Cardiac Rehabilitation Improves Functional Capacity and Patient-Reported Health Status in Patients With Continuous-Flow Left Ventricular Assist Devices

The Rehab-VAD Randomized Controlled Trial

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ABSTRACT

OBJECTIVES This study examined the effects of a cardiac rehabilitation (CR) program on functional capacity and health status (HS) in patients with newly implanted left ventricular assist devices (LVADs).

BACKGROUND Reduced functional capacity and HS are independent predictors of mortality in patients with heart failure. CR improves both, and is related to improved outcomes in patients with heart failure; however, there is a paucity of data that describe the effects of CR in patients with LVADs.

METHODS Enrolled subjects (n = 26; 7 women; age 55 ± 13 years; ejection fraction 21 ± 8%) completed a symptom-limited cardiopulmonary exercise test, the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 6-min walk test (6MW), and single-leg isokinetic strength test before 2:1 randomization to CR versus usual care. Subjects in the CR group underwent 18 visits of aerobic exercise at 60% to 80% of heart rate reserve. Within-group changes from baseline to follow-up were analyzed with a paired t-test, whereas an independent t-test was used to determine differences in the change between groups.

RESULTS Within-group improvements were observed in the CR group for peak oxygen uptake (10%), treadmill time (3.1 min), KCCQ score (14.4 points), 6MW distance (52.3 m), and leg strength (17%). Significant differences among groups were observed for KCCQ, leg strength, and total treadmill time.

CONCLUSIONS Indicators of functional capacity and HS are improved in patients with continuous-flow LVADs who attend CR. Future trials should examine the mechanisms responsible for these improvements, and if such improvements translate into improved clinical outcomes. (Cardiac Rehabilitation in Patients With Continuous Flow Left Ventricular Assist Devices: Rehab VAD Trial [RehabVAD]; NCT01584895) (J Am Coll Cardiol HF 2014;2:653–9) © 2014 by the American College of Cardiology Foundation.

Although heart transplantation is the treatment of choice for patients with end-stage heart disease, because of limited donor availability (1), the left ventricular assist device (LVAD) has become an established therapeutic option in appropriately selected patients. Continuous-flow LVADs are used as a bridge to recovery, a bridge to cardiac transplantation, and increasingly, as
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ABBREVIATIONS AND ACRONYMS

6MW = 6-min walking distance
CPX = cardiopulmonary treadmill test
CR = cardiac rehabilitation
HF = heart failure
HS = health status
KCCQ = Kansas City Cardiomyopathy Questionnaire
LVAD = left ventricular assist device
UC = usual care
VO2 = peak oxygen uptake

ASSIST DEVICE

destination therapy in which the device remains in use for the life of the patient (2). In addition to improved survival, some studies have shown improvements in functional capacity and health status (HS) following LVAD implantation (3,4). However, despite these improvements, many patients with LVADs continue to experience exercise intolerance and other heart failure (HF)-related symptoms (5,6). Leibner et al. (7) observed that cardiorespiratory fitness, as measured by peak oxygen uptake (VO2), and ventilatory efficiency remained unchanged 1 year after LVAD implantation. Persisting functional limitations in this population can affect HF-related symptoms, HS, and, potentially, clinical outcomes (e.g., hospitalization) (8). As the durability of LVADs improve and duration of support is extended, the assessment and optimization of functional capacity and HS become key components in the long-term management of these patients.

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In patients with cardiovascular disease, cardiac rehabilitation (CR) improves survival, functional capacity, and quality of life (9-11). Among patients with stable HF, exercise training improves peak VO2, reduces HF-related symptoms, and is associated with a lower risk for all-cause death or all-cause hospitalization (8,11-14).

Methods and Study Design

Patients who underwent LVAD implantation between June 2011 and September 2012 for any indication at Henry Ford Hospital were screened for participation. Eligibility criteria included a recently implanted continuous-flow LVAD (i.e., 1 to 6 months from surgery date), age older than 18 years, and patients had to be free of any major comorbidities or limitations that might interfere with exercise training. Exclusion criteria included patients who declined to attend CR or who attended a CR program outside of the Henry Ford Health System. The protocol was reviewed and approved by the Henry Ford Health System Institutional Review Board, and all subjects provided written informed consent.

Following baseline testing, patients were randomized in a 2:1 fashion to either 6 weeks of CR or usual care (UC). Randomization was conducted using a computer random number generator, with group assignments transferred to allocation cards sealed in opaque sequential envelopes. Staff members who conducted the follow-up testing at 6 weeks after baseline were blinded to group assignment.

Patient Testing

Before group assignment, all patients underwent initial testing that consisted of a self-reported patient HS questionnaire, a symptom-limited cardiopulmonary treadmill test (CPX), a 6-min walk (6MW) test, and a maximal single-leg isokinetic test to measure strength. The order of administrating these tests remained the same for all patients at both time points (i.e., at baseline and follow-up). Patient-reported HS was obtained using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item questionnaire to evaluate patient responses across 5 domains (i.e., physical function, symptoms, social function, self-efficacy, and quality of life) (16). The symptom-limited CPX test was then completed using the modified Naughton protocol (i.e., 1 metabolic equivalent increase per each 2-min stage).Expired air was sampled breath-by-breath and analyzed using a Medgraphics Ultima (Minneapolis, Minnesota) metabolic cart. Heart rate and blood pressure were measured in the supine and standing positions before exercise, at the end of each 2-min exercise stage, at peak exercise, and during recovery.

Gas exchange data were analyzed by a CPX core laboratory that was blinded to subject assignment. Gas exchange data were reported using 20-s interval averages. Peak values were identified from the highest interval value during the final minute of exercise. Ventilatory-derived anaerobic threshold was determined using the modified V-slope method by 3 independent reviewers. Minute ventilation to carbon dioxide slope was calculated using data from the
start of exercise up to recovery. Following the CPX test, subjects rested for a minimum of 30 min, then completed a standardized 6MW test, which was performed using the American Thoracic Society guidelines (17).

On the same day, subjects also performed a single-leg extension peak torque test using an isokinetic dynamometer (Biodex, Shirley, New York). The test consisted of 15 maximal concentric knee extensions at 90°/s. To ensure a maximal effort was given, peak torque was identified as the highest value observed (Newton meters) within the first 5 repetitions. If the peak torque occurred after the fifth repetition, then the subject was asked to return on a separate day to repeat the test.

**EXERCISE TRAINING**

Patients randomized into the CR group had 18 visits that included supervised exercise, group educational classes, and individualized treatment plans. The supervised exercise consisted of 3 sessions per week for 6 weeks. Following a 5-min warm up, exercise training was completed mainly with treadmill walking and a secondary modality (e.g., stationary cycle, arm ergometer, recumbent stepper) for a total of 30 min at a training intensity initially set at a heart rate corresponding to 60% of the heart rate reserve (difference between peak and heart rate at rest). Exercise training duration did not change throughout the program; however, staff encouraged patients to progress exercise intensity as tolerated up to 80% of the heart rate reserve.

**USUAL CARE**

Patients randomized into the UC group were not given an individualized exercise prescription to follow or counseled about physical activity, but were told to continue to follow physician instructions regarding care, including the standard recommendation to perform daily walking. To partially control for patient contact, both UC and CR patients received follow-up calls at weeks 2, 4, and 6. The follow-up calls consisted of questions asking about new signs or symptoms, medications, hospitalizations, and any changes to activity levels.

**OUTCOME MEASURES**

The primary outcome was change in peak VO₂. Secondary outcomes included: 1) KCCQ summary score; 2) peak torque from the single-leg extension isokinetic test; 3) 6MW distance; and 4) total treadmill time. Untoward clinical events were determined by a review of the electronic medical records (K.B.) and defined as any unexpected complication that resulted in an emergency department visit or hospitalization. Any events outside of the hospital were confirmed during the patient follow-up calls. Scheduled hospitalizations (e.g., right heart catheterization) were not included as an untoward event.
TABLE 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rehabilitation (n = 18)</th>
<th>Standard (n = 8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>7 (39%)</td>
<td>1 (14%)</td>
<td>0.300</td>
</tr>
<tr>
<td>Black race</td>
<td>12 (67%)</td>
<td>2 (29%)</td>
<td>0.070</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53 ± 13</td>
<td>60 ± 12</td>
<td>0.225</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 14</td>
<td>83 ± 13</td>
<td>0.575</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 5</td>
<td>27 ± 4</td>
<td>0.808</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>21 ± 7</td>
<td>21 ± 9</td>
<td>0.874</td>
</tr>
<tr>
<td>Days from implantation</td>
<td>91 ± 33</td>
<td>73 ± 32</td>
<td>0.192</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>6 (33%)</td>
<td>2 (25%)</td>
<td>0.671</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>12 (67%)</td>
<td>6 (75%)</td>
<td></td>
</tr>
<tr>
<td>INTERMACS level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (22%)</td>
<td>0 (0%)</td>
<td>0.475</td>
</tr>
<tr>
<td>II</td>
<td>2 (11%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8 (44%)</td>
<td>6 (75%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4 (22%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td>Device type</td>
<td>HeartMate II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (83%)</td>
<td>5 (63%)</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>HeartWare</td>
<td>3 (17%)</td>
<td>3 (40%)</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (55%)</td>
<td>3 (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beta blockers</td>
<td>15 (83%)</td>
<td>3 (40%)</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>10 (55%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>3 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>18 (100%)</td>
<td>7 (88%)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; INTERMACS = Interagency Registry for Mechanical Circulatory Support.

SUBANALYSIS. Within the 26 subjects who participated, a cohort of 7 male subjects had previous CPXs performed <6 months before LVAD implantation. We present these data to provide context and description of cardiorespiratory values before and following LVAD surgery.

TABLE 2 Gas Exchange and Exercise Performance Measures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rehabilitation (n = 16)</th>
<th>Standard Care (n = 7)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill time (min)</td>
<td>7.9 ± 1.6</td>
<td>11.0 ± 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>VO₂ (l/min)</td>
<td>1.05 ± 0.44</td>
<td>1.19 ± 0.43*</td>
<td>0.91 ± 0.18</td>
</tr>
<tr>
<td>Oxygen uptake (ml/kg/min)</td>
<td>13.6 ± 3.3</td>
<td>15.3 ± 4.4*</td>
<td>11.2 ± 2.0</td>
</tr>
<tr>
<td>VAT (ml/kg/min)</td>
<td>10.0 ± 2.1</td>
<td>10.9 ± 2.1*</td>
<td>9.1 ± 0.7</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>1.17 ± 0.08</td>
<td>1.18 ± 0.08</td>
<td>1.24 ± 0.09</td>
</tr>
<tr>
<td>Minute ventilation (l/min)</td>
<td>46.0 ± 13.8</td>
<td>50.9 ± 17.8</td>
<td>43.0 ± 6.2</td>
</tr>
<tr>
<td>V₄₋VCO₂ slope</td>
<td>36.8 ± 8.7</td>
<td>37.8 ± 8.8</td>
<td>38.8 ± 8.0</td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>350.1 ± 64.7</td>
<td>402.4 ± 89.3*</td>
<td>336.6 ± 59.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Difference between groups <0.05. †Difference within groups ≥ 0.05.
VAT = ventilatory-derived anaerobic threshold; V₄ – VCO₂ slope = change in ventilation to change in carbon dioxide slope; VO₂ = oxygen uptake.

STATISTICAL ANALYSIS

A paired t-test was used to assess within-group changes from baseline to 6 weeks. An independent sample t-test was used to compare the differences in change from baseline to follow-up between UC and CR patients. The Student’s t-test and the chi-square test were used to compare groups at baseline for continuous and nominal data, respectively. Alpha level was set at 0.05 for all analyses. All statistical analyses were performed with IBM SPSS version 21.0 (Armonk, New York).

RESULTS

During the study, 26 of 39 eligible patients consented to participate. The flow of participants is shown in Figure 1. The most common reason for nonparticipation was travel distance to the rehabilitation site. Individuals who chose not to participate in the study (n = 13) were similar across all reported demographic and clinical characteristics (e.g., ejection fraction, heart failure etiology, and so on) compared with the 26 who did undergo randomization, except for body mass index (27 kg/m² vs. 31 kg/m²; p = 0.025). Baseline characteristics of the study participants can be found in Table 1.

Of the patients who were randomized into the CR group all but 1 completed 18 visits, with 84% completing all visits by week 6. The single patient in the intervention group who did not complete all 18 CR visits dropped out of the study due to relocation. All attempts to contact this patient for follow-up testing were unsuccessful. A second CR patient who finished all 18 visits was unable to complete follow-up testing due to acute cholecystitis, and shortly afterwards, a driveline infection that led to an extended hospital stay. In addition, 1 patient in the UC group had an extended hospital stay for an infection and also did not return for follow-up testing.

The CR group had a significant improvement (10%) in peak VO₂ from baseline to follow-up (p = 0.007); however, compared with the UC group, there were no differences in the change between groups (Table 2, Figure 2). Similarly, the increase in 6MW distance was significant in the CR group only (p = 0.001), but no significant difference was found compared with the control group (Table 2). The KCCQ summary score, leg strength, and total treadmill time all showed significant improvements both within the CR group and compared with the UC group (Figures 3 and 4, Table 2). Other notable improvements observed only in the CR group included improvements in ventilatory-derived anaerobic threshold, heart rate during submaximal...
exercise, and heart rate at minute one of recovery (Tables 2 and 3).

Overall, the exercise sessions were well-tolerated and safe. Of the 313 total exercise visits, there was only 1 untoward event that required the patient to be transferred to the emergency department. This was due to a syncopal episode immediately following the completion of an exercise session. Electrocardiographic telemetry revealed a wide complex tachycardia that might have precipitated this event. No other signs or symptoms were reported before, during, or within 3 h following an exercise session in patients in the CR group.

Three other patients in the CR group also had visits to the ED that occurred outside of exercise (i.e., >3 h after last exercise session), with 1 requiring an overnight hospitalization for epistaxis. In addition, 4 of the control subjects had visits to the emergency department, with 3 requiring overnight hospitalization. The reasons for hospitalization for the UC group patients were edema, bacterial infection, and anemia.

Changes in peak VO₂, for all subjects combined, were moderately to strongly associated to changes in the 6MW test (r = 0.605; p = 0.03), ventilatory-derived anaerobic threshold (r = 0.774; p < 0.001), and treadmill time (r = 0.882; p < 0.001). Changes in the KCCQ score were found to be weakly associated with changes in the treadmill time (r = 0.417; p = 0.047). No other associations were found to be significant.

We observed no changes in cardiorespiratory fitness before and following LVAD implantation (VO₂ = 14.0 ± 2.8 ml/kg/min vs. 12.5 ± 1.6 ml/kg/min; p = 0.272) in the 7 patients (age 60 ± 11 years, body mass index 24 ± 2 kg/m², ejection fraction 24 ± 8%) who completed a CPX within 6 months before LVAD implantation.

**DISCUSSION**

We demonstrated in this randomized, single-blind trial that CR improves cardiorespiratory fitness (10%), muscle strength (17%), and KCCQ scores (23%) in patients with continuous flow LVADs. In addition, we observed that standard CR appeared to be well tolerated within our patient cohort, which participated in >300 patient-hours of exercise training and attended 99% of the planned sessions. Although a difference in change in peak VO₂ was not observed between the groups, only the CR group had a clinically meaningful (i.e., >1 ml/kg/min or >8%) improvement in peak VO₂.

Further, when all metrics of functional capacity were examined in their entirety, CR was favorably associated with improved exercise tolerance.

Muscular strength is a known correlate to patient quality of life and physical disability in patients with HF (18). Compared with an aged-matched group of healthy 50 to 60 year olds, with an average knee extension torque of 179 ± 40 N-m, our cohort of patients, who had newly implanted LVADs, averaged only 51% of this normative value (19). However, following training, the CR group demonstrated a 17% improvement in peak leg torque compared with no change in the UC group. Although the CR intervention did not consist of strength training exercises, the observed improvement might have been due to structured moderate intensity and/or modalities of exercise (e.g., stationary cycle) not available to the UC group. Given the severe muscle atrophy and histochemical changes that occur in end-stage heart failure, the stimulus due to aerobic exercise might have been sufficient to improve leg strength. In patients with HF, aerobic exercise training improves skeletal muscle
The resting hemodynamic measures are as follows:

- Peak MAP (mm Hg): 100
- Submaximal MAP (mm Hg): 94
- Resting MAP (mm Hg): 85
- Resting HR (beats/min): 88
- Submaximal HR (beats/min): 105
- Heart rate recovery (HR recovery): 24

These values are mean ± SD. *Difference between groups ≤ 0.05. **Difference within groups ≤ 0.05.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) Summary Score for CR and Usual Care Group Subjects:

For CR group, changes at follow-up were significant (\(p = 0.001\)) and significantly different from changes in the usual care group (\(p = 0.005\)). Abbreviation as in Figure 2.

The KCCQ score is a composite measure of patient-reported symptoms and quality of life, and is associated with mortality and morbidity (21). Previously, Rodgers et al. (3) demonstrated significant improvements in the KCCQ score from baseline (i.e., pre-implantation) compared with 1, 3, and 6 months post-implantation. This suggested a time-dependent improvement in clinical symptoms and quality of life in patients with newly implanted LVADs. However, the association between daily physical activity levels and KCCQ score improvement was not accounted for.

A change of 5 points in the KCCQ score is considered clinically meaningful and more predictive of patient clinical status than B-type natriuretic peptide and 6MW distance (22). Patients randomized into the CR group demonstrated an average KCCQ score increase of 14.4 points compared with a 0.5 point change in the UC group. This marked improvement was in concordance with previous studies that showed improvement in patient-reported symptoms and quality of life with CR participation (23). The components within a structured exercise program that affect this improvement are likely multifaceted (e.g., enhanced social support, improved cardiovascular fitness, increased muscular strength).

An analysis of the KCCQ subcomponents revealed significant within-group improvements in the CR group for physical limitations (\(p = 0.002\)), symptom frequency (\(p = 0.013\)), symptom burden (\(p = 0.042\)), quality of life (\(p = 0.002\)), and social limitations (\(p = 0.021\)). No within-group improvements were seen in the control group. Between-group changes were found only for the quality of life subcomponent, with a 30% improvement in the CR group versus no change in the control group (\(p = 0.018\)).

A clinically significant improvement (i.e., >1.0 ml/kg/min) in peak VO\(_2\) was observed for the CR group. However, similar to findings from Hayes et al., we were unable to demonstrate a significant difference between the groups (15). Improvement in peak VO\(_2\), following LVAD implantation might simply be the result of improved hemodynamics, resulting in increased oxygen transport to skeletal muscles (3,24). However, similar to the study by Leibner et al. (7), we found severe deconditioning that was persistent in most of our patients, with only 1 patient with a peak VO\(_2\) at baseline >14 ml/kg/min.

In addition, in the 7 subjects who had a cardiorespiratory test before LVAD implantation, only 1 had an improved peak VO\(_2\) following LVAD implantation (before training). The 6 other subjects had either no change or a decrease in cardiorespiratory fitness.

Despite improved circulatory support from the LVAD, the lack of improved exercise tolerance might have been due to the extended hospital stay following implantation (i.e., bed rest) and might partly explain why subjects in the UC group showed a trend toward improved fitness with the resumption of daily home physical activities.

Another contributing factor that might explain a lack of difference between groups in fitness was that the UC group had no restrictions regarding performing exercise on their own, and although it was not quantified, anecdotally, many UC subjects reported regular walking.

However, despite a lack of significant difference between groups for change in peak VO\(_2\), improvements in peak VO\(_2\), 6MW distance, treadmill time, ventilatory-derived anaerobic threshold, submaximal heart rate, and heart rate recovery were only
observed in the CR group, suggesting an accentuated improvement in fitness due to the intervention.

**STUDY LIMITATIONS.** The small sample size for this study might have contributed to a lack of statistical differences between both groups for some variables. Conversely, because of the small sample size, multiple comparison adjustments were not made. Although this was done with the intention of decreasing the likelihood of a type II error, it must also be acknowledged that this could also inversely increase the chance of a type I error. In addition, because the intervention group was not blinded to the intervention, there was a possibility of the Hawthorne effect, with patients expecting to see an improvement. Finally, because this was a small, single-site trial, final conclusions regarding the safety of exercise training must be interpreted with caution.

**CONCLUSIONS**

Participation in CR has been shown to improve symptoms and function across a range of cardiovascular conditions (10). This study adds to the literature that shows improvements in functional capacity and HS for individuals with continuous-flow LVADs who participate in CR (vs. usual care). In addition, this is the first study to report that participation in CR can also lead to improvements in strength in this population. As mechanical assist devices become more common place, the utilization of CR should be considered to help these individuals regain physical function and improve their HS.

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**REFERENCES**


**KEY WORDS** cardiopulmonary exercise testing, cardiac rehabilitation, end-stage heart failure, exercise training, Kansas City Cardiomyopathy Questionnaire, left ventricular assist device.