

BMJ Open Effects of high-intensity interval training on vascular function in breast cancer survivors undergoing anthracycline chemotherapy: design of a pilot study

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ABSTRACT

Introduction Cardiovascular disease (CVD) mortality is higher among breast cancer survivors (BCS) who receive chemotherapy compared with those not receiving chemotherapy. Anthracycline chemotherapy is of particular concern due to anthracycline-related impairment of vascular endothelial cells and dysregulation of the extracellular matrix. One strategy proven to offset these impairments is a form of exercise known as high-intensity interval training (HIIT). HIIT improves endothelial function in non-cancer populations by decreasing oxidative stress, the main contributor to anthracycline-induced vascular dysfunction. The purpose of this pilot study is to assess the feasibility of an 8-week HIIT, as well as the HIIT effects on endothelial function and extracellular matrix remodelling, in BCS undergoing anthracycline chemotherapy.

Methods and analysis Thirty BCS are randomised to either HIIT, an 8-week HIIT intervention occurring three times per week (seven alternating bouts of 90% of peak power output followed by 10% peak power output), or delayed group (DEL). Feasibility of HIIT is assessed by (1) the percentage of completed exercise sessions and (2) the number of minutes of exercise completed over the course of the study. Vascular function is assessed using brachial artery flow-mediated dilation and carotid intima media thickness. Extracellular matrix remodelling is assessed by the level of matrix metalloproteinases in the plasma. A repeated-measures analysis of covariance model will be performed with group (HIIT and DEL group) and time (pre/post assessment) as independent factors. We hypothesise that HIIT will be feasible in BCS undergoing anthracycline chemotherapy, and that HIIT will improve endothelial function and extracellular matrix remodelling, compared with the DEL group. Success of this study will provide evidence of feasibility and efficacy to support a larger definitive trial which will impact cancer survivorship by decreasing anthracycline-induced vascular dysfunction, thereby benefiting cardiovascular markers that are related to CVD risk.

Ethics and dissemination This trial was approved by the University of Southern California Institutional Review Board (HS-15-00227).

Trial registration number NCT02454777; Pre-results.

Strengths and limitations of this study

- This manuscript presents that high-intensity interval training (HIIT) is a novel exercise strategy for breast cancer survivors undergoing anthracyclines since lower volumes of HIIT compared with higher volumes of moderate continuous intensity exercise elicit better cardiovascular outcomes such as endothelial function and maximal oxygen uptake.
- Given the barrier of compliance of breast cancer survivors to regular exercise participation, HIIT is an intriguing time-efficient alternative to traditional endurance-based exercise training for preventing cardiovascular side effects induced by anthracycline chemotherapy.
- Another strength of the proposed study is our focus on measuring vascular function using ultrasound imaging, as well as molecular approaches in measuring matrix metalloproteinases; these measurements allow to identify whether HIIT can be used to improve extracellular matrix remodelling by targeting matrix metalloproteinases in breast cancer survivors undergoing treatment with anthracyclines.
- Although this study will provide the first evidence of HIIT targeting vascular function in breast cancer survivors undergoing anthracycline chemotherapy, it is possible that we may demonstrate that endothelial function is maintained and not worsened during the HIIT intervention when compared with the delayed group.
- We recognise that poor adherence is a possibility given the time and effort needed to participate in an intervention study, in particular while undergoing anthracycline chemotherapy.

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of mortality in women diagnosed with early-stage breast cancer; breast cancer survivors (BCS) have 1.8-fold increased risk of CVD mortality in comparison with age-matched counterparts.^{1,2} BCS undergoing

chemotherapy are at even greater risk for CVD mortality.³ BCS who receive chemotherapy have a 1.7-fold increased risk of CVD mortality than those who receive only radiotherapy and endocrine therapy.¹ In particular, anthracyclines, used in the treatment of early and advanced stage breast cancer, have negative cardiovascular consequences, including increased risk for coronary heart disease and heart failure.^{4,5} Despite the potential cardiotoxicity, anthracyclines lead to higher survival and lower recurrence compared with non-anthracycline chemotherapy such as cyclophosphamide, methotrexate and fluorouracil.⁶

While the exact mechanisms by which anthracyclines cause cardiovascular dysfunction are still unknown, it is plausible that anthracyclines-induced oxidative stress may be responsible for endothelial dysfunction.⁷ Anthracyclines' major mechanism of action is intercalation, in which the anthracycline inserts itself and binds to the DNA structure of a cell, inhibiting replication of cancer cells.⁸ During anthracycline intercalation, oxidative stress is caused by the increased production of reactive oxygen species (ROS), which disrupts the regulation of nitric oxide, a major vasodilator.⁹ The bioavailability of nitric oxide is reduced due to anthracycline-generated ROS that scavenge the nitric oxide. This aspect of vascular endothelial dysfunction results in reduced brachial artery flow-mediated dilation (baFMD) and thickening of the carotid intima media (cIMT), both of which can be assessed via ultrasound imaging.¹⁰ Reduced baFMD and increased cIMT are evident in patients with CVD, including hypertension, stroke and heart failure.^{11–13} Oxidative stress further increases damage in the extracellular matrix (ECM), which structurally supports surrounding endothelial cells.¹⁴ ECM surrounding endothelial cells is mainly regulated by matrix metalloproteinases (MMPs). In particular, MMP-2 and MMP-9 are overactivated by ROS during anthracycline intercalation; this is another pathway contributing to endothelial dysfunction and thickening of the arterial wall by degrading the connective tissue and basement membrane.^{15–17} For example, anthracyclines markedly increased the activity of MMP-2 and MMP-9 in the carotid artery and peripheral blood following 8 weeks of treatment in rats.¹⁸

Exercise is a safe and cost-effective strategy targeting many health outcomes (ie, cardiorespiratory fitness and endothelial function) in BCS,¹⁹ and therefore is a candidate to offset cancer treatment side effects given the burden of pharmaceutical treatments experienced by BCS in 8 weeks.^{20–22} The benefits of exercise in BCS are well established, and include improvements in physical function, quality of life and activities of daily living.^{23,24} Exercise promotes vascular shear stress, which decreases oxidative stress,²⁵ and thereby increases endothelial function measured by baFMD in CVD populations.^{26,27} High-intensity interval training (HIIT) is an exercise strategy that maximises exercise intensity by using bursts of concentrated effort alternated with active recovery periods.²⁸ HIIT allows patients to perform vigorous-intensity exercise due to the 'on-off' pattern of

exercise. The 'on' portion of HIIT typically lasts 1–4 min performed at 80%–90% of peak power output (PPO) or maximum heart rate (MHR), followed by the 'off' period of 1–3 min active break (10% PPO, or 40%–50% to 60% of MHR).²⁹ HIIT is a clinically proven, safe and cost-effective intervention in patients with stroke or heart failure.^{29–32} This strategy has been shown to be more effective than moderate continuous intensity aerobic exercise for improving endothelial function among healthy adults and patients with CVD.^{19,30,33} Overall, HIIT is a time-efficient exercise strategy that successfully increases endothelial function measured by baFMD in patients with severe CVD, such as coronary heart disease,¹⁹ heart failure³⁴ and stroke,³⁰ without serious adverse events. Therefore, HIIT may have the capacity to improve endothelial function and atherosclerosis in BCS who are undergoing anthracycline chemotherapy. While the benefits of HIIT have been investigated on cancer-related fatigue^{29,35} and health-related quality of life³⁶ in patients with cancer, there is no specific evidence demonstrating the feasibility of HIIT in BCS undergoing anthracycline chemotherapy. Further, novel aspects of our exercise programme design warrant an assessment of feasibility. Specifically, the prescribed HIIT intensity in our pilot study is based on PPO, which differs from previous studies which quantified intensity using the predicted MHR³⁷ or ratings of perceived exertion.³⁵

Objectives

This pilot study was designed to determine the feasibility of an 8-week HIIT intervention in BCS undergoing anthracycline chemotherapy. We hypothesise that an 8-week HIIT exercise intervention will be a feasible exercise training approach, whereby more than 50% of patients randomised to the HIIT intervention are able to complete an average of 70% (63/90 min) of total prescribed weekly minutes of exercise and >70% (17/24 sessions) of total exercise sessions. Our second aim is to investigate the effect of an 8-week supervised HIIT intervention on endothelial function. We hypothesise that an 8-week HIIT exercise intervention will increase baFMD compared with the delayed (DEL) group. Lastly, we seek to investigate the effect of an 8-week HIIT exercise intervention on ECM remodelling measured as levels of MMPs. We hypothesise that an 8-week HIIT exercise intervention will improve circulating plasma MMP-2 and MMP-9, compared with the DEL group.

METHODS AND ANALYSIS

Experimental design

Participants are recruited from the breast cancer clinics at the Norris Comprehensive Cancer Center (NCCC) and the Los Angeles County Medical Center. Our recruitment strategy is to closely collaborate with our medical oncology team. Specifically, when the patients come for their medical oncology appointment, they are informed about the study by the medical staff including medical

oncologists, fellow, nurse or the principal investigator (PI), with the PI on hand at all clinic times to ensure successful screening and consent of eligible participants. Following informed consent and determination of eligibility at the screening visit, eligible and consenting participants complete their baseline test at the Integrative Center for Oncology Research in Exercise (ICORE) within 1–2 weeks prior to the start of the intervention period in a 1:1 ratio of allocation. Participants are randomly assigned using computer-generated, investigator-blinded randomisation to the HIIT group or the DEL group. Participants randomised to the HIIT group visit the ICORE to complete three exercise sessions for a total of 90 min of weekly exercise during the 8-week intervention period. Participants randomised to the DEL group are asked to maintain their current level of physical activity, which should not exceed 30 min of total structured exercise per week. All participants return to the ICORE within 1 week following completion of the 8-week study period for post-testing. Outcome measures are obtained at baseline within 1 week prior to the first cycle of anthracyclines (week 0), at week 9, within 2–5 days from the last exercise session, and week 17 (8 weeks following poststudy assessment) (figure 1).^{22 38}

Study status

Study enrolment, intervention and data collection are ongoing.

Patient and public involvement

Patients or the public were not involved in the development of the research question, study design and recruitment process.

PARTICIPANTS

Eligibility criteria

Participants who meet the following requirements are eligible: (1) women ≥ 18 years of age diagnosed (stages I–III) with a first primary invasive breast cancer; (2) receiving (neo)adjuvant anthracycline; (3) able to initiate exercise programme within 1–2 weeks of initiation of chemotherapy; (4) less than 30 min of physical activity per week; (5) non-smokers in the previous 12 months; (6) willing to travel to the exercise facility at the University of Southern California (USC); and (7) able to provide physician clearance to participate in the exercise programme. The following are the exclusion criteria: (1) history of chronic disease including diabetes, uncontrolled hypertension or thyroid disease; (2) weight reduction $\geq 10\%$ within the past 6 months; (3) metastatic disease; (4) overt CVD (myocardial infarction, stroke, angina); (5) contraindications to exercise; and (6) participation in regular exercise defined as greater than 30 min exercise per week screened by medical oncologist and PI and/or participation in other lifestyle interventions such as psychosocial or diet interventions.

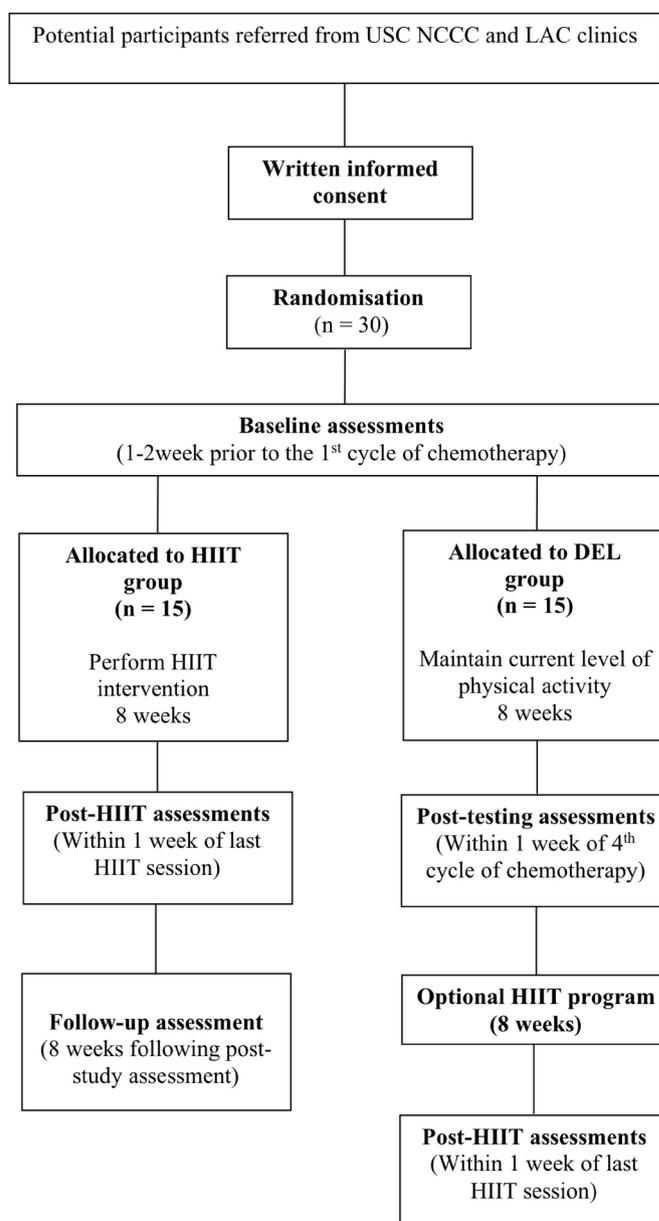


Figure 1 Study flow. DEL, delayed; HIIT, high-intensity interval training; LAC, Los Angeles County Hospital; NCCC, Norris Comprehensive Cancer Center; USC, University of Southern California.

Recruitment strategy

We aim to recruit roughly three participants per month based on the estimated number of eligible patients who visit the breast clinics at USC; thus, we anticipate reaching the targeted sample size within 10 months. Recruitment occurs primarily at the Los Angeles County Hospital and the USC NCCC Breast Cancer Clinic via onsite recruitment by the PI. Eligible patients scheduled for anthracycline are informed about the study at their medical oncology appointments to ensure successful screening and consent of eligible participants. Oncologists inform the PI when eligible participants who are interested in participating are identified. Interested participants are informed of the study details by the PI and patient eligibility is confirmed.

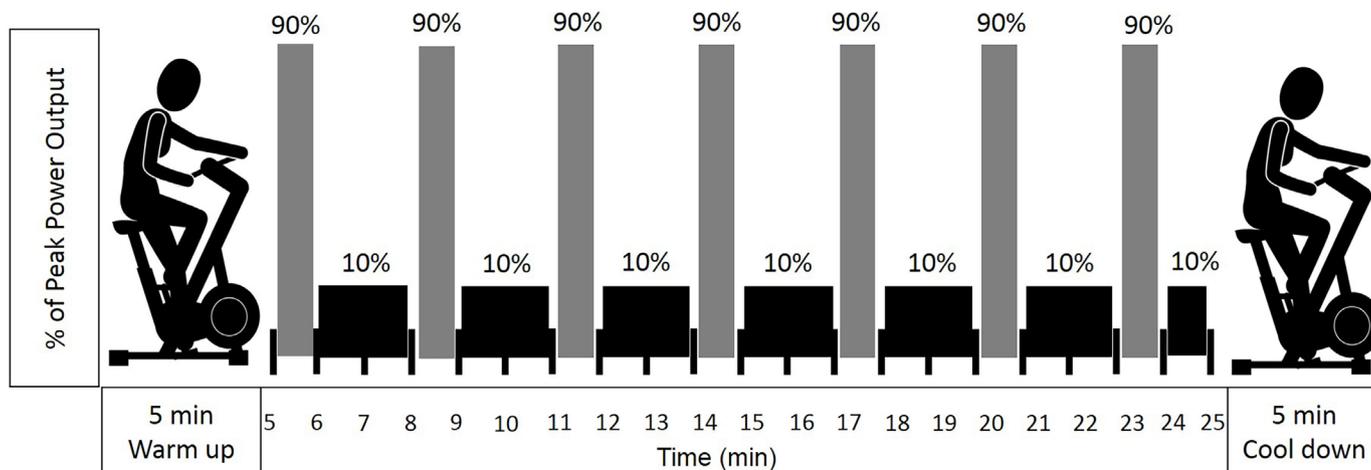


Figure 2 Sample high-intensity interval training intervention per session. Grey bars indicate high-intensity intervals at 90% peak power output and black bars indicate the 2 min active rest interval at 10% peak power output.

The conversation between the PI and the potential participants takes place in a private room at the hospital. Written informed consent is obtained prior to study procedures.

Intervention

The HIIT protocol includes seven bouts of 1 min high-intensity exercise followed by 2 min of active recovery (figure 2). A similar protocol was used by Boyne *et al*,³⁰ who reported that HIIT significantly improved endothelial function in patients with chronic stroke compared with moderate aerobic exercise. All exercise sessions are supervised by the PI, a certified exercise trainer, are performed on a stationary bike and take place at USC ICORE. Based on peak PPO measured by a maximal oxygen uptake (VO_2max) fitness test, exercise intensity is individually prescribed for HIIT intensity. Each session consists of a 5 min warm-up performed at 10% PPO followed by a 21 min HIIT stimulus (90% PPO/10% PPO) and 5 min cool-down (10% PPO).³⁰ The HIIT bouts consist of seven 1 min high-intensity intervals performed at 90% PPO followed by a 2 min low-intensity recovery interval performed at 10% PPO for the 21 min HIIT duration.

Participants are encouraged to complete each exercise session with one full day of rest in between sessions, and are completed on days when participants have not received anthracyclines infusion. If a participant prefers to perform two or three consecutive sessions in a given week (vs one session every other day) due to anthracyclines-induced side effects (eg, fatigue), this is documented on the exercise session form and the number of consecutive sessions in a week is counted. Power output, heart rate, rating of perceived exertion (Borg Scale of 6–20) and the total minutes of exercise completed are documented during each exercise session for each interval. Participants are encouraged to make up any missed sessions in the same week or during a 2-week make-up period (extending the intervention period to 10 weeks if needed), and have the ability to schedule their exercise sessions at days and times convenient for

the participants alongside their individual treatment schedule. The DEL group is asked not to initiate a structured exercise programme during the first 8 weeks of the study period and to maintain their current level of physical activity (<30 min of total structured exercise per week). During this time the DEL group is asked to document their weekly physical activity on exercise logs. Following the first 8 weeks of intervention, the DEL group is provided the same HIIT intervention.

OUTCOMES

All outcome assessments (table 1) are performed by the PI.

Feasibility

Overall feasibility of HIIT is assessed using the average weekly exercise completion (min/week) of all participants in the HIIT group. Perceived limitations of enrolment in a previous study were lack of interest, too far to travel and too busy.³⁹ Chemotherapy-induced fatigue can be another barrier to adherence. Thus, the HIIT programme is considered feasible if more than 50% of patients randomised to the given condition are able to complete 70% (63/90 min) of prescribed weekly exercise (17/24 sessions).⁴⁰ This method of feasibility was set forth based on previous studies in BCS that reported the adherence of exercise intervention ranges from 68% to 80%. Particularly, exercise adherence is lower in the studies which included cancer survivors undergoing chemotherapy, whereas higher adherence was reported in cancer survivors who completed cancer treatment.³⁹ If at least half of the participants do not complete an average of 70% of the weekly exercise time, the exercise intervention is not classified as feasible. In the event that a participant is not able to complete the entire exercise session, the number of minutes (out of 30 min) completed during each exercise session is documented.

Table 1 Study visit timeline and assessment

	Preintervention (visit 1) Week 0-a HIIT and DEL groups	Preintervention (visit 2) Week 0-b HIIT and DEL groups	Intervention (HIIT only) (visits 3–27; HIIT only) Weeks 1–8	Post-testing (visit 28) Week 9 HIIT and DEL groups	Intervention (DEL only) (visits 4–28) Weeks 10–17	Follow-up testing (visit 29) Week 17 HIIT and DEL groups
Eligibility/informed consent/randomisation	X					
Height, weight, body mass index		X		X		X
Blood draw		X		X		X
Body compositions		X		X		X
Blood pressure/heart rate		X		X		X
baFMD/cIMT		X		X		X
Cardiopulmonary fitness		X		X		X
Questionnaires		X		X		X

baFMD, brachial artery flow-mediated dilation; cIMT, carotid intima media thickness; DEL, delayed; HIIT, high-intensity interval training.

Arterial wall thickening: cIMT

After a 12-hour fast and abstinence from alcohol, caffeine and vitamins, arterial wall thickening is evaluated measuring cIMT. Participants lie in the supine position on the plinth to non-invasively image common carotid arteries (left and right) using B-mode ultrasound (GE LOGIQ e). The ultrasound scan is used to measure the lumen diameter, intima media thickness, and the presence and extent of carotid plaques. Large interventional studies have shown that cross-sectional cIMT is positively associated with CVD risk including stroke.^{41 42} To measure cIMT, the carotid bifurcation is detected as a reference; a region of interest (ROI) is identified by the far (posterior) arterial wall along a 10 mm section proximal to the carotid bifurcation (the average value of three measurements). Using autodetection software developed by GE Healthcare, an ultrasound calliper automatically detects the ROI (where a bright-dark bright pattern corresponds to the intima media adventitia layers of the arterial walls).⁴³ This autodetection technique provides an accurate measure of the cIMT and reduces the subjectivity of manual approaches by detecting the cIMT throughout the artery length, rather than using only a few points of cIMT (intraclass correlation coefficient of repeated measurements over a week: 0.95).⁴³

Endothelial function: baFMD

Following carotid ultrasonography for cIMT measurement, endothelial function is evaluated using baFMD while the participant is in the supine position. A rapid inflation and deflation blood pressure cuff is positioned on the contralateral arm from mastectomy or lumpectomy immediately distal to the antecubital fossa to provide a stimulus to forearm ischaemia, 1 cm below the antecubital fossa.⁴⁴ If the participant had bilateral surgery, the study oncologist determines which arm to test. A 10 MHz multifrequency linear array probe, attached to a high-resolution ultrasound machine (GE LOGIQ e), is used to

image the brachial artery in the distal third of the upper arm. A single-lead ECG recording is obtained concurrently during acquisition of brachial artery images. The B-mode image of the brachial artery and Doppler images of flow are recorded for 20 s at baseline (P0). Extravascular landmarks are identified and labelled to assure that the imaged segment of the brachial artery is reproduced within and across participants. After baseline images, the cuff is inflated to 250 mm Hg for 5 min.⁴⁵ Following limb ischaemia, there is a rapid increase in forearm blood flow, which slowly returns to baseline values, and is termed reactive hyperaemia. Digitised images of the brachial artery are captured continuously for 30 s before cuff inflation and for 5 min following cuff release, to document the endothelial-dependent vasodilator response. baFMD is calculated from the brachial artery diameter at baseline (D0) and 1 min after cuff deflation (D1). baFMD is the percentage change of brachial artery diameter 1 min after cuff deflation relative to the baseline (baFMD=100 × (D1–D0)/D0).⁴⁵

ECM remodelling: MMP analyses

A fasting venous blood sample is drawn by a licensed phlebotomist, separated into plasma and serum to be stored at –80°C until later processing. MMP-2 and MMP-9 are assessed, as well as other CVD risk-related MMPs (MMP-1, MMP-7, MMP-10 and MMP-14) and tissue inhibitor of matrix metalloproteinases (TIMP-1 and TIMP-2). MMPs and TIMPs are processed using the MagPlex suspension bead array immunoassays on a Luminex 100 Bioanalyzer (Luminex 100, Luminex Corporation, Austin, Texas) according to the kit manufacturer's instructions (Milliplex ELISA kits, Millipore, Massachusetts) by the USC Metabolic Assay Core. Briefly, 50 mL plasma samples are incubated with fluorokine-coloured microspheres coated with specific antibodies, and analytes are allowed to bind to the specific antibody-coated microspheres, as previously described.⁴⁶ Samples are then washed and

incubated with biotinylated antibodies and phycoerythrin-conjugated streptavidin. Finally, fluorescence is detected using a flow cytometry technique (Luminex 100, Luminex Corporation). Although we do not target the activity of TIMPs, the concentration of TIMPs is used to conduct a sensitivity analysis of the ratio of MMPs/TIMPs, which represents a single value of MMPs at the global proteolytic balance.⁴⁷ All samples are assayed in duplicate wells (25 μ L per well), and the mean of these results is used. MMP concentrations are calculated by reference to an eight-point spline fit curve. We store additional blood samples for future analysis of biomarkers related to insulin sensitivity.

ADDITIONAL OUTCOMES

Cardiorespiratory fitness

All participants complete a baseline cardiorespiratory fitness test (week 0) using a maximal effort cycling protocol to measure VO_2max , used in order to prescribe the relative exercise intensity.^{48 49} The specific protocol comprises a 10W increase in workload every 1min, starting at 40W. This testing is performed with standard equipment for indirect calorimetry (Parvo Medics, Salt Lake City, Utah) in an incremental protocol until exhaustion (respiratory exchange ratio >1.10 , heart rate $\pm 10/\text{min}$ predicted MHR, ratings of perceived exertion 17; in 6–20 ratings) on a recumbent bike. Before the fitness test is performed, participants are familiarised with the testing protocol using standardised verbal instructions indicating the duration of each stage, maintaining the same RPM throughout the test, and increases of torque during the test. Participants are instructed on proper pedalling, high-intensity and low-intensity periods, with a resistance corresponding to 10%–20% of PPO and a pedal rate of 60 RPM.⁵⁰ Following this testing, PPO is obtained at the last stage of maximal cycling testing, and the PPO is used to prescribe the intensity of HIIT.

Body composition

Body compositions (lean body mass and fat mass) are measured using an InBody 770 bioelectrical impedance scale (Biospace, Cerritos, California). These measures will be used as possible covariates and to determine if the improvement in vascular function is independent of body composition. Participants are scanned using standard imaging and positioning protocols recommended by the manufacturer. Body mass index in kg/m^2 is calculated from height and weight measurements using a medical scale (Detecto 437, Webb City, Missouri).

Lifestyle measures

These are obtained using validated questionnaires at baseline, 8-week postintervention and 16-week follow-up, and include the following: International Physical Activity Questionnaire, 3Day Dietary Recall, Functional Assessment of Cancer Therapy-Breast and Functional Assessment of Cancer Therapy-Fatigue.

DATA SAFETY AND MONITORING

All data are securely managed by the PI and are regularly monitored by the USC NCCC Data and Safety Monitoring Committee. This ensures the safety of participants, validity of data, appropriate termination of study, evaluation of the current accrual relative to the planned total accrual, examination of all reported protocol violations and review of past audits. The safety of the exercise intervention is assessed and documented on the participant's exercise training chart by study personnel by recording of adverse events. Adverse events are identified at every exercise session and testing time point. Serious adverse events (events resulting in hospitalisation) are reported within 24 hours to research governance committees (Institutional Review Boards and Data and Safety Monitoring Committee).

SAMPLE SIZE

Data from this pilot trial will provide estimates of group means, SDs and group differences for use in designing a larger definitive efficacy. With a sample size of 30 subjects (15 per group) in this pilot study, we are able to estimate the means for our outcome variables (within either group of 15) with a 95% CI of ± 0.51 SD units. At a two-sided alpha level of 0.05, we are able to estimate treatment group difference in the outcome means with a 95% CI of ± 0.72 SD units. Since this study is conducted as a pilot study, it is designed to inform feasibility and provide estimates of intervention effects.

RANDOMISATION

Once the patient has signed the informed consent and trial eligibility is confirmed, participants are randomly assigned by computer-generated, investigator-blinded randomisation assignments; randomisation is stratified by neoadjuvant versus adjuvant anthracyclines treatment in a 1:1 allocation ratio by the Clinical Investigation Support Office at USC NCCC. To prevent potential bias, study personnel do not have access to the randomisation list.

DATA MANAGEMENT

Data are collected in a confidential format on paper charts and case report forms that are stored securely before and after being entered electronically into the secure web-based Research Electronic Data Capture application (REDCap, Vanderbilt University).

STATISTICAL ANALYSIS

Feasibility of this study will be assessed using descriptive statistics (percentage of protocol-specified sessions and minutes completed). Paired t-tests will be used to evaluate the differences before and after intervention in each group. Repeated-measures ANOVA on the trial outcomes

will use a 2 (group: HIIT, DEL) \times 2 (time: preintervention, postintervention, follow-up intervention) analysis. In a secondary analysis, participant baseline characteristics that are different across groups will be included as covariates in the statistical analyses with a repeated-measures analysis of covariance model. Residual analyses will be performed to test whether the assumptions of the model were met. If the residuals do not meet the assumptions (ie, linearity, homoscedasticity and normality), data transformations will be performed.

DISCUSSION

Within clinical settings, HIIT is traditionally prescribed using predicted MHR or ratings of perceived exertion in previous clinical settings.^{33 37 51–53} However, given that individuals have different resting/maximal heart rates and heart rate recovery, especially during chemotherapy treatment, using heart rate as an indicator of intensity in this population does not guarantee a similar absolute or relative intensity to individuals not undergoing chemotherapy. PPO has become a more precise measure to prescribe and monitor exercise intensity during HIIT, because it is not only objective, but is a direct measure of the rate of external work performed which has not been proven in this population.^{54 55}

This pilot trial was designed to determine the feasibility of HIIT in BCS undergoing anthracyclines, and secondarily assess exercise-induced changes in vascular function. HIIT is a novel exercise strategy for BCS undergoing anthracyclines, which may allow clinical populations to perform vigorous-intensity exercise due to the ‘on-off’ pattern of exercise. Importantly, lower volumes of HIIT compared with higher volumes of moderate continuous intensity exercise elicit better cardiovascular outcomes such as endothelial function and VO_2max ; therefore HIIT is an effective and time-efficient exercise option.⁵⁶ Given the barrier of compliance of BCS to regular exercise participation, HIIT is an intriguing alternative to traditional endurance-based exercise training for increasing cardiovascular benefits requiring a shorter exercise duration.⁵⁷

Another innovative feature of this study is our focus on improving vascular function in BCS undergoing anthracyclines. HIIT in comparison with moderate continuous intensity exercise has successfully improved endothelial function in patients with CVD, such as coronary heart disease,¹⁹ heart failure⁵³ and stroke.³⁰ Thus, HIIT may have the capacity to improve endothelial function and atherosclerosis in BCS undergoing anthracyclines. Increased atherosclerosis and endothelial dysfunction are major detrimental impacts of anthracyclines which impair cardiovascular function, including cardiac autonomic dysfunction, decreased diastolic pressure and coronary perfusion.⁵⁸ These detrimental impacts are significantly correlated with the dysregulation of ECM remodelling measured by the level of MMPs; it is unclear whether dysregulation of MMPs is improved by exercise

in BCS undergoing treatment with anthracyclines. This study allows us to identify whether HIIT can be used to improve ECM remodelling by targeting MMPs in BCS undergoing treatment with anthracyclines.

We hypothesise that the HIIT intervention is feasible in this population. The method of feasibility we set forth was based on previous studies that reported 68%–80% adherence to exercise intervention in patients with breast cancer.^{39 59 60} Exercise adherence was notably lower in studies which included patients with cancer undergoing chemotherapy (68%–72%),^{39 59} whereas higher adherence was reported in patients who had completed cancer treatment (83%–95%).^{38 60} Because exercise adherence may be disrupted by cancer treatment and its adverse effects, it is important to know whether BCS are able to complete the prescribed minutes of HIIT, along with prescribed number of exercise sessions while they are undergoing anthracyclines. Previous studies determined the feasibility by the number of exercise sessions attended and did not report the number of exercise minutes completed per session.^{39 59} Therefore we defined the feasibility of this study as an average of 70% (63/90 min) completion of exercise minutes and 70% completion of the total number of exercise session (17/24 sessions).

We acknowledge potential limitations in our study design. Although this study will provide the first evidence of HIIT targeting vascular function in BCS undergoing AC, it is possible that we may demonstrate that endothelial function is maintained and not worsened during the HIIT intervention when compared with the DEL group. However, this is an important clinical finding given that HIIT may prevent worsening of CVD risk factors. Second, we recognise that poor adherence is a possibility given the time and effort needed to participate in an intervention study, in particular while undergoing chemotherapy. Therefore, we have accounted for a 15% attrition rate to allow for dropout participants; we do not expect a higher dropout rate using data from previous studies that have conducted exercise training during chemotherapy.⁶¹ Finally, recruitment of BCS can be challenging.^{62–64} However, given our ongoing successful recruitment strategies including collaboration with the medical oncology team at USC, we believe a successful support team and recruitment plan are in place for the proposed study.

ETHICS AND DISSEMINATION

This trial is registered at ClinicalTrials.gov (NCT02454777). All study participants are consented to participate in the study prior to data collection without any element of force, fraud and duress. Sufficient knowledge and comprehension of research procedures including purpose, methods and means by which it is to be conducted are provided. Any potential risk, benefits, discomfort and hazards are reasonably explained by the PI. Participants are not excluded from the study based on race, religion or socioeconomic status.

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Contributors KL, IK, CMD-C, LAF, FS, JM, GS and WJM: study conception and design. KL: study coordinator, exercise trainer, endpoint assessments and data manager. KL and CMD-C: study management, and writing and reviewing of the manuscript. JM and FS: study physicians and medical advice, and writing and reviewing of the manuscript. KL and CMD-C: exercise intervention and performance testing conception. KL: biospecimen collection and analysis. WJM: statistical analyses. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study has been approved by the University of Southern California Institutional Review Board (HS-15-00227), and follows the Health Insurance Portability and Accountability Act (HIPAA) mandate.

Provenance and peer review Not commissioned; externally peer reviewed.

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