8-4-2022

Cardiac Rehabilitation Improves Fitness in Patients With Subclinical Markers of Cardiotoxicity While Receiving Chemotherapy: A RANDOMIZED CONTROLLED STUDY

Dennis J. Kerrigan
Henry Ford Health, dkerrig1@hfhs.org

Madhulata Reddy
Henry Ford Health, mreddy1@hfhs.org

Eleanor M. Walker
Henry Ford Health, EWALKER1@hfhs.org

Bernard Cook
Henry Ford Health, bcook10@hfhs.org

James McCord
Henry Ford Health, JMCCORD1@hfhs.org

See next page for additional authors

Recommended Citation

Kerrigan DJ, Reddy M, Walker EM, Cook B, McCord J, Loutfi R, Saval MA, Baxter J, Brawner CA, and Keteyian SJ. Cardiac Rehabilitation Improves Fitness in Patients With Subclinical Markers of Cardiotoxicity While Receiving Chemotherapy: A RANDOMIZED CONTROLLED STUDY. J Cardiopulm Rehabil Prev 2022.

Authors
Dennis J. Kerrigan, Madhulata Reddy, Eleanor M. Walker, Bernard Cook, James McCord, Randa Loutfi, Matthew A. Saval, Jodi Baxter, Clinton A. Brawner, and Steven J. Keteyian

Cardiac Rehabilitation Improves Fitness in Patients With Subclinical Markers of Cardiotoxicity While Receiving Chemotherapy

A RANDOMIZED CONTROLLED STUDY

Dennis J. Kerrigan, PhD; Madhulata Reddy, MD; Eleanor M. Walker, MD; Bernard Cook, PhD; James McCord, MD; Randa Loutfi, MD; Matthew A. Saval, MS; Jodi Baxter, BS; Clinton A. Brawner, PhD; Steven J. Keteyian, PhD

Purpose: Heart failure (HF) due to cardiotoxicity is a leading non–cancer-related cause of morbidity and mortality in cancer survivors. Cardiac rehabilitation (CR) improves cardiorespiratory fitness (CRF) and reduces morbidity and mortality in patients with HF, but little is known about its effects on cardiotoxicity in the cancer population. The objective of this study was to determine whether participation in CR improves CRF in patients undergoing treatment with either doxorubicin or trastuzumab who exhibit markers of subclinical cardiotoxicity.

Methods: Female patients with cancer (n = 28: breast, n = 1: leiomyosarcoma) and evidence of subclinical cardiotoxicity (ie, >10% relative decrease in global longitudinal strain or a cardiac troponin of >40 ng·L^{-1}) were randomized to 10 wk of CR or usual care. Exercise consisted of 3 d/wk of interval training at 60-90% of heart rate reserve.

Results: Cardiorespiratory fitness, as measured by peak oxygen uptake ($\dot{V}O_{2peak}$), improved in the CR group (16.9 + 5.0 to 18.5 + 6.0 mL·kg^{-1} ·min^{-1}) while it decreased in the usual care group (17.9 + 3.9 to 16.9 + 4.0 mL·kg^{-1} ·min^{-1}) (P = .009). No changes were observed between groups with respect to high-sensitivity troponin or global longitudinal strain.

Conclusion: This study suggests that the use of CR may be a viable option to attenuate the reduction in CRF that occurs in patients undergoing cardiotoxic chemotherapy. The long-term effects of exercise on chemotherapy-induced HF warrant further investigation.

Key Words: aerobic exercise training • cancer • cardiotoxicity • global longitudinal strain • high-sensitivity troponin

Author Affiliations: *Division of Cardiovascular Medicine (Drs Kerrigan, Reddy, McCord, Brawner, and Keteyian, Mr Saval, and Ms Baxter) and Department of Pathology (Dr Cook), Henry Ford Hospital, Detroit, Michigan; and Departments of Radiation Oncology (Dr Walker) and Medical Oncology (Dr Loutfi), Henry Ford Cancer Institute at Henry Ford Health System, Detroit, Michigan.*

This study was supported by the Helen L. Key Charitable Trust and the Henry Ford Health System Game on Cancer Fund.

Dr James McCord has received consultant payments from Beckman, Roche, and Siemens, and has research grants as well with those three companies along with Abbott. None of the other authors have conflicts of interest to disclose. All authors have read and approved the article.

Correspondence: *Dennis J. Kerrigan, PhD, Division of Cardiovascular Medicine, Henry Ford Hospital, 6525 Second Ave, Detroit, MI 48187 (Dkerrig1@hfhs.org).*

DOI: 10.1097/HCR.0000000000000719

With approximately 16 million cancer survivors in the United States, more patients are living beyond their initial cancer diagnosis.[1] However, the increased numbers of cancer survivors have created new challenges associated with treatment-related side effects, many of which can impact quality of life long after treatment. Particularly concerning is cancer-related cardiotoxicity (CRC), which is the leading noncancer cause of morbidity and mortality in cancer survivors.[2,3] Although CRC can include cardiac-related disorders such as arrhythmias, acute coronary syndrome, and valvular disorders, the most common form of CRC that interrupts cancer treatment is heart failure (HF) or a decline in left ventricular ejection fraction.[4] Although other factors can contribute to this increased risk (eg, left-sided radiation, pre-existing risk factors), HF due to CRC is often attributed to exposure from the anticancer drugs doxorubicin and trastuzumab.[5,6]

The known risk for HF due to doxorubicin and trastuzumab has led to evidence-based guidelines for the surveillance and detection of cardiac dysfunction.[7] However, uncertainty exists relative to who may or may not develop HF, leading to a delicate balance between withholding these life-saving drugs and possibly increasing the risk of irreversible heart damage. Emerging subclinical markers such as global longitudinal strain (GLS) and high-sensitivity cardiac troponin (hs-cTn) have helped identify patients at increased risk for CRC[8,9] but not on deciding the course of preventative treatment. And while the use of prophylactic HF-specific medications has been proposed, the potential for additional unwanted side effects (eg, fatigue, lightheadedness) may negatively affect patient compliance to these HF drugs and thus limit their efficacy.

Exercise training has shown promise as a strategy to attenuate or improve many cancer-related side effects.[10,11] Specific to cardiotoxicity, preliminary studies involving animals showed cardioprotective benefits of exercise training when exposed to doxorubicin.[12-14] The few studies in humans that have examined the effects of exercise on heart function have involved either mostly younger individuals with few risk factors for cardiovascular disease or have been nonrandomized trials.[15,16] There is, however, a wealth of studies in patients with stable HF of mixed etiologies showing that exercise training can improve exercise capacity and may favorably effect morbidity and mortality.[17-20]

Given the aforementioned text and the increasing evidence for exercise to attenuate certain cancer-related side effects (eg, fatigue), we sought to determine whether cardiac rehabilitation (CR) exercise training could improve both exercise capacity and subclinical markers of CRC in

individuals at risk for chemotherapy-induced HF. Our primary aim was to determine whether CR improves exercise capacity in patients who have exhibited subclinical markers of myocardial damage due to doxorubicin or trastuzumab. We hypothesized that exercise training would increase exercise capacity among these patients.

METHODS

In this randomized controlled trial (ClinicalTrials.gov NCT02796365), we recruited patients on the anticancer therapies doxorubicin and/or trastuzumab within the Henry Ford Health System between June 2016 and December 2018. Eligibility criteria included the ability to exercise, age >18 yr, and a positive subclinical CRC test defined as (1) a recent relative drop in GLS of ≥10%, or (2) a detectable standard cardiac troponin value of ≥40 ng/L. Exclusion criteria included patients with an ejection fraction of <50%, or those with a history of either HF or coronary artery disease. The protocol was reviewed and approved by the Henry Ford Health System Institutional Review Board. All subjects provided written consent.

Following baseline testing, the patients were randomized in a 1:1 fashion to either 10 wk of CR or usual care (UC) (Figure 1). Randomization was conducted using a computer random number generator, with group assignment transferred to allocation cards sealed in opaque sequential envelopes. Staff members who conducted the follow-up testing at 10 wk after baseline were blinded to group assignment.

STUDY MEASURES

After providing written informed consent, the subjects completed the International Physical Activity Questionnaire and Functional Assessment of Cancer Therapy: General (FACT-G) questionnaires to assess physical activity status and self-reported health, respectively. Blood samples were collected using two 8.5-mL lithium heparin tubes: one for immediate analysis using the standard contemporary cTnI assay (Siemens Healthineers), and one stored at −70° C for high-sensitivity hs-cTnI. The ADVIA Centaur high-sensitivity cTnI assay (Siemens Healthineers) was used to measure changes in troponin. This assay meets the requirements for an hs-cTnI assay, as defined by the International Federation of Clinical Applications of Cardiac Bio-Markers and the American Association for Clinical Chemistry Academy.[21]

Global longitudinal strain, which characterizes left ventricular contractile function, was taken at three time points: prior to chemotherapy (T0), at the time subclinical CRC was detected (T1), and 10 wk following randomization (T2) (Figure 1). The relative percent change in GLS was calculated using the T0 measurement as the reference. All subjects had a GLS (which is expressed as a negative number) prior to chemotherapy at T0. A relative reduction of 10% when compared with the pre-treatment echocardiogram (T0) was considered eligible for the study (example GLS at T0 = −20%, GLS at T1 = −17%, relative change −3/−20 = 15% reduction). All echocardiographic testing was done at Henry Ford Hospital by an experienced technician, using a Vivid E9 system (General Electric Company). Digital images were saved and off-line 2D-STE analyses were performed using the ECHOPAC, version 201. For all patients, optimal apical 2D images were obtained with frame rates between 50 and 80 Hz in grayscale. The software did not quantify strain if there was significant heart rate variability. Left ventricular ejection fraction was calculated using the biplane Simpson method. The LV longitudinal strain parameters were measured from the apical four-chamber, two-chamber, and three-chamber views. The region of interest was kept off the blood pool and adjusted to cover at least 90% of the myocardial wall thickness. Global longitudinal strain was reported using the same software (ECHOPAC) on all follow-up studies. Studies were performed and reported according to the document of the European Association of Cardiovascular Imaging/American Society of Echocardiography/Industry Task Force.[22]

Prior to cardiopulmonary exercise testing (CPX), resting heart rate and resting oxygen uptake ($\dot{V}O_2$) were measured during the last minute of 3 min of seated rest. Expired air was sampled breath by breath and analyzed using an MGC Diagnostics metabolic cart. The CPX was performed using the Haskell treadmill protocol (ie, two metabolic equivalents of task increase for every 3-min stage). During the CPX, the patients were encouraged to exercise until reaching a sign or symptom-limited maximum. Gas exchange and heart rate data were reported in 30-sec interval averages. Peak values were the highest interval value during the last minute of exercise or the first interval of recovery. The CPX data were analyzed by the Henry Ford core laboratory using standardized procedures. Core laboratory staff were blinded to treatment group and not involved in the conduct of the CPX.

INTERVENTION

Exercise training was performed at three Henry Ford Health System CR sites in the Detroit Metropolitan area (ie, one urban and two suburban locations). Subjects participated in the phase II CR program offered 2 or 3 d/wk, for 10 wk (30 visits) and had the option to attend CR education lectures on various wellness topics (eg, nutrition, stress management, cardiac medications). Exercise training consisted of interval training protocol with 4-min high-intensity intervals alternated by 3 min of moderate intensity. Exercise intensity was guided using the heart rate reserve method with high intensity set at 71-90% heart rate reserve and moderate intensity at 60-70%. The exercise sessions were 40-50 min of duration and subjects performed one to two exercise modalities (eg, treadmill, stationary cycle, elliptical trainer). A 5-min warm-up and cooldown was performed at the beginning and end of each workout session.

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 any physical

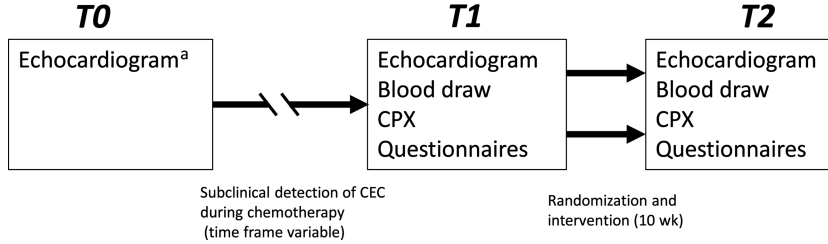

Figure 1. HF PROACTIVE study design. [a]Echocardiogram obtained prior to chemotherapy. Abbreviations: CRC, cancer related cardiotoxicity; CPX, cardiopulmonary exercise test.

activity recommendations. To partially control for patient contact, both groups received a biweekly follow-up call from the research coordinator asking about any changes in health. Untoward events were recorded during biweekly follow-up phone calls by research staff or sent directly via electrical medical records notification (ie, EPIC research alerts).

STATISTICAL ANALYSIS

Utilizing a Per Protocol Analysis, a Student *t* test and the χ^2 test were used to compare groups at baseline for continuous and nominal data, respectively. A paired *t* test was used to assess within-group changes from T1 to T2. An independent sample *t* test was used to compare the differences in change from baseline to follow-up between UC and CR groups. Alpha level was set at .05. All statistical analyses were performed with SPSS version 21.0 (IBM Corp).

RESULTS

As shown in Figure 2, the main reasons candidates were ineligible were due to not being on a cardiotoxic anticancer drug (ie, doxorubicin or trastuzumab), already completed cancer treatment, or did not have a ≥10% relative drop in GLS from the echocardiography done before chemotherapy. Of those who met the eligibility criteria but declined participation, 23% stated concerns regarding the inability to exercise during treatment, while 36% were not available to exercise because of work/schedule conflicts or distance/travel reasons (Figure 2). Baseline characteristics of all participants can be found in Table 1.

The attrition rate between the CR group and the UC group was similar (21% UC vs 27% CR) and was related to health concerns/treatment side effects, work schedule conflicts, or travel/distance concerns. Of those randomized into the CR group, the average attendance rate was 70% of all scheduled visits. Adherence to the high intensity interval training exercise protocol was 59%, based on the percentage of CR sessions where subjects achieved at least one interval within the exercise training heart rate between 70% and 90% of heart rate reserve. Reasons for not reaching the prescribed heart rate reserve include chemotherapy-induced peripheral neuropathy, fatigue, and joint/orthopedic pain. However, despite one-third of the exercise sessions not reaching the prescribed high-intensity zone, in 81% of the CR sessions a heart rate reserve of ≥60% was achieved, which was the minimally prescribed training target.

MEASURES

The effects of exercise training for the CR group are shown in Table 2 and Figures 3 and 4. In general, the CR group showed improvements in CRF as measured by within- and between-group increases in $\dot{V}O_{2peak}$ and within-group improvements for CPX duration and ventilatory threshold. Conversely, the control group showed a within-group decrease in $\dot{V}O_{2peak}$, as well as trends suggesting decreases in exercise time and ventilatory threshold.

The decrease in GLS for the UC group dropped from −21% to −16.7% (20% reduction) and for the CR group changed from −19.3% to −16.4% (15% reduction) (Figure 4). And although both groups showed time-dependent within-group improvements in GLS from T1 to T2, no statistical differences were found between groups. The HscTnI showed a within-group trend toward improvement for the CR group; however, this was not significant and there were no differences between groups ($P = .230$).

Patient-reported quality of life, as defined by the FACT-G questionnaire, showed a trend toward improvement among both the control and CR groups (Table 2); however, there was no significant difference in changes between groups ($P = .556$). No differences were found within or between the subdomains of the FACT-G (ie, functional, physical, social/family, and emotional).

ADVERSE EVENTS

Untoward events were defined as any unexpected condition requiring medical attention, which necessitated a visit

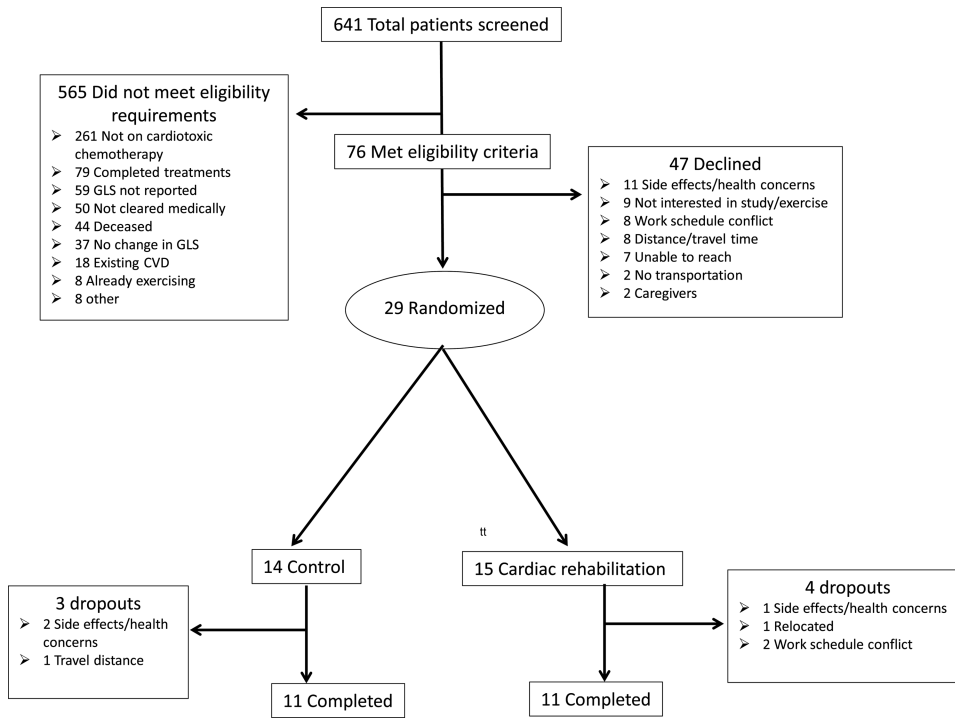

Figure 2. Consort diagram of study participant flow. Abbreviations: CVD, cardiovascular disease; GLS, global longitudinal strain.

Table 1

Demographics[a]

Variable	Treatment	Control	*P* Value
Total, N	11	11	
Age, yr	58 ± 11	52 ± 13	.756
Rest systolic blood pressure, mm Hg	121 ± 13	115 ± 13	.314
Rest diastolic blood pressure, mm Hg	76 ± 8	68 ± 8	.030[b]
Rest heart rate, bpm	71 ± 10	74 ± 13	.599
Body mass index, $kg \cdot m^{-2}$	31 ± 7	34 ± 5	.377
Breast cancer	10 (92)	11 (100)	.702
Cancer stage			
Stage 1	0 (0)	3 (27)	
Stage 2	8 (72)	5 (45)	
Stage 3	2 (18)	2 (18)	
Stage 4	1 (9)	1 (9)	
Ejection fraction, %	62 ± 6	58 ± 3	.100
Global longitudinal strain, %	−16.7 ± 4.0	−16.4 ± 1.6	.809
High-sensitivity troponin, $ng\ L^{-1}$	24.9 ± 43.8	15.6 ± 25.3	.490
Cardiovascular medication			
β-blockers	4 (36)	3 (27)	.647
ACEI/ARBs	6 (55)	4 (36)	.392
Doxorubicin	6 (55)	4 (36)	.201
Trastuzumab	8 (72)	11 (100)	.331

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers.
[a]Data presented as mean ± SD or n (%).
[b]Differences between groups: ≤0.05.

Table 2

Exercise Performance, Patient-Reported Health Status, and Troponin Measures[a]

	Cardiac Rehabilitation		Usual Care		
Characteristic	T1	T2	T1	T2	*P* Value
$\dot{V}O_{2peak}$, $L \cdot min^{-1}$	1.5 ± 0.2	1.6 ± 0.3[b]	1.5 ± 0.3	1.4 ± 0.3	.012[c]
$\dot{V}O_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$	16.9 ± 5.0	18.5 ± 6.0[b]	17.9 ± 3.9	16.9 ± 4.0	.005[c]
Percent-predicted $\dot{V}O_{2peak}$, %	85 ± 15	92 ± 18[b]	85 ± 13	81 ± 10	.004[c]
Ventilatory threshold, $mL \cdot kg^{-1} \cdot min^{-1}$	11.4 ± 3.2	12.5 ± 3.7[b]	12.2 ± 2.1	11.3 ± 1.5	.092
Peak RER	1.15 ± 0.09	1.17 ± 0.08	1.16 ± 0.1	1.21 ± 0.1	.491
VE/VCO_2	33.2 ± 5.6	34.2 ± 4.4	32.7 ± 4.3	31.8 ± 4.1	.141
Peak HR, bpm	150 ± 16	148 ± 19	150 ± 20	150 ± 15	.819
Total exercise time, min	9.1 ± 2.5	11.5 ± 4.3[b]	9.6 ± 2.2	10.1 ± 2.7	.060
FACT-G	82.6 ± 11.6	86.2 ± 14.4	72.4 ± 11.7	79.6 ± 13.6	.556
High-sensitivity troponin, $ng \cdot L^{-1}$	24.6 ± 43.8	13.9 ± 14.9	15.6 ± 25.3	27.1 ± 60.8	.211

Abbreviations: FACT, Functional Assessment of Cancer Therapy—General; HR, heart rate; RER, respiratory exchange ratio; VE/VCO_2, slope of the ratio of minute ventilation to carbon dioxide; $\dot{V}O_2$, oxygen uptake.
[a]Data are presented as mean ± SD.
[b]Differences within groups ≤0.05.
[c]Differences between groups: ≤0.05.

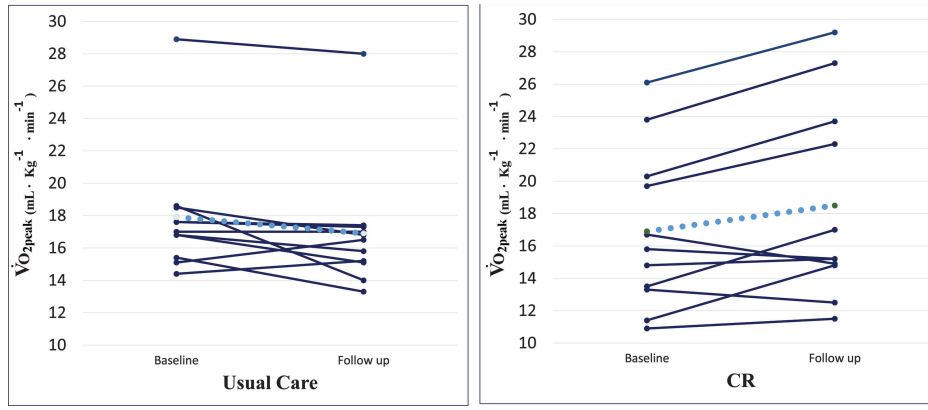

Figure 3. Individual $\dot{V}O_{2peak}$ changes over 10 wk. Dotted lines indicate group mean. Abbreviation: CR, cardiac rehabilitation. This figure is available in color online (www.jcrpjournal.com).

to a physician or the emergency department. None of the patients, regardless of study assignment, were admitted to the hospital during this study. Furthermore, aside from adjusting workload and/or exercise modality due to fatigue or neuropathy pain, no exercise session was stopped because of an untoward event. A total of six non–exercise-related untoward events were recorded (three in each group). The nature of these events was as follows: for the control group, these included hypokalemia, dermatitis, and dehydration; for the CR group, this included a near syncopal episode, an urinary tract infection, and a fall at home.

DISCUSSION

This study supports the utilization of CR to perform exercise training in patients exposed to cardiotoxic cancer treatments and is the first to our knowledge to demonstrate improvement of $\dot{V}O_{2peak}$ among individuals with early signs and symptoms of cardiotoxicity. The improvement of $\dot{V}O_{2peak}$ in the CR group is potentially important because of the known association with mortality and poor CRF[23]; thus, increases in CRF may reduce the risk of HF as well as other CV events.

The lack of improvement observed for the GLS (Figure 4) may be due to several factors including the timing of the intervention, the sensitivity of these tests, and/or the length of the training stimulus itself. Regarding the timing of the exercise intervention, it may be that exercise training prior to exposure to the toxic agent (ie, the so-called "pre-hab") might have more of an impact with respect to the GLS and troponin values. This is supported by Chicco et al,[12] who showed that exercise training performed before doxorubicin exposure in rats attenuated the loss in left ventricular function observed in the control group.

The relatively short length of the training as well as the follow-up may be another reason why no difference was found between groups. A recent study by Ansund et al[24] found that NT-pro-BNP levels were improved at 1-yr follow-up in a group of individuals who self-selected to participate in high-intensity interval training.

Alternatively, a reason why cardiopulmonary fitness improved independent of GLS or troponin is that the observed improvements with exercise training might be a result of peripheral adaptations (eg, improved capillary density, aerobic enzymes, and mitochondria density). This is supported in studies showing a discordance between $\dot{V}O_{2peak}$ and left ventricular function.[25,26]

Furthermore, there is potential concern that exercise while actively undergoing cardiotoxic chemotherapy may

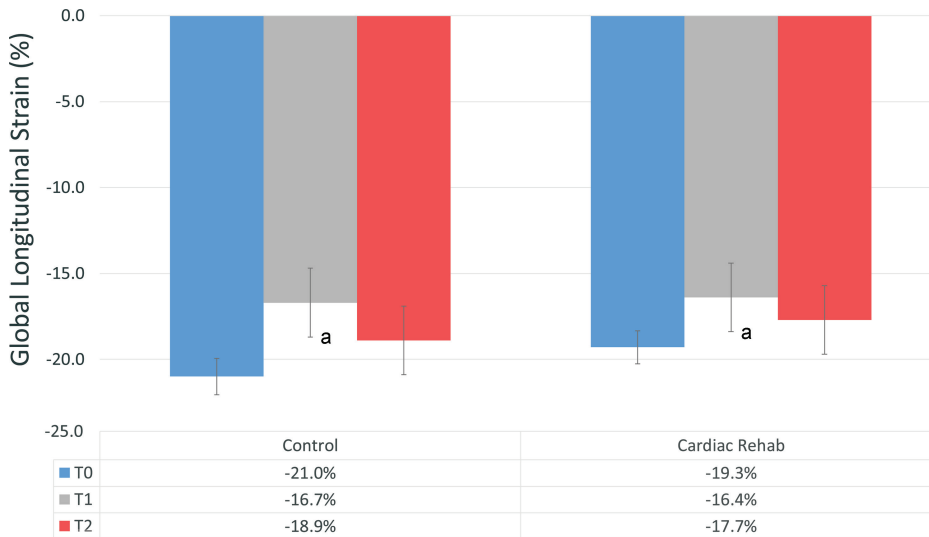

Figure 4. Change in global longitudinal strain. [a]Differences within groups ≤ 0.05. This figure is available in color online (www.jcrpjournal.com).

be detrimental to the heart. This is supported by an observational study by Haykowsky et al[16] reporting a modest, but significant, reduction in left ventricular ejection fraction in patients while exercise training during treatment with trastuzumab. Despite that finding, we did not observe any decrease in cardiac function with exercise training.

In addition to the direct effects of cancer-related cardiotoxicity, there is growing interest with respect to the greater downstream heart disease risk in patients with cancer.[27,28] Because exercise training has been shown to improve many CV risk factors, it has been promoted to potentially mitigate heart disease in the cancer population. The barrier, however, that many patients, and referring oncologists, face is that there are not very many cancer-specific exercise programs in the country. However, the existing network of CR programs can help bridge this gap, providing them with facilities and staff in a scalable fashion to meet the growing demands of an increasing survivorship population. Our study demonstrated from a feasibility standpoint that CR can fill that need.

The strengths of this study were that we had a clearly defined higher-risk cohort, it was a randomized controlled trial, and that the exercise training was supervised by clinical exercise physiologists in an evidence-based setting (ie, CR). Potential limitations to this study include the small sample size, the short duration of training (10 wk), the short follow-up period (ie, 3 mo), and perhaps the transient nature of these biomarkers, which often trend back to normal as the time increases from the insult to the myocardium. In addition, the small number of patients with elevated troponins at baseline may have been a large contributing factor to why no differences were observed between groups.

In conclusion, our study suggests that CR is potentially a viable pathway to improve exercise capacity in patients undergoing treatment with known cardiotoxic agents. Future studies should include a larger number of participants across multiple health locations and have a longer follow-up period.

REFERENCES

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289.
2. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25, pt A):2751-2768.
3. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. *CA Cancer J Clin*. 2016;66(4):309-325.
4. Yu AF, Moskowitz CS, Lee Chuy K, et al. Cardiotoxicity surveillance and risk of heart failure during HER2 targeted therapy. *JACC CardioOncol*. 2020;2(2):166-175.
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(36):2768-2801.
6. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*. 2012;104(17):1293-1305.
7. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35(8):893-911.
8. De Iuliis F, Salerno G, Taglieri L, et al. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. *Tumour Biol*. 2016;37(3):3379-3387.
9. Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *Am J Cardiol*. 2011;107(9):1375-1380.
10. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25(28):4396-4404.
11. Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical activity and cancer outcomes: a precision medicine approach. *Clin Cancer Res*. 2016;22(19):4766-4775.
12. Chicco AJ, Hydock DS, Schneider CM, Hayward R. Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity. *J Appl Physiol (1985)*. 2006;100(2):519-527.
13. Dickinson JM, D'Lugos AC, Mahmood TN, et al. Exercise protects skeletal muscle during chronic doxorubicin administration. *Med Sci Sports Exerc*. 2017;49(12):2394-2403.
14. Kirkham AA, Eves ND, Shave RE, et al. The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: a RCT. *Breast Cancer Res Treat*. 2018;167(3):719-729.
15. Howden EJ, Bigaran A, Beaudry R, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. *Eur J Prev Cardiol*. 2019;26(3):305-315.
16. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res*. 2009;15(15):4963-4967.
17. Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. *J Am Coll Cardiol*. 2012;60(16):1521-1528.
18. Flynn KE, Lin L, Ellis SJ, et al. Outcomes, health policy, and managed care: relationships between patient-reported outcome measures and clinical measures in outpatients with heart failure. *Am Heart J*. 2009;158(4 suppl):S64-S71.
19. Keteyian SJ, Leifer ES, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol*. 2012;60(19):1899-1905.
20. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail*. 2018;20(12):1735-1743.
21. Wu AHB, Christenson RH, Greene DN, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem*. 2018;64(4):645-655.
22. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr*. 2015;28(2):183-193.
23. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.
24. Ansund J, Mijwel S, Bolam KA, et al. High intensity exercise during breast cancer chemotherapy—effects on long-term myocardial damage and physical capacity—data from the OptiTrain RCT. *Cardiooncology*. 2021;7(1):7.
25. Kraemer MD, Kubo SH, Rector TS, Brunsvold N, Bank AJ. Pulmonary and peripheral vascular factors are important determinants of peak exercise oxygen uptake in patients with heart failure. *J Am Coll Cardiol*. 1993;21(3):641-648.
26. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. *Circulation*. 1988;78(3):506-515.
27. Gilchrist SC, Barac A, Ades PA, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation*. 2019;139(21):e997-e1012.
28. Shultz AM, Squires RW, Shin JY, Durani U, Pophali PA. Cardio-Oncology Rehabilitation (CORE) exercise prescription and programming. A practical guide. *J Cardiopulm Rehabil Prev*. 2021;41(5):341-344.