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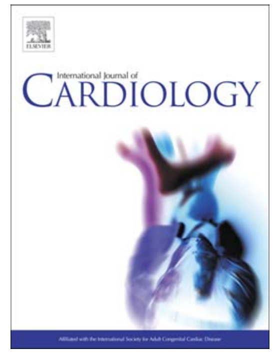

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Comparing exercise training modalities in heart failure: a systematic review and meta-analysis.

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1. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abstract

Exercise training (ET) is suggested to improve exercise capacity, prognosis, quality of life (QOL) and functional modifications of the heart in patients with heart failure (HF). However, it is not clear which modality is best. In order to assess the effectiveness of different ET modalities on prognostic cardiopulmonary exercise test (CPET) parameters, QOL and left ventricular remodeling, a systematic review and meta-analysis was performed. Randomized clinical trials (RCTs) were selected in three databases. The primary outcome data were peak oxygen uptake, ventilation over carbon dioxide slope, oxygen uptake efficiency slope, exercise oscillatory ventilation, rest and peak pulmonary end-tidal CO_2. Secondary variables were QOL, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD). Twenty RCTs (n=811) met the a priori stated inclusion criteria. Studies were categorized into four different groups: “interval training (IT_1) versus combined interval and strength training (IT_1S)” (n=156), “continuous training (CT_1) versus combined continuous and strength training (CT_1S)” (n=130), “interval training (IT_2) versus continuous training (CT_2)” (n=501) and “continuous training (CT_3) versus strength training (S_3)” (n=24). No significant random effects of exercise modality were revealed assessing the CPET parameters. There was a significant improvement in QOL applying CT_1S ($P<0.001$). Comparing IT_2 with CT_2, LVEDD and LVEF were significantly improved favoring IT_2 ($P<0.001$). There is some evidence to support that interval training is more effective to improve LVEF and LVEDD. The fact that patients with HF are actively involved in any kind of ET program seems sufficient to improve the prognosis, QOL and anatomic function.

Key words: Heart failure; Exercise; Training; Meta-analysis

Systematic review registration number: PROSPERO CRD42015030012

Abbreviation list

HF: Heart Failure

QOL: Quality of Life

ET: Exercise Training

VO_2: Oxygen Uptake

LVEF: Left Ventricular Ejection Fraction

CPET: Cardiopulmonary Exercise Test

AT: Anaerobic Threshold

HRR: Heart Rate Reserve

MCT: Moderate Continuous Training

HIIT: High Intensity Interval Training

IT: Interval Training

IMT: Inspiratory Muscle Training

S: Strength Training

VE/VCO_2: Ventilation over Carbon Dioxide

$PetCO_2$: Pulmonary End-Tidal Carbon Dioxide

OUES : Oxygen Uptake Efficiency Slope

EOV : Exercise Oscillatory Ventilation

LVEDD : Left Ventricular End-Diastolic Diameter

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Mesh: Medical Subject Headings

PICO: Population Intervention Comparison Outcome

RCT: Randomized Controlled Trial

SD: Standard Deviation

BMI: Body Mass Index

NYHA: New York Heart Association class

Pedro: Physiotherapy Evidence Database score

CI: Confidence Intervals

IT: Interval Training

ITS: Combined Interval and Strength Training

CT: Continuous Training

CTS: Combined Continuous and Strength Training

SRT: Steep Ramp Test

WR: Work Rate

VAT: ventilator anaerobic threshold

VE: Minute Ventilation or Ventilatory Equivalent

VCO_2: Ventilatory Carbon Dioxide

HR : Heart Rate

RM: Repetition Maximum

MLwHFQ: Minnesota Living with Heart Failure Questionnaire

HFpEF: Heart Failure preserved Ejection Fraction

HFrEF: Heart Failure reduced Ejection Fraction

Introduction

It is generally recognized that heart failure (HF) incidence rates are still increasing on a large-scale, especially in an ageing society(1, 2). Despite the slight decrease in mortality rates, patients with HF have an increased risk for early mortality and a poor quality of life (QOL)(1). In general, this syndrome has a huge counter impact on psychosocial wellbeing, fall injuries, autonomy and independence(3). Exercise training (ET) is generally recommended in stable outpatients in addition to optimal medical treatment(1, 4). The main assumption is that ET could benefit exercise capacity and QOL, mainly by increasing peak oxygen uptake (VO_2)(5). Furthermore, peripheral changes induced by ET could prevent muscle wasting and decrease catecholamine concentrations(6). It is also stated that ET could induce left ventricular remodeling, alteration in cardiac volumes and an augmented left ventricular ejection fraction (LVEF)(7). Furthermore, prognosis towards morbidity and mortality has been shown to improve(8).

The gold standard and preferred method to clinically quantitate exercise capacity is conducting a cardiopulmonary exercise test (CPET) and assessing peak VO_2(9). Additional established prognostic parameters in HF have been evaluated with CPET at baseline and during follow-up(10). Moreover, CPET allows calculation of an effective and safe training intensity, a functional and risk classification, and an assessment of benefit following a training program(9). Usually, training intensity is prescribed relative to the peak VO_2 or the anaerobic threshold (AT)(11). When CPET is not available, indirect methods such as the six minutes walking test and heart rate reserve (HRR) have been proposed.

Nowadays, the variety in exercise intensities and modalities has been increased in an attempt to select the most effective and individualized ET. In current clinical trials, attention is given towards comparing moderate continuous training (MCT) with high intensity interval training (HIIT)(12, 13). Up until now, the most evaluated ET is MCT as it approves to be efficient, safe and well tolerated by the patients(11). Therefore, MCT is also recommended by the HF association guidelines(11). Recently, it was suggested that interval training (IT) and especially HIIT, is more effective(11). This assumption was corroborated by the publication of a renowned study(14) in which the effect of HIIT i.e. on exercise capacity was stupendous. It was stated that applying high intensity during short bouts of exercise might challenge the heart’s pumping ability, the endothelial system and the mitochondrial functions in skeletal muscles and could therefore explain this outstanding increase in peak VO_2(14). Indeed, it was shown that a higher exercise intensity leads to larger improvements in peak VO_2 when compared to low exercise intensities, respectively 23% and 7%(5). Despite from intensity also modalities such as inspiratory muscle training (IMT) (enhances functional capacity), strength training (S) (prevents muscle wasting) or a combination of these could boost the positive results towards exercise capacity, prognosis, QOL and left ventricular remodeling. Therefore, this systematic review and meta-analysis aims to assess the effect of the exercise training modality on (1) prognostic CPET parameters i.e. peak VO_2, ventilation over carbon dioxide (VE/VCO_2) slope, rest and peak pulmonary end-tidal CO_2 ($PetCO_2$), oxygen uptake efficiency slope (OUES) and exercise oscillatory ventilation (EOV), (2) left ventricular remodeling i.e. LVEF and left ventricular end-diastolic diameter (LVEDD) and (3) QOL.

Methods

This systematic review and descriptive meta-analysis was registered in the PROSPERO database CRD42015030012. It was edited following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Medical subject headings (Mesh) and keywords were combined to describe the patient population, intervention and outcome (adapted PICO search). The search strategy as inserted in PubMed: ((“Heart Failure”[Mesh]) AND (“Physical education and training”[Mesh] OR “Motor activity”[Mesh] OR “Exercise”[Mesh] OR “Physical rehabilitation”) AND (“Oxygen consumption”[Mesh] OR “Pulmonary Gas Exchange”[Mesh] OR “Respiration”[Mesh] OR “VE/VCO2” OR “ventilatory efficiency” OR “peakVO2” OR “VO2peak” OR “oxygen uptake” OR “PetCO2” OR “fluctuat*” OR “oscillatory breathing” OR “periodic breathing” OR “oscillatory ventilation”)). The search strategy was modified for each database in case of differences in indexing terms. Other, non-reported keywords and Mesh terms were inserted, however, these did not deliver supplementary results. Three databases (PubMed, the Cochrane Library and Web of Science) were systematically searched up until the 19th of October 2015.

Selection criteria were established a priori. Citations were included if (1) the population was diagnosed with HF; (2) the population was aged 18 years or older; (3) peak or maximal VO_2 was assessed; (4) two different training modalities were compared; (4) the studies were published in English, Spanish, French, German or Dutch; (5) the study design was a randomized controlled trial (RCT). Exclusion criteria were (1) physical interventions not given in a constant regime (2) no evaluation of the exercise intervention (3) heart transplantation (4) no CPET evaluation was performed or the patients were not able to perform a CPET (5) no post-exercise CPET evaluation was executed. Reference lists were checked for any topic-related studies. Expert opinions and recommendations on on-going (unpublished) studies or other relevant data were gathered. The corresponding author of a study was contacted to obtain any missing information or data. If means and/or standard deviations (SD) were not mentioned in the tables and in case the authors did not reply, these values were obtained by extracting them from the provided figures.

All identified studies were organized and the duplicates were deleted. Initially, two investigators (T.C. & T.V.) screened the results from the electronic searches in order to select potentially relevant citations based on titles and abstracts. Full-text articles were retrieved and evaluated based on the proposed selection criteria. In case of uncertainty, a second, third and fourth investigator (J.C., D.V. & J.T.) evaluated the citation and consensus was sought during a meeting. The final determination to include or exclude an article was based on common agreement.

The following study characteristics were extracted, if appropriate coded, from the articles by one researcher (J.C.): author, publication year, training i.e. intensity, repetitions, modality, duration, frequency and number of sessions; study size, sex, age, body mass index (BMI), New York Heart Association (NYHA) class, LVEF, etiology of HF, medication, CPET protocol, CPET intensity, peak VO_2 (ml/kg/min), VE/VCO_2 slope, OUES, rest and peak $PetCO_2$ (mmHg), EOV, LVEDD (mm) and QOL.

The methodological quality of each eligible study was assessed by two researchers (T.V. & T.C.) using the Physiotherapy Evidence Database (Pedro) score for RCTs ranging from zero to 11(15). If the score deferred, the article was rated by a third reviewer (J.C.) and consensus was sought during a meeting. As the studies included in this meta-analysis were RCTs, the post intervention means and SD were extracted. Because all values were reported in the same unit, effect sizes were expressed as raw mean differences. The extracted data were meta-analyzed using the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, NJ, USA). Meta-analyses with a priori chosen random-effects model were conducted to calculate the overall weighted effect estimates. The 95% confidence intervals [95%CI] were expressed around the weighted mean estimates. The Cochran's Q statistic and its corresponding P-value were calculated to assess the presence of heterogeneity across studies. To assess the part of the total observed variability that can be acquaint by true between-studies variability, Higgins' I^2 (%) was used and bench-marked as low (around 25%), moderate (around 50%) or high (around 75%) heterogeneity. To explain heterogeneity, meta-regression analysis was applied. A sensitivity analysis was executed to estimate the robustness of the overall weighted estimate against extreme effect sizes observed in two trials(14, 16). For all analyses, the limit for statistical significance was set at $P \leq 0.05$.

Results

Description of the included studies and population

The initial search yielded 841 articles, which were assessed for eligibility. After de-duplication, 518 records were screened on title and abstract, retaining 85 full-text articles. Ultimately, full-text screening resulted in 19 citations. One study protocol(17) was identified through searching the reference lists of the retrieved studies. Authors were contacted to ask permission for inclusion of their unpublished study results. Therefore, 20 RCTs met the a priori stated inclusion criteria (Figure 1), accounting for 811 patients diagnosed with HF (Table 1). Studies were categorized into four different groups i.e. “interval training (IT_1) versus combined interval and strength training (IT_1S)”, “continuous training (CT_1) versus combined continuous and strength training (CT_1S)”, “interval training (IT_2) versus continuous training (CT_2)” and “continuous training (CT_3) versus strength training (S_3)” including five, three, eleven and one studies and assessing 156, 130, 501 and 24 patients respectively. Sex distribution was mainly male (82.9%). The average age of the patients ranged between 45.7 and 76.5 years while BMI ranged from 24.1 to 30.4 kg/m². The LVEF assessed during rest and the percentage of HF with ischemic origin at baseline amounted between 23 to 41.7% and 20 to 100% respectively. An optimal medication strategy i.e. β-blockers, diuretics and ACE-inhibitors was opposed in all studies to a majority of the patients. No patients of NYHA class IV were included, however two studies(14, 18) did not mention the severity score.

Description of exercise assessment and training

In order to assess exercise capacity, two different protocols were described in literature. On the one hand, peak values were investigated using a symptom-limited CPET(14, 16, 18-30) of eight to 12 minutes(31) executed on a bicycle(18, 21-25, 27, 29, 30, 32-35), treadmill(14, 16, 20, 26, 28) or a combination of both(19). The majority of the studies applied a ramp protocol(14, 16, 18-23, 27-30, 32-35), however a modified Bruce(26), Dargie(19) and step protocol(24, 25) were also described. On the other hand, a steep ramp test (SRT)(28-30, 32-35) was conducted. It was assumed that 50% of peak work rate (WR) assessed with a SRT corresponds to more than 100% peak VO_2 evaluated with CPET(34). In the majority of the studies, a re-test was performed on regular basis to adjust for training intensity(18, 20, 32-35). Based on the CPET and SRT results at baseline and during follow-up, researchers could estimate intensity for optimal ET. The ventilatory anaerobic threshold (VAT) was mainly assessed using the v-slope method(14, 19, 22, 23, 27-30, 32-35) and occasionally confirmed by the equivalent method(22, 23). When performing a SRT, 50%(28-30, 32-35) to 80%(28) of the baseline achieved peak WR was applied. Also HRR was calculated (%(HR peak-HR rest)+HR rest)(16, 21, 26). To estimate peak VO_2, the average values of the last 15s(28), 20s(22, 24, 27, 32-35), 30s(16, 18, 26, 30) or 60s(19) were obtained. The highest value of the last 30s(20) or 60s(21) of the exercise test could also be used. Peak WR was defined as the highest achieved load and maintained at a pedaling frequency of at least 50rpm during 30s(22, 27, 32-35). The VE/VCO_2 slope was considered by plotting VE against VCO_2 from baseline until AT(20-22, 27, 34, 35) i.e. the linear regression slope. The following regression (y = mx + b, m = slope)(23, 26) was also applied to estimate VE/VCO_2 slope. The OUES was defined as the slope of linear regression of VO_2 versus the log-transformed VE values for all exercise variables according following equation (VO_2 = a (log10VE) ± b, a = slope)(23). The peak and rest $PetCO_2$ were calculated at baseline and during the CPET(35). During ET, the warm-up protocol was vaguely or not described. Mainly, the warm-up consisted out of a short (3'(23), 5'(16, 19, 20), 9'(26),10'(14, 16, 28) or not defined(30)) period of stretching(33), breathing(16) or light resistance(16) exercises and cycling at low intensity(33) (5W(28), 30%(23) or 50-60% peak VO_2(14)). The cool-down period consisted out of stretching(33), relaxation(16), resistance(28) or endurance(28) exercises at low intensity(30) (30% peak VO_2(23) or 50-70% peak HR(14)) during 3(14, 23) to 5(16, 19, 20, 28) minutes. If the patient could not attain training sessions, the missed sessions were added at the end of the program(32-35). A detailed overview of the applied core ET is provided in table 2.

Assessment of skeletal muscle strength was mainly done by performing an one repetition maximum (RM) test(20, 21, 25, 32, 33, 35). Moreover, isokinetic strength was assessed with an isokinetic dynamometer(18, 20) and also muscular endurance tests were performed(18, 21).

Inspiratory muscle training (IMT) was executed using an inspiratory-incremental resistive loading device (TRAINAIR®, Project Electronics Ltd, UK). The authors(19) indicated that the training protocol was according the skeletal muscle training principles i.e. test of incremental respiratory endurance. Therefore, it was opted to include this article in the meta-analysis.

Meta-analyses and meta-regression results

Five studies compared interval training (IT_1) with a combined interval-strength training (IT_1S). The meta-analysis for peak VO_2 showed an overall weighted raw mean difference of -0.47 ml/kg/min (95%CI: -1.78 to 0.85; P=0.489) favoring IT_1. There was low heterogeneity (Q=4.7; P=0.326; I^2 =13.9). Only one out of these five studies described the VE/VCO_2 slope (34). No mean difference between the post-intervention values of both groups was observed (Table 3).

Three studies compared continuous training (CT_1) with a combined continuous-strength training (CT_1S). The meta-analysis for peak VO_2 showed an overall weighted raw mean difference of -1.45 ml/kg/min (95%CI: -3.47 to 0.56; P=0.158) with low heterogeneity (Q=0.4; P=0.824; I^2 =0.0) in favor of CT_1. In these studies, the overall weighted estimate for VE/VCO_2 slope was 0.61 (95%CI: -3.10 to 4.32; P=0.747) with moderate heterogeneity (Q=4.1; P=0.127; I^2 =51.6) indicating a higher VE/VCO_2 slope with CT_1, thus favoring CT_1S.

Eleven studies compared continuous training (CT_2) with interval training (IT_2). The meta-analysis for peak VO_2 showed an overall weighted raw mean difference of 0.73 ml/kg/min (95%CI: -0.24 to 1.70; P=0.138) with low heterogeneity (Q=11.7; P=0.390; I^2 =5.6) favoring IT_2 (Figure 2). Seven out of these eleven studies analyzed the VE/VCO_2 slope. The overall weighted raw mean difference was 0.96 (95%CI: -0.58 to 2.50; P=0.221) with low heterogeneity (Q=4.2; P=0.648; I^2=0.0) indicating a higher VE/VCO_2 slope with $CT_{2,}$ hence favoring IT_2.

Only one study(25) compared continuous training (CT_3) with strength training (S_3) and found a raw mean peak VO_2 difference of 0.41 ml/kg/min (95%CI: -3.64 to 4.46; P=0.843) in favor of CT_3.

A meta-regression of the amount of sessions over peak $VO_{2,}$ assessing the CT_2-IT_2 group, revealed a slope of 0.03 (P=0.498).

One study(23) showed that OUES improved significantly from 1250±297.9 to 1230.8±297.9 and from 1192.3±163.9 to 1500±297.9 in CT_2 and IT_2 respectively, resulting in a post intervention raw mean difference of -269.2 (95%CI: -494.1 to -44.3; P=0.019) favoring IT_2. Rest $PetCO_2$(35) improved from 34.7±4.7 mmHg and 32.0±5.8 mmHg before training to 35.1±5.8 mmHg and 35.6±4.6 mmHg after training, respectively, when comparing IT_1-IT_1S, resulting in -0.50 mmHg (95%CI: -3.51 to 2.51; P=0.744) difference favoring IT_1S. Peak $PetCO_2$(35) improved from 32.0±5.8 mmHg and 32.3±5.3 mmHg before training to 35.0±6.3 mmHg and 37.3±6.9 mmHg after training comparing IT_1-IT_1S, resulting in raw mean difference of -2.30 mmHg (95%CI: -6.15 to 1.55; P=0.241) favoring IT_1S. Exercise oscillatory ventilation (EOV) was not assessed in the included studies.

Two dimensional echocardiography combined with Doppler using the Simpson's method(14, 17, 19, 24, 26, 29) was applied to assess LVEF(%) and LVEDD(mm). The other studies used echocardiography with ultrasound to calculate LVEF(18, 21, 23) and LVEDD(18, 20). Gated Blood Pool Scan through analysis of the ECG-triggered acquisition data was applied to estimate LVEF in one study(20). Exercise echocardiography was executed(24), however due to uniformity only the data during rest were reported.

The effect of the ET modality on cardiac modification objectified by LVEF and LVEDD was evaluated. One study(18) compared IT_1-IT_1S for LVEF and mentioned a raw mean difference of 4.40% (95%CI: 1.48 to 7.32; P=0.003) favoring significantly IT_1S. Moreover, a small increase in LVEDD, respectively 68.3mm and 68.2mm, was found for IT_1S resulting in a raw mean difference of 0.10 mm (95%CI: -0.19 to 0.39; P=0.491), hence favoring IT_1. In the CT_1-CT_1S group (n=3), the overall weighted raw mean difference for LVEF was 0.25% (95%CI: -3.49 to 4.00; P=0.895) with low heterogeneity (Q=0.2; P=0.888; I^2=0.0) favoring CT_1S. For LVEDD (n=2), the overall weighted raw mean difference was -2.44 mm (95%CI:-5.69 to 0.81; P=0.141) with low heterogeneity (Q=0.1; P=0.786; I²=0.0) indicating a higher LVEDD applying CT_1S, hence favoring CT_1. In the CT_2-IT_2 group, the overall weighted raw mean difference for LVEF (n=6) was 3.39% (95%CI: 1.62 to 5.16; P<0.001) with low heterogeneity (Q=2.9; P=0.712; I^2 =0.0) significantly favoring IT_2 (Figure 3). Also, the overall raw mean difference for LVEDD (n=4) was significantly increased (3.79 mm (95%CI: 1.18 to 6.40; P=0.004)) with low heterogeneity (Q=4.8; P=0.186; I²=37.6) applying CT_2, thus favoring IT_2 (Figure 4).

The QOL was described through the data provided by the Minnesota Living with Heart Failure Questionnaire (MLwHFQ)(36) as it is a self-assessment measure of therapeutic response to interventions applied in HF. It contains 21 questions and the score can range from 0-105 with higher scores indicating greater perception of severity and intrusiveness of HF related symptoms. It contains a physical and emotional dimension score. The QOL, applying MLwHFQ, was described in six studies. Comparing CT_1-CT_1S (n=2), the overall weighted raw mean difference was significantly higher in CT_1 10.86 (95%CI: 5.25 to 16.48; P<0.001) with low heterogeneity (Q=0.1; P=0.806; I²=0.0) significantly favoring CT_1S (Figure 5). In the CT_2-IT_2 group (n=4), the overall weighted raw mean difference was 4.21 (95%CI: -2.89 to 11.30; P=0.245) with low heterogeneity (Q=1.3; P=0.736; I²=0.0) indicating a higher score in CT_2, thus favoring IT_2.

Methodological quality and publication bias

The Pedro-scale of all published studies was assessed and the general results were listed in table 1. The score ranged between three and 11, with five as average. All studies mentioned random allocation however the precise method was only specified in one study(21). Allocation concealment through an off-shore investigator or opaque envelopes was mentioned in few studies(14, 21, 32). The majority of the compared population groups within a study were stated to be equal and comparable at baseline. Little information was provided concerning blinding of participants, investigators and assessors. In the majority of the studies, at least 15% of the randomized patients did not complete the study. Intention-to-treat analysis was only specified in one study(21), however few studies explicitly stated the patients were treated as allocated. Statistical information concerning between group analysis was provided. Inclusion and exclusion criteria were not explicitly mentioned in two studies(18, 28). A meta-regression of the Pedro-score over peak VO_2 assessing the CT_2-IT_2 group revealed a slope of 0.44 (P=0.379). Because of the low number of studies included in the meta-analysis on the subgroups of LVEF and QOL, a risk for publication bias cannot be excluded.

Discussion

Systematic reviews and meta-analyses that evaluated the effect of ET on peak VO_2(5, 37, 38), VE/VCO_2 slope(8, 38), N terminal-pro brain natriuretic peptide (NT-proBNP)(8) and LVEF(37) had already been conducted. However, two of these studies included also a non-active control group(5, 8). The other two meta-analyses partially compared the effect of specific exercise modalities i.e. IT versus CT(37, 38) and IT versus ITS(38) on selected parameters. This is the first systematic review and meta-analysis that has been obtained to provide a complete overview of RCTs that compared the available exercise training modalities(11) i.e. IT versus ITS, CT versus CTS, IT versus CT and CT versus S, on an extended number of prognostic CPET parameters i.e. peak VO_2, VE/VCO_2 slope, rest and peak $PetCO_2$, OUES and EOV. Moreover, LVEF, LVEDD and QOL were inserted in the assessment. In this study only active control patients were evaluated.

The key findings of this meta-analysis were: (i) an increase in exercise capacity, represented by the peak VO_2, was not significantly favored by a specific training modality; (ii) the influence of a certain training modality on VE/VCO_2 slope was not found to be significant different from other training modalities; (iii) only OUES seemed to improve significantly with IT_2, yet, only one study reported on this variable; (iv) towards the other prognostic parameters, insufficient data were reported in order to draw conclusions; (v) QOL seems to improve significantly with CT_1S; (vi) investigating left ventricular remodeling i.e. LVEF and LVEDD, revealed significant improvements when conducting IT_2.

Comparing interval training (IT_1) and combined interval-strength training (IT_1S) did not provide significant results. Besides, very similar training and population were described in four out of five of the included studies(32-35). It could be questioned if indeed the studies described the same population since the studies were published around the same period and reported similar authors. In a previous meta-analysis(38), a significant difference towards peak VO_2 was noted in favor of IT_1S, however, only four studies were assessed. It was shown that aerobic training could improve QOL in patients with HF(39). In a recent RCT, it was stated that QOL improved with 66% by applying HIIT compared to a control group(40). The effect of ET on QOL is already stated long time before and therefore it is more interesting and important to compare different exercise modalities to clarify which ET modality is most effective(5). The meta-analysis showed that combined continuous-strength training (CT_1S) significantly improve QOL compared to continuous training (CT_1). Nevertheless, it should be stated that these results were only described in two studies(19, 21). Furthermore, one study(25) evaluated CT_3 with strength training (S) only. No significant effect towards exercise capacity was noted. Using strength training exclusively is rarely applied but is often combined with CT or IT. In people with combined HF and significant muscle wasting, training should focus initially on increasing muscle mass and force by applying mainly strength training during the first weeks sessions(9). Skeletal muscle weakness of the upper limbs can often complicate daily tasks and therefore reduce QOL. A combination of endurance and resistance training has been shown to improve submaximal exercise intolerance and therefore boosts the ability to conduct daily tasks at submaximal effort(20). For these reasons and because these results showed no significant difference towards a single exercise modality, except for CT_1S, it could be advised to always include strength training in combination with another training modality i.e. CT or IT, to improve exercise capacity and prognosis.

The majority of the studies (n=11) compared interval training (IT_2) with continuous training (CT_2). Previous meta-analyses found significant (i) results with regard to peak VO_2(37, 38) being 2.14ml/kg/min and 1.04ml/kg/min respectively, and (ii) results in decrease of VE/VCO_2 slope(38). A trend favoring IT for gain in LVEF (P=0.11) was noted(37). These studies only assessed seven, five, four and five studies respectively. Moreover, it could be assumed that in these meta-analyses one clinical trial(14) outperformed the other RCTs, directing the results in favor of IT. In the current meta-analysis, the study of Wisloff et al. (2007)(14) was included, describing a small population with only nine patients in each group, with a major significant result towards peak VO_2 (6 ml/kg/min) favoring IT. On the contrary, the study of Piotrowicz et al. (2010)(16), which was also included, described a large population with 75 versus 56 patients, showing controversially a small improvement in peak VO_2 (1.9 ml/kg/min) in favor of CT when compared to IT (1.1 ml/kg/min). It was noticed that the results of these studies could offset each other. Therefore, sensitivity analyses were performed which revealed that excluding Piotrowicz et al. (2010)(16) significantly influenced the results. Excluding both trials did not significantly influence the results. Despite the fact that the setting in which ET is performed i.e. hospital based versus home based environment, could also influence the results(11), the study(16) addressing telemonitoring was included in this meta-analysis. The initially established selection criteria did not allow us to exclude this trial. Recently, more attention has been drawn to telerehabilitation as it can have multiple advantages such as ease of accessibility and improved cost-effectiveness(41). Similar improvements in QOL were seen and adherence to training was enhanced in the included study(16). It is suggested that in the future more extensive trials will be performed in order to assess the effect of telerehabilitation in patients with HF(13, 42) but also with other chronic pathologies(43-45) that benefit from long-term ET and follow-up. The current meta-analysis showed that applying IT improved significantly LVEF and lowered significantly LVEDD.

Therefore, these results seem to confirm the assumption that (HI)IT improves the heart's pumping ability(14). Despite the fact that LVEF was significantly higher and LVEDD significantly lower in IT, there was no significant improvement in exercise capacity, prognosis and QOL on short term. Previous studies have suggested that measurements of left ventricular systolic function do not predict maximal exercise capacity in individuals with normal or impaired left ventricular systolic function(46-49). Furthermore, many studies(50-53) have failed to show a significant link between exercise performance and left ventricular performance. More recently, it was showed that HF patients with preserved ejection fraction (HFpEF) had a deteriorated exercise capacity, prognosis and QOL which could improve with ET(54, 55). It appears that the peripheral system is the limiting factor of exercise capacity and therefore prognosis in the majority of HF patients(46, 56). It could be possible that the physiologic consequences of improved LVEF and LVEDD need more time and therefore longer follow-up to appear and positively influence exercise capacity, prognosis and QOL. In general, there was a low heterogeneity reported in the meta-analysis results.

In general, evidence-based ET under supervision is accepted as a highly effective and safe treatment(3). Yet, as the variety of exercise modalities and intensities increases, questions are being raised again concerning safety in especially HIIT. This topic was only addressed in limited number of studies and therefore no recommendations can be given(57). Are we asking the right questions? Perhaps instead it should be questioned if such short bouts of high intensity are necessary and useful to be performed in patients with HF knowing that daily activities often require an adequate submaximal performance, indicating the ability to exercise with an intensity lower than VAT without presenting dyspnea or fatigue(9). It is likely that not all patients will tolerate training at a high intensity for a very short duration of time(57). It was suggested that larger trials were needed to reveal the added clinical relevance for HIIT(57). Indeed, in a recently conducted extended trial(17) significant difference towards HIIT was reported, however results were not as prominent as initially found in the study of Wisloff et al. (2007)(14). Currently, another European supported multicenter study is evaluating the effect of moderate CT and HIIT combined with telerehabilitation on an extensive cohort (n=180) of patients with HFpEF(13). In the present meta-analysis, no patients with HFpEF were included, since they are often systematically excluded from exercise trials(3), providing no information about the effect of different exercise modalities on exercise capacity, prognosis and QOL in this population. However, it was illustrated that these patients responded just as well to exercise training(58, 59). Furthermore, similar established prognostic CPET parameters in HFrEF(60) estimated also the prognosis in HFpEF i.e. peak VO_2, VE/VCO_2 slope and EOV respectively(61). Recently, it was found that peak atrial-venous oxygen difference was a major determinant of exercise capacity in HFpEF which reflects impaired oxygen extraction and intrinsic abnormalities in skeletal muscle or peripheral microvascular function(56). Specifically targeting this limitation by including appropriate exercise training modalities could be an important therapeutic intervention.

Limitations

Meta-analysis of the results was conducted based on the post-exercise values as included studies stated to be RCTs. However, it was checked if randomization was correctly performed at baseline by conducting pre-post analyses of the change values. No differences in significance were seen. Hence, it was opted to assess only the post-exercise values.

The RCTs included in this study, reported a wide range of executed ET towards frequencies, intensities and repetitions. The extended variety of exercise intensities and parameters to calculate intensity from i.e. HRR, AT, peak VO_2 etc., made it impossible to distinguish HIIT from low, moderate and vigorous intensity interval training in this study, as executed in a previous meta-analysis(5). Therefore, it was chosen to include studies that compared at least two exercise modalities. To be able to make statements about intensity, specific clinical trials should be performed in a standardized way in which high, vigorous, moderate and low intensity are adequately defined based on general recommendations.

In general, few studies compared different training modalities in patients with HF. Accordingly, it is not possible to state which training modality is outstanding to apply in patients with HF. More standardized, high qualitative, rigorous (multicenter) clinical trials should be executed in the near future in order to estimate the most effective training modality and intensity.

Conclusions

There is some evidence to support that interval training is more effective to improve LVEF and LVEDD. Regarding CPET parameters and QOL however, it is not clear which training modality is the best. The fact that patients with HF are actively involved in any kind of exercise training program seems sufficient to improve the prognosis, QOL and anatomic function.

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Figure legends

Figure 1: Four-phase flow diagram of the systematic reviewing process.

Figure 2: Meta-analysis results of the peak VO_2 comparing continuous training and interval training.

Figure 3: Meta-analysis results of the left ventricular ejection fraction comparing continuous training and interval training.

Figure 4: Meta-analysis results of the left ventricular end-diastolic diameter comparing continuous training and interval training.

Figure 5: Meta-analysis results of the quality of life comparing continuous training and combined continuous-strength training.

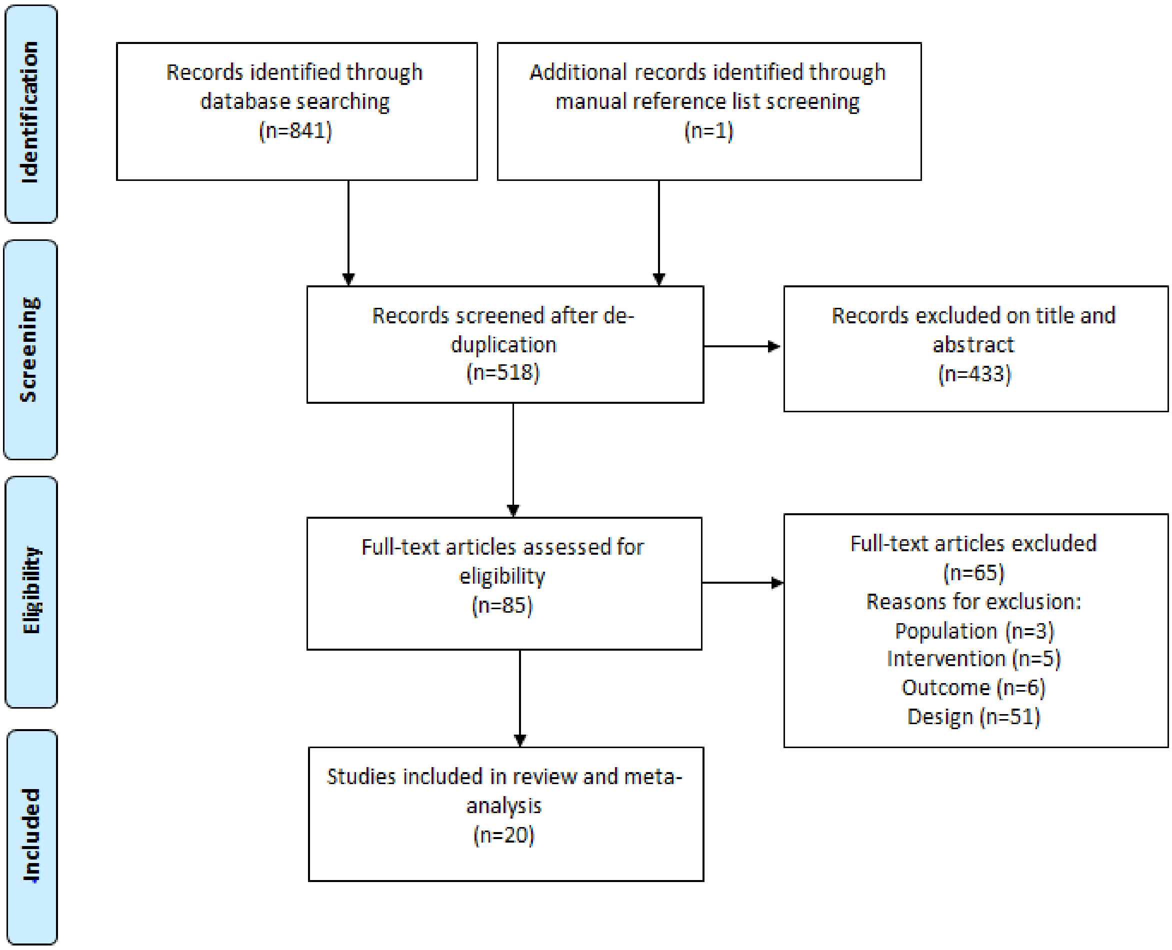
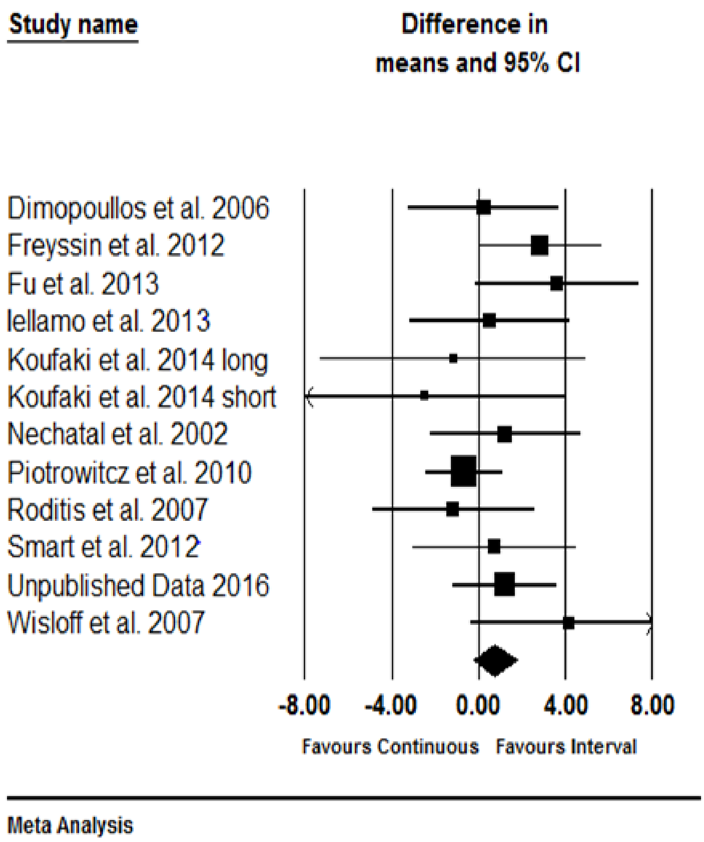

Identification
Screening
Eligibility
Included
Records identified through database searching (n=841)
Additional records identified through manual reference list screening (n=1)
Records screened after de-duplication (n=518)
Records excluded on title and abstract (n=433)
Full-text articles assessed for eligibility (n=85)
Full-text articles excluded (n=65)
Reasons for exclusion:
Population (n=3)
Intervention (n=5)
Outcome (n=6)
Design (n=51)
Studies included in review and meta-analysis (n=20)

Figure 1



Study name
Difference in means and 95% CI
Dimopoullos et al. 2006
Freyssin et al. 2012
Fu et al. 2013
Iellamo et al. 2013
Koufaki et al. 2014 long
Koufaki et al. 2014 short
Nechatal et al. 2002
Piotrowitcz et al. 2010
Roditis et al. 2007
Smart et al. 2012
Unpublished Data 2016
Wisloff et al. 2007
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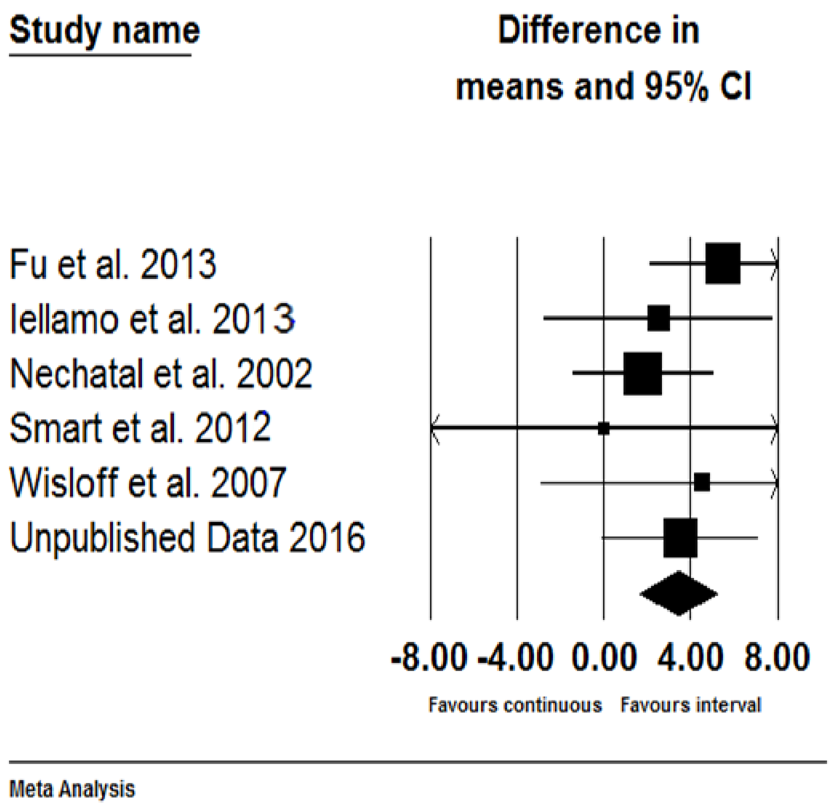
0.00
4.00
8.00
Favours Continuous
Favours Interval
Meta Analysis

Figure 2


Study name
Difference in means and 95% CI
Fu et al. 2013
Iellamo et al. 2013
Nechatal et al. 2002
Smart et al. 2012
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Unpublished Data 2016
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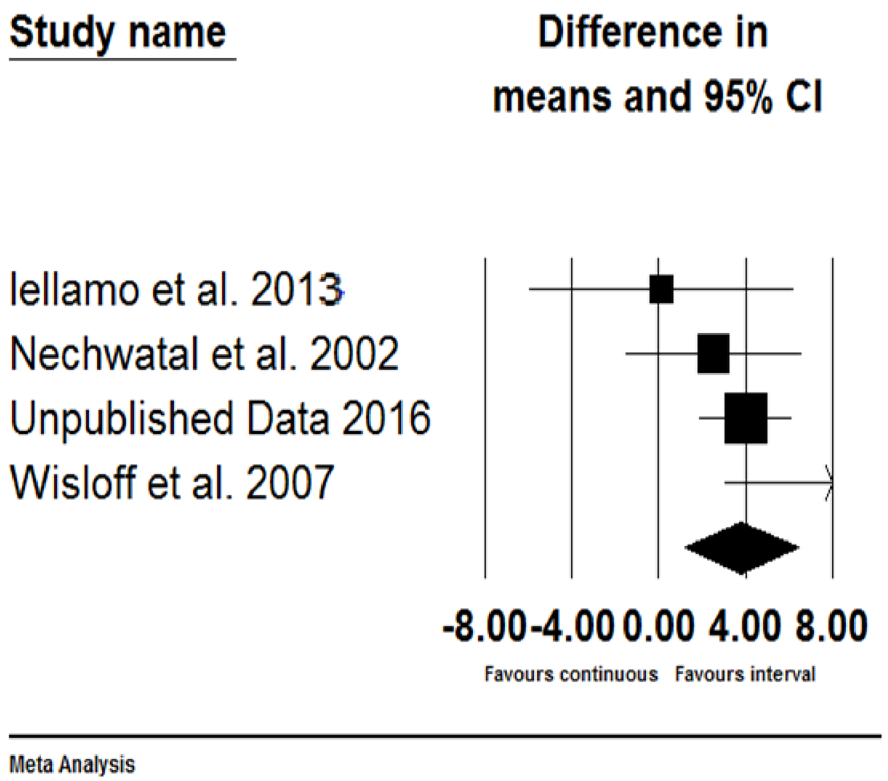
Favours continuous
Favours interval
Meta Analysis

Figure 3


Study name
Difference in means and 95% CI
Iellamo et al. 2013
Nechwatal et al. 2002
Unpublished Data 2016
Wisloff et al. 2007
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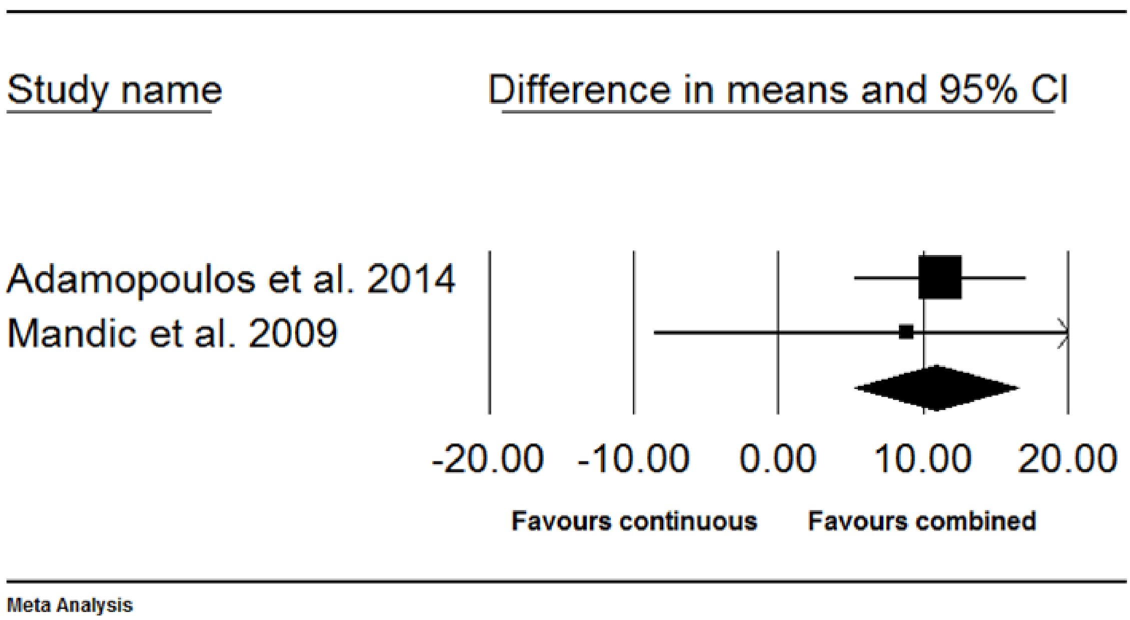
4.00
8.00
Favours continuous
Favours interval
Meta Analysis

Figure 4


Study name
Difference in means and 95% CI
Adamopoulos et al. 2014
Mandic et al. 2009
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-10.00
0.00
10.00
20.00
Favours continuous
Favours combined
Meta Analysis

Figure 5

Table 1: General characteristics and the methodological quality score of the included studies.

Author, Year	PEDro	TM	Patients (m/f)	Age (y)	LVEF (%)	BMI (kg/m²)	β-blocker (%)	ACE (%)	Diuretics (%)	Etiology Ischemic (%)	NYHA
TM: IT_1 versus IT_1S											
Anagnostakou, 2011	7	IT_1	14 (12/2)	52	36	28,6	93	79	86	29	1,9
		IT_1S	14 (11/3)	54	39	28,1	71	71	100	50	1,8
Bouchla, 2011	5	IT_1	10 (9/1)	50,5	37,8	28,1	100	90	80	20	2,0
		IT_1S	10 (7/3)	56,7	33,4	28,6	90	90	90	40	1,9
Georgantas, 2014	5	IT_1	20 (19/1)	53	34	27,4	90	85	95	35	1,8
		IT_1S	22 (16/6)	55	35	28,1	87	82	87	36	1,9
Tasoulis, 2010	4	IT_1	21 (19/2)	53	34,1	27,0	90	81	95	52	1,8
		IT_1S	25 (19/6)	53	35,6	27,4	88	80	88	64	1,9
Delargardelle, 2002	3	IT_1	10 (10/0)	60,4	30,7	27,7	50	90	80	100	2,5

		IT_1S	10 (10/0)	56,3	26,7	27,8	60	100	80	70	2,7
TM: C_1 versus CT_1S											
Adamopoulos, 2014	4	CT_1	22 (17/5)	58,3	30,1	27,2	94	82	82	36	2,5
		CT_1S	21 (19/2)	57,8	27,7	28,6	86	93	100	48	2,6
Beckers, 2008	7	CT_1	30 (24/6)	59	23,4	26,2	90	100	70	60	2,6
		CT_1S	28 (18/10)	58	25,8	25,7	57	96	85	57	2,7
Mandic, 2009	9	CT_1	14 (11/3)	63	29,3	29,8	100	100	71	50	I-III
		CT_1S	15 (11/4)	59	30,9	32,1	100	87	93	53	I-III
TM: C_2 versus IT_2											
Dimopoulos, 2006	4	CT_2	14 (14/0)	61,5	30,7	27,2	86	93	79	36	1,9
		IT_2	10 (9/1)	59,2	34,5	26,5	80	100	100	40	1,8
Freyssin, 2012	5	CT_2	14 (7/7)	55	30,7	24,1	100	86	100	86	-
		IT_2	12 (6/6)	54	27,8	24,8	100	83	100	83	-

Fu, 2013	6	CT_2	15 (9/6)	66,3	38,6	24,5	93	80	47	60	II-III
		IT_2	15 (10/5)	67,5	38,3	24,5	93	80	53	67	II-III
Koufaki, 2014	5	CT_2	17 (13/4)	59,7	35,2	29,5	59	76	65	-	I-III
		IT_2	16 (14/2)	59,8	41,7	28,9	69	63	56	-	I-III
Iellamo, 2013	5	CT_2	8 (8/0)	62,6	31,5	27,2	100	88	63	-	II-III
		IT_2	8 (8/0)	62,2	33,7	27,8	100	100	50	-	II-III
Nechwatal, 2002	5	CT_2	20 (19/1)	47,7	27,3	-	90	100	85	30	2,0
		IT_2	20 (18/2)	45,7	29,3	-	90	100	90	20	2,1
Piotrowitcz, 2010	6	CT_2	75 (64/11)	56,4	30,2	27,7	100	92	77	73	2,5
		IT_2	56 (53/3)	60,5	30,8	26,5	100	93	73	86	2,5
Roditis, 2007	4	CT_2	10 (9/1)	61	34,5	27,4	90	90	90	40	1,7
		IT_2	11 (10/1)	63	30,7	25,9	91	100	82	27	1,8

Smart, 2012	6	CT_2	10 (8/2)	62,9	29,5	28,1	80	90	-	70	2,6
		IT_2	10 (10/0)	59,1	27	28,9	100	100	-	50	2,6
Wisloff, 2007	7	CT_2	9 (7/2)	74,4	32,8	24,7	100	100	44	-	-
		IT_2	9 (7/2)	76,5	28,0	24,5	100	100	56	-	-
Unpublished data, 2016		CT_2	65 (53/12)	60	29	27,5	61	60	49	39	-
		IT_2	77 (63/14)	65	29	27,6	73	71	58	46	-
TM: CT_3 versus S_3											
Maiorana, 2011	6	CT_3	12 (11/1)	61,3	29	30,4	100	100	83	58	1,8
		S_3	12 (10/2)	58,8	26	28,4	92	75	100	58	2,0

Training modality (TM); interval training (IT); continuous training (CT); strength (S); combined continuous and strength training (CTS); combined interval and strength training (ITS); male (m); female (f), year (y); left ventricular ejection fraction (LVEF); body mass index (BMI); New York Health Association (NYHA); Angiotensin I converting enzyme (ACE)

Table 2: Detailed description of the opposed exercise training programs.

Author, Year	TM	I; Rep (E''/R''); Duration (')	F; We; Se
TM: IT_1 versus IT_1S			
Anagnostakou, 2011	IT_1	50% peakWR; 30"E/60"R; 40'	3; 12; 36
	IT_1S	(IT) 50% peakWR; 30"E/60"R; 20' (S) Q: 55-65% 2RM, H: I(Q) - 1kg, UE: 10RM; 3x10-12rep/30"R; 20'	
Bouchla, 2011	IT_1	50% peakWR; 30"E/60"R; 40'	3; 12; 36
	IT_1S	(IT) 50% peakWR; 30"E/60"R; 20' (S) Q: 55-65% 2RM, H: I(Q) – 0.5-1kg, UE: 10RM; 3x10-12rep/30"R; 20'	
Georgantas, 2014	IT_1	50% peakWR; 30"E/60"R; 40'	3; 12; 36
	IT_1S	(IT) 50% peakWR; 30"E/60"R; 20' (S) Q: 55-65% 2RM, H: I(Q) – 0.5-1kg, UE: 10RM; 3x10-12rep/30"R; 20'	
Tasoulis, 2010	IT_1	50% peakWR; 30"E/60"R; 40'	3; 12; 36
	IT_1S	(IT) 50% peakWR; 30"E/60"R; 20' (S) Q: 55-65% 2RM, H: I(Q) - 1kg, UE: 10RM; 3x10-12rep/30"R; 20'	
Delargardelle, 2002	IT_1	75% $peakVO_2$ / 50% $peakVO_2$; 2'E/2'E; 40'	2-3; 16; 40
	IT_1S	(IT) 75%/50% $peakVO_2$; 2'E/2'E; 20' (S) Q, H, P, LD, R, D: 60% 1RM; 3x10rep/60"R; 20'	

TM: CT_1 versus CT_1S			
Adamopoulos, 2014	CT_1	70-80% peakHR & 10% maxSPi; 6 levels of 6 inspiratory efforts; R↓ per level: 60", 45", 15", 10", 5"; 75'	3; 12; 36
	CT_1S	70-80% peakHR & 60% maxSPi; 6 levels of 6 inspiratory efforts; R↓ per level: 60", 45", 15", 10", 5"; 75'	
Beckers, 2008	CT_1	90% HR@VT2; 5x8'E/2'R (0-4m) I↑(3-4m), 3x15'E/2'R (5-6m) (T, B, St, AC, RC); 40' (0-4m), 45' (5-6m)	3; 24; 70
	CT_1S	(CT) 90% HR@VT2; 40' (0-2m), 30' (3-4m), 10' (5-6m) (T, B, St, AC, RC) (S) 50% 1RM (0-2m), 60% 1RM (2-6m) (Q, P, SA, LD); 1-2x10-15rep (1' R); 10' (0-2m), 2x8' (3-4m), 3x15' (5-6m)	
Mandic, 2009	CT_1	50-70% HRR (15'B/15'T); 30'	3; 12; 36
	CT_1S	(CT) 50-70% HRR T (S) 50-70% 1RM; 1-2x10-15rep (CP, SP, VR, BC, TE, LE)	
TM: CT_2 versus IT_2			
Dimopoulos, 2006	CT_2	50% peakWR (5%↑/m); 40'	3; 12; 36
	IT_2	100% peakWR (10%↑/m); 30"E/30"R; 40'	
Freyssin, 2012	CT_2	HR@VT1; 22'B/22'T; 45’	5; 8; 40
	IT_2	50% (0-4w), 80% (4-8w) peakWR; 3x12x30"E/60"R, 5'R between sets; 71'	
Fu, 2013	CT_2	60% $peakVO_2$ (≈HRR); 30'	3; 12; 36
	IT_2	80% $peakVO_2$ / 40% $peakVO_2$; 5x3'E/3'E; 30'	

Koufaki, 2014	CT_2	90% VT (≈40-60% peakVO_2); 3x7-10'(1-2m) → 1x40' (5-6m); 40'	3; 12; 36 3; 24; 72
	IT_2	50% peakWR (≈100% PPO)/25-40% peakWR (≈30-40% PPO); 2x15' (30''E/60''E); 30'	
Iellamo, 2013	CT_2	45-60% HRR; 30-45'	2→5 (↑ every 3w); 12; 42
	IT_2	75-80% HRR/ 45-50% HRR; 2-4x 4'E/3'E	
Nechwatal, 2002	CT_2	75% maxHR; 15'	6; 3; 18
	IT_2	50% peakWR/15W; 30''E/60''E; 15'	
Piotrowicz, 2010	CT_2	40-70%HRR; 20-30'	3; 8; 24
	IT_2	40-70% HRR; 1-3'/1-2'; 30'	
Roditis, 2007	CT_2	50% peakWR to 55-60%; Rep; 40'	3; 12; 36
	IT_2	100% peakWR to 110%; 30''E/30''R; 40'	
Smart, 2012	CT_2	70% peakVO2 I↑2-5W/We; 30'	3; 16; 48
	IT_2	70% peakVO2 I↑2-5W/We; 60''E/60''R; 60'	
Wisloff, 2007	CT_2	70-75% peakHR; Rep; 47'	3; 12; 36
	IT_2	90-95% peakHR / 50-70% peakHR; 4'E/3'E; 38'	
Unpublished data, 2016	CT_2	70-75% peakHR; Rep; 47'	3; 12; 36
	IT_2	90-95% peakHR / 50-70% peakHR; 4'E/3'E; 38'	
TM: CT_3 versus S_3			
Maiorana, 2011	CT_3	50-60% peakVO_2 (0-6We), 60-70% peakVO_2 (6-12We); 20'B, 6.5'R, 20'T; 46.5'	3; 6; 18

	S_3	50-60% 1RM (0-6We), 60-70% 1RM (6-12We); 60"E/30"R (0-6We), 45"E/45"R (6-12We); 3x9 3'R; 46.5'	3; 12; 36

Training modality (TM); interval training (IT); watt (W); continuous training (CT); strength (S); combined continuous and strength training (CTS); combined interval and strength training (ITS); intensity (I); repetitions (Rep); exercise (E); rest (R); frequency, number of sessions per week (F); number of weeks (We); total number of sessions (Se); work rate (WR); oxygen uptake (VO_2); repeated measure (RM); hamstrings (H); quadriceps (Q); upper extremity (UE); pectoralis (P); latissimus dorsi (LD); rhomboidus (R); deltoidus (D); heart rate (HR); inspiratory muscle strength (SPi); ventilatory threshold (VT); stair or step (St); arm-cycling (AC); reclined cycling (RC); serratus anterior (SA); bicycle (B); treadmill (T); heart rate reserve (HRR); peak power output (PPO); month (m); chest press (CP); shoulder press (SP); vertical row (VR); bicep curl (BC); triceps extension (TE); leg extension (LE)

Table 3: Before and after exercise training mean values for the different exercise training modalities.

Author, Year	TM	PeakVO2 (ml/kg/min)		VE/VCO2 slope		LVEF (%)		LVEDD (mm)		MLWHFQ	
		B	A	B	A	B	A	B	A	B	A
TM: IT_1 versus IT_1S											
Anagnostakou, 2011	IT_1	15,7±4,0	17,2±3,7	-	-	-	-	-	-	-	-
	IT_1S	15,7±6,0	18,3±6,3	-	-	-	-	-	-	-	-
Bouchla, 2011	IT_1	15,9±3,6	17,2±4,3	-	-	-	-	-	-	-	-
	IT_1S	13,7±4,7	16,0±4,9	-	-	-	-	-	-	-	-
Georgantas, 2014	IT_1	16,6±4,2	17,9±4,7	31,8±6,6	31,0±6,3	-	-	-	-	-	-
	IT_1S	15,8±5,4	18,6±5,9	32,1±6,1	31,0±5,9	-	-	-	-	-	-
Tasoulis, 2010	IT_1	16,4±4,1	17,8±4,6	-	-	-	-	-	-	-	-
	IT_1S	16,2±5,3	19,1±5,8	-	-	-	-	-	-	-	-
Delargard	IT_1	19,3	19,4	-	-	30,7	27,2	65,6	68,3	-	-

elle, 2002	IT_1S	16,7	17,8	-	-	26,7	31,6	70,4	68,2	-	-
TM: CT_1 versus CT_1S											
Adamopoulos, 2014	CT_1	18,6±4,4	20,2±5,5	37,5±6,9	36,2±6,4	30,1±5,0	36,0±9,0	63,0±7,0	62,0±6,0	42,2±8,1	38,8±8,4
	CT_1S	17,3±5,6	18,9±5,3	36,4±5,6	35,8±6,6	27,7±6,7	36,0±11,0	65,0±9,0	64,0±9,0	38±10,4	27,7±11,3
Beckers, 2008	CT_1	21,2±6,2	22,2±6,2	33,2±8,7	31,7±7,4	23,4±9,4	29,0±13,5	60,8±13,9	62,3±9,3	-	-
	CT_1S	18,1±4,5	20,2±5,2	34,4±7,2	33,6±6,3	25,8±6,9	28,5±9,7	65,7±8,9	65,2±8,7	-	-
Mandic, 2009	CT_1	16,0±5,1	17,3±6,4	32,5±5,1	33,5±10,1	29,3±11,8	32,6±11,0	-	-	45,9±16,8	41,4±23,2
	CT_1S	16,1±6,0	17,2±6,9	27,9±3,9	27,6±5,4	30,9±11,4	34,5±9,6	-	-	40,0±19,8	32,6±20,2
TM: CT_2 versus IT_2											
Dimopoulos, 2006	CT_2	15,5±3,7	16,4±3,8	32,7±4,9	33,2±6,2	-	-	-	-	-	-
	IT_2	15,4±4,7	16,6±4,9	34,2±5,6	33,4±5,2	-	-	-	-	-	-
Freyssin, 2012	CT_2	10,6±4,1	10,8±4,1	-	-	-	-	-	-	-	-
	IT_2	10,7±2,9	13,6±3,2	-	-	-	-	-	-	-	-

Fu, 2013	CT_2	15,9±2,7	16,0±5,4	34,8±8,0	35,6±8,6	38,6±4,8	43,1±5,9	-	-	34,8±19,0	28,3±14,3
	IT_2	16,0±3.9	19,6±4,5	35,2±5,2	30,4±5,2	38,3±3,5	48,6±3,3	-	-	34,3±13,9	21,3±13,2
Koufaki, 2014	CT_2	17,6±7,1	19,8±7,8 18,9±7,5	-	-	-	-	-	-	22,8±12,9	24,6±20,3 37±24
	IT_2	15,3±4,7	17,3±5,4 17,7±4,9	-	-	-	-	-	-	26,6±18,3	29,1±15,7 33,3±17,6
Iellamo, 2013	CT_2	18,4±4,3	22,5±3,1	30,9±4,5	30,1±4,1	31,5±6,9	32,1±5,2	68,5±6,7	66,8±6,3	-	-
	IT_2	18,8±4,6	23,0±4,3	30,0±2,9	28,0±2,9	33,7±4,8	34,6±5,6	67,6±5,6	66,6±6,1	-	-
Nechwatal, 2002	CT_2	17,2±6,0	18,8±6,5	-	-	26,9±6,0	27,9±5,4	68,3±5,0	64,8±7,0	-	-
	IT_2	18,5±4,1	20,0±4,5	-	-	29,0±7,0	29,7+-5,0	63,1±6,0	62,3±6,0	-	-
Piotrowitcz, 2010	CT_2	17,8±4,1	19,7±5,2	-	-	-	-	-	-	-	-
	IT_2	17,9±4,4	19,0±4,6	-	-	-	-	-	-	-	-
Roditis,	CT	15,3±	16,6±	32,8±	33,7±7	-	-	-	-	-	-

2007	2	4,4	4,5	5,8	,2						
	IT_2	14,2±3,1	15,4±4,2	34,2±4,0	34,6±4,6	-	-	-	-	-	-
Smart, 2012	CT_2	12,4±2,5	14,0±4,0	32,0±4,5	30,3±5,6	29,5±7,2	29,3±12,2	-	-	47,2±14,1	34,6±19,5
	IT_2	12,2±6,5	14,7±4,5	35,5±6,4	30,2±4,4	27,0±7,9	32,8±9,7	-	-	41,9±21,4	30,1±17,3
Wisloff, 2007	CT_2	13,0±3,3	14,9±2,7	-	-	32,8±4,8	33,5±5,7	69,1±8,6	68,2±6,5	-	-
	IT_2	13,0±4,8	19,0±6,3	-	-	28,0±7,3	38,0±9,8	66,7±6,8	59,0±6,8	-	-
Unpublished data, 2016	CT_2	16,2±7,0	17,0±8.0	-	-	29,0±12,3	27,0±12,3	69,0±12,3	67,0±8,2	-	-
	IT_2	16,8±4,5	18,2±8,3	-	-	29,0±11,2	31,0±9,0	68,0±8,2	63,0±4,4	-	-
TM: CT_3 versus S_3											
Maiorana, 2011	CT_3	14,5±4,5	15,7±6,2 17,2±5,5	-	-	-	-	-	-	-	-
	S_3	13,7±4,2	15,8±4,5 16,4±3,8	-	-	-	-	-	-	-	-

Training modality (TM); interval training (IT); continuous training (CT); strength (S); combined continuous and strength training (CTS); combined interval and strength training (ITS); baseline (B); after conducting the exercise training program (A); oxygen uptake (VO2); ventilation over carbon dioxide (VE/VCO2); left ventricular ejection fraction (LVEF); left ventricular end-diastolic diameter (LVEDD); Minnesota living with heart failure questionnaire (MLWHFQ); mean ± standard deviation (mean ± SD)

Highlights for review

- Different exercise modalities were compared.
- Interval training significantly improved left ventricular remodelling.
- It is important to involve heart failure patients in any kind of exercise training.