DOI: 10.1590/1809-2950/16416224012017

Effectiveness of resistance training on the improvement of functional capacity and quality of life in heart failure patients: a systematic review and meta-analysis

Eficácia do treinamento resistido na melhora da capacidade funcional e na qualidade de vida de pacientes com insuficiência cardíaca: uma revisão sistemática e metanálise

El entrenamiento de resistencia puede mejorar la capacidad funcional y la calidad de vida de pacientes con insuficiencia cardíaca: revisión sistemática y metanálisis

Jasiel Frutuoso do Nascimento Júnior[1], Armèle Dornelas de Andrade[2], Adriane Borba Cardim[1], Daniella Cunha Brandão[2]

ABSTRACT | This study aimed to evaluate the effectiveness of resistance training (RT) on the improvement of functional capacity (FC) and quality of life (QOL) in heart failure (HF) patients. An electronic search was performed in databases (PubMed/Medline, SCOPUS, Web of Science, CINAHL, Lilacs, and Cochrane), without restrictions of language or year of publication, using the following keywords: heart failure, resistance training, exercise tolerance, quality of life, fatigue, dyspnea, and muscle strength. Clinical trials were included, with a sample composed of individuals with HF in the functional classes I, II, or III of the New York Heart Association; with average age < 65; sedentary; clinically stable and pharmacologically optimized; with ejection fraction (EF) < 45% of the predicted. The intervention should be the exclusive RT. We described the methodological aspects by the bias risk and a meta-analysis with subgroup analysis. Seven studies were included for qualitative analysis. The agreement (Kappa index – k) between researchers was k=0.74. Most studies that assess FC and QOL showed increase in VO_2 max (maximal oxygen consumption) and in the final scores of the QOL questionnaires for the intervention group. The results of FC enabled a meta-analysis, showing a final increase of 0.52 (0.17-0.87) ml×kg−1×min−1 (milliliters×kilogram−1×min−1) in the VO_2 max after RT, with low heterogeneity. However, statistical limitations and diversity of interventions were evidenced after the analysis by subgroups. The limitations found in the selected studies still do not allow considering RT effective in improving FC and QOL in HF patients.

Keywords | Heart Failure; Resistance Training; Exercise Tolerance; Quality of Life.

RESUMO | Avaliou-se a eficácia do treinamento resistido (TR) na melhoria da capacidade funcional (CF) e na qualidade de vida (QV) de pacientes com insuficiência cardíaca (IC). Uma busca eletrônica foi realizada em bancos de dados (PubMed, MEDLINE, Scopus, Web of Science, CINAHL, LILACS e Cochrane), sem restrições de linguagem ou ano de publicação, utilizando como descritores "heart failure", "resistance training", "exercise tolerance", "quality of life", "fatigue", "dyspnea" e "muscle strength". Foram incluídos ensaios clínicos, com amostra composta por indivíduos com IC, classe funcional I, II ou III da New York Heart Association; idade média <65 anos, sedentários, clinicamente estáveis e farmacologicamente otimizados; com fração de ejeção (FE) <45% do predito. A intervenção deveria ser o TR exclusivo. A descrição dos aspectos metodológicos pelo risco de viés e uma metanálise com uma análise por subgrupo foram executados. Sete estudos foram incluídos para análise qualitativa. O nível de concordância (índice *kappa* – k) entre

This study was neither partly nor totally presented in any scientific event, such as congress or symposium.
[1]Physical Therapists graduated by Universidade Federal de Pernambuco (UFPE), masters in Physical Therapy by UFPE.
[2]Professors of the Department of Physical Therapy (UFPE).

Corresponding address: Daniella Cunha Brandão – Centro de Ciências Exatas e da Natureza – Av. Jornalista Aníbal Fernandes, s/n, Cidade Universitária – Recife (PE) – Zip Code: 50740-560 – Phone: +55 (81) 2126-8496 – E-mail: daniellacunha@hotmail.com – Financial support: National Council for Scientific and Technological Development (CNPq)/Coordination of Higher Education and Graduate Training (Capes)/Pernambuco Research Foundation (FACEPE-APQ) - 0154-4.08/15 – Conflicts of interest: Nothing to declare – Presentation: Nov. 2016 – Accepted for publication: Mar. 2017 – Approved by the Ethics Committee: not applicable (systematic review).

os pesquisadores foi k=0,74. A maioria dos estudos que avalia CF e QV mostrou aumento no VO_2 pico (pico de consumo de oxigênio) e nas pontuações finais dos questionários de QV para o grupo de intervenção. Os resultados de CF possibilitaram uma metanálise, exibindo um aumento final de 0,52 (0,17-0,87) mL.kg-1.min-1 (mililitros.quilograma-1.minuto-1) no VO_2 pico depois do TR, com baixa heterogeneidade. Contudo, limitações estatísticas e diversidade de intervenções foram evidenciadas depois da análise por subgrupos. As limitações encontradas nos estudos selecionados ainda não permitem considerar o TR eficaz na melhoria da CF e da QV em pacientes com IC.

Descritores | Insuficiência Cardíaca; Treinamento de Resistência; Tolerância ao Exercício; Qualidade de Vida.

RESUMEN | Se evalúo si el entrenamiento de resistencia (ER) es eficaz para mejorar la capacidad funcional (CF) y la calidad de vida (CV) de pacientes con insuficiencia cardíaca (IC). Se buscó estudios en las bases de datos electrónicas (PubMed, MEDLINE, Scopus, Web of Science, CINAHL, LILACS y Cochrane), sin restricciones de idiomas o de años de publicación, empleando las siguientes palabras clave: "heart failure", "resistance training", "exercise tolerance", "quality of life", "fatigue", "dyspnea" y "muscle strength". Para un muestreo se incluyeron ensayos clínicos, con muestras formadas por sujetos con IC, clase funcional I, II o III de la *New York Heart Association*; un promedio de edad de <65 años, sedentarios, clínicamente estables y farmacológicamente optimizados; con fracción de eyección (FE) <45% del predicho. La intervención debería ser un ER exclusivo. Se realizaron la descripción de los marcos teóricos por el riesgo del sesgo y un metanálisis con un análisis por subgrupo. Se incluyeron siete estudios para analizarlos cualitativamente. El nivel de concordancia (el índice kappa) entre investigadores fue de k=0,74. La mayoría de los estudios que evalúan la CF y la CV develan un aumento en el VO_2 pico (pico de consumo de oxígeno) y en los puntajes finales del cuestionario de la CV en el grupo intervención. Los resultados de la CF posibilitaron un metanálisis, que tuvo un aumento final de 0,52 (0,17-0,87) ml.kg-1.min-1 (mililitros.quilogramo-1.minuto-1) en el VO_2 pico tras el ER, de baja heterogeneidad. Se observaron limitaciones estadísticas y de diversidad de intervenciones tras el análisis por subgrupos. Pero estas limitaciones no permiten todavía considerar que el ER es eficaz para mejorar la CF y la CV en los pacientes con IC.

Palabras clave | Insuficiencia Cardíaca; Entrenamiento de Resistencia; Tolerancia al Ejercicio; Calidad de Vida.

INTRODUCTION

Cardiometabolic rehabilitation is the main non-pharmacological tool for the clinical management of heart failure (HF) patients[1]. In its scope of activities, physical training, especially resistance training (RT), gained notoriety recently, mainly because of studies that show its benefits in various outcomes. Recent researches have suggested that the association of RT with aerobic exercise leads to physical and functional improvement of HF patients[2-5].

However, the most recent systematic reviews on the RT effects do not present conclusive data on its effectiveness in improving the quality of life and functional capacity of these patients, which are the main physical and functional impairments reported by this population[6,7]. A previous systematic review aimed to give an overview of the effects of moderate to high intensity RT in individuals with HF, and, although finding information that could support the safety of this intervention, its conclusion does not establish sufficient subsidies to use it in cardiometabolic rehabilitation. In addition, the quality of the evidence presented in the study is limited by the linguistic restriction and the reduced number of used databases[6].

In 2010, another systematic review also evaluated the RT effects on the quality of life and functional capacity of HF patients, noting its positive effect after quali-quantitative analysis. However, the authors conducted the six-minute walk test (6MWT) as a clinical tool for measuring functional capacity, and it is known that the 6MWT is an indirect method for its measurement. In addition, another compromising factor in the interpretation of their conclusions relates to the analysis process of the quality of the studies, which affects the interpretation of these results[7].

Therefore, this study aimed to investigate whether resistance training is effective in improving functional capacity and quality of life in heart failure patients.

METHODOLOGY

From July to August 2014, two independent reviewers selected articles by an electronic search in the databases PubMed, Medline, Lilacs, CINAHL, Web of Science,

Scopus, and Cochrane. No restriction of language or year of publication was applied. Functional capacity – measured directly by the VO_2max (maximal oxygen consumption), which is in turn measured by cardiopulmonary exercise testing (CPET) – and quality of life (measured by specific validated questionnaires) were defined as primary outcomes. For secondary outcomes, dyspnea and fatigue (measured by scales of visual perception), as well as muscular strength (measured by dynamometry or maximum repetition tests) were established.

The following keywords in English and their combinations were selected to perform the research process: "heart failure," "resistance training," "exercise tolerance," "quality of life," "fatigue," "dyspnea," and "muscle strength."

Only studies that met the following inclusion criteria were registered for further evaluation: clinical trials, with sample composed of individuals with HF diagnosis in the functional classes I, II, or III, according to the New York Heart Association (NYHA); patients with average age < 65; sedentary; clinically stable and pharmacologically optimized; with ejection fraction (EF) < 45% of the predicted. The intervention should be composed exclusively of RT (i.e., activities with muscular contraction carried out against a force generated from any form of resistance, such as weights, stretch bands, water, or immovable objects).

At the end of the search, duplicate articles were excluded by title from the total articles initially found by the keywords. After reading the abstracts, we excluded studies that did not address the proposed topic and review studies. Thus, after reading the full text, studies that did not fit the inclusion criteria were not included in the qualitative analysis. Finally, for a possible quantitative analysis, studies that did not evaluate the possible outcomes chosen for this statistical approach were excluded. The reference lists of the preselected articles were also examined to find those with possible relevance to be added to the complete reading.

Statistical analysis

At the end of the systematic search, the Kappa index was calculated based on the results of the studies selected for the qualitative analysis to establish the agreement between the two independent researchers. The main methodological aspects of these studies (as well as the characteristics of samples, interventions, and main outcomes and results of each study) were qualitatively described, being summarized in charts and tables.

The bias risk of the selected studies was classified as low, uncertain, or high based on the criteria established by the Cochrane Collaboration[8] tool, by RevMan software (version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). The quality of the evidence for the variable VO_2 max was determined by GRADE profiler software (version 3.6.1, The Grading of Recommendations Assessment, Development and Evaluation – GRADE workgroup, 2011-2004).

The results of VO_2 max allowed the conduction of a fixed effect meta-analysis, by the standardized mean difference, from five of the seven studies evaluated. The heterogeneity between the studies was assessed using Cochran's Q test and Higgins' I^2 test[9], considered significant when $p<0.05$ and moderate when $I^2>30\%$. The RevMan software was used for this evaluation.

RESULTS

Selection of studies

Systematic search results are summarized by the flowchart in Figure 1. Of all 2,368 articles selected by the combinations of keywords, 18 were selected to be fully read, and only seven articles were included in the qualitative analysis, since 11 were excluded for presenting a different intervention than RT (6) or presenting sample with average age > 65 years (5). The Kappa index was k=0.74, resulting in substantial agreement between the search results of the independent researchers.

Qualitative analysis

Table 1 qualitatively describes the main methodological aspects of the selected studies, such as the protocols, selected sample, and executed intervention characteristics. The main outcomes (primary and secondary) and their conclusions are summarized in Table 2.

Regarding functional capacity, six of the seven selected studies presented data on the variable in question, and in five of them VO_2 max improved in the intervention group[11-16]. However, one of these studies[16] compared the results of the intervention group before and after RT, without making any comparison between intervention and control groups[16]. Another of these five studies, in turn, showed no difference between groups after RT[13].

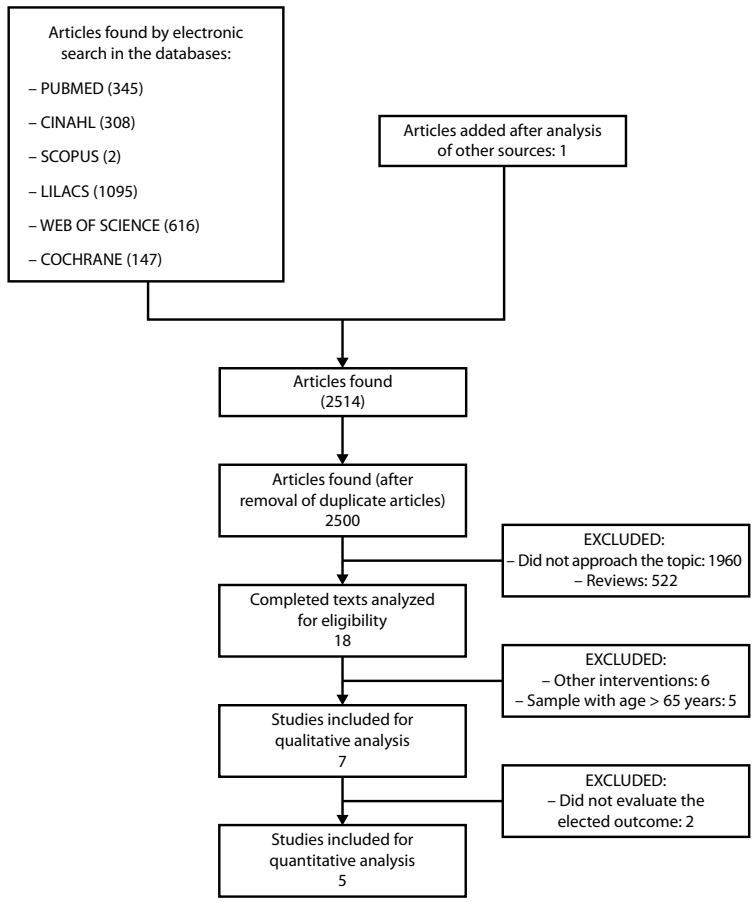


Figure 1: Flowchart of the selection of studies

Concerning quality of life, from the seven selected studies, five presented information on this variable, all reporting an increase in the final scores of the specific questionnaires used to measure the perception of quality of life[10-13,15]. Nevertheless, two of these studies[12,13] only compared initial and final scores from the intervention group before and after RT, and, once again, there was no description of statistical analysis regarding the comparison between the groups at the end of the intervention.

Data on the secondary outcomes (dyspnea, muscle strength, and fatigue) are also described in Table 2. However, the frequency of how they were studied seems to differ substantially from the results obtained for the primary outcomes. Concerning muscle strength, of the seven studies included in the qualitative analysis, only three mentioned this variable. Even so, all of them reported an increase in its value[12,14,16], and only one study described methodologically (i.e., comparing the results of intervention and control groups after training) and statistically (data as mean ± confidence interval) the analyses related to this variable, showing an increase in knee flexion torque with mean value of 12 Nm (–28.73-4.73) ($p<0.05$)[14].

Concerning the "dyspnea" outcome, two of the seven selected studies presented data for this variable[12,13]. One of them describes that, when compared to the baseline, the intervention group improved their perception of dyspnea ($p<0.05$)[12]. Another one showed no difference when comparing both groups[13]. We found no study comparing the groups after RT and no studies that examined fatigue in this population.

Figure 2 shows the graph of bias risk of the selected studies. Since this type of intervention (RT) does not allow blinding the volunteers, and since we did not find, so far, studies that have described the blinding of researchers, we established that, for this domain, the bias risk was uncertain for all articles analyzed. For the other analysis fields, the absence of description of the sample calculation, randomization, or blinding of the evaluators, as well as compromised description of the results (i.e., not providing the mean difference between intervention and control groups or their confidence intervals) determined the final result of the qualitative analysis.

Table 1. Methodological aspects of the selected studies

AUTHORS	TYNI-LENNÉ et al. (1996)	TYNI-LENNÉ et al. (1997)	GORDON et al. (1997)	TYNI-LENNÉ et al. (2001)	SELIG et al. (2004)	LEVINGER et al. (2005)	MAIORANA et al. (2010)
STUDY DESIGN	RCT	COT	CT	RCT	RCT	CT	RCT
SAMPLE	21 ♂ with HF (NYHA II and III); 60Y (42-73); EF 28±11%.	16 ♀ with HF (NYHA II and III); 62±10Y and EF 28 ± 10% FE (first stage – INTERVENTION) and 63±10Y and EF 30±8% (second stage –CONTROL)**.	20 ♂ with HF (NYHA II AND III); 56±3Y; EF 27 ±3%**.	24 (13 ♂ and 11 ♀) with HF (NYHA II and III); 63±9Y; EF 30±10%**.	39 (33 ♂ and 6 ♀) with HF (NYHA II and III); 65±11Y; EF 28±7%**.	15 ♂ (NYHA?); 57.0±10.2Y; EF 34.7±7.2%**.	24 ♂ (NYHA I, II, and III); 64.4±4.4Y; EF 37±3% (CONTROL group) and 58.8±5Y; EF 26±3% (INTERVENTION group)**.
INTERVENTION	***ETIOLOGY:*** NM.	***ETIOLOGY:*** CORONARY (11); CARDIOMYOPATHY (6).	***ETIOLOGY:*** CORONARY (8); DILATED (10); HYPERTENSIVE (2).	***ETIOLOGY:*** NM.	***ETIOLOGY:*** ISCHEMIC (24); DILATED (16).	***ETIOLOGY:***NM.	***ETIOLOGY:*** ISCHEMIC (16); DILATED (8).
	DIAGNOSIS TIME: 3M.	***DIAGNOSIS TIME:*** MINIMUM 3M.	***DIAGNOSIS TIME:*** 58± 5M.	***DIAGNOSIS TIME:*** NM.	***DIAGNOSIS TIME:*** NM.	***DIAGNOSIS TIME:*** NM.	***DIAGNOSIS TIME:*** NM.
	TYPE: bilateral (Group 1) and unilateral (Group 2) knee extension exercise with modified cycle ergometer.	***TYPE***: bilateral knee extension exercises with modified cycle ergometer.	***TYPE***: bilateral knee extension exercises with quadriceps isolation in modified cycle ergometer.	***TYPE***: bilateral exercises with exercise bands.	***TYPE:*** Bilateral exercises of flexion and extension of the knees, elbows, and shoulders (30s); going up 5 steps (0.5-2 min); and cycle ergometer of the upper and lower limbs (0.5-2 min).	***TYPE:*** 8 exercises (no information about modalities) for the main muscle groups.	***TYPE:*** 8 sets of 9 exercises (no information on modalities)
	INTENSITY: 70% (Group 1) and 35% (Group 2) of 1RM.	***INTENSITY:*** 65% of 1RM with progression to 70% in 4 weeks.	***INTENSITY:*** 65% of 1RM with progression to 70% in 4 weeks.	***INTENSITY:*** < 13 at Borg fatigue scale and between 13 and 16 at Borg dyspnea scale.	***INTENSITY:*** HRmax - 10BPM.	***INTENSITY AND TIME:*** 40-60% of 1RM, one set, 15 to 20 reps with a gradual increase of 80-90% of 1RM during weeks 7-8 and, at the same time, a decrease in the number of reps between weeks 8-12, for the three sets.	***INTENSITY:*** in the first ones, 6s-60% 1RM and, in the last six, 70% 1RM.
	TIME: 60 rpm, 15 min.	***TIME:*** 60 rpm, 15 min.	***TIME:*** 3 min, with 1 min intervals.	***TIME:*** 60 min of activities such as the warm-up and cooldown and periods of 45 minutes of RT.	***TIME:*** varies.		***TIME:*** Not defined. Interval of 3 minutes between sets.
	FREQUENCY: 3 ×/week.	***FREQUENCY:*** 3 ×/week.	***FREQUENCY:*** 3 ×/week.	***FREQUENCY:*** 3 ×/week.	***FREQUENCY:*** 3 ×/week.	***FREQUENCY:*** 3 ×/week.	***FREQUENCY:*** 3 ×/week.
	DURATION: 8 weeks.	***DURATION:*** 8 s.	***DURATION:*** 8 weeks.	***DURATION:*** 8 weeks.	***DURATION:*** 3M.	***DURATION:*** 8 weeks.	***DURATION:*** 12 weeks.
	WARM-UP: 3 min of walking and stretching.	***WARM-UP:*** 6 min of walking and stretching.	***WARM-UP:*** 6 min of walking on the usual speed of the volunteer.	***WARM-UP:*** 6 min of large movements of the 4 members.	***WARM-UP:*** 6 min of walking and stretching.	***WARM-UP:*** NM.	***WARM-UP:*** NM.
	COOLDOWN: 3 min of walking and stretching.	***COOLDOWN:*** 3 min of walking and stretching.	***COOLDOWN:*** NM.	***COOLDOWN:*** 6 min of large movements of the 4 members.	***COOLDOWN:*** 5 min of walking and stretching.	***COOLDOWN:*** NM.	***COOLDOWN:*** NM.

RCT: randomized clinical trial; CO: cross-over trial; CT: clinical trial; HF: heart failure; ♂: male; ♀: female, NYHA: New York Heart Association; EF: ejection fraction of left ventricular; NM: not mentioned; rpm: rotations per minute; ×: times; 1RM: one-repetition maximum; RT: resistance training; HRmax: maximum heart rate; HRrest: resting heart rate; BPM: beats per minute; Y: years; M: months; min: minutes; s: seconds.

Table 2. Results of the primary and secondary outcomes in the selected studies

AUTHORS	TYNI-LENNÉ et al. (1996)	TYNI-LENNÉ. et al. (1997)	GORDON et al. (1997)	TYNI-LENNÉ. et al. (2001)	SELIG et al. (2004)	LEVINGER et al. (2005)	MAIORANA et al. (2010)
OUTCOMES PRIMARY	NA	***FC*** (CPET): increase of 1.2 (0.6-1.7) ml×kg^{-1}×min^{1} (p=0.0005)* in the VO_2 max.	***FC*** (CPET): no difference.	***FC*** (CPET): increase of 1.5 (1.9-4.9) ml×kg^{-1}×min^{-1} (p<0.05)* in the VO_2 max.	***FC*** (CPET): increase of 2 (0.53-4.53) ml×kg^{-1}×min^{-1} (p<0.01)* in the VO_2 max.	***FC*** (CPET): increase of 3 (0.35-5.35) ml×kg^{-1}×min^{-1} (p=0.01)* in the VO_2 max.	***CF*** (CPET): compared with the initial values, there was an increase in the intervention group in the VO_2 max (p<0.01)†.
	QOL (SIP): improvement in 4 points on the scale (−5.32-13.32) (p<0.01)*.	***QOL*** (SIP): improvement in 1.2 points on the scale (−3.0-0.6) (p<0.01)*.	***QOL*** (SIP): compared with the initial values, the intervention group showed improvement in all domains of SIP (p<0.05–0.01)**†.	***QOL*** (MLWHFQ): improvement on the final score (p<0.01)$^{\circ}$.		***QOL*** (MLWHFQ): improvement in 23.1 (2.85-43.35) points on the scale (p=0.03)*.	
			MS (peak knee extension torque): Compared with initial values, the intervention group showed an increase in muscle strength of 19 Nm ± 13% (p<0.01)**†.		***MS*** (flexor and extensor torque measures of knees and elbows): increased muscle strength of knee extension in 12 Nm (4.73-28.73) (p<0.05)*.	***MS*** (RM): increase in muscular strength (p<0.001)$^{\circ}$.	***MS*** (RM): Compared with initial values, the intervention group showed an increase in RM (p<0.05)†.
SECONDARY OUTCOMES	NA	NA	***DISP*** (Borg scale): Compared with initial values, the intervention group showed an increase in the perception of dyspnea (p<0.01)**†.	***DISP*** (Borg scale): no difference.			

FC: functional capacity; QOL: quality of life; DISP: dyspnea; SIP: Sickness Impact Profile Questionnaire; MLHFQ: Minnesota Living with Heart Failure Questionnaire; MS: muscular strength; CPET: cardiopulmonary exercise test; VO_2 max: maximal oxygen consumption; ml × kg^{-1} × min^{-1}: milliliters per kilogram per minute; NA: not applicable; NM: not mentioned; Nm: Newton meter; RM: repetition maximum; $^{\circ}$: did not present mean differences; *: data expressed in means and confidence intervals (95%); **: data expressed as mean ± standard deviation; †: there was no comparison between intervention and control groups after resistance training.

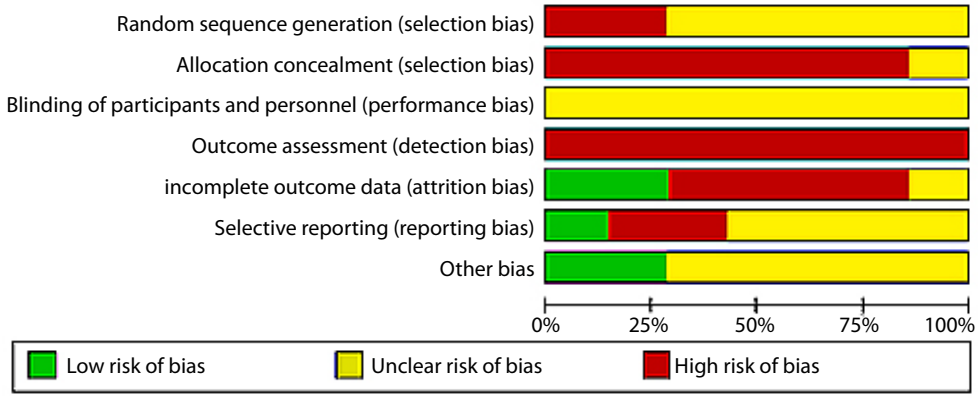


Figure 2. Graph of the bias risk of the selected studies.

Quantitative analysis

After analyzing the selected studies, we conducted a meta-analysis with six articles that analyzed the VO_2 max. (results presented in Figure 3). The selected studies differed methodologically regarding the type of protocol used in the cardiopulmonary exercise testing and in the RT prescription method, and, therefore, we performed two subgroup analyses to explore the heterogeneity of these studies. Standardized mean difference was used for all analyses. When the level of heterogeneity was higher than 30%, the random effect model was applied on the fixed effect model.

Based on the critical analysis of the included studies, five domains were analyzed to generate the final score of the evidence quality: bias risk; publication bias; inconsistency; "indirectness"; and data inaccuracy. For all studies, the poor quality of the methodological and statistical processes, the heterogeneity of the selected studies, and the indirect comparisons and selective description of results impaired the final result, leading to a very low evidence quality.

We were not able to apply the quantitative analysis for the quality of life outcome because of the differences in the type of questionnaire applied to achieve the final score of perception of dyspnea. Moreover, from the three studies that used SIP – Sickness Impact Profile Questionnaire, one presented a selective description of the outcome[11] and another presented its results in median and interquartile range[12]. The studies that used the MLWHFQ (The Minnesota Living With Heart Failure Questionnaire) reported significant differences regarding the RT prescription method, which also limited the interpretation of those results.

DISCUSSION

RT has been incorporated into the cardiometabolic rehabilitation to enhance the physical performance of heart failure patients. Even so, the systematic reviews on this topic have methodological limitations and do not provide sufficient data support to such practices[6,7]. More than 2,000 studies were selected in this review, but, of these, only seven actually conducted clinical trials that examined the RT effects, and none of them provided sufficient data to calculate the dose-response gradient for RT or allowed a possible analysis of the associated confounding effects, thus limiting the evidence of this intervention.

Of the seven listed studies, only two mentioned the presence of adverse effects after RT in HF patients. Tyni-Lenné et al.[10] reported an increase in lower limb edema in volunteers of their study. Another study mentions a sudden death event and the emergence of a non-cardiac disease in one of its participants during the intervention period[17]. On the other hand, there are no numeric reports of loss of volunteers, which limits the possibility of executing an analysis by intention to treat.

All evaluated studies presented uncertain or high risk for selection bias when the absence of randomization, masking, and allocation concealment was perceived. The appropriate allocation of volunteers in the different branches of the clinical trial is able to balance the characteristics of the groups[19]. The act of masking intends to keep the allocation confidential for volunteers and researchers, and it is used to avoid the possibility of knowledge about the allocation affecting the patient's response to the treatment, the researchers' behavior (performance bias), or the verification of outcomes (detection bias)[20]. The implementation

of randomization and maintenance of allocation concealment minimize the mentioned selection bias, making sure that the treatment effect occurred because of the intervention and not by other factors[21,22]. When there is no allocation concealment and randomization, the intervention effect can be overestimated in 16-40%.

Six of the seven selected studies evaluated the primary outcome "functional capacity," measured by the VO_2 max. In five of them, this variable improved for the intervention group[11-16]. However, there are limitations in the interpretation of these data, especially because of the clinical heterogeneity of the studies, since the researches use different methods for measuring VO_2 max and different protocols to conduct the cardiopulmonary exercise test (such as Balke and ramp protocol) or instruments used for it (cycle ergometer and treadmill).

Methodological differences were also found regarding the resource and prescription method employed to apply RT, limiting the statistical comparisons. One of the studies[13] used exercise bands, with nonspecific and not detailed resistance degree. Another study[16] did not compare the outcomes of the two groups after RT. In addition, the same study provides no precise description of the exercise carried out by the intervention group, also including in its sample patients with functional class I (NYHA), with a better physical-functional performance, which may have changed the results for VO_2 max. Gordon et al.[13] conducted a clinical trial without randomization, which showed no difference between the groups.

Our study is the first systematic review assessing qualitatively and quantitatively the effectiveness of resistance training on the functional capacity measured directly by the VO_2 max obtained by the cardiopulmonary exercise test, gold standard in the evaluation of exercise tolerance. We verified an increase of 0.52 $ml \times kg^{-1} \times min^{-1}$ of VO_2 max for the studies analyzed, by a fixed effect meta-analysis, with good heterogeneity index (Figure 3, part A). Although there are no data in the researched literature until April 2015 reporting the minimum detectable difference for the VO_2 max after a RT protocol, Swank et al.[22] showed that an increase of 0.4 $ml \times kg^{-1} \times min^{-1}$ (6%) in VO_2 max led to a 7% reduction in the final cutoff points for all causes of mortality in the population with HF. Despite this result, the study found this effect after aerobic training in treadmill, thus limiting the inference and relevance of the analogies.

Aiming to explore the methodological heterogeneity of the selected studies, we performed a subgroup analysis (Figure 3, part B) by a fixed effect meta-analysis, to investigate whether the VO_2 max values obtained by different protocols or instruments – such as cycle ergometer and treadmill – would lead the results to different clinical outcomes. Studies that evaluated the exercise tolerance by cycle ergometer presented higher VO_2 max values when compared to those that used treadmills, indicating that aspects of the evaluation methodology probably induced different metabolic demands and, consequently, different values for maximal oxygen consumption. However, both methods were able to detect the change of the VO_2 max favoring the intervention group after RT.

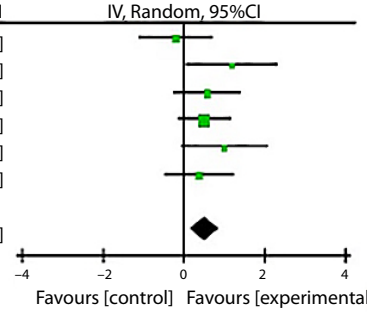
When the studies were analyzed in subgroups according to their form of exercise prescription (Figure 3, part C), the results were less promising. Random effect meta-analyses, which assessed the standardized mean differences, showed that both groups presented values close to the 0.52 $ml \times kg^{-1} \times min^{-1}$ initially found when the studies were analyzed together (0.59 $ml \times kg^{-1} \times min^{-1}$ and 0.46 $ml \times kg^{-1} \times min^{-1}$). However, both groups presented negative confidence intervals, indicating the inaccuracy of the results. In addition, a separate analysis of the first group of studies, when the prescription was based on the one-repetition maximum test (1RM), showed a moderate heterogeneity index. In turn, in the other study group, in which the prescription was based on methods different from the 1RM, the final VO_2 max increase ($p>0.05$) was not significant.

Despite recent recommendations for RT directing its prescription based on the 1RM, there is a report suggesting that patients with cardiovascular diseases should receive RT prescribed based on the effort perception[24]. In addition, some authors describe that, in HF patients, a wide range of resistance training methods is also conducted, showing how dissonant are the recommendations of prescription and implementation of the various modalities of this intervention[25]. This scenario collaborates to limit our findings, which is reflected in the quality of the evidence examined by the six studies that evaluated the VO_2 max. In addition to the heterogeneity of these studies, other methodological failures also contributed to the low-quality evidence for the increased functional capacity in HF patients after RT.

Part A.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95%CI
GORDON, A. et al; 1997	13.3	0.7	13	13.6	2.3	7	14.4%	−0.20 [−1.12, 0.72]
LEVINGER, I. et al; 2005	17.7	1.3	8	14.7	3.2	7	9.6%	1.19 [0.06, 2.32]
MAIORANA, A. J. et al; 2010	16.4	3.81	12	14.1	3.81	12	18.2%	0.58 [−0.24, 1.40]
SELIG, S. E. et al; 2004	16.9	3.8	19	14.9	4	20	30.1%	0.50 [−0.14, 1.14]
TYNI-LENNÉ, R. et al; 1997	11	2.3	8	8.8	1.8	8	10.9%	1.01 [−0.05, 2.07]
TYNI-LENNÉ, R. et al; 2001	15.9	4.3	16	14.4	2.8	8	16.7%	0.37 [−0.48, 1.23]
Total (95%CI)			76			62	100.0%	0.52 [0.17, 0.87]

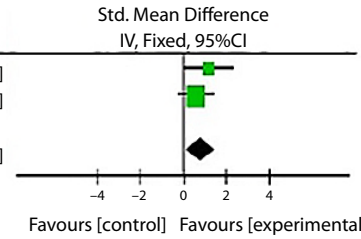
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.64$, df = 5 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 2.88 (P = 0.004)



Part B.

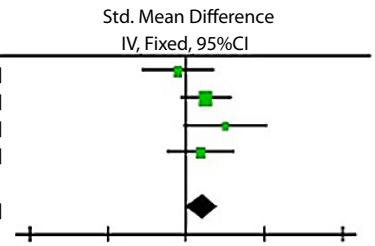
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95%CI
LEVINGER, I. et al; 2005	17.7	1.3	8	14.7	3.2	7	34.5%	1.19 [0.06, 2.32]
MAIORANA, A. J. et al; 2010	16.4	3.81	12	14.1	3.81	12	65.5%	0.58 [−0.24, 1.40]
Total (95%CI)			20			19	100.0%	0.79 [0.13, 1.46]

Heterogeneity: $Chi^2 = 0.73$, df = 1 (P = 0.39) $I^2 = 0\%$
Test for overall effect: Z = 2.34 (P = 0.02)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95%CI
GORDON, A. et al; 1997	13.3	0.7	13	13.6	2.3	7	20%	−0.20 [−1.12, 0.72]
SELIG, S. E. et al; 2004	16.9	3.8	19	14.9	4	20	41.7%	0.50 [−0.14, 1.14]
TYNI-LENNÉ, R. et al; 1997	11	2.3	8	8.8	1.8	8	15.2%	1.01 [−0.05, 2.07]
TYNI-LENNÉ, R. et al; 2001	15.9	4.3	16	14.4	2.8	8	23.2%	0.37 [−0.48, 1.23]
Total (95%CI)			56			43	100.0%	0.52 [0.17, 0.87]

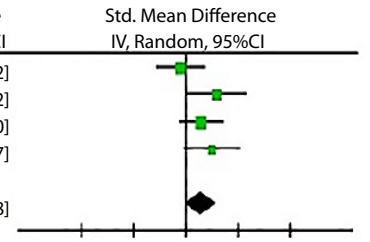
Heterogeneity: $Chi^2 = 2.98$, df = 3 (P = 0.39); $I^2 = 0\%$
Test for overall effect: Z = 1.94 (P = 0.05)



Part C.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95%CI
GORDON, A. et al; 1997	13.3	0.7	13	13.6	2.3	7	26.7%	−0.20 [−1.12, 0.72]
LEVINGER, I. et al; 2005	17.7	1.3	8	14.7	3.2	7	20.2%	1.19 [0.06, 2.32]
MAIORANA, A. J. et al; 2010	16.4	3.81	12	14.1	3.81	12	30.9%	0.58 [−0.24, 1.40]
TYNI-LENNÉ, R. et al; 1997	11	2.3	8	8.8	1.8	8	22.2%	1.01 [−0.05, 2.07]
Total (95%CI)			41			34	100.0%	0.59 [−0.00, 1.18]

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 4.49$, df = 3 (P = 0.21); $I^2 = 33\%$
Test for overall effect: Z = 1.95 (P = 0.05)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95%CI
SELIG, S. E. et al; 2004	16.9	3.8	19	14.9	4	20	64.3%	0.50 [−0.14, 1.14]
TYNI-LENNÉ, R. et al; 2001	15.9	4.3	16	14.4	2.8	8	35.7%	0.37 [−0.48, 1.23]
Total (95%CI)			35			28	100.0%	0.46 [−0.06, 0.97]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 1.74 (P = 0.08)

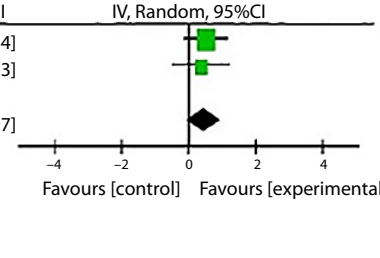


Figure 3. Forest plots: meta-analyses between control groups and intervention groups in relation to the maximal oxygen consumption (VO_2 max): Part A: Analysis of all selected studies; Part B: Subgroup analysis according to the instrument used for measuring (cycle ergometer x treadmill); Part C: Subgroup analysis according to the method of exercise prescription (1RM × other methods). Mean: mean of the groups; SD: standard deviation; Weight: statistical relevance of the study; Std Mean Difference: Standardized Mean Difference; IV: inverse variance; CI: confidence interval; Fixed: fixed effect; Random: random effect; I^2: heterogeneity index; Z: test for overall effect; Chi^2: Chi-square test; Tau^2: Kendall Tau test; df: degree of freedom; *P*: p-value.

Another important clinical result – quality of life – was evaluated by visual perception scales. Of the seven selected studies, five presented data on the variable in question, all showing an increase in the final scores of the questionnaires applied for measuring the quality of life[10-13,15]. On the other hand, only two of the three selected studies compared initial and final scores of the intervention group before and after RT, without presenting statistical analysis regarding the comparison between the groups at the end of the intervention[12,13]. Furthermore, only two studies used questionnaires specific to the HF population[13,15], and only one of these studies compared intervention with control groups after a RT program[15].

Data on other secondary outcomes, such as muscle strength and dyspnea, were measured by visual perception scales and muscle torque of knee flexors and extensors, respectively. Concerning muscle strength, of the seven studies included in the quality analysis, only three mentioned this variable and all reported increase[12,14,16]. Only one study shows quality of methods (comparing the results between the groups after RT) and statistics (data expressed as mean ± confidence interval), describing an increase of 12 Nm in the peak knee flexion torque (–28.73-4.73) ($p<0.05$)[14]. A clinical trial conducted without randomization compared only the peak of the knee flexion torque before and after RT, and only for the intervention group[13]. In another one, a randomized clinical trial examined the muscle strength of heart failure patients after RT, but its method of exercise prescription was not clear in terms of time and type of physical performance[16].

Only two of the seven selected studies evaluated the outcome for dyspnea. The first describes that, in comparison to the baseline, dyspnea perception improved in the intervention group, without presenting the mean difference between the groups before and after RT ($p<0.05$)[12]. The second, which used exercise bands (with nonspecific and not detailed resistance degree) as intervention, showed no intragroup difference after RT[13]. Until the writing of this systematic review, we found no articles in which control and intervention groups had their dyspnea perception compared after RT.

CONCLUSION

Based on the systematic review of the literature, resistance training seems to be a reliable clinical tool to be incorporated into cardiometabolic rehabilitation, for improving the exercise tolerance of heart failure patients. In particular, a fixed effect meta-analysis showed the increase in the maximal oxygen consumption between control and intervention groups. However, the methodological characteristics of the selected studies still do not allow such conclusions, mainly because of statistical limitations, such as the absence of clarity on methodological procedures (randomization, allocation concealment, standardization of the methods of RT prescription and its detailed execution).

As implications for clinical practice, randomized clinical trials, with adequate statistical power, sample calculation, and methodological rigor, must be carried out. Studies with follow-up, description of losses and possible adverse effects should also be included in the methodological scope of future studies. Thus, we suggest comprehensive and precise systematic reviews on the effects of this intervention, not only about functional capacity, but also about other critical outcomes for heart failure patients, such as dyspnea and fatigue.

REFERENCES

1. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-based rehabilitation for heart failure. Cochrane Database of Syst Rev. 2014;27(4): CD003331.
2. Braith RW, Beck DT. Resistance exercise: training adaptations and developing a safe exercise prescription. Heart Fail Rev. 2008;13(1):69-79.
3. Smart NA, Steele M. Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. Int J Cardiol. 2010;140(3):260-5.
4. Gary RA, Cress ME, Higgins MK, Smith AL, Dunbar SB. Combined aerobic and resistance exercise program improves task performance in patients with heart failure. Arch Phys Med Rehabil. 2011;92(9):1371-81.
5. Schwarz S, Halle M. Exercise training in heart failure patients. Dtsch Med Wochenschr. 2014;139(16):845-50.
6. Hwang CL, Chien CL, Wu YT. Resistance training increases 6-minute walk distance in people with chronic heart failure: a systematic review. J Physiother. 2010;56(2):87-96.
7. Spruit MA, Eterman RMA, Hellwig VACV, Janssen PP, Wouters EFM, Uszko-Lencer NHMK. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. Heart. 2009;95(17):1399-408.
8. Carvalho APV, Silva V, Grande AJ. Avaliação do risco de viés de ensaios clínicos randomizados pela ferramenta da colaboração Cochrane. Diagn Tratamento. 2013;18(1):38-44.
9. Higgins J, Green S, editors. The Cochrane handbook for systematic reviews of interventions version 5.3 [Internet].

The Cochrane Collaboration, 2011 [cited 2017 Mar 28]. Available from: http://handbook.cochrane.org

10. Tyni-Lenné R, Gordon A, Sylvén C. Improved quality of life in chronic heart failure patients following local endurance training with leg muscles. J Card Fail. 1996;2(2):111-7.
11. Tyni-Lenné R, Gordon A, Jansson E, Bermann G, Sylvén C. Skeletal muscle endurance training improves peripheral oxidative capacity, exercise tolerance, and health-related quality of life in women with chronic congestive heart failure secondary to either ischemic cardiomyopathy or idiopathic dilated cardiomyopathy. Am J Cardiol. 1997;80(8):1025-9.
12. Gordon A, Tyni-Lenné R, Jansson E, Kaijser L, Theodorsson-Norheim E, Sylvén C. Improved ventilation and decreased sympathetic stress in chronic heart failure patients following local endurance training with leg muscles. J Card Fail. 1997;3(1):3-12.
13. Tyni-Lenné R, Dencker K, Gordon A, Jansson E, Sylvén C. Comprehensive local muscle training increases aerobic working capacity and quality of life and decreases neurohormonal activation in patients with chronic heart failure. Eur J Heart Fail. 2001;3(1):47-52.
14. Selig SE, Carey MF, Menzies DG, Patterson J, Geerling RH, Williams AD, et al. Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. J Card Fail. 2004;10(1):21-30.
15. Levinger I, Bronks R, Cody DV, Linton I, Davie A. Resistance training for chronic heart failure patients on beta blocker medications. Int J Cardiol. 2005;102(3):493-9.
16. Maiorana AJ, Naylor LH, Exterkate A, Swart A, Thijssen DH, Lam K, et al. The impact of exercise training on conduit artery wall thickness and remodeling in chronic heart failure patients. Hypertension. 2001;57(1):56-62.
17. Borry P, Schotsmans P, Dierickx K. Evidence-based medicine and its role in ethical decision-making. J Eval Clin Pract. 2006;12:306-11. DOI: 10.1111/j.1365-2753.2006.00548.x.
18. Schulz KF. Unbiased research and the human spirit: the challenges of randomized controlled trials. CMAJ. 1995;153(6):783-6.
19. Day SJ, Altman DG. Statistcs notes: bliding in clinical trials and other studies. BMJ. 2000;321(7259):504. oi: https://doi.org/10.1136/bmj.321.7259.504.
20. Altman DG, Schulz KF. Statistcs notes: concealing treatment allocation in randomised trials. BMJ. 2001;323:446-7. DOI: 10.1136/bmj.323.7310.446.
21. Altman DG, Bland, JM. Statistcs notes. Treatment allocation in randomised trials: why randomise? BMJ. 1999;18:1209. doi: https://doi.org/10.1136/bmj.318.7192.1209.
22. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, et al. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail. 2012;5(5):579-85.
23. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43:1334-59. doi: 10.1249/MSS.0b013e318213fefb.
24. Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. Circulation. 2000;101(7):828-33.
25. Volaklis KA, Tokmakidis SP. Resistance exercise training in patients with heart failure. Sports Med. 2005;35(12):1085-103.