EFFECTS OF EXERCISE TRAINING ON MAXIMAL OXYGEN UPTAKE IN HEART FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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SUMMARY

Aims. Low cardiorespiratory fitness is a common physical status among patients with heart failure. Several studies have examined the effects of exercise training on maximal oxygen uptake (VO_{2max}) in heart failure. Though, these studies had relatively small sample sizes and highly variable results. Therefore the aim of this study was to systemically review the effects of exercise training on VO_{2max} in heart failure patients.

Methods. Database search of randomized controlled trials was conducted from Ovid MEDLINE and Cochrane Central Register of Controlled Trials. Search was allocated to studies with patients with heart failure, structured exercise intervention, control group receiving usual medical care, at least eight weeks duration and direct VO_{2max} measurement method.

Results. Seventeen studies with eighteen comparisons met the inclusion criteria. The pooled results indicated that VO2max changed by 17.2±13.2% in the training groups and 0.4±5.4% in control groups. The absolute change in VO_{2max} was 2.9±2.3 in the exercise groups and 0.1±0.9 in the control groups. Thus, the net change in VO_{2max} between the groups was 2.8 mL/kg/min. Aerobic training led to a larger change in VO_{2max} between the groups than other training modes. Studies with higher exercise intensities and longer durations tended to produce larger improvements in VO_{2max}. Additionally, gradually increasing workload was found effective method when targeting increase in VO_{2max} through training.

Conclusions. Long, moderate to moderate to high intensity aerobic exercise training with gradually increasing workload has statistically and clinically most significant effect on VO_{2max} in heart failure patients.

Keywords: heart failure, exercise, maximal oxygen uptake

Liikuntaharjoittelun vaikutus maksimaaliseen hapenottokykyyn sydämen vajaatoimintapotilailla: systemaattinen katsaus ja meta-analyysi

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TIIVISTELMÄ

Tarkoitus. Huono hengitys- ja verenkiertoelimistön kunto on yleinen fyysinen ongelma sydämen vajaatoimintapotilailla. Useat tutkimukset ovat tutkineet liikuntaharjoittelun vaikutuksia maksimaaliseen hapenottokykyyn sydämen vajaatoimintapotilailla. Näiden tutkimusten otoskoko on kuitenkin ollut suhteellisen pieni ja tulokset vaihtelevia. Tästä johtuen tämän tutkielman tavoite oli tehdä systemaattinen katsaus ja meta-analyysi aihetta koskien sekä koota yhteen liikuntaharjoittelun vaikutukset sydämen vajaatoimintapotilaan maksimaaliseen hapenottokykyyn (VO_{2max}).

Metodit. Tiedonhaku satunnaistetuista kontrolloiduista tutkimuksista tehtiin Ovid MEDLINE- sekä Cochrane Central Register of Controlled Trials –tietokannoista. Haku kohdennettiin sydämen vajaatoimintapotilaille tehtyihin tutkimuksiin, jotka sisälsivät jäsennellyn liikuntaintervention, tavanomaista hoitoa saavan kontrolliryhmän, suoran maksimaalisen hapenottokyvyn mittauksen sekä kestivät vähintään kahdeksan viikkoa.

Tulokset. Seitsemäntoista tutkimusta sisältäen kahdeksantoista vertailua täytti mukaanottokriteerit. Yhdistetyt tulokset osoittivat VO_{2max} muuttuneen 17.2±13.2% liikuntainterventioryhmissä sekä 0.4±5.4% kontrolliryhmissä. Absoluuttinen muutos VO_{2max} todettiin olevan 2.9±2.3 liikuntainterventioryhmissä sekä 0.1±0.9 kontrolliryhmissä sekä nettomuutoksen ryhmien välillä 2.8 mL/kg/min. Aerobisen harjoittelun todettiin johtavan muita liikuntainterventioita suurempaan VO_{2max} muutokseen ryhmien välillä. Harjoitusintervention korkeammalla intensiteetillä ja pidemmällä kestolla näyttäisi olevan yhteys maksimaalisen hapenottokyvyn suurempaan kehitykseen. Lisäksi harjoitusintervention aikana asteittain lisääntyvä kuormitus vaikuttaisi olevan tehokas menetelmä pyrittäessä parantamaan maksimaalista hapenottokykyä liikuntaharjoittelun avulla.

Johtopäätökset. Tilastollisesti sekä kliinisesti merkittävimmäksi maksimaalista hapenottokykyä lisääväksi harjoitusmuodoksi osoittautui pitkäkestoinen, intensiteetiltään keskitasoinen tai korkea aerobinen harjoittelu asteittaisella kuorman lisäyksellä toteutettuna.

Asiasanat: sydämen vajaatoiminta, liikunta, maksimaalinen hapenotto

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1 INTRODUCTION

Chronic heart failure (CHF) has become one of the most common cardiovascular disorders in Western societies (Tyni-Lenné et al. 2001, Jónsdóttir et al. 2006). Whilst improved management of hypertension has reduced this condition as an aetiological factor developing heart failure (Kostis et al. 2007), increasing longevity (Lip et al. 2000, Rees et al. 2000) and increased survival rate (Lip et al. 2000) from myocardial infarction have led to increased numbers of cases of chronic heart failure (Kostis et al. 2007). Thus, heart failure is primarily a disorder of elderly people, with more than 75% of patients aged 65 or over (Vuori & Kesäniemi 2005, Wisløff et al. 2007, Kitzman et al. 2010).

Chronical heart failure is a condition with poor prognosis (Coats 2000). It is described as an imbalance in pumping function in which heart fails to maintain sufficient circulation of blood due to many cardiac disorders that cause either systolic or diastolic dysfunction with reduced myocardial contractility and ventricular filling (Kupari et al. 2000, Besnick 2004, Vuori & Kesäniemi 2005). It is associated with debilitating limiting symptoms even with optical modern medical management (Coats 2000). Patients with heart failure have a variety of symptoms, mostly non-specific (Watson et al. 2000). Major symptoms such as dyspnea, muscle fatigue (Kiilavuori et al. 1996, Kupari et al. 2000, Koukouvou et al. 2004), breathlessness (Kupari et al. 2000, Koukouvou et al. 2004) and reduced functional capacity are restricting daily living activities and affecting the quality of life (Rees et al. 2000).

Prevailing exercise intolerance (Kiilavuori et al. 1996, Rees et al. 2000, Brubaker et al. 2009) due to impaired skeletal muscle function (Rees et al. 2000) is declared by excessive, ineffective ventilation (Kiilavuori et al. 1996), reduced peripheral circulation and capillary density (Kiilavuori et al. 1996, Hämäläinen 2000, Kupari et al. 2000) restricting blood flow and thus causing lack of oxygen in skeletal muscles (Kiilavuori et al. 1996, Sturm et al. 1999, Hämäläinen 2000, Kupari et al. 2000). The mitochondrial amount and capacity in muscle cells (Kupari et al. 2000, Vuori & Kesäniemi 2005) and activity of enzymes needed in fatty acids oxidation are decreasing (Hämäläinen 2000, Kupari et al. 2000, Vuori & Kesäniemi 2005). Low peak oxygen consumption is associated with impaired exercise tolerance (Williams et al. 2007) and partly caused by increased amount of anaerobic muscle cells in striated muscles

(Mancini et al. 1989, Kupari et al. 2000, Vuori & Kesäniemi 2005) causing early anaerobic metabolism (Kiilavuori et al. 1996, Kupari et al. 2000, Vuori & Kesäniemi 2005) and progressive functional deterioration (Kiilavuori et al. 1996, Belardinelli et al. 1999, Brubaker et al. 2009).

The management for chronic heart failure is a combination of drugs and lifestyle changes. Because the concepts of heart failure mechanisms and treatment have greatly changed over the past decades, nowadays patients with this disease are being physically more active than ever before (Klocek et al. 2005). Lifestyle management includes diet and exercise training while drug therapy aims at controlling symptoms by policing fluid balance and blocking neurohormonal activation (Rees et al. 2000). Historically patients have been advised to avoid physical exercise believing that it might be harmful and aggravate pre-existing cardiac condition (Willenheimer et al. 1998, Wielenga et al. 1999, Kulcu et al. 2007). It was not until the late 1980s (Dubach et al. 1997, Willenheimer et al. 1998) that it was reported that exercise training is safe for patients with impaired ventricular function (Erbs et al. 2003, Mandic et al. 2009) and can prospectively increase exercise capacity (Coats et al. 1994, Keteyian et al. 1996, Dubach et al. 1997, Afzal et al. 1998, Wielenga et al. 1999, Erbs et al. 2003, Mueller et al. 2007, Wisløff et al. 2007, Kujala 2009, Erbs et al. 2010). If estimating overall clinical effects of exercise training on patients, exercise could also have many other potential benefits to cardio-metabolic risk factors than only improvement in cardiorespiratory fitness, such as delaying the onset of anaerobic metabolism (Coats et al. 1994, Keteyian et al. 1996, Dubach et al. 1997, Afzal et al. 1998, Wielenga et al. 1999, Jónsdóttir et al. 2006, Mueller et al. 2007, Erbs et al. 2010), leading to a widening of the arteriovenous oxygen difference (Dubach et al. 1997), decreasing neurohormonal activation (Tyni-Lenné et al. 2001) and reducing mortality (Belardinelli et al. 1999, Kujala 2009). Studies indicate also improvements in glucose disposal, insulin signaling and lipid profile, reduction of vascular inflammation as reflected by reduced C-active protein, improved endothelial function, facilitation of weight maintenance (Boulé et al 2003) and last but not least, improvements in perceived quality of life (Collins et al. 2004, Klocek et al. 2005) or not (Gottlieb et al. 1999).

The maximal amount of oxygen consumed during exercise (VO_{2max}) has been used by exercise physiologists to determinate the maximum exercise capacities for athletes. In recent decades, it has had a growing importance in clinical use and has become a significant method

measuring cardiovascular fitness and exercise capacity (Fletcher et al. 2001). Several studies have indicated that exercise training improves VO_{2max} also in patients with heart failure. Within those patients, oxygen uptake has been established as a good predictor of prognosis (Cohen-Solal et al. 1998, Belardinelli et al. 1999, Maiorana et al. 2000) and also efficacy of such programs (Gottlieb et al. 1999), but only patients with NYHA I or II (Opasich et al. 1998). Maiorana et al. (2000) have also stated that improvement in VO_{2peak} is associated with enhanced survival in patients awaiting cardiac transplantation. After all, the mechanisms underlying a reduced oxygen uptake during exercise may help to improve its prognostic power (Cicoira et al. 2004).

In spite of that, synthesis by a systematic review and meta-analysis has not, to current knowledge, been published yet and should be made to comprehensively evaluate changes in VO_{2max}. The conclusive evidence on the effects of exercise in the treatment of patients with chronic diseases should be based on randomized controlled trials (Kujala 2009) and this review is made to meet those needs. The purpose of this study was to evaluate the effects of exercise training on VO_{2max} on patients with cardiac failure based on randomized controlled trials. In this review, not only studies concerning aerobic training intervention, but also studies from resistance training have been included, because of few interesting trials (Ades et al. 1996, Delagardelle et al. 2002, Shaw & Shaw 2005) reporting positive effects of resistance training to VO_{2max}.

2 BACKGROUND

2.1 Factors causing heart failure

Acute heart failure can be caused by sudden heart disease, such as myocardial infarction, myocarditis, heart valve rupture or arrhythmia (Remes 2000, Vuori & Kesäniemi 2005) but also sudden physical effort may cause acute heart failure and even death (Vuori & Kesäniemi 2005). Chronical heart failure can begin in an acute event, but usually symptoms are developed and worsened gradually (Remes 2000, Vuori & Kesäniemi 2005). Chronical heart failure occurs most commonly in left ventricular function. Right ventricular dysfunction is usually consequence from left ventricular dysfunction, but it may also be independent caused by infarction of right ventricle or pulmonary embolism (Vuori & Kesäniemi 2005). Damage of the heart muscle causes immediate weakening in pumping activity and arterial contracting, causing blood congestion in lungs (Guyton and Hall 2000, 235, Remes 2000, Vuori & Kesäniemi 2005) and leading to quickly worsening shortness of breath with possible shock (Remes 2000, Vuori & Kesäniemi 2005).

In western societies about 80% (Remes 2000) to 90% (Vuori & Kesäniemi 2005) of patients' chronic heart failure is caused by coronary artery disease or/and hypertension. Almost invariably the rest is caused by some disease of heart or lungs and their arterial disease. (Remes 2000, Vuori & Kesäniemi 2005).

2.2 Haemodynamic forms of heart failure

As a haemodynamic aspect, heart failure is divided in two forms. Systolic heart failure is impaired contracting ability of heart muscle, which is rising cardiac filling pressure and diminishing cardiac stroke volume because of infarct, inflammation, chronic heart disease or chronic hypertension that are destroying muscle cells in function (Kupari et al. 2000, Vuori & Kesäniemi 2005). Diastolic heart disease or failure in fulfillment is caused by retardation of active relaxation or impaired passive elasticity in heart muscle or both (Kupari et al. 2000). Behind that impairment is usually found ischemic factors, hypertrophy and fibrosis of heart

muscle and/or mechanic impediments, like tumor or fluid-filled pericardium (Vuori & Kesäniemi 2005).

Usually heart failure is about systolic and diastolic malfunction together. Especially systolic heart failure occurs almost without exception with diastolic malfunction, when defective contraction of ventricle induces weak elastic countermotion. Also many conditions that are paralyzing contractions, like ischemia in heart muscle, are weakening relaxation at the same time. Diastolic heart failure instead, is encountered without changes in heart contraction ability, thus the systolic heart function may be normal or even over current like for example in hypertrophic cardiomyopathy or constriction of the heart (Kupari et al. 2000).

2.3 Pathophysiology of heart failure

Weakened pumping activity of the heart is diminishing circulations regulation ability, when the capacity may become insufficient to meet the needs of metabolism. At the time, system tries to return heart's function ability with compensatory mechanisms, which are for example changes in heart structure, like expansion of left ventricle, hypertrophy of heart muscle and activation of local neurohumoral mechanisms. With these compensatory mechanisms blood flow reserve may be adequate to meet the needs of daily bases and the patient may remain asymptomatic. However, by the time these mechanisms may become insufficient and even expedite damaging of heart muscle (Kupari et al. 2000). Essential pathophysiological mechanisms in chronic heart failure are seen in Figure 1.

Sympathetic nervous system is significant in heart failure. Its function is agitated even in asymptomatic status and is strengthening as the disease proceeds (Kupari et al. 2000, Vuori & Kesäniemi 2005) inhibiting parasympathetic function (Guyton and Hall 2000, 235). When sympathetic function accelerates, muscle function of the heart strengthens and venous function improves increasing filling pressure of the right atrium and facilitating pumping work of the heart (Guyton and Hall, 2000, 235, Kiilavuori 2000). Sympathetical overcurrency is seen as raise of noradrenalin in plasma and accession of sympathetic impulses in peripheral nerves (Kiilavuori 2000, Kupari et al. 2000, Vuori & Kesäniemi 2005). Excited activity is preserved and enhanced by several reflexes originating from heart, muscles and renin-

angiotensin-aldosteronsystem (RAA) (Kupari et al. 2000, Vuori & Kesäniemi 2005). Although enhanced sympathetic activity is restoring pumping ability of heart at first, it is eventually causing negative effects related to hypertrophy and fibrosis of heart muscle and strengthening of neurohumoral reflexes (Kupari et al. 2000, Vuori & Kesäniemi 2005). When overactive status continues, heart muscles response to sympathetic excitement is weakening because the amount of beta-receptors is decreasing and disconnecting from intracellular mechanisms though the other circulatory responses to sympathetic irritation are strengthening. Although contraction of peripheral arteries and veins was enhancing heart pumping activity at first, it is causing oxygen depletion, accelerating anaerobic metabolism, enhancing systolic and diastolic stress of left ventricle and raising oxygen requirement of heart muscle when prolonged (Kupari et al. 2000).

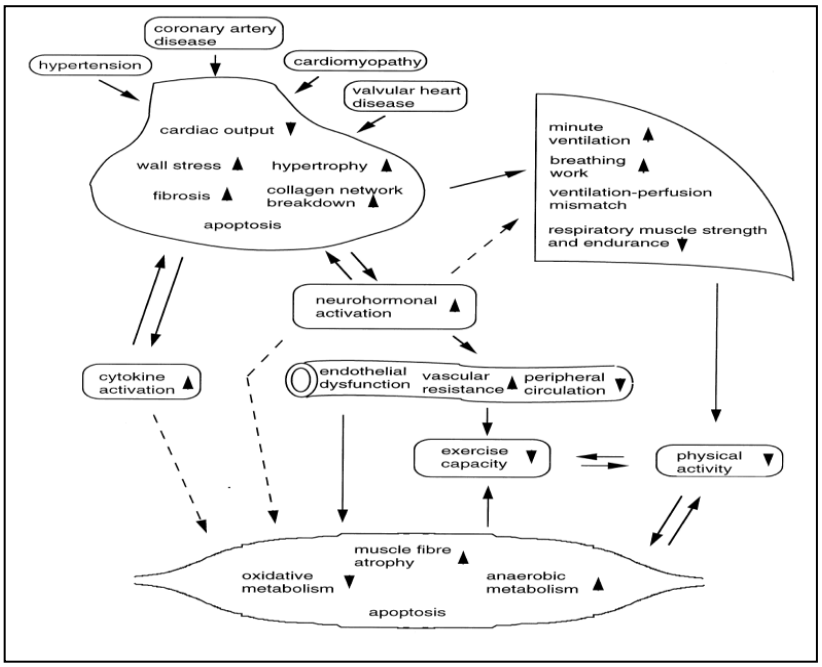


Figure 1: Essential pathophysiological mechanisms in chronic heart failure. Solid lines are describing known effects and dotted lines possible effects of disease. (Kiilavuori 2000).

Increasing stress is causing hypertrophy in heart muscle because of neurohormonal activation and mechanical tension (Kiilavuori 2000, Kupari et al. 2000). Growing length of muscle cells is causing enlargement and shape change of the left ventricle when pumping activity is supported at first by Frank-Starling mechanism. In turn, when diastolic volume is growing, smaller ejection fraction is sufficient for normal stroke volume. Over time, changes remain insufficient to balance enlargement and the muscle is unable to stretch more, contraction of the ventricle is weakening (Kupari et al. 2000). Mechanical stress is also multiplying collagen in heart muscle (Vuori & Kesäniemi 2005) and forming connective tissue in interstitial space whilst RAA-system is stimulating activity of fibrotic cells (Kiilavuori 2000, Vuori & Kesäniemi 2005).

Ventricular hypertrophy is therefore momentarily replacing heart's pumping activity, but in longer term, thick and fibrotic heart muscle is impairing diastolic (Kiilavuori 2000, Kupari et al. 2000, Vuori & Kesäniemi 2005) and systolic (Kiilavuori 2000) function. Enlarged heart muscle needs more oxygen, but on the other hand oxygenation becomes more difficult because of prolonged diffusion. At the same time, slowed relaxation and elevated filling pressure of left ventricle are shortening the duration of coronary flow and reducing perfusion pressure, causing lack of oxygen in heart muscle (Kupari et al. 2000, Vuori & Kesäniemi 2005).

Ventricular enlargement and change in the form of heart muscle are stretching valvular ring causing mitral leakage, and further reduction in circulatory minute volume and systematic blood pressure (Kupari et al. 2000). Whilst reduction in blood pressure, the primary goal of replacing mechanisms becomes to secure perfusion pressure in vital tissues instead of support pumping activity of heart. To reduce perfusion pressure peripheral blood vessels are contracting and blood flow is diminishing particularly in skeletal muscles, kidneys and skin. Reduced circulation in kidneys induces activation of neurohumoral regulation, when kidneys start to reserve water and sodium thus increasing extracellular fluid. Increase in extracellular fluid and intravenous blood volume leads to heart failure characteristic swelling in foots and ankles (Kupari et al. 2000, Vuori & Kesäniemi 2005).

2.4 Physical performance limiting factors in heart failure

In heart failure, physical performance is limited by shortness of breath, muscle fatigue and rapid exhaustion (Kupari et al. 2000, Koukouvou et al. 2004). Reasons caused by heart's pumping disorders, like high vein pressure in lungs and small minute volume combined with changes in lung function, skeletal muscle, muscle structure (Hämäläinen 2000, Kupari et al. 2000) and metabolism (Sturm et al. 1999, Kupari et al. 2000) together with problems with blood flow in muscles (Hämäläinen 2000, Sturm et al. 1999) are explaining drop in functional capacity. Shortness of breath is worsening because of increased work in respiration caused by rise in vein pressure, congestion, swelling and petrifaction in lungs combined with bronchial

obstruction and decreased blood flow in respiration muscles (Kupari et al. 2000, Vuori & Kesäniemi 2005).

Impaired peripheral circulation and diminished capillary density are restricting blood flow in skeletal muscles causing lack of oxygen particularly during physical stress (Kiilavuori 2002, Kupari et al. 2000). Slow structural and functional changes in skeletal muscles and reduction in muscle mass are promoting fatigue as well (Kupari et al. 2000). Mitochondrial amount and volume decreases (Kupari et al. 2000, Vuori & Kesäniemi 2005) and enzyme activity needed in fatty acids oxidation weakens (Hämäläinen 2000, Kupari et al. 2000, Vuori & Kesäniemi 2005). Also distribution of striated muscle cells changes so that percentage of anaerobic cells grows in relation to oxidative cells (Mancini et al. 1989, Kupari et al. 2000, Vuori & Kesäniemi 2005). As a result of these changes anaerobic energy production is easily overriding aerobic energy production which is explaining fatigue and weak physical performance once again (Kupari et al. 2000, Vuori & Kesäniemi 2005).

2.5 Physical effects of exercise in heart failure

Traditionally, even until 1980's (Coats 2000, Vuori & Kesäniemi 2005), patients with chronic heart failure have been recommended to avoid physical exercise, due to a general belief that physical stress might be harmful and aggravate the pre-existing cardiac condition (Willenheimer et al. 1998) and also because of its general impacts to endurance and differences in those factors (Vuori & Kesäniemi 2005). Nowadays, when heart failure has been revealed to be more complicated syndrome with significant changes in peripheral circulation and muscle activity (Kiilavuori 2000, Vuori & Kesäniemi 2005), it has been shown that physical exercise has beneficial effect to patients condition while harms remain minor (Willenheimer et al. 1998, Sturm et al. 1999, Coats 2000, Kiilavuori 2000, Vuori & Kesäniemi 2005.). The most congruent response in studies on this topic has been improvement in aerobic capacity and muscular strength (Kujala 2004, Kujala 2009). This is important when population is aging; exercise therapy may have important resorts by reducing disability and increasing the number of older people living independently (Kujala 2009).

Long-term physical inactivity of patients with clinically stable heart failure is noted to worsen the state of health and cause greater morbidity (Sturm et al. 1999). Many studies have shown that properly implemented physical exercise at least not shorten forecast in patients' lifetimes but actually lowers morbidity compared with controls (Vuori & Kesäniemi 2005). However, in Finnish evidence-based treatment recommendations concerning heart failure, physical activity could not be established preventive itself (Käypä hoito 2008).

Physical exercise affects positively to endothelium that covers the inner surface of blood vessels, lymphatic vessels and heart and also decreases sympathetic activation (Vuori & Kesäniemi 2005), when problematic physiological factors in heart failure, aerobic capacity and blood flow improve (Keteyian et al. 1996, Vuori & Kesäniemi 2005, Mueller et al. 2007). These changes act an essential basis to other physiological changes. Left ventricle growth stops and its size may even shrink. Hearts minute volume grows 8-15% in maximal strain, which is consequence from increment in heart rate and stroke volume. Growth in stroke volume, in turn, is caused by decrease in sympathetic nervous system activation and strengthening of vagal tonus. As a result of these, patients' maximal and submaximal endurance are raising 15-20% (European Heart Failure Training Group 1998, Piepoli et al. 1998) to 25% (Vuori & Kesäniemi 2005) and fatigue and shortness of breath in exercise decreasing (Vuori & Kesäniemi 2005).

2.6 Exercise recommendation in heart failure

According general physical activity recommendations, exercise training should be focused on endurance training for the best benefit (Vuori & Kesäniemi 2005). Endurance training has been noted to improve left ventricular pumping activity, skeletal muscle blood flow, strength and aerobic energy production, cardiovascular performance in submaximal and maximal stress, and also reducing fatigue and shortness of breath in patients with heart failure (Käypä hoito 2008).

Along aerobic exercise, also muscular strength training is important to stop muscle depletion, maintain the level of muscle strength, strengthen aerobic energy production (Vuori & Kesäniemi 2008) and enhance heart rate variability (Käypä hoito 2008). Together these two

exercise modes are generating larger effort to muscle strength and cardiovascular performance in maximal and submaximal stress than neither of them separately (Delagardelle et al. 2002). On the other hand, it has been noted that strength training alone may also increase heart rate variation in patients with mild or moderate heart failure (Käypä hoito 2008).

Patients with heart failure are usually aged and have multifarious sicknesses. Therefore the most important thing is to pay attention to individual, safe guides and smooth start. Patients' maximal heart beat without medication is typically about 130-150 beats per minute, which is 20% lower than among healthy people in same age. Regulation of exercise strain is defined by clinical exercise stress test before beginning of exercise training (Hämäläinen 2000). Because of factors such as leg fatigue and discomfort, a plateau of oxygen consumption is rarely achieved even with an increase in exercise intensity in a clinical setting with older sedentary patients. Therefore, it is customary to refer to VO_{2max} as the peak oxygen consumption during incremental exercise (Fletcher et al. 2001).

However, exercise testing enables load to be set 60-85% of the maximal heart rate (Hämäläinen 2000, Vuori & Kesäniemi 2005), which is about 40 (Hämäläinen 2000, ACSM 2006) -75% from maximal oxygen uptake (Hämäläinen 2000). According Finnish guidelines for fair treatment (Käypä hoito 2008), exercise training should be started at lower heart rate and increased later to about 60% of maximal heart rate, that means staying considerably lower heart rates during the whole exercise training. Training should be started from a few minutes period, leading to over a half an hour duration. Resulting effective training, maximal heart beat rate should increase among patients with heart failure, vice versa healthy people (Vuori & Kesäniemi 2005).

Exercise implemented in high intensity, 90-95% maximal oxygen uptake (Wisløff et al. 2007) or maximal heart rate (Käypä hoito 2008), could have larger effects on heart failure patient's physiology than endurance-type, lower intensity training. Practically that means interval-type training, in which short high-intensity periods are followed by recovery periods the same length (Wisløff ym 2007, Käypä hoito 2008). Both Käypä hoito (2008) and Wisløff et al. (2007) note that exercise implemented in high intensity is leading to greater changes in left ventricular pumping activity, skeletal muscle blood flow, strength, circulatory function

(Käypä hoito 2008), contraction of muscle cells and restraining hypertrophy of the heart muscle (Wisløff ym 2007).

2.7 The effect of exercise on maximal oxygen uptake in healthy people

Maximal oxygen uptake is reflection of cardiovascular fitness and its ability to carry oxygen to produce energy during maximal physical stress. It can be expressed as absolute volume liter per minute (l/min), or more usually as body weight regarding relative oxygen uptake (mL/kg/min). Oxygen uptake grows linearly with stress until maximal oxygen uptake is achieved and the growth stops. When strenuous exercise continues, additional energy production is achieved by anaerobic glycolysis. Aerobic capacity may increase 15 to 25% in few months and possibly improve by 50% in long-term training (McArdle et al. 2001, 159, 162, 477).

3 METHODS

3.1 Search strategy

Search was made from Ovid MEDLINE(R) (1948 to February week 2 2011) and Cochrane Central Register of Controlled Trials (1st Quarter 2011) using the strategy described in Table 1. As seen in the end of the search strategy, search was limited to concern only humans and language limitation picked up only articles in English. Search strategy was comprehended to cover also PubMed (Medline). From the searches, the title and abstract of each paper were reviewed and potentially relevant references retrieved. Following this initial screening, current reviewer (H. K.) selected trials to be included in this review using predetermined inclusion criteria.

Table 1. Search strategy.

1. cardiac failure.mp.	16. maximal vo2.mp.
2. cardiac insufficiency.mp.	17. aerobic capacity.mp.
3. myocardiac failure.mp.	18. randomised controlled trial*.mp.
4. myocardial failure.mp.	19. randomized controlled trial*.mp.
5. heart failure.mp.	20. rct.mp.
6. 1 or 2 or 3 or 4 or 5	21. 18 or 19 or 20
7. exercise.mp.	22. oxygen consumption.mp. or Oxygen Consumption/
8. exercise therapy.mp.	23. peak vo2.mp.
9. sport*.mp.	24. peakvo2.mp.
10. physical exercise.mp.	25. vo2 peak.mp.
11. 7 or 8 or 9 or 10	26. vo2peak.mp.
12. max* oxygen intake.mp.	27. 12 or 13 or 14 or 15 or 16 or 17 or 22 or 23 or 24 or 25 or 26
13. max* oxygen uptake.mp.	28. 6 and 11 and 27
14. vo2 max*.mp.	29. 21 and 2830. limit 29 to (english and humans)
15. VO_{2max}*.mp.	

In potentially eligible studies, authors were contacted when necessary for ambiguities in their reported methodologies or results. In addition, reference lists of articles found were reviewed to find other potential material.

3.2 Inclusion and exclusion criteria

The search strategy was developed to indentify all relevant randomized controlled trials that included structured exercise intervention in patients with heart failure. Reviews, editorials and comments, as well as studies other than parallel group design, were excluded.

Adults of all ages with chronic heart failure were included. Criteria for diagnosis of heart failure based on clinical findings or objective indices were demanded for inclusion. Myocardial infarction, uncontrolled hypertension or diabetes, recent stroke, renal dysfunction, pulmonary disease or any other condition limiting exercise duration were criteria to exclusion.

All exercise based interventions, lasting eight or more weeks were included. Trial must had non-exercising control group receiving usual medical care or attention-placebo. An exercise intervention had to be predetermined supervised program consisting of aerobic training, combined aerobic and resistance training, or resistance training and must been described within the corresponding manuscript. Studies in which people were exercising on their own with given instructions were excluded, because of problematic estimating of intensity and volume in unsupervised exercise training. Included studies in which personnel did not directly supervise the whole exercise intervention, a hospital- or rehabilitation centre -based period and a strict training program at home were required.

VO_{2max} measurements at baseline and at the end of the intervention period were required. To be considered valid, the VO_{2max} values were claimed to be obtained during a maximal exercise test with direct measures of oxygen consumption.

3.3 Data extraction and methodological quality assessment

The main outcome measure was maximal or peak oxygen uptake (VO_{2max} or VO_{2peak} mL/min/kg). Sample sizes and pre- and post-intervention means and standard deviations were extracted by reviewer (H. K). The extracted characteristics of the subjects included age, gender and diagnosis and the extracted characteristics of the exercise interventions contained exercise mode, frequency, duration, intensity and the duration of one exercise session. Additionally, the description of the exercise stress test protocol was extracted.

The Compendium of Physical activities (Ainsworth et al. 1993) was used to estimate the intensity of the exercise in terms of metabolic equivalents (METs) to promote comparability of coding across studies (seen in Appendix 1, Appendix Table 1). One MET corresponds to

an oxygen consumption of 3.5 mL O_2*kg^{-1}*min^{-1}, and is the amount of energy required to sleep. Total volume of training during the study was calculated by multiplying the intensity in METs by total time (minutes) spent exercising. Total volume of training per one week was also calculated dividing the total MET by duration (weeks) of intervention. Relative exercise intensity (%VO_{2max}) needed estimating METs was extracted directly from studies or estimated from the exercise heart rates according to guidelines (ACSM 2006, Swain & Leutholtz 2007) established earlier.

The methodological quality of each included trial was evaluated by reviewer (H. K) according to a validated three-point scale by Jadad et al. (1996). Jadad-scale is an instrument to measure the likehood of bias in reported randomization, blinding and withdrawals. In addition, adequate allocation concealment was also viewed according to Schulz et al. (1995).

3.4 Data synthesis and statistical analysis

Statistical analyses were performed using PASW Statistics Data Editor (PASW Statistics 18, release 18.0.0 July 30, 2009) and Review Manager (RevMan) [Computer program] Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. In each study, intention to treat data was analyzed whenever possible. The effect size for the intervention was calculated by the difference between the means of the exercise and control groups at the end of the intervention. When standard deviation was not reported, it was converted from standard error (SD = SE * square root of the sample size per group) and used in statistical runs when needed. When absence of the exact values of increase in duration or in METs, needed values were calculated with the average amount of increase. Percentage of heart rate reserve used in a few included studies was considered as percentage of VO_{2max} according to the general principles. The I^2 was used to measure the heterogeneity of the included studies.

4 RESULTS

4.1 Description of included studies

The computer search initially yielded 364 potential articles, from which 52 potential references were screened. 25 separate studies met the inclusion criteria. Of these, eight studies were later excluded since unacceptable study design or exercise intervention, incomplete description of intervention, incomplete data, too short intervention, submaximal exercise test, selective randomization and/or patients not facing the inclusion criteria (Appendix 1, Appendix Table 2). Eventually there were 17 acceptable articles with 18 comparisons as seen in Table 2. Sixteen studies reported a comparison between one intervention and one control group, and one study (Mandic et al. 2009) presented data for two comparisons, in which two different interventions were compared with one control group.

A total of 717 participants were included in 17 trials, 366 in training groups and 351 in control groups. 644 participants (89.8%) completed trials, 331 from training groups and 313 from control groups, which means 9.6% drop-outs in experimental groups and 10.9% in control groups. The mean age of participants was 60.6 years and they were mainly men. The majority of trials included patients with both primary and secondary heart failure and the results were not reported separately. The ejection fraction (LVEF) among the patients was usually <40% and/or NYHA -classification II or III.

4.2 Methodological quality of studies

The methodological quality of the included studies was moderate to low according to a previously validated scale (Jadad et al. 1996). Mean score was 1.5 out of a possible 3 points as seen in Table 3. Only two of the studies scored 3/3 (Mandic et al. 2009, Willenheimer et al. 1998). Although all 17 studies were reported to have randomized designs, only seven studies described the randomization method adequately. None of the studies were double blinded or had adequate allocation concealment. Three of the studies reported trials to be blinded in some way

Table 2. Characteristics of included studies.

Study	No. of participants	Patient description	Mean age	Exercise intervention						More
				Sub-group	Type	No. of weeks	No. of times/week	Length (min)	Intensity	
Belardinelli et al. 1999	E 48/50, C 46/49	Mixed HF - 85% ischaemic cardiomyopathy, 15% idiopathic DCM, LVEF <40%	55	Aerobic	Warm-up stretching, cycling	48	Phase 1 (8 weeks): 3, Phase 2: 2	55-60min	60% VO2max	89% men, compliance 89%, follow up at month 2 and 14. Patients monitored for 3,3 years
Brubaker et al. 2009	E 23/30, C 21/29	Diagnosted HF by LVEF <45%, NYHA 2 or 3	70,2	Aerobic	Walking, cycling	16	3	First 2 weeks 60min, from 3rd week gradually to 75-80min	40-50% HRR, from 3rd week gradually to 60-70 HRR	66% men
Dubach et al. 1997	E 12/12, C 13/13	CHF caused by MI, LVEF <40%, NYHA 2 or 3	55,5	Aerobic	Walking, cycling	8	Walking 2x/day, cycling 4x/week	2x60min/day + 4x45min/week	70%-80% HRR, increasing progressively as tolerated	100% men
Dziekan et al. 1998	E 10/10, C 10/10	HF caused by MI, LVEF <40%, NYHA 2or 3	56	Aerobic	Walking, cycling	8	Walking 2x/day, cycling 4x/week	2x60min/day, 4x45min/week	70%-80% HRR, increasing progressively as tolerated	100% men, gas exchange ang plethysmographic tests after 1 year
Erbs et al. 2010	E 18/18, C 19/19	Mixed CHF-IHD and DCM	70	Aerobic	Phase 1: cycling, phase 2: walking, cycling, calisthenics, ball games	12	Phase 1 (3 weeks): 3-6x/day, phase 2: 1x/day, 1 group session/week	Phase 1: 3-6x5-20min/day, phase 2: 20-30min/day, 1x60min group session/week	Phase 1: 50% VO2max, phase 2: target HR	100% men, phase 1 in hospital, phase 2 at home.

Hambrecht et al. 1995	E 9/12, C 9/10	Majority DCM (86%), remainders IHD. NYHA 2 or 3, LVEF<40%	51	Aerobic	Phase 1: cycling, phase 2: cycling, group sessions	24	Phase 1: 6x/day, phase 2: 2x/day, 2 group sessions/week	Phase 1: 6x10min, phase 2: 2x40min/day, 2x60min/group session week	Phase 1: 70% VO2max, phase 2: target HR	100% men, follow up at month 3 and 6
Jónsdóttir et al. 2006	E 22/22, C 21/21	Majority IHD (73%) rest AF or valvular, LVEF mean 40%, NYHA 2 or 3	68	Combined	Cycling, circuit resistance training	20	2	2x50min/week	Stimulus gradually increasing	79% men
Keteyian et al. 1996	E 15/21, C 14/19	Mixed CHF-IHD (9) and DCM (20). NYHA 2 or 3, LVEF<35%	54	Aerobic	Aerobic exercise equipments	24	3	3x45min/week	60-80% HRR, increasing as tolerated	100% men
Kitzman et al. 2010	E 24/26, C 22/27	Diagnosted HF, HFPEF >50%, NYHA 2 or 3	70	Aerobic	Walking, cycling	16	3	Phase 1 (2 weeks): 3x60min/week, phase 2: gradually increasing to 3x75-80min/week	Phase 1: 40-50% HRR, phase 2: gradually increasing to 60-70% HRR	25% men
Koukouvou et al. 2004	E 16/18, C 10/11	Mixed CHF - IHD or DCM, LVEF <40%, NYHA 2 or 3	52,6	Combined	Institution-based training, walking, cycling, jogging, calisthenics, stair climber, step aerobic, resistance training with therabands or small weights	24	3 or 4	3-4x60min/week	50-70% VO2peak/Borg scale 12-14	100% men, first 2-4 weeks institution-based training, after 3 months added some resistance training
Kulcu et al. 2007	E 23/27, C 21/26	Diagnosted HF - NYHA 2 or 3	59,4	Aerobic	Walking	8	3	3x60min/week	60-70% MHR	73% men

Mandic et al. 2009	E 13/14, C 13/13	LVEF mean 30,4, NYHA 1-3	62	Aerobic	Walking, cycling	12	3	3x30min/week	50-70%HRR, Borg scale 11-14	Sex not reported
Mandic et al. 2009	E 14/14, C 13/13	LVEF mean 30,4, NYHA 1-3	62	Combined	Walking, arm/leg ergometer, resistance exercises	12	3	3x30min/week + time spent during resistance exercises	50-70% HRR, Borg scale 11-14, resistance training 50-70%1RM	Sex not reported, resistance exercises: 6 types with commercially available weight machines, 1-2 sets 10-15 reps
Myers et al. 2002	E 12/12, C 12/12	CHF - all DCM - LVEF mean 26,6%	52,8	Aerobic	Cycling	8	5	5x45min/week	60-80% VO2max/Borg scale 13-15, intensity progressed as tolerated	42% men
Tyni-Lenné et al. 2001	E 16/16, C 8/8	CHF - CHD, DCM - LVEF<40%, NYHA 2 or 3	62,5	Resistance	Resistance/strenght training with rubber bands	8	3	3x60min/week	Borg scale 13-16	54% men
Wielenga et al. 1999	E 35/35, C 32/32	Mixed CHF - CHD and DCM. LVEF<40%, NYHA 2 or 3	56,6	Aerobic	Cycling, walking, ball games	12	3	3x30 (45)min/week	60% HRmax	100% men, compliance 85,4%. Comparising all 3 exercise types for 10 min each separated by 5 min rest
Willenheimer et al. 1998	E22/23, C 27/27	Mixed CHF - CHD (75%) and DCM (25%). Boston HF criteria, LVEF<45%	64	Aerobic	Cycling	16	2 or 3	2x15min/week gradually increasing to 3x45min/week	80% Vo2max, Borg scale 15	71% men, interval training
Williams et al. 2007	E6/7, C 5/6	CHF diagnosted - LVEF<40%, NYHA 2 or 3	70,5	Resistance	Resistance training	12	3	3x30min/week	< 5 beats/minute of peak heart rate	Sex not reported, time spent exercising estimated by reviewer (work 0,5-2 min/muscle (group), rest between intervals)

* Patients in the study: E= exercise group, C= control group, end/beginning.
Letter after the year of publication: A= aerobic training group, C= combined training group, R= resistant training group. Other abbreviations seen in Appendix 1, Appendix Table 3.

(single-blinded study design in Kitzman et al 2010, blinded outcome assessors in Mandic et al. 2009 and Willenheimer et al. 1998). Eleven studies had adequately (or at least in some way) described dropouts. There were no dropouts in four studies, and one study did not report dropouts at all (Dziekan et al. 1998). The compliance to exercise interventions, when reported, was relatively high, 81% on average within nine studies. Of those, only two had compliance under 80%. One study simply indicated that compliance was high and remain seven did not mention the compliance at all. Only two studies reported statistical analysis to be performed according to intention-to-treat principle (Belardinelli et al. 1999, Mandic et al. 2009). Keteyian et al. 1996 reported only results of the patients who completed the exercise test at the end of the study.

Table 3. Methodological quality of the included studies.

Study	Year	1	2	3	Total	AC
Belardinelli et al.	1999	N	N	Y	1	N
Brubaker et al.	2009	N	N	Y	1	N
Dubach et al.	1997	N	N	Y	1	N
Dziekan et al.	1998	Y	N	Y	2	N
Erbs et al.	2010	N	N	Y	1	N
Hambrecht et al.	1995	Y	N	Y	2	N
Jónsdóttir et al.	2006	N	N	Y	1	N
Keteyian et al.	1996	Y	N	Y	2	N
Kitzman et al.	2010	N	Y	Y	2	N
Koukouvou et al.	2004	N	N	N	0	N
Kulcu et al.	2007	Y	N	Y	2	N
Mandic et al.	2009	Y	Y	Y	3	N
Myers et al.	2002	N	N	Y	1	N
Tyni-Lenné et al.	2001	N	N	Y	1	N
Wielenga et al.	1999	N	N	Y	1	N
Willenheimer et al.	1998	Y	Y	Y	3	N
Williams et al.	2007	Y	N	Y	2	N

1: adequate sequence generation, 2: blinding, 3: description of dropouts; Total: maximal score 3 points in reported features; AC: allocation concealment; Y: yes, N: no.

4.3 Exercise interventions

4.3.1 Exercise mode and intensity

The exercise interventions in each study are described in Table 2. Twelve studies used aerobic training, typically stationary cycling or walking. Two studies (Jónsdóttir et al. 2006, Koukouvou et al. 2004) used combination of aerobic training and light resistance training, and two studies (Tyni-Lenné et al. 2001, Williams et al. 2007) used resistance training. One study (Mandic et al. 2009) had both aerobic and combined aerobic-resistance training interventions, from which both groups (aerobic-control, combination-control) were analyzed in this study.

Therefore 18 comparisons were included to the meta-analysis. The intensity of aerobic training was determined according to the maximal oxygen consumption (seven trials; 50-80% VO_{2max}), the maximal heart rate (three trials; 60-80% MHR) and heart rate reserve (five trials; 40-80% HRR). The intensity of strength training was set according to individuals exertion RPE 13-16 (Tyni-Lenné et al. 2001) or heart rate range >HR_{rest}+10, <95% HR_{peak} (Williams et al. 2007).

4.3.2 Length of the exercise period

The length of the training period varied between 8 weeks and 14 months (20 weeks at the average). The average length of the training programs was 29 weeks in the aerobic training studies, 18.6 weeks in the combined training studies and 10 weeks in the resistance training studies.

4.3.2 Exercise frequency and duration of an exercise session

Exercise frequency varied from six times per day to two times per week (Table 2). The average of exercise session frequency was 3.5 per week (6.7 if multiple sessions per day are calculated) in all studies, 4.3 times per week in the aerobic training groups, 2.8 times per week in the combined training groups and 3 times per week in the resistance training groups. The average duration of one session was 45 minutes in all studies. Average minutes spent exercising in one week were 297 minutes in aerobic training groups, 175 minutes in combined training groups and 105 minutes in resistance training groups.

4.4 Effects of exercise training on maximal oxygen uptake

4.4.1 Measurement of maximal oxygen uptake

In 14 studies maximal or peak oxygen uptake was measured using a bicycle ergometer and in three studies it was measured by a treadmill. Respiratory gases were simultaneously measured by direct measurement in all studies.

4.4.2 Change in VO_{2max} in all studies

At baseline, there were no significant differences observed between exercise and control groups in 18 comparisons of the results of VO_{2max} as seen in Table 4. The pooled results of the 18 comparisons indicated that VO_{2max} changed by 17.2±13.2% in the training groups and 0.4±5.4% in the control groups. The absolute change in VO_{2max} was 2.9±2.3 in the exercise groups and 0.1±0.9 in the control groups (Table 5). Thus, the net change in VO_{2max} between the groups was 2.8 mL/kg/min. Table 4 shows that the statistical heterogeneity of the studies was low at baseline (I^2=0%), but after intervention I^2 was 79%, indicating substantial heterogeneity.

4.4.3 Change in VO_{2max} in sub-groups

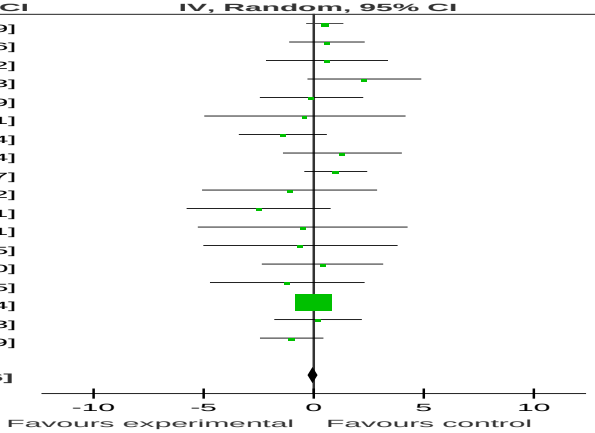
As mentioned earlier, VO_{2max} did not differ from each other in the exercise groups and control groups (Table 4). The post-intervention results indicated that VO_{2max} increased in all training modes. The change was greatest (19.0%) in the aerobic training groups, next in the combined aerobic and resistance training groups (13.9%) and smallest (9.9%) in the resistance training groups (Table 6). As expected, each training mode was found to be more effective than non-exercising control mode with only 0.4% change in VO_{2max}.

Table 4. VO_{2max} before (A) and after (B) the intervention periods in all included studies.

A

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Belardinelli 1999	15.7	2	50	15.2	2	49	7.4%	0.50 [-0.29, 1.29]
Brubaker 2009	14.1	3.3	30	13.5	3.2	29	1.7%	0.60 [-1.06, 2.26]
Dubach 1997	19.4	3	12	18.8	3.9	13	0.6%	0.60 [-2.12, 3.32]
Dziekan 1998	19.9	2.4	10	17.6	3.3	10	0.7%	2.30 [-0.23, 4.83]
Erbs 2010	15.3	3.3	18	15.4	3.8	19	0.9%	-0.10 [-2.39, 2.19]
Hambrecht 1995	17.5	5.1	12	17.9	5.6	10	0.2%	-0.40 [-4.91, 4.11]
Jónsdóttir 2006	14.9	3.4	22	16.3	3.1	21	1.2%	-1.40 [-3.34, 0.54]
Keteyian 1996	16	4.1	21	14.7	4.4	19	0.7%	1.30 [-1.34, 3.94]
Kitzman 2010	13.8	2.5	26	12.8	2.6	27	2.4%	1.00 [-0.37, 2.37]
Koukouvou 2004	22.3	4.9	16	23.4	5	10	0.3%	-1.10 [-5.02, 2.82]
Kulcu 2007	20.1	5.6	27	22.6	6.3	26	0.4%	-2.50 [-5.71, 0.71]
Mandic 2009 (1)	16.1	6	12	16.6	6	13	0.2%	-0.50 [-5.21, 4.21]
Mandic 2009 (2)	16	5.1	12	16.6	6	13	0.2%	-0.60 [-4.95, 3.75]
Myers 2002	12.8	4	12	12.4	2.6	12	0.6%	0.40 [-2.30, 3.10]
Tyni-Lenné 2001	14.8	4.2	16	16	4	8	0.4%	-1.20 [-4.65, 2.25]
Wielenga 1999	15.2	0.5	41	15.2	0.6	39	78.3%	0.00 [-0.24, 0.24]
Willenheimer 1998	16.6	3.1	22	16.4	3.8	27	1.2%	0.20 [-1.73, 2.13]
Williams 2007	13.8	1.1	7	14.8	1.4	6	2.4%	-1.00 [-2.39, 0.39]
Total (95% CI)			**366**			**351**	**100.0%**	**0.04 [-0.17, 0.26]**

Heterogeneity: Tau² = 0.00; Chi² = 15.61, df = 17 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

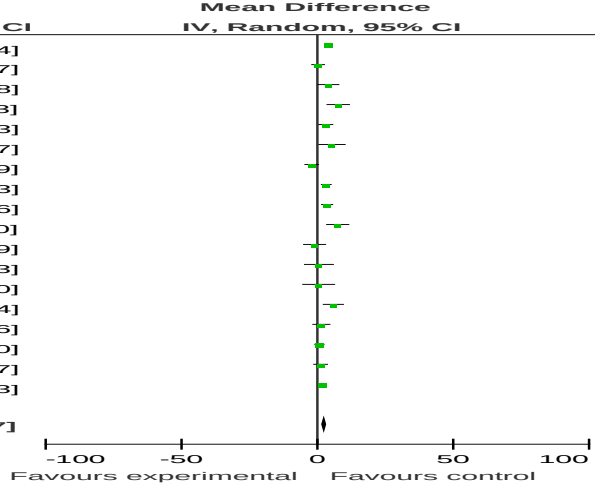


(1) Aerobic training group
(2) Combined aerobic and resistance training group

B

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Belardinelli 1999	19.9	1	48	15.6	2	46	8.4%	4.30 [3.66, 4.94]
Brubaker 2009	13.9	3.8	23	13.6	3.2	21	6.6%	0.30 [-1.77, 2.37]
Dubach 1997	23.9	4.8	12	19.8	4.3	13	4.5%	4.10 [0.52, 7.68]
Dziekan 1998	25.4	4.8	10	17.7	3.9	10	4.2%	7.70 [3.87, 11.53]
Erbs 2010	17.8	3.2	17	14.7	3.7	17	6.2%	3.10 [0.77, 5.43]
Hambrecht 1995	23.3	4.2	9	17.9	5.6	9	3.4%	5.40 [0.83, 9.97]
Jónsdóttir 2006	14.8	3	22	16.9	4	19	6.4%	-2.10 [-4.29, 0.09]
Keteyian 1996	18.5	2.3	15	15.2	1.9	14	7.4%	3.30 [1.77, 4.83]
Kitzman 2010	16.1	2.6	24	12.5	3.4	22	7.1%	3.60 [1.84, 5.36]
Koukouvou 2004	30.3	4.3	16	22.8	5.1	10	4.2%	7.50 [3.70, 11.30]
Kulcu 2007	23.6	7	23	24.6	5.8	21	4.2%	-1.00 [-4.79, 2.79]
Mandic 2009 (1)	17.3	6.4	11	16.7	6.1	13	3.0%	0.60 [-4.43, 5.63]
Mandic 2009 (2)	17.2	6.9	9	16.7	6.1	13	2.6%	0.50 [-5.10, 6.10]
Myers 2002	19	5.1	12	13.1	3.3	12	4.6%	5.90 [2.46, 9.34]
Tyni-Lenné 2001	15.9	4.3	16	14.4	2.8	8	5.4%	1.50 [-1.36, 4.36]
Wielenga 1999	16.72	3	35	15.96	3	32	7.5%	0.76 [-0.68, 2.20]
Willenheimer 1998	17.5	4.2	22	16.3	3.8	27	6.3%	1.20 [-1.07, 3.47]
Williams 2007	15.5	0.6	7	13.5	1.3	6	7.9%	2.00 [0.87, 3.13]
Total (95% CI)			**331**			**313**	**100.0%**	**2.58 [1.49, 3.67]**

Heterogeneity: Tau² = 3.57; Chi² = 80.65, df = 17 (P < 0.00001); I² = 79%
Test for overall effect: Z = 4.64 (P < 0.00001)



(1) Aerobic training group
(2) Combined aerobic and resistance training group

Table 5. Changes in VO_2 in the training and control groups.

Group		N	Minimum	Maximum	Mean	Std. Deviation
Training	Pre	18	12.80	22.30	16.35	2.56
	Post	18	13.90	30.30	19.25	4.35
	Change, %	18	-1.42	48.44	17.15	13.28
	Change	18	-0.20	8.00	2.90	2.34
	Valid N (listwise)	18				
Control	Pre	17	12.40	23.40	16.45	3.00
	Post	17	12.50	24.60	16.54	3.31
	Change, %	17	-10.00	8.85	0.43	5.01
	Change	17	-1.60	2.00	0.09	0.86
	Valid N (listwise)	17				
Combined	Pre	3	14.92	22.30	17.77	3.96
	Post	3	14.76	30.30	20.75	8.36
	Change, %	3	-1.07	35.87	13.88	19.46
	Change	3	-0.16	8.00	2.98	4.39
	Valid N (listwise)	3				
Resistance	Pre	2	13.80	14.80	14.30	0.71
	Post	2	15.50	15.90	15.70	0.28
	Change, %	2	7.43	12.32	9.88	3.46
	Change	2	1.10	1.70	1.40	0.42
	Valid N (listwise)	2				
Aerobic	Pre	13	12.80	20.10	16.34	2.32
	Post	13	13.90	25.40	19.46	3.53
	Change, %	13	-1.42	48.44	19.03	13.06
	Change	13	-0.20	6.20	3.12	2.017
	Valid N (listwise)	13				

4.5 Meta-regression analyses

The associations between different variables are seen in Figure 2. Associations between total duration of exercise and mean change in VO_{2max} (r=0.486, p=0.020, Fig 1A), and total METs of exercise and mean change in VO_{2max} (r=0.512, p=0.015, Fig 1B) were significant. Also the associations between intensity and mean change in VO_{2max} (r=0.351, p=0.077, Fig 1C) and exercise volume per week and mean change in VO_{2max} (r=0.367, p=0.067, Fig 1D) were of borderline significance.

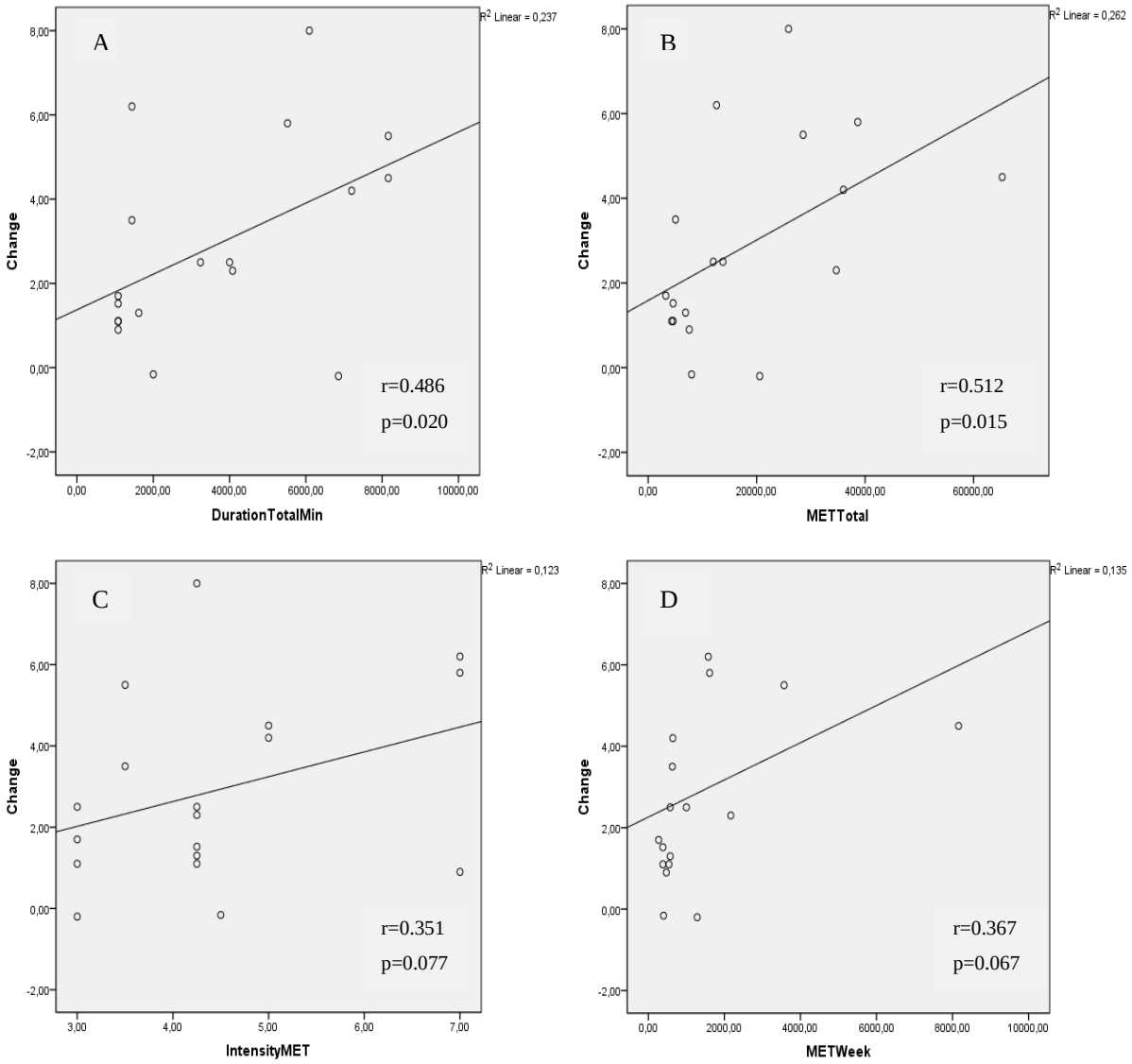


Figure 2. Associations between exercise intensity (MET) or exercise volume (MET hours/week) and post-intervention change in VO_{2max} between the exercise and control groups.

Table 6. Results of the sub-group analyses.

		No. of studies	No. of participants		VO_{2max} (exe)	VO_{2max} (cont)	Random model MD (95% CI)	I^2(%)	*P* value
Training mode	Aerobic	13	264/290	Pre	16.3	16.4	-0.11 [-2.01, 1.79]	0	0.91
				Post	19.4	16.5	2.90 [0.42, 5.38]	72	0.06
				Change%	19.0				
	Combined	3	52/54	Pre	17.8	16.4	1.33 [-3.38, 6.03]	0	0.58
				Post	20.8	16.5	4.21 [-5.38, 13.80]	0	0.84
				Change%	13.9				
	Resistance	2	22/23	Pre	14.3	16.4	-2.15 [-3.88, -0.42]	0	0.01
				Post	15.7	16.5	-0.84 [-2.46, 0.78]	14	0.02
				Change%	9.9				

exe= exercise training group, cont= control group, MD= mean difference.

DISCUSSION

Low cardiorespiratory fitness is a large risk factor associated with increased mortality also within people without any cardiac disease. Thus, it is obvious that with a modifiable risk factor like that, it is clinically important to determine the extent to which the low cardiorespiratory fitness often observed in people with heart failure is also modifiable. Its benefits in advanced stages of chronic heart failure with regard to hemodynamics and exercise capacity are already shown in recently published retrospective analysis (Erbs et al. 2003). The present review is, to this knowledge, the most comprehensive meta-analysis to date to examine the effectiveness of exercise training on VO_{max2} in heart failure patients.

The present meta-analysis determined that VO_{2max} can be improved in patients with heart failure. Overall, the absolute change of 2.8 mL/kg/min VO_{2max} between exercise and control groups was observed after the exercise training interventions. The strongest effect was achieved with aerobic training mode with 19.0% (3.1 mL/kg/min, p=0.06) change in VO_{2max}. Also other training modes were established impressive with results of 13.9% (3.0 mL/kg/min) in combined aerobic and resistance training groups, and 9.9% (1.4 mL/kg/min) in resistance training groups. Change in the control groups was 0.4% (0.1 mL/kg/min). Results are rather similar with previously published meta-analyses among patients with other chronic diseases (Boulé et al. 2003, Rees et al. 2004, Kujala 2009, Valkeinen et al. 2010).

Touching on this review, Kodama et al. (2009) have summarized the results of observational studies in recent meta-analysis and concluded that about 1 MET (about 3.5 mL/kg/min) increase in aerobic capacity is associated with 13-15% decrease in risk of mortality and coronary heart disease in healthy men and women. According Boulé et al (2003) increase only about 2.1 mL/kg/min less than 70% of VO_{2max} is enough to have beneficial consequences on morbidity and mortality. Earlier observational studies have shown that exercise training programs giving at least 3.5 mL/kg/min improvement in VO_{2max} are beneficial to patients with chronic heart disease, but benefits of smaller increases of VO_{2max} are not well known (Valkeinen et al. 2010 according Myers et al. 2002, Gulati et al. 2003, Kokkinos et al. 2008). It can only be suggested that the greater the improvements are in the exercise capacity, the greater is the reduction in the risk of death. Viewing that relationship, it should be

remembered that it is not known if the relationship from observational studies corresponds to the relationship of changes in intervention studies. As this review revealed, exercise induced changes in VO_{2max} were however quite small in patients with heart failure, 2.8 mL/kg/min, which is only about 0.8 MET. Though, seven trials out of 18 comparisons are reporting ≥3.5 mL/kg/min improvement in VO_{2max} (Belardinelli et al. 1999, Dubach et al.1997, Dziekan et al. 1998, Hambrecht et al. 1995, Koukouvou et al. 2004, Kulcu et al. 2007, Myers et al. 2002) (Appendix 1, Appendix Table 4). Discussing the results of improvements in VO_{2max} and its effects mentioned earlier in this paragraph, it should be kept in mind that this review is not actually dealing with mortality but rather with maximal oxygen uptake and possible improvements in it. Thus, it is certainly sure that even improvements with 0.8 MET are effective when dealing with cardiorespiratory fitness.

Klocek et al. (2005) suggest in their study that more intensive physical training with gradually increasing workload can improve quality of life more than training with constant workload. In this review, all seven studies mentioned earlier (VO_{2max} ≥3.5 mL/kg/min) were implemented with such exercise training program and as noted, were found the most effective also concerning VO_{2max} (Belardinelli et al. 1999, Dubach et al.1997, Dziekan et al. 1998, Hambrecht et al. 1995, Koukouvou et al. 2004, Kulcu et al. 2007, Myers et al. 2002). Six (not Kulcu et al 2007) of those seven were carried out by highest intensities (~5-7 MET), highest METs in week (not Belardinelli et al. 1999) and highest total durations (Appendix 1, Appendix Table 1). Also meta-regression analyses in this study confirmed that changes in VO_{2max} across studies tended to be associated with exercise intensity and duration. Belardinelli et al. (1999) that was far below in METs per week, reached the others by the length of training period. In turn, five of the studies implemented with gradually increasing workload, were not found as effective on VO_{2max} (Brubaker et al. 2009, Jónsdóttir et al. 2006, Kulcu et al. 2007, Wielenga et al. 1999, Willenheimer et al. 1998). That can be explained by substantially lower METs and duration of the training program. Of those five, Brubaker et al. (2009) was the only study with METs and duration similar to effective ones. It was though separating those ones by a long, and even increasing length of one training session. Judging from that, it might be deduced that one training session must not be too long at a time.

Walking and cycling were used as training method in every study with aerobic intervention. A great popularity of those has probably due to their effectiveness and safety as training method

when improving aerobic capacity. Exercising is known to improve circulation and it can be found number of studies concerning connections between heart failure and blood flow in lower limbs. Inter alia Hambrecht et al. (1995) are stating that Vo_{2peak} measured from leg increased significantly and changes in cytochrome c oxidase-positive mitochondria were significantly related to changes in oxygen uptake at the ventilator threshold and at peak exercise. That means that regular physical training increases maximal exercise tolerance and delays anaerobic intolerance during sub-maximal exercise. Improved functional capacity is closely linked to an exercise induced increase in the oxidative capacity of skeletal muscle.

Certain possible factor limiting improvement in oxygen uptake among patients with heart failure compared with improvements possible among healthy people may be the effect of medication. Especially β-blockers are known to inhibit an increase in heart rate and may affect also VO_{2max} in that way. In this review, medication was accepted in every included study. In turn, exercise training is known to improve heart's pumping mechanism when blood flow is improving and heart rate is decreasing. Thus, exercising can be considered as a natural β-blocker when successfully implemented. Unfortunately, a quick search for studies concerning effects of medication as VO_2-limiting factor in exercise training among heart failure patients yielded no results and connections remain unexplained. The lack of studies presumably derives from the existing risk of death while exercising without proper medication.

Meta-regression analyses of this study were slightly unsuccessful. Regression analysis is a method, which tries to describe dependence ratio between variables. In other words, variable (y) is tried to be explained by number of other variables (x_1, x_2…). It would have been more pertinent if the other kinds of factors were selected to the meta-regression analysis in this study. First of all, it could have been more felicitous to try to estimate the exercise intensity in percentage of VO_{2max} instead of conversion to METs. Determination of exercise intensity to METs was difficult because of possible subjectivity of evaluating person. Also percentage of heart rate reserve considered as percentage of VO_{2max}, as presented in the method part of the study, could have been converted more accurately. Correlation is extensively found incomplete (Swain & Leutholtz 1997, Brown et al. 2006, Lounana et al. 2007), most prominently in older, less fit adults (Brown et al. 2006). Secondly, instead of viewing associations of chosen factors, there would possibly have been more preferable factors to

explain variations. In present case, the factor "change" was used in meta-regression. In retrospect, it is too vague factor to be used in scientific research. Better choice could have been post-intervention mean difference (MD) or standardized mean difference (SMD) in VO_{2max} between the exercise and control groups. Also intensity (in estimated METs) and volume (MET hours/week) could have been enough in estimating associations instead of used Total Duration/min, Intensity/METs, MET Total and MET/Week.

The most severe deficiency was done with absence of comparison between mean differences in different subgroups. Only changes in the whole exercise group are seen by used comparisons, whilst the changes between different sub-groups were the object of interest. A sensitivity analysis might also have been helpful to determine whether the specific types of interventions influenced the results by calculating the effect sizes of the outcome assessed. Still, it should also have been included more factors in sub-group analyses, like intensity, the length of training period and time elapsed since last cardiac event. The last one would have been important factor in analyzing not only efficacy, but also safety of the exercise training. The right timing while starting exercise training may have strong impacts to effectiveness of training, and should be taken into account in defining recommendable exercise training program in heart failure. Factor, which would have been interesting to investigate, is interval-type training mode. Simply, the higher was the intensity, the better were the results. That kind of high intensity training is possible to implement only by interval-type training mode.

Limitations of the current study

Studies that met the inclusion criteria of this review were mostly small and of relatively poor methodological quality according validated Jadad scale (Jadad et al. 1996). The mean score was 1.5 out of possible three points. Blinding of the care providers and participants is difficult in exercise intervention studies. If this criterion of blinding had been left out, the result would certainly have been better. Allocation concealment, randomization methods, compliance and drop-out rate were incompletely described among all included studies or were not described at all. Though, insufficient documentation rather than problems in the actual study protocol might have been the reason for the poor quality score in many cases. It is revealed that more

high quality RCTs with proper documentation is needed on researching the effects of exercise training in patients with heart failure.

As mentioned earlier, the size of included studies was mostly small. That is followed by a problem of the small size of the sub-groups. There were 13 studies in the aerobic group, but only three in the combined training group and two in the resistance training group. This leads directly to generalisability problems with the results of those two groups. Though, reading the results of the current review, outcomes should be treated with some caution because the limited material of those two groups does not give reliable results of training mode efficacy. If this review is used as part of the further investigation, search strategy should be modified to get more studies fulfilling the criteria. For example, search could be extended to include not only terms oxygen intake and uptake, but also term oxygen consumption. Those three could be handled as the same, and this would help to achieve more extensive and comprehensive material.

During the search of this current study, also methodological limitations were confronted. Two interesting studies were found that were not in reach in any of the available channels through, even when asked directly from the authors (Coats et al. 1990, Klecha et al. 2007). Also one study (Wisløff et al. 2007) met the inclusion criteria as well, but was incorrectly excluded at an early stage due to human error; inclusion criteria were found eventually fulfilled after all the statistical results when using study as a reference.

Conclusion

Although there can be found many reports concerning heart failure and training, only few have prospectively compared the elements of the training program. On the basis of this current meta-analysis, moderate to moderate-high intensity aerobic exercise training is the most preferred in increasing VO_{2max} among patients with heart failure, as expected. Differences in VO_{2max} were found to be higher when intensity and duration were high. Unexpectedly but reasonably, gradually increasing workload was also found to be effective method when targeting increase in VO_{2max} through training. As previously stated, the start must be smooth because the patients are usually aged and have multifarious sicknesses. For

the same reason, the most important thing to do is to pay attention to individuality and safety when designing exercise training program for patient with heart failure.

This review was made to determine which kind of exercise training will help patients with heart failure to improve their cardiorespiratory fitness. Because the distribution between men and women in this review was usually unknown, findings of this review are best generalized for men around 60 years of age and may not be generalisable to all patients with heart failure. Benefits of exercise training were certified and improvements witnessed in this study, but accurate instructions of implementation remained incomplete. Important points that need to be clarified in future are the optimal intensity, frequency and necessary duration for obvious training effects. As well questions concerning higher intensities permitting interval-type exercise training and the stability of the results achieved by any type of training are requiring more detailed investigation.

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Appendix Table 1. Intensity of the exercise in included studies converted in terms of metabolic equivalents (METs).

Study	Major headings	Specific activity	Intensity (MET)	Duration,total (min)	MET/total	MET/week
Belardinelli et al. 1999	Conditioning exercise	Bicycling, stationary, general	5	7200	36000	643
Brubaker et al. 2009	Walking	Walking, firm surface	3	6855	20565	1285
Dubach et al. 1997	Conditioning exercise	Bicycling, stationary, general	5	8160	65280	8160
Dziekan et al. 1998	Walking	Walking, moderate pace, firm surface	3,5	8160	28560	3570
Erbs et al. 2010	Conditioning exercise, walking	Bicycling, stationary, very light effort	3	4000	12000	1000
Hambrecht et al. 1995	Conditioning exercise	Bicycling, stationary, moderate effort	7	5520	38640	1610
Jónsdóttir et al. 2006	Conditioning exercise	Bicycling, stationary, general; weight lifting, light or moderate, general	3,0-5,0	2000	8000	400
Keteyian et al. 1996	Conditioning exercise, walking	Bicycling, stationary, general; walking, moderate pace, firm surface	3,5-5,0	3240	13770	574
Kitzman et al. 2010	Conditioning exercise, walking	Bicycling, stationary, general; walking, moderate pace, firm surface	3,5-5,0	4080	34680	2168
Koukouvou et al. 2004	Conditioning exercise, walking	Bicycling, stationary, general; walking, moderate pace, firm surface; weight lifting, light or moderate, general	3,5-5,0	6090	25883	1078
Kulcu et al. 2007	Walking	Walking, moderate pace, firm surface	3,5	1440	5040	630
Mandic et al. 2009 (1)	Conditioning exercise, walking	Bicycling, stationary, general; walking; weight lifting, light or moderate, general	3,5-5,0	1620	6885	574
Mandic et al. 2009 (2)	Conditioning exercise, walking	Bicycling, stationary, general; walking, moderate pace, firm surface	3,5-5,0	1080	4590	383
Myers et al. 2002	Conditioning exercise	Bicycling, stationary, moderate effort	7	1800	12600	1575
Tyni-Lenné et al. 2001	Conditioning exercises	Weight lifting, general	3	1440	4320	540
Wielenga et al. 1999	Conditioning exercise, walking	Bicycling, stationary, general; walking, moderate pace, firm surface	3,5-5,0	1080	4590	383
Willenheimer et al. 1998	Conditioning exercise	Bicycling, stationary, moderate effort (interval)	7	1080	7560	473
Williams et al. 2007	Conditioning exercises	Weight lifting, general	3	1080	3240	270

Appendix Table 2. Characteristics of excluded studies.

Study	Reason for exclusion
Collins et al.. 2004	Intervention and outcomes incompletely described
Erbs et al.. 2003	Data incomplete. Outcome reported but no follow up data presented in the publication. Written to authors to try to obtain missing data, but no help because of confusion with asked information. No answer to further ask.
Gottlieb et al. 1999	Intervention not acceptable. Baseline exercise test not maximal.
Kiilavuori et al. 1996	Intervention incompletely described. No contact details.
Klocek et al. 2005	Data inadequate. No standard deviation (SD) reported. No active address for contact.
Maiorana et al. 2000	Cross-over study, not accepted.
Mueller et al. 2007	Intervention too short, selective randomization.
Sturm et al. 1999	Patients do not meet the inclusion criteria.

Appendix Table 3. Abbreviations.

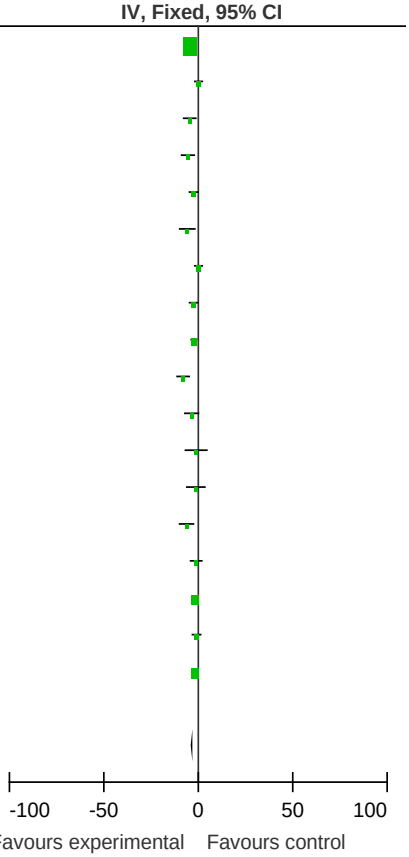
CHF	Chronic heart failure
CHD	Coronary heart disease
DCM	Dilated cardiomyopathy
HF	Heart failure
HFPEF	Heart failure with a preserved left ventricular ejection fraction
HR	Heart rate
MHR	Maximal heart rate
HRR	Heart rate reserve ($HR_{max} - HR_{rest}$)
IHD	Ischemic heart disease
LVEF	Left ventricular ejection fraction
MD	Mean difference
MET	Metabolic equivalent
MI	Myocardial infraction
Min	Minutes
NYHA	New York Heart Association classification
Sec	Seconds
SMD	Standardized mean difference
RCT	Randomized controlled trial
Reps	Repetitions
RPE	The Borg RPE Scale
VO_{2max}	Maximal oxygen uptake or intake
VO_{2peak}	Peak oxygen uptake or intake

Appendix Table 4. Changes in $VO2_{max}$ in exercise groups.

	Pre			Post				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Belardinelli 1999	15.7	2	50	19.9	1	48	36.3%	-4.20 [-4.82, -3.58]	
Brubaker 2009	14.1	3.3	30	13.9	3.8	23	3.7%	0.20 [-1.75, 2.15]	
Dubach 1997	19.4	3	12	23.9	4.8	12	1.4%	-4.50 [-7.70, -1.30]	
Dziekan 1998	19.9	2.4	10	25.4	4.8	10	1.3%	-5.50 [-8.83, -2.17]	
Erbs 2010	15.3	3.3	18	17.8	3.2	17	3.0%	-2.50 [-4.65, -0.35]	
Hambrecht 1995	17.5	5.1	12	23.3	4.2	9	0.9%	-5.80 [-9.78, -1.82]	
Jónsdóttir 2006	14.92	3.44	22	14.76	3.02	22	3.8%	0.16 [-1.75, 2.07]	
Keteyian 1996	16	4.1	21	18.5	2.3	15	3.2%	-2.50 [-4.60, -0.40]	
Kitzman 2010	13.8	2.5	26	16.1	2.6	24	7.0%	-2.30 [-3.72, -0.88]	
Koukouvou 2004	22.3	4.9	16	30.3	4.3	16	1.4%	-8.00 [-11.19, -4.81]	
Kulcu 2007	20.1	5.6	27	23.6	7	23	1.1%	-3.50 [-7.06, 0.06]	
Mandic 2009 (1)	16.1	6	12	17.2	6.9	9	0.4%	-1.10 [-6.74, 4.54]	
Mandic 2009 (2)	16	5.1	12	17.3	6.4	11	0.6%	-1.30 [-6.06, 3.46]	
Myers 2002	12.8	4	12	19	5.1	12	1.0%	-6.20 [-9.87, -2.53]	
Tyni-Lenné 2001	14.8	4.2	16	15.9	4.3	16	1.6%	-1.10 [-4.05, 1.85]	
Wielenga 1999	15.2	0.5	41	16.72	3	35	13.9%	-1.52 [-2.53, -0.51]	
Willenheimer 1998	16.6	3.1	22	17.5	4.2	22	3.0%	-0.90 [-3.08, 1.28]	
Williams 2007	13.8	1.1	7	15.5	0.6	7	16.3%	-1.70 [-2.63, -0.77]	
Total (95% CI)			**366**			**331**	**100.0%**	**-2.77 [-3.15, -2.40]**	

Heterogeneity: Chi² = 74.30, df = 17 (P < 0.00001); I² = 77%

Test for overall effect: Z = 14.48 (P < 0.00001)



(1) Combined aerobic and resistance training group

(2) Aerobic training group