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CLINICAL TRIAL

Effects of high-intensity interval training on vascular endothelial function and vascular wall thickness in breast cancer patients receiving anthracycline-based chemotherapy: a randomized pilot study

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Abstract

Purpose The purpose of this study was to determine the effects of an 8-week high-intensity interval training (HIIT) intervention on vascular endothelial function, measured as brachial artery flow-mediated dilation (baFMD), and vascular wall thickness measured by carotid intima media thickness (cIMT) in breast cancer patients undergoing anthracycline-based chemotherapy.

Methods Thirty women were randomized to either HIIT or non-exercise control groups (CON). The HIIT group participated in an 8-week HIIT intervention occurring three times per week on a cycle ergometer. The CON group was offered the HIIT intervention after 8 weeks. baFMD was measured from the brachial artery diameter at baseline (D0) and 1 min after cuff deflation (D1); percent change was calculated by measuring brachial artery diameter after cuff deflation relative to the baseline [baFMD = (D1 − D0)/D0 × 100]. The cIMT was obtained from the posterior wall of common carotid artery 10 mm below the carotid bulb. Paired *t* test and repeated measures ANCOVA were performed to assess changes in baFMD and cIMT.

Results At baseline, the HIIT ($n=15$) and CON ($n=15$) groups did not differ by age (46.9 ± 9.8 years), BMI (31.0 ± 7.5 kg/m^2), and blood pressure (123.4 ± 16.8/72.3.9 ± 5.6 mmHg). Post-exercise, baFMD significantly increased [4.3; 95% confidence interval (CI): (1.5, 7.0), $p=0.005$] in HIIT versus CON group. cIMT did not significantly change [0.003, 95% CI − 0.004, 0.009), $p=0.40$] in HIIT group, while IMT significantly increased from baseline to post-intervention (0.009, 95% CI 0.004, 0.010, $p=0.003$) in CON group.

Conclusion This study may suggest that HIIT improved vascular endothelial function and maintained wall thickness in breast cancer patients undergoing anthracycline-based chemotherapy.

Trial registration: ClinicalTrials.gov: NCT02454777.

Keywords Vascular endothelial function · High-intensity interval training · Anthracycline-based chemotherapy · Breast cancer patients

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Abbreviations

baFMD Brachial artery flow-mediated dilation
CVD Cardiovascular disease
cIMT Carotid intima media thickness
CON Non-exercise control
HIIT High-intensity interval training

Introduction

Breast cancer mortality has been reduced by 20–30% over the last two decades with the use of anthracycline-based chemotherapy [1, 2]. However, congestive heart failure is reported in 5% of patients whose cumulative lifetime dose of bolus drug is 400 mg/m^2 and higher cumulative doses are tolerable when administered as a 96-h infusion [3, 4]. Less well recognized are the toxic effects of anthracycline-based chemotherapy on the vascular system. Anthracycline-related cardiotoxicity reduces vascular endothelial function and increases vascular wall thickness [5]. This is of particular concern because endothelial cells in the vasculature regulate blood circulation and fluidity, vascular tone, coagulation, and inflammatory responses [6]. For example, in leukemia patients treated with anthracycline-based chemotherapy, vascular endothelial function assessed by brachial artery flow-mediated dilation (baFMD) was reduced (~ 95%) compared to leukemia patients who did not receive anthracycline-based chemotherapy [7]. The negative alterations of vascular endothelial function and wall thickness caused by anthracyclines are associated with the development of cardiovascular diseases including atherosclerosis [8], hypertension [9], and heart failure [10].

Exercise is a well-known approach to improve vascular endothelial function in clinical populations [11–13]. High-intensity interval training (HIIT) is more effective than moderate continuous intensity aerobic exercise for improving vascular endothelial function among patients with heart failure [11] and stroke [14]. HIIT is a novel exercise strategy that maximizes exercise intensity by using bursts of higher-intensity efforts alternated with recovery periods, which allows patients to perform high-intensity exercise due to the ‘on–off’ pattern of exercise. The “on” portion of HIIT typically involves 1–4 min performed at 80–90% of peak power output (PPO) or maximum heart rate (MHR), followed by the “off” period (1–3 min active break at 10% PPO or 40–60% of MHR) [11, 15]. Among various types of HIIT, 1-min HIIT with stationary bike has been chosen in this study due to the side effects induced by cancer treatment such as loss of balance, neuropathy [16], fatigue, and low upper extremity muscle endurance influenced by surgery [17]. Further, individuals have different resting/maximal heart rates and heart rate recovery, especially during chemotherapy treatment [18], and therefore prescribing HIIT with heart rate in this population may not be ideal to guarantee a consistent absolute or relative intensity. In particular, 1-min HIIT has higher compliance (up to 100%) to the prescribed intensity in obese individuals [19] than other types of HIIT such as 4-min HIIT in patients with heart failure [20]. The protective effect of HIIT on vascular endothelial function has, to date, largely focused on patients with cardiovascular disease (CVD). HIIT has not been evaluated in clinical oncology settings to specifically test that HIIT may offset the negative changes caused by anthracycline-based chemotherapy on vascular endothelial function. Given the importance of these agents in cancer treatment, it is important to identify ways to minimize potential vascular toxicity.

The purpose of this pilot study was to determine the effects of an 8-week supervised HIIT intervention on vascular endothelial function and wall thickness in early-stage breast cancer patients receiving anthracycline-based chemotherapy. We hypothesized that an 8-week HIIT intervention would significantly increase baFMD in the HIIT group compared to the non-exercise control (CON) group. Due to the extended duration (6–12 months) needed to improve carotid intima media thickness (cIMT) [21–23], we explored whether an 8-week HIIT intervention would maintain cIMT in the HIIT group compared to the CON group.

Methods

Participants/consent

Eligible participants were (1) women > 18 years of age diagnosed with a primary invasive breast cancer (stage I–III); (2) planned (neo)adjuvant anthracycline-based chemotherapy; (3) able to start the exercise program within a week of initiation of anthracycline-based chemotherapy; (4) nonsmokers (i.e., not smoking during the previous 12 months); (5) willing to travel to the exercise facility at USC; (6) able to provide physician clearance to participate in the exercise program; and (7) speak English or Spanish as a primary language. The exclusion criteria were (1) history of chronic disease including diabetes, uncontrolled hypertension, or thyroid disease; (2) weight reduction > 10% within the past 6 months; (3) metastatic disease; (4) overt cardiovascular disease (CVD; myocardial infarction, stroke, angina, etc.); (5) contra-indications to exercise; and (6) participation in regular exercise defined as greater than 30-min exercise per week. Recruitment occurred between August 15, 2017 and August 6, 2018 from the USC Norris Comprehensive Cancer Center and the Los Angeles County Hospital. The protocol and informed consent were IRB-approved (HS-15-00227) and registered (ClinicalTrials.gov: NCT02454777). A signed informed consent was obtained from each participant. Participants randomized to the CON group were asked to maintain their current level of physical activity and were offered the same HIIT intervention upon completion of the initial 8-week study period.

Experimental design

Detailed methods and outcome measures were published elsewhere [24]. This pilot study was designed to compare baseline to 8-week changes in vascular endothelial function and vascular wall thickness in the HIIT versus CON groups in 30 sedentary women undergoing potentially curative (neo)adjuvant chemotherapy for the treatment of early-stage breast cancer, with doxorubicin and cyclophosphamide administered every 2 weeks for 4 cycles. All participants received white cell growth factors 24 h after chemotherapy. Trial outcomes were assessed at baseline (week 0) and post-intervention (week 9). Outcomes were measured after a 12-h fast and abstinence from alcohol, caffeine, and vitamins [25]. To enhance participation, participants in the CON group were offered the same HIIT intervention following the initial 8-week study period.

Endothelial function

Endothelial function was measured using baFMD while the participant was in the supine position. Prior to assessing baFMD, participants rested for a minimum of 15 min, and systolic and diastolic blood pressures were measured during the rest period to ensure that no fluctuation of blood pressure occurred [26]. A rapid inflation and deflation blood pressure cuff was positioned on the unaffected (from mastectomy or lumpectomy) arm 1 cm distal to the antecubital fossa to provide a stimulus to forearm ischemia. A 7.5–10 MHz multi-frequency linear array probe, attached to a high-resolution ultrasound machine (GE LOGIQ e), was used to image the brachial artery in the distal third of the upper arm. A single-lead ECG recording was obtained concurrently during acquisition of brachial artery images. The B-mode image of the brachial artery and Doppler images of flow were recorded for the average of 15 s for four times at baseline (D0) [25]. Extra-vascular landmarks were identified and labeled to assure that the imaged segment of the brachial artery was reproduced within and across participants. After baseline images were obtained, the cuff was inflated to 250 mmHg for 5 min, and then deflated immediately after the 5 min [25]. Following limb ischemia, there was a rapid increase in forearm blood flow, which slowly returned to baseline values. Each participant had a different time point of peak diameter, which ranged from 40 to 90 s after deflation. The peak diameter was detected by an automated edge detection software system (FMD Studio, Quipu, Italy). This is termed reactive hyperemia. Digitized images of the brachial artery were captured continuously for 30 s before cuff inflation and for 5 min following cuff release, to document the endothelial-dependent vasodilator response. The baFMD was calculated from the brachial artery diameter at baseline (D0) and peak diameter after cuff deflation (D1), and expressed as the percent change of brachial artery diameter relative to the baseline [$\text{baFMD} = 100 \times (\text{D1} - \text{D0})/\text{D0}$; D0 = diameter at baseline, D1 = peak diameter after cuff deflation].

Vascular wall thickness

Vascular wall thickness was evaluated by cIMT and a total of 10 min was used to measure cIMT; three measures were obtained at each visit (baseline, post-intervention). Each measure was taken for approximately 3 min. Participants lied in the supine position with the head turned slightly away from the side that was scanned on the plinth to assess both common carotid arteries (left and right) using a linear array 7.5–10 MHz transducer attached to B-mode ultrasound (GE LOGIQ e, Chicago, IL). Multiple angles (anterior, lateral, and posterior) were used to detect cIMT. When an optimal image was obtained, the probe was held stable and the ultrasound parameters were set to optimize the longitudinal, B-mode image of the lumen-arterial wall interface. To measure cIMT, the carotid bifurcation was used as a reference. The same depth of field, gain, input power, dynamic range, monitor intensity, and all other instrumentation settings were maintained for baseline and post-intervention visits. Following imaging, ultrasound auto-detection caliper software (GE Healthcare, Chicago, IL) was used to automatically detect the posterior wall along a 10-mm-long section proximal to the carotid bifurcation, where a bright-dark-bright pattern corresponded to the intima media adventitia layers of the vascular walls. By means of auto-detection of the ultrasound caliper, we were able to reduce the subjectivity of manual approaches and measure the cIMT throughout the artery length, which provided more precise measurements. The ultrasound scan provided measures of lumen diameter, intima media thickness, and presence and extent of plaques in millimeters [27].

Exercise intervention

All exercise sessions took place at the Integrative Center for Oncology Research in Exercise (ICORE) in the Division of Biokinesiology and Physical Therapy at the University of Southern California (USC). Participants in the HIIT group received 3 supervised one-on-one exercise sessions/week and performed their exercise on a cycle ergometer (Life Fitness, Rosemont IL). Exercise intensity was individually prescribed for the HIIT group based on peak power output (PPO), which was measured by a VO_2max fitness test. VO_2max fitness test was performed with standard equipment for indirect calorimetry (Parvo Medics Inc, Salt Lake City, UT) in an incremental protocol to determine VO2max based on the following criteria: respiratory exchange ratio > 1.10, heart rate ± 10/min predicted MHR, ratings of perceived exertion 17, in 6–20 ratings on recumbent bike. The specific protocol comprised a 10 W increase in workload every one minute, starting at 40 W. This testing was performed with standard equipment for indirect calorimetry (Parvo Medics Inc, Salt Lake City, UT) in an incremental protocol until exhaustion on the bike. PPO was defined as the highest power output generated during a maximal cycling test [14, 15]. Before the fitness test was administered, participants were familiarized with the testing protocol using the same standardized verbal instructions which indicated the duration of each stage, maintaining the same cadence throughout the test, and increases of torque during the test. Each exercise session consisted of a 5-min warm-up performed at 10% PPO, followed by a 20-min HIIT protocol. The HIIT protocol consisted of seven bouts of 1-min high-intensity exercise (90% of PPO) followed by 2 min of active recovery (10% of PPO). Participants were encouraged to complete each exercise session with at least 24 h of rest between each session and to complete sessions on days when they did not receive anthracycline infusions. Power output, heart rate, rating of perceived exertion (RPE; rated on the Borg scale of 6–20), and total minutes of exercise were documented for each session and for each interval. Participants were encouraged to make up any missed sessions in the same week. Participants in the CON group were asked to maintain less than 30 min of total structured exercise per week during the 8-week study period. After the 8 weeks of intervention, the CON group was provided the HIIT intervention (optional).

Statistical analysis

Participant characteristics were analyzed by descriptive statistics. Distribution of outcomes were evaluated and presented as mean (SD) for continuous outcomes and frequency (%) for categorical outcomes. Comparisons of baseline participant characteristics between groups were made using t test or a non-parametric corollary for continuous outcomes and χ^2 test for categorical outcomes. Baseline variables (e.g., age, BMI, level of physical activity, and blood pressure) with a group difference of $p < 0.05$ were considered as covariates in the models. However, no baseline variables met this threshold and therefore we report unadjusted models. For vascular outcomes, the changes in baFMD and cIMT from baseline to post-intervention were examined by a paired t test (to test changes within each group). Repeated measures ANCOVA on the trial outcomes was a 2 (group: HIIT, CON) × 2 (time: baseline, post-intervention) analysis. Although there were no statistical group differences at baseline, age was included as an a priori covariate as a conservative approach [standardized group difference (mean difference/standard deviation) was higher than 0.1]. Cohen's d effect sizes (ES) for the changes in baFMD and cIMT were calculated using the group difference in mean changes from baseline to post-intervention and the pooled standard deviations of change. All analyses were performed with SPSS (v.22).

Results

The study CONSORT diagram is presented in Fig. 1. Briefly, we assessed 58 women for eligibility of which 30 were enrolled and randomized to the HIIT or CON group. Baseline characteristics are reported in Table 1; no statistical differences were identified across the two groups. On average (SD), participants were 46.9 (9.8) years old, Hispanic white (73%), with a BMI 31.0 (7.5) kg/m^2. Participants were diagnosed primarily with stage II (30%) or III (63%) breast cancer and largely treated with neoadjuvant chemotherapy (77%). High attendance of 82.3% (overall average 19.2 of 24 sessions) was attained by the HIIT group. No adverse events were reported over the duration of the intervention and there were no drop-outs.

baFMD

baFMD outcomes are displayed in Table 2. At baseline, there were no differences in baFMD between the two groups ($p = 0.87$). Post-intervention, baFMD significantly increased [within-group mean change from baseline to post-intervention: 4.3%; 95% confidence interval (CI): (1.55%, 7.02%), $p = 0.005$] in the HIIT group [wk 0: 12.65 (6.83)%, wk 9: 16.90 (9.07)%] when compared to the baseline and to the CON group (between groups $p < 0.001$). In the CON group, baFMD significantly decreased from baseline to post-intervention [within-group mean change: 13.21 (1.84)%, to 6.06 (2.96)%; − 7.15% decrease; 95% CI: (4.94%, 9.35%), $p < 0.001$]. The Cohen's d effect size using the pooled standard deviation for the changes in baFMD was 0.63 (SD of change = 4.5%).

cIMT

cIMT outcomes are displayed in Table 2. At baseline, there was no difference in cIMT between the two groups ($p = 0.52$). Post-intervention, no significant change in cIMT [within-group mean change from baseline to post-intervention: − 0.003 mm, 95% CI: (− 0.004, 0.009), $p = 0.40$] was observed in the HIIT group [wk 0:0.591 (0.084), wk 9: 0.589 (0.092) mm] compared to the baseline and to the CON group (between groups $p = 0.23$). However, cIMT significantly increased from baseline to post-intervention [within-group mean change: 0.009 mm, 95% CI: (0.004, 0.014), $p = 0.003$]

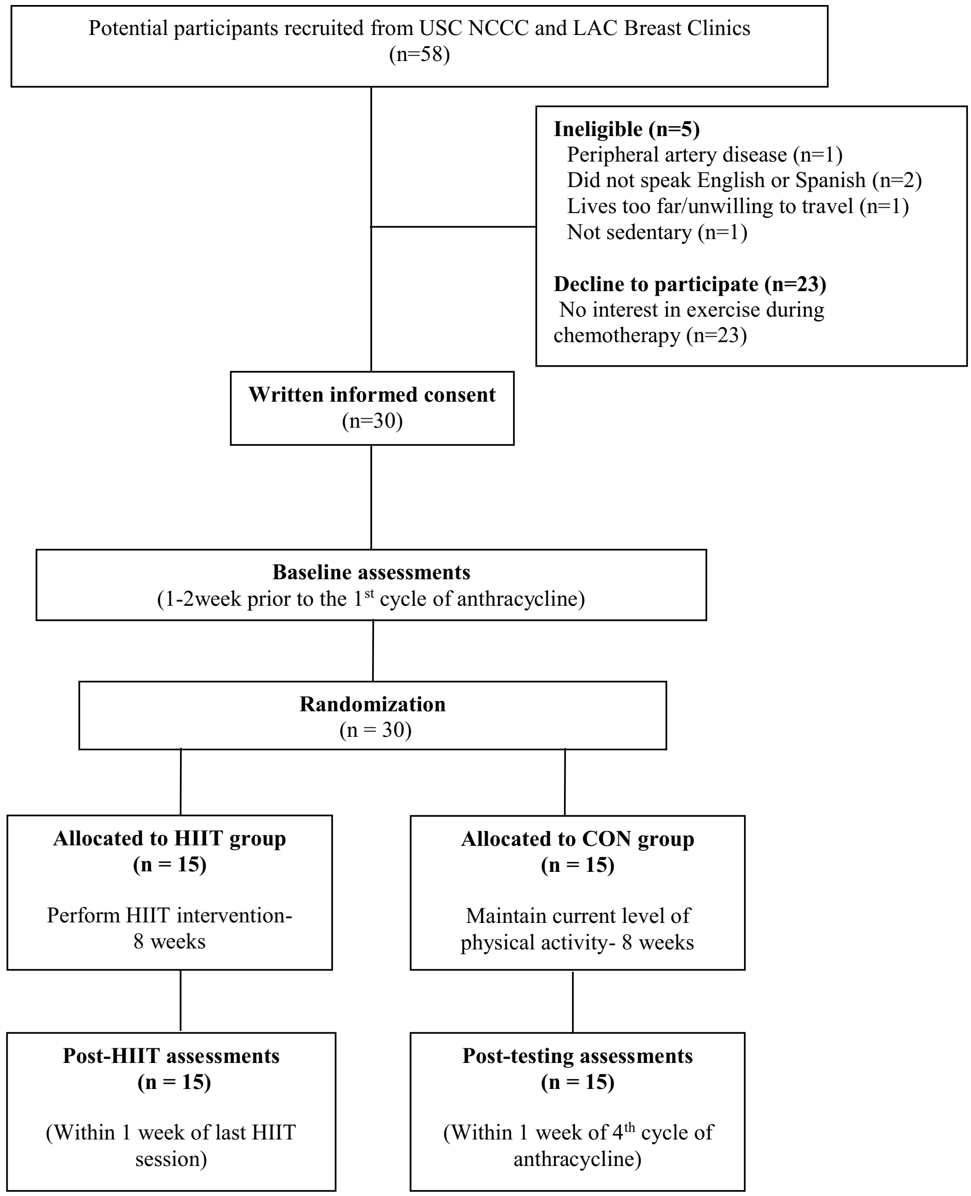

Fig. 1 CONSORT diagram of HIIT intervention. *HIIT* high-intensity interval training, *CON* delayed, *USC* University of Southern California, *NCCC* Norris Comprehensive Cancer Center, *LAC* Los Angeles Country

in the CON group [0.623 (0.091) to 0.631 (0.111) mm]. The Cohen's d effect size using the pooled standard deviation for the changes in cIMT was 0.6 (SD of change = 0.02 mm).

Discussion

A supervised 8-week HIIT intervention led to significant improvements in baFMD and the maintenance of cIMT among breast cancer patients receiving anthracycline-based chemotherapy, compared to significant reductions in baFMD and increases in cIMT in patients not receiving HIIT. This is the first study to our knowledge to demonstrate significantly improvement in vascular endothelial function with HIIT in an ethnically diverse sample of breast cancer patients receiving anthracycline chemotherapy.

Despite this being a pilot study, our findings are promising given that vascular endothelial function significantly improved (4.3%) in breast cancer patients within a relatively short time frame of 8 weeks during anthracycline-based chemotherapy. In contrast, participants in the CON group experienced worsened vascular endothelial function (−7.15%). Our results align with those of Jones et al. [28] who reported that a 12-week aerobic exercise intervention (cycle ergometer 30–45 min/session; progressively increased intensity of 60–100 VO_2max) increased baFMD (0.7%; $p = 0.07$) in 20 neoadjuvant breast cancer patients undergoing 12 weeks of anthracycline-based chemotherapy. It is plausible that our study resulted in a greater increase

Table 1 Baseline participant characteristics

	All ($N=30$)	HIIT group ($N=15$)	CON Group ($N=15$)
Age (years), mean (SD)	46.9 (9.8)	49.1 (7.9)	44.7 (11.2)
Menopausal status			
Premenopausal	11 (37)	5 (33)	6 (40)
Postmenopausal	19 (63)	10 (67)	9 (60)
Body weight (kg), mean (SD)	77.7 (18.3)	80.9 (17.7)	74.5 (18.8)
Height (cm), mean (SD)	158.4 (8.2)	156.5 (6.6)	160.3 (9.9)
BMI (kg/m^2), mean (SD)	31.6 (7.7)	33.1 (7.6)	30.1 (7.7)
Race/ethnicity			
Non-Hispanic white	4 (13)	3 (20)	1 (6)
Hispanic white	22 (73)	11 (74)	11 (74)
African American	2 (7)	0 (0)	2 (14)
Asian/Pacific Islander	2 (7)	1 (6)	1 (6)
Disease stage			
I	2 (7)	1 (6)	1 (6)
II	9 (30)	5 (30)	4 (24)
III	19 (63)	9 (64)	10 (70)
Chemotherapy			
Neoadjuvant	23 (77)	11 (73)	12 (80)
Adjuvant	7 (23)	4 (27)	3 (20)
International physical activity questionnaire			
MET min per week of moderate to vigorous intensity recreational activity, mean (SD)	462.5 (101.2)	480.9 (85.3)	441.9 (93.2)

Data are presented as No. (%) unless otherwise indicated. No significant baseline differences between groups were observed ($p > 0.05$) by independent sample *t* tests for continuous variables and Pearson X^2 and Fisher's exact tests for categorical variables. *BMI* body mass index, *HIIT* high-intensity interval training, *DEL* delayed, *MET* metabolic equivalents, *SD* standard deviation

in baFMD due to the interval training nature of the exercise prescription, duration of exposure to anthracycline-based chemotherapy and intervention, and diverse sample in the present study.

We found that baFMD was significantly reduced in the CON group. This finding is consistent with previous studies in patients with leukemia in whom significant impairments in baFMD occurred following anthracycline-based chemotherapy [5.6 (3.5) to 0.3 (1.6) %; decrease of 5.3%] [7]. The more negative changes of baFMD reported in the CON group of our sample compared to the previous study may partly be due to higher baFMD at baseline, and the different inclusion of patients with advanced clinical conditions since the previous study included five metastatic cancer patients of 27 patients.

Although we did not observe significant reductions in cIMT following the 8-week HIIT intervention, cIMT was maintained in the HIIT group following the 8-week chemotherapy. This finding is important in that cIMT did not worsen during anthracycline-based chemotherapy, while cIMT in the CON group significantly worsened. The lack of significant improvements in cIMT in the HIIT group may be due to the short duration of the exercise intervention; direct comparisons to published literature are not possible since this is the first study to examine cIMT with an exercise intervention in breast cancer patients undergoing chemotherapy. However, the effects of exercise on cIMT have been studied in non-cancer populations. Park et al. [29] reported a decrease in cIMT in obese older women (65–77 years old) without a history of breast cancer following 6 months of aerobic and resistance exercise (40–50-min walking, 20–30-min resistance band exercise; 5 days per week). Similarly, Byrkjeland et al. [23] reported that 12 months of resistance and aerobic exercise (150 min weekly) significantly decreased cIMT in patients with type 2 diabetes and coronary artery disease. Notably, the duration of these two studies suggest that a minimum of 6–12 months of exercise may be necessary to elicit a positive effect on cIMT. Further, study participants in the previous studies did not undergo any cancer treatment during the intervention, and thus improvements in cIMT in cancer patients may take longer to induce than non-cancer populations without a history of cancer treatment. While the specific mechanism of increased cIMT induced by anthracycline-based chemotherapy is unknown, previous studies suggested that anthracyclines generate excessive oxidative stress. It is

Table 2 Mean differences in baFMD and cIMT between HIIT and CON groups across the 8-week intervention

Variable	Baseline, mean (SD)	Post-intervention, mean (SD)		Between-group difference post-intervention	
	Mean (SD)	Mean (SD)	P	Mean (95% CI)	p
Brachial artery diameter (mm)					
HIIT group	3.62 (0.83)	3.69 (0.83)	0.59	–	–
CON group	3.31 (0.65)	3.29 (0.66)	0.67		
baFMD (%)					
HIIT group	10.43 (4.70)	12.15 (6.97)	0.005[a]	6.04 (2.18, 9.89)	0.001[b]
CON group	11.21 (4.45)	6.11 (2.13)	<0.001[a]		
Shear rate ($s^{-1} \times 10^3$)					
HIIT group	18.4 (9.5)	18.7 (7.4)	0.76	1.88 (− 2.08, 5.42)	0.35
CON group	17.1 (8.8)	16.8 (6.9)	0.81		
cIMT (mm)					
HIIT group	0.591 (0.084)	0.589 (0.098)	0.40	− 0.04 (− 0.11, 0.03)	0.23
CON group	0.623 (0.091)	0.631 (0.111)	0.003*		
Systolic blood pressure (mmHg)					
HIIT group	120.9 (13.9)	119.0 (10.9)	0.50	− 9.60 (− 10.9, 2.4)	0.12
CON group	125.7 (19.2)	127.7 (19.9)			
Diastolic blood pressure (mmHg)					
HIIT group	72.4 (9.6)	74.1 (8.9)	0.19	− 5.93 (− 12.5, 0.65)	0.08
CON group	76.7 (7.9)	80.2 (8.6)			

Values are presented as mean and SD. *p* values are reported from within-group difference by paired *t* test and between-group and between-time point repeated measures ANCOVA

baFMD brachial artery flow-mediated dilation, *cIMT* carotid intima media thickness, *HIIT* high-intensity interval training, *CON* control

[a] *p* value for within-group baseline versus post-intervention values

[b] *p* value for group × time interaction

plausible that oxidative stress may have increased cIMT in the CON group following anthracycline-based chemotherapy, whereas oxidative stress may have been reduced in the HIIT group. Future studies are necessary to identify the exact mechanisms related to anthracycline-induced vascular wall thickening.

Strengths of this study include a focus on a single cardio-toxic chemotherapy with a lower volume exercise intervention, an ethnically diverse sample, and a randomized controlled design. Although this study provides the first evidence of a novel exercise approach targeting vascular endothelial function in breast cancer patients undergoing anthracycline-based chemotherapy, we acknowledge limitations in our design. In this pilot trial, we were not adequately powered to detect statistically significant improvements in all of our outcome measures. We did not include a non-HIIT exercise (i.e., moderate continuous exercise) group in our study design because this study was designed to assess the feasibility of HIIT given the potent effects of HIIT on vascular function. Future studies are warranted to compare the effects of HIIT to other forms of exercise to determine whether HIIT induces a greater impact on vascular function in breast cancer patients. A possible mechanism to improve baFMD may result from improved insulin sensitivity in addition to the exercise. Since our patient population was obese, it is important to consider this mechanism as a means for any observed improvements in endothelial function, as the exercise may have improved insulin resistance and subsequently endothelial function. Insulin resistance is a central mediator in developing endothelial dysfunction, and previous studies have shown that HIIT improves endothelial dysfunction in patients with type 2 diabetes [30–32]. While upregulation of nitric oxide pathway due to increased shear rate may be a potential mechanism, shear rate in our study was not significantly changed, implying there would be other mechanism improving baFMD found in our study.

In summary, the results of the current study demonstrate that HIIT improves baFMD in breast cancer patients undergoing anthracycline-based chemotherapy while maintaining cIMT. This finding underscores the value of HIIT as a means to improve vascular endothelial function in breast cancer patients undergoing anthracycline-based chemotherapy and provides evidence to support the adoption of exercise during chemotherapy. Future studies are needed to elucidate the mechanisms of anthracycline-related vascular endothelial function and to identify effective exercise interventions to protect the endothelium against anthracycline-related toxicity.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

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

Ethical approval The protocol and informed consent were approved by the University of Southern California Institutional Review Board (HS-1500227).

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