The role of exercise training on cardiovascular peptides in patients with heart failure: A systematic review and meta-analysis

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ABSTRACT

Background: The purpose of this systematic review & meta-analysis was to determine the roles of aerobic, resistance or concurrent exercises vs. control (CON) group on B-type natriuretic peptide (BNP) and N-terminal-pro hormone BNP (NT-proBNP) in patients with heart failure.

Methods: The electronic databases of PubMed, Scopus, Web of Science, and Google Scholar were searched up to May 2022 for aerobic vs. CON, resistance vs. CON, and concurrent vs. CON studies on circulating (serum or plasma) levels of BNP and NT-proBNP in patients with heart failure. Non-randomized or randomized controlled trial studies were included. Standardized mean difference (SMD) and 95% confidence intervals (95% CIs) were calculated. This systematic review & meta-analysis was registered in PROSPERO at the University of York with the registration number [CRD42021271632].

Results: A total of 28 articles (37 intervention arms), 26 aerobic intervention arms, 3 resistance intervention arms, and 8 concurrent intervention arms were included. A total of 2563 participants (exercise groups = 1350 and CON groups = 1213) were included. Exercise training significantly decreased NT-proBNP marker [-0.229 (SMD and 95% CI: 0.386 to −0.071), p = 0.005], irrespective of overweight/obesity status. Analysis of subgroup by type of exercise training revealed that there was a significant reduction in the NT-proBNP marker for aerobic exercise group compared to the CON group [-0.336 (SMD and 95% CI: 0.555 to −0.071), p = 0.005], whereas concurrent exercise did not show significant changes in the NT-proBNP marker [-0.134 (SMD and 95% CI: 0.350 to 0.083), p = 0.227]. In addition, exercise training did not significantly change the BNP marker [-0.122 (SMD and 95% CI: 0.322 to 0.079), p = 0.235].

Conclusions: The results suggested that exercise training, especially aerobic exercise can be improved the NT-proBNP concentrations in patients with HF (irrespective of overweight/obesity status), which may be a sign of positive physiological adaptations to aerobic exercise.

1. Introduction

Heart failure (HF) is a heterogeneous syndrome, causing significant mortality and morbidity worldwide (Metra and Teerlink, 2017; Groeneveld et al., 2020). Recently, the results of clinical studies have shown that B-type natriuretic peptide (BNP) and N-terminal-pro hormone BNP (NT-proBNP), as myocardial stretch markers (Chow et al., 2017; Pearson et al., 2018), are recognized as the gold standard circulating markers for the diagnostic, prognostic, prevention, management, and assessment of HF disease (Chow et al., 2017). BNP or ventricular/brain natriuretic peptide is a 32-amino acid hormone/polypeptide (Xu-Cai and Wu, 2010; Hall, 2004) secreted by cardiomyocytes in response to an increase in left ventricular stretching and wall stress (Topf et al., 2020). NT-proBNP is a 76-amino acid prohormone that is cleaved from the molecule to release the BNP (Hall, 2004). A number of studies demonstrated that serum levels of BNP and NT-proBNP increase significantly in response to pathophysiological conditions such as acute HF, chronic HF, ventricular hypertrophy, cardiac ischemia, atrial fibrillation, hypertension, hypoxia, diabetes mellitus, and infection (Topf et al., 2020; Xu-Cai and Wu, 2010). The primary and secondary prevention of cardiovascular diseases (CVDs),
pharmacological interventions and medications, lifestyle changes, physical activity and exercise training and/or cardiac rehabilitation are important approaches to the HF (Piepoli et al., 2019). The American Heart Association (AHA) guidelines have demonstrated that exercise training (as a non-pharmacological intervention) or cardiac rehabilitation is now a class 1 recommendation in patients with HF (Pearson et al., 2018; Piña et al., 2003; Piepoli et al., 2019). In general, exercise training is an important non-pharmacological intervention that is effective and safe (Malandish et al., 2020a, 2020b; Khalafi et al., 2021a; Khalafi et al., 2021b), and is often recommended as a class 1 treatment of CVDs, especially for the HF patients (Pearson et al., 2018; Piña et al., 2003; Piepoli et al., 2019). Regular physical activity also improves cardiac function (Adamopoulos et al., 2014; Aksoy et al., 2015; Pearson et al., 2018), VO2max (Conraads et al., 2004), and quality of life (Adamopoulos et al., 2014; Kawachi et al., 2017) in patients with HF, and thus may be an effective non-pharmacological intervention to improve myocardial stretch function and cardio-metabolic risk factors in HF patients. It seems that an optimal reduction in serum levels of BNP and NT-proBNP may contribute to the beneficial role of exercise intervention on myocardial stretch function and cardio-metabolic risks in patients with HF (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Wislaff et al., 2007; Fu et al., 2013; Yeh et al., 2004), irrespective of overweight/obese status. A number of studies have reported that aerobic exercise intervention (Fu et al., 2013; Yeh et al., 2004; Abolahrari-Shirazi et al., 2018; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Melo et al., 2019; Wislaff et al., 2007) and as well as concurrent or combined aerobic and resistance interventions (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004) can reduce serum levels of BNP and NT-proBNP in patients with HF compared to the control group, while other studies have reported no change (Karavidas et al., 2008; Kawachi et al., 2017; Kobayashi et al., 2003; Yeh et al., 2011; Ahmad et al., 2014; Aksoy et al., 2015; Eleuteri et al., 2013; Giallauria et al., 2006-b; Marco et al., 2013; Nilsson et al., 2010; Prescott et al., 2009; Sandri et al., 2012; Van Berendoncks et al., 2010). In this regard, there is the systematic review and meta-analysis-based evidence supporting a favorable effect in serum levels of BNP (Smart and Steele, 2010; Smart et al., 2012) and NT-proBNP (Smart and Steele, 2010; Smart et al., 2012; Pearson et al., 2018) in patients with HF. It seems that the roles of aerobic (Fu et al., 2013; Yeh et al., 2004; Abolahrari-Shirazi et al., 2018; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Wislaff et al., 2007), resistance (Karavidas et al., 2008) and/or concurrent (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004) interventions on serum levels of BNP and NT-proBNP have contradictory results in HF patients compared to the control group. Therefore, the purpose of this systematic review and meta-analysis was to clarify the roles of aerobic, resistance, and concurrent exercise interventions vs. control group on cardiovascular peptides including BNP and NT-proBNP in patients with HF.

2. Methods

2.1. Search strategy

The international prospective registration of our systematic review and meta-analysis protocol was registered in PROSPERO at the University of York [CRD42021271632]. This systematic review and meta-analysis was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (Page et al., 2021) and the Cochrane Handbook for Systematic Reviews of Interventions. The electronic databases of PubMed, Scopus, Web of Science, and Google Scholar were searched to identify original published articles up to May 2022 by four independent researchers (A M, N Gh, A K, and M N). The search strategy for exercise training interventions, BNP and NT-proBNP markers, and HF patients included the keywords as follows: ((((concurrent OR combined OR combination OR concurrent OR combination) OR Circuit) AND (resistance OR strength))) AND (aerobic OR endurance OR HIIT/high intensity interval training OR SIT/sprint interval training OR Continuous)) AND (training OR exercise OR exercise training OR physical activity OR cardiac rehabilitation) AND (“BNP” OR “B-type natriuretic peptide” OR “brain natriuretic peptide” OR “ventricular natriuretic peptide” OR “NT-proBNP” OR “N-terminal-pro hormone B-type natriuretic peptide”)) AND (“HF/EF” OR “heart failure with reduced ejection fraction” OR “HFpEF” OR “heart failure with preserved ejection fraction” OR “heart failure” OR “acute heart failure” OR “chronic heart failure”) (Kawachi et al., 2017). The keywords were combined by using the Boolean operator “OR”. The five different sets of keywords were combined by using “AND”. The keywords used could be found in the main title, abstract, different sections of the abstract, and/or in the keywords of each original article. In addition, systematic reviews and meta-analyses, and reference lists of all extracted articles were scrutinized for eligibility and to ensure that no relevant articles have been missed. The titles and abstracts of all articles were screened after removing duplicate publications and then full-text of articles were assessed for eligibility. All extracted articles were scrutinized independently by four reviewers (A M, N Gh, A K, and M N).

2.2. Study selection

Non-randomized and randomized controlled trials of exercise training interventions and/or cardiac rehabilitation programmes were considered for eligibility of inclusion criteria as follows: (a) only English language and peer-reviewed original articles, (b) original research with human participants (males and females), (c) patients with HF aged 18 yrs or older, (d) HF patients with maintaining routine medications or usual care such as chronic HF, acute HF, left ventricular dysfunction after myocardial infarction, chronic systolic HF, moderate systolic dysfunction after myocardial infarction, HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and compensated congestive HF, (e) measuring serum levels of BNP and NT-proBNP at baseline and after intervention, (f) duration of exercise training >2 weeks, (g) having at least one exercise training group (aerobic, resistance or concurrent) with HF vs. control group with HF or healthy control group, (b) usual care or routine medications for control group with and without exercise prescription and/or home-based exercise training intervention. The modality of exercise training in this
systematic review and meta-analysis included aerobic (‘aerobic training; endurance training; exercise-based cardiac rehabilitation; cardiac rehabilitation programme; low and moderate-intensity inspiratory; physical training; aerobic interval training; HIIT; Tai Chi’), resistance (‘resistance training; functional electrical stimulation; inspiratory muscle training; peripheral resistance training’), concurrent (‘concurrent training’, combined training’). It should be noted that there were no restrictions on the duration of exercise training or used training protocols in the studies. Exclusion criteria included (a) non-original articles (letters to the editors, short reports, case studies, methodologies, review articles and systematic review & meta-analysis articles), (b) non-English language articles, (c) animal studies, (d) studies without exercise group, (e) studies without control group, (f) studies with caloric restrictions in exercise group and/or control group, (g) studies with dietary interventions, (h) studies with exacerbate HF-related medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers (CCBs), and most antiarrhythmic drugs.

2.3. Data extraction

Data extraction was performed by four independent reviewers (A. M. N Gh, A K, and M N) and any disagreement was resolved by discussion among all teamwork reviewers (A. M, N Gh, A K, and M N). The characteristics of the data for each study were extracted as follows: (a) study design, (b) participant characteristics including age, sex, body mass index (BMI) and sample size, (c) exercise training characteristics including mode, duration and frequency, (d) outcome markers including circulating BNP and NT-proBNP markers. The pre- and post-test values (mean and standard deviation) or mean differences and associated standard deviations were entered into the meta-analysis in order to generate forest plots. If means and standard deviations were not reported, they were calculated from standard errors, median, range and/or interquartile range (Wan et al., 2014; Higgins et al., 2019). The Getdata Graph Digitizer software was used for the data extraction from figures. If studies had multiple arms of exercise interventions, data for the aerobic vs. control group, resistance vs. control group and concurrent vs. control group were included. In addition, for the studies with more than one evaluated post-test intervention period, only the last period of post-test intervention was considered. When insufficient information was available from the published articles and/or additional information was required, the corresponding author was contacted.

2.4. Quality assessment and sensitivity analysis

The PEDro scale was used to assess the risk of bias (Higgins et al., 2019), which included as follows: (1) eligibility criteria specified, (2) random allocation of participants, (3) allocation concealed, (4) groups similar at baseline, (5) assessors blinded, (6) outcome measures assessed in 85% of participants, (7) intention to treat analysis, (8) comparing between-groups for statistical differences, (9) point measures and measures of variability reported for main effects, (10) activity monitoring in control group, (11) relative exercise intensity reviewed (12) non-supervised or supervised (Table 1). To evaluate the robustness of the results was used of sensitivity analysis.

2.5. Statistical analysis

The comprehensive meta-analysis (CMA) software was used for data analysis and as well as calculating the standardized mean difference and 95% confidence intervals (CIs) by fixed and random-effects models. Significance level was considered at a P < 0.05. The effect size was calculated to compare the effects of exercise training interventions (aerobic, resistance and concurrent) vs. control group on circulating BNP and NT-proBNP markers. The Cochrane guidelines for interpreting effect sizes were considered as follows: small effect size (0.2–0.49), medium effect size (0.5–0.79), and large effect size (more than 0.8) (Cohen, 2013). Heterogeneity was assessed by using the $I^2$ statistic. Furthermore, the Cochrane guidelines in the interpretation of the $I^2$ statistic were considered as follows: low heterogeneity (25%), medium heterogeneity (50%), and high heterogeneity (75%). The visual interpretation of funnel plots was considered to identify publication bias. In addition, Egger’s test was used as a secondary determinant test; significant publication bias was considered apparent if P < 0.1 (Egger et al., 1997).

3. Results

3.1. Included studies

The initial search in the electronic databases of PubMed, Scopus, Web of Science, and Google Scholar identified 1550, 235, 228, and 1285 articles, respectively. After removing duplicates and screening articles based on the title/abstract, 84 full-text papers were included for final screening based on the inclusion and exclusion criteria. Of those 84 papers, 28 full-text articles met the inclusion criteria and 56 full-text articles were excluded with reasons as follows: (1) three articles with “letters to the editor”, (2) sixteen articles without control group, (3) four articles with hormone therapy in exercise group, (4) two articles with combined dietary supplementation plus exercise interventions in HF patients, (5) two articles were measured serum levels of BNP and NT-proBNP in obese hypertension patients and athletes, (6) six articles with measured serum levels of BNP and NT-proBNP at baseline, (7) ten articles without reporting BNP and NT-proBNP values in HF patients, (8) four articles without any exercise training interventions in HF patients, (9) seven article with acute exercise training interventions in HF patients, and (10) two articles did not have specific and enough information in exercise training intervention and BNP and NT-proBNP values in patients with HF, and no additional information was provided after contacting the corresponding author. Nine articles included two arms of exercise training intervention (Abolarrayhi-Shirazi et al., 2018; Aksoy et al., 2015; Delagardelle et al., 2008; Giallauria et al., 2006-a; Fu et al., 2013; Kawauchi et al., 2017; Melo et al., 2019; Sandri et al., 2012; Wislöff et al., 2007). A total of 28 articles (37 intervention arms), 26 aerobic intervention arms, 3 resistance intervention arms, and 8 concurrent intervention arms were included. A total of 2563 participants (exercise groups = 1350 and CON groups = 1213) were included. The flowchart of study selection is shown in Fig. 1.

3.2. Participant characteristics

The participant characteristics of included articles are presented in Table 2. As mentioned above, total sample sizes including 2563 participants (1350 participants in exercise groups and 1213 participants in control groups) were included in our meta-analysis. The sample size, mean age, and mean BMI for each article ranged between 8 and 477 participants (Conraads et al., 2007; Ahmad et al., 2014), 49 ± 19.36 and 76.5 ± 9 yrs (Sandri et al., 2012; Wislöff et al., 2007), and between 24.5 ± 3 and 30 ± 11.61 kg/m² (Wislöff et al., 2007; Sandri et al., 2012), respectively. A total of 28 included articles, 27 articles were included both male and female genders, and one article was included only male gender (Eleuteri et al., 2013).

3.3. Characteristics of interventions in exercise and control groups

The characteristics of exercise training interventions and control group-related interventions are illustrated in Table 3. Types of exercise interventions including aerobic (Abolarrayhi-Shirazi et al., 2018; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2007; Eleuteri et al., 2013; Fu et al., 2013; Giallauria et al., 2006-a; Giallauria et al., 2006-b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Melo et al., 2019; Nilsson et al., 2010; Passino et al., 2006; Radi et al., 2017; Sandri et al., 2012; Wislöff et al., 2015).
Table 1
Risk of bias assessment.

| Authors et al. (yrs) | eligibility criteria specified | Random allocation of participants | allocation concealed | groups similar at baseline | assessors blinded | outcome measures assessed in 85% of participants* | intention to treat analysis | reporting of between group statistical comparison# | point measures and measures of variability reported for main effects | Activity monitoring in control group | Relative exercise intensity reviewed | Supervised/Non-supervised | Total PEDRO score |
|----------------------|--------------------------------|----------------------------------|----------------------|---------------------------|------------------|---------------------------------|--------------------------|---------------------------------|---------------------------------|-----------------------------|----------------------------|-----------------|-----------------|
| Abolahrari-Shirazi et al., 2018 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓✓✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 15 |
| Adamopoulos et al. (2014) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Ahmad et al. (2014) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Aksoy et al. (2015) | ✓ | ✓ | – | ✓ | – | – | – | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Conrads et al. (2004) | ✓ | ✓ | – | ✓ | – | – | – | – | – | – | – | ✓ | 8 |
| Conrads et al. (2007) | ✓ | ✓ | ✓ | ✓ | – | – | – | – | – | ✓ | – | ✓ | 11 |
| Delagardelle et al. (2008) | ✓ | ✓ | ✓ | ✓ | – | – | – | – | – | – | – | – | 11 |
| Eleuteri et al. (2013) | ✓ | ✓ | ✓ | ✓ | – | – | – | – | – | – | – | – | 13 |
| Fu et al. (2013) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 10 |
| Giallauria et al., 2006-a | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Giallauria et al., 2006-b | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 13 |
| Giallauria et al. (2008) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 13 |
| Karavidas et al. (2008) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Kawauchi et al. (2017) | ✓ | ✓ | ✓ | ✓ | – | – | – | – | – | – | – | – | 9 |
| Kobayashi et al. (2003) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 11 |
| Marco et al. (2013) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Maria-Sarullo et al. (2006) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Masterson-Creber et al. (2015) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 11 |
| Melo et al. (2019) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 11 |
| Nilsson et al. (2010) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| Passino et al. (2006) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 9 |
| Prescott et al. (2009) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 10 |
| Raff et al. (2017) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 9 |
| Sandri et al. (2012) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 11 |
| Van Berendoncks et al. (2010) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 9 |
| Wisloff et al. (2007) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 13 |
| Yeh et al. (2004) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 12 |
| Yeh et al. (2011) | ✓ | ✓ | ✓ | ✓ | – | ✓✓ | – | ✓ | ✓ | ✓ | ✓ | ✓ | 10 |

Note: Total PEDRO score out of 15 points; ✓ = one point; (–) = not reported or unclear; *Three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported; #Two points possible—one point if primary outcome is reported, one point if all other outcomes reported.
2007; Yeh et al., 2004; Yeh et al., 2011), resistance (Karavidas et al., 2008; Kawauchi et al., 2017), and concurrent (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Delagardelle et al., 2008; Marco et al., 2013; Prescott et al., 2009; Van Berendoncks et al., 2010) were studies included in our meta-analysis. The intensity ranges for the aerobic exercise interventions were performed from 40% VO2peak (Abolahrari-Shirazi et al., 2018), 60% HRmax reserve (Ahmad et al., 2014; Masterson-Creber et al., 2015), increased heart rate up to 20 bpm above resting (Radi et al., 2017) and 15–18 on the Borg scale (Nilsson et al., 2010) to 70% HRmax reserve (Masterson-Creber et al., 2015), 80% VO2peak (Fu et al., 2013; Prescott et al., 2009), 90% of the ventilator threshold level (Conraads et al., 2004; Conraads et al., 2007; Eleuteri et al., 2013; Kobayashi et al., 2003; van Berendoncks et al., 2010) and as well as 90–95% HRmax (Melo et al., 2019; Wisloff et al., 2007), with the most common exercise intensity 60–75% VO2peak (Delagardelle et al., 2008; Fu et al., 2013; Giallauria et al., 2006a,b; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Passino et al., 2006; Sandri et al., 2012) or 60–70% HRmax reserve (Ahmad et al., 2014; Masterson-Creber et al., 2015). The intensity ranges for the resistance training interventions were performed from 50% of 1RM/one-repetition maximum (Conraads et al., 2004; Kawauchi et al., 2017; van Berendoncks et al., 2010) and 4–5 on the modified Borg scale (Prescott et al., 2009) to 60% of 1RM (Abolahrari-Shirazi et al., 2018; Conraads et al., 2004; Delagardelle et al., 2008; van Berendoncks et al., 2010), 60% of individual sustained maximal inspiratory pressure (Adamopoulos et al., 2014), functional electrical stimulation 25 Hz (Karavidas et al., 2008), 70% of 1RM (Delagardelle et al., 2008) and 100% of 10RM (Marco et al., 2013), with the most common exercise intensity 50–60% of 1RM (Conraads et al., 2004; van Berendoncks et al., 2010). The duration of exercise intervention protocols was varied from 1 month (4 weeks) (Marco et al., 2013; Radi et al., 2017) to 12 months (Masterson-Creber et al., 2015), with the most common period of 3 months (12 weeks) (Adamopoulos et al., 2014; Ahmad et al., 2014; Eleuteri et al., 2013; Fu et al., 2013; Giallauria et al., 2006a; Giallauria et al., 2006b; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Wisloff et al., 2007; Yeh et al., 2004; Yeh et al., 2011). The duration of 6 weeks (Karavidas et al., 2008), 7 weeks (Abolahrari-Shirazi et al., 2018), 8 weeks (Kawauchi et al., 2017; Prescott et al., 2009), 10 weeks (Aksoy et al., 2015), 4 months (Conraads et al., 2004; Delagardelle et al., 2008; Nilsson et al., 2010; Sandri et al., 2012; Van Berendoncks et al., 2010), 5 months (Conraads et al., 2007), 6 months (Giallauria et al., 2008; Melo et al., 2019), and 9 months (Passino et al., 2006) were used in other
The participant characteristics included articles at baseline. | Source, yrs | Country | Exercise + Control | Sex | Participant characteristics | Groups | Age (yrs) (Baseline) Mean ± SD | BMI (kg/m²) (Baseline) Mean ± SD | BNP or proBNP |
|------------|---------|-------------------|-----|---------------------------|--------|-----------------------------|----------------------------------|------------------|
| Abolahrari-Shirazi et al., 2018 | Iran | 25 (Concurrent) + 25 (Aerobic) + 25 (Control) | Male/ Female | Patients with heart failure | Concurrent Control | Concurrent: 56.76 ± 8.71 Aerobic: 57.64 ± 7.85 Control: 57.32 ± 9.41 | Concurrent: 25.69 ± 3.65 Aerobic: 26.71 ± 2.91 Control: 26.10 ± 3.86 | NT-proBNP |
| Adamopoulos et al. (2014) | Belgium | 21 + 22 = 43 | Male/ Female | Patients with chronic heart failure | Concurrent Control | Concurrent: 57.8 ± 11.7 Control: 58.3 ± 13.2 Aerobic: 59.0 (51.2, 67.9) Control: 59.0 (50.7, 68.0) | NT-proBNP |
| Ahmad et al. (2014) | England | 477 + 451 = 928 | Male/ Female | Patients with chronic heart failure | Aerobic Control | Aerobic: 57 ± 2 Control: 61 ± 4 Concurrent: 59.3 ± 5.9 Control: 55.5 ± 7.5 Aerobic: 66 ± 2 Control: 63 ± 2 | Unknown | NT-proBNP |
| Aksoy et al. (2015) | Turkey | 15 (Continuous) + 15 (Intermittent) + 15 (Control) | Male/ Female | Patients with chronic heart failure | Aerobic Control | Aerobic: 63.7 ± 8.8 Intermittent: 59.6 ± 6.9 Control: 57.5 ± 11.2 | Aerobic: 28.4 ± 4.9 Intermittent: 30.1 ± 5.1 Control: 29.1 ± 4.2 | NT-proBNP |
| Conraads et al. (2004) | Belgium | 27 + 22 = 49 | Male/ Female | Patients with chronic heart failure | Concurrent Control | Concurrent: 59 ± 2 Control: 61 ± 4 Aerobic: 59.3 ± 5.9 Control: 55.5 ± 7.5 | Unknown | NT-proBNP |
| Conraads et al. (2007) | Belgium | 8 + 9 = 17 | Male/ Female | Patients with chronic heart failure | Aerobic Control | Aerobic: 57 ± 2 Control: 61 ± 4 Concurrent: 59.3 ± 5.9 Control: 55.5 ± 7.5 | Unknown | NT-proBNP |
| Delagardelle et al. (2008) | Luxembourg | 45 + 15 = 60 | Male/ Female | Patients with and without ischemic chronic heart failure | Concurrent Control | Concurrent: 59.3 ± 5.9 Control: 55.5 ± 7.5 | Concurrent: 28.56 ± 4.9 Control: 28.2 ± 4.8 | NT-proBNP |
| Eleuteri et al. (2013) | Italy | 11 + 10 = 21 | Male | Patients with chronic heart failure | Aerobic Control | Aerobic: 66 ± 2 Control: 63 ± 2 | Unknown | NT-proBNP |
| Fu et al. (2013) | Taiwan | 15 (Aerobic interval) + 15 (Aerobic continuous) + 15 (Control) | Male/ Female | Patients with heart failure | Aerobic Interval Continuous Control | Aerobic Interval: 67.5 ± 1.8 Continuous: 66.3 ± 2.1 Control: 67.8 ± 2.5 Aerobic: 55 ± 2 Control: 54 ± 3 | Unknown | BNP |
| Gallauria et al., 2006-a | Italy | 22 + 22 = 44 | Male/ Female | Patients with left ventricular dysfunction after myocardial infarction | Aerobic Control | Aerobic: 68.6 ± 2.3 Control: 68.2 ± 2.6 | Aerobic: 55.9 ± 3.1 Control: 55.1 ± 3.7 | Unknown | NT-proBNP |
| Gallauria et al., 2006-b | Italy | 20 + 20 = 40 | Male/ Female | Patients after acute myocardial infarction | Aerobic Control | Aerobic: 68.6 ± 2.3 Control: 68.2 ± 2.6 | Aerobic: 55.9 ± 3.1 Control: 55.1 ± 3.7 | Unknown | NT-proBNP |
| Gallauria et al. (2008) | Italy | 30 + 31 = 61 | Male/ Female | Patients with moderate systolic dysfunction after myocardial infarction | Aerobic Control | Aerobic: 55.9 ± 3.1 Control: 55.1 ± 3.7 | Aerobic: 25.6 ± 2.4 Control: 25.3 ± 2.9 | NT-proBNP |
| Karavidas et al. (2008) | Greece | 20 + 10 = 30 | Male/ Female | Patients with chronic heart failure | Resistance/ Functional electrical stimulation Control | Resistance: 62 ± 12 Control: 64 ± 8 | Resistance: 27 ± 5 Control: 28 ± 4 | BNP |
| Kawasuchi et al. (2017) | Brazil | 13 + 9 = 22 | Male/ Female | Patients with heart failure | Resistance Control | Low resistance: 54 ± 10 Moderate resistance: 56 ± 7 Control: 56 ± 7 Aerobic: 55 ± 7.48 | Low resistance: 28 ± 6 Moderate resistance: 28 ± 5 Control: 25 ± 4 | BNP |
| Kobayashi et al. (2003) | Japan | 14 + 14 = 28 | Male/ Female | Patients with chronic heart failure | Aerobic Control | Aerobic: 55 ± 7.48 | Aerobic: 25.6 ± 2.4 Control: 25.3 ± 2.9 | BNP |

(continued on next page)
Table 2 (continued)

| Source, yrs | Country  | Exercise + Control | Sex          | Participant characteristics | Groups                        | Age (yrs) | BMI (kg/m²) | BNP or NT-proBNP |
|-------------|----------|--------------------|--------------|-----------------------------|-------------------------------|-----------|-------------|------------------|
| (Baseline)  | (Baseline) |                    |              |                             |                               | Mean ± SD | Mean ± SD   |                  |
| **Control** | **Control** |                    |              |                             |                               |           |             |                  |
| Marco et al. (2013) | Spain       | 11 + 11 = 22       | Male/ Female | patients with chronic heart failure | Concurrent Control               | 62 ± 7.48|             |                  |
| Maria-Sarullo et al. (2006) | Italy     | 30 + 30 = 60       | Male/ Female | Patients with chronic heart failure | Aerobic Control                 | 68.5 ± 8.08|             |                  |
| Masterson-Creber et al. (2015) | USA       | 163 + 157 = 320    | Male/ Female | Patients with chronic heart failure | Aerobic Control                 | 58.66 ± 11.91|             |                  |
| Melo et al., 2019-a | Portugal  | 7 + 9 = 16         | Male/ Female | Patients with chronic heart failure (atrial fibrillation) | Aerobic Control | 69.4 ± 7.2 |             |                  |
| Nilsson et al. (2010) | Norway     | 39 + 39 = 78       | Male/ Female | Patients with chronic heart failure | Aerobic Control               | 66.2 ± 14.57|             |                  |
| Passino et al. (2006) | Italy       | 44 + 41 = 85       | Male/ Female | Patients with heart failure | Aerobic Control | 71.5 ± 7.9  |             |                  |
| Prescott et al. (2009) | Denmark  | 20 + 23 = 43       | Male/ Female | Patients with chronic systolic heart failure | Concurrent Control | 68 ± 11  |             |                  |
| Raci et al. (2017) | Indonesia | 48 + 65 = 113      | Male/ Female | Patients with heart failure | Aerobic Control | 51.8 (49.3-54.4) |             |                  |
| Sandri et al. (2012) | Germany   | 15 (Aerobic) + 15(Control) | Male/ Female | Patients with chronic heart failure | Aerobic Control | 51.7 (49.6-53.7) |             |                  |
| Van Berendoncks et al. (2010) | Belgium  | 46 + 34 = 80       | Male/ Female | Patients with chronic heart failure | Concurrent Control | 57.5 ± 10.8 |             |                  |
| Wisloff et al. (2007) | Norway     | 9 (Aerobic/moderate continuous) + 9 (Aerobic/interval) + 9(Control) | Male/ Female | Patients with heart failure | Aerobic Control | 61.1 ± 11.6 |             |                  |
| Yeh et al. (2004) | USA        | 15 + 15 = 30       | Male/ Female | Patients with chronic heart failure | Aerobic Control | 74.4 ± 12 interval |             |                  |
| Yeh et al. (2011) | USA        | 50 + 50 = 100      | Male/ Female | Patients with chronic heart failure | Aerobic Control | 68.1 ± 11.9 |             |                  |

Note: B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP).

Studies. The exercise frequency was performed from 2 (Melo et al., 2019; Nilsson et al., 2010; Prescott et al., 2009; Yeh et al., 2004, 2011) to 7 (Kawauchi et al., 2017; Marco et al., 2013) day/week, with the most common exercise frequency of 3 day/week (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Delagardelle et al., 2008; Fu et al., 2013; Giallauria et al., 2006–a; Giallauria et al., 2006–b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Master-son-Creber et al., 2015; Passino et al., 2006; Radi et al., 2017; van Berendoncks et al., 2010; Wisloff et al., 2007). In addition, the exercise frequency of 4 day/week (Sandri et al., 2012) and as well as 5 day/week (Eleuteri et al., 2013; Karavidas et al., 2008) was performed in other studies. The session duration per session for the aerobic exercise interventions was consisted of 15 min (Ahmad et al., 2014; Kobayashi...
### Table 3
Characteristics of exercise intervention and control group in patients with heart failure.

| Source, yr | Exercise intervention | Type | Frequency (days/week) | Follow-up (Duration) | Mode | Supervised or Unsupervised | Control group |
|------------|------------------------|------|-----------------------|----------------------|------|-----------------------------|---------------|
| Abolahrari-Shirazi et al., 2018-a | Combined (cycle + weight training) | 3 | 7 weeks | Endurance training: 45 min at 40%-70% peak VO2 predicted; exercising on a cycle ergometer for 20 min, an arm ergometer for 10 min, and a treadmill for 15 min; Resistance training – knee extension, knee flexion, elbow flexion, and shoulder abduction. Initial intensity was set as 40% one repetition maximum (1RM) and then increased gradually to 60% 1RM. | Supervised | Control group (patients) only received a pamphlet for daily exercising at home including ten types of active exercises, 10 repetitions and each exercise session at home lasted 15–20 min. |
| Abolahrari-Shirazi et al., 2018-b | Endurance (cycle) | 3 | 7 weeks | Endurance training: 45 min at 40%-70% peak VO2 predicted; exercising on a cycle ergometer for 20 min, an arm ergometer for 10 min, and a treadmill for 15 min. | Supervised | Control group (patients) only received a pamphlet for daily exercising at home including ten types of active exercises, 10 repetitions and each exercise session at home lasted 15–20 min. |
| Adamopoulos et al. (2014) | Concurrent (cycle + inspiratory muscle training) | 3 | 12 weeks | Patients in the concurrent group underwent aerobic training for 45 min on an ergometer at 70–80% HRmax with warm-up and cool down periods lasted 5 min Resistance training including an inspiratory-incremental resistive loading device was performed at 60% of individual sustained maximal inspiratory pressure (SPImax) with six inspiratory efforts at each level. Initially, the first level presented templates at 60 s rest intervals over its six inspiratory efforts, but at the second level through to the sixth level, this rest period was reduced to 45, 30, 15, 10, and 5 s. After the sixth level, the rest period was kept at 5 s. The duration of training was 30 min. | Supervised | Patients in control group underwent aerobic + resistance trainings similar to the concurrent group. However, control group was exercised at only 10% of their sustained maximal inspiratory pressure (SPImax). |
| Ahmad et al. (2014) | Aerobic (walking, treadmill or cycling) | 3 | 12 weeks | Patients in aerobic group performed walking, treadmill, or stationary cycling as their primary training mode. Aerobic exercise was initiated at 15–30 min per session at a heart rate corresponding to 60% of heart rate reserve. Patients in the aerobic group were also provided home exercise equipment, and home exercise adherence and amount were formally measured. | Supervised | Control group (patients) in the usual care group received detailed self-management educational materials that included information on medications, fluid management, symptom exacerbation, sodium intake, and amount of activity recommended. |
| Aksoy et al. (2015) | Aerobic (cycle) | 3 | 10 weeks | Aerobic training: Intermittent aerobic + Continuous aerobic: Both group started with power attained at 50% of peak VO2 and continued with increments of power in every 2 wks until achievement of power attained at 75% of peak VO2; a single session consisted of 35 min of aerobic exercise (by ergometers with an electromagnetic brake at a constant pedal rate of 50 revolutions per min) including 10 min of warm-up and cool down. Intermittent aerobic: worked for 60-sec bouts of cycling at a determined intensity and worked for 30-sec intervals of low intensity cycling at 30 W, making a total of 17 cycles of low- and high-intensity bouts in a session. Continuous aerobic: worked without any change in the intensity of the exercise during a single session. | Supervised | Control group (patients) was on optimal medical therapy without any particular regular physical activity before. |
| Conraads et al. (2004) | Combined (cycling & jogging + weight training) | 3 | 4 months | Combined group was performed endurance/resistance exercise programme in the hospital for 60 min. Endurance – at 90% of the ventilator threshold including 20–30 min of cycling and/or jogging. Resistance – | Supervised | Control group was patients with the untrained heart failure and unchanged medication during 4 months. |

(continued on next page)
| Source, yr | Exercise intervention | Frequency (days/week) | Follow-up (Duration) | Mode | Supervised or Unsupervised | Control group |
|-----------|------------------------|-----------------------|----------------------|------|-----------------------------|---------------|
| Conraads et al. (2007) | Aerobic (cycle & waking) | 3 | 5 months | Patients attended an ambulatory exercise programme consisting of 3 sessions/week, 90% of the ventilatory threshold, and each lasting for 1 h. Each session started with a 5 min warming-up and stretching period, followed by endurance training (cycling, walking) and a period of 5 min cool-down. Resistance training was set at 60% of 1-RM during the 20 first sessions and then increased to 70% of 1-RM, ensuring that one series of ten repetitions lasted exactly 1 min for a total work time of 40 min. | Supervised | Control group (patients) undergo standard therapy only. |
| Delagardelle et al. (2008) | Concurrent (cycle & treadmill + strength training) | 3 | 3–4 months | The concurrent group was performed an intensive ambulatory training program of 40 sessions, 3 times per week, and at 60–75% VO2 peak during 3–4 months. Every training session consisted of 45 min of exercise, with 5 min of warm-up and 40 min of training. Resistance training was set at 60% of 1-RM during the 20 first sessions and then increased to 70% of 1-RM, ensuring that one series of ten repetitions lasted exactly 1 min for a total work time of 40 min. | Supervised | Control group (patients) was not able to participate in the ambulatory training program because of geographic constraints. |
| Eleuteri et al. (2013) | Aerobic (cycle) | 5 | 3 months | The training protocol consisted of 5 sessions a week of 30-min cycle ergometry (60 rev/min) at a power and heart rate corresponding to ventilatory anaerobic threshold (VAT), preceded and followed by a 5-min warm-up and cool-down unloaded period, respectively. | Supervised | Control group (patients) was continued their optimal medical therapy without exercise intervention. |
| Fu et al. (2013) | Aerobic (cycle) | 3 | 12 weeks | Aerobic training including 2 groups: Aerobic interval training group warmed up for 3 min at 30% of VO2peak (≈30% HRR) before exercise five 3-min intervals at 80% of VO2peak (≈80% HRR). Each interval was separated by 3-min exercise at 40% of VO2peak (≈40% HRR). The exercise session was terminated by 3-min cool-down at 30% of VO2peak. Moderate-continuous training group comprised a warm-up at 30% of VO2peak for 3 min, followed by continuous 60% of VO2peak (≈60% HRR) for 30 min, then a cool-down at 30% of VO2peak for 3 min. The two protocols were isocaloric at the same exercise duration. | Supervised | Control group (patients) only engaged in general home-based health care. |
| Giallauria et al., 2006-a | Aerobic (cycle) | 3 | 3 months | Aerobic training was performed for 30 min on a bicycle ergometer at 70% of the VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test, which was preceded by a 5-min warming-up and followed by a 5-min cooling-down. | Supervised | Patients in control group were discharged with routine instructions to continue physical activity and maintain a correct lifestyle. |
| Source, yr | Type | Frequency | Follow-up | Mode | Supervised or Unsupervised | Control group |
|-----------|------|-----------|-----------|------|-----------------------------|--------------|
| Giallauria et al., 2006-b | Aerobic (cycle) | 3 | 6 months | Training sessions, preceded by a 5-min warming-up and followed by a 5-min cooling-down, were performed by pedalling for 30 min on a bicycle ergometer at 60% of the VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test. | Supervised | Patients in control group were discharged with routine instructions to continue physical activity and maintain a correct lifestyle. |
| Giallauria et al. (2008) | Resistance (functional electrical stimulation) | 5 | 6 weeks | Resistance group was trained for 30 min a day the stimulator was configured to deliver a direct electrical current at 25 Hz for 5 s followed by 5 s of rest. The intensity of the stimulation was adjusted to achieve a visible muscle contraction that was not sufficiently strong to cause discomfort or a significant movement at either the knee or the ankle joints. When the muscles of the right leg were contracted, the muscles of the left leg were relaxing and vice versa. | Supervised | Control group patients were exposed to the same regimen as the functional electrical stimulation group, using a lower intensity of stimulation (5 Hz) that did not lead to visible or palpable contractions, as judged objectively or subjectively. |
| Karavidas et al. (2008) | Resistance (inspiratory and peripheral resistance training) | 7 | 8 weeks | Combined training — moderate-intensity inspiratory and peripheral resistance training group (MIPRT): low-intensity inspiratory and peripheral resistance training group (LIPRT): performed a combination of IMT at 15% of the maximum inspiratory pressure (MIP) and peripheral muscle training with 0.5 kg for 30 min. Moderate-intensity inspiratory and peripheral resistance training group (MIPRT): trained their inspiratory muscles at 30% of the MIP combined with peripheral muscle training at 50% of one maximum repetition (1RM) for 30 min. | Supervised | Control patients maintained daily medication use and self-controlled salt/fluid ingestion during the 8-week. |
| Kawauchi et al. (2017) | Aerobic (cycle) | 2-3 | 3 months | Aerobic group was performed cycle ergometer training that exercise speed was adjusted to maintain the heart rate equivalent to the ventilator threshold level for 15 min. | Supervised | Control group (patients) was continued their optimal medical therapy without exercise intervention for the same time period. |
| Marco et al. (2013) | Concurrent (inspiratory muscle endurance & strength) | 7 | 4 weeks | Concurrent group performed high-intensity inspiratory muscle training with 10 consecutive maximal repetitions (10RM), five sets of 10 repetitions followed by 1–2 min of unloaded recovery breathing off the device and training intensity with 100% of their 10RM twice a day at a 15–20 breaths/ min. | Supervised | Control group (patients) received sham inspiratory muscle training at an initial workload of 10 cmH2O which was increased 2.5 cmH2O every week. |
| Maria-Sarlo et al. (2006) | Aerobic (cycle) | 3 | 3 months | Aerobic group underwent using a bicycle ergometer for 30 min at 60–70% of their VO2 peak. | Supervised | Control group (patients) did not change their optimal medical therapy and previous physical activity. |
| Masterson-Creber et al. (2015) | Aerobic (walking & cycling) | 3 | 12 months | Aerobic group performed walking or cycling at a 60–70% HRmax reserve for 30–35 min. | Supervised | Control group patients in the usual care group were not provided with a formal exercise prescription. |
| Melo et al. (2019) | Aerobic (walking) | 2 | 6 months | HIT group performed of 4 interval training periods (high intensity: 90–95% of maximal heart rate if below the device threshold, and if not, 90–95% of the device threshold was used) with 3 lower-intensity active periods (moderate intensity: 60–70% of maximal heart rate if below the device threshold) between interval training | Supervised | Control group patients received usual care. |

(continued on next page)
| Source, yr | Type | Frequency (days/week) | Follow-up (Duration) | Mode | Supervised or Unsupervised | Control group |
|-----------|------|-----------------------|----------------------|------|---------------------------|---------------|
| Nilsson et al. (2010) | Aerobic (cycle) | 2 | 4 months | Aerobic group was performed group-based simple aerobic exercises, including three intervals of high intensity (15-18 on the Borg scale). The total duration of the exercise program was 50 min. | Supervised | Control group (patients) was referred to follow-up care by their primary care physician and was not discouraged from regular physical activity. |
| Passino et al. (2006) | Aerobic (cycle) | 3 | 9 months | Aerobic group was performed cycling on a bike for a minimum of 3 days per week, 30 min per day. Patients were instructed to exercise at 60 rpm, keeping heart rate constantly monitored at 65% of peak VO2 heart rate, by a wearable device. | Supervised | Control group (patients) underwent follow-up visits at the third and ninth month to exclude changes in their usual lifestyle and physical activity. |
| Prescott et al. (2009) | Concurrent (walking, cycling, step machine, and step board) | 2 | 8 weeks | Concurrent group was performed 1.5-h training session comprised of 20 min warm-up period followed by four 6-min series of aerobic training (walking, cycling, step machine, and step board) and two posts of resistance endurance exercises (leg press and exercises with rubber bands for quadriceps, gluteus/hamstring region, and arms; three sets of 20 repetitions with each arm/leg). Each patient’s training intensity was adjusted to achieve 70-80% of peak oxygen consumption, corresponding to 4-5 on the Modified Borg Scale (range 0 (no breathlessness at all) to 10 (maximal breathlessness)). | Supervised | Control group patients with usual care were encouraged to keep on training at home but were not offered group sessions or to keep diaries. |
| Radd et al. (2017) | Aerobic (cycle, walking or treadmill) | 3 | 1 month | Aerobic group was trained personnel’s, three sessions per week for 20-40 min per session; the exercise consisted of warming up, low to moderate intensity of endurance training (leg ergocycle and walking or treadmill), with electrocardiogram telemetry when necessary, the exercise program was expected to increase the heart rate up to 20 bpm above resting, and was completed after cooling down. | Supervised | Control group patients continued the standard care without early exercise program. |
| Sandri et al. (2012) | Aerobic (cycle) | 4 | 4 months | Aerobic group was performed per weekday each for 20 min (excluding 5 min of warming up and cooling-down) using a bicycle ergometer interrupted by recreation intervals of at least 60 min after each session. Workloads were adjusted to heart rate so that 70% of the symptom-limited maximum oxygen uptake was reached. | Supervised | Control group patients received usual clinical care by their physicians. |
| van Berendoncks et al., 2010 | Concurrent (treadmill, cycle, stair or step, arm-cycling, half recumbent or reclined cycling + weight training) | 3 | 4 months | Concurrent group was performed aerobic and resistance trainings. Aerobic training THR (target heart rate) was calculated as 90% of the heart rate achieved at the anaerobic threshold. The initial resistance training intensity was set at 50% of 1RM (1 repetitive maximum) (for the nine different muscle groups), with an increase to 60% after 2 months. Repetitions were slowly increased from $1 \times 10, 1 \times 15, 2 \times 10$ to $2 \times 15$ repetitions. Between each series of repetitions, rest for 1 min was allowed. Aerobic group trained for 8 min on five different training devices (treadmill, bicycle, stair or step, arm-cycling, half recumbent or reclined cycling). When changing from one device to another, 2 min of recuperation time was introduced. During the first 2 months, | Supervised | Control group or untrained patients maintained their optimal medical therapy. |

(continued on next page)
patients assigned to the concurrent group trained for almost 40 min on the fitness equipment, whereas only 10 min were spent on aerobic. The next 2 months, resistance training was reduced to 30 min (nine muscle groups, 2 × 15 repetitions each) and ET was increased to 2 × 8 min. Aerobic interval training group warmed up for 10 min at 50%-60% of Vo2peak (≥60%-70% of peak heart rate) before walking four 4-min intervals at 90%-95% of peak heart rate. Each interval was separated by 3-min active pauses, walking at 50%-70% of peak heart rate. The training session was terminated by a 3-min cool-down at 50%-70% of peak heart rate. Performed four 4-min intervals with an exercise intensity that made them breathe heavily without becoming too stiff in their legs once a week. Moderate continuous training group walked continuously at 70%-75% of peak heart rate for 47 min each session to make sure the training protocols were isocaloric. Walked continuously for 47 min without breathing heavily once a week. Control group was told to follow advice from their family doctor with regard to physical activity; in addition, they met for 47 min of continuous treadmill walking at 70% of peak heart rate every 3 weeks.

A standard protocol of meditative warm-up exercises followed by five simplified tai chi movements (adapted from Master Cheng Man-Ch'ing's Yang-style short form). Traditional warm-up exercises included weight shifting, arm swinging, visualization techniques, and gentle stretches of the neck, shoulders, spine, arms, and legs. Each class was supervised by a physician, 35-min instructional videotape outlining the warm-up exercises and tai chi movements. Patients were encouraged to practice at home at least three times per week.

The characteristics of control group-related interventions were used without exercise interventions (Aksoy et al., 2015; Conraads et al., 2004; Delagardele et al., 2008; Eleuteri et al., 2013; Giallauria et al., 2006-a, 2006-b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; van Berendoncks et al., 2010; Passino et al., 2006), optimal medical or standard therapy (Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Kawauchi et al., 2017; Radi et al., 2017), general home-based health care (Fu et al., 2013), usual care (Ahmad et al., 2014; Masterson-Creber et al., 2015; Melo et al., 2019; Nilsson et al., 2010; Prescott et al., 2009; Sandri et al., 2012-a; Yeh et al., 2004), time-matched education (Yeh et al., 2011), pamphlet for daily exercising at home (Abolahrari-Shirazi et al., 2018-a; Abolahrari-Shirazi et al., 2018-b), aerobic + resistance trainings similar to the exercise group at only 10% of their sustained maximal inspiratory pressure (Adamopoulos et al., 2014), functional electrical stimulation using a lower intensity of stimulation (5 Hz) (Karavidas et al., 2008), sham-inspiratory muscle training at an initial workload of 10 cmH2O (Marco et al., 2013), and advice from their family doctor with regard to physical activity (Wisløff et al., 2007).

| Source, yr | Exercise intervention | Frequency (days/week) | Follow-up (Duration) | Mode | Supervised or Unsupervised | Control group |
|------------|-----------------------|-----------------------|----------------------|------|-----------------------------|---------------|
| Wisløff et al. (2007) | Aerobic (treadmill walking) | 3 | 12 weeks | Supervised | Control group patients received usual care. |
| Yeh et al. (2004) | Aerobic (Tai Chi) | 2 | 12 weeks | Supervised | Control group patients received usual care. |
| Yeh et al. (2011) | Aerobic (Tai Chi) | 2 | 12 weeks | Supervised | Control group patients received time-matched education without exercise intervention. |
3.4. BNP and NT-proBNP markers

In this systematic review and meta-analysis, the gold standard circulating markers of HF disease including serum/plasma BNP and NT-proBNP levels were measured in eight (Fu et al., 2013; Karavidas et al., 2008; Kawauchi et al., 2017; Kobayashi et al., 2003; Melo et al., 2019; Passino et al., 2006; Yeh et al., 2004, 2011) and 20 (Abolsharabi-Shirazi et al., 2018; Adamopoulos et al., 2014; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Delagardelle et al., 2008; Eleuteri et al., 2013; Giallauria et al., 2006a,b; Giallauria et al., 2008; Marco et al., 2013; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Nilsson et al., 2010; Passino et al., 2006; Prescott et al., 2009; Radi et al., 2017; Sandri et al., 2012; Van Berendonck et al., 2010; Wisloff et al., 2007) articles, respectively.

3.5. Meta-analysis

3.5.1. BNP

According to eight exercise intervention arms compared to the control group, exercise training intervention did not significantly change the BNP marker [−0.122 (SMD and 95% CI: 0.322 to 0.079), p = 0.235] (Fig. 2). Heterogeneity analysis showed that there was no significant heterogeneity, thereby I-squared was less than 50% (I-squared = 58%), Analysis of subgroup by type of exercise training intervention did not show significant changes for both aerobic [−0.136 (SMD and 95% CI: 0.352 to 0.081), p = 0.220] and resistance [−0.036 (SMD and 95% CI: 0.574 to 0.501), p = 0.895] exercise interventions compared to the control group (Fig. 2).

3.5.2. NT-proBNP

According to 21 exercise intervention arms compared to the control group, exercise training intervention significantly decreased NT-proBNP marker [−0.229 (SMD and 95% CI: 0.386 to −0.071), p = 0.005] (Fig. 3), irrespective of overweight/obesity status. Heterogeneity analysis showed that I-squared was more than 50% (I-squared = 64.68, P = 0.001) and therefore heterogeneity was significant. Analysis of subgroup by type of exercise training revealed that there was a significant reduction in the NT-proBNP marker for aerobic exercise compared to the control group [−0.336 (SMD and 95% CI: 0.555 to −0.105), p = 0.004], whereas concurrent exercise did not show significant changes in the NT-proBNP marker [−0.134 (SMD and 95% CI: 0.350 to 0.083), p = 0.227], (Fig. 3).

3.5.3. Quality assessment and publication bias

The quality assessment of included studies (Pedro scores ranged between 15 and maximum 15 scores) is illustrated in Table 1. The visual interpretation of funnel plot was used to assess the publication bias. In addition, the Egger’s test was used as another technique for assessing publication bias. Assessment of visual interpretation in the funnel plot showed symmetry, suggesting that there was no significant publication bias for BNP (Fig. 4). Egger’s test for BNP was carried out to confirm this symmetry, which was confirmed to be non-significant (p = 0.752). In contrast, the visual interpretation of funnel plot showed asymmetry (no significant publication bias) for NT-proBNP (Fig. 5), which Egger’s test was also carried out to confirm this asymmetry at a significance level (p = 0.041).

4. Discussion

The results of our systematic review and meta-analysis showed that exercise training improved NT-proBNP marker in patients with HF aged 49 ± 19.36 to 76.5 ± 9 yrs, irrespective of overweight/obesity status. In other words, our results indicated that aerobic exercise intervention has a small sized effect for reducing NT-proBNP marker in patients with HF. Therefore, the results of our study confirmed that aerobic exercise intervention was effective in improving NT-proBNP marker in patients with HF, whereas concurrent exercise intervention was not effective for NT-proBNP marker. In addition, our results indicated that exercise training interventions such as aerobic and resistance exercises were no effective for the BNP marker in patients with HF.

Recent investigations reported that endogenous peptide markers such as BNP and NT-proBNP are secreted mainly from heart tissue. The endogenous peptides have numerous beneficial effects on cardiovascular system such as vasodilation and natriuresis (Maeder et al., 2008). The results of studies showed that myocardial BNP release is inversely associated with peak VO2 in healthy humans (Maeder et al., 2018), which may be due to non-cardiac and cardiac mechanisms. The mechanism of beneficial effects of endogenous peptides would counteract the adverse adaptations of the activation of renin-angiotensin-aldosterone and sympathetic nervous systems (Maeder et al., 2018). In contrast, recent clinical studies on the BNP and NT-proBNP markers report a pathophysiological role in response to an increase in left ventricular stretching and wall stress and as well as myocardial stretch in patients with HF (Chow et al., 2017; Pearson et al., 2018; Topf et al., 2020). Recently, European society cardiology (ESC) guidelines revealed that BNP ≥100 and NT-proBNP ≥ 300 pg/ml values for confirmed acute HF and BNP ≥ 35 and NT-proBNP ≥ 125 pg/ml values for suspected HF are pathologic and diagnostic conditions for HF (McDonagh et al., 2021). These findings suggest that endogenous peptides, especially BNP and NT-proBNP play important roles in the pathologic and physiologic responses of the heart. It is possible that an optimal increase in BNP and NT-proBNP following exercise training intervention resulted in the regulation of cardiac function, increased physiological adaptations in left ventricular function, vasodilation and natriuresis in healthy humans.

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**Table 1**

| Study name | Type of exercise | SMD | 95% CI | p-value |
|------------|------------------|-----|--------|---------|
| Fu et al., 2013a | Aerobic | -0.705 | -3.871 | 0.277 |
| Karavidas et al., 2013 | Aerobic | -0.855 | -4.011 | 0.211 |
| Kobayashi et al., 2003 | Aerobic | 0.257 | 0.128 | 0.037 |
| Melo et al., 2019 | Aerobic | 0.386 | 0.011 | 0.501 |
| Passino et al., 2006 | Aerobic | 0.315 | -0.034 | 0.001 |
| Yeh et al., 2004 | Aerobic | 0.200 | 0.001 | 0.005 |
| Yeh et al., 2011 | Aerobic | 0.300 | 0.001 | 0.001 |

**Fig. 2** Forest plot of the effects of exercise training on BNP. Data are standardized mean difference (SMD) (95% confidence intervals).
(Maeder et al., 2008). However, a decrease in BNP and NT-proBNP values following exercise training has a positive adaptation on CVS in HF patients (McDonagh et al., 2021; Santoso et al., 2020; Pearson et al., 2018), which was observed after aerobic exercise training for NT-proBNP marker, irrespective of overweight/obese status, in our systematic review and meta-analysis. The findings of our systematic review and meta-analysis were consistent with the results of previous systematic review and meta-analysis studies (Santoso et al., 2020; Pearson et al., 2018; Cipriano et al., 2014; Smart et al., 2012; Smart and Steele, 2010) and were inconsistent with others (Pearson et al., 2018; Smart et al., 2012; Smart and Steele, 2010).

The findings of our study were consistent with the results of Santoso et al. that aerobic exercise training was significant in lowering NT-proBNP values compared to the control group (Santoso et al., 2020). In addition, Pearson et al. reported that conventional exercise training (exercises that incorporate an individual body part with single or multi-joint movements such as presses, rows, fly, squats, etc.) has a significant improvement in NT-proBNP biomarker in HF patients (Pearson et al., 2018). Cipriano et al. demonstrated that aerobic exercise training was effective at improving NT-proBNP values in systolic HF patients (Cipriano et al., 2014). Smart et al. showed that aerobic and resistance exercise trainings had favorable roles on NT-proBNP marker in HF (Smart et al., 2012). Moreover, Smart and Steele reported that resistance and aerobic exercises were effective in lowering NT-proBNP values in patients with HF (Smart and Steele, 2010). In contrast, Pearson et al. demonstrated that exercise training was significant in improving BNP values in patients with HF (Pearson et al., 2018). Smart et al. reported that resistance and aerobic exercise interventions were
significant in lowering BNP in HF patients (Smart et al., 2012). In addition, Smart and Steele indicated that resistance and aerobic exercises were significant at improving BNP marker in HF patients (Smart and Steele, 2010), which were inconsistent with the results of our systematic review and meta-analysis.

The results of studies indicate that higher concentrations of BNP and NT-proBNP markers are associated with a higher risk of morbidity and mortality from any cause, pump failure and cardiac sudden death and as well as HF (Korth et al., 2020). In addition, circulating BNP and NT-proBNP levels are inversely associated with serum insulin (Neeland et al., 2013; Mehra et al., 2004; Hamasaki, 2016), visceral fat (Neeland et al., 2013; Hamasaki, 2016), body mass index (BMI) (Neeland et al., 2013; Hamasaki, 2016), waist circumference (Hamasaki, 2016) and as well as overweight/obesity status (Neeland et al., 2013; Mehra et al., 2004; Hamasaki, 2016). It seems that the effects of pathologic and physiologic conditions on circulating BNP and NT-proBNP values are contradictory. In other words, the results of acute exercise showed that circulating BNP and NT-proBNP levels significantly increase immediately after exercise training, a reduction on the following day, and return to baseline values after one week (Hamasaki, 2016). It is possible that an increase in circulating BNP and NT-proBNP levels is related to the exercise-induced physiological endocrine responses in response to an increase in the myocardial stress (Hamasaki, 2016), suggesting that BNP and NT-proBNP releases during and after exercise training are related to the cytoprotective and growth-regulating responses as well as physiological reaction of cardiomyocytes, but not myocardial damage (D’Souza et al., 2003; Hamasaki, 2016). However, the physiological mechanism of exercise training-induced BNP and NT-proBNP releases remain unclear.

The results of systematic review and meta-analysis studies indicated that a reduction in NT-proBNP by aerobic exercise is associated with improved cardiacpulmonary function, increased peak VO2, improved workload and increased left ventricular ejection fraction (LVEF) in patients with HF (Santoso et al., 2020), which was consistent with the results of our systematic review and meta-analysis. Since the exercise training, especially aerobic exercise plays an important role in improving myocardial stretch markers such as BNP and NT-proBNP, it is possible that aerobic exercise training as a non-pharmacological intervention can be considered as a cardiac rehabilitation programme (a class 1 recommendation) in HF patients. It has been reported that BNP and NT-proBNP values did not change after resistance training in elderly subjects (Beltran Valls et al., 2014). However, some studies demonstrated that muscle mass inversely related to the BNP levels (Yamashita et al., 2014). It is possible that the changes in BNP and NT-proBNP concentrations by resistance training are not related to the myocardial stress-induced NP secretion (Hamasaki, 2016). Based on the science of training in exercise physiology, optimal protocol and intensity, frequency and duration of exercise trainings are related to the release of cardiac biomarkers and as well as BNP and NT-proBNP markers (Hamasaki, 2016) although differential effects of exercise interventions on NPs secretions in HF and/or healthy subjects are not fully understood.

4.1. Strengths and limitations

The mean age 49–76.5 yrs, BMI 24.5–30 kg/m², the most common period of 3 months (12 weeks), a focus on HF patients, subgroup analysis based on type of exercise and as well as lack of reports of morbidity and mortality associated with the supervised exercise training programmes in HF patients were strengths of our meta-analysis. However, the current systematic review and meta-analysis had some limitations. The lack of concurrent exercise for BNP marker, lack of resistance training for NT-proBNP marker, low number of included studies based on subgroup by type of exercise training, and as well as heterogeneity and publication bias according to the data were limitations of this meta-analysis.

5. Conclusions

In conclusion, exercise training, especially aerobic exercise was useful in improving (lowering) circulating NT-proBNP concentrations in patients with HF, irrespective of overweight/obesity status, although the BNP marker remained unchanged.

The main clinical implications of our systematic review and meta-analysis were a reduction in circulating NT-proBNP levels after exercise training, especially aerobic exercise training in HF patients. Therefore, exercise training, especially aerobic training as a non-pharmacological intervention and as well as a cardiac rehabilitation programme (a class 1 recommendation) can be used at improving NT-proBNP marker for the prevention, management, and assessment of HF, irrespective of overweight/obesity status.

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CRediT authorship contribution statement

Abbas Malandish: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing. Niloufar Ghadamary: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing. Asma Karimi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, draft, Writing – review & editing. Mahdi Naderi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abolahrari-Shirazi, S., Kojari, J., Bagheri, Z., Rojhani-Shirazi, Z., 2018. Efficacy of combined endurance-resistance training versus endurance training in patients with heart failure after percutaneous coronary intervention: a randomized controlled trial. J. Res. Med. Sci. 23, 12. https://doi.org/10.4103/jrms.JRMS_743_17.

Adamopoulos, S., Schmid, J.P., Dendale, P., Poerschke, D., Hansen, D., Dritsas, A., Kouloubinis, A., Alders, T., Ghouziouita, A., Reyckers, I., Vartela, V., Pleiss, N., Doulaptsis, S., Saner, H., Laoustaris, I.D., 2014. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: the Vent-HeFT trial: a European prospective multicentre randomized trial. Eur. J. Heart Fail. 16 (5), 574–582. https://doi.org/10.1002/ejhf.70.

Ahmad, T., Fiuzaat, M., Mark, D.B., Neely, B., Neely, M., Kraus, W.E., Kitzman, D.W., Whellan, D.J., Donahue, M., Zannad, F., Piña, I.L., Adams, K., O’Connor, C.M., Felker, G.M., 2014. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. Am. J. Heart J. 167 (2), 193–202. https://doi.org/10.1016/j.ajhj.2013.10.018.

Akyoz, S., Findikoglu, G., Ardic, F., Rota, S., Dursunoglu, D., 2015. Effect of 10-week supervised moderate-intensity intermittent vs. Continuous aerobic exercise programs on vascular adhesion molecules in patients with heart failure. Am. J. Phys. Med.
exercise training in heart failure (ExTraHF) survey. Eur. J. Heart Fail. 21 (9), 1142–1148. https://doi.org/10.1002/ejhf.1539.

Pina, I.I., Apstein, C.S., Balady, G.J., Bel ardinelli, R., Chaitman, B.R., Duscha, B.D., Fletcher, B.J., Fleg, J.L., Myers, J.N., Sullivan, M.J., 2003. American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 107 (8), 1210–1225. https://doi.org/10.1161/01.ATH.0000105513.92097.40.

Prescott, E., Hjardem-Hansen, R., Delfa, D., Ørskild, B., Teiner, A.S., Nielsen, H., 2009. Effects of a 14-month low-cost maintenance training program in patients with chronic systolic heart failure: a randomized study. Eur. J. Cardiovasc. Prev. Rehabil. 16 (4), 430–437. https://doi.org/10.1097/HJR.0b013e3283e494R.

Radi, B., Santoso, A., Siiswanto, B.B., Mansyur, M., Ibrahim, N., Kusmana, D., 2017. Early exercise program for patients with heart failure after hospital discharge. nt J Phys Med Rehabil 5 (2), 1–6. https://doi.org/10.4172/2329-9096.1000392.

Rorth, R., Jhund, P.S., Yilmaz, M.B., Kristensen, S.L., Welsh, P., Desai, A.S., Keber, L., Prescott, M.F., Rouleau, J.L., Solomon, S.D., Swedberg, K., Zile, M.R., Packer, M., McMurray, J.J.V., 2020. Comparison of BNP and NT-proBNP in patients with heart failure and reduced ejection fraction. Heart 106 (13), e006541. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006541.

Sandri, M., Kozarek, I., Adams, V., Mangner, N., Helgerud, J., Erbs, S., Linke, A., Mobius-Winkler, S., Thiyen, J., Kratzsch, J., Teu per, D., Mende, M., Hambrecht, R., Schulter, G., Gielen, S., 2012. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the leipzig exercise intervention in chronic heart failure and aging (LEICA) diastolic dysfunction study. Eur. Heart J. 33 (14), 1758–1768. https://doi.org/10.1093/eurheartj/ehr469.

Santoso, A., Maulana, R., Afza hra, F., Prameswar i, H.S., Ambari, A.M., Hortapob, A.B., Arso, I.A., Radi, B., 2020. The effects of aerobic exercise on N-terminal pro-B-type natriuretic peptide and cardiopulmonary function in patients with heart failure: a meta-analysis of randomized clinical trials. Heart Lung Circ. 29 (12), 1790–1798. https://doi.org/10.1016/j.hrthc.2020.05.098.

Smart, N.A., Steele, M., 2010. Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. Int. J. Cardiol. 140 (3), 260–265. https://doi.org/10.1016/j.ijcard.2009.07.004.

Smart, N.A., Meyer, T., Butterfield, J.A., Faddy, S.C., Pissino, C., Malfatto, G., Jonsdottir, S., Sarulllo, F., Winhoff, U., Vigorito, C., Giallauria, F., 2012. Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure. Eur J Prev Cardiol 19 (3), 428–435. https://doi.org/10.1177/1741826711409171.

Topf, A., Mirna, M., Ohnwein, B., Jirak, P., Kopp, K., Fejzic, D., Haslinger, M., Motloch, L.J., Hoppe, U.C., Berezin, A., Lichtenuer, M., 2020. The diagnostic and therapeutic value of multimarker analysis in heart failure. An approach to biomarker-targeted therapy. Front Cardiovasc Med 7, 579567. https://doi.org/10.3389/fcvm.2020.579567.

Van Berendonck, A.M., Beckers, P., Hoymans, Y.V., Posemers, N., Wuyts, F.L., Vrints, C.J., Conraads, V.M., 2010. Exercise training reduces circulating adiponectin levels in patients with chronic heart failure. Clin. Sci. 118 (4), 281–289. https://doi.org/10.1042/CS20090213.

Wan, X., Wang, W., Liu, J., Tong, T., 2014. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med. Res. Methodol. 14, 135. https://doi.org/10.1186/1471-2288-14-135.

Wislaff, U., Støylen, A., Lønnechen, J.P., Bruvold, M., Rogmann, Ø., Haram, P.M., Tjonna, A.E., Helgerud, J., Sildahl, S.A., Lee, S.J., Viden, V., Bye, A., Smith, G.L., Najjar, S.M., Ølling, S., Skjaerpe, T., 2007. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 115 (24), 3086–3094. https://doi.org/10.1161/CIRCULATIONAHA.106.675041.

Xu-Cai, Y.O., Wu, Q., 2010. Molecular forms of natriuretic peptides in heart failure and their implications. Heart 96 (6), 419–424. https://doi.org/10.1136/hrt.2008.164145.

Yamashita, T., Kohara, K., Tabara, Y., Ochi, M., Nagai, T., Okada, Y., Igane, M., Miki, T., 2014. Muscle mass, visceral fat, and plasma levels of B-type natriuretic peptide in healthy individuals (from the J-SHIPP Study). Am. J. Cardiol. 114 (4), 635–640. https://doi.org/10.1016/j.amjcard.2014.05.050.

Yeh, G.Y., Wood, M.J., Loeell, B.H., Stevenson, L.W., Eisenberg, D.M., Wayne, P.M., Goldeberger, A.L., Davis, R.B., Phillips, R.S., 2004. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. Am. J. Med. 117 (8), 541–548. https://doi.org/10.1016/j.amjmed.2004.04.016.

Yeh, G.Y., McCarthy, E.P., Wayne, P.M., Stevenson, L.W., Wood, M.J., Forman, D., Davis, R.B., Phillips, R.S., 2011. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. Arch. Intern. Med. 171 (8), 750–757. https://doi.org/10.1001/archinternmed.2011.150.