The effect of an aerobic exercise bout 24 hours prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: a RCT

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Abstract

Purpose: In rodents, a single exercise bout performed 24 hours prior to a single doxorubicin treatment provides cardio-protection. This study investigated whether performing this intervention prior to every doxorubicin treatment for breast cancer reduced subclinical cardiotoxicity and treatment symptoms.

Methods: Twenty-four women with early stage breast cancer were randomly assigned to perform a 30-minute, vigorous-intensity treadmill bout 24 hours prior to each of four doxorubicin-containing chemotherapy treatments or to usual care. Established echocardiographic and circulating biomarkers of subclinical cardiotoxicity, as well as blood pressure and body weight were measured before the first and 7-14 days after the last treatment. The Rotterdam Symptom Checklist was used to assess patient-reported symptoms.

Results: The exercise and usual care groups did not differ in the doxorubicin-related change in longitudinal strain, twist, or cardiac troponin. However, the four total exercise bouts prevented changes in hemodynamics (increased cardiac output, resting heart rate, decreased systemic vascular resistance, $p<0.01$) and reduced body weight gain, prevalence of depressed mood, sore muscles, and low back pain after the last treatment ($p<0.05$) relative to the usual care group. No adverse events occurred.

Conclusions: An exercise bout performed 24 hours prior to every doxorubicin treatment did not have an effect on markers of subclinical cardiotoxicity, but had a positive systemic effect on hemodynamics, musculoskeletal symptoms, mood, and body weight in women with breast cancer. A single exercise bout prior to chemotherapy treatments may be a simple clinical modality to reduce symptoms and weight gain among women with breast cancer.

Keywords: doxorubicin, breast cancer, cardiotoxicity, exercise, treatment symptoms

Introduction

The anthracycline chemotherapy agents doxorubicin and epirubicin are important components of third generation breast cancer regimens [1]. Despite their antineoplastic effects, anthracyclines are associated with dose-related, potentially irreversible cardiotoxicity defined as a drop in left ventricular ejection fraction (LVEF) of 10 percentage points to <53% [2], among other severe treatment symptoms [3]. Markers of anthracycline-related subclinical cardiotoxicity that predict a drop in LVEF or development of cardiotoxicity (defined as a >10 percentage point drop in LVEF to below the lower limit of normal) include a deterioration in left ventricular (LV) longitudinal strain and twist or elevated levels of cardiac troponin [4, 5]. Anthracycline-related cardiac injury may be an important contributor to increased risk of cardiovascular-related death among breast cancer survivors [6].

A substantial body of preclinical evidence demonstrates that various volumes of aerobic exercise mitigate doxorubicin-related myocardial injury [7]. In two studies in rodents, a single 60-minute bout of vigorous-intensity treadmill running performed 24 hours prior to doxorubicin treatment completely prevented or attenuated deleterious changes in systolic and diastolic cardiac function, as well as markers of cardiomyocyte oxidative stress, mitochondrial dysfunction, and apoptotic signaling [8, 9]. In breast cancer patients, we reported the acute effect of a single 30-minute, vigorous-intensity treadmill walking bout performed 24 hours prior to the first doxorubicin treatment [10]. Relative to usual care, the exercise bout resulted in a significant attenuation of the circulating biomarker that is prognostic for anthracycline-related cardiac injury and events, NT-proBNP, and a 46% absolute risk reduction of this biomarker exceeding a clinical cut-point for overt acute heart failure. The exercise bout also resulted in a small but

significant improvement from pre-chemotherapy in LVEF and longitudinal systolic strain rate, suggesting increased systolic function.

The purpose of this study was to elucidate the clinical relevance of a single exercise session 24 hours prior to doxorubicin treatment by determining the cumulative effect of performing this intervention prior to every doxorubicin treatment received by breast cancer patients. The primary aim was to investigate the effect of this intervention on established markers of subclinical cardiotoxicity at the end of treatment. It was hypothesized that the exercise intervention would attenuate the change in LV longitudinal strain and twist, as well as increased circulating cardiac troponin as compared to usual care. The secondary aim was to investigate another important aspect of the clinical utility of this intervention, namely, whether it could also reduce patient-reported treatment symptoms.

Methods

Design and participants

This study was a randomized controlled trial (clinicaltrails.gov NCT02006979) where participants were allocated with a 1:1 ratio, stratification by age ≥50/<50, and random block sizes of four and six, to perform a supervised exercise bout 24 hours prior to each doxorubicin treatment or to usual care without supervised exercise. The randomization sequence was generated by a spreadsheet random function by a party external to the study, and implemented with sequentially numbered envelopes. We previously reported the acute effect of one bout of exercise on cardiac function and biomarkers [10], and here we present the cumulative effects of one exercise bout prior to every treatment on cardiac function, biomarkers, treatment symptoms, as well as other descriptive variables throughout chemotherapy treatment in the same cohort. As acute changes with a single chemotherapy treatment (i.e. within 24-48 hours) may differ from those occurring 7-14 days after completion of several treatments, the analyses of cardiac function

and biomarkers were performed separately. We recruited English or Chinese-speaking adult women with stage I-III breast cancer who were scheduled to receive doxorubicin-containing chemotherapy and were able to complete the baseline assessment prior to their first treatment. In order to isolate the effect of our acute intervention and minimize confounding factors in this first-in-man proof-of-concept trial, exclusion criteria were conditions that may be associated with abnormal baseline cardiac function or increased risk of developing anthracycline cardiotoxicity. Patients were excluded if they were current smokers, unable to perform sustained exercise, had a body mass index (BMI) >35 kg/m^2 or history of cardiovascular disease, previously received anthracyclines, trastuzumab, or thoracic radiation, or were concurrently enrolled in studies involving exercise training or pharmacological cardio-protection. Patients reporting a history of hypertension, diabetes, or respiratory disease were only included if they self-reported that the conditions were well controlled over the past year (i.e. stable blood pressure <140/90 mmHg, glycemic control, or dyspnea). This study was approved by the Clinical Research Ethics Board of the University of British Columbia and was performed in accordance with the Declaration of Helsinki. Participants provided written informed consent.

Descriptive variables

Demographics, diagnosis and treatment information were self-reported at baseline. Baseline physical activity habits were assessed as the average weekly moderate-to-vigorous minutes of physical activity (MVPA) over the previous six months [11]. Height and weight were measured at baseline and the end of the study. Doxorubicin dose received and hemoglobin levels pre- and post-treatment were extracted from clinical records.

Intervention

Participants randomized to the exercise group completed a supervised treadmill bout approximately 24 hours (within a 22-26 hour window) prior to each doxorubicin treatment. The session consisted of a 10-minute warm-up, 30 minutes at a vigorous intensity (70% of age-predicted [12] heart rate reserve (HRR)), and a 5-minute cool-down. Resting heart rate (HR) used to calculate the target HR was measured prior to each session following five minutes of quiet, seated rest. For the 30 minutes of exercise, average HR was recorded, and participants reported a rating of perceived exertion (RPE).

Both the exercise and the usual care control groups were asked to abstain from vigorous-intensity aerobic exercise for 72 hours prior to, and 48 hours after each treatment. Vigorous-intensity exercise was described as "aerobic exercise where your heart is beating rapidly, you are sweating a fair amount, and are breathing hard." In alignment with current exercise guidelines for cancer survivors [13], participants were free to perform light or moderate-intensity exercise at any time. MVPA for the week prior to and after each treatment was obtained using the Godin Leisure Time Exercise Questionnaire [14]. Participants were asked whether exercise was performed during the 72 hours prior to and the 48 hours after each treatment to determine compliance.

Outcome measures

Echocardiograms and circulating biomarkers were obtained 0-14 days prior to the first (baseline) and 7-14 days after the last doxorubicin treatment. The primary outcome measures were LV longitudinal strain, twist, and cardiac Troponin T (cTnT) based on their sensitivity in detecting subclinical anthracycline-related cardiotoxicity [4, 5]. NT-proBNP was not a primary outcome as it is most sensitive in the acute setting for anthracycline treatment.

Resting two-dimensional transthoracic echocardiograms (Vivid i Ultrasound, 3S-RS 2.0-3.6 MHz probe, GE Healthcare, Mississauga, ON) were performed according to current guidelines [15]. A certified cardiac sonographer, who was blinded to group assignment, acquired images from the parasternal and apical views with patients in the left lateral decubitus position. Images were acquired at 80 fps with depth and focal point standardized within each participant. A single trained investigator performed all analyses blinded on Echopac Version 112 (GE Healthcare, Mississauga, ON). All values were averaged over three cardiac cycles.

LV dimensions and wall thicknesses were acquired from the parasternal long axis view to calculate LV mass using the linear method [15]. The modified Simpson's Biplane method was used to assess LV volumes and ejection fraction (LVEF). E/A ratio was measured from pulsed wave Doppler at the tips of the mitral valve leaflets. Longitudinal strain was measured in the apical 4-chamber view using 2D speckle tracking. Basal and apical rotation were measured in the apical short-axis view at the levels of the mitral leaflets and distal to the papillary muscles at the level proximal to luminal obliteration [16], respectively. Twist was calculated as the difference between peak apical and basal rotation. Poorly tracking segments (determined via visual inspection) were excluded with ≥4 segments retained. Custom-made software was used for the strain analysis (2D Strain Analysis Tool, Stuttgart, Germany), where cubic spline interpolation was used to produce 600 data points each for systolic and diastolic periods [17].

Resting HR was measured from the ultrasound electrocardiogram during acquisition of the apical 4-chamber image after ≥10 minutes of rest. Blood pressure was measured after ≥20 minutes of supine rest by manual auscultation as the average of two measurements 60-seconds apart. Systemic vascular resistance (SVR) was calculated as: 80*(mean arterial pressure /cardiac output).

cTnT and NT-proBNO were measured by the TroponinT high-sensitive short-turnaround-time proBNP II electrochemiluminescence sandwich immunoassays, respectively (Roche Diagnostics, Laval, Quebec).

The Rotterdam Symptom Checklist [18] was administered at the baseline and end of treatment assessments, as well as the day prior to the 2^{nd}-4^{th} treatments in reference to symptoms since the prior treatment. Standardized physical and psychological distress scores were calculated. The prevalence of individual symptoms was calculated after the last treatment only to capture the greatest cumulated symptoms.

Statistical analyses

Independent t-tests or the Mann-Whitney U test were used to compare age, anthropometrics, hemoglobin, as well as all MVPA measures between groups. Generalized linear mixed model analyses were otherwise used based on the longitudinal study design and ability to model between-subject variance and non-normally distributed residuals. The model terms included participant as a random effect, time as a repeated term and fixed effect, group as a fixed effect, and a group*time interaction. For significant interactions, contrasts were used to assess differences over time within each group and between groups at baseline and follow-up. In order to not miss real effects, these constrasts were performed on non-significant interactions for variables that are potentially explanatory for other significant effects noted. This practice is recommended when there is biological relevance of a potential difference between the treatment and control groups [19]. For the Rotterdam Symptom Checklist standardized scores, contrasts were performed between groups at each time point. As an exploratory analysis, prevalence of individual symptoms was compared between groups after the last treatment using chi-squared tests. SPSS Version 24.0 (IBM Corporation, Armonk, NY) and $p \leq 0.05$ were used.

The effect size used for sample size calculation was estimated as the weighted average of the effect sizes from six previously published studies measuring longitudinal strain before and within 1 month after anthracycline treatment of a similar dose (~240 mg/m^2) for similar early breast cancer populations [20-25]. Pre and post chemotherapy longitudinal strain were used to calculate effect size for each study. To acquire 80% power to detect the average effect size (Cohen's f=0.59) at α=0.05 with a repeated measures (2 repetitions), between factor design, n=20 total (randomized to one of two groups) is required (G*Power version 3.0.10, Düsseldorf, Germany). This effect size assumes that the intervention would result in complete prevention of the deterioration in longitudinal strain. In the preclinical versions of this study, the exercise bout completely prevented or attenuated the various doxorubicin-related changes measured. Therefore, an additional 33% were recruited (n=27 total) to account for the potential for partial (rather than complete) prevention of the change in strain, as well as withdrawal and imaging quality.

Results

Participants

Twenty-seven participants enrolled in the study between June 2013 and March 2016 (Figure 1). One usual care participant became ineligible after not receiving any anthracycline treatment and was excluded. One participant each in the usual care and exercise groups withdrew immediately prior to and after completion of the baseline assessment, respectively. The latter participant who withdrew after the baseline assessment was excluded because carrying the baseline values through to follow-up was not appropriate given the expected change with chemotherapy, leaving n=13 in the exercise and n=11 in the usual care groups. Longitudinal strain was not measurable at follow-up due to image quality in one participant in the usual care group.

Participant characteristics are described in Table 1. All participants were prescribed 240 mg/m^2 of doxorubicin and 2400 mg/m^2 of cyclophosphamide over four treatments. No participants received trastuzumab during the study. Five participants (two usual care, three exercise) received four paclitaxel treatments prior to doxorubicin. The end of treatment assessment was performed 9.9±2.3 and 11.5±4.7 days after the last doxorubicin for the usual care and exercise groups, respectively (p=0.31). One exercise group assessment was delayed to 25 days due to hospitalization for an acute infection.

At baseline, there were no differences between groups in weight, height, BMI, average MVPA in the previous six months, or hemoglobin (Table 2). Weight gain at end of treatment was significantly higher in the usual care group relative to the exercise group (p=0.03) (Table 2). The reduction in hemoglobin over time was not different between groups (p=0.30). There were no differences between groups in MVPA performed during the week prior to or after each treatment (Table 2). One participant in the exercise group reported performing one vigorous exercise session 48 hours prior to one treatment, but otherwise participants reported compliance with the study protocol.

Exercise bouts

For the 52 prescribed exercise bouts, there was 100% attendance; 94% adherence to timing (24±2 hours before treatment) for an average timing of 23.9±1.1 hours; 83% adherence to intensity (average heart rate was within 3 bpm of target heart rate) for an average intensity of 71±3% HRR and RPE of 13±1; and 98% adherence to duration. No adverse events occurred.

Cardiac function and hemodynamics

There were no differences between groups at baseline. The primary outcome markers of subclinical cardiotoxicity did not differ by group over time (Table 3). Regarding change from

baseline to end of treatment in both groups together, longitudinal strain and twist did not change, while cTnT and NT-proBNP significantly increased ($p<0.05$). The change in cardiac output over time differed between groups ($p=0.05$), where it increased significantly in the usual care ($p<0.01$) but not in the exercise group (Table 3). Resting HR, mean arterial pressure, and SVR all increased with time (all $p<0.01$), but based on the group difference in the related cardiac output variable, the post hoc contrasts were explored. The increase in resting HR and decreases in both SVR and mean arterial pressure were significant for the usual care group (all $p<0.01$) but not for the exercise group (Table 3). There were no significant changes for LV mass, LVEF, LV volumes, or E/A ratio. The change in systolic and diastolic pressure over time did not differ by group, but decreased in both groups together ($p<0.01$, $p=0.02$).

Patient-reported symptoms

There were no significant differences between groups in the standardized scores of physical or psychological distress at baseline or following any treatments. For individual symptoms after the last treatment, the exercise group was less likely to have depressed mood ($p=0.05$), sore muscles ($p=0.02$), or low back pain ($p=0.04$), but more likely to have lack of appetite ($p=0.05$) relative to usual care (Table 4).

Discussion

Based on the cardio-protective benefits of a single vigorous-intensity aerobic exercise session performed 24 hours prior to a single doxorubicin treatment demonstrated in rodents [8, 9], we investigated whether this intervention had a cumulative effect in humans when performed prior to every treatment. Our hypothesis that this intervention would attenuate negative changes in longitudinal strain, twist, and cTnT was not supported. However, there was an effect of the intervention on cardiovascular hemodynamics, namely cardiac output, systemic vascular

resistance, mean arterial pressure, and resting HR, as well as body weight, and prevalence of four patient-reported symptoms.

There was no effect of the intervention on longitudinal strain, a consistent marker of subclinical cardiotoxicity [4], nor twist, which has also shown preliminary promise for prediction of cardiotoxicity [23, 26, 27]. Furthermore, in contrast to all previous observational studies of adults receiving anthracycline treatment [4, 23], both parameters did not change over time. A potential explanation for this discrepancy may relate to the LV afterload dependency of longitudinal strain and twist [28, 29]. Baseline systolic and diastolic blood pressures were substantially lower and the magnitude of reduction during treatment was greater in the current study compared with previous studies. Blood pressure lowering medications taken concurrent to cardiotoxic treatments have been shown to prevent subclinical cardiotoxicity [30, 31]. Of note in the current study, only one participant in each group was on blood pressure medication at baseline. It is plausible that the participants in the current study were protected from deterioration in longitudinal strain and twist (and also LVEF) by either their low baseline blood pressure or the reduction in blood pressure that occurred during treatment, or both. The cause of the reduction in blood pressure is unknown, but could be exercise-related, as the selection bias of enrolling in an exercise study may mean that participants in both groups performed more exercise on their own throughout chemotherapy than participants in an observational study.

Similarly, there was no intervention effect on cTnT, but there was an overall significant increase at end of treatment. The mechanism of cTnT release following anthracycline treatment is not fully understood [5], but it would appear that the exercise intervention did not mitigate this response. Although measurement of the circulating biomarker NT-proBNP 24 hours following anthracycline treatments has prognostic utility [32, 33], a single measurement >1 week after

completion of treatment has generally not been an important predictor of cardiotoxicity or clinical events [34, 35]. Despite this, NT-proBNP was assessed in the current study to standardize outcomes across time points with our previous work and was also not affected by the intervention.

While we hypothesized, based on the available literature, that the exercise intervention would have cardio-protective effects, the cumulative benefits when performed across the duration of treatment were systemic. Specifically, the cumulative effects included prevention of the increase in cardiac output, resting HR, and body weight, and the decrease in SVR that occurred in the usual care group, as well as reduced prevalence of depressed mood, sore muscles, and low back pain. The increased cardiac output and decreased SVR that occurred in the usual care group are expected responses to anemia or reduced hemoglobin [36]. We did not measure resting oxygen consumption, but it is not known to increase with chemotherapy [37]. Therefore, the absence of increased cardiac output in the exercise group despite the same reduction in hemoglobin suggest improved oxygen extraction capacity of skeletal muscle. Indeed, improved skeletal muscle metabolism is a hypothesized mechanism for the prevention of exercise intolerance by exercise training during cancer treatment [38]. Increased skeletal muscle metabolism could also help to explain the changes in body weight [39] and reduced prevalence of muscle-related symptoms [40] occurring in the exercise group. Future research is planned to explore a potential effect of this intervention on skeletal muscle metabolism to help explain these systemic effects.

The elevation of resting HR that occurred in the usual care group only has been shown to remain years after chemotherapy treatment for breast cancer survivors relative to healthy controls [41], and is prognostic of cardiovascular events and mortality in non-cancer populations [42].

Resting HR can be used as a rough indicator of autonomic balance between sympathetic and parasympathetic nervous system activations [42]. Although resting HR is also influenced by several nonautonomic factors, the changes in cardiac output and systemic vascular resistance in the usual care group, which are also regulated by autonomic balance, provide further support for a potential autonomic-mediated protective effect. Furthermore, moderate-to-high intensity aerobic exercise three times/week during anthracyclines treatment also prevented elevation of resting HR in breast cancer patients [43]. Although likely acting through differing mechanisms, these findings together provide proof-of-principle that targeted aerobic exercise can positively impact resting HR in women with breast cancer.

The weight gain occurring with usual care is common during breast cancer treatment, and is linked to increased risk of recurrence and worse survival [44]. Although exercise training is an effective tool to prevent weight gain [44], the weight reduction in the exercise group of the current study was unexpected given that the intervention consisted of only four supervised exercise bouts across 6-9 weeks. A potential explanation is that the increased prevalence of lack of appetite that occurred in the exercise group (which is a well-documented effect of acute exercise [45]), contributed to their weight loss. Other speculative explanations for the difference in weight are that fluid status or health habits (e.g., nutritional intake quality) differed between groups. However, because differences in weight gain were not expected, we did not collect any data related to hydration status, edema, blood volume, or health habits other than physical activity that might help to explain this speculation. While this finding is of interest, it will need to be confirmed by additional studies, ideally with assessment of the composition of associated weight changes (i.e., fat vs. lean mass).

A key implication of this study was translating the benefits of an exercise intervention observed in preclinical work into a clinical model feasible for adoption within clinical care. We chose a lower dose of exercise than the preclinical models that would be feasible for sedentary women to perform while receiving chemotherapy treatment. A single exercise session the day before the next treatment may be an ideal exercise format, as patients are often scheduled for medical oncology appointments that day, and may feel their best symptom-wise. Therefore, this type of exercise programming may be more palatable to both cancer treatment centers and patients than that requiring multiple visits per week. While the exercise prescription was feasible as indicated by excellent adherence, and had positive systemic and patient-reported effects, the intervention failed to elicit a cumulative positive effect on markers of subclinical cardiotoxicity. Follow-up studies on cardio-protection could consider a more potent acute exercise stimulus (i.e., higher dose). Further evaluation of potential effects of the current prescription on systemic markers is also warranted.

Strengths of the current study include investigation of a novel and clinically feasible intervention for cancer patients via a RCT design with high fidelity to the research protocol. Limitations include small sample size, multiple statistical comparisons, and potential selection bias.

In summary, this study demonstrated that while performing a 30-minute, vigorous-intensity, aerobic exercise bout 24 hours prior to each doxorubicin treatment was feasible and safe, there was no effect on markers of subclinical cardiotoxicity. The cumulative invention effects were systemic rather than localized to the heart, including prevention of changes in hemodynamics, and importantly from a patient perspective, prevention of body weight gain and reduced prevalence of depressed mood, sore muscles and low back pain.

Financial support: This work was supported by an Anita Cochrane Memorial Fund Award from the British Columbia Cancer Foundation. AK was supported by the Canadian Institutes of Health Research. We also acknowledge the support of GE Healthcare.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

All experiments complied with the current laws in the country in which the study was performed.

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Table 1: Study participant demographics and cancer diagnosis and treatment characteristics

	Total n=24	Usual care n=11	Exercise n=13
Age (years) (mean±SD)	50±9	50±10	51±9
Menopausal status n (%)			
Pre-menopausal	8 (33%)	4 (36%)	4 (31%)
Post-menopausal	10 (42%)	6 (55%)	4 (31%)
Peri-menopausal	6 (25%)	1 (9%)	5 (38%)
Ethnicity (n (%))			
Caucasian	18 (75%)	7 (64%)	11 (85%)
Asian	5 (21%)	3 (27%)	2 (15%)
Other	1 (4%)	1 (9%)	0
Marital status (n (%))			
Married/common-law	16 (67%)	8 (73%)	8 (62%)
Divorced/separated/widowed	3 (13%)	2 (18%)	1 (8%)
Single	5 (21%)	1 (9%)	4 (31%)
Education (n (%))			
Bachelor's degree or above	15 (63%)	5 (45%)	10 (77%)
Below Bachelor's degree	9 (37%)	6 (55%)	3 (23%)
Comorbid conditions (n (%))			
Angina	1 (4%)	0	1 (8%)
Diabetes	1 (4%)	1 (9%)	0
Asthma	4 (17%)	2 (18%)	2 (15%)
Arthritis	4 (17%)	0	4 (31%)
Hypertension	2 (8%)	1 (9%)	1 (8%)
Dyslipidemia	0	0	0
Medications (n (%))			
Thyroid replacement	4 (17%)	1 (9%)	3 (23%)
Statin	3 (13%)	1 (9%)	2 (15%)
Calcium channel blocker	1 (4%)	0	1 (8%)
Beta-blocker	1 (4%)	1 (9%)	0
Metformin	1 (4%)	1 (9%)	0
ACE-inhibitor	0	0	0
Angiotensin receptor blocker	0	0	0
Stage (n (%))			
I	4 (17%)	3 (27%)	1 (8%)
II	12 (50%)	5 (45%)	7 (54%)
III	8 (33%)	3 (27%)	5 (38%)
Treatment type (n (%))			
Three-week protocol	5 (21%)	1 (9%)	4 (31%)
Dose dense protocol	19 (79%)	10 (91%)	9 (69%)
Adjuvant	16 (67%)	7 (64%)	9 (69%)
Neoadjuvant	8 (33%)	4 (36%)	4 (31%)
Dose reductions (n (%))	3 (13%)	2 (18%)	1 (8%)
Doxorubicin dose (mean±SD mg/m^2)	236±10	234±12	238±8

Abbreviations: ACE = angiotensin converting enzyme; n = sample size; SD = standard deviation

Table 2: Body size and physical activity

Variable	Usual care	Exercise	p-value
Baseline body mass index (kg/m^2)	26.7±5.1	25.0±4.8	0.19
Height (cm)	165±6	167±6	0.13
Weight (kg)			
Baseline	72.2±12.7	69.7±11.7	0.35
Change	0.8±3.3	-2.1±3.3	0.03*
Hemoglobin (g/dL)			
Baseline	12.7±1.1	13.0±1.0	0.33
Change	-2.5±1.5	-2.3±1.0	0.30
	median (min, max)	median (min, max)	
6-month average MVPA (minutes/week)	124 (0, 701)	214 (0, 619)	0.78
7-day MVPA (minutes)			
Post cycle 1	0 (0, 225)	0 (0, 200)	0.19
Pre cycle 2	0 (0, 450)	60 (0, 350)	0.49
Post cycle 2	0 (0, 180)	0 (0, 120)	0.53
Pre cycle 3	20 (0, 420)	50 (0, 240)	0.91
Post cycle 3	0 (0, 630)	0 (0, 180)	0.78
Pre cycle 4	0 (0, 465)	60 (0, 350)	0.57
Post cycle 4	0 (0, 600)	0 (0, 200)	0.83

Abbreviations: cm = centimeter; kg = kilogram; m = meter; MVPA = moderate-to-vigorous physical activity; SD = standard deviation

Table 3: Cardiac function, circulating biomarkers, and hemodynamics. All baseline data has been previously reported [10]

Parameter	Group	Baseline	End of treatment	Interaction p-value	Time p-value
Longitudinal strain (%)	Usual care	-19.6±1.9	-20.3±1.6	0.15	0.76
	Exercise	-19.2±1.9	-18.7±1.4		
Twist (°)	Usual care	16.4±5.9	15.6±6.6	0.94	0.63
	Exercise	16.4±7.6	15.7±6.5		
Cardiac troponin T (pg/mL)	Usual care	1.5±2.3	11.6±8.3	0.12	<0.01*
	Exercise	1.3±2.1	13.6±11.2		
NT-proBNP (pg/mL)	Usual care	59±35	77±39	0.08	<0.01*
	Exercise	52±30	106±78		
Resting HR (bpm)	Usual care	69±12	75±10 [a]	0.46	<0.01*
	Exercise	69±11	73±9		
Systolic blood pressure (mmHg)	Usual care	102±12	93±9	0.73	<0.01*
	Exercise	102±12	95±11		
Diastolic blood pressure (mmHg)	Usual care	63±12	59±9	0.83	0.03*
	Exercise	62±10	59±9		
Mean arterial blood pressure (mmHg)	Usual care	76±11	70±8	0.68	<0.01*
	Exercise	75±10	71±9		
Systemic vascular resistance (dynes·sec·cm^{-5})	Usual care	2074±514	1630±207 [a]	0.08	<0.01*
	Exercise	1933±445	1771±320		
LVEF (%)	Usual care	58±3	58±3	0.56	0.95
	Exercise	57±4	57±4		
End-diastolic volume (mL)	Usual care	77±10	80±14	0.25	0.93
	Exercise	83±17	80±14		
End-systolic volume (mL)	Usual care	33±6	33±7	0.74	0.96
	Exercise	36±9	35±8		
Stroke volume (mL)	Usual care	44±6	47±8	0.05	
	Exercise	47±9	45±7		
Cardiac output (L/min)	Usual care	3.0±0.5	3.5±0.5 [a]	0.05	
	Exercise	3.2±0.6	3.3±0.4		
E/A ratio	Usual care	1.27±0.32	1.10±0.25	0.08	0.42
	Exercise	1.20±0.37	1.26±0.37		
LV mass (g)	Usual care	124±25	131±27	0.56	0.32
	Exercise	120±22	122±23		

*Significant main effect for time at $p \leq 0.05$

[a] Significantly different from baseline with pairwise contrast at $p \leq 0.05$

Data are mean±SD. Abbreviations: bpm = beats per minute; cm = centimeter; HR = heart rate; LV = left ventricular; LVEF = left ventricular ejection fraction; mL = milliliter; mmHg = millimeters of mercury; ms = millisecond; m/s = meters per second; pg = picogram; sec = second;

Table 4: Prevalence of symptoms following the last (fourth) doxorubicin treatment

	Total n=24	Usual care n=11	Exercise n=13	p-value*
Physical Symptoms				
Lack of appetite	14 (58%)	4 (36%)	10 (77%)	0.05*
Tiredness	23 (96%)	10 (91%)	13 (100%)	0.27
Sore muscles	11 (46%)	8 (73%)	3 (23%)	0.02*
Lack of energy	23 (96%)	10 (91%)	13 (100%)	0.27
Low back pain	8 (33%)	6 (55%)	2 (15%)	0.04*
Nausea	19 (79%)	8 (73%)	11 (85%)	0.48
Difficulty sleeping	19 (79%)	9 (82%)	10 (77%)	0.77
Headaches	14 (58%)	6 (55%)	8 (62%)	0.73
Vomiting	5 (21%)	2 (18%)	3 (23%)	0.77
Dizziness	8 (33%)	5 (46%)	3 (23%)	0.25
Abdominal aches	13 (54%)	6 (55%)	7 (54%)	0.97
Constipation	14 (58%)	6 (55%)	8 (62%)	0.73
Diarrhea	10 (42%)	5 (46%)	5 (39%)	0.73
Acid indigestion	17 (71%)	6 (55%)	11 (85%)	0.11
Shivering	10 (42%)	5 (46%)	5 (39%)	0.73
Tingling hands or feet	9 (38%)	6 (55%)	3 (23%)	0.11
Sore mouth/pain when swallowing	14 (58%)	7 (64%)	7 (54%)	0.63
Loss of hair	12 (50%)	7 (64%)	5 (39%)	0.22
Burning/ sore eyes	14 (58%)	7 (64%)	7 (54%)	0.63
Shortness of breath	15 (63%)	8 (73%)	7 (54%)	0.34
Dry mouth	18 (75%)	9 (82%)	9 (69%)	0.48
Pyschological Symptoms				
Depressed mood	10 (42%)	7 (64%)	3 (23%)	0.05*
Nervousness	9 (38%)	6 (55%)	3 (23%)	0.11
Worrying	17 (71%)	7 (64%)	10 (77%)	0.48
Irritability	16 (67%)	8 (73%)	8 (62%)	0.56
Despairing about the future	8 (33%)	5 (46%)	3 (23%)	0.25
Decreased sexual interest	12 (50%)	6 (55%)	6 (46%)	0.68
Tension	13 (54%)	4 (36%)	9 (69%)	0.11
Anxiety	15 (63%)	8 (73%)	7 (54%)	0.34
Difficulty concentrating	18 (75%)	8 (73%)	10 (77%)	0.81

* Indicates significant difference in prevalence between groups

Figure legends:

Fig. 1 Participant flow through study: 48 patients were both screened and eligible, 27 (56%) enrolled, and 24 (89%) completed the study