Effect of eccentric exercise on quality of life and function in people with chronic heart failure: a pilot randomised controlled trial

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Abstract

Purpose: To determine if eccentric exercise was effective, safe and feasible in increasing function and quality of life in people with heart failure compared to usual care and a waitlist control group.

Methods**:** A prospective, three-armed, parallel-design, assessor-blind pilot randomised controlled trial with 1:1:1 allocation. Forty-seven participants (16 female; mean age 66 years) with mild to moderate heart failure were randomly allocated to either eccentric exercise, concentric exercise or a waitlist control group. Participants in the exercise groups completed twice-weekly exercise for eight weeks. Primary outcome was walking capacity. Secondary outcomes were quality of life, leg strength and fatigue. Outcomes were assessed at baseline, post intervention and three-month follow-up. Attendance, tolerability and adverse events were used to determine safety and feasibility.

Results: Intention-to-treat analysis showed no differences between eccentric exercise and either concentric exercise or waitlist for any outcome. Per-protocol analysis found improvements identified by the Minnesota living with heart failure questionnaire were significantly greater post-intervention for eccentric exercise compared to concentric exercise (-17.99 units, 95% confidence interval -35.96 to -0.01). No major adverse events were reported.

Conclusion: In this small trial, eccentric exercise did not demonstrate superior outcomes to concentric exercise or a waitlist control group.

Keywords

Chronic heart failure, heart failure, exercise, eccentric exercise, rehabilitation, quality of life, function.

Implications for Rehabilitation:

- Regular physical activity and referral to rehabilitation is recommended for people with chronic heart failure, however exercise can be challenging for this group.
- Eccentric exercise was safe and feasible for participants with heart failure.
- In this study there were no differences between groups who received eccentric exercise, concentric exercise or no exercise.

Introduction

Current clinical guidelines recommend regular physical activity for people with chronic heart failure and referral to rehabilitation for patients who are medically stable (1). Rehabilitation programs primarily comprise moderate intensity, continuous, endurance exercise as well as weightlifting with the aim of improving physical function, quality of life and hospitalisation rates (1). Individuals with chronic heart failure show obstructive and restrictive deficits on respiratory function tests (2) as well as skeletal muscle dysfuction (3) which leads to exercise intolerance. For this reason, there is interest in determining if eccentric exercise with its low energy costs, may be used safely to achieve strength and functional gains in people with significant intolerance to exercise.

Eccentric exercise produces high forces but with low energy costs (4). During eccentric contractions, the muscle lengthens and stores elastic recoil energy which can then be used to create high forces with little metabolic demand (4). Eccentric contractions require 50% to 86% less oxygen than concentric contractions (5, 6). While eccentric exercise has traditionally been used in younger populations for its ability to increase muscle strength and size using high force production and to rehabilitate soft tissue injuries, (7) research trialing eccentric exercise with an endurance dosage suggests older people may also benefit from low energy-cost exercise (8).

Previous research of eccentric exercise in people with chronic diseases such as Parkinsons disease, diabetes, chronic obstructive pulmonary disease, and coronary heart disease have demonstrated comparable functional outcomes with low metabolic demand and no adverse outcomes (9-11). Specifically, in coronary heart disease, eccentric exercise was reported to be safe as it caused minimal cardiovascular or respiratory stress, was perceived by patients as "fairly light" exertion and when compared with concentric exercise resulted in comparable

improvements in muscle strength and walking distance, often with reduced oxygen consumption (12, 13).

Four previous trials (14-18) investigated the effect of eccentric exercise on physiological and functional outcomes in people with heart failure. One trial showed a single bout of eccentric exercise was safe, with minimal impact on the cardiovascular and ventilatory systems when compared to concentric exercise (14, 15). Three trials implementing a rehabilitation dosage (three times weekly for 6-7 weeks), found eccentric exercise resulted in comparable walking and strength outcomes to concentric exercise but with lower levels of work (heart rate, ventilatory demand or ratings of percieved exertion) (16-18). Although these trials provide useful information, there were methodological limitations identified such as small sample sizes (11 to 50 participants), single group design (14, 15), limited information about randomisation and concealed allocation (17), non-blinded assessment (17), no follow-up analysis (17) and no intention to treat analysis (16, 17).

The overall aim of this trial was to investigate the effect of eccentric exercise in people with mild to moderate heart failure, of any origin. The primary aim was to determine if eccentric exercise increases physical function in people with heart failure. The secondary aim was to investigate its effect on quality of life as well as the feasibility and safety of eccentric exercise.

Materials and methods

A prospective, three-armed, parallel-design, assessor-blind pilot randomised controlled trial with a 1:1:1 ratio for group allocation was completed. Participants were randomly allocated to one of three groups: (1) an eccentrically biased rehabilitation program (eccentric exercise);

(2) a traditional rehabilitation program (concentric exercise); or (3) a waitlist control group. Allocation was achieved using an electronic block randomisation method (19). An assistant otherwise uninvolved in the trial generated the allocations and concealed them in numbered, opaque, sealed envelopes. Randomisation occurred after baseline assessment by opening the next envelope in the sequence. All participants gave informed written consent. Ethics approval was obtained from the relevant hospital and university human ethics committees (NH LR 49.2013).

Patients were included if they were: (1) aged 18 years or above; (2) had a clinical diagnosis of mild to moderate heart failure (systolic or diastolic, reduced or preserved ejection fraction); (3) were medically stable; and (4) had no contraindications to exercise. Where there were concerns about an individual taking part, medical clearance was sought from the treating cardiologist. Participants whose preferred language was not English were not excluded from the trial. Interpreters were employed to facilitate these participants providing consent, completing assessments and outcome measures and for taking part in exercise sessions.

Patients were excluded if they were: (1) hospitalised for an exacerbation of chronic heart failure within the previous month; (2) had severe heart failure (New York Heart Association class IV, i.e. short of breath at rest); (3) had a concurrent unstable medical condition such as uncontrolled angina, diabetes or hypertension; (4) had dementia or a psychological disorder that would interfere with participation in group exercise; (5) had participated in a cardiac or heart failure rehabilitation program in the previous six months; (6) had a contraindication to exercise (i.e. aneurysm, valvular disease, severe aortic stenosis), or, (7) had any pre-existing

neurological or musculoskeletal condition that on assessment was deemed to interfere with exercise participation.

All exercise was performed in a hospital outpatient gymnasium in a group setting. It was completed twice a week for eight weeks on regular days, at the same time each day. If participants missed an exercise session, they were given up to two extra weeks to make up that session. Program completion was defined as having attended 12 out of a possible 16 exercise sessions (75%). Each exercise group was supervised by two registered physiotherapists, or by one physiotherapist and one experienced allied health assistant. The group physiotherapist may have been a junior physiotherapist who completed an orientation to group supervision. All exercise sessions were individually tailored with ratings of perceived exertion on the BORG scale (6-20 scale), and shortness of breath on BORG scale (0-10) taken for each participant for each exercise. For both exercise groups, exercise intensity was progressed over the course of the program to maintain symptom ratings of 11-13 (fairly light – somewhat hard) on the perceived exertion scale (20, 21).

***Eccentric exercise*:** Sessions typically included a 10-minute warm-up (whole body stretches and walking gentle laps of the gymnasium (1-2 minutes), 20 minutes on the eccentric stepper (Eccentron^{TM} see figure 1), walking on a treadmill for 10 minutes at a moderate pace, and upper limb and lower limb free weights (1-3 sets, 8-10 repetitions) addressing all major upper and lower limb muscle groups (i.e. biceps curls, upward row, shoulder abduction and elevation, hip abduction and extension, hip and knee flexion, ankle plantarflexion, seated knee extension with cuff weights). On the Eccentron^{TM}, participants were provided with visual feedback via a television screen about their technique of resisting the pedals, which moved toward them (i.e. a negative resistance trainer). Where participants were unable to

complete 20 minutes of continuous exercise on the Eccentron^{TM}, the aim was for them to complete two 10-minute bouts of eccentric exercise with rest as necessary within the 60-minute session.

Concentric exercise: Participants completed the same warm-up, walking and upper limb and lower limb weights. They also completed 20 minutes of concentric exercise comprising 10 minutes cycling on an exercise bike and climbing over and back on four steps (5-10 minutes, typically completed in sets of 10 repetitions). At the end of each exercise session each participant rested and their pulse rate and oxyhaemoglobin saturation was recorded.

Waitlist control: Participants completed two assessments, eight weeks apart, with no care provided during the wait period. After the wait period they were invited to participate in the usual care rehabilitation program but did not provide any further data to the study.

At baseline, all participants received advice about managing their condition. This included encouragement to maintain an active lifestyle and to walk regularly, and information on monitoring their fluid balance and weight as a means of monitoring their condition. Participants in the two exercise groups had access to once weekly, one-hour, multidisciplinary, group education sessions. The following topics were presented by health professionals: nutrition and healthy eating, stress management, energy conservation and relaxation, physical activity, socialising and self-management in chronic heart failure, medications, legal considerations (e.g. enduring power of attorney) and emotional reactions to heart failure.

Outcome measures were taken at baseline, immediately after the intervention period and three months after the intervention period. A physiotherapist, blinded to group allocation and not involved in delivering the intervention, conducted all assessments.

The primary outcome was:

Walking capacity- the 6-minute walk test was conducted along a 25m corridor and participants were asked to walk as far as possible in six minutes during which they were allowed to take rests but encouraged to continue as soon as able. Standardised encouragement and information was provided each minute, in line with recommendations (22). This test has demonstrated high test-retest reliability (ICC 0.9) (23) and shown higher correlation with quality of life questionnaires than peak oxygen uptake in people with chronic heart and lung disease (22).

The secondary outcomes were:

Minnesota Living with Health Failure Questionnaire- is a 21-item questionnaire with a 0 to 5 rating scale of how much participants perceive their heart failure affects aspects of their life. It provided a total score (range 0–105, from best to worst quality of life), as well as scores for two dimensions: physical (range 0–40) and emotional (range 0–25). Lower scores indicate better quality of life. It has evidence of validity and reliability with high test-retest reliability ($r = 0.87$) and internal consistency (Cronbach's alpha = 0.92) (24).

Assessment of Quality of Life- is a 15-item multiple-choice questionnaire with five domains: illness, independent living, social relationships, physical senses and psychological well-being. Each item has four response options scored from 0-3; higher scores (maximum 45) indicated lower quality of life. This outcome is sensitive to change in a variety of people- different sex, age, education level and health status- and has high internal consistency (alpha = 0.8) (25).

Lower limb strength- measured by one repetition maximum during a seated leg press. Participants completed a warm-up of 10 repetitions of a weight estimated to be approximately 50% of their maximum. The weight used for the warm-up was estimated using information from the baseline assessment (such as the 6-minute walk test and qualitative reports of physical activity levels and/or previous experience with weight training) as well as clinical experience. A near maximum weight was then estimated using the warm-up weight as a guide and lifted through range. Weight was progressively increased in increments of 5kg or 5% (whichever was greater) until the weight was no longer able to be correctly lifted fully. Rests of at least three minutes were allowed between attempts and the one repetition maximum was aimed to be determined within five attempts (26, 27). This technique has excellent inter-rater reliability in people with heart failure (ICC 0.93) (28).

Fatigue- measured using the 9-item Dutch Exertion Fatigue Scale (DEFS). This measure rates the level of fatigue during everyday activities including walking for 10 minutes, walking for 30 minutes, standing in the shower, climbing stairs, vacuuming, cleaning up rubbish, visiting a friend and attending a birthday party. Higher scores indicate greater fatigue. This scale has high internal consistency (Cronbach's alpha 0.91) in people with heart failure (29).

The number of exercise sessions attended was documented for each participant. The tolerability of the program was measured using ratings of perceived exertion and shortness of breath. Pulse rate and oxyhaemoglobin saturation via pulse oximetry were monitored before, during and on completion of each exercise session with any within-session adverse events recorded by the treating physiotherapist. Participants were also asked to report any adverse events between sessions, as well as pain or muscle soreness, rated on a 0-10cm visual

analogue scale (0= no pain to 10= worst pain imaginable) to the treating physiotherapist prior to starting each exercise session. Hospital admissions and deaths were monitored for all participants.

Assuming a between-group difference in the six-minute walk test of 60m is clinically important (12) and the baseline standard deviation is 74.2m (12) for a power of 0.8, with a two-tailed alpha of 0.5 a sample of 19 participants was required in each group. Based on historical completion rates for this heart failure rehabilitation program of approximately 75%, to allow for drop-outs we attempted to recruit a total of 25 participants to each group (75 participants total).

To determine whether the eccentric exercise group improved more than the concentric exercise group or waitlist control group immediately after the 8-week program, data were analysed with analysis of covariance using the baseline measures as covariates. A deviation from protocol, was that multiple imputation was used to account for missing data instead of the carry forward technique, as it is a superior method (30). Categorical outcome variables (death or hospital admission) were analysed with relative risk ratios. Intention to treat analysis was used, with follow-up of withdrawals where possible. A per-protocol analysis was also completed including only those participants who completed the program (minimum 12 sessions over 10 weeks). Effect sizes were calculated using Cohen's d by subtracting the mean change over time for the control group (both concentric exercise and waitlist control) from the mean change for the eccentric exercise group, and dividing the result by the pooled standard deviation (31). Cohen's convention was used to determine the strength of effect sizes, with effect sizes of d = 0.20 considered small, d = 0.50 considered medium and d = 0.8 considered large (31).

Planned secondary analyses related to type of heart failure and correlations between primary and secondary outcomes were not conducted as the sample recruited was smaller than anticipated and insufficient for meaningful analysis.

Results

Recruitment occurred between July 2014 and August 2018. Three hundred and six people were assessed for eligibility and 47 were randomised (figure 2). Recruitment was much slower than expected due to large numbers of participants failing to attend hospital assessments, declining to participate or not meeting the eligibility criteria. Due to staffing changes, recruitment was ceased before the target sample size was achieved. The 47 participants were randomly assigned to the eccentric exercise group (n = 16), concentric exercise group (n = 16) and waitlist control group (n= 15). Participants were predominantly male and most were New York Heart Association (NYHA) class 2 (table 1). Exercise was delivered to all participants as planned except for one participant randomised to the eccentric exercise group (during a period of Eccentron™ equipment repair) who received the concentric intervention.

There was no difference between the eccentric exercise group and concentric exercise group, or the eccentric exercise group and the waitlist control for any outcome in the intention to treat analysis (table 2). Effect sizes were small, ranging from 0 to -0.37 (6-minute walk test) for the eccentric exercise compared with the waitlist control and from 0 to -0.48 (Minnesota living with heart failure questionnaire) for the eccentric exercise compared with the concentric exercise groups, with a negative score indicating an improvement in quality of life.

The per-protocol analysis (table 3) included only participants that completed the program and accounted for the participant allocated to the eccentric group but who received concentric exercise due to equipment breakdown (figure 2). This analysis found no between group differences for the primary outcome of 6-minute walk test or secondary strength outcome. Significant between-group differences favouring the eccentric exercise group compared to concentric exercise group for quality of life at the post intervention assessment were found. The effect sizes for these two outcomes; Minnesota living with heart failure questionnaire-Total and Emotional, were -0.55 (-1.24 – 0.17) for both. These differences were not maintained at the three-month follow-up. Overall, effect sizes for the per-protocol analysis were largely similar to the intention to treat analysis.

Participants in the eccentric exercise and concentric exercise groups attended a mean of 12 exercise sessions (range 2 to 16). Twenty out of 32 participants completed the exercise program, with non-completers split equally between the eccentric exercise (n = 6) and concentric exercise (n = 6) groups. Exercise was well tolerated by participants in both groups. The protocol for the eccentric exercise group allowed participants to set their own work rate of 'somewhat hard' and their range of scores for rating of perceived exertion averaged 13 (range 7 to 17). The target time of 20 minutes spent on performing eccentric exercise was achieved for 11 of the 15 participants with the remaining four participants achieving 5, 10, 12 and 15 minute bouts of exercise. In the concentric exercise group, the average rating of perceived exertion was 12 (range 9 to 17). Shortness of breath averaged 2 on BORG scale (0-10) (slight to moderate) for the eccentric exercise group and 3 (moderate) for the concentric exercise group. Progression was comparable for the shared content (walking and free weights) of both groups. Exercise progression in the concentric exercise group was on

average 173% in the levels of resistance for static bicycling. Exercise progression in the eccentric exercise group was an average change in force of 47%.

There were no major adverse events. Across the two exercise groups there were five unexpected hospital admissions, unrelated to the intervention. One participant in the eccentric exercise group was hospitalised for a urinary tract infection and sustained a fall between completing their program and the post-intervention assessment. Four participants in the concentric exercise required hospitalisation; one for delirium and a fall, one for postural hypotension, one for insertion of an Automatic Implantable Cardioverter Defibrillator and one for gastroenteritis and later for insertion of an Automatic Implantable Cardioverter Defibrillator. The latter participant withdrew from the trial, but all other participants who required hospitalisation continued with the intervention despite their medical conditions. The relative risk for hospital admission during rehabilitation tended to be higher in the concentric exercise group (RR 4, 95% CI: 0.50 to 31.98) when compared to the eccentric exercise group. Pain scores were monitored for 23 participants (9 out of the 16 concentric exercise group participants and 14 of the 16 eccentric exercise group participants). The average VAS pain score was 1.4cm (concentric exercise group mean 0.8cm vs eccentric exercise group mean 1.8cm) suggesting only mild pain was experienced by participants in either group.

Discussion

This trial demonstrated that eccentric exercise can be delivered in selected people with heart failure, however the results suggest eccentric exercise is not superior to traditional heart failure rehabilitation for outcomes of functional capacity or quality of life. Per protocol analysis found no difference for functional outcomes. A significant difference in quality of life favouring eccentric exercise was found when compared to concentric exercise, but not

compared to no exercise. Eccentric exercise was tolerated equally well as concentric exercise in terms of program attendance and completion rates, participation during the exercise sessions, and reported symptoms of pain, exertion or shortness of breath during exercise.

The lack of difference between the groups may have been due to the rate at which exercise was progressed. While some recommend that exercise prescription in heart failure be determined using a symptom-limited cardiopulmonary exercise test and progressed according to this testing (32) others suggest exercise intensity be progressed gradually as fitness improves (33) or often have used patient reported ratings of perceived exertion to progress exercise (21). Based on these suggestions, we aimed to progress exercises based on a rating of perceived exertion of 'somewhat hard' or 11 -13 on the Borg scale (21). While this was achieved and appeared comparable between groups, it is a limitation of the study as progression as a percentage change in workload was varied and for some participants was low. For future trials, it is recommended that in addition to rating of perceived exertion, all exercise components of the program be progressed according to a protocol, with regular percentage increases in exercise intensity or documented progressions, such as has been applied in pulmonary rehabilitation (34). The use of protocols for people with heart failure would assist researchers consider exercise intensity when developing trial protocols and/or clinicians to prescribe exercises which result in maximum change for the individual.

A further limitation of the study was that data were not collected that would allow for normalising the total amount of work completed by the two exercise groups. This would have aided in confirming if for the same intensity, eccentric participants were able to achieve a greater output. Although the duration of exercise was the same for each participant, and the intensity of exercise was measured on the BORG scale for all participants, due to varying

information available from the equipment used, questions remain as to the dose-response relationship of the intervention and if this was the reason for the lack of difference found between both exercise groups and the waitlist control.

Physical activity completed by participants outside of rehabilitation may have also impacted the results. All participants were not asked how much exercise they completed prior to commencing the study or during the study, but they were encouraged during the initial assessment and education session lead by a physiotherapist to maintain an active lifestyle, to walk regularly or commence regular exercise at home. Although education can lead to increases in physical activity and studies show people with heart failure have low activity levels, there is also the potential for a ceiling effect if people were already active or rehabilitation simply substituted another activity.

In addition to considering if the intervention groups completed sufficient exercise to evoke meaningful changes, it must also be considered if the waitlist control group increased their physical activity levels while waiting for rehabilitation. Waitlist participants were not asked to report their physical activity levels during the waitlist period. At initial assessment, no education was provided on how to commence exercise at home during the wait period, but participants were encouraged to maintain an active lifestyle. In a large study of people with heart failure over a period of up to four years, only eight per cent of usual care participants reported exercising at every telephone check after the first three months despite being provided with self-management education and then regular (fortnightly for the first nine months and then decreasing frequency) telephone calls to check if they were exercising (35). Given participants were randomised, the limited education provided during the initial assessment and no further intervention during the wait period, the probability of improvement

in the waitlist group due to increasing their levels of physical activity is considered to be low. Information regarding activity levels would have assisted in comparing the intervention group with this waitlist group, who may have commenced exercising in preparation for their rehabilitation program following their enrolment in the trial. Information regarding other lifestyle changes or medical input participants received during the waitlist period was also not collected.

In comparing the eccentric and concentric interventions the degree of overlap between the two groups needs to be considered. Due to the preliminary nature of the eccentric exercise intervention with this population, and well-established guidelines for aerobic exercise as part of heart failure rehabilitation, it was deemed important to keep some aspects of the rehabilitation program consistent. The exercise tolerance of the participants was also considered and therefore twenty minutes of continuous eccentric exercise was deemed suitable. Given the results of this and other recent studies in this population which show equivalent results for eccentric and concentric exercise, future non-inferiority trials might consider if rehabilitation might comprise solely or of a greater proportion of eccentric exercise.

The primary limitation of this trial was the inability to reach the proposed sample size of 75 participants, leaving it underpowered. Recruitment took place over a four-year period and was slow. The main difficulty was that only 56% of people assessed were eligible to participate due to wanting to attend rehabilitation exercise programs just once weekly (n= 35/134), musculoskeletal limitations (n= 20), more appropriate for a different service e.g. Cardiac or Pulmonary rehabilitation (n= 18) and already completing rehabilitation or physiotherapy elsewhere (n= 16). Effect sizes were calculated in considering the effect of the

sample size on the results. With the exception of the moderate effect size of 0.55 for quality of life for eccentric exercise compared with concentric exercise, all of the effect sizes were small.

For those excluded due to musculoskeletal limitation such as back and knee pain, it was felt these participants would not be capable of participating in either the exercise bike or EccentronTM interventions. Whereas in usual practice, an alternative exercise program would be devised, with eccentric exercise requiring one specific piece of equipment, alternatives were limited. The cost of the EccentronTM equipment may also limit widespread feasibility in real-world clinical environments. Due to cost, only one device was purchased which subsequently limited participant numbers and throughput, as well as hindering widespread roll-out across sites. It is recommended other cost-effective ways of facilitating eccentric contractions, such as downhill treadmill walking or eccentric cycling on an ergometer (upper limb or lower limb), could be considered. Previous studies using eccentric exercise in people with heart failure have implemented eccentric exercise with either treadmill or ergometers rather than a recumbent stepper. While the stepper in some respects can mimic downhill walking, it differs from a treadmill in that users are prompted to resist the force plates as they move towards them. A dosing test is completed prior to its use, which measures the level of resistance provided by the participant. Then during the exercise session, visual feedback on the screen supports the participant to exert the correct force to remain in the target range based on the dosing test. As such, it was considered in this respect to be different to downhill walking on a treadmill however the complexity of movement may have prevented early uptake in an aging population with up to 40% requiring an interpreter or having a preferred language to English. In this population, downhill walking may be more intuitive.

To date, the evidence around eccentric exercise in heart failure is limited. The extension from those with chronic heart and respiratory disease to heart failure is a logical one but with only three other trials using this exercise modality in therapy (16-18) in this population, the field of knowledge is growing but remains small. These previous trials reported comparable outcomes with concentric exercise but with lower work levels. The consequence of this finding was not well explored. The results of our trial and the limitations involved, namely the inadequate sample size, means further research is required to determine if eccentric exercise can be used to improve functional and quality of life outcomes for people with heart failure greater than those achieved with traditional rehabilitation programs. At this stage, the seemingly equivalence of this intervention with concentric exercise means that it is unlikely to replace concentric exercise but may be considered as an adjunct or alternative exercise for select people who have difficulty participating in a traditional program. Lastly, the inability to easily complete eccentric contractions without also completing concentric contractions means that specific exercise equipment is required and this limits feasibility. For eccentric exercise to truly be considered as an ongoing exercise modality for this population, a means of completion in the home environment is required.

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Figure 1. Eccentron^{TM} negative resistance trainer.

Figure 2. Number of participants at each stage of the trial (enrolment, allocation, follow- up, analysis) based on Consolidated Standards of Reporting Trials (CONSORT).

Table 1: Demographic Data for Intervention and Control Groups

Characteristic	Eccentric exercise group (n=16)	Concentric exercise group (n=16)	Waitlist group (n=15)
Sex (male/female)	10/6	13/3	8/7
Mean age (SD) (y)	66 (14)	68 (10)	65 (9)
Language (English/non-English speaking	13/3	15/1	9/6
Mean height (SD) (2)	168 (11)	169 (10)	165 (12)
Mean weight (SD) (kg)	92.8 (18.6)	97.2 (30.0)	84.7 (17.0)
Mean BMI (SD) (kg/m2)*	33 (8)	35 (11)	31 (6)
NYHA Classification (n) (Class 1-3)	4/11/1	1/13/2	3/9/3
Mean EF (%) (SD) (n)	34(12) (n= 13)	27 (18) (n= 10)	42 (18) (n= 15)
Medications (number)			
Beta blocker	15	15	13
ACE inhibitor	6	7	6
Calcium channel blocker	3	3	3
Nitrate	2	3	3
Diuretic	13	12	12
Statin	7	14	12
Anticoagulant	14	14	12
Digoxin	2	4	1
ARA 2	6	5	4
Aldosterone antagonist	6	8	6
Amioderone	0	1	2
Potassium	1	2	1
Diabetes medications	4	6	5
Depression/ Anxiety medications	0	5	2
Respiratory medications	5	7	3
Reflux medications	4	6	8

Abbreviations: SD, standard deviation; BMI, body mass index; NYHA; New York Heart Association; EF, ejection fraction; ARA 2, angiotension II receptor agonists.
*Average BMI is 18.5–24.9kg/m^2, overweight is 25–29.9kg/m^2, obese is 30kg/m^2 (36)

Table 2: Intention to treat analysis: Mean (SE) of groups at baseline, post intervention and 3 months, mean difference (95% CI) in change between groups and Cohen's d (95% CI) for difference between groups.

	Group Scores: Mean (SE)							
	Baseline			Post Intervention			Follow-Up	
Outcome (units)	Eccentric	Concentric	Waitlist	Eccentric	Concentric	Waitlist	Eccentric	Concentric
6MWT (m)	391.5 (30.8)	298.3 (30.8)	338.2 (31.8)	387.4 (33.3)	322.4 (31.5)	373.6 (33.5)	406.6 (33.2)	343.8 (32.0)
MLWHFQ Total	37.63 (5.57)	35.00 (5.57)	36.87 (5.75)	26.42 (5.94)	39.06 (5.68)	25.37 (6.00)	31.39 (6.46)	39.78 (6.22)
MLWHFQ Physical	16.88 (2.50)	16.56 (2.50)	18.07 (2.58)	12.82 (2.69)	18.61 (2.55)	12.74 (2.71)	14.35 (2.79)	17.16 (2.77)
MLWHFQ Emotional	8.25 (1.72)	7.13 (1.72)	6.80 (1.78)	5.90 (1.86)	8.93 (1.76)	4.57 (1.87)	6.36 (2.01)	8.25 (1.91)
AQOL	15.00 (1.43)	13.44 (1.43)	14.10 (1.52)	13.33 (1.55)	15.39 (1.46)	13.21 (1.56)	12.23 (1.82)	14.10 (1.66)
1-RM Leg strength (kg)	52.68 (6.83)	43.86 (6.67)	44.33 (6.73)	55.23 (6.98)	49.88 (6.71)	46.97 (6.89)	52.83 (7.08)	46.64 (6.91)
DEFS	13.63 (2.49)	15.63 (2.49)	15.73 (2.57)	11.32 (2.73)	17.64 (2.56)	10.97 (2.74)	11.71 (2.81)	15.18 (2.77)

	Difference between groups									
	Baseline to Post Intervention				Baseline to Follow-Up				Post Intervention to Follow-Up	
Outcome (units)	Concentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Concentric	d
6MWT (m)	-11.3 (-62.3 to 39.7)	-0.11 (-0.81 to 0.60	-28.1 (-81.2 to 24.9)	-0.26 (-0.95 to 0.44)	-39.5 (-93.4 to 14.5)	-0.37 (-1.07 to 0.35)	-30.3 (-87.3 to 26.7)	-0.26 (-0.95 to 0.44)	-2.2 (-40.0 to 35.6)	-0.03 (-0.72 to 0.67)
MLWHFQ Total	15.56 (-0.17 to 31.29)	0.50 (-0.23 to 1.20)	-15.27 (-31.00 to 0.46)	-0.48 (-1.17 to 0.24)	0.29 (-15.69 to 16.28)	0.01 (-0.70 to 0.71)	-11.02 (-28.92 to 6.88)	-0.30 (-0.99 to 0.40)	4.25 (-10.36 to 18.85)	0.14 (-0.55 to 0.83)
MLWHFQ Physical	7.38 (0.35 to 14.40) **	0.53 (-0.20 to 1.23)	-6.11 (-13.14 to 0.93)	-0.43 (-1.12 to 0.29)	1.27 (-5.88 to 8.42)	0.09 (-0.62 to 0.79)	-3.12 (-10.86 to 4.62)	-0.20 (-0.89 to 0.50)	2.99 (-2.48 to 8.45)	0.25 (-0.45 to 0.94)
MLWHFQ Emotional	4.03 (-1.15 to 9.22)	0.39 (-0.33 to 1.09)	-4.15 (-9.34 to 1.03)	-0.39 (-1.08 to 0.32)	-0.12 (-5.39 to 5.15)	-0.01 (-0.72 to 0.69)	-3.02 (-8.84 to 2.81)	-0.26 (-0.94 to 0.45)	1.14 (-3.66 to 5.94)	0.12 (-0.58 to 0.81)
AQOL	2.85 (-1.59 to 7.29)	0.32 (-0.39 to 1.03)	-3.62 (-8.00 to 0.76)	-0.41 (-1.09 to 0.30)	0.77 (-5.28 to 3.74)	0.09 (-0.62 to 0.79)	-3.43 (-8.64 to 1.79)	-0.33 (-1.01 to 0.38)	0.20 (-4.71 to 5.10)	0.02 (-0.67 to 0.71)
1-RM Leg strength (kg)	3.38 (-9.30 to 16.07)	0.13 (-0.57 to 0.84)	-3.48 (-16.58 to 9.62)	-0.13 (-0.82 to 0.57)	-0.10 (-13.11 to 12.92)	0.00 (-0.71 to 0.70)	-2.64 (-16.47 to 11.18)	-0.09 (-0.78 to 0.60)	2.85 (-3.28 to 8.97)	0.04 (-0.66 to 0.73)
DEFS	6.78 (1.14 to 12.43) **	0.61 (-0.13 to 1.31)	-4.32 (-10.08 to 1.45)	-0.37 (-1.06 to 0.34)	2.46 (-3.39 to 8.32)	0.21 (-0.50 to 0.91)	-1.47 (-8.02 to 5.08)	-0.11 (-0.80 to 0.59)	0.84 (-10.82 to 12.49)	0.23 (-0.47 to 0.92)

a Based on repeated measures mixed model, with multiple imputations for each outcome
** p-value, <0.05
Abbreviations: CI - confidence interval; MLWHFQ - Minnesota Living with heart failure questionnaire
AQOL - Assessment of Quality of Life; 6MWT - six-minute walk test, 1-RM - one-repetition maximum, DEFS - Dutch exertion fatigue scale

Table 3: Per-Protocol Analysis: Mean (SE) of groups at baseline, post intervention and 3 months, mean difference (95% CI) in change between groups and Cohen's d (95% CI) for difference between groups.

	Group Scores: Mean (SE)							
	Baseline			Post Intervention			Follow-Up	
Outcome (units)	Eccentric	Concentric	Waitlist	Eccentric	Concentric	Waitlist	Eccentric	Concentric
6MWT (m)	413.6 (34.0)	307.7 (37.3)	338.2 (31.8)	414.8 (35.8)	337.4 (37.3)	373.6 (33.5)	434.9 (35.9)	343.8 (37.6)
MLWHFQ Total	40.92 (6.30)	34.20 (6.90)	36.87 (5.64)	26.13 (6.57)	37.4 (6.90)	25.37 (5.89)	31.38 (7.02)	38.06 (7.06)
MLWHFQ Physical	17.33 (2.81)	15.60 (3.08)	18.07 (3.08)	12.04 (2.95)	16.90 (3.08)	12.74 (2.64)	14.21 (3.04)	15.28 (3.14)
MLWHFQ Emotional	9.67 (1.94)	6.40 (2.13)	6.80 (1.74)	6.38 (2.04)	9.20 (2.13)	4.57 (1.83)	6.18 (2.17)	7.75 (2.18)
AQOL	14.83 (1.68)	13.00 (1.84)	14.10 (1.55)	13.00 (1.77)	14.80 (1.84)	13.21 (1.58)	11.76 (2.00)	13.42 (1.91)
1-RM Leg strength (kg)	59.17 (7.42)	46.61 (8.43)	44.33 (6.64)	63.21 (7.82)	52.65 (8.48)	46.97 (6.79)	59.60 (7.87)	51.44 (8.61)
DEFS	11.83 (2.66)	14.40 (2.92)	15.73 (2.38)	9.42 (2.85)	14.90 (2.92)	10.97 (2.56)	10.55 (2.93)	14.74 (2.98)

	Difference between groups									
	Baseline to Post Intervention						Baseline to Follow-Up		Post Intervention to Follow-Up	
Outcome (units)	Concentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Waitlist	d	Eccentric vs Concentric	d	Eccentric vs Concentric	d
6MWT (m)	5.7 (-45.1 to 56.5)	0.06 (-0.64 to 0.75)	-28.5 (-82.1 to 25.1)	-0.27 (-0.96 to 0.43)	-34.2 (-88.0 to 19.6)	-0.32 (-1.04 to 0.41)	-14.8 (-69.3 to 39.6)	-0.14 (-0.83 to 0.56)	13.7 (-24.0 to 51.3)	0.19 (-0.52 to 0.88)
MLWHFQ Total	14.70 (-2.42 to 31.81)	0.43 (-0.28 to 1.13)	-17.99 (-35.96 to -0.01) **	-0.55 (-1.24 to 0.17)	-3.29 (-20.00 to 13.42)	-0.10 (-0.81 to 0.62)	-13.40 (-32.61 to 5.82)	-0.35 (-1.04 to 0.35)	4.59 (-9.84 to 19.02)	0.16 (-0.54 to 0.85)
MLWHFQ Physical	6.63 (-1.22 to 14.47)	0.43 (-0.28 to 1.12)	-6.59 (-14.83 to 1.65)	-0.40 (-1.10 to 0.31)	0.04 (-7.64 to 7.71)	0.00 (-0.71 to 0.72)	-2.81 (-11.37 to 5.76)	-0.17 (-0.86 to 0.53)	3.79 (-1.65 to 9.22)	0.36 (-0.35 to 1.05)
MLWHFQ Emotional	5.03 (-0.32 to 10.38)	0.48 (-0.24 to 1.17)	-6.09 (-11.71 to -0.47) **	-0.55 (-1.24 to 0.17)	-1.06 (-6.31 to 4.19)	-0.10 (-0.82 to 0.62)	-4.84 (-10.82 to 1.15)	-0.41 (-1.10 to 0.30)	1.25 (-3.15 to 5.65)	0.14 (-0.55 to 0.84)
AQOL	2.68 (-2.44 to 7.79)	0.27 (-0.44 to 0.96)	-3.63 (-8.94 to 1.69)	-0.35 (-1.04 to 0.36)	-0.95 (-5.94 to 4.03)	-0.10 (-0.81 to -0.62)	-3.49 (-9.32 to 2.34)	-0.30 (-0.99 to 0.40)	0.14 (-5.52 to 5.79)	0.01 (-0.68 to 0.71)
1-RM Leg strength (kg)	3.40 (-10.34 to 17.14)	0.13 (-0.57 to 0.82)	-2.00 (-16.99 to 12.99)	-0.07 (-0.76 to 0.63)	1.40 (-12.07 to 14.87)	0.05 (-0.66 to 0.77)	-4.41 (-20.19 to 11.38)	-0.14 (-0.83 to 0.56)	-2.41 (-14.45 to 9.63)	-0.10 (-0.79 to 0.60)
DEFS	5.27 (0.02 to 10.51) **	0.51 (-0.21 to 1.20)	-2.91 (-8.44 to 2.61)	-0.27 (-0.96 to 0.44)	2.35 (-3.07 to 7.77)	0.22 (-0.50 to 0.93)	-1.62 (-7.61 to 4.36)	-0.14 (-0.83 to 0.56)	1.29 (-4.29 to 6.87)	0.12 (-0.58 to 0.81)

a Based on repeated measures mixed model, with multiple imputations for each outcome
** p-value, <0.05
Abbreviations: CI - confidence interval; MLWHFQ - Minnesota Living with heart failure questionnaire
AQOL - Assessment of Q