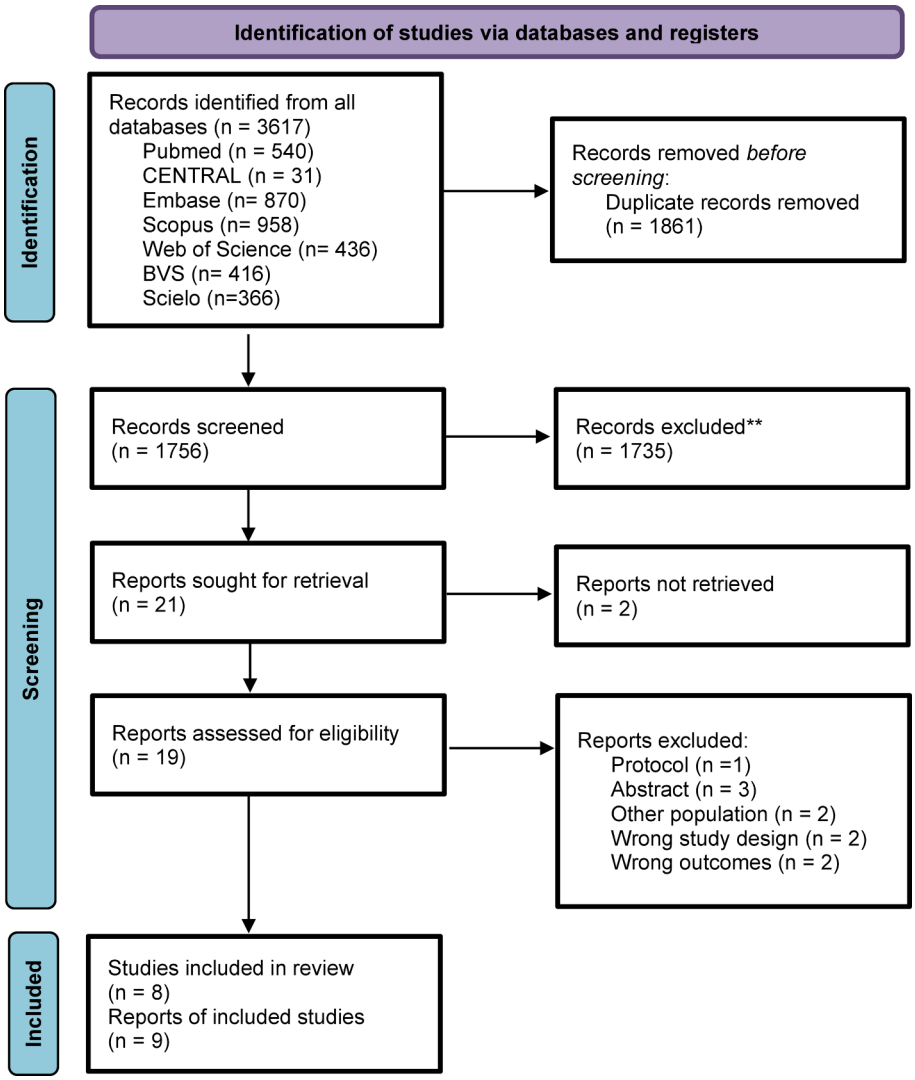

Fig. 1. PRISMA diagram flow of the study selection process.

Functional Classification, most patients (n = 57) were assigned to class II, indicating a mild limitation of physical activity. Furthermore, a smaller number of patients were classified as class I, indicating no limitation of physical activity (n = 39), and class I/II (n = 24). Notably, information regarding the disease severity was not available for 24 patients. Baseline peak VO2 and LVEF varied among studies. Importantly, no major adverse effects related or not related to EBTP were described [14,16,20] **(**Table 1**)**. The intervention involved physical exercise training alone (without any cointervention) or exercise-based cardiac rehabilitation (plus nutritional and pharmaceutical counseling), comprising different types of physical activities (strength, aerobic, stretching, etc.). Additionally, three studies explicitly mentioned the incorporation of nutritional and pharmacological counseling as part of the intervention [12,14,16] **(**Table 1**, and Supplementary Table S3)**.

3.3. Risk of bias assessment

The overall risk of bias in the RCTs was rated low for one study [14], and high for the other two [13,19] due to important problems related to deviations from intended interventions **(**Fig. 2**A)**. Regarding NRIS, two studies [17,18] were rated as having a moderate risk of bias due to issues with bias related to missing data, and the other three [12,16,20] were considered to have a serious risk due to considerable problems with confounding, missing data, and selection in the reported results **(**Fig. 2**B)**.

3.4. Effect of EBTP on primary outcomes

The main findings are summarized in Table 2. Only 2 studies reported data on HRQoL. One was an RCT that used the 36-Item Short Form Survey (SF-36) and reported an intergroup comparison (experimental vs. control). It found significant differences in the domains of vitality [7.5 (0–16.2 points) vs. 0 (−5.0 to 5.0 points), p = 0.013], emotional aspects [16.7 (0–41.7 points) vs. 0 (−66.7 to 0 points), p = 0.012], and mental health [16.1 (−1 to 26 points) vs. 0 (−8 to 16 points), p = 0.031] in favor of the experimental group [19]. The other study was a single-arm study that used two different tools: the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the SF-36. The MLHFQ found that EBTP showed a non-statistically significant improvement, while the SF-36 showed a statistically significant increase in different domains, such as physical functioning (β = +5.7, p = 0.003), role-physical (β = +1.9, p = 0.03), and body pain (β = +3.5, p = 0.02), as well as in the summary physical health score (β = +1.4, p = 0.001) [15,16].

The studies included referred indirectly to all-cause mortality and cardiovascular mortality data, and reported one death caused by decompensated HF, but within the control (no exercise) group [14], and another death due to a complicated acute respiratory infection in the experimental group [16].

3.5. Effect of EBTP on secondary outcomes

Secondary results are shown in the summary table (Table 2), and we also provide information about the changing outcomes over time (exercise capacity measured by peak VO2 and LVEF) **(**Supplementary Table S4**)**.

All studies reported data on increases in exercise capacity measured by peak VO2, but Mitelman *et al.* reported a significant increase from 18 to 20–25 mL/kg/min, which was not clearly understood [20]. The *meta*-analysis pooling four studies showed that the peak VO2 was significantly higher (MD 4.45, 95% CI 3.50 to 5.39 mL/kg/min, I2 = 0%) in the EBTP group compared to the control group. **(**Fig. 3**)**.

There was no information about HFRHA in any study. Four studies provided information about changes in the LVEF (2 RCTs and 2 NRIS) as measured by transthoracic echocardiogram, of which two found no significant changes [13,14], one a statically significant change of 5.4% ± 6.4 [16], and one reported a significant increase of 10% after one year of follow-up, but the standard deviation was not reported [20].

3.6. Certainty of evidence

The outcomes proposed for evaluation using the GRADE approach had very low certainty **(**Table 3**)** and the reasons for the assessment are shown in **Supplementary Table S5**.

4. Discussion

4.1. Main findings

The objective of this study was to systematically review and quantify the effects of EBTP in patients with CCC. The evidence available on the intervention was limited and heterogeneous. Despite this, we found that EBTP had positive effects on HRQoL and exercise capacity. The *meta*-analysis demonstrated that EBTP resulted in a significant change in peak VO2 after receiving the intervention. However, there was insufficient reporting of hard outcomes to ascertain the impact of EBTP on their occurrence.

4.2. Effect of EBTP on primary outcomes

HRQoL is a subjective perception of health status regarding overall functioning and well-being [21]. Regardless of their etiology, in general, cardiomyopathies cause several physical symptoms, including fatigue, edema, dyspnea, chest pain, and a significant decline in functionality [22]. This affects the physical, emotional, and social well-being of patients (and their families), resulting in poor quality of life [23]. Therefore, measuring HRQoL in patients with cardiovascular disease is highly recommended [24]. Nevertheless, among all types of cardiomyopathies, CCC has particular features, including chronic myocarditis involving all cardiac chambers and damage to the excitation-conducting system of the intrinsic autonomic innervation. There are potential complications such as HF, ventricular aneurysms, complex supraventricular and ventricular arrhythmias, advanced heart blocks, thromboembolic phenomena, and sudden cardiac death. In addition to the scarcity of randomized data specific to this condition, the result is a worse prognosis compared to idiopathic dilated cardiomyopathy [6,25]. Some studies reported the level of HRQoL in CCC patients, showing that they scored lower than patients with other types of cardiomyopathies, as well as the general population [25].

Our results show that EBTP had benefits on HRQoL when assessed either through intragroup changes (after 8 months of follow-up) or intergroup differences (after 12 weeks of follow-up) using validated tools to measure this outcome [15,19]. It is noteworthy that the reported effect of EBTP on HRQoL is not the same across all cardiovascular diseases. On one hand, systematic reviews and *meta*-analyses did not find clinically relevant differences in coronary heart disease and atrial fibrillation [26,27]. On the other hand, our findings could be consistent with the evidence that EBTP considerably improved HRQoL in patients with HF due to etiologies other than Chagas disease (standardized MD 0.60 lower, 95% CI 0.82 to 0.39) on a scale with which lower points indicate better HRQoL for a follow-up period of up to 12 months [8,28]. Although the follow-up times in those studies are not comparable to those in our review, the benefits perceived by patients could indicate an early effect on this outcome in patients with CCC. However, the interpretation of the change in HRQoL in CCC is still uncertain due to the differences between CCC patients and those with other types of HF. Randomized controlled trials that evaluate changes in HRQoL in CCC patients are still necessary to ascertain the true impact on this outcome.

Chadalawada *et al.* published a *meta*-analysis showing an annual all-cause mortality rate of 7.9% (95% CI 6.3 to 10.1) and an annual cardiovascular mortality rate of 6.3% (95% CI 4.9 to 8.0) in CCC patients.

Table 1
Characteristics of the studies included.

Study	Country	Design	Intervention	Control	Length of follow-up	Arm	Sample size	Age (years)	Male (%)	Severity of CCC	Baseline peak VO2 (mL/kg/min)	Baseline LVEF (%)	Number of attritions	Adverse effects
Viana AMN, 2023	Brazil	Retrospective single-arm NRIS	Exercise-based cardiac rehabilitation*	NA	6–8 months	NA	36	58.1 ± 11.7	63.9	CCC stages: B2 (n = 7, 19.4%); C (n = 29, 80.6%)	16.4 ± 4.7	33.3 ± 9.3		NR
Sarmento AO, 2021	Brazil	RCT	Physical exercise alone	No exercise	17 weeks	Exercise	12	47.8 ± 2.4	37.5	NR	24.3 ± 2.4	59.8 ± 1.0	4 (reasons NR)	NR
						Control	12	51.0 ± 1.9	50	NR	25.2 ± 1.8	59.6 ± 1.3	2 (reasons NR)	NA
Mendes Fde S, 2020	Brazil	RCT	Exercise-based cardiac rehabilitation*	No exercise	6 months	Exercise	15	57.8 ± 9.4	73.3	CCC stages: B2 (n = 4, 26.7%); C (n = 11, 73.3%)	17.6 ± 4.7	32.3 ± 8.7	2 dropouts from training sessions	1 atrial fibrillation with hospitalization
						Control	15	60.7 ± 10.7	60	B2 (n = 4, 26.7%); C (n = 11, 73.3%)	15.4 ± 6.3	33.9 ± 7.0	1 died of decompensated HF	NA
Mediano MFF, 2016	Brazil	Prospective single-arm NRSI	Exercise-based cardiac rehabilitation*	NA	8 months	NA	12	56.1 ± 13.8	25	CCC stages: C (n = 10, 83.3%); D (n = 2, 16.7%)	15.8 ± 5.2	31.9 ± 7.7	5 (1 complicated acute respiratory infection, 3 decompensated HF, and 1 dropped out)	2 symptomatic exertional hypotension
Fialho PH, 2012	Brazil	Prospective single-arm NRSI	Physical exercise alone	NA	6 months	NA	24	56.7 ± 9.5	27.8	NYHA:I and II (number NR)	21.11 (18.7 to 26.9)	Mean: 54	6 (1 severe pneumonia, 1 transitory ischemic accident, 1 lumbago related to work activities, 1 acute peripheral vascular disease, and 2 dropped out)	NR
Mendes M de FA, 2011	Brazil	Prospective two-arm NRSI	Physical exercise alone	No exercise	6 weeks	Exercise	7	48.0 ± 5.0	0	NYHA:I (n = 7, 100%)	31.1 ± 4.3	NR	NR	NR
						Control	7	53.6 ± 6.2	0	NYHA:I (n = 7, 100%)	22.2 ± 6.3	NR	NR	NA
Lima MM, 2010	Brazil		Physical exercise alone	No exercise	12 weeks	Exercise	21	48.9 ± 8.8	52	NYHA:I (n = 11, 52%); II (n = 10, 48%)	26.2 (23.8 to 31.4)	35.7 ± 8.1	3 (1 pacemaker implantation, 1 hyperthyroidism, 1 discontinuation of medication)	NR
						Control	19	50.0 ± 6.6	63	NYHA:I (n = 14, 74%); II (n = 5, 26%)	31.1 (24.8 to 37.8)	37.0 ± 7.6	NR	NA
Mitelman J, 2008	Argentina	Prospective single-arm NRSI	Exercise-based cardiac rehabilitation	NA	1 year	NA	42	51.1 ± 3.6	40.5	NYHA:II (n = 42, 100%)	Mean: 18	Mean:35	12 (5 complex arrhythmias and 7 dropped out)	5 complex arrhythmias

CCC, chronic Chagas cardiomyopathy; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not applicable; NR, not reported; NRSI, non-randomized study of interventions; NYHA, New York Heart Association Functional Classification; RCT, Randomized controlled trial.

* Exercise plus nutritional and pharmaceutical counseling.

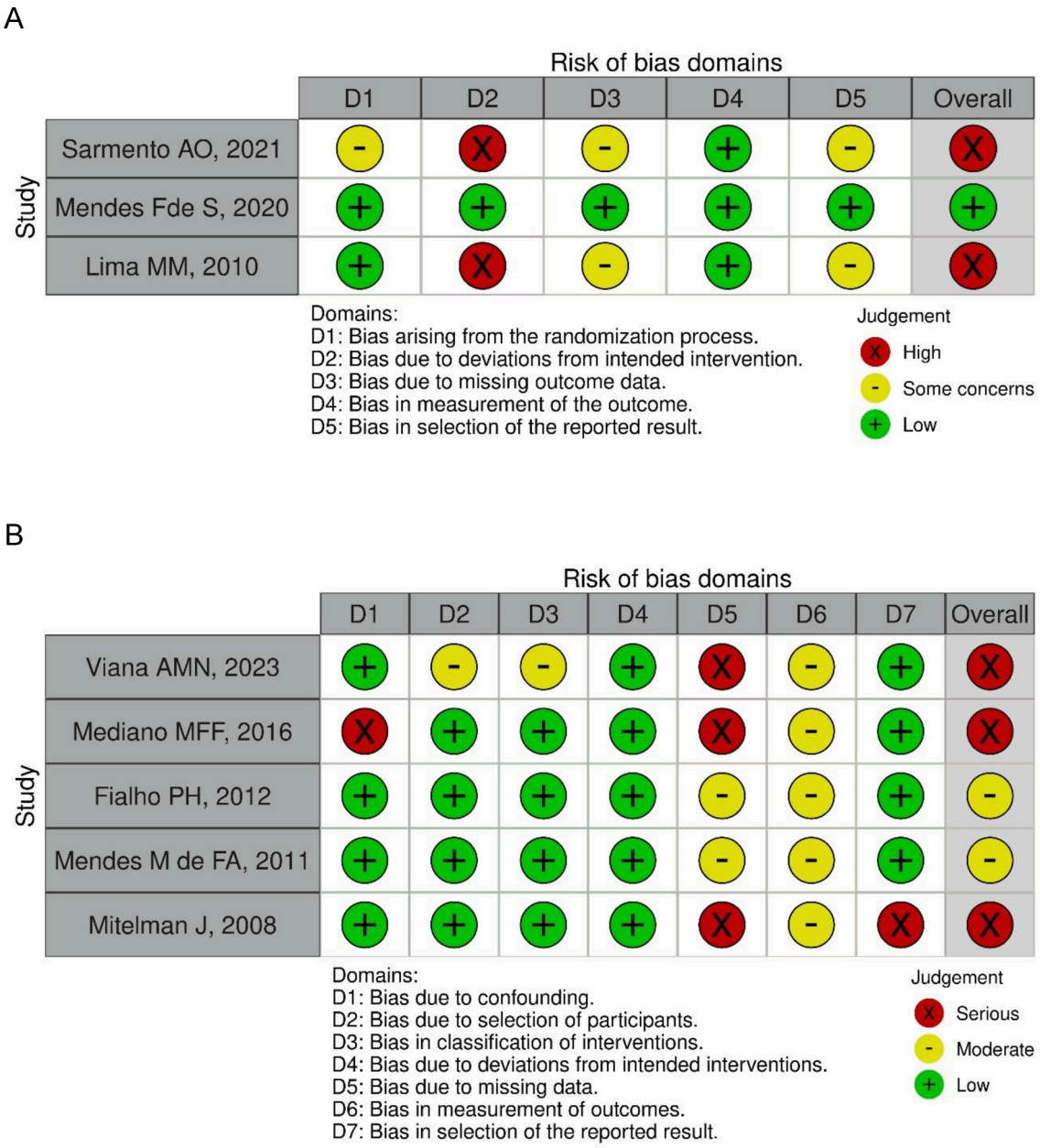

Fig. 2. Risk of bias assessment for randomized controlled trials (A) and non-randomized intervention studies (B).

They also showed that the mortality attributable to CCC is higher than that of other common forms of cardiomyopathy, indicating that the impact of interventions on this outcome is substantial [29]. In addition, Vieira *et al.* conducted a retrospective analysis to investigate mortality in patients with CCC undergoing EBTP. They found that 14% of the participants died while enrolled in EBTP, but this figure increased to 34% for those patients who discontinued the program. The causes of death were attributed to complications of CCC, such as decompensated heart failure and sudden death. However, it is important to note that these deaths did not occur during the training sessions, which supports the safety of the intervention. Instead, it is suggested that sociodemographic factors and the stage of CCC in each patient may have influenced the results [30]. In our review, the included studies did not report mortality data with appropriate effect measures, such as RR or HR, to draw solid conclusions. This could be due to the way the studies reported all-cause or cardiovascular mortality. They only mentioned two deaths of individuals who were in contact with the EBTP [14,16].

Conversely, some patients dropped out of the EBTP, and in some studies, end data on these patients were not reported, thus leaving the survival of this group unknown. Additionally, the evidence suggests that the duration of follow-up may be related to our lack of information about mortality. For example, Long *et al.* showed that EBTP made little or no difference in all-cause mortality at short-term follow-up (≤12 months) in HF due to etiologies other than Chagas disease (RR 0.89, 95% CI 0.66 to 1.21), despite a potential reduction in all-cause mortality at long-term follow-up (>12 months) (RR 0.88, 95% CI 0.75 to 1.02) [8]. We did not identify studies with follow-ups longer than 12 months. Furthermore, cardiovascular mortality is not necessarily consistent with all-cause mortality. Dibben *et al.* found little or no difference in all-cause mortality at short, medium, and long-term follow-ups in coronary heart disease; in contrast, a large reduction in cardiovascular mortality at medium and long-term follow-up was reported [26]. It is necessary to have better reporting of mortality data and longer follow-up lengths in future studies to better understand the survival benefit of EBTP.

Table 2
Summary of main outcomes.

Study	All-cause mortality	Cardiovascular mortality	HRQoL (SF-36 domains)	Peak VO2	HFRHA	LVEF
Viana AMN, 2023	NR	NR	NR	t3-4 Yes * t6-8 Yes *	NR	NR
Sarmento AO, 2021	NR	NR	NR	Yes*†	NR	NSC
Mendes Fde S, 2020	1 (decompensated HF in the control group)	1 (decompensated HF in the control group)	NR	t3 NSC t6 Yes†	NR	NSC
Mediano MFF, 2016	1 (complication of an acute respiratory infection in the experimental group)	NR	Physical functioning* Role-physical* Improvement in body pain* Physical health score*	t4 Yes* t8 NSC	NR	t8 Yes *
Fialho PH, 2012	NR	NR	NR	Yes*	NR	NR
Mendes M de FA, 2011	NR	NR	NR	Yes*	NR	NR
Lima MM, 2010	NR	NR	Vitality† Emotional aspects† Mental health†	Yes*†	NR	NR
Mitelman J, 2008	NR	NR	NR	Yes*	NR	Yes*

HF, heart failure; HFRHA, heart failure-related hospital admissions; HRQoL, health-related quality of life; LVEF, left ventricular ejection fraction; NR, not reported; NSC, no significant change; SF-36 = 36-Item Short Form Survey; t3, at 3 months; t4, at 4 months; t6, at 6 months; t8, at 8 months; t3-4, at 3 to 4 months; t6-8, at 6 to 8 months.

* $p \leq 0.05$ in intragroup comparison (end vs. baseline).

† $p \leq 0.05$ in intergroup comparison (experimental vs. control).

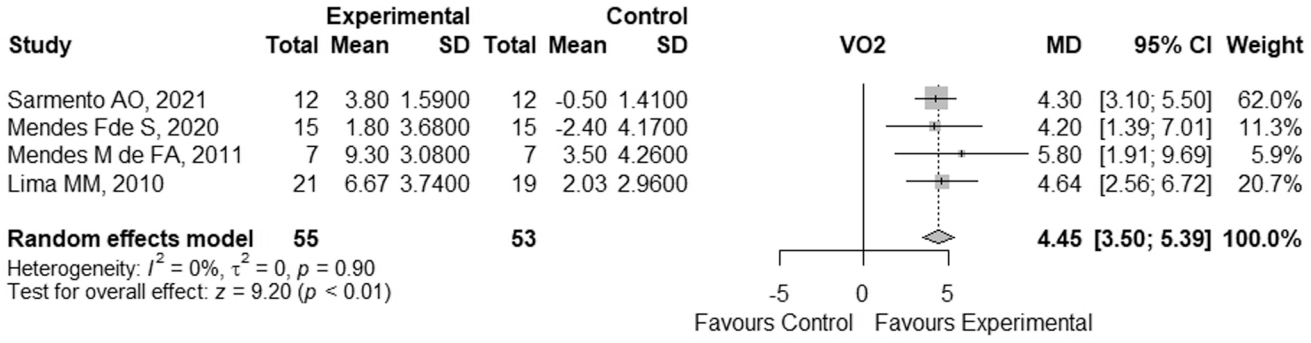

Fig. 3. Forest plot showing the effect of exercise-based training programs on exercise capacity measured by peak VO2. Abbreviations: MD, median difference; CI, confidence interval; SD, standard deviation.

4.3. Effect of EBTP on secondary outcomes

Peak VO2 is the gold standard measurement of functional and aerobic capacity as well as the strongest predictor of mortality and cardiovascular events [31,32]. Therefore, improvement in peak VO2 has become a major treatment goal for cardiovascular diseases [32]. Continuous physical training of moderate intensity is recommended in patients with HF due to etiologies other than Chagas disease to improve exercise capacity [33]. Our review shows that EBTP produces benefits in the exercise capacity of patients with CCC. This improvement in functional capacity observed in cardiomyopathies may arise from a favorable response in peripheral vascular and coronary endothelial function, myocardial contractility, and the autonomic balance or stress of the systolic and diastolic walls [34]. Similarly, in animal models, exercise training has been shown to promote increased efficiency of the electron transport system and mitochondrial biogenesis, as well as the elimination of toxic molecules, including reactive oxygen species and aldehydes, in cardiomyocytes. This favors a decrease in parasitemia, improvement in immune response, and antioxidant defenses in cardiac tissue, as well as a reduction in cardiac fibrosis in mice with CCC [35]. Thus, physical training could be an effective therapeutic option that could be implemented in clinical practice to increase the functional capacity of patients with CCC.

The benefit on exercise capacity was one of the first to be observed in patients with HF due to etiologies other than Chagas disease. Rees *et al.* reported a mean increase of 2.16 mL/kg/min (95% CI 1.49 to 2.82) in peak VO2 after a mean follow-up of 20 ± 14 weeks. More recently, Taylor *et al.* reported an increased range in peak VO2 of 1.6 to 4.6 mL/kg/min after follow-up periods ranging from 4 to 120 weeks [36,37]. We obtained a mean difference of 4.45 mL/kg/min in our calculations, which could be considered consistent with the previously mentioned studies due to the increases observed.

LVEF is a known predictor of mortality in HF patients, and therefore therapies focus on attenuating the remodeling process [38]. In the present review, EBTP improved LVEF in two studies, while the other two showed no significant changes. Nonetheless, the increases observed could be related to the length of follow-up. In a study with the shortest length (17 weeks), Sarmento *et al.* reported a minimum change of 0.3 ± 0.7% for this outcome, whereas the study by Mitelman *et al.* with the longest length (1 year), reported a mean increase of 10% [13,20]. This relationship between LVEF and the length of EBTP was previously identified in patients with HF due to etiologies other than Chagas disease [38].

Table 3
GRADE assessment of the certainty of evidence.

Outcomes	Impact	N° of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality follow-up: range 12 weeks to 6 months	Studies showed no significant decrease or no difference	94 (3 RCTs)	⊕◯◯◯ Very low[a,b,c,d]
Cardiovascular mortality follow-up: range 12 weeks to 6 months	Studies showed no significant decrease or no difference	94 (3 RCTs)	⊕◯◯◯ Very low[a,b,c,d]
Health-related quality of life (HRQoL) assessed with: SF-36 follow-up: median 12 weeks	The study showed significant improvement in domains such as vitality, emotional aspects, and mental health	40 (1 RCT)	⊕◯◯◯ Very low[a,e,f,g]
Exercise capacity assessed with: peak VO2 (mL/kg/min) follow-up: range 12 weeks to 6 months	Studies showed a significant improvement	94 (3 RCTs)	⊕◯◯◯ Very low[a,c,d]
Health-related quality of life (HRQoL) assessed with: SF-36 follow-up: mean 8 months	The study showed significant improvement in domains such as physical functioning, role-physical, improvement in bodily pain, and physical health	12 (1 NRIS)	⊕◯◯◯ Very low[a,e,f,g]
Exercise capacity assessed with: peak VO2 (mL/kg/min) follow-up: range 6 weeks to 1 year	Studies showed a significant improvement	128 (5 NRIS)	⊕◯◯◯ Very low[a,c,d]

NRIS, non-randomized intervention studies; RCT, randomized clinical trial.
[a] Decreases two levels due to high risk of bias;
[b] Decreases one level for inconsistency;
[c] Decreases one level for indirectness,
[d] Decreases one level for imprecision,
[e] Decreases two levels for inconsistency,
[f] Decreases two levels for indirectness,
[g] Decreases two levels for imprecision.

4.4. Clinical and public health implications

Although there are evidence-based recommendations to implement exercise-based cardiac rehabilitation in the management of patients with HF, regardless of their etiology [39], CCC could behave differently from HF due to etiologies other than Chagas disease. Clinical data on interventions in CCC are limited, and currently, there is no effective treatment for CCC [40]. Indeed, when terminal heart transplantation is indicated, it carries unique challenges, including the risk of parasite reactivation in the graft and a potentially worse prognosis [40]. Given that EBTP offers a different and potentially more cost-effective alternative compared to conventional treatments, it is worth considering. Studies such as PEACH, which evaluated the cost-effectiveness of an exercise-based cardiovascular rehabilitation program in patients with CCC in Brazil, have demonstrated that EBTP can be a cost-effective tool to improve patients' condition [41]. Furthermore, the implementation of home-based cardiac rehabilitation (EBTP at home) has been associated with better outcomes, including improvements in health-related quality of life and physical fitness, compared to conventional, center-based cardiac rehabilitation (EBTP at healthcare centers). This suggests that considering the implementation of home-based programs could further enhance cost-effectiveness and promote greater adherence to this intervention [42].

4.5. Strengths and limitations

Our systematic review has some limitations. Firstly, the studies included involved different stages of CCC and medication. The variation in the severity of CCC among the included studies poses a potential limitation. The differing stages of CCC and NYHA classifications may influence the response to EBTP and the observed outcomes. It is crucial to consider this heterogeneity when interpreting the overall findings and generalizing them to the broader population of individuals with CCC. Consequently, future trials are needed to evaluate the specific effects of EBTP at each stage of the disease.

Secondly, it is important to highlight that the interventions in the included studies exhibited variation in their composition. In other words, each program implemented different types of exercises, and some even incorporated co-interventions as part of a more complex intervention, such as cardiac rehabilitation programs. These differences in EBTP can lead to some confusion regarding the true effect of physical exercise as a standalone intervention, as well as the specific type of physical exercise being referred to. However, overall, this systematic review provides evidence that physical exercise, in any of its modalities, has a positive effect on patients with CCC.

Thirdly, the studies included had heterogeneous follow-up times, which may explain the heterogeneity of the findings. The variability in follow-up durations is an important factor to consider when interpreting the findings and assessing the overall impact of EBTP. It is important to note that a longer follow-up period allows for a more comprehensive evaluation of the sustained effects of the intervention. While some studies reported positive outcomes during shorter follow-up periods, it is possible that the effects of the intervention may diminish or stabilize over time.

Furthermore, five out of the eight studies did not have a control group. The absence of a control group significantly limits the ability to establish a cause-and-effect relationship and accurately attribute the observed effects solely to the exercise-based treatment. A control group serves as a vital benchmark for comparison, enabling researchers to assess the true impact of the intervention by accounting for confounding factors and measuring changes relative to a non-intervention or placebo group. Future studies should prioritize the inclusion of appropriate control groups to strengthen the evidence base and enable a more comprehensive evaluation of the benefits of exercise-based interventions in the context of CCC.

Lastly, it is important to note that the sample sizes of the included studies were relatively small, which imposed limitations on the ability to assess robust and conclusive hard outcomes.

Despite these limitations, this is the first published systematic review of the effect of EBTP on patients with CCC, showing a benefit on functional capacity (measured by peak VO2). Similarly, in the qualitative synthesis, we found an improvement in HRQoL. Additionally, there was a low frequency of adverse effects in patients with CCC who underwent EBTP.

5. Conclusions

The evidence available on EBTP was limited and heterogeneous. Despite this, EBTP could be an accessible intervention with important effects on HRQoL and exercise capacity (peak VO2) in clinically stable CCC patients. In addition, there is no conclusive information about the impact on all-cause mortality, cardiovascular mortality, HFRHA, and LVEF. These positive effects present an opportunity to provide treatment to CCC patients in low- and middle-income countries, where the incidence of Chagas disease is high and resources are limited. Further randomized controlled trials are needed to ascertain the effects of EBTP on hard outcomes in this population.

Authors' contributions

PMCR, CSMG, and CDA were involved in conceiving and designing the systematic review. PMCR, DFG, BCC, CSMG, and CDA participated in the acquisition and analysis of the data. PMCR, DFG, BCC, CDA, and HMM interpreted the results. PMCR, DFG, BCC, CSMG, CDA, and HMM contributed to drafting the manuscript. All authors provided their approval for the submission of the final manuscript.

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CRediT authorship contribution statement

Pablo M. Calderon-Ramirez: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Daniel Fernandez-Guzman:** Methodology, Investigation, Writing – review & editing. **Brenda Caira-Chuquineyra:** Methodology, Writing – review & editing. **Carlos S. Mamani-García:** Methodology, Investigation, Writing – review & editing. **Héctor M. Medina:** Writing – review & editing. **Carlos Diaz-Arocutipa:** Methodology, Investigation, 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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Appendix A. Supplementary data

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