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# Endurance Exercise Training in Older Patients with Heart Failure: Results from a Randomized, Controlled, Single-Blind Trial

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## Abstract

**OBJECTIVES—**To test the hypothesis that exercise training (ET) improves exercise capacity and other clinical outcomes in older persons with heart failure with reduced ejection fraction (HfrEF).

**DESIGN—**Randomized, controlled, single-blind trial.

**SETTING—**Outpatient cardiac rehabilitation program.

**PARTICIPANTS—**Fifty-nine patients aged 60 and older with HFrEF recruited from hospital records and referring physicians were randomly assigned to a 16-week supervised ET program (n = 30) or an attention-control, nonexercise, usual care control group (n = 29).

**INTERVENTION—**Sixteen-week supervised ET program of endurance exercise (walking and stationary cycling) three times per week for 30 to 40 minutes at moderate intensity regulated according to heart rate and perceived exertion.

**MEASUREMENTS—**Individuals blinded to group assignment assessed four domains pivotal to HFrEF pathophysiology: exercise performance, left ventricular (LV) function, neuroendocrine activation, and health-related quality of life (QOL).

**RESULTS—**At follow-up, the ET group had significantly greater exercise time and workload than the control group, but there were no significant differences between the groups for the primary outcomes: peak exercise oxygen consumption ($VO_2$ peak), ventilatory anaerobic threshold (VAT), 6-minute walk distance, QOL, LV volumes, EF, or diastolic filling. Other than serum aldosterone, there were no significant differences after ET in other neuroendocrine measurements. Despite a lack of a group “training” effect, a subset (26%) of individuals increased $VO_2$ peak by 10% or more and improved other clinical variables as well.

**CONCLUSION—**In older patients with HFrEF, ET failed to produce consistent benefits in any of the four pivotal domains of HF that were examined, although the heterogeneous response of older

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patients with HFrEF to ET requires further investigation to better determine which patients with HFrEF will respond favorably to ET.

### Keywords

rehabilitation; functional capacity; exercise physiology; cardiac function

Exercise intolerance is the primary symptom in patients with chronic heart failure and reduced ejection fraction (HFrEF), is a major contributor to their severely reduced health-related quality of life (HRQOL), and often persists even after full guidelines-based pharmacological therapy is implemented. A number of studies have suggested that endurance exercise training (ET) can improve important outcomes in patients with HFrEF.[1–3] A small study,[3] a meta-analysis,[4] and now a randomized, controlled trial[5] suggest that ET may also reduce morbidity and mortality in patients with HFrEF. In contradiction to these "positive" ET studies, there are also several published reports[6,7] suggesting that a significant percentage of patients with HFrEF do not respond favorably to ET. The large Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF ACTION) trial demonstrated that 3 months of supervised ET resulted in a modest, albeit statistically significant, 4% improvement in exercise capacity in well-managed patients with HFrEF.[5]

An important limitation of currently published studies is that few have included significant proportions of elderly patients with HFrEF, even though elderly people constitute the majority of the population with HFrEF. This limits the generalizability of the currently available studies, including the HF ACTION study, in which the median age of subjects was just 59. Furthermore, uncertainty regarding the effect of ET in older persons with heart failure has contributed to the lack of Medicare reimbursement for medically supervised ET in this population.

Therefore, the primary objective of the present study was to perform an adequately powered, randomized, controlled, single-blind trial to test the hypothesis that ET improves exercise capacity and HRQOL in older persons with HFrEF. Four domains pivotal to the pathophysiology of the HF syndrome were assessed before and after the 16-week ET intervention: exercise performance, left ventricular (LV) structure and function, neuroendocrine activation, and HRQOL.

## METHODS

### Study Participants

Prospective patients were recruited and screened as described in Figure 1, as well as in a previous report.[8] The diagnosis of HF was based on clinical criteria modified from the National Health and Nutrition Examination Survey I[9] plus a left ventricular ejection fraction (EF) of 45% or less. Patients with the following conditions were excluded from the study: valvular heart disease as the primary etiology of HFrEF, recent stroke or myocardial infarction, uncontrolled hypertension, and any other condition limiting exercise duration. Of those assessed for eligibility, nearly 80% were excluded, because they did not meet inclusion or exclusion criteria or were unwilling to participate. This high percentage of ineligibility is not unexpected, considering the nature of the intervention (participate in ET 3 times per week) and a target population of elderly patients with HFrEF with multiple comorbidities and that recruitment was conducted at a large tertiary-care medical center where a large percentage of patients live a significant distance from the institution. This study was conducted between 1995 and 1999.

## Protocol Overview

The Wake Forest institutional review board approved the study protocol, and written informed consent was obtained from all subjects. The outcome measures of exercise function, LV structure and function, neuroendocrine function, and HRQOL were obtained during a single visit at baseline before randomization and at a follow-up visit after completion of the 16-week intervention. Testing was performed in the morning, with participants not having taken any medication or eaten or ingested caffeine since midnight. The ET group participated in 16 weeks of center-based ET, whereas the control group did not but received telephone follow-up every other week. Individuals blinded to group assignment and other clinical information related to the patient performed all testing and analyzed all results.

**ET Protocol—**Details of the ET have been previously described in detail.[8,10] Breath-by-breath expired gas analysis was performed using a commercially available system with on-line computer calculation of variables (CPX/D, MedGraphics, Minneapolis, MN). Complete calibration of expired gases and volume analyzers (pneumotach) was performed before each exercise test, as outlined in the user manual.

Each patient performed the exercise test in the upright position on an electronically braked bicycle. The initial workload was 12.5 W for 2 minutes, followed by 25 W for 3 minutes and advanced thereafter by 25-W increments in 3-minute stages. Heart rate and blood pressure were measured in standard fashion. Peak values ($VO_2$ peak and all other expired gas parameters) were averaged during the final 30 seconds of the exercise test for all analyses. A 6-minute walk test (6 MWT) was performed in a university gymnasium using standard procedures as previously described.[11,12]

**Echocardiography—**Echo-Doppler examinations were performed under resting conditions at baseline and follow-up as previously described[8] using a Hewlett-Packard Sonos 5500 ultrasound imaging system (Palo Alto, CA) with a multiple frequency transducer.[13,14] Standard two-dimensional images were obtained in the parasternal long and short axes and in the apical four- and two-chamber views. Pulsed-wave Doppler tracings of mitral valve inflow were recorded.[14] Blinded personnel analyzed left ventricular volumes and Doppler tracings using a digital echocardiography workstation as previously described.[8,13] Cardiac volumes, including end-diastolic and end-systolic volumes, measured at rest were used to determine cardiac output.

**Neurohormones—**At baseline and follow-up testing visits, after at least 15 minutes of quiet, supine rest, venous blood samples were drawn into prepared, chilled ethylenediaminetetraacetic acid vacutainers, placed on ice, and then centrifuged to separate plasma. Samples were then stored at −70°C. Commercially available radioimmunoassays were used for C-terminal atrial natriuretic peptide (ANP) and for brain natriuretic peptide (BNP)-32. Angiotensin II, aldosterone, and norepinephrine were measured using standardized techniques as previously described.[15]

**Health-Related Quality of Life—**The standardized Medical Outcomes Study 36-item Short Form Health Survey (SF-36) was administered at baseline and follow-up to assess general health limitations. This instrument provides subscores for physical, general health, social function, role physical, role emotional, pain, mental, and vitality. The Minnesota Living with Heart Failure (MLHF) questionnaire, a condition-specific measure, was administered at baseline and follow-up to assess the effect of HF on the patients' well-being.[16] In addition to a total score, the questionnaire contains emotional and physical subscores.

**ET Intervention—**Patients randomized to the ET intervention group exercised three times per week for 16 weeks for a total of 48 session. The exercise sessions were conducted from

7:45 to 9:00 a.m. on Monday, Wednesday, and Friday. Before each session subjects' heart rate (HR) and blood pressure (BP) were measured and recorded. Each session lasted 1 hour and consisted of warm-up, stimulus, and cool-down phases. The stimulus phase consisted of walking on a track and lower extremity cycling on a Schwinn Airdyne (Madison, WI). During the initial period of training (2 weeks), patients exercised at 40% to 50% of HR reserve (HRR); the duration of the exercise was gradually increased for each of the two modes of exercise (walking and cycle ergometry). Over the next several weeks, the intensity of exercise was increased to 60% to 70% HRR, and exercise duration was increased to 15 to 20 minutes on each training mode. During the stimulus phase, subjects were asked to monitor and record responses (HR and rating of perceived exertion) at four intervals (after 10, 20, 30, and 40 minutes) during each exercise session. The exercise prescription (intensity and duration) was adjusted as needed based on medical considerations and clinical responses. Missed exercise sessions were made up so that each patient completed no less than 40 of the 48 (> 80%) ET sessions.

Patients randomized to the attention control group received phone calls every 2 weeks throughout the 16 weeks of follow-up. This served to provide attention and interaction with the study staff of a nature similar to what the ET group received but without exercise. The telephone conversations focused on adherence to the study protocol and reminders and encouragement to keep upcoming study visits and ascertained whether there were any new medical events since the prior contact. The discussion intentionally did not address exercise behaviors of the control participants.

### Statistical Analysis

Two-sample *t*-tests and Fisher exact tests were used to examine baseline differences in demographic characteristics, New York Heart Association (NYHA) classification, medication use, echocardiography variables, and exercise function measures between the two groups.

Separate analyses of covariance (ANCOVAs), adjusting for baseline differences in that variable, were used to compare exercise function, LV structure and function, neuroendocrine function, and HRQOL outcomes between the two groups at follow-up. Least-square means and standard errors were obtained from the ANCOVA models and were used to represent differences between treatment groups. SPSS software (SPSS, Inc., Chicago, IL) was used for all statistical analyses. All reported *P*-values were two-sided and had to be <.05 to be considered significant. The primary outcome for this study was $VO_2$ peak, because the study was powered for this measure. Power analysis conducted during planning and design of the trial indicated that the present sample size would yield more than 80% power to detect as little as a 10% change in $VO_2$ peak. Other exercise performance measures (peak exercise time and workload, 6-MWT), HRQOL measures, resting LV volumes, and plasma neurohormones were the secondary outcomes.

## RESULTS

### Patient Characteristics

At baseline (Table 1), the study population was closely representative of patients with HFrEF reported in large, population-based observational studies.[17,18] The mean age of 70 ± 5; (range 60–80) is substantially greater than reported in most prior studies of ET in HFrEF, including HF ACTION. Furthermore, the mean EF of 31% in the present investigation was higher than in many HFrEF studies, including HF ACTION, in which median EF was 25%. At the time of entry, all patients had HF symptoms rated as NYHA class II to III. The frequency of beta-blocker usage was relatively modest, because this investigation was conducted between 1995 and 1999, before its establishment as standard therapy. All medical therapy remained constant

for the duration of the study. The ET and control groups were well matched on most characteristics at baseline.

### ET Adherence

Patients in the ET group attended an average of 45 ET session (range 40–48). From the initial 4 weeks to the final 4 weeks of the ET intervention, mean cycle ergometer distance per session (3.03 ± 0.88 vs 3.67 ± 0.98 miles/session) and combined walking and cycle distance (4.11 ± 1.09 vs 4.81 ± 0.99 miles/session), increased significantly ($P = .001$) in the ET group. Walk distance also increased in the ET group during the intervention, albeit nonsignificantly ($P = .48$), from 1.08 + 0.42 to 1.14 + 0.59 miles/session. Sixty-five percent of heart rates recorded on exercise logs during the ET session were within the prescribed range of intensity.

### Effect of ET on Exercise Capacity

The peak exercise workload achieved (watts) and exercise time (seconds) on the bicycle ergometer at follow-up were significantly greater in the ET than in the control group, as shown in Table 2. In contrast, $VO_2$ peak was not significantly different in the ET than the control group at follow-up. Peak exercise respiratory exchange ratio (RER), an objective index of effort, was not significantly different between the groups at baseline or follow-up and reached a level of 1.0 or greater in 91% and 1.05 or greater in 70% of the ET group and 93% and 66%, respectively, of the control group.

Peak carbon dioxide production ($VCO_2$ peak) during exercise, peak ventilation (VE), and VE/$VCO_2$ slope, an important prognostic index, were not significantly different in the ET and control groups at follow-up. Peak exercise heart rate, systolic and diastolic blood pressure, and pulse pressure were not significantly different between the groups at follow-up.

The ventilatory anaerobic threshold (VAT), a measure of submaximal exercise performance that is independent of effort, was not significantly different between the ET and control groups at follow-up. Similarly, there were no significant differences in 6-MWD, a commonly used measure of exercise performance, between the two groups at follow-up.

### Health-Related Quality of Life

There were no significant differences between the ET and control groups at follow-up for the MLHF (total or sub-scores including physical) or general life functioning scores as assessed using the standardized SF-36.

### Resting LV Structure and Function

There were no significant differences in any of the resting echocardiographic or Doppler measures between the ET and control groups at follow-up.

### Neuroendocrine Function

Aldosterone was significantly lower ($P = .04$) at follow-up in the ET than the control group, and there was a trend ($P = .07$) for lower angiotensin II levels in the ET group as well (Table 2). There were no significant differences between the ET and control groups for other neurohormones (renin, epinephrine, vasopressin, ANP, or BNP) at follow-up.

### Events

Of the 59 patients who completed baseline testing, six ET and seven control subjects did not complete follow-up testing. The most common reason for not completing follow-up testing in the ETand control groups were non-HFrEF illness (n = 4) and lost to follow-up (n = 3). Both

groups had one death during the 16-week intervention period. Neither of the deaths or any other events were temporally or otherwise related to the intervention or the testing procedures.

### Individual Responses to ET

Although there was no significant mean increase in $VO_2$ peak from baseline to follow-up in the responder or non-responder ET group (Table 2), there were individuals who demonstrated significant improvement in $VO_2$ peak at follow-up. Figure 2A and B shows the mean group change (dashed line) and individual changes from baseline to the 16-week follow-up in the ET and control groups. These individual data reveal that, in 23 patients in the ET group, $VO_2$ peak increased by 10% or more in six (26%) and 0% to 9.9% in nine (39%) and decreased in eight (35%). Thus, based on the criteria employed previously[7] (an increase in $VO_2$ peak of ≥10%), slightly more than one-fourth of the older patients with HF in this trial had an improvement in peak exercise $VO_2$ after ET, whereas nearly three-fourths of the patients demonstrated no significant increase. An additional analysis was performed to determine whether any demographic, hemodynamic, or neuroendocrine variables were predictive of those that responded to ET with an increase in $VO_2$ peak. Of the many potential predictors evaluated, only peak exercise cardiac output (9.3 ± 1.5 vs 8.5 ± 1.3 L/min, $P = .11$) and mitral valve Doppler inflow deceleration time (210 ± 33 vs 177 ± 38 ms, $P = .08$) on baseline echocardiogram showed a trend toward a significant difference between responders and nonresponders to ET. Of equal interest and importance are the three ET subjects who demonstrated a significant decrease in $VO_2$ peak from baseline to follow-up (Figure 2A). Several participants in the control group also demonstrated unexpected, and unexplained, variability in $VO_2$ peak responses from baseline to follow-up.

## DISCUSSION

This study was designed to address important gaps in the literature regarding ET in HFrEF by focusing exclusively on elderly people, who constitute the majority of this population.[19–21] The study succeeded in that the demographic composition of the study group, including age, sex, and body size, reflected those in population-based studies of HFrEF.[19–21] Using the proper demographic group and unbiased methods, it was found that, after 16 weeks, the ET group had 12% longer exercise time on the bike and 13% greater exercise workload than the control group, although there was no increase in peak exercise $VO_2$, which was the prospectively planned primary outcome. In addition, relatively few significant differences were found between ET and control at follow-up in the other domains assessed. Submaximal exercise performance, measured according to VAT (an effort independent measure) and 6-MWD were not significantly different; nor were HRQOL, echocardiographic LV volumes, ejection fraction, mass, or LV remodeling as assessed according to mass:volume ratios. Furthermore, none of the Doppler-derived LV diastolic function variables were significantly different between ET and control at follow-up. There was a significant reduction in aldosterone concentration and a trend in angiotensin II but not in the other neurohormones measured, including BNP.

Consequently, the overall findings of this study may be interpreted as “neutral” or “negative,” because the primary outcome ($VO_2$ peak) did not improve significantly in the ET group. In contrast to several prior studies of younger patients with HFrEF,[1–3,22,23] few significant changes were observed in any of the four pivotal domains (exercise function, resting LV function and volumes, resting neurohormones, and HRQOL) after 16 weeks of ET in older patients with HFrEF. In contrast, another study evaluated a cohort of older patients with HFrEF and reported a significant increase in exercise time after an ET intervention,[24] although metabolic gas analysis was not performed, and therefore the change in $VO_2$ peak was not assessed.

The testing protocol, including errors in the expired gas measurements; an inadequate ET stimulus; and greater dependence by the ET group at follow-up on anaerobic non-oxidative metabolism or greater "efficiency" during exercise could explain a lack of change in $VO_2$ peak in the ET group despite an increase in workload and exercise time, as observed in the present investigation. Related to these potential confounding issues, the bicycle testing protocol employed was standardized for all patients, although small increases in exercise time could allow the subjects to reach a higher workload and result in a significant increase in this parameter (e.g., increasing from 50 to 75 W = 50% increase in workload).

Moreover, the ET stimulus was also standardized for each patient through an individualized exercise prescription that was adjusted, based on individual adaptations, to provide an appropriate training stimulus. Additionally, if patients could not attend an ET session, they were required to make up these sessions by extending the 16-week training period until a minimum of 40 sessions had been completed. The RER values, which tended to be higher in ET subjects, rather than lower, at follow-up than in the control group does not support inadequate effort on follow-up tests in the ET subjects. A final possible explanation could be that nonoxidative muscle metabolic adaptation, which would not be reflected in $VO_2$ peak measurement; an improvement in efficiency; or both could be responsible for the increase in exercise time and workload, although the ET program was conducted at a moderate intensity with a goal of increasing exercise duration rather than increasing exercise intensity. This moderate-intensity training is unlikely to induce improvements in anaerobic capacity. Furthermore, significant improvements in submaximal exercise variables, including 6 MWT distance and VAT were not observed. By assessing an effort-independent variable such as VAT, any patient learning effect or bias can be eliminated, with only the actual physiologic response being measured, but there was still no significant training effect observed with either of these variables.

The lack of significant improvement in $VO_2$ peak after ET in HFrEF is not unprecedented and has been observed in several studies of subjects with HFrEF.[6,25] Whereas an increase in $VO_2$ peak of more than 10% is often used as the criterion value for a "training effect" in patients with HFrEF, the HF ACTION trial employed a similar ET intervention and demonstrated a median increase in $VO_2$ peak of just 4% more in the ET than the control group after 3 months.[5] In contrast to the present study, the inclusion of younger HFrEF participants (median age 59, vs 70 in the present study) and the use of nonblinded exercise test administrators aided HF ACTION results. Furthermore, despite highly standardized ET programs, several studies[26–28] have demonstrated a range of improvement in $VO_2$ peak from 0% to 40% in healthy adults. Although numerous factors, including sex, age, baseline fitness, and genetics, appear to contribute to this variability in adaptation to ET, autonomic nervous system status has been shown to be the most powerful predictor of improvement in $VO_2$ peak after ET.[29] The relationship between autonomic nervous system status and adaptation to ET in HFrEF has not been established but clearly warrants further investigation.

Although the present investigation (and most others reported in the literature) used a traditional ET intervention, based primarily on moderate-intensity continuous ET, emerging research suggests that high-intensity interval ET may be more beneficial in improving peak $VO_2$ in older HF patients.[30] It has been reported that high-intensity interval training had a significantly greater effect on peak $VO_2$ than did traditional continuous training (41% improvement vs 14%). Although this type of exercise program may be more physiologically beneficial, the safety and long-term adherence to this approach has not been sufficiently studied.

Likewise, no significant improvement in LV structure and function was observed after 16 weeks of ET in older patients with HFrEF. Another study also observed little to no change in cardiac structure or function after ET.[31] The cohort evaluated was considerably younger (mean

age 62 vs 70) than in the present study and consisted more predominately of men (92% vs 66%) than the present study, which was 34% female.

The present investigation indicated that patients randomized to ET had significantly lower aldosterone levels and a trend toward lower angiotensin II after ET. These two neuroendocrine measures are thought to be among the most pivotal in the pathophysiological genesis and progression of heart failure. Furthermore, patients in the ET arm of the trial who showed an increase in peak exercise $VO_2$ peak also had a significantly greater ($P = .003$) decline in aldosterone levels than patients with no change in exercise capacity. Although a specific mechanism is unclear, this suggests a possible causal relationship between improvements in physical function and decline in aldosterone levels. The effect of ET on neurohormonal activation in HF has previously been examined and a significant decrease in angiotensin II, aldosterone, and vasopressin found after ET,[32] but that study consisted of younger patients with HF (mean age 61) than in the present study (mean age 70), although that study reported no significant correlations between improvements in exercise capacity and neurohormonal responses.

In the present trial, there were no significant changes in quality-of-life scores on the condition-specific MLHF questionnaire or the more general SF-36 in the ET or control groups. Several previous studies have failed to observe significant changes in HRQOL in HFrEF after participation in ET, despite improvement in overall exercise capacity.[33–35] The lack of improvement on the "physical" subscales in the present investigation is in contrast to a previous study, which reported a significant improvement in the MLHF and the physical function and role function categories of the SF-36.[31] The contrast in findings might be related to differing baseline QOL scores in the two studies. Subjects in the previous study had higher baseline MLHF scores, indicating worse QOL and a greater potential for change than subjects in the present study. The lack of change in the QOL "physical" subscores may also be related to the potential confounding issues discussed earlier or to the older age of the subjects used in this investigation.

A primary limitation of this study was that it was conducted a decade ago, before beta-blockers and aldosterone antagonists became standard pharmacotherapy for treating patients with HFrEF. Although use of these medications was low at baseline, their frequency may have increased during the study period and affected the study outcomes. Furthermore, the results of this study must be reviewed in the context of a single-center design that focused on increasing ET duration and frequency while maintaining a moderate exercise intensity stimulus. Therefore, the results of this study of older patients with HFrEF cannot be generalized to younger patients with HFrEF or those employing alternative ET regimens.

In summary, in this randomized, controlled, single-blind trial, ET failed to produce consistent benefits in a cohort of exclusively elderly patients with HFrEF that included a significant proportion of women. Exercise time and peak workload increased significantly, but $VO_2$ peak, the primary outcome did not. In this investigation, a subgroup of approximately one-fourth of the ET group that responded favorably to the intervention with an increase in $VO_2$ peak of 10% or more was identified. Patients in this subgroup also had suppression of aldosterone activation and a trend toward suppression of angiotensin II and tended to demonstrate better diastolic function. Thus, these find-ings suggest that, despite similar adherence to ET, older patients with HFrEF have a heterogeneous response to ET. Although the mechanism(s) responsible for this variability in adaptation to ET remain(s) unclear, the ability to identify potential responders and nonresponders to ET has important implications in the management of older patients with HFrEF and warrants further attention.

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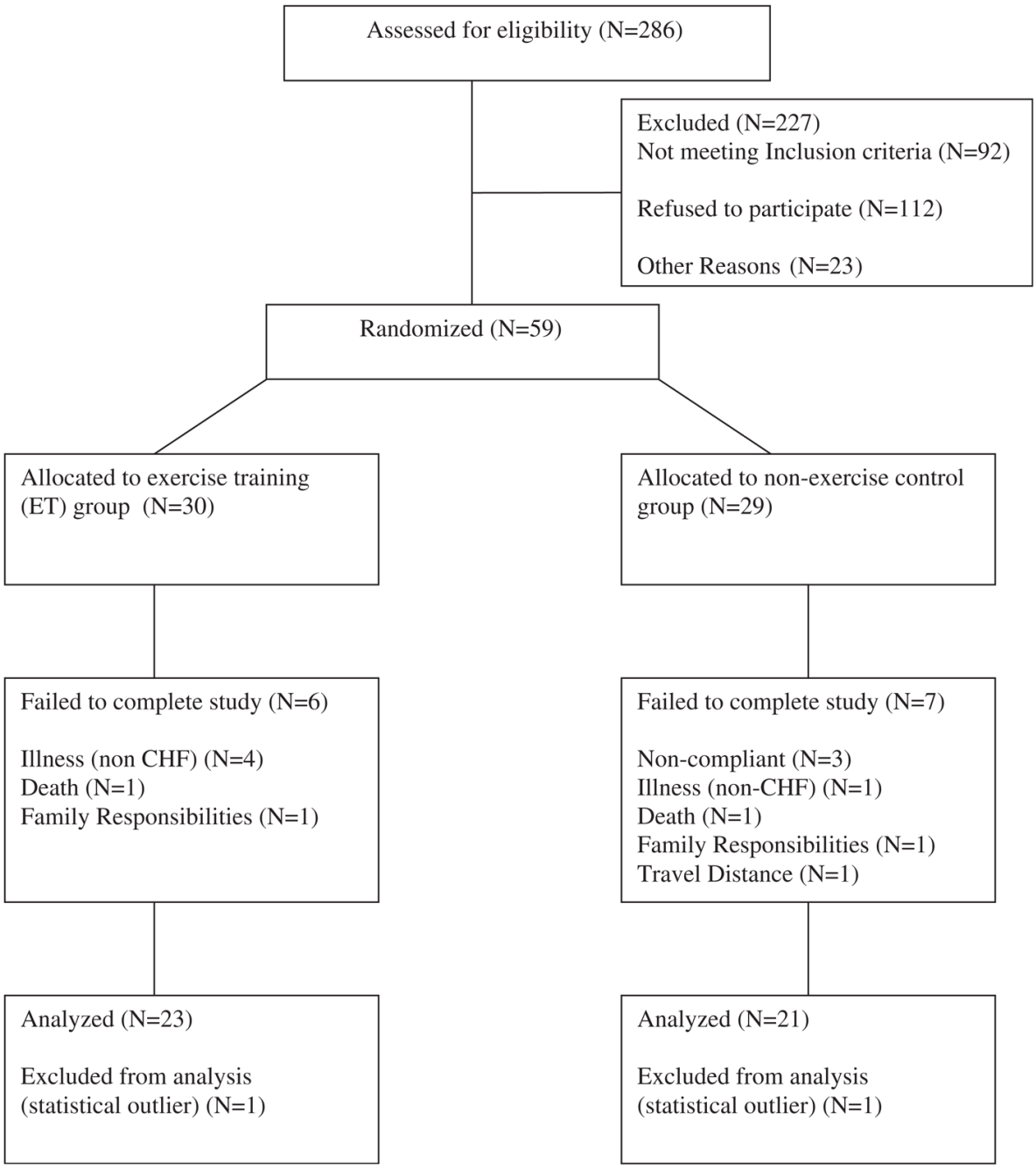


**Figure 1.**
Flow of the trial.

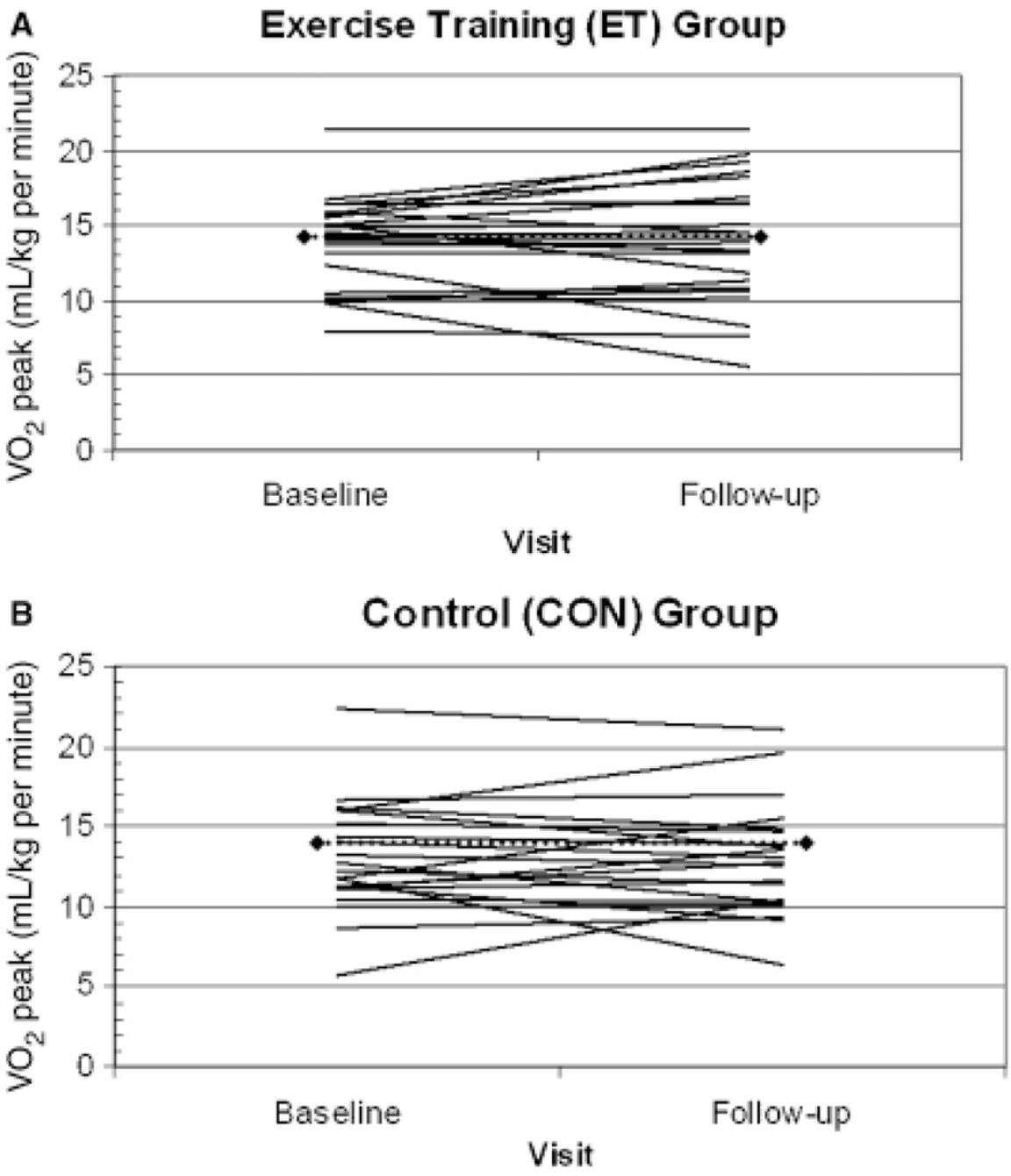


**Figure 2.**
Individual patient's changes in peak exercise oxygen consumption ($VO_2$) peak from baseline to follow-up (16 weeks) in the (A) exercise training (ET) and (B) control (CON) groups.

## Table 1

Patient Demographics

| Characteristic | All N = 59 | ET n = 30 | Control n = 29 | *P*-Value |
|---|---|---|---|---|
| Age, mean ± SD | 70.2 ± 5.1 | 70.4 ± 5.3 | 69.9 ± 6.3 | .83 |
| Women, n (%) | 20 (33.9) | 11 (36.7) | 9 (31.0) | .48 |
| Caucasian, n (%) | 48 (81.4) | 11 (36.7) | 9 (31.0) | .84 |
| Body weight, kg, mean ± SD | 77.8 ± 14.2 | 80.4 ± 13.6 | 77.3 ± 14.1 | .50 |
| Body surface area, $m^2$, mean ± SD | 1.91 ± 0.2 | 1.92 ± 0.2 | 1.90 ± 0.2 | .46 |
| Body mass index, $kg/m^2$, mean ± SD | 26.4 ± 4.1 | 27.0 ± 4.8 | 26.3 ± 4.2 | .36 |
| Body fat, %, mean ± SD | 24.1 ± 5.1 | 24.3 ± 5.1 | 23.4 ± 5.8 | .48 |
| Left ventricular ejection fraction, %, mean ± SD | 30.7 ± 9.0 | 32.1 ± 9.1 | 30.4 ± 8.8 | .38 |
| Sinus rhythm, n (%) | 53 (89.8) | 26 (86.7) | 27 (93.1) | .23 |
| New York Heart Association Class, n (%) | | | | |
| II | 27 (45.7) | 15 (50.0) | 16 (55.2) | .68 |
| III | 31 (52.5) | 15 (50.0) | 12 (41.4) | .62 |
| IV | 1 (1.7) | 0 (0.0) | 1 (3.4) | .77 |
| Diabetes mellitus, n (%) | 17 (28.8) | 6 (20.0) | 11 (37.9) | .50 |
| History of hypertension, n (%) | 30 (50.8) | 16 (53.3) | 14 (48.3) | .67 |
| History of pulmonary edema, n (%) | 34 (57.6) | 17 (56.7) | 17 (58.6) | .80 |
| Systolic blood pressure mmHg, mean ± SD | 137.1 ± 20.8 | 133.3 ± 19.4 | 140.9 ± 24.1 | .17 |
| Diastolic blood pressure, mmHg, mean ± SD | 77.4 ± 10.2 | 77.1 ± 9.8 | 77.9 ± 10.4 | .81 |
| Current medication, n (%) | | | | |
| Angiotensin-converting enzyme inhibitors | 49 (83.1) | 24 (80.0) | 25 (86.2) | .85 |
| Digoxin | 42 (71.2) | 21 (70.0) | 21 (72.4) | .95 |
| Diuretics | 51 (86.4) | 26 (86.7) | 25 (86.2) | .59 |
| Beta-blockers | 10 (16.9) | 6 (20.0) | 4 (13.8) | .61 |
| Calcium channel blockers | 15 (25.4) | 9 (30.0) | 6 (20.6) | .32 |
| Nitrates | 19 (32.2) | 7 (23.3) | 12 (41.3) | .16 |

Baseline characteristics and medical history of all participants and the comparison of those randomized to the exercise training (ET) and control groups. No significant differences were observed in these variables between the groups at baseline.

SD = standard deviation.

**Table 2**

Selected Outcome Measures

| | Baseline | | Follow-Up | | Change | | Adjusted * | | |
|---|---|---|---|---|---|---|---|---|---|
| | ET | Control | ET | Control | ET | Control | ET | Control | |
| **Variable** | **Mean ± SE** | | | | **%** | | **Mean ± SE** | | ***P*-Value** |
| Time, minutes | 6.6 ± 0.6 | 6.4 ± 0.6 | 7.4 ± 0.7 | 6.7 ± 0.8 | 12.1 | 4.7 | 7.5 ± 0.2 | 6.5 ± 0.2 | .007 |
| Work, W | 51.1 ± 5.3 | 50.7 ± 5.2 | 58.4 ± 6.1 | 51.2 ± 7.3 | 14.3 | 0.9 | 58.6 ± 2.2 | 49.4 ± 2.4 | .002 |
| Heart rate at peak exercise, beats per minute | 135.3 ± 3.9 | 126.1 ± 3.3 | 142.2 ± 3.5 | 129.3 ± 4.2 | 5.1 | 2.3 | 138.2 ± 3.3 | 133.0 ± 2.9 | .25 |
| $VO_2$, mL/kg per minute | 14.1 ± 0.6 | 13.5 ± 0.6 | 13.9 ± 0.8 | 13.6 ± 0.7 | −1.4 | 0.7 | 13.8 ± 0.4 | 13.7 ± 0.4 | .91 |
| Respiratory exchange ratio at peak exercise | 1.12 ± 0.02 | 1.11 ± 0.02 | 1.17 ± 0.03 | 1.11 ± 0.03 | 4.5 | 0.0 | 1.15 ± 0.02 | 1.13 ± 0.03 | .51 |
| Peak ventilation/peak carbon dioxide production slope | 36.8 ± 1.2 | 38.4 ± 1.7 | 38.5 ± 2.3 | 36.3 ± 1.3 | 4.6 | −5.4 | 38.7 ± 1.4 | 36.1 ± 1.6 | .23 |
| $VO_2$ at ventilatory anaerobic threshold, in mL/min (mL) | 720.2 ± 30.7 | 702.8 ± 29.1 | 746.3 ± 44.7 | 785.4 ± 39.1 | 3.6 | 11.8 | 759.9 ± 24.3 | 758.2 ± 27.4 | .96 |
| Six-minute walk distance, feet | 1,333.3 ± 99.6 | 1,232.4 ± 130.2 | 1,515.9 ± 98.1 | 1,388.7 ± 78.1 | 13.6 | 12.7 | 1,516.3 ± 85.1 | 1,430.0 ± 100.1 | .52 |
| Angiotensin II, pg/mL** | 50.3 ± 2.9 | 49.5 ± 6.1 | 45.9 ± 3.5 | 49.2 ± 5.0 | −8.7 | −0.6 | 46.8 ± 3.2 | 49.1 ± 4.2 | .07 |
| Aldosterone, pg/mL** | 11.5 ±1.5 | 12.1 ± 1.4 | 11.1 ± 1.4 | 14.1 ± 1.4 | −3.4 | 16.5 | 11.3 ± 1.3 | 13.5 ± 1.4 | .047 |
| Left ventricular mass (g) | 248.4 ±15.2 | 247.9 ± 11.1 | 232.4 ± 16.2 | 261.8 ± 16.3 | −6.6 | 5.6 | 251.2 ± 7.9 | 258.3 ± 7.1 | .53 |
| Ejection fraction (%) | 31.1 ±2.2 | 32.8 ± 2.4 | 29.4 ± 1.8 | 29.1 ± 2.3 | −5.4 | −11.2 | 29.4 ± 1.2 | 29.3 ± 1.4 | .86 |
| Early mitral velocity:atrial mitral velocity | 0.9 ±0.1 | 1.2 ± 0.2 | 1.2 ± 0.2 | 1.0 ± 0.1 | 33.3 | −16.7 | 1.3 ± 0.2 | 1.0 ± 0.2 | .34 |
| Minnesota Living with Heart Failure Questionnaire, total score | 39.9 ±4.2 | 44.1 ± 4.9 | 35.3 ± 4.2 | 37.9 ± 4.3 | −11.5 | −14.1 | 36.1 ± 2.8 | 37.3 ± 3.2 | .84 |

Peak exercise testing responses for exercise training (ET) and control groups at baseline and 16-week follow-up.

* Adjusted for age, sex, and baseline values.

** *P*-values are based on analysis conducted on log-transformed data because of nonnormal distribution.

SE = standard error; $VO_2$ = oxygen uptake at peak exercise.