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Geovana de Almeida Righi

COMBINAÇÃO DE TREINO AERÓBICO E DE FORÇA EM PACIENTES COM INSUFICIÊNCIA CARDÍACA: META-ANÁLISE E META-REGRESSÃO

Santa Maria, RS
2019

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Dissertação apresentada ao **Programa de Pós-Graduação em Reabilitação Funcional** da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para obtenção do título de **Mestre em Reabilitação Funcional.**

Orientador: Prof. Dr. Antonio Marcos Vargas da Silva
Co-orientador: Prof. Dr. Felipe Barreto Schuch
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Santa Maria, RS
2019

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“Há 5 tipos de pessoas que você deve apreciar:

- As que se preocupam com você;

- As que te corrigem;

- As que ficam nos momentos bons e ruins;

- As que querem te ver bem;

- As que te dizem a verdade”.

Mãe e Pai, estes dois anos foram intensos. Nos momentos difíceis vocês sempre se fizeram presente. É incrível como vocês apoiam e fazem de tudo para que nossos sonhos, meus e do Migui, se realizem. Vocês vibram conosco, mesmo que isso custe momentos longe de vocês, como quando decidimos fazer intercâmbio. Vocês fizeram nosso caráter e perfil para que fossemos pessoas capazes de praticar o bem e de fazer escolhas sábias na vida, bem como assumir elas e arcar com as consequências. Independente da escolha que fizermos, eu sei que se estivermos felizes, vocês estarão também. ***As que querem te ver bem;***

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RESUMO

COMBINAÇÃO DE TREINO AERÓBICO E DE FORÇA EM PACIENTES COM INSUFICIÊNCIA CARDÍACA: META-ANÁLISE E META-REGRESSÃO

AUTORA: Geovana de Almeida Righi
ORIENTADOR: Prof. Dr. Antonio Marcos Vargas da Silva
CO-ORIENTADOR: Prof. Dr. Felipe Barreto Schuch

Pacientes com insuficiência cardíaca (IC) tendem a apresentar dispneia, fadiga e diminuição da tolerância ao exercício, alterações que repercutem na qualidade de vida. O treino aeróbico (TA) em combinação com o treino de força demonstrou ser benéfico para VO_2 pico e força muscular quando comparado a um grupo controle. Ao comparar o treino combinado (TC), definido pela associação de treino de força com o TA, padrão-ouro para tratamento não farmacológico desta população, os resultados são controversos e maiores elucidações se fazem necessárias devido a limitações presentes em revisões prévias como classificação inadequada de estudos, não exploração da heterogeneidade, baixa sensibilidade de pesquisa, algumas com baixo número de artigos incluídos e etc. O objetivo do estudo foi revisar sistematicamente os efeitos do TC *versus* TA ou controle sobre capacidade funcional, medida pelo VO_2 pico, e força muscular de quadríceps. Utilizou-se as bases de dados Pubmed/MEDLINE, EMBASE, Cochrane CENTRAL, PEDro, SPORTDiscus e Lilacs. Foram incluídos ensaios clínicos randomizados com indivíduos com IC, que compararam os efeitos do TC *versus* TA ou controle no VO_2 pico e força muscular de quadríceps. Foram incluídos 28 artigos, divididos em quatro análises. O TC aumentou VO_2 pico e força muscular de quadríceps em comparação com o controle. O TC foi similar ao TA na melhora do VO_2 pico, porém com melhores efeitos sobre a força de quadríceps. Não houve diferenças entre modalidades de TA. Baixo número de estudos incluídos, falta de consenso e descrição detalhada dos protocolos de reabilitação dificultaram maiores especulações por parte das análises de subgrupo e meta-regressão. TC melhora capacidade funcional e força muscular, porém não difere do TA quanto à melhora no VO_2 pico. O treino de força deve ser encorajado nos programas de reabilitação cardíaca, porém quando inviável, o TA pode ser realizado isoladamente visando o aumento de capacidade funcional.

Palavras-chave: insuficiência cardíaca, exercício, reabilitação cardíaca.

ABSTRACT

COMBINATION OF AEROBIC AND STRENGTH TRAINING IN PATIENTS WITH HEART FAILURE: META-ANALYSIS AND META-REGRESSION

AUTHOR: Geovana de Almeida Righi
ADVISOR: Prof. Dr. Antonio Marcos Vargas da Silva
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Patients with heart failure (HF) tend to present dyspnea, fatigue and decreased exercise intolerance, changes that affect quality of life. Isolated aerobic training (AT) in combination with strength training has been shown to be beneficial for VO_2 peak and muscle strength when compared to a control group. When comparing the combined training (CT), defined by the association of strength training with AT, gold standard for non-pharmacological treatment of this population, the results are controversial and more elucidations are necessary due to limitations present in previous reviews such as inadequate classification of studies, non-exploration of heterogeneity, low sensitivity of research, some reviews with low number of included articles and etc. The objective of the study was to systematically review the effects of CT *versus* AT or control on functional capacity, by the measurement of VO_2 peak, and quadriceps muscle strength. The databases Pubmed/MEDLINE, EMBASE, Cochrane CENTRAL, PEDro, SPORTDiscus and Lilacs were used. Randomized clinical trials with subjects with HF were included, who compared the effects of CT *versus* AT or control on VO_2 peak and quadriceps muscle strength. We included 28 articles, divided into four analyzes. The CT increased VO_2 peak and quadriceps muscle strength compared to the control. CT was similar to TA in improving VO_2 peak but with better effects on quadriceps strength. There were no differences between AT modalities. Low number of studies included, lack of consensus and detailed description of rehabilitation protocols made it more difficult to speculate on subgroup and meta-regression analyzes. CT improves functional capacity and muscle strength, but does not differ from AT for improvement in VO_2 peak. Strength training should be encouraged in cardiac rehabilitation programs, but when infeasible, AT can be performed in isolation to increase functional capacity.

Palavras-chave: Heart Failure; Exercise; Cardiac Rehabilitation.

SUMÁRIO

1 INTRODUÇÃO

A insuficiência cardíaca (IC) é a doença cardiovascular de crescimento mais rápido mundialmente. É um problema de saúde pública global e está associada ao aumento da mortalidade e morbidade. Estima-se uma prevalência de mais de 37,7 milhões de casos no mundo (VOS et al., 2012). Aproximadamente 80% dos casos de doença cardíaca ocorrem em países de baixa e média renda (ZIAEIAN; FONAROW, 2016). Há relatos de que a mortalidade total por IC está diminuindo em todas as regiões do Brasil, porém os autores atribuem esse resultado a falta de qualidade das informações coletadas (GAUI; OLIVEIRA; KLEIN, 2014).

A IC é caracterizada pela diminuição do débito cardíaco (DC) (ROGERS; BUSH, 2015). As alterações hemodinâmicas, como aumento da pressão venosa sistêmica, estão entre as principais causas de alteração do DC, levando a inadequada perfusão tecidual (BOCCHI et al., 2009). As alterações dos níveis glicêmicos também causam lesões nos vasos cardíacos e em consequência diminuição do fluxo sanguíneo e função miocárdica. No caso das doenças coronarianas, as placas de aterosclerose impedem ou obstruem a passagem sanguínea levando a hipóxia, que é caracterizada pelo desequilíbrio entre a demanda e a oferta de oxigênio no músculo cardíaco (ROGERS; BUSH, 2015; YANCY et al., 2013). Os principais fatores de risco para o desenvolvimento da IC são: hipertensão, diabetes mellitus, doença coronariana, obesidade, dislipidemia e tabagismo (ROGERS; BUSH, 2015). A principal alteração decorrente desses processos fisiopatológicos envolvidos na IC é o enfraquecimento do miocárdio, incapaz de atender às demandas metabólicas (ROGERS; BUSH, 2015). Inicialmente o comprometimento do DC pode ser é visto apenas durante o exercício, ao passo que a doença progride é possível evidenciar esforço durante o repouso (BOCCHI et al., 2009).

Congestão pulmonar, anemia, aumento da resistência pulmonar, fadiga de diafragma e musculatura periférica são fatores responsáveis pela dispneia e intolerância ao exercício nesta população (TANAI; FRANTZ, 2015). A atrofia muscular é muito comum, com redução das fibras do tipo I (contração lenta, para exercícios de longa duração), enquanto ocorre a hiperplasia das fibras do tipo II (contração rápida, para exercícios de curta duração), mas com hipotrofia das mesmas. Além disso, há redução de enzimas aeróbicas e aumento de enzimas glicolíticas. Essas alterações indicam uma mudança do metabolismo aeróbico para o anaeróbico, que resulta no início precoce da fadiga e intolerância ao exercício (OKITA; KINUGAWA; TSUTSUI, 2013). A intolerância ao exercício é quantificada pelo teste cardiopulmonar, importante medida para avaliar grau de comprometimento cardíaco e otimizar o tratamento do paciente com IC. A medida de VO_2 pico representa os limites do sistema cardiopulmonar (MYERS et al., 2015) e se mostrou associada com prognóstico de pacientes com IC candidatos ao transplante cardíaco. Em estudo clássico, aqueles que obtiveram um VO_2 pico ≤ 14 ml/kg/min no teste cardiopulmonar apresentaram taxa de sobrevida de 47% a 32% em dois anos comparado a 84% a 94% dos que apresentaram VO_2 pico > 14 ml/kg/min (MANCINI et al., 1991).

O tratamento do paciente com IC é baseado em duas linhas, farmacológica e não farmacológica. As terapias não farmacológicas compreendem educação, suporte social, restrição ao sódio, tratamento de desordens do sono, tratamento para perda de peso e reabilitação cardíaca. O exercício físico regular é recomendado para melhora da funcionalidade, sendo a reabilitação cardíaca uma estratégia segura para melhora da capacidade funcional, tolerância ao exercício (AUSTIN et al., 2005, 2008), qualidade de vida (DAVIES et al., 2010; SAGAR et al., 2015) e diminuição da mortalidade (PIEPOLI et al., 2004; SAGAR et al., 2015) e número de hospitalizações (DAVIES et al., 2010; PIEPOLI et al., 2004).

O exercício físico, de forma geral, é responsável por diversas modificações, como: melhora da função cardíaca, função endotelial, muscular e diminuição do processo inflamatório (MANDIC et al., 2012). O exercício aeróbico foi a primeira modalidade de treinamento físico a ser investigada em pacientes com IC, capaz de aumentar tempo de exercício e VO_2 pico (COATS et al., 1990). Além disso, melhorias na função ventricular esquerda também foram observadas, resultante de reduções na resistência vascular sistêmica (HAMBRECHT et al., 2000). O treino aeróbico de moderada intensidade, entre 40 a 70% do VO_2 pico, é recomendado para pacientes com IC (SELIG et al., 2010). Outra alternativa de tratamento que vem ganhando destaque é o treino intervalado de alta intensidade (HIIT), o qual demonstrou, em pacientes com IC, melhora da capacidade aeróbica (HAYKOWSKY et al., 2013), função endotelial e qualidade de vida em comparação ao treino de moderada intensidade (WISLOFF et al., 2007).

O treino de força é indicado para minimizar a perda de massa muscular, visto que essa variável é preditora independente de prognóstico em pacientes com IC (CICOIRA et al., 2001). Nesse sentido, o treino de força pode ser superior ao treino aeróbico para evitar atrofia muscular (BRAITH; STEWART, 2006). Em comparação ao grupo controle, o treino de força isolado foi capaz de melhorar capacidade aeróbica e força (SELIG et al., 2004). As modalidades recomendadas para esta população compreendem treinamento com peso em circuito, com o peso do corpo ou com elásticos. (MANDIC et al., 2012). Sugere-se que esse treino seja incorporado ao treino aeróbico, com o objetivo de otimizar o tratamento da IC (SELIG et al., 2010).

O TC apresenta inúmeros benefícios para os pacientes com IC, como aumento do VO_2 pico, FEVE, melhora da função endotelial e estresse oxidativo, aumento de força e resistência muscular (MANDIC et al., 2012). Quando comparado com grupo controle, o TC foi capaz de melhorar função física e qualidade de vida (GARY et al., 2011; OKA et al., 2000), VO_2 pico, função endotelial e força muscular (MAIORANA et al., 2000a, 2000b).

Diversos ensaios clínicos demonstram os efeitos do TC em comparação com o TA. O TC parece apresentar aumentos superiores ao TA no VO_2 pico (AGAPITOU et al., 2017; DELAGARDELLE et al., 2002) e força muscular (AGAPITOU et al., 2017; BARNARD et al., 2000; BECKERS et al., 2008; BOUCHLA et al., 2011; DEGACHE et al., 2007; DELAGARDELLE et al., 2002; MANDIC et al., 2009). Em relação ao desfecho VO_2 pico, o resultado dos dois estudos citados anteriormente são controversos em relação à maioria dos estudos publicados, que demonstraram não haver diferença entre os grupos (ANAGNOSTAKOU et al., 2011; BECKERS et al., 2008; BOUCHLA et al., 2011; GEORGANTAS et al., 2014; MANDIC et al., 2009; TZANIS et al., 2017).

Revisões sistemáticas conduzidas anteriormente investigaram os efeitos do TC sobre o VO_2 pico e apresentam limitações no que diz respeito a sensibilidade da estratégia de pesquisa, não definição dos grupos que foram estudados, algumas com baixo número de artigos incluídos, necessitam de atualização, todas abrangem um leque de modalidades de treino, sem foco específico em TC e não utilizaram de análises adicionais para explicar as altas heterogeneidades encontradas (CORNELIS et al., 2016; JEWISS; OSTMAN; SMART, 2016; SANTOS et al., 2018). A primeira incluiu apenas três estudos na análise TC *versus* TA, um deles considerou treino muscular inspiratório como TC, nenhuma diferença foi encontrada (CORNELIS et al., 2016). A segunda, na comparação TC *versus* controle, com dez artigos na análise, incluiu estudo com pacientes com IC e comorbidades associadas. Na comparação TC *versus* TA, inclusão de apenas seis estudos, sem diferença entre os grupos. Esta foi a única revisão que realizou análise de risco de publicação para estas comparações (JEWISS; OSTMAN; SMART, 2016). A terceira e última, quando comparado TC e controle, 13 estudos foram incluídos, dois ensaios clínicos não randomizados. TC *versus* TA, oito estudos incluídos, dentre eles um que considerou treino muscular inspiratório como TC (SANTOS et al., 2018). Em relação a força muscular, apenas uma revisão foi conduzida até o momento, incluiu apenas quatro estudos, não diferenciou força muscular de membros superiores e membros inferiores e formas de avaliação (WANG et al., 2019)

Assim, destaca-se a nossa questão de pesquisa: o TC é capaz de melhorar o VO_2 pico e força muscular em comparação ao controle e/ou ao TA, padrão-ouro de tratamento não farmacológico, em pacientes com IC? Quais seriam os possíveis moderadores do efeito do exercício?

Esta dissertação foi estruturada em cinco partes. A primeira, destinada à introdução geral e revisão de literatura; a segunda, ao artigo científico formatado conforme normas do periódico ao qual será submetido; a terceira, às conclusões do estudo; a quarta, ao referencial bibliográfico utilizado, e a quinta, aos apêndices e anexos do estudo.

O artigo científico será apresentado segundo as normas do periódico JACC Heart Failure (ANEXO A), com Fator de Impacto 8.202 definido pela Thompson Reuters.

2 ARTIGO CIENTÍFICO

TITLE PAGE

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COMBINATION OF AEROBIC AND STRENGTH TRAINING IN PATIENTS WITH HEART FAILURE: META-ANALYSIS AND META-REGRESSION

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COMBINED TRAINING IN HEART FAILURE: META-ANALYSIS

The authors report that they have no conflict of interest.

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ABSTRACT

OBJECTIVES: To compare the effects of combined training (CT) *versus* aerobic training (AT) or *versus* control group on VO_2 peak and quadriceps muscle strength.

BACKGROUOND: AT is a fundamental part of cardiac rehabilitation for patients with heart failure (HF), and the CT may confer additional benefits. However, previous reviews comparing CT *versus* AT has some inconsistencies.

METHODS: Major electronic databases PubMed/MEDLINE, EMBASE, Cochrane CENTRAL, PEDro, SPORTDiscus e Lilacs were searched, without year restraint until August 2018. Randomized clinical trials comparing the effects of CT against AT or control on VO_2 peak and/or quadriceps muscle strength were included. Random effects meta-analyses, calculating the standardized mean difference (SMD) for each outcome and comparison group (AT or control), were conducted. Heterogeneity was tested and, whenever significant, was explored with subgroup and meta-regression analysis.

RESULTS: A total of 28 articles were included (1306 subjects, 69.5% men, median age 57.4, median LVEF 30.9%). An increase on VO_2 peak (SMD = 0.77, 95%CI 0.39 to 1.14, I^2 = 80.1%) and quadriceps muscle strength (SMD = 0.67, 95%CI 0.18 to 1.16, I^2 = 0%) was found in CT compared to control. CT increased quadriceps muscle strength, as expected, *versus* AT (SMD = 0.44, 95% CI 0.15 to 0.74, I^2=0%). No differences between CT and AT on VO_2 peak were founded (SMD = 0.16, 95% CI -0.06 to 0.37, I^2 = 0%).

CONCLUSIONS: CT promotes additional gains on muscular strength and VO2 peak, however when compared with AT, only muscular strength improved. Longer time of session and length of training are associated with greater benefits on aerobic capacity.

ABBREVIATIONS LIST

HF	Heart Failure
AT	Aerobic training
CT	Combined training
ES	Effect size
SMD	Standardized mean difference
CI	Confidence intervals
LVFE	Left ventricular fraction of ejection
1RM	One maximal repetition

INTRODUCTION

Cardiac rehabilitation is indicated for patients with cardiovascular diseases. It is composed of non-pharmacological interventions based on a multi-professional team evaluation (1). It is recommended for patients with stable heart failure (HF) to improve quality of life (2,3), decrease mortality (2), number of hospitalizations (2–4), hospitalization time (5) and increase functional capacity and exercise tolerance (5,6).

Traditionally, aerobic training (AT) consists the main focus of rehabilitation, being continuous moderate training on treadmill or bicycle, the most recommended prescription (7). Systematic review has demonstrated that patients with HF undergoing moderate continuous training, when compared to a control group, improve exercise capacity, being this result dependent on the frequency, duration of the session and treatment and intensity (8).

Strength exercises are also highlighted in cardiac rehabilitation programs. When compared to a control group, the isolated strength training was able to increase the distance in the 6-minute walk test (9,10) and VO_2 peak (11) in patients with HF.

The combination of these two trainings (aerobic and strength), defined as combined training (CT), has been widely studied in HF patients. When comparing this modality with a control group, CT demonstrates to improve VO_2 peak and muscle strength (12). Previous systematic reviews evidenced the benefit of CT over the control group on VO_2 peak (11,13,14), and calculated the magnitude of the effects, however, some reviews included of non-randomized clinical trials (11), studies that evaluated VO_2 peak indirectly (14), as well as, studies with HF patients and multiple comorbidities such as sleep apnea (13) which might introduce some bias on the effect estimative. In addition, the reviews have found high heterogeneity on their analyzes that were not fully explored or explained.

AT is a fundamental part of cardiac rehabilitation for patients with HF (15). Previous systematic reviews have compared several training modalities on VO_2 peak for patients with HF (9,11,13,16), none with focus in CT. Some shortcomings in the reviews cited above as low sensitivity of the research (9,13,16) and lack of definition of the intervention group and comparison (inclusion of inspiratory muscle training as part of the CT) (11,16) were founded.

Regarding muscle strength, there is one review which compared CT against control (14), which did not differentiate methods of assessing muscle strength and upper and lower limb muscle strength, including only four studies.

The objectives of this systematic review were to: 1) update the literature, considering the shortcomings of previous reviews comping the effects of CT against AT or control group on VO_2 peak and quadriceps muscle strength; 2) explore moderators through meta-regression and subgroup analysis that could impact the effects of exercise, including sample characteristics and exercise intervention variables; 3) evaluate the presence of publication bias, and to adjust the effect whenever.

METHODS

Systematic review of randomized clinical trials, conducted in compliance with the recommendations of PRISMA (17) and Cochrane Handbook (18), registered in the PROSPERO database under number CRD42018105764.

ELIGIBILITY CRITERIA

We included studies that: 1) included participants of all ages, with a diagnosis of HF; 2) had one arm CT (aerobic and strength); 3) compared CT with AT or control; 4) have assessed VO_2 peak or quadriceps muscle strength as outcomes; 5) were randomized controlled trials. We did not include studies that: 1) evaluated only acute effects of exercise; 2) included patients with heart transplantation, cardiac pacemaker or sleep apnea; 3) used of inspiratory muscle training as a combined treatment; 4) evaluated VO_2 peak indirectly; 5) theses and dissertations.

AT was defined as repetitive exercises over an extended period that produce dynamic contractions of various muscle groups, such as walking, running, pedaling. To be considered physical exercise and not physical activity, it should contain two of the following parameters: frequency, intensity and time (19). Strength training was defined as a method of muscle strengthening or conditioning that involves the use of resistance with the goal of increasing strength, power, endurance and muscle mass, and includes both isometric contraction and isotonic contraction, eccentric or concentric (20,21). Resistance protocols involving free weights, body weight, elastic bands and weight machines were considered. CT is the join of AT with strength training. The control group was defined as none of the interventions mentioned above, usually consisting of drug therapy and patient education.

SOURCES OF DATA

Search strategy were performed in the following databases: PubMed/MEDLINE, EMBASE, Cochrane CENTRAL, PEDro, SPORTDiscus e Lilacs, from inception to 20th August 2018.

SEARCH STRATEGY

The term "participant" and "intervention" of the "PICO" model was used for the research strategy, without including "comparison" or "outcome", in order to maximize sensitivity. The search combined words based on the PubMed/MEDLINE database search strategy. For the term "participant": *heart failure, heart diseases, cardiomyopathy, coronary disease*. For the term "intervention": *rehabilitation, cardiac rehabilitation, exercise therapy, resistance training, exercise, resistance exercise, physical endurance, progressive resistance training, concurrent training, concurrent strength.* In addition, the terms *animals, rat, mice* were excluded. The search was performed without restriction of year of publication or language. The full strings can be seen on Appendix A.

DATA EXTRACTION

Two reviewers (GAR and TT) independently analyzed articles by title and abstract, and then read the full text. Were extracted from eligible studies: publishing details (author, year, journal, country), study methodology (sample characterization and size, description group intervention and comparison; professionals who oversaw the training, characteristics of intervention of treatment, including frequency, intensity, time and modality), loss data, and outcomes (mean and standard deviation). Any disagreement between the reviewers was resolved by consensus and, if necessary, by a third reviewer (AMVS). To solve the lack of information of extracted data, we contact the authors. In case of overlapping (articles reporting outcome data from the same trial) we included only one with the largest sample size and most recent published.

The lists of references of the articles included and of previous revisions were verified with intention to recover all the relevant documents (9,11,13,14,16). The corresponding author of each unpublished study was contacted for missing information or data, and was performed once a week for three consecutive weeks.

RISK OF BIAS ASSESSMENT

We considered low risk of bias those studies who had adequate allocation concealment AND analysis of outcome data according to intention-to-treat principles AND have blinding of outcome assessors (22).

META-ANALYSIS

Statistical analysis was conducted by the *Comprehensive Meta-Analysis software* (CMA; Version 3, Biostat, Englewood, New Jersey). We pooled the studies using a random model effect. The effect size (ES) estimation was calculated through the standardized mean differences (SMD) and 95% confidence intervals (IC). The heterogeneity was calculated by Cochran Q and I-squared (I^2) (18) and an $\alpha < 0.05$ was be considered statistically significant and an I^2 test with values higher than 50% were indicative of high heterogeneity. Meta-regression and subgroup analysis were conducted, testing potential moderators, selected a-priori, according to the previous literature. Sex, age, body mass index, left ventricular ejection fraction (LVFE), frequency, duration and time of session were analyzed through meta-regression. Modality and intensity of exercise, qualification of professional supervising the exercise sessions, group or individual, by subgroup analysis. The publication bias was trough inspection of the funnel plot and the Egger regression test method (23) and the Begg-Mazumdar Kendall´s Tau test (24). When detected the presence of potential publication bias, we applied the Duval and Tweedie (25). The fail-safe of number of negative studies that would require to nullify the ES was calculated.

RESULTS

SEARCH RESULTS

A total of 2605 articles were identified. Of these, 252 articles were read on full text stage, and 11 were included in analysis of CT *versus* AT and 19 in analysis of CT *versus* control (Fig 1). Previous reviews and list of references of included studies were reviewed, details of reasons for exclusion are summarized in Table 1.

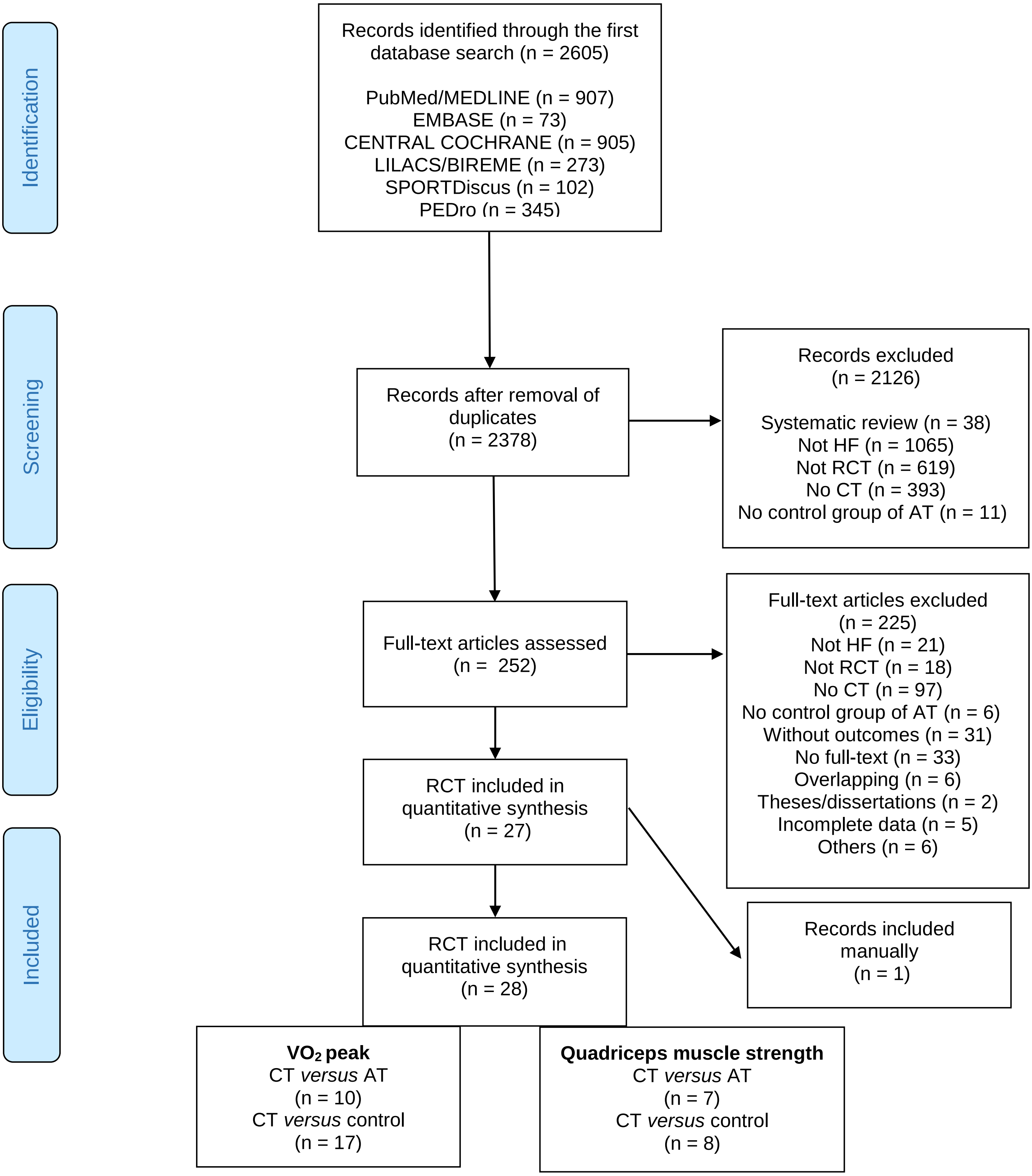


Fig. 1. Flowchart of studies selection

Table 1. Reasons for exclusion of articles

Articles	Reason	Revisions that included
Servantes, 2012	Patients with sleep apnea	Wang, 2019; Jewiss, 2016
Agiboye, 2015	Indirect measure of VO_2 peak	Wang, 2019
Andersen, 2006	Same trial published by Jónsdóttir, 2005	Jewiss, 2016
Williams, 2007	Circuit resistance training	Jewiss, 2016
Sabelis, 2004	Same trial published by Senden, 2005	Santos, 2019
Stolen, 2003	Non-randomized CT	Santos, 2019
Groehs, 2015	Non-randomized CT	Santos, 2019
Laoutaris, 2013	CT with inspiratory muscle training	Santos, 2019
Adamopoulos, 2014	CT with inspiratory muscle training	Cornelis, 2016
Maiorana, 2000	Incomplete outcome data	-
Pozehl, 2003	Incomplete outcome data	-
Scheffers, 2004	Aerobic training was extended only to patients who achieved better physical condition	-
Whitam, 2012	Incomplete outcome data	-
Kaltsatou, 2014	Different AT between groups	-
Evangelista, 2006	RT added after 6 weeks of AT	-
Reeves, 2017	Decompensated acute HF	-
Santos, 2010	Incomplete outcome data	-

CHARACTERISTICS OF INCLUDED TRIALS AND PARTICIPANTS

The total sample size accounted in our analysis were 1306 individuals (69.5% men, median age 57.4, median LVEF 30.9%), of these 367 in comparison of CT *versus* AT, 939 were included in the analysis of CT *versus* control. One study contained all patients with HF and preserved ejection fraction (NOLTE, 2014). Full details of studies characteristics can be found in Table 2.

Table 2. Summary of included studies in CT *versus* AT and CT *versus* control analysis

Study CT *versus* AT	Duration (month)	Frequency (week)	NYHA	Participants	Combined training	Aerobic training	Outcomes	Assessment	Dropouts
Barnard, 2000	2	3	?	Congestive HF **CT** (n=14, ♂ 100%, mean age 60.3, LVEF 25%) **AT** (n=7, ♂ 100%, mean age 55.4, LVEF 22.9%)	30min **AT:** continuous, 60 - 80% HRmax **ST:** progressive**,** 60 - 80% 1RM	30min Continuous, 60 - 80% HRmax	Quadriceps muscle strength	1RM	**CT:** 2 **AT:** 0
Beckers, 2008	6	3	II, III	CHF **CT** (n=28, ♂64%, mean age 58, LVEF 26%) **AT** (n=30, ♂ 80%, mean age 59, LVEF 23%)	60 min **AT:** continuous, 90% HR achieved at anaerobic threshold **ST:** progressive, 50 - 60% 1RM	60min Continuous, 90% HR achieved at anaerobic threshold	VO_2 peak, quadriceps muscle strength	CPT, 1RM	**CT:** 0 **AT:** 0
Bouchla, 2011	4	3	I, II, III	CHF **CT** (n=10, ♂ 70%, mean age 56.7, LVEF 33.4%) **AT** (n=10, ♂ 90%, mean age 50.5, LVEF 37.8%)	40min **AT:** interval, 50% peak WR on SRT **ST:** progressive, 55 - 65% 2RM	40min Interval, 50% peak WR on SRT	VO_2 peak, quadriceps muscle strength	CPT, 2RM	**CT:** 0 **AT:** 0
Georgantas, 2014	4	3	I, II, III	CHF **CT** (n=22, ♂ 72%, mean age 55, LVEF 35%) **AT** (n=20, ♂ 95%, mean age 53, LVEF 34%)	40min **AT:** interval, 50% peak WR on SRT **ST:** progressive, 55 - 65% 2RM	40min Interval, 50% peak WR on SRT	VO_2 peak	CPT	**CT:** 6 **AT:** 7
Anagnostakou, 2011	3	3	I, II, III	CHF **CT** (n=14, ♂ 86%, mean age 54, LVEF 39%) **AT** (n=14, ♂ 79%, mean age 52, LVEF 36%)	40min **AT:** interval, 50% peak WR on SRT **ST:** 55 - 65% 2RM	40min Interval, 50% peak WR on SRT	VO_2 peak, quadriceps muscle strength	CPT, 2RM	**CT:** 4 **AT:** 5
Mandic, 2009	3	3	I, II, III	CHF **CT** (n=15, ♂ 73%, mean age 59, LVEF 33.4%) **AT** (n=14, ♂ 79%, mean age 63, LVEF 30.1%)	**AT:** continuous, 50 - 70% HHR, Borg 11 - 14/20 **ST:** progressive, 50 - 70% 1RM	30min Continuous, 50 - 70% HRR, RPE 11 - 14/20	VO_2 peak, quadriceps muscle strength	CPT, 1RM	**CT:** 0 **AT:** 0
Tasoulis, 2010	3	3	I, II, III	CHF **CT** (n=25, ♂ 76%, mean age 53, LVEF 35.6%) **AT** (n=21, ♂ 90%, mean age 53, LVEF 34.1%)	40min **AT:** interval, 50% do baseline **ST:** 55 – 65% 2RM	40min Interval, 50% of baseline SRT	VO_2 peak	CPT	**CT:** 0 **AT:** 0
Tzanis, 2017	3	3	I, II, III	CHF **CT** (n=7, ♂ 100%, mean age 53, LVEF 38%) **AT** (n=6, ♂ 100%, mean age 47, LVEF 37%)	**AT:** interval, 3min 50% VO_2 peak, 4min 80% VO_2 peak **ST:** progressive, 60 - 70% 1RM	31min Interval, 3min 50% VO_2 peak, 4min 80% VO_2 peak	VO_2 peak, quadriceps muscle strength	CPT, 1RM	**CT:** 0 **AT:** 0
Feiereisen, 2007	3	3	II, III	CHF **CT** (n=15, ♂ 87%, mean age 60.6, LVEF 23%) **AT** (n=15, ♂ 73%, mean age 59.4, LVEF 25%)	45min **AT:** continuous, 60% - 75% VO_2 peak **ST:** progressive, 60% - 70% 1RM	45min Continuous, 60% - 75% VO_2 peak	VO_2 peak	CPT	**CT:** 0 **AT:** 0
Keast, 2013	3	**3**	**CT:** III **AT:** II, III	Moderate to severe HF **CT** (n=27, ♂ 81%, mean age 62.8, LVEF 26.3%) **AT** (n=27, ♂ 81%, mean age 62.1, LVEF 27.6%)	60min **AT:** continuous, 60 - 70% HRR **ST:** ?	60min Continuous, 60 - 70% HRR	VO_2 peak	CPT	**CT:** 5 **AT:** 6
Agapitou, 2017	3	3	I, II, III	CHF **CT** (n=16, ♂ 94%, mean age 52, LVEF 32%) **AT** (n=10, ♂ 90%, mean age 53, LVEF 30%	40min AT: interval, 50% peak WR on SRT ST: 55-65% 2RM	40min Interval, 50% peak WR on SRT	VO_2 peak, quadriceps muscle strength	CPT, 2RM	**CT:** 0 **AT:** 0

Study CT *versus* control	Duration (month)	Frequency (week)	NYHA	Participants	Combined training	Outcomes	Assessment	Dropouts
Oka, 2005	3	2-3	II	HF Mean age 60 **CT** (n=12) **C** (n=12)	40-60min **AT:** continuous, 70% HRmax **ST:** progressive, free weights	VO_2 peak	CPT	**CT:** 0 **C:** 0
Roveda, 2003	4	3	II, III	Advanced HF Mean age 53 **CT** (n=7, ♂ 71%, LVEF 35) **C** (n=9, ♂ 67%, LVEF 35)	60min **AT:** continuous and interval, HR corresponded to anaerobic threshold up to 10% below the respiratory compensation point on CPT **ST:** 10 min local exercises	VO_2 peak	CPT	**CT:** 0 **C:** 0
Senden, 2005	6	4	?	CHF Mean age 59.8 **CT** (n=25, ♂ 80% LVEF 29) **C** (n=36, ♂ 69%, LVEF 26)	11min at home, 60min at ambulatory **AT:** continuous, 50% peak WR on SRT, 70% HRmax (5BX protocol) **ST:** progressive, 5BX protocol	VO_2 peak, quadriceps muscle strength	CPT, hand dynamometer	**CT:** 8 **C:** 8
Jonsdottir, 2005	5	2	II, III	CHF **CT** (n=21, ♂ 76%, mean age 68, LVEF 41.5) **C** (n=22, ♂ 82%, mean age 69, LVEF 40.6)	**AT:** continuous, 50% W peak **ST:** progressive, 20 - 25% 1RM, 35 - 40% 1RM	VO_2 peak, quadriceps muscle strength	CPT, 1RM	**CT:** 0 **C:** 2
Drakup, 2007	3	3-4	II, III, IV	HF **CT** (n=87, ♂ 73%, mean age 53.3, LVEF 26.7) **C** (n=86, ♂ 70%, mean age 54.6, LVEF 26.1)	**AT:** continuous, 60% HRmax **ST:** progressive, 80% 1RM	VO_2 peak	CPT	**CT:** 1 **C:** 1
Mckelvie, 2002	3	1-2	I, II, III	HF **CT** (n=90, ♂ 82%, mean age 64.8) **C** (n=91, ♂ 80%, mean age 66.1)	30min **AT:** continuous, 60 - 70% HRmax **ST:** progressive, 40 - 60% 1RM	Quadriceps muscle strength	1RM	**CT:** 10 **C:** 8
de Mello Franco, 2006	4	3	II, III	HF **CT** (n=17, ♂ 76%, mean age 56, LVEF 29) **C** (n=12, ♂ 75%, mean age 52, LVEF 27)	60min **AT:** continuous, HR corresponded to anaerobic threshold up to 10% below the respiratory compensation point on CPT **ST:** 10 min local exercises	VO_2 peak	CPT	**CT:** 2 **C:** 2
Stevens, 2015	3	2-3	I, II, III	CHF **CT** (n=15, ♂ 67%, mean age 66.6, LVEF 39) **C** (n=7, ♂ 86%, mean age 64.4, LVEF 35)	**AT:** interval, RPE 14 – 16/20 **ST:** progressive, 50 - 70% 1RM	VO_2 peak, quadriceps muscle strength	CPT, isokinetic dynamometer	**CT:** 3 **C:** 3
Fraga, 2007	4	3	II, III	CHF **CT** (n=15, ♂ 53%, mean age 57, LVEF 27) **C** (n=12, ♂ 75%, mean age 53, LVEF 26)	60min **AT:** continuous, HR corresponded to anaerobic threshold up to 10% below the respiratory compensation point on CPT **ST:** 10min local exercises	VO_2 peak	CPT	**CT:** 0 **C:** 0
Antunes, 2014	4	3	II, III	CHF **CT** (n=17, ♂ 77%, mean age 56, LVEF 28) **C** (n=17, ♂ 88%, mean age 54, LVEF 29)	60min **AT:** continuous, 60-72% do VO_2 peak **ST:** 10min local exercises	VO_2 peak	CPT	**CT:** 11 **C:** 11
Gary, 2012	3	2-3	II, III	HF	45-60min	Quadriceps	Handheld	**CT:** 0

				CT (n=12, ♂ 58%, mean age 59, LVEF 23) **C** (n=12, ♂, 42%, mean age 61, LVEF 27)	**AT:** 50 - 70% HRR on 6MWT **ST:** progressive, elastic bands, less than 15 (RPE)	muscle strength	dynamometer	**C:** 0
Chryshoou, 2015	3	3	I, II, III	CHF **CT** (n=33, ♂ 88%, mean age 63, LVEF 31) **C** (n=39, ♂ 72%, mean age 56, LVEF 32)	45min **AT:** interval, 80% - 100% W peak **ST:** progressive, 30-50-90% 1RM	VO_2 peak	CPT	**CT:** 17 **C:** 11
Meirelles, 2014	6	3	II, III	HF **CT** (n=15, ♂ 47%, mean age 54, LVEF 31.2) **C** (n=15, ♂47%, mean age 55, LVEF 31.7)	90min **AT:** continuous, 5 - 15% acima do limiar ventilatório **ST:** local exercises for major muscle groups	VO_2 peak	CPT	**CT:** 0 **C:** 0
Mandic, 2009	3	3	I, II, III	HF **CT** (n=15, ♂ 73%, mean age 59, LVEF 33.4) **C** (n=13, ♂ 77%, mean age 62, LVEF 27.8)	**AT:** continuous, 50 - 70% HRR, Borg 11 - 14/20 **ST:** progressive, 50 - 70% 1RM	VO_2 peak, quadriceps muscle strength	CPT, 1RM	**CT:** 2 **C:** 2
Evans, 2010	2	2-3	II, III, IV	CHF **CT** (n=37, ♂ 68%, mean age 69.8, LVEF 31.2) **C** (n=20, ♂ 70%, mean age 73.2, LVEF 30.7)	120min **AT:** continuous, 85% VO_2 peak on SWT **ST:** free weights	Quadriceps muscle strength	Isokinetic dynamometer	**CT:** 10 **C:** 3
Nolte, 2014	3	2-3	II, III	HFpEF **CT** (n=44, ♂ 55%, mean age 64, LVEF 68) **C** (n=21, ♂ 40%, mean age 65, LVEF 67)	**AT:** continuous, 50-70% VO_2 peak **ST:** 60-65% 1RM	VO_2 peak	CPT	**CT:** 2 **C:** 1
Safiyari, 2016	3	1-3	I, II, III	HF **CT** (n=20, ♂ 75%, mean age 57.8, LVEF 27.8) **C** (n=20, ♂ 70%, mean age 58.9, LVEF 26)	**AT:** interval, 40-50% off 80-85% on VO_2 peak **ST:** progressive, 40 - 75% 1RM	VO_2 peak	CPT	**CT:** 6 **C:** 5
Feiereisen, 2007	3, 3	3	II, III	CHF **CT** (n=15, ♂ 87%, mean age 60.6, LVEF 23) **C** (n=15, ♂ 87%, mean age 55.5, LVEF 25)	45min **AT:** continuous, 60% - 75% VO_2 peak **ST:** progressive, 60% - 70% 1RM	VO_2 peak, quadriceps muscle strength	CPT, isokinetic dynamometer	**CT:** 0 **C:** 0
Tzanis, 2017	3	3	I, II, III	CHF **CT** (n=7, ♂ 100%, mean age 53, LVEF 38%) **C** (n=13, ♂ 100%, mean age 53, LVEF 37%)	**AT:** interval, 3min 50% VO_2 peak, 4min 80% VO_2 peak **ST:** progressive, 60 - 70% 1RM	VO_2 peak	CPT	**CT:** 0 **AT:** 0

CT: combined training; AT: aerobic training; C: control; RCT: randomized controlled trial; CHF: chronic heart failure; SRT: steep ramp test; HR: heart rate; HRmax: maximum heart rate; HRR: HR reserve; W: work; WR: work rate; RM: maximum repetition; CPT: cardiopulmonary test; RPE: rated perceived exertion; HFpEF: heart failure with preserved ejection fraction; 6MWT: 6 minutes walking test.

RISK OF BIAS

Most studies were scored as having a low risk of bias for “Incomplete outcome data”. The unclear risk of bias predominated. Only two studies, in each comparison, were classified as low risk of bias. Full details of the quality of studies can be found in Table 3.

Table 3. Risk of bias of included studies in systematic review and meta-analysis concerting the effects of CT *versus* AT and CT *versus* control.

Study **CT *versus* AT**	Randomization	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Selective reporting	Other sources of bias
Barnard, 2000	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Beckers, 2008	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Bouchla, 2011	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Georgantas, 2014	Low	Unclear	Unclear	Low	High	Low	Unclear
Anagnostakou, 2011	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Mandic, 2009	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Tasoulis, 2010	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Tzanis, 2017	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Feiereisen, 2007	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Keast, 2013	Low	Low	Unclear	Low	Low	Unclear	Unclear
Agapitou, 2017	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study **CT *versus* control**							
Oka, 2005	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
Roveda, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Senden, 2005	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Jónsdóttir, 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Drakup, 2007	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
de Mello Franco, 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Stevens, 2015	High	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Fraga, 2007	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Antunes, 2014	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Koukouvou, 2004	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Gary, 2012	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Chryshoou, 2015	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear
Meirelles, 2014	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Mandic, 2009	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Evans, 2010	Low	Low	Unclear	Low	High	Unclear	Unclear
Nolte, 2014	Low	Low	Unclear	Low	Low	Unclear	Unclear
Safiyari-Hafizi, 2016	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Feiereisen, 2007	High	High	Unclear	Unclear	Low	Unclear	Unclear
Tzanis, 2017	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

“Low” (low risk of bias), “High” (high risk of bias) or “Unclear” (no information or uncertainty over the potential for bias).

MAIN ANALYSIS

CT *versus* AT

VO_2 peak

Data pooled from 10 studies (26–34) (AT n = 165, CT n = 176) showed no difference between the groups in VO_2 peak (SMD = 0.16, 95% CI -0.06 to 0.37, Q = 2.92, p = 0.145, I^2 = 0%) (Fig. 2). The Begg-Mazumdar Kendall´s Tau (-0.13, p = 0.591) and the Egger tests indicated no publication bias (intercept = -0.40, p = 0.653).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Beckers, 2008	0.192	0.263	0.069	-0.325	0.708	0.728	0.467
Bouchla, 2011	0.217	0.449	0.201	-0.662	1.096	0.484	0.629
Georgantas, 2014	0.280	0.310	0.096	-0.329	0.888	0.901	0.368
Anagnostakou, 2011	0.213	0.379	0.144	-0.530	0.956	0.562	0.574
Mandic, 2009	-0.030	0.408	0.167	-0.830	0.770	-0.074	0.941
Tasoulis, 2010	0.284	0.297	0.088	-0.299	0.867	0.953	0.340
Tzanis, 2017	-0.369	0.561	0.315	-1.468	0.731	-0.657	0.511
Feiereisen, 2007	0.130	0.366	0.134	-0.587	0.846	0.355	0.722
Keast, 2013	-0.060	0.272	0.074	-0.593	0.474	-0.219	0.826
Agapitou, 2017	0.525	0.410	0.168	-0.278	1.327	1.281	0.200
	0.159	0.109	0.012	-0.055	0.373	1.458	0.145

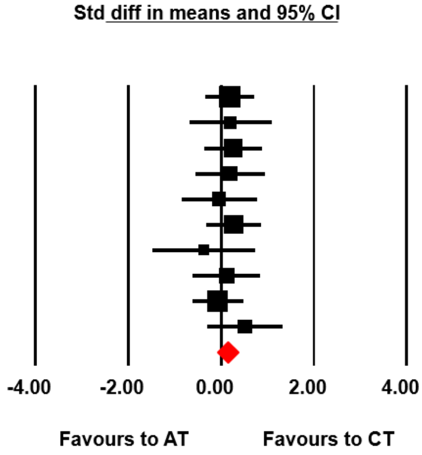


Figure 2. Effect of CT *versus* AT on VO_2 peak

Quadriceps muscle strength

Data pooled from 7 studies (26–29,31,35,36) (AT n = 96, CT n = 94) evaluating quadriceps muscle strength through 1RM (one maximal repetition) test showed a moderate significant improvement favoring CT (SMD = 0.44, 95% CI 0.15 to 0.74, Q = 4.12, p = 0.003, I^2 = 0%) (Fig. 3). The Begg-Mazumdar Kendall’s Tau (0.47, p = 0.133) and the Egger tests indicated no publication bias (intercept = 2.26, p = 0.080). The fail-safe number of additional negative studies required to nullify the significance of main analysis was 12 studies with negative results. Only one study use dynamometer to evaluate quadriceps muscle strength (SMD = 0.25, 95% CI -0.45 to 0.97, p = 0.480).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Barnard, 2000	0.981	0.487	0.237	0.027	1.936	2.014	0.044
Beckers, 2008	0.112	0.263	0.069	-0.403	0.628	0.428	0.669
Bouchla, 2011	0.740	0.462	0.214	-0.166	1.646	1.601	0.109
Anagnostakou, 2011	0.637	0.387	0.150	-0.123	1.396	1.643	0.100
Mandic, 2009	0.218	0.409	0.168	-0.584	1.021	0.533	0.594
Tzanis, 2017	0.368	0.561	0.315	-0.732	1.468	0.656	0.512
Agapitou, 2017	0.685	0.414	0.172	-0.127	1.497	1.654	0.098
	0.443	0.149	0.022	0.151	0.735	2.972	0.003

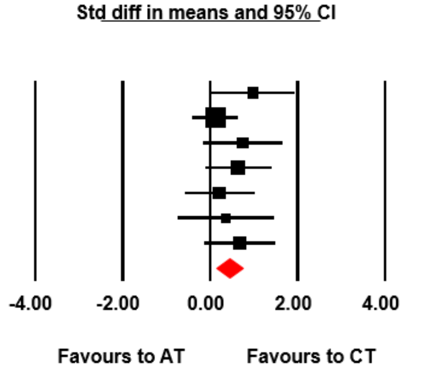


Figure 3. Effect of CT *versus* AT on quadriceps muscle strength evaluated by 1RM

CT *versus* control

VO_2 peak

Data pooled from 17 studies (32,34,35,37–50) (control n = 350, CT n = 368) showed a large significant improvement favoring CT in VO_2 peak (SMD = 0.77, 95%CI 0.39 to 1.14, Q = 80.7, $p < 0.01$, I^2 = 80.1%) (Fig.4). The Begg-Mazumdar Kendall’s Tau (0.35, p = 0.052) and the Egger tests indicated the presence of publication bias (intercept = 3.66, p = 0.004). Therefore, the ES was recalculated using Duval and Tweedie’s trim and fill method with three studies being adjusted a new ES of 1.001 (95% CI 0.58 to 1.42). The fail-safe number of additional negative studies required to nullify the significance of main analysis was 267 studies with negative results.

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Oka, 2005	0.122	0.409	0.167	-0.679	0.922	0.298	0.766
Roveda, 2003	1.977	0.613	0.376	0.775	3.179	3.224	0.001
Senden, 2005	0.290	0.262	0.068	-0.223	0.803	1.107	0.268
Jónsdóttir, 2005	-0.199	0.317	0.100	-0.820	0.423	-0.627	0.531
Drakup, 2007	0.072	0.152	0.023	-0.226	0.370	0.474	0.635
de Mello Franco, 2006	0.540	0.415	0.173	-0.274	1.354	1.301	0.193
Stevens, 2015	0.246	0.459	0.211	-0.655	1.146	0.535	0.593
Fraga, 2007	1.162	0.418	0.175	0.342	1.981	2.777	0.005
Antunes, 2014	0.732	0.354	0.126	0.037	1.426	2.065	0.039
Koukouvou, 2004	1.863	0.479	0.229	0.925	2.801	3.891	0.000
Chryshoou, 2015	0.892	0.248	0.061	0.406	1.378	3.597	0.000
Meirelles, 2014	7.210	1.000	1.000	5.250	9.170	7.211	0.000
Mandic, 2009	0.154	0.401	0.161	-0.632	0.940	0.384	0.701
Nolte, 2014	0.590	0.275	0.075	0.052	1.129	2.149	0.032
Safiyari-Hafizi, 2016	0.641	0.381	0.145	-0.106	1.388	1.682	0.093
Feiereisen, 2007	0.828	0.380	0.145	0.082	1.573	2.176	0.030
Tzanis, 2017	0.356	0.472	0.223	-0.569	1.281	0.754	0.451
	0.766	0.191	0.037	0.391	1.142	4.003	0.000

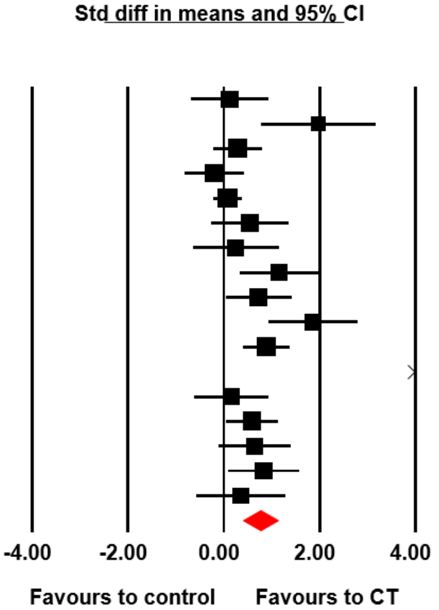


Figure 4. Effect of CT *versus* control on VO_2 peak

Due the high heterogeneity found, a subgroup analysis was performed and is presented in Table 4. There was no difference between modality of AT, however, continuous AT presents a large ES when compared to interval, but high heterogeneity. There is difference between the modality of strength training, progressive presents a moderate ES. Supervised and group session increase the effect size, but no difference between the subgroups.

Duration of rehabilitation and time of session alone moderate the effect of CT on VO_2 peak. When both are added in the model of regression, only time of session (β = 0.0869, 95% IC 0.01 to 0.16, p = 0.031) moderate the effect. Meta-regression is present in Table 5.

Table 4. Subgroup meta-analysis in all studies - CT *versus* control on VO_2 peak

Analysis	Number of RCTs	Meta-analysis				Heterogeneity
		SMD	95% IC		P value	
Main analysis	17	0.76	0.03	1.14	<0.001	80.1
Modality AT					0.620	
Continuous	12	0.91	0.42	1.41	<0.001	85.7
Interval	4	0.55	-0.28	1.39	0.193	0
Both	1	0.28	-1.28	1.86	0.718	0
Modality ST					0.001	
Unclear	6	1.41	0.76	2.05	1.857	88.9
Progressive	11	0.45	0.01	0.89	0.040	58.1
Intensity AT					0.464	
Light	1	0.07	-1.70	1.84	0.936	0
Moderate	2	0.21	-1.11	1.53	0.755	0
Vigorous	3	0.41	-0.70	1.54	0.464	0
Near maximal	1	0.89	-0.92	2.70	0.335	0
Moderate to vigorous	5	0.81	-0.03	1.66	0.060	49.9
Intensity ST					0.403	
Light	1	-0.19	-1.98	1.59	0.827	0
Moderate	1	0.59	-1.17	2.35	0.511	0
Vigorous	1	0.07	-1.63	1.77	0.933	0
Moderate to vigorous	4	0.40	-0.53	1.33	0.402	0
Light to vigorous	2	0.77	-0.49	2.03	0.231	0
Supervision					0.441	
Yes	7	0.67	0.03	1.32	0.039	63.6
No	1	0.07	-1.49	1.64	0.928	0
Both	2	0.40	-0.78	1.59	0.503	0
Professional who supervised					0.145	
Physical exercise professional	2	0.05	-0.98	1.09	0.921	29.1
Group or individual					0.209	
Group	1	1.86	0.24	3.48	0.024	0
Individual	3	0.27	-0.57	1.11	0.526	0

CT: combined training; AT: aerobic training; ST: strength training; RCT: randomized controlled trial.

Table 5. Meta-regression of moderators/correlates of effects of exercise - CT *versus* control on VO_2 peak

Moderator	Number of RCTs	β	95% CI		P value	R^2
Mean age CT	14	0.0838	0.17	0.01	0.082	0.22
Mean age controls	14	0.0725	0.15	0.01	0.088	0.07
% men CT	16	0.0246	0.05	0.01	0.111	0.09
%men controls	16	0.0210	0.04	0.01	0.132	0.09
BMI CT	12	0.0623	0.29	0.17	0.605	0.11
BMI controls	11	0.0010	0.23	0.23	0.993	0.18
LVFE CT	15	0.0100	0.04	0.02	0.604	0.15
LVFE controls	15	0.0041	0.04	0.03	0.834	0.15
Duration	17	0.3662	0.03	0.69	0.031	0.09
Frequency of AT on CT	17	0.0804	0.94	0.78	0.855	0.12
Frequency of ST on CT	17	0.3704	0.43	1.17	0.369	0.09
Time of session	10	0.0660	0.01	0.11	0.005	0.17
Multivariate model						
Time of session Duration	10	2.6838	5.51	0.14	0.063	0.31

CT: combined training; BMI: body mass index; AT: aerobic training; ST: strength training; LVFE: left ventricular fraction of ejection

Quadriceps muscle strength

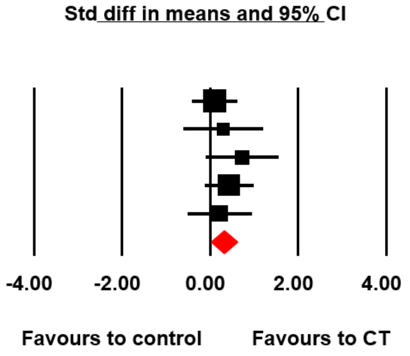
Data pooled from 5 studies (32,46,50–52) (control n = 90, CT n = 104) that evaluated quadriceps muscle strength by dynamometer showed a small significant improvement favoring CT (SMD = 0.32, 95% CI 0.03 to 0.61, Q = 1.82, p = 0.03, I^2 = 0%) (Fig. 5A). The Begg-Mazumdar Kendall's Tau (0.30, p = 0.462) and the Egger tests indicated no publication bias (intercept = 1.34, p = 0.405). The fail-safe number of additional negative studies required to nullify the significance of main analysis was 2 studies with negative results.

Only two studies (35,47) (CT n = 33, control n = 35) use 1RM test to evaluate quadriceps muscle strength. A moderate significant improvement favoring CT (SMD = 0.67, 95% CI 0.18 to 1.16, p = 0.007, I^2 = 0%) was found (Fig. 5B).

A

Study name — **Statistics for each study**

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Senden, 2005	0.114	0.261	0.068	-0.396	0.625	0.439	0.661
Stevens, 2015	0.308	0.460	0.212	-0.593	1.210	0.670	0.503
Gary, 2012	0.736	0.422	0.178	-0.091	1.563	1.744	0.081
Evans, 2010	0.436	0.281	0.079	-0.114	0.986	1.555	0.120
Feiereisen, 2007	0.230	0.366	0.134	-0.488	0.949	0.629	0.529
	0.321	0.149	0.022	0.030	0.613	2.162	0.031



B

Study name — **Statistics for each study**

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jónsdóttir, 2005	0.840	0.318	0.101	0.217	1.464	2.640	0.008
Mandic, 2009	0.414	0.405	0.164	-0.379	1.207	1.023	0.306
	0.677	0.250	0.063	0.187	1.168	2.708	0.007

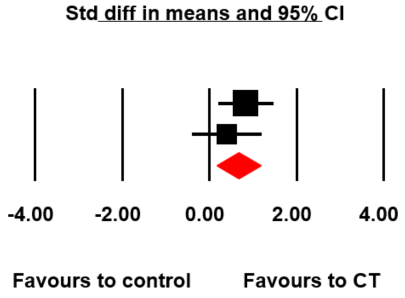


Figure 5. Effect of CT *versus* control on quadriceps muscle strength evaluated by dynamometer (A) and 1RM (B)

DISCUSSION

This systematic review is, to the best of our knowledge, the first focusing on the effects of CT on VO_2 peak and quadriceps muscle strength. The main results are the addition of resistance training did not improve functional capacity, evaluated by VO_2 peak, when compared to AT. Otherwise, quadriceps muscle strength enhanced, as expected, in comparison with AT or control group. The result of subgroup analysis illustrates the lack of protocols to standardize modality of training. Time of session and duration of rehabilitation are important variables that influence on effects of exercise.

VO_2 peak and quadriceps muscle strength are considered functional measures. This present systematic review did not analyses outcomes as quality of life and mortality, but recent evidence shows that VO_2 peak may be appropriate surrogate outcomes for these variables (53). Besides that, improvement in quadriceps muscle strength is required. Sarcopenia is an independent predictor of 3 year mortality in elderly subjects (54) and it is prevalence 20% higher in HF patients compared with healthy controls with the same age (55).

Previous meta-analysis studied different modalities for training in HF patients and no difference between CT and AT on VO_2 peak were observed (9,11,13). The present systematic review included ten studies in analysis, more than previous reviews. Even the results suggest no preference for any training to improve VO_2 peak, the addiction of strength training is recommended for these population, especially those patients who had significant muscle wasting (56,57). Evidence supports that muscle mass influences exercise performance, as an independent predictor of exercise performance (58,59). The quality of included studies in this analysis, however, is low, and more high quality RCTs are needed to futher address this question.

People with HF, similarly to people with COPD and coronary heart disease, presents muscle weakness which can influence quality of life, exercise tolerance and functional capacity (60). Two meta-analysis demonstrated an improvement of leg muscle strength, favoring CT against AT in those populations (19,61). Same results were found in our research. Even if these results are expected, this is the first meta-analysis with HF patients that explored quadriceps muscular strength. Quadriceps muscle strength was chosen as an outcome because it is one of the main muscles of the lower limbs and because it is correlated with functional performance (62). A recent systematic review, with only four studies included, did not partitioned upper and lower body muscular strength, reported a progress in favor of CT against control (14).

The comparison of CT *versus* control included 368 patients and demonstrated an improvement of VO_2 peak. Others meta-analysis (11,13) also showed superiority of CT on functional capacity, with larges EF and high heterogeneity, same as ours. This is the first meta-analysis that included a greater number of studies and tried to explain the high heterogeneity with additional analysis. The subgroup analysis suggests that continuous AT still are the focus of cardiac rehabilitation, some studies support these findings (63,64). Our results can be attributed to the large number of RCTs that used this form of training. The high heterogeneity does not allow to make greater speculations of which is the best modality for HF patients, but interval training should not be discarded from future analysis and protocols of rehabilitation, considering it also has positive results favoring this type of training (65–67). Previous meta-analysis compared types of exercise training modalities for HF patients and the results showed an increase in exercise capacity, evaluated by VO_2 peak, was not significantly favored by a specific training modality (16).

Our results indicate that only time of session seems to be a very important moderator of exercise effect. A previous meta-analysis with 18 studies comparted only continuous AT programs to usual care in HF patients. Session frequency, time of session and training intensity were significantly associated with VO_2 peak improvement (8). Unfortunately, the number of studies included in our meta-regression analysis is low.

The literature leaves no doubt about the implementation of the strength training in cardiac rehabilitation (68–70). Situations when strength training may not be viable, AT can be performed with the aim of improve exercise performance.

The limitations of the present studied are the low number of studies with low risk of bias, lack of statistical power in subgroup and meta-regression analysis due low number of included studies (less than ten). Also the high number of cardiac rehabilitation protocols and the lack of consensus and detailed description of the trainings made it difficult to characterize the moderators (in subgroup analysis). Risk of bias was detected in the analysis of VO_2 peak, CT *versus* control, but it was adjusted.

In conclusion, CT provides additional gains in quadriceps muscle strength and not in VO_2 peak when compared to AT, but when compared to control, it provides an increase in both outcomes. Thus, CT should be recommended in cardiac rehabilitation, as both VO_2 peak and muscle strength are predictors of survival in these patients. However, when strength training is not possible, AT should be recommended to increase functional capacity. Time of session appear to be an important moderator of exercise effect. More RCTs with better quality are needed.

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3 CONCLUSÃO

O TC demonstrou ser eficaz no aumento da capacidade funcional, avaliada pelo VO_2 pico, e da força muscular de quadríceps. Quando comparado com o TA, o TC foi capaz de aumentar apenas a força muscular de quadríceps. Nossos achados reforçam a implementação do TC dentro de programas de reabilitação cardíaca, principalmente para pacientes com IC. Porém, quando inacessível o treino de força, o TA deve ser utilizado com o objetivo de aumentar capacidade aeróbica.

A inatividade física é um fator altamente prevalente e facilmente modificável. Aumentar a taxa de referência para a reabilitação parece ser um desafio enfrentado por profissionais da saúde constantemente. A mudança dos hábitos de vida reflete diretamente na qualidade de vida, o acompanhamento de uma equipe multiprofissional para orientação adequada é fundamental. A reabilitação cardíaca é considerada uma alternativa de baixo risco e baixo custo. Cabe a nós, profissionais da saúde, seguirmos normas de triagem, elegibilidade, avaliação e tratamento baseadas em evidência científica, com o objetivo de popularizar o exercício físico regular como parte integral do paradigma de tratamento padrão da IC.

APÊNDICES

APÊNDICE A – ESTRATÉGIA DE PESQUISA

RESEARCH STRATEGY

August 20th, 2018

- Pubmed (MEDLINE)

(((((((((((((("Heart Failure"[Mesh] OR “Cardiac Failure” OR “Heart Decompensation” OR “Heart Failure, Right-Sided” OR “Heart Failure, Right Sided” OR “Right-Sided Heart Failure” OR “Right Sided Heart Failure” OR “Myocardial Failure” OR “Congestive Heart Failure” OR “Heart Failure, Congestive” OR “Left-Sided Heart Failure” OR “Left Sided Heart Failure”)) OR ("Heart Diseases"[Mesh] OR “Disease, Heart” OR “Diseases, Heart” OR “Heart Disease” OR “Cardiac Diseases” OR “Cardiac Disease” OR “Disease, Cardiac” OR “Diseases, Cardiac”)) OR ("Cardiomyopathies"[Mesh] OR “Cardiomyopathy” OR “Myocardial Diseases” OR “Disease, Myocardial” OR “Diseases, Myocardial” OR “Myocardial Disease” OR “Myocardiopathies” OR “Myocardiopathy” OR “Secondary Cardiomyopathies” OR “Secondary Cardiomyopathy” OR “Secondary Myocardial Diseases” OR “Secondary Myocardial Disease” OR “Cardiomyopathies, Primary” OR “Primary Cardiomyopathies” OR “Primary Cardiomyopathy” OR “Primary Myocardial Diseases” OR “Myocardial Diseases, Primary” OR “Diseases, Primary Myocardial” OR “Primary Myocardial Disease”)) OR ("Coronary Disease"[Mesh] OR “Coronary Diseases” OR “Disease, Coronary” OR “Diseases, Coronary” OR “Coronary Heart Disease” OR “Coronary Heart Diseases” OR “Disease, Coronary Heart” OR “Diseases, Coronary Heart” OR “Heart Disease, Coronary”)))) AND (((((((((((((((((("Rehabilitation"[Mesh] OR “Disability Evaluation” OR “Halfway Houses” OR “Early Intervention (Education)” OR “Recovery of Function” OR “Sports for Persons with Disabilities”)) OR ("Cardiac Rehabilitation"[Mesh] OR “Cardiac Rehabilitations” OR “Rehabilitation, Cardiac” OR “Cardiovascular Rehabilitation”)) OR ("Exercise Therapy"[Mesh] OR “Therapy, Exercise” OR “Exercise Therapies” OR “Therapies, Exercise” OR “Rehabilitation Exercise” OR “Exercise, Rehabilitation” OR “Rehabilitation Exercises”)) OR ("Resistance Training"[Mesh] OR “Training, Resistance” OR “Strength Training” OR “Training, Strength” OR “Weight-Lifting Exercise Program” OR “Weight Lifting Exercise Program” OR “Weight-Lifting Exercise Programs” OR “Weight-Bearing” OR “Strengthening Program” OR “Weight Bearing Strengthening Program” OR “Weight-Bearing Strengthening Programs” OR “Weight-Bearing Exercise Program” OR “Weight Bearing Exercise Program” OR “Weight-Bearing Exercise Programs”)) OR ("Exercise"[Mesh] OR “Exercises” OR “Physical Activity” OR “Activities, Physical” OR “Activity, Physical” OR “Physical Activities” OR “Exercise, Physical” OR “Exercises, Physical” OR “Physical Exercise” OR “Physical Exercises” OR “Exercise, Isometric” OR “Isometric Exercises” OR “Isometric Exercise” OR “Exercise, Aerobic” OR “Aerobic Exercise” OR “Aerobic Exercises” OR “Exercise Training” OR “Exercise Trainings” OR “Training, Exercise”)) OR Resistance exercise) OR ("Physical Endurance"[Mesh] OR “Endurance, Physical”)) OR Endurance training) OR Progressive resistance training) OR ("Weight Lifting"[Mesh] OR “Weight Liftings”)) OR ("Circuit-Based Exercise"[Mesh] OR “Circuit Based Exercise” OR “Circuit-Based Exercises” OR “Circuit Training”)) OR Combined exercise training) OR Combined training) OR Combined physical exercise) OR Concurrent training) OR Concurrent strength)))))) NOT ("Animals"[Mesh] OR “Animalia” OR “Animal” OR “Metazoa”)) NOT Rat) NOT Rats) NOT Mice

Total of articles founded: 907

- Cochrane CENTRAL

#1 "Cardiac Failure" OR "Myocardial Failure" OR "Congestive Heart Failure" OR "Heart Failure"

#2 "Coronary Disease" OR “Coronary Heart Disease”

#3 "Cardiac Rehabilitation"

#4 "Resistance Training" OR “Strength Training”

#5 “Aerobic Exercise”

#6 "Physical Endurance"

#7 "Endurance Training"

#8 "Progressive resistance training"

#9 "Combined exercise training"

#10 "Combined training"

#11 "Combined physical exercise"

#12 "Animal" OR "Rats" OR "Rat" OR "Mice"

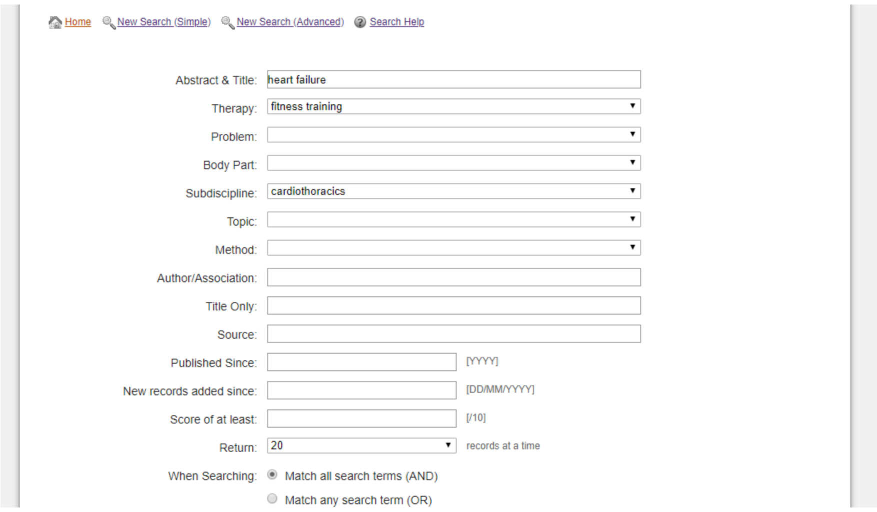
Total of articles founded: 905

- LILACS

(("insuficiencia cardiaca" or "insuficiencia cardiaca congestiva" or "insuficiencia cardiaca diastolica" or "insuficiencia cardiaca sistolica") or "cardiopatia CORONARIANA" or "doenca da arteria CORONARIANA" or "sindrome CORONARIANA aguda") or "CARDIOPATIA coronariana" or "CARDIOPATIA grave" or "CARDIOPATIA isquemica" or "CARDIOPATIAs" or "CARDIOPATIAs congenitas" [Descritor de assunto] and ((("reabilitacao" or "exercicio de reabilitacao" or "medicina fisica e reabilitacao" or "reabilitacao cardiaca" or "reabilitacao cardiovascular") or "exercicio" or "terapia por exercicio" or "tolerancia ao exercicio" or "exercicio aerobico" or "exercicio fisico" or "exercicios em circuitos") or "TREINAMENTO" or "TREINAMENTO de resistencia" or "TREINAMENTO fisico") or "RESISTENCIA" or "RESISTENCIA fisica" [Descritor de assunto] and not "ANIMAL" or "experimentacao ANIMAL" [Descritor de assunto]

Total of articles found: 273

- PEDro



Total of articles found: 345

- SPORTDiscus

"Heart Failure" OR “Cardiac Failure” OR “Heart Decompensation” OR “Heart Failure, Right-Sided” OR “Heart Failure, Right Sided” OR “Right-Sided Heart Failure” OR “Right Sided Heart Failure” OR “Myocardial Failure” OR “Congestive Heart Failure” OR “Heart Failure, Congestive” OR “Left-Sided Heart Failure” OR “Left Sided Heart Failure” OR "Heart Diseases" OR “Disease, Heart” OR “Diseases, Heart” OR “Heart Disease” OR “Cardiac Diseases” OR “Cardiac Disease” OR “Disease, Cardiac” OR “Diseases, Cardiac” OR "Cardiomyopathies" OR “Cardiomyopathy” OR “Myocardial Diseases” OR “Disease, Myocardial” OR “Diseases, Myocardial” OR “Myocardial Disease” OR “Myocardiopathies” OR “Myocardiopathy” OR “Secondary Cardiomyopathies” OR “Secondary Cardiomyopathy” OR “Secondary Myocardial Diseases” OR “Secondary Myocardial Disease” OR “Cardiomyopathies, Primary” OR “Primary Cardiomyopathies” OR “Primary Cardiomyopathy” OR “Primary Myocardial Diseases” OR “Myocardial Diseases, Primary” OR “Diseases, Primary Myocardial” OR “Primary Myocardial Disease” OR "Coronary Disease" OR “Coronary Diseases” OR “Disease, Coronary” OR “Diseases, Coronary” OR “Coronary Heart Disease” OR “Coronary Heart Diseases” OR “Disease, Coronary Heart” OR “Diseases, Coronary Heart” OR “Heart Disease, Coronary”

AND "Rehabilitation" OR “Disability Evaluation” OR “Halfway Houses” OR “Early Intervention (Education)” OR “Recovery of Function” OR “Sports for Persons with Disabilities” OR "Cardiac Rehabilitation" OR “Cardiac Rehabilitations” OR “Rehabilitation, Cardiac” OR “Cardiovascular Rehabilitation” OR "Exercise Therapy" OR “Therapy, Exercise” OR “Exercise Therapies” OR “Therapies, Exercise” OR “Rehabilitation Exercise” OR “Exercise, Rehabilitation” OR “Rehabilitation Exercises” OR "Resistance Training" OR “Training, Resistance” OR “Strength Training” OR “Training, Strength” OR “Weight-Lifting Exercise Program” OR “Weight Lifting Exercise Program” OR “Weight-Lifting Exercise Programs” OR “Weight-Bearing” OR “Strengthening Program” OR “Weight Bearing Strengthening Program” OR “Weight-Bearing Strengthening Programs” OR “Weight-Bearing Exercise Program” OR “Weight Bearing Exercise Program” OR “Weight-Bearing Exercise Programs” OR "Exercise" OR “Exercises” OR “Physical Activity” OR “Activities, Physical” OR

“Activity, Physical” OR “Physical Activities” OR “Exercise, Physical” OR “Exercises, Physical” OR “Physical Exercise” OR “Physical Exercises” OR “Exercise, Isometric” OR “Isometric Exercises” OR “Isometric Exercise” OR “Exercise, Aerobic” OR “Aerobic Exercise” OR “Aerobic Exercises” OR “Exercise Training” OR “Exercise Trainings” OR “Training, Exercise” OR “Resistance exercise” OR "Physical Endurance" OR “Endurance, Physical” OR “Endurance training” OR “Progressive resistance training” OR "Weight Lifting" OR “Weight Liftings” OR "Circuit-Based Exercise" OR “Circuit Based Exercise” OR “Circuit-Based Exercises” OR “Circuit Training” OR “Combined exercise training” OR “Combined training” OR “Combined physical exercise” OR “Concurrent training” OR “Concurrent strength”

AND Clinical Trails

NOT "Animals" OR “Animalia” OR “Animal” OR “Metazoa” OR "Rat" OR "Rats" OR "Mice"

Total of articles found: 102

- EMBASE

“Heart Failure” OR “Cardiomyopathy” OR “Coronary Artery disease” AND “Rehabilitation” OR “Exercise” OR “Resistance Training” OR “Circuit training” AND “Clinical Trial” NOT “Animal” **Total of articles found: 73**

ANEXOS

ANEXO A – NORMAS PARA SUBMISSÃO NO PERIÓDICO “JACC – HEART FAILURE”

JACC: Heart Failure publishes peer-reviewed articles on all aspects of heart failure, including original clinical studies, experimental investigations with clear clinical relevance, and state-of-the-art papers. Case reports will not be considered for publication. The journal will be predominantly focused on human heart failure, including heart failure clinical trials, (Phases I to IV); heart failure registries (including methodology and design papers); and personalized medicine (including the areas of pharmacogenetics, biomarkers, and metabolomics). We also believe that interdisciplinary relationships with neuroscience, pulmonary medicine, nephrology, electrophysiology, and surgery as they relate to heart failure will be of particular interest.

We request that all manuscripts be submitted online at www.jaccsubmit-heartfailure.org**.**

Manuscript submissions should conform to the guidelines set forth in the ‘‘Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals,’’ available from http://www.icmje.org/recommendations and most recently updated in December 2016.

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Ethics

Studies should be in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines.

Human studies must be performed with the subjects' written informed consent. Authors must provide the details of this procedure and indicate that the institutional committee on human research has approved the study protocol. If radiation is used in a research procedure, the radiation exposure must be specified in the Methods.

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in your paper. Patients have a right to privacy. Therefore, identifying information, including patients' images, names, initials, or hospital numbers, should not be included in videos, recordings, written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and you have obtained written informed consent for publication in print and electronic form from the patient (or parent, guardian or next of kin where applicable). If such consent is made subject to any conditions, the editorial office must be made aware of all such conditions.

Written consents must be provided to the editorial office on request. Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note. If such consent has not been obtained, personal details of patients included in any part of the paper and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Animal investigation must conform to the ''Position of the American Heart Association on Research Animal Use,'' adopted by the AHA on November 11, 1984. If equivalent guidelines are used, they should be indicated. The AHA position includes: 1) animal care and use by qualified individuals, supervised by veterinarians, and all facilities and transportation must comply with current legal requirements and guidelines; 2) research involving animals should be done only when alternative methods to yield needed information are not possible; 3) anesthesia must be used in all surgical interventions, all unnecessary suffering should be avoided and research must be terminated if unnecessary pain or fear results; and 4) animal facilities must meet the standards of the American Association for Accreditation of Laboratory Animal Care (AAALAC).

The *JACC* Journals have an ethics committee comprised of 7 members, which oversees quality control and will look into the issues of concern, if any.

Authorship/Cover Letter

Each author must have contributed significantly to the submitted work. If there are more than 4 authors, the contribution of each must be substantiated in the cover letter. If authorship is attributed to a group (either solely or in addition to 1 or more individual authors), all members of the group must meet the full criteria and requirements for authorship. To save space, if group members have been listed in *JACC: Heart Failure*, the article should be referenced rather than reprinting the list. The Editors consider authorship to include all of the following: 1) conception and design or analysis and interpretation of data, or both; 2) drafting of the manuscript or revising it critically for important intellectual content; 3) final approval of the manuscript submitted. Participation solely in the collection of data does not justify authorship but may be appropriately acknowledged in the Acknowledgment section; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html)

Manuscripts must be submitted with a cover letter stating that: 1) the paper is not under consideration elsewhere; 2) none of the paper's contents have been previously published; 3) all authors have read and approved the manuscript; and 4) the full disclosure of any relationship with industry (see "Relationship with Industry Policy"). Exceptions must be explained.

The corresponding author should be specified in the cover letter. All editorial communications will be sent to this author. The corresponding author will be whom we contact for submission queries. A short paragraph telling the editors why the authors think their paper merits publication priority may be included in the cover letter. Potential reviewers may be suggested in the cover letter, as well as reviewers to avoid. In order to add or remove any authors after acceptance of their paper, all listed authors at the time of acceptance need to provide written approval to the JACC Journals' editorial office prior to the scheduling and publication of the paper.

General Guidelines for Submission of Original Research Papers

Original research papers should present original research conducted by the investigators which resulted in reportable findings. Such papers should contribute new information that is important to the field of study. Original research papers should include an introduction, hypothesis and purpose, methods, results, discussion, and implications for clinical practice. Because of the printed page limitations, the Editors require that manuscripts not exceed 4,500 words (the word count begins at the Introduction of the text and includes references and figure legends). Note that if you are asked to revise your paper an alternate word limit may be specified by the Editors. Illustrations and tables should be limited to those necessary to highlight key data. Please provide gender-specific data, when appropriate, in describing outcomes of epidemiologic analyses or clinical trials; or specifically state that no gender-based differences were present. For original research dealing with genetic associations authors should refer to the following article: Ginsburg GS, Shah SH, McCarthy JJ. Taking cardiovascular genetic association studies to the next level. J Am Coll Cardiol 2007;50:930–2.

The manuscript should be arranged as follows: 1) title page; 2) structured abstract and key words; 3) abbreviations list; 4) text; 5) Clinical Perspectives; 6) acknowledgments (if applicable); 7) references; 8) figure titles and legends; and 9) tables.

Page numbering should begin with the title page.

Other Paper Categories

The following information should be noted for these paper types:

STATE-OF-THE-ART PAPERS. State-of-the-Art review papers should focus on a specific topic and review original research on that topic. Authors should summarize the state of current research on a topic, provide analysis and comparison, identify gaps and inconsistencies, and suggest future steps to solve identified problems. The Editors will consider both invited and uninvited review articles. Manuscripts should be no more than 5,000 words and require an unstructured abstract of no more than 250 words (the word count begins at the Introduction of the text and includes references and figure legends). Authors should detail in their cover letters how their submission differs from existing reviews on the subject.

CENTRAL ILLUSTRATION. All state-of-the-art reviews should include at least 1 central illustration drawing or figure (that may be a simple/rough hand-drawn figure), which summarizes the entire manuscript or at least a major section of the manuscript. Our in-house medical illustrators will create the final printable versions of these figures in consultation with the authors and the editors. The purpose of these illustrations is to provide a snapshot of your paper in a single visual, conceptual manner. This illustration must be accompanied by a legend.

EXPEDITED PUBLICATIONS. Manuscripts in this category should report important original findings of high-potential clinical impact or research significance. Authors must apply for expedited publication consideration in their cover letter at the time of submission. The Editors commit to a decision regarding suitability for expedited publication processing within 5 days, and will make an effort to provide an initial decision within 14 days. Those manuscripts not deemed appropriate for the expedited publication track will be eligible for consideration according to the standard review process. Online publication will occur within 10 days of receiving the approved galley prints.

EDITORIAL COMMENTS. The editors invite all Editorial Comments published in the Journal.

LETTERS TO THE EDITOR. A limited number of letters will be published. Letters to the Editor should have no more than 500 words, 5 references, 1 figure/table, and no more than 5 authors. They should focus on a specific article that has appeared in *JACC: Heart Failure*. Letters must be submitted within 3 weeks of the print issue date of the article. No original data may be included. Type letters double-spaced and include the cited article as a reference. Provide a title page that includes authors' names and institutional affiliations and a complete address for correspondence. These can be submitted online at www.jaccsubmit-heartfailure.org. Replies will generally be solicited by the Editors.

Manuscript Content

Title Page

Include the full title (no more than 15 words, hyphenated words count as a single word and single terms [e.g., de novo, in vivo, etc.] count as a single word), authors' names (including full first name and middle initial and degrees), total word count, and a brief title of no more than 45 characters. List the departments and institutions with which the authors are affiliated, and indicate the specific affiliations if the work is generated from more than one institution (use the footnote symbols given under "Tables"). Also provide information on grants, contracts, and other forms of financial support, and list the cities and states of all foundations, funds and institutions involved in the work. Include any relationship with industry (see "Relationship with Industry Policy"). If there are no relationships with industry, this should be stated. Under the heading, "Address for correspondence," give the full name and complete postal address of the author to whom communications, printer's proofs, and reprint requests should be sent. Also provide telephone and fax numbers and an e-mail address.

Structured Abstract

Provide a structured abstract of no more than 250 words, presenting essential data in 5 paragraphs introduced by separate headings in the following order: Objectives, Background, Methods, Results, and Conclusions. Use complete sentences. *All data in the abstract must also appear in the manuscript text or tables*. For general information on preparing structured abstracts, see ''Haynes RB, Mulrow CD, Huth EJ, Altman DG, Gardner MJ. More informative abstracts revisited. Ann Intern Med 1990;113:69–76.'' A nonstructured abstract is appropriate for review articles.

Text

The text should be structured as Introduction, Methods, Results, and Discussion. Use headings and subheadings in the Methods, Results, and, particularly, Discussion sections. Every reference, figure and table should be cited in the text in numerical order according to order of mention.

To save space in the Journal, up to 10 abbreviations of common terms (e.g., ECG, PTCA, CABG) or acronyms (GUSTO, SOLVD, TIMI) may be used throughout the manuscript. On a separate page following the abstract, list the selected abbreviations and their definitions (e.g., TEE = transesophageal echocardiography). The Editors will determine which lesser known terms should not be abbreviated. Consult ‘‘Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication,’’ available from http://www.ICMJE.organd most recently updated in April 2010, for appropriate use of units of measure.

Statistics

All publishable manuscripts will be reviewed for appropriateness and accuracy of statistical methods and statistical interpretation of results. We subscribe to the statistics section of the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication," available from http://www.ICMJE.org and most recently updated in April 2010. In the Methods section, provide a subsection detailing the statistical methods, including specific methods used to summarize the data, methods used for hypothesis testing (if any), and the level of significance used for hypothesis testing. When using more sophisticated statistical methods (beyond *t* tests, chi-square, simple linear regression), specify the statistical package, version number, and nondefault options used. For more information on statistical review, see ‘‘Glantz SA. It is all in the numbers. J Am Coll Cardiol 1993;21:835–7.’’

Acknowledgments

Acknowledgments or appendices must contain 100 words or less. Anything exceeding this limit will appear in the online version only. Letters of permission from all individuals listed in the acknowledgments are the responsibility of the corresponding author.

Clinical Perspectives

The authors should outline the clinical relevance and translational outlook recommendations for their manuscripts. These should be listed in the manuscript after the Text and before the Acknowledgments and References. Please review the examples provided below. The perspectives describe the implications of the study for current practice. The translational outlook places the work in a futuristic context, emphasizing directions for additional research, or clinical utility of the work. These should be no longer than 1 paragraph, i.e. 3-4 sentences.

Authors are asked to consider the clinical implications of their paper and identify areas of clinical relevance that could be used by clinician readers as professional caregivers.

This applies not only to physicians in training, but to the sustained commitment to education and continuous improvement across the span of their professional careers.

Translational Outlook

Translating biomedical research from the laboratory bench, clinical trials or global observations to the care of individual patients can expedite discovery of new diagnostic tools and treatments through multidisciplinary collaboration. Effective translational medicine facilitates implementation of evolving strategies for prevention and treatment of disease in the community. The Institute of Medicine identified two areas needing improvement: testing basic research findings in properly designed clinical trials and, once the safety and efficacy of an intervention has been confirmed, more efficiently promulgating its adoption into standard practice (Sung NS, Crowley WF, Genel M. The meaning of translational research and why it matters. JAMA 2008;299:3140–3148).

The National Institutes of Health (NIH) has recognized the importance of translational biomedical research, emphasizing multifunctional collaborations between researchers and clinicians to leverage new technology and accelerate the delivery of new therapies to patients (www.ncats.nih.gov/about/about.html).

Authors are asked to place their work in the context of the scientific continuum, by identifying impediments and challenges requiring further investigation and anticipating next steps and directions for future research.

References

Identify references in the text by arabic numerals in parentheses on the line. The reference list should be typed double-spaced on pages separate from the text; references must be numbered consecutively in the order in which they are mentioned in the text.

Do not cite personal communications, manuscripts in preparation, or other unpublished data in the references; these may be cited in the text in parentheses. *Do not cite abstracts that are older than 2 years*. Identify abstracts by the abbreviation ‘‘abstr’’ in parentheses. If letters to the editor are cited, identify them with the word ‘‘letter’’ in parentheses.

Use *Index Medicus* (National Library of Medicine) abbreviations for journal titles. It is important to note that when citing an article from the *JACC: Heart Failure*, the correct citation format is J AmColl Cardiol HF.

e the following style and punctuation for references:

Periodical

List all authors if 6 or fewer, otherwise list the first 3 and add et al.; do not use periods after the authors’ initials. Please do provide inclusive page numbers as in example below.

5. Glantz SA. It is all in the numbers. J Am Coll Cardiol 1993; 21:835–7.

Doi-based citation for an article in press

If the ahead-of-print date is known, provide as in example below.

16. Winchester D, Wen X, Xie L, et al. Evidence for pre-procedural statin therapy: meta-analysis of randomized trials. J Am Coll Cardiol 2010 Sept 28 [E-pub ahead of print], http://dx.doi.org/10.1016/j.jacc.2010.09.028.

If the ahead-of-print date is unknown, omit as in example below.

16. Winchester D, Wen X, Xie L, et al. Evidence for pre-procedural statin therapy: meta-analysis of randomized trials. J Am Coll Cardiol 2010 [E-pub ahead of print], http://dx.doi.org/10.1016/j.jacc.2010.

Chapter in book

Provide authors, chapter title, editor(s), book title, publisher location, publisher name, year, and inclusive page numbers.

27. Meidell RS, Gerard RD, Sambrook JF. Molecular biology of thrombolytic agents. In: Roberts R, editor. Molecular Basis of Cardiology. Cambridge, MA: Blackwell Scientific Publications, 1993:295–324.

Book (personal author or authors)

Provide a specific (not inclusive) page number.

23. Cohn PF. Silent Myocardial Ischemia and Infarction. 3rd edition. New York, NY: Marcel Dekker, 1993:33.

Online media

Provide specific URL address and date information was accessed.

10. Henkel J. Testicular Cancer: Survival High With Early Treatment. FDA Consumer magazine [serial online]. January–February 1996. Available at: http://www.fda.gov/fdac/features/196_test.html. Accessed August 31, 1998.

Material presented at a meeting but not published

Provide authors, presentation title, full meeting title, meeting dates, and meeting location.

20. Eisenberg J. Market forces and physician workforce reform: why they may not work. Paper presented at: Annual Meeting of the Association of Medical Colleges; October 28, 1995; Washington, DC.

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