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Feasibility and Outcomes of an Exercise Intervention for Chemotherapy-Induced Heart Failure

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Abstract

Purpose: Cancer treatment-related heart failure (HF) is an emerging health concern, as the number of survivors is increasing rapidly, and cardiac health issues are a leading cause of mortality in this population. While there is general evidence for the efficacy of exercise rehabilitation interventions, more research is needed on exercise rehabilitation interventions for patients specifically with treatment-induced HF, and if such interventions are safe and well-accepted. This study provides feasibility and health outcomes of a pilot exercise intervention for cancer survivors with chemotherapy-induced HF.

Methods: Twenty-five participants were randomized to a clinic-based exercise intervention or a wait-list control group, or alternatively allowed to enroll in a home-based exercise intervention if they declined the randomized study. For purposes of analysis, both types of exercise programs

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were combined into a single intervention group. Repeated measures ANOVA was conducted assessing for significant time and treatment group main effects separately, and time-by-treatment group interaction effects.

Results: Significant improvements in VO_{2max} were observed in the intervention group. Intervention satisfaction and adherence were high for both clinic and home-based interventions, with no reported serious adverse events. Enrollment was initially low for the clinic-based intervention, necessitating the addition of the home-based program as an intervention alternative.

Conclusions: Results suggest exercise rehabilitation interventions are feasible in terms of safety, retention, and satisfaction, and have the potential to improve VO_{2max}. To maximize adherence and benefits while minimizing participant burden, an ideal intervention may incorporate elements of both clinic-based supervised exercise sessions and a home-based program.

Condensed abstract:

General evidence for efficacy of exercise rehabilitation interventions exists, but more research is needed on intervention feasibility and efficacy for those with treatment-induced heart failure. This study demonstrates that an exercise program has the potential to improve VO_{2max}, along with being safe and well-accepted by this cancer survivor population.

Keywords

Exercise; heart failure; cancer; intervention; feasibility

Although more cancer patients now survive the disease, the cost can include lasting effects of treatment, such as chemotherapy-induced cardiovascular toxicity leading to adverse effects such as arrhythmias, cardiomyopathy, endothelial dysfunction, and heart failure (HF).[1] Chemotherapy agents like anthracyclines (a class of highly effective cytotoxic agents for hematopoietic and solid tumors) have been significantly associated with increased risk of HF and cardiomyopathy.[2,3] Studies also show this association with targeted therapies including trastuzumab and bevacizumab, while newer antiangiogenic agents (bevacizumab, sunitinib, sorafenib) have also been found to lead to cardiovascular toxicity and hypertension, which are contributing factors to HF.[4,5,6]

These effects are often clinically silent until their severity causes symptoms and mandates treatment, often years after chemotherapy. For anthracyclines, over half of patients treated show effects of cardiac dysfunction up to 20 y post-treatment, while anthracyclines combined with trastuzumab have been linked to cardiac complications in 27% of patients up to 51 mo if receiving combined therapy.[7] A study of leukemia survivors treated with anthracyclines reported left ventricular fractional shortening and systolic dysfunction up to 12 y post-diagnosis.[8]

RCTs have demonstrated the potential for improvement in cardiovascular health in non-cancer patients with HF through exercise rehabilitation.[9,10,11] Meta-analyses of these programs have demonstrated positive effects on cardiac functioning, physical performance, and quality of life.[12,13,14,15,16] Cochrane Reviews reported those receiving exercise showed a 27% reduction in all-cause mortality and a 31% reduction of total cardiac-specific related

mortality compared to those not receiving exercise.[17,18] Results from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), a large-scale RCT, showed participants receiving exercise had significantly lower rates of all-cause mortality and hospitalization, cardiovascular mortality, and HF hospitalization compared to standard care.[19] Despite potential benefits, there is a lack of studies demonstrating positive effects of exercise for adult patients with chemotherapy-related HF, and it is unclear if these interventions can be delivered with the same efficacy and positive effects as in non-survivor populations.[20]

This study provides feasibility (recruitment, adherence, safety, satisfaction) and health outcomes of an exercise intervention for patients with chemotherapy-induced HF.

METHODS

We recruited participants for randomization to a control or a 16-wk clinic-based exercise intervention. After initial low-enrollment, a home-based exercise condition was added as an alternative only to those declining to participate after offered the original study of randomization to the control or clinic-based intervention (Figure 1). Due to limited sample size, for the purposes of analysis, the clinic and home-based groups were combined into a single intervention comparison group.

Participant Eligibility

Patients seen by the MD Anderson Cancer Center (MDACC) cardiology service for chemotherapy-related cardiomyopathy and HF were recruited. Eligibility criteria included: (1) HF diagnosis with New York Heart Association (NYHA) class I, II, or III functional classification; (2) previous treatment with potentially cardio-toxic anticancer agents contributing to HF; (3) living in the Houston area; (4) cancer survivor with no evidence of disease; and (5) completed treatment, or on long-term adjuvant/maintenance chemotherapy only. Therefore, patients could be survivors with no evidence of disease, or evidence of disease but in stable long-term maintenance. Patients were treated with standard-of-care maximally tolerated medical therapy of ACE inhibitors and beta-blockers and when necessary, diuretics, based on the American College of Cardiology (ACC) guidelines for management of chronic HF.[21]

Patients were excluded if: (1) remained in NYHA class IV HF despite optimal guideline directed medical therapy; (2) had health problems or current treatments making exercise unsafe; (3) were unable to provide informed consent.

Exercise Intervention

The exercise program was based on HF-ACTION and consisted of supervised 30-min exercise sessions 3 times/wk for 16 wk.[19] The initial session was conducted by cardiologists and subsequent sessions were supervised by an exercise physiologist. Exercise training was done on a Cybex recumbent exercise bike. Sessions focused on improving exercise duration, intensity, and tolerance (working up to 30 min of continued activity at intensity level of 50% heart rate reserve). Starting intensity was prescribed and monitored using the Borg “6–20” RPE (rating of perceived exertion) scale.[22] During initial sessions, participants were

instructed to cycle at an RPE of 12 (between “fairly light” and “somewhat hard”). The progression plan involved increasing exercise duration and then intensity incrementally as tolerance improved. Participants were monitored with ECGs during sessions. Intervention development details have been previously reported.[19,23]

After 78% of eligible candidates declined potential randomization to a clinic-based program, a 12-wk home-based intervention was developed for reduced participant burden and potentially greater feasibility. The home-based program involved an initial supervised exercise session before starting home-based exercise to establish appropriate exercise intensity/duration. The exercise physiologist instructed participants how to assess/monitor intensity by going through an aerobic exercise session. Additionally, participants were trained to use the RPE method, and given a logbook to record exercise and intensity, as well as a pedometer to measure daily steps. Participants were then prescribed an aerobic exercise and walking program. Each participant was telephoned 1/wk to report progress, monitor for adverse events, and set exercise goals for the upcoming week.

Measures/Instruments

Feasibility measures included recruitment rates, adherence to sessions, retention, adverse events, and patient satisfaction questions. Participant satisfaction was assessed at 16-wk follow-up using items measuring difficulty attending sessions (1=not at all difficult to 5=very difficult), intervention satisfaction (1=satisfied to 5=not at all satisfied), and likelihood of recommending the intervention (1=likely to 5=not at all likely).

Outcomes of VO_{2max}, left ventricular ejection fraction (LVEF), HF symptom severity, physical/role functioning, and physical activity were collected at baseline and 16-wk follow-up. VO_{2max} was obtained through respiratory gas exchange analysis using cycle ergometry and LVEF was determined through echocardiograms. The biplane area-length method was utilized to calculate LVEF. Echocardiography and ergometry procedures have been previously reported.[23] HF symptom severity and burden were assessed through the MD Anderson Symptom Inventory Heart-Failure (MDASI-HF)[24], physical/role functioning were assessed by the Medical Outcomes Study Short Form-*36* (SF-36)[25], and the Community Health Activities Model Program for Seniors (CHAMPS)[26] questionnaire assessed physical activity.

Data Analysis

For recruitment, percentages against total eligible at each recruitment step were calculated, while retention percentage was obtained similarly. Adherence was determined through proportion of total planned sessions attended. Repeated measures analysis of variance (ANOVA), were conducted to assess intervention effects on cardiovascular health, symptoms, QOL, and physical activity[27]. Models included main effects of time and intervention group, and also a time-by-group interaction, which tested the effects of the intervention on outcomes. A significant time-by-group interaction indicates the intervention has an effect. Additionally, differences in baseline characteristics between groups are controlled for, as both changes between groups and changes within groups are accounted for. We also calculated standardized mean group differences (Cohen’s *d*) in the change from

baseline to follow-up for each outcome. This metric of effect size can be interpreted as a standardized measure of intervention effects, which can be communicated across different studies. Also, effect sizes can help determine sample size in follow-up studies.

RESULTS

A total of 155 potentially eligible were identified in the 36-mo recruitment period. After closer screening by cardiologists, 87 (56%) were eligible, of whom 25 (29%) consented and were enrolled. Among the enrolled, 3 (12%) dropped out before baseline, leaving 22 participants. Characteristics for the 22 participants who completed at least the baseline are summarized in Table 1. Of these 22, 17 (77%) remained and completed follow-up; 2 of the 8 participants in the randomized intervention arm and 1 of the 8 control participants dropped out before final assessment. Six participants were enrolled in the non-randomized home-based condition, and 4 completed participation (Figure 1).

Regarding feasibility, a low proportion of participants were willing to attend an in-clinic exercise intervention. Out of participants recruited in the greater Houston area, over 1/3 eligible but declining participation cited travel (>20 miles) as a major barrier. For the clinic-based group, adherence was assessed through attendance to exercise sessions (# of sessions attended/# of sessions planned), where mean completion was 73% (completing ≥ 8 out of 11 sessions), and all but 1 participant completed ≥2/3 of their 48 in-clinic sessions. For the home-based group, adherence was assessed through proportion of counseling calls completed and activity in the walking program; mean percent of total counseling sessions completed was 84% (completing ≥ 9 out of 11 sessions) and 75% of participants walked ≥ 10,000 steps/d.

For satisfaction items, mean score for difficulty attending sessions was 1.87, 1.00 for overall intervention satisfaction, and 1.13 for likelihood of recommending the intervention. Only 1 participant reported that the intervention was “difficult”.

Regarding adverse events, 2 documented cases were related to exercise. In 1 case, premature ventricular contractions were observed during exercise, however, this participant was cleared to continue after full re-evaluation. In the second case, a participant exhibited increased fatigue with minimal exertion during exercise. After examination by the cardiologist, this participant was cleared to continue and did not demonstrate elevated fatigue subsequently.

Statistically significant changes for the time main effect for both intervention and control groups were observed for QOL physical functioning (P =.001) and role functioning (P =.0279) (Table 2). In addition, a statistically significant time-by-group interaction effect (difference in change between groups over time taking into account baseline measurements) was observed for VO_{2max}, (P =.042) (Table 2). There were no statistically significant differences in LVEF, symptom scores (MDASI-HF), or physical activity. Observed standardized mean differences between intervention and control groups (Cohen’s d) in the change from baseline to follow-up ranged from large (MDASI-HF Cardiac Health: .83), to small (VO_{2max}: .28; LVEF(%): .40; MDASI-HF Symptom Burden: .05; SF-36 Physical

Functioning: .34; SF-36 Role Functioning: .01; CHAMPS Total hours: .45; CHAMPS High intensity hours: .13).

DISCUSSION

This study demonstrates the potential of an exercise intervention to improve cardiorespiratory health (through change in the surrogate endpoint of VO_{2max}) in patients with treatment-induced HF. Additionally, the study informs feasibility of clinic and home-based interventions that may be useful in developing future programs.

Among participants attending the clinic-based program, adherence and retention were high, indicating the exercise program may be feasible for a subset of participants. Given greater patient burden for the clinic-based intervention, but also observed long-term adherence issues with home-based programs in the literature (e.g. the HF-ACTION home component), an optimal intervention would likely involve a combination of these, for example, supervised sessions offered at locations close to the participant's home like community centers.[28] This reflects current recommendations for incorporating cardiac rehabilitation into oncology programs for patients who have completed treatment and no longer frequent clinical settings.[29]

Despite limited appeal during recruitment, satisfaction of those in the exercise intervention was high, and serious adverse events were not observed, which converges with evidence that exercise is safe for HF patients (although one study observed increased risk of clinical events in a cancer population).[19,28]

Several limitations are noted, inherent to the exploratory nature of the study. These include a small sample size, lack of random assignment to the home-based condition influencing internal validity, absence of long-term follow-up, and combination of the home-based and clinic-based groups for analysis, ergo, results should be interpreted considering limitations. Recruiting only through the cardiology clinic was likely a limiting factor for enrollment, and may be improved through recruiting more broadly (e.g., additionally through oncologists) and using a searchable EMR. Significant improvements were observed in QOL functioning (SF-36), however, this may be attributable to participants in both conditions receiving normal follow-up care or natural improvement in function over time.

VO_{2max} improvements indicate that an exercise program shows potential in improving cardiorespiratory fitness, while feasibility results inform implementation for future intervention studies. Subsequent research with a larger population could further investigate these changes and if they can be sustained.

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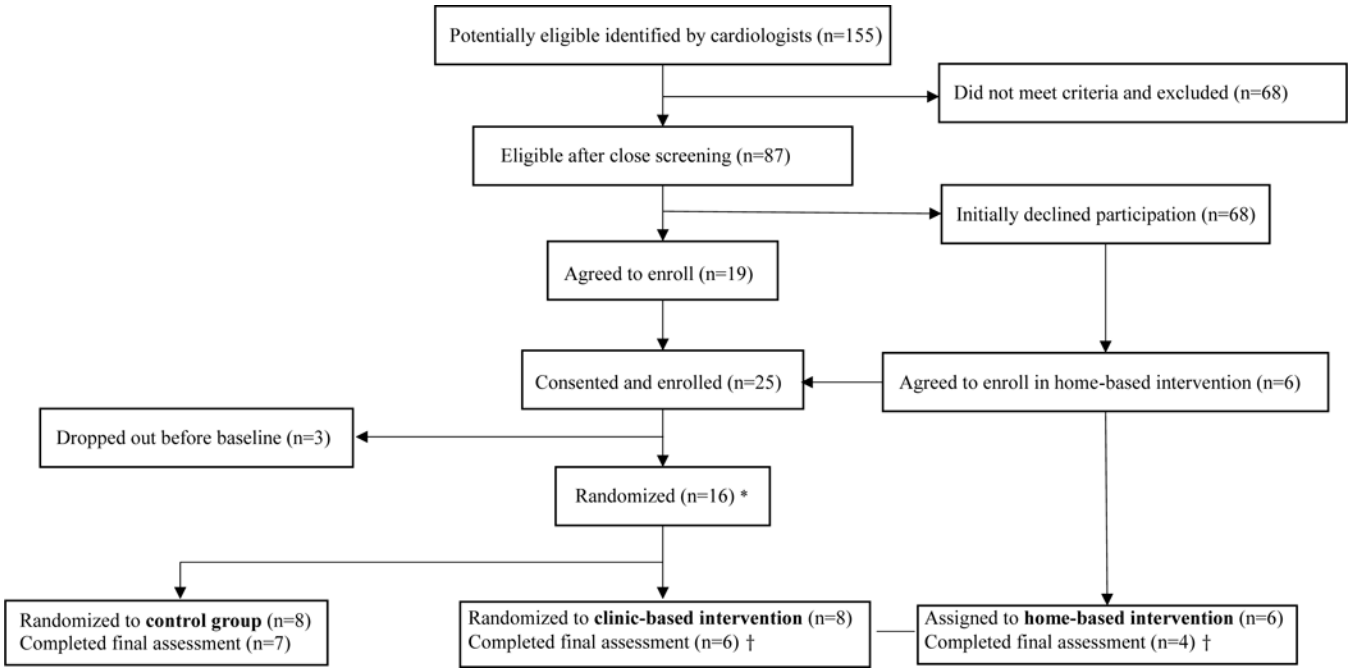

Figure 1.

Study flow diagram

* Only participants agreeing to enroll after first being approached with the randomized study to either a control or clinic-based exercise group were randomized. Participants in the home-based group were directly assigned to this group without being randomized, as they were individuals who refused the randomized study initially, but were offered the chance to still participate by being allowed to directly enroll in a home-based program.

† For purposes of analyses, the clinic-based and home-based group were combined into a single intervention comparison group.

Table 1.

Participant characteristics.

Characteristic		Intervention		Control
		Clinic-based n = 8	Home-based n = 6	n = 8
Gender	Male	0 (0)	1 (17)	2 (25)
	Female	8 (100)	5 (83)	6 (75)
Race	Black/non-Hispanic	3 (38)	3 (50)	2 (25)
	White/non-Hispanic	4 (50)	1 (17)	4 (50)
	Asian/non-Hispanic	0 (0)	1 (17)	0 (0)
	Hispanic	1 (12)	1 (17)	2 (25)
Marital Status	Single	1 (12)	1 (17)	1 (12)
	Married	5 (62)	4 (67)	4 (50)
	Divorced	2 (25)	1 (17)	1 (12)
	Separated	0 (0)	0 (0)	2 (25)
Cancer Site	Breast	5 (62)	4 (67)	5 (62)
	Sarcoma hip/thigh	1 (12)	0 (0)	0 (0)
	Lymphoma	0 (0)	2 (33)	1 (12)
	Multiple myeloma	1 (12)	0 (0)	0 (0)
	Osteosarcoma	0 (0)	0 (0)	0 (0)
	Hodgkin’s disease	0 (0)	0 (0)	1 (12)
	Leukemia	1 (12)	0 (0)	0 (0)
	Tongue	0 (0)	0 (0)	1 (12)
Age (y)	28 – 76	56.1 (10.5)	51.2 (9.5)	55.2 (13.5)
BMI (kg/m^2)	21.4 – 57.4	31.1 (11.4)	30.6 (5.6)	30.2 (5.7)

Abbreviation: BMI, body mass index.

Data are presented as n (%) or range, mean ± SD.

Table 2.

Repeated measures ANOVA for intervention group[†], time, and interaction effects

	Group (n)	Baseline	Follow-Up	Group *P* Value	Time *P* Value	Group by Time *P*-Value
Cardiac Health						
VO_{2max} (mL/kg/min)	Control (7)	14.8 (2.0) 9.4–23.2	14.1 (2.0) 8.4–22.8	0.62	0.98	0.042*
	Intervention (8)	13.5 (1.9) 6.9–17.5	14.3 (2.0) 8.4–29.5			
LVEF (%)	Control (6)	53.3 (3.6) 42.0–62.0	52.8 (3.0) 40.0–62.0	0.17	0.62	0.46
	Intervention (7)	45.0 (3.6) 32.0–58.0	48.0 (3.0) 40.0–58.0			
MDASI-HF						
Symptom severity	Control (6)	30.7 (3.5) 14.0–41.0	33.3 (2.8) 27.0–39.0	0.41	0.18	0.97
	Intervention (10)	27.2 (2.7) 18.0–40.0	30.2 (2.2) 16.0–45.0			
Symptom burden	Control (6)	13.3 (1.9) 4.0–18.0	13.8 (1.4) 11.0–16.0	0.87	0.66	0.91
	Intervention (10)	13.1 (1.5) 7.0–18.0	13.4 (1.1) 7.00–18.0			
Cardiac health	Control (6)	5.00 (1.5) 0.0–12.0	2.83 (1.4) 0.00–6.00	0.22	0.30	0.053
	Intervention (10)	1.40 (1.1) 0.0–4.00	2.10 (1.01) 0.00–11.0			
SF-36						
Physical functioning	Control (8)	37.0 (8.5) 10.0–65.0	53.8 (9.8) 25.0–100	0.17	0.001*	0.15
	Intervention (10)	58.5 (7.6) 20.0–100	66.5 (8.8) 30.0–95.0			
Role functioning	Control (8)	35.9 (8.4) 0.00–68.0	49.2 (10.7) 12.5–100	0.09	0.03*	0.99
	Intervention (10)	57.5 (7.5) 12.5–100	70.6 (9.6) 12.5–100			
CHAMPS						
Total hours	Control (8)	13.7 (3.3) 2.2–35.3	11.4 (2.3) 2.80–21.5	0.25	0.82	0.40
	Intervention (10)	8.03 (3.0) 0.5–21.0	9.38 (2.1) 3.00–21.3			
High intensity hours	Control (8)	4.25 (1.6) 0.0–9.75	4.72 (1.8) 0.00–14.0	0.92	0.60	0.83
	Intervention (10)	3.75 (1.5) 0.0–15.5	4.85 (1.6) 0.00–14.5			

*$P < .05$

†For purposes of analysis, the clinic-based exercise condition was combined with the home-based exercise condition to form a single intervention comparison group.

Data are presented as mean ± SE, range