Aerobic Fitness Is Related to Myocardial Fibrosis Post–Anthracycline Therapy

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[1]Department of Biomedical Engineering, University of Alberta, Edmonton, AB, CANADA; [2]Division of Cardiology, University of Alberta, Edmonton, AB, CANADA; [3]Faculty of Nursing, University of Alberta, Edmonton, AB, CANADA; [4]College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, TX; and [5]Department of Oncology, University of Alberta, Edmonton, AB, CANADA

ABSTRACT

KIRKHAM, A. A., D. I. PATERSON, M. J. HAYKOWSKY, R. I. BEAUDRY, J. R. MACKEY, E. PITUSKIN, J. G. GRENIER, and R. B. THOMPSON. Aerobic Fitness Is Related to Myocardial Fibrosis Post–Anthracycline Therapy. *Med. Sci. Sports Exerc.*, Vol. 53, No. 2, pp. 267–274, 2021. Adjuvant anthracycline chemotherapy for breast cancer is associated with cardiotoxicity and reduced cardiorespiratory fitness ($\dot{V}O_{2peak}$). **Purpose:** We evaluated the impact of anthracyclines on left ventricular function and myocardial tissue characteristics using cardiovascular magnetic resonance (CMR) imaging to determine their relationship with $\dot{V}O_{2peak}$. **Methods:** Women with breast cancer who had not yet received treatment (No-AT, n = 16) and had received anthracycline treatment ~1 yr earlier (Post-AT, n = 16) and controls without cancer (CON, n = 16) performed a maximal exercise test and a comprehensive 3T CMR examination, including native myocardial T_1 mapping, where elevated T_1 times are indicative of myocardial fibrosis. ANOVA and linear regression were used to compare CMR variables between groups and to determine associations with $\dot{V}O_{2peak}$. Subgroup analysis was performed by categorizing participants as "fit" or "unfit" based on whether their $\dot{V}O_{2peak}$ value was greater or less than 100% of reference value for age, respectively. **Results:** Left ventricular end-diastolic volume, ejection fraction, and mass were similar between groups. Post-AT, T_1 times were elevated (1534 ± 32 vs 1503 ± 28 ms, $P < 0.01$), and $\dot{V}O_{2peak}$ was reduced (23.1 ± 7.5 vs 29.5 ± 7.7 mL·kg^{-1}·min^{-1}, $P = 0.02$) compared with CON. In No-AT, T_1 times and $\dot{V}O_{2peak}$ were similar to CON. In the Post-AT group, T_1 time was associated with $\dot{V}O_{2peak}$ (R^2 = 64%), whereas in the absence of anthracyclines (i.e., No-AT and CON groups), T_1 time was not associated with $\dot{V}O_{2peak}$. Regardless of group, all fit women had similar T_1 times, whereas unfit women Post-AT had higher T_1 than unfit CON (1546 ± 22 vs 1500 ± 33 ms, $P < 0.01$). **Conclusions:** After anthracycline chemotherapy, an elevated T_1 time suggesting greater extent of myocardial fibrosis, was associated with lower $\dot{V}O_{2peak}$. However, those who were fit did not have evidence of myocardial fibrosis after anthracycline treatment. **Key Words:** HEART FUNCTION TESTS, CARDIOTOXICITY, BREAST NEOPLASMS, CARDIORESPIRATORY FITNESS

Cardiorespiratory fitness, measured as the peak volume of whole-body oxygen consumption ($\dot{V}O_{2peak}$), is the strongest independent predictor of cardiovascular disease and all-cause mortality and an important indicator of functional ability (1). Women with breast cancer have reduced $\dot{V}O_{2peak}$ before, during, and after chemotherapy treatment (2–4), but the contributors to chemotherapy-related deterioration of $\dot{V}O_{2peak}$ have not been well studied. Anthracyclines are commonly used in adjuvant treatment of breast cancer but are associated with dose-dependent myocardial oxidative stress, manifesting as cardiac dysfunction and heart failure (5,6). In addition, emerging evidence suggests that cardiac function may be impaired before the receipt of cardiotoxic treatment in cancer patients (7). The relationship between the cardiac injury resulting from anthracyclines and the reduced $\dot{V}O_{2peak}$ is not well characterized.

Cardiovascular magnetic resonance (CMR) is an important imaging modality for the assessment of cardiac injury from cancer treatment (8). CMR is the gold standard imaging technique to assess left ventricular (LV) ejection fraction and mass and can also assess vascular stiffness (aortic distensibility), as well as quantitative noninvasive estimates of interstitial fibrosis and edema using T_1 and T_2 mapping techniques. Given the ability of CMR to precisely quantify several complimentary metrics of myocardial injury, it is the optimal modality to evaluate relationships between myocardial injury and $\dot{V}O_{2peak}$.

The purpose of this study was to determine the influence of anthracycline treatment for breast cancer on potential cardiac determinants of $\dot{V}O_{2peak}$. The primary objective was to compare CMR measures of LV morphology and function, aortic stiffness, and $\dot{V}O_{2peak}$ among women with breast cancer who have received anthracycline chemotherapy (post–anthracycline treatment [Post-AT]), women with breast cancer who have not yet

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received treatment (No-AT), and controls without a history of cancer (CON). The secondary objective was to determine associations among these CMR measures and $\dot{V}O_{2peak}$ in each of these groups.

METHODS

Design and Ethics

This study was a cross-sectional comparison between the three age-matched and body mass index (BMI)-matched groups described above. Ethical approval was obtained from the University of Alberta Research Ethics Board, and participants provided written informed consent.

Participants

Inclusion criteria and recruitment methods are described for each group below. Exclusion criteria for all groups were self-report of a diagnosis of cardiovascular disease, diabetes, and lung disease, as these conditions could alter cardiac function/cardiorespiratory fitness independent of cancer status, as well as CMR contraindications.

Breast cancer, Post-AT group. We mailed study invitation letters to 75 women who were randomly selected using a random spreadsheet function from the 240 patients who had received anthracycline-based chemotherapy for breast cancer at the Cross Cancer Institute (Edmonton, Canada) in the previous calendar year. Of the 22 women who responded, 2 declined after learning more about the study, and 4 were excluded after telephone screening (CMR contraindication, $n = 2$; diabetes, $n = 2$); thus, 16 participants were enrolled. All participants had finished anthracycline treatment ≥3.5 months earlier (median onset of anthracycline-related cardiotoxicity) (9).

Breast cancer, No-AT group. A treatment-naïve breast cancer group were included to account for the potential confounding of the influence of a breast cancer diagnosis alone on cardiovascular function and health. Women for this group were recruited from an ongoing longitudinal trial of individuals with newly diagnosed, early stage breast cancer (10). The assessments used in this study occurred at baseline, before receipt of any nonsurgical cancer treatment. Participants from the longitudinal study were selected to match each participant in the Post-AT group to within 2 yr of age and whenever possible, to within 3.0 $kg \cdot m^{-2}$ of BMI.

No cancer, CON group. Women without a history of cancer were recruited via word of mouth and recruitment posters and were matched to the Post-AT group using the same criteria as above.

Cardiopulmonary Exercise Test

All participants performed an incremental to maximum exercise test on a cycle ergometer (Ergoselect II 1200 Ergoline, Germany). Testing procedures were explained in detail to the participant in advance of the test. The initial workload was 20 W with a 5-W increase every 20 s, and participants were verbally encouraged to continue until volitional exhaustion. Heart rate and electrocardiography were continuously monitored, and blood pressure and Borg rating of perceived exertion were collected every 2 min. Continuous gas analysis was performed to capture $\dot{V}O_{2peak}$, defined as the highest 20-s average volume of oxygen consumption (Encore229 Vmax; SensorMedics, Yorba Linda, CA). A $\dot{V}O_{2peak}$ reference value was predicted for each participant using the Jones and Campbell equation for females according to age $[2.6 - (0.014 \times \text{age})]$ (11). The measured $\dot{V}O_{2peak}$ for each participant was calculated as percentage of their reference value, which was then used to categorize them as "fit" if they met/exceeded 100% of their $\dot{V}O_{2peak}$ reference value or "unfit" for <100%.

CMR Examination

CMR was performed on a 3T Siemens Prisma system (Siemens Healthcare, Erglangen, Germany). The CMR examination was typically performed before the cycle ergometer test on the same day due to the living distance of the participants from the testing facility. In all cases, participants were asked not to perform exercise for 24 h before the exam. Gated, balanced, steady-state free precession cine imaging was performed in the long- and short-axis orientation across the entire LV as well as an axial slice through the aorta at the level of bifurcation of the pulmonary artery for the visualization of the ascending and descending aortic cross section. The saturation recovery single-shot acquisition (SASHA) and the modified look-locker inversion recovery (MOLLI) pulse sequences were both used to acquire native (noncontrast) T_1 mapping for a single midbasal short-axis slice (12,13). Typical acquisition parameters are described in the supplemental material (see Document, Supplemental Digital Content 1, Acquisition parameters, http://links.lww.com/MSS/C54).

CMR Analysis

All analyses were performed by a single, experienced interpreter who was blinded to group and $\dot{V}O_{2peak}$. LV volumes and mass were measured from short-axis cine images covering the entire LV using Segment V2.0 (http://segment.heiberg.se) (14). Longitudinal strain was measured from the two-, three-, and four-chamber long-axis cine images using a feature tracking approach, similar to other previously reported methods (15). Analysis of strain, T_1 and T_2 times, and aortic distensibility were performed using custom in-house software (MATLAB, The MathWorks, Natick, MA).

For LV volumes and strain, the LV endocardial and epicardial borders were traced, excluding the papillary muscles on the end-diastolic and end-systolic frames. Global longitudinal strain (GLS) was calculated as the average of the fractional change in length, from end-diastole to end-systole, of the endocardial contour from the three long-axis slices. Aortic distensibility was calculated as the fractional change in aortic area from end-diastole to end-systole divided by the brachial pulse pressure (the average of two measurements taken 60 s apart at the time of cine acquisition) (16). T_1 and T_2 maps were reconstructed on the scanner. Reported T_1 and T_2 values are the average of all segments from the middle layer of the

myocardium (2 mm thickness) as anthracycline-related myocardial damage is expected to be diffuse (8).

Descriptive Data

Hemoglobin was assessed by complete blood count from a venipuncture before exercise. Demographics and cardiovascular risk factors were self-reported. Height and weight were measured by electronic scale and standiometer (Health-o-meter Professional 500KL; Pelstar LLC, McCook, IL). BMI was calculated and used to categorize participants as overweight (25.0–29.9 $kg \cdot m^{-2}$) or obese (30.0+ $kg \cdot m^{-2}$). The Godin Leisure Time Exercise Questionnaire was used to capture typical moderate and vigorous intensity aerobic activity for "a typical week in the last month" (17). Total moderate and vigorous aerobic minutes per week were used to categorize participants as sedentary (0 $min \cdot wk^{-1}$) or inactive (<150 $min \cdot wk^{-1}$) to describe cardiovascular risk factors. The physical activity questionnaires were not collected in the longitudinal study, so this descriptive data are not available for the No-AT group.

Statistical Analyses

Categorical descriptive variables were compared by Fisher exact tests. The Shapiro–Wilk test was used to confirm normal distributions of dependent variables to meet statistical assumptions. Normally distributed, continuous descriptive and outcome variables were compared between groups using one-way ANOVA, with significant findings investigated using independent *t*-tests. In the case of nonnormal distribution, the Kruskal–Wallis *H*-test was used to compare the medians, with between group differences investigated using the Mann–Whitney *U*-test. No adjustments were made for multiple comparisons. Next, linear regression with an ordinary least square estimator was used to examine the relationship between CMR variables and relative $\dot{V}O_{2peak}$ within each group. For the CMR variables with significant univariate linear relationships with $\dot{V}O_{2peak}$, age and aerobic activity (when available) were individually added to a multivariate model to determine whether the CMR variable remained a significant predictor of $\dot{V}O_{2peak}$. Finally, as women in the Post-AT group may also receive left-sided radiation therapy, which can also cause myocardial injury, we performed univariate linear regression within this group to determine whether this potential confounding variable predicts $\dot{V}O_{2peak}$ or any of the CMR variables.

RESULTS

Participants. All participants completed the CMR and CPET assessments. The three groups were well matched for age, BMI, and cardiovascular risk factors (Table 1). Although there were more participants in the No-AT group with a self-reported history of hypertension, blood pressure was well controlled (<140/90 mm Hg) in all cases, including on the day of the CMR examination. The majority (88%) of participants in the No-AT group had received surgery approximately 4–6 wk earlier. In the Post-AT group, the most common anthracycline regimen was epirubicin (n = 15), and one was treated with doxorubicin. The cumulative median epirubicin dose received was 300 $mg \cdot m^{-2}$, with the last treatment received 12.8 ± 4.7 months prior. Eleven and four patients received radiation therapy to their left and right sides, respectively; none received trastuzumab; all were considered clinically stable with respect to disease.

TABLE 1. Descriptive characteristics.

	CON (n = 16)	BC No-AT (n = 16)	BC Post-AT (n = 16)	P
Demographics				
Age (mean ± SD), yr	56 ± 10	55 ± 9	56 ± 10	0.94
BMI (mean ± SD), $kg \cdot m^{-2}$	28 ± 5	28 ± 4	29 ± 4	0.71
Caucasian ethnicity	16 (100%)	14 (88%)	15 (94%)	0.76
Cardiovascular risk factors				
Hypertension	0 (0%)	6 (38%)	2 (13%)	**0.02**
Hypercholesterolemia	2 (13%)	2 (13%)	0 (0%)	0.53
Former smoker	8 (50%)	4 (25%)	7 (44%)	0.43
Current smoker	0 (0%)	0 (0%)	0 (0%)	–
Diabetes	0 (0%)	0 (0%)	0 (0%)	–
Overweight	8 (50%)	9 (56%)	5 (31%)	0.44
Obese	7 (44%)	5 (31%)	7 (44%)	0.81
Sedentary (MVPA = 0 $min \cdot wk^{-1}$)	2 (13%)	NA	4 (25%)	0.65
Inactive (MVPA<150 $min \cdot wk^{-1}$)	5 (31%)	NA	10 (63%)	0.16
Breast cancer				
Stage				
I		2 (13%)	0 (0%)	
II		11 (69%)	8 (50%)	
III		3 (19%)	7 (44%)	
IV		0 (0%)	1 (6%)	
Epirubicin dose, median (min, max), $mg \cdot m^{-2}$			300 (200, 570)	
Months since last epirubicin (mean ± SD)			12.8 ± 4.7	
Radiation				
Left			11 (69%)	
Right			5 (31%)	
Trastuzumab			0 (0%)	
Hormone therapy				
Aromatase inhibitor			7 (44%)	
Tamoxifen			6 (38%)	

Data are presented as sample size (percentage) unless otherwise indicated.
CON, no cancer controls; BC No-AT, breast cancer No-AT yet; BC Post-AT, breast cancer Post-AT; NA, data are not available.

$\dot{V}O_{2peak}$. During the cardiopulmonary exercise test, 47 participants (98%) exceeded a respiratory exchange ratio of 1.10 (18), and all participants reached volitional exhaustion. Both absolute and relative $\dot{V}O_{2peak}$ values were approximately 20% lower in Post-AT relative to CON (1.69 ± 0.37 vs 2.13 ± 0.41 $L \cdot min^{-1}$, $P < 0.01$; 23.1 ± 7.5 vs 29.5 ± 7.7 $mL \cdot kg^{-1} \cdot min^{-1}$, $P = 0.02$; respectively). Absolute and relative $\dot{V}O_{2peak}$ for the No-AT group (1.87 ± 0.46 $L \cdot min^{-1}$, 25.7 ± 8.2 $mL \cdot kg^{-1} \cdot min^{-1}$) were not significantly different from the Post-AT and CON groups (Table 2).

Between group differences in cardiovascular variables. Resting heart rate, blood pressure, and aortic distensibility were not different between groups. Although hemoglobin was higher in the No-AT group versus other groups, all values were normal (i.e., not anemic/below 120 $g \cdot L^{-1}$) except for one participant (116 $g \cdot L^{-1}$) in the Post-AT group. LV end-diastolic and end-systolic volumes, ejection fraction, mass, and myocardial T_2 times were similar in all groups. LV ejection fraction was normal (i.e., >53% [19], range of 56%–72%) in all participants.

SASHA T_1 times were higher (1534 ± 32 vs 1503 ± 28 ms, $P < 0.01$) and endocardial GLS was reduced (−22.1% ± 2.1% vs

TABLE 2. Comparison of resting cardiovascular and cardiopulmonary data between groups.

Variable	CON (n = 16)	BC No-AT (n = 16)	BC Post-AT (n = 16)	P
Resting circulation				
Heart rate (bpm)	65 ± 10	64 ± 8	71 ± 12	0.12
Systolic blood pressure (mm Hg)	114 ± 11	114 ± 14	117 ± 12	0.79
Diastolic blood pressure (mm Hg)	69 ± 6	67 ± 9	69 ± 8	0.72
Ascending aortic distensibility ($\times 10^{-3}$ mm Hg^{-1})	3.3 ± 2.3	3.2 ± 1.8	3.1 ± 2.5	0.87
Descending aortic distensibility ($\times 10^{-3}$ mm Hg^{-1})	4.0 ± 1.6	3.8 ± 1.7	3.3 ± 1.9	0.26
Hemoglobin (g·L^{-1})	134 ± 8	141 ± 7*	133 ± 11**	**0.02**
LV morphology and function				
LV mass (g·m^{-2})	45 ± 4	46 ± 7	46 ± 6	0.89
T_1 (SASHA, ms)	1503 ± 28	1519 ± 36	1534 ± 32*	**0.02**
T_1 (MOLLI, ms)	1212 ± 27	1210 ± 39	1231 ± 24*	**0.04**
T_2 (ms)	42 ± 1	42 ± 1	41 ± 1	0.27
Ejection fraction (%)	64 ± 5	64 ± 4	62 ± 4	0.19
End-diastolic volume (mL·m^{-2})	75 ± 10	71 ± 11	72 ± 12	0.58
End-systolic volume (mL·m^{-2})	27 ± 6	25 ± 4	27 ± 5	0.45
GLS (%)	−24.2 ± 2.2	−22.1 ± 2.1*	−22.1 ± 2.1*	**0.01**
Cardiopulmonary exercise test				
$\dot{V}O_{2peak}$ (L·min^{-1})	2.13 ± 0.41	1.87 ± 0.46	1.69 ± 0.37*	**0.01**
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	29.5 ± 7.7	25.7 ± 8.2	23.1 ± 7.5*	**0.05**
Percent of reference value	108 ± 20	93 ± 24	84 ± 22*	**0.01**
Descriptive test data				
Peak power output (W)	165 ± 30	128 ± 38	132 ± 31	
Peak heart rate (bpm)	142 ± 15	158 ± 18	142 ± 16	
Peak ventilation (L·min^{-1})	83 ± 13	75 ± 19	71 ± 17	
Peak respiratory exchange ratio	1.27 ± 0.08	1.21 ± 0.11	1.29 ± 0.09	
Peak rating of perceived exertion (0–10)	9.2 ± 1.0	8.4 ± 1.7	9.3 ± 0.9	

Bold indicates significant differences ($P \leq 0.05$).
Data are presented as mean ± SD.
*Significantly different with $P < 0.05$ from no cancer controls.
**Significantly different with $P < 0.05$ from breast cancer—no anthracycline treatment yet.
CON, no cancer controls; BC No-AT, breast cancer No-AT yet; BC Post-AT, breast cancer Post-AT; $\dot{V}O_{2peak}$, peak volume of oxygen consumption.

−24.2% ± 2.2%, $P = 0.01$) in the Post-AT group compared with CON (Table 2). SASHA T_1 times for the No-AT group (1519 ± 36 ms) were not statistically different from the Post-AT and CON groups. Results were similar for MOLLI T_1 times. GLS was also reduced in the No-AT group relative to CON (−22.1% ± 2.1% vs −24.2% ± 2.2%, $P < 0.01$) but was similar to the Post-AT group.

Relationship between CMR variables and $\dot{V}O_{2peak}$. Within the breast cancer Post-AT group, previous left-sided radiation treatment was not a significant categorical predictor of $\dot{V}O_{2peak}$ or any of the CMR variables (data not shown). T_1 times were highly inversely associated with $\dot{V}O_{2peak}$ (SASHA: $R^2 = 64\%$, Figure 1A; MOLLI: $R^2 = 56\%$; Table 3). Adjustment for age or aerobic activity did not modify this relationship. The moderate associations between aortic distensibility (R^2 = 32% and 38% for ascending and descending), GLS ($R^2 = 30\%$), and indexed end-diastolic volume ($R^2 = 45\%$) with $\dot{V}O_{2peak}$ were no longer significant with adjustment for age.

Because of the greater prevalence of hypertension and higher hemoglobin in the breast cancer No-AT group, all analyses were performed with and without independent adjustment for these variables. The positive associations of indexed end-diastolic volume ($R^2 = 56\%$) and mass ($R^2 = 45\%$) with $\dot{V}O_{2peak}$ were no longer significant when adjusted for hypertension, but hypertension did not modify any other variables. In both the No-AT and the CON groups, the association of aortic distensibility with $\dot{V}O_{2peak}$ (R^2 range of 30%–39%; Table 3) was no longer significant after adjustment for age. The adjustment for hemoglobin also removed the significant relationship between aortic distensibility and $\dot{V}O_{2peak}$ in the No-AT group.

Influence of fitness on myocardial T_1 times. Exploratory *post hoc* analysis was performed to further examine the new finding of a strong association between T_1 times and $\dot{V}O_{2peak}$ in the breast cancer Post-AT group. First, it was confirmed that the relationship between T_1 time and $\dot{V}O_{2peak}$ in the Post-AT group remained an independent predictor with adjustment for the other identified predictor variables (i.e., GLS, end-diastolic volume, and aortic distensibility; data not shown). Second, given the 31-yr age range in our study, we aimed to determine the role of relative cardiorespiratory fitness level by categorization of participants into "fit" and "unfit" subgroups based on whether or not they met/exceeded 100% of the $\dot{V}O_{2peak}$ value for their age and sex. Those meeting the fit criterion also self-reported greater typical aerobic physical activity compared with the unfit participants (median, 275 vs 75 min·wk^{-1}; $P < 0.001$). SASHA T_1 times were compared between the fit and the unfit participants in each group using the same analyses for group comparisons described earlier.

T_1 was similar among all fit women in each group (CON: n = 10, 1504 ± 27 ms; No-AT: n = 6, 1501 ± 38; P = 0.99; Post-AT: n = 4, 1503 ± 36 ms; Fig. 1B). However, T_1 differed among the unfit groups (P = 0.02), where unfit CON (n = 6) still had T_1 times within normal ranges (1500 ± 33 ms) and unfit Post-AT (n = 12) had significantly elevated T_1 times (1546 ± 22, $P < 0.01$) in comparison (Fig. 1B). Among unfit women with breast cancer, T_1 times trended toward being higher Post-AT compared with No-AT (n = 10) (1546 ± 22 vs

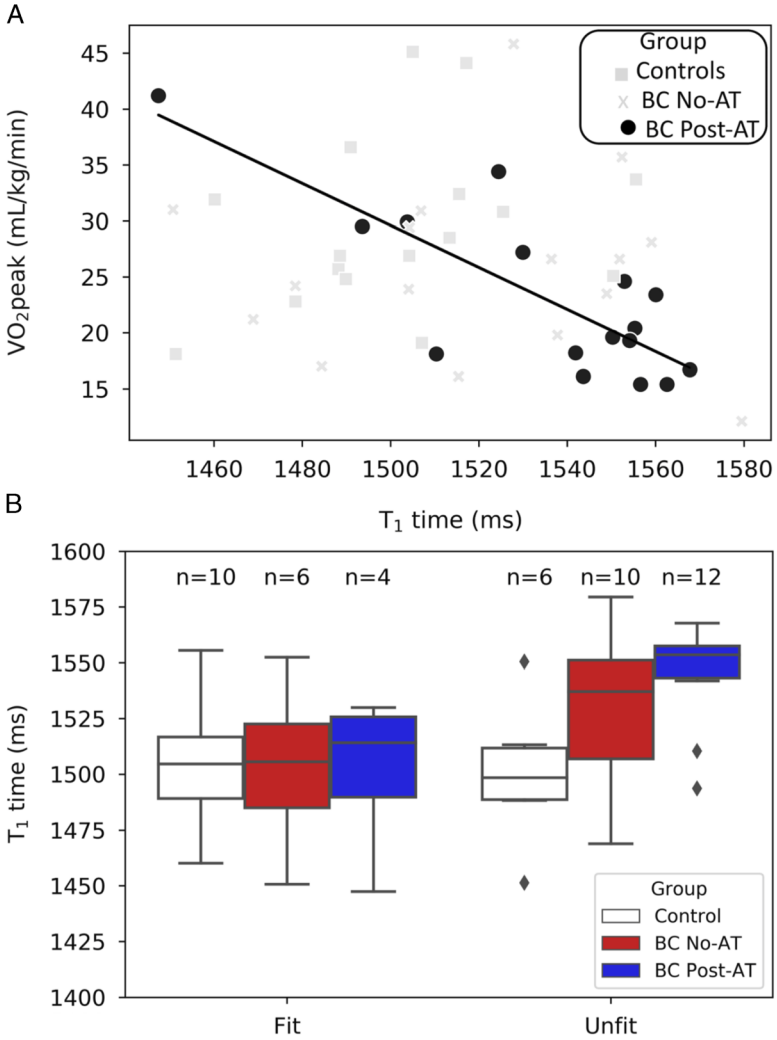

FIGURE 1—Relationships between relative $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1}) and myocardial SASHA T_1 times. A, Correlation of $\dot{V}O_{2peak}$ and T_1 time with significant trend line for breast cancer Post-AT group only. B, Box plot comparing native T_1 times between fit (≥100% of $\dot{V}O_{2peak}$ reference value) and unfit (<100% of $\dot{V}O_{2peak}$ reference value) women. BC No-AT, breast cancer No-AT yet; BC Post-AT, breast cancer Post-AT; Control, no cancer controls.

1529 ± 35, $P = 0.07$). There was no difference between unfit CON and unfit No-AT ($P = 0.13$).

DISCUSSION

A primary finding of this study is that women with a recent history of low-moderate dose anthracycline treatment for breast cancer with normal ejection fraction have significantly reduced $\dot{V}O_{2peak}$ and elevated myocardial T_1 times relative to matched women without a history of cancer. A robust independent relationship between the extent of myocardial T_1 time elevation and the impairment in $\dot{V}O_{2peak}$ was identified in this group. Women with breast cancer who have not yet received nonsurgical cancer treatment and also have normal ejection fraction did not have significantly different $\dot{V}O_{2peak}$ or myocardial T_1 time from matched controls.

Elevated native myocardial T_1 times have been associated with all-cause mortality, heart failure mortality, and hospitalization in noncancer populations (20). T_1 times vary with tissue water content and microstructure and have been correlated with histological assessment of collagen volume fraction, where longer times are associated with a greater degree of biopsy-quantified fibrosis (21). Myocardial T_2 values, which are more sensitive specifically to water mobility, were consistent between groups, suggesting no difference in myocardial edema or inflammation among these three groups (22). In the current study, the average T_1 time for the Post-AT group was 31 ms greater than the CON group. This difference is likely clinically relevant as it is similar in size to the difference noted in a case–control study of non-cancer-related dilated cardiomyopathy (where myocardial fibrosis is a hallmark pathologic feature) (23). We excluded for history of other common comorbid conditions that could impair the myocardium and confirmed that left-sided radiation therapy was not a significant predictor of CMR parameters or $\dot{V}O_{2peak}$. In composite, these findings suggest that the elevated T_1 times in the Post-AT group is likely consistent with anthracycline-related myocardial fibrosis.

TABLE 3. Unadjusted associations between CMR variables and cardiorespiratory fitness (relative $\dot{V}O_{2peak}$ in milliliters per kilogram per minute) between groups.

	CON (n = 16)		BC No-AT (n = 16)		BC Post-AT (n = 16)	
Variable	**ß (95% CI)**	**R^2 (%)**	**ß (95% CI)**	**R^2 (%)**	**ß (95% CI)**	**R^2 (%)**
Myocardial T_1 (SASHA)	0.08 (–0.07 to 0.23)	9	–0.01 (–0.14 to 0.12)	0	**–0.19 (–0.27 to –0.11)**	64
Myocardial T_1 (MOLLI)	–0.06 (–0.22 to 0.10)	5	0.01 (–0.11 to 0.13)	1	**–0.24 (–0.36 to –0.12)**	56
Myocardial T_2	–0.91 (–3.97 to 2.14)	3	–3.15 (–6.71 to 0.42)	20	–2.81 (–5.64 to 0.02)	25
LV mass	0.46 (–0.51 to 1.43)	7	**0.76 (0.27 to 1.23)**[a]	45	0.61 (–0.01 to 1.23)	24
LV end-diastolic volume	0.30 (–0.13 to 0.73)	14	**0.57 (0.28 to 0.86)**[a]	56	**0.42 (0.16 to 0.69)**[b]	45
LV end-systolic volume	0.12 (–0.67 to 0.91)	1	0.87 (–0.11 to 1.85)	21	0.56 (–0.24 to 1.36)	14
LV ejection fraction	0.45 (–0.48 to 1.38)	7	0.54 (–0.52 to 1.61)	8	0.81 (–0.23 to 1.85)	17
GLS	–0.82 (–2.73 to 1.10)	6	–0.80 (–3.02 to 1.42)	4	**–1.91 (–3.59 to –0.23)**[b]	30
Ascending aortic distensibility	**2.07 (0.57 to 3.57)**[b]	39	**2.59 (0.50 to 4.68)**[b,c]	34	**1.70 (0.27 to 3.13)**[b]	32
Descending aortic distensibility	**2.86 (0.67 to 5.04)**[b]	36	**2.7 (0.34 to 5.07)**[b,c]	30	**2.39 (0.63 to 4.15)**[b]	38

Bold indicates significant predictors before adjustment for confounding variables. Adjustment for age (all groups), physical activity (CON, BC Post-AT only), hemoglobin, and hypertension (No-AT only) did not modify relationships unless otherwise noted.
[a]No longer significant after adjustment for hypertension.
[b]No longer significant after adjustment for age.
[c]No longer significant after adjustment for hemoglobin.
CON, no cancer controls; BC No-AT, breast cancer No-AT yet; BC Post-AT, breast cancer Post-AT; ß, unstandardized beta coefficient; CI, confidence interval; R^2, coefficient of variation.

We have further demonstrated the clinical relevance of the effect of elevated T_1 times in an anthracycline-treated population by reporting a strong inverse coupling of T_1 time and $\dot{V}O_{2peak}$. Cardiorespiratory fitness commonly deteriorates with adjuvant cancer therapy (2–4). After anthracycline treatment in the current study, those with higher T_1 times (suggesting greater cardiomyocyte loss and more fibrosis) have lower $\dot{V}O_{2peak}$ values (indicating lower fitness), even after adjustment for current aerobic physical activity levels and age. This finding suggests that aerobic physical activity levels Post-AT do not alter the relationship between myocardial injury and $\dot{V}O_{2peak}$, perhaps due to the irreversibility of anthracycline-related myocardial injury. Our findings demonstrate that after anthracyclines, a 19-ms higher T_1 time was associated with one metabolic equivalent (i.e., 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) lower $\dot{V}O_{2peak}$. This magnitude of $\dot{V}O_{2peak}$ change has been associated with a 17% increased mortality risk among women after adjustment for cardiovascular risk factors (24). One other study has compared T_1 mapping and $\dot{V}O_{2peak}$ in survivors of childhood cancer 7.6 ± 4.5 yr after anthracycline treatment (25). In children, extracellular volume fraction, calculated using contrast-enhanced T_1 mapping, but not native T_1, was significantly associated with $\dot{V}O_{2peak}$ (25). Potential reasons for the discrepancy from the current study include the length of time since treatment, a younger myocardium at treatment and time of assessment, and mixed gender (50% male). These findings regarding T_1 mapping and $\dot{V}O_{2peak}$ in both studies suggest that anthracycline-related myocardial fibrosis may be an important determinant of exercise intolerance. This stresses the importance of cardioprotective strategies at the time of treatment, including potentially exercise training, or in the posttreatment setting, a targeted exercise training program to enhance noncardiac peripheral determinants of $\dot{V}O_{2peak}$.

We performed a *post hoc* analysis to further explore the relationship between fitness and T_1 time. T_1 times of unfit women who had not had previous anthracycline treatment (CON and No-AT groups) did not differ from fit women. It was only the subgroup with the combination of being unfit and receipt of previous anthracycline treatment that had significantly elevated T_1 times, indicative of fibrosis. Importantly, we found that the small subgroup of women who were fit Post-AT did not have elevated T_1 times. This subgroup included a competitive ultramarathoner and a professional fitness instructor among others, who were likely at the extreme end of physical activity levels before, during, and after anthracycline treatment. This finding is in line with preclinical data suggesting that higher levels of exercise (i.e., daily, moderate-intensity, 60 min per session) may be required concurrent to doxorubicin treatment to attenuate myocardial fibrosis, whereas lower volume was not sufficient (i.e., 5 $d \cdot wk^{-1}$, low-intensity, 45 min per session) (26,27). Similarly, in women with breast cancer, moderate adherence to two to three aerobic exercise sessions per week had no effect on the significant increase in myocardial T_1 time during anthracycline treatment (28). Taken together, this discrepancy and the finding of lower physical activity reported by the unfit group suggests that future longitudinal studies should explore the role of cardiorespiratory fitness (rather than exercise training alone) as a protective mechanism from the myocardial insult associated with anthracyclines. The small subgroup sample sizes should be noted as this warrants caution in interpretation of these results and the results should only be considered for hypothesis generating. Furthermore, our cross-sectional study design does not allow us to infer causation, but our careful selection of participants and analyses did confirm that the potential confounding factors of aging, overweight/obesity, cardiovascular risk associated with a cancer diagnosis, and receipt of left-sided radiation did not influence our T_1 time results. In addition, we found similar results using two different commonly used MRI methods for T_1 mapping of the myocardium, which reinforces our primary findings around T_1 times after anthracycline treatment and their relationship with $\dot{V}O_{2peak}$. We plan to test these hypotheses generated in this study with data being collected in our ongoing longitudinal trial among women scheduled to receive cardiotoxic therapies (10).

Breast cancer and cardiovascular disease share a number of modifiable risk factors (e.g., obesity, physical inactivity, and diabetes) and biological pathways related to disease development and progression (e.g., chronic inflammation, oxidative stress, upregulation of growth factors or enzymes) (29,30). The potential intersection of these conditions was the primary motivation for inclusion of the No-AT group in this study. The lack of statistical difference between the No-AT and the CON groups for both $\dot{V}O_{2peak}$ and T_1 time helps to isolate the influence of anthracycline treatment on the findings in the Post-AT group. Likewise, the numerical difference between the No-AT and the Post-AT groups in these metrics did not reach statistical difference. Yet, GLS was similar and significantly lower compared with the CON group in both the No-AT and the Post-AT groups. This suggests that the diffuse fibrosis in the Post-AT group did not significantly affect GLS relative to the No-AT group and potentially that distinct processes influence T_1 time and GLS in women with breast cancer. In mice, Sturgeon et al. (27) also demonstrated that a clinically relevant dose of doxorubicin induced myocardial fibrosis in the absence of overt functional changes in the heart. This finding of depressed GLS in treatment-naïve individuals with cancer has been previously reported using echocardiography (7) and predicts symptomatic heart failure, cardiac and all-cause mortality after treatment completion (31,32). The underlying biological pathways influencing both cancer and cardiovascular disease and their potential role in these findings require further investigation.

Two studies have reported short-term deteriorations (by ~25% and 50%) in aortic distensibility with anthracycline and/or trastuzumab treatment using similar CMR techniques (33,34). Our finding that aortic distensibility was not different in women ~12 months Post-AT relative to women with breast cancer before treatment or to controls is in line with one of these studies that reported recovery toward pretreatment levels within 12 months posttreatment (34). These findings suggest that the anthracycline-related increased stiffness of the large artery may be temporary. Aortic distensibility was the only cardiovascular function variable that was associated with $\dot{V}O_{2peak}$ in all three groups. Anthracycline treatment did not appear to affect this relationship as the strength of this relationship was similar in the Post-AT group. Age is well known to have a strong influence on aortic distensibility in women (35). In all three groups, after adjustment for age, this relationship was no longer significant, suggesting that aortic distensibility may partially mediate the relationship between age and cardiorespiratory fitness in women.

A limitation of this study is the cross-sectional design that does not allow us to draw conclusions on causality. Another limitation is the small sample size per group, which may introduce bias, yet the high reproducibility of CMR allows detection of small differences in function and T_1 values (23,36). Our recruitment approach for all groups described exercise tests, which may have positively biased our results toward more fit participants. Participants in this study were predominantly white and relatively healthy, which may limit generalizability.

CONCLUSION

In women with breast cancer who have received anthracycline chemotherapy treatment 1 yr earlier, native myocardial T_1 times are elevated and $\dot{V}O_{2peak}$ is depressed despite normal resting LV ejection fraction compared with age- and BMI-matched controls. In these women, the higher the native T_1 times, which may suggest greater myocardial fibrosis, the lower the measured $\dot{V}O_{2peak}$. Treatment-naïve women with breast cancer did not have elevated T_1 times or significantly lower $\dot{V}O_{2peak}$ but did have lower GLS compared with matched controls. Importantly, fit women from all groups had similar and low T_1 times, whereas unfit women who had received anthracyclines had elevated T_1 compared with unfit controls. A longitudinal study is needed to confirm this finding, suggesting that high levels of cardiorespiratory fitness may be associated with protection from anthracycline-related myocardial fibrosis.

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The authors declare that there is no conflict of interest.

The results of the present study do not constitute endorsement by the American College of Sports Medicine. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

REFERENCES

1. Kaminsky LA, Arena R, Beckie TM, et al. The importance of cardiorespiratory fitness in the United States: the need for a national registry. *Circulation*. 2013;127:652–62.
2. Klassen O, Schmidt ME, Scharhag-Rosenberger F, et al. Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy. *Acta Oncol*. 2014;53:1356–65.
3. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*. 2012;30:2530–7.
4. Jones LW, Haykowsky M, Pituskin EN, et al. Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor positive operable breast cancer. *Oncologist*. 2007;12:1156–64.
5. Monsuez JJ. Detection and prevention of cardiac complications of cancer chemotherapy. *Arch Cardiovasc Dis*. 2012;105:593–604.
6. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. *Ann Intern Med*. 1996;125:47–58.
7. Tadic M, Genger M, Baudisch A, et al. Left ventricular strain in chemotherapy-naive and radiotherapy-naive patients with cancer. *Can J Cardiol*. 2018;34:281–7.
8. Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from

cancer chemotherapy a systematic review. *Circ Cardiovasc Imaging*. 2013;6:1080–91.
9. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131:1981–8.
10. Pituskin E, Haykowsky M, McNeely M, Mackey J, Chua N, Paterson I. Rationale and design of the multidisciplinary team intervention in cardio-oncology study (TITAN). *BMC Cancer*. 2016;16:733.
11. Jones NL, Campbell EJ. *Clinical Exercise Testing*. Philadelphia: Saunders; 1982. p. 202.
12. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified look-locker inversion recovery (MOLLI) for high-resolutionT1 mapping of the heart. *Magn Reson Med*. 2004;52:141–6.
13. Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T1mapping. *Magn Reson Med*. 2013;71:2082–95.
14. Heiberg E, Sjögren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of segment—freely available software for cardiovascular image analysis. *BMC Med Imaging*. 2010;10:1.
15. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. *J Cardiovasc Magn Reson*. 2016;18:51.
16. Metafratzi ZM, Efremidis SC, Skopelitou AS, de Roos A. The clinical significance of aortic compliance and its assessment with magnetic resonance imaging. *J Cardiovasc Magn Reson*. 2002;4:481–91.
17. Godin G, Shephard RJ. Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*. 1997;29:S36.
18. Robergs RA, Dwyer D, Astorino T. Recommendations for improved data processing from expired gas analysis indirect calorimetry. *Sports Med*. 2010;40:95–111.
19. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911–39.
20. Puntmann VO, Carr-White G, Jabbour A, et al, International T1 Multicentre CMR Outcome Study. T1-mapping and outcome in nonischemic cardiomyopathy: all-cause mortality and heart failure. *JACC Cardiovasc Imaging*. 2016;9:40–50.
21. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart.* 2013;99:932–7.
22. Lota AS, Gatehouse PD, Mohiaddin RH. T2 mapping and T2* imaging in heart failure. *Heart Fail Rev*. 2017;22:431–40.
23. Costello BT, Springer F, Hare JL, et al. SASHA versus ShMOLLI: a comparison of T1 mapping methods in health and dilated cardiomyopathy at 3 T. *Int J Cardiovasc Imaging*. 2017;33:1551–60.
24. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women. *Circulation*. 2003;108:1554–9.
25. Tham EB, Haykowsky MJ, Chow K, et al. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson*. 2013;15:48.
26. Yang HL, Hsieh PL, Hung CH, et al. Early moderate intensity aerobic exercise intervention prevents doxorubicin-caused cardiac dysfunction through inhibition of cardiac fibrosis and inflammation. *Cancers (Basel)*. 2020;12:1102.
27. Sturgeon K, Schadler K, Muthukumaran G, et al. Concomitant low-dose doxorubicin treatment and exercise. *Am J Physiol Regul Integr Comp Physiol*. 2014;307:R685–92.
28. Costello BT, Roberts TJ, Howden EJ, et al. Exercise attenuates cardiotoxicity of anthracycline chemotherapy measured by global longitudinal strain. *JACC CardioOnc*. 2019;1:298–301.
29. Kirkham AA, Beaudry RI, Paterson DI, Mackey JR, Haykowsky MJ. Curing breast cancer and killing the heart: a novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer. *Prog Cardiovasc Dis*. 2019;62:116–26.
30. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133:1104–14.
31. Ali MT, Yucel E, Bouras S, et al. Myocardial strain is associated with adverse clinical cardiac events in patients treated with anthracyclines. *J Am Soc Echocardiogr*. 2016;29:522–527.e3.
32. Rhea IB, Uppuluri S, Sawada S, Schneider BP, Feigenbaum H. Incremental prognostic value of echocardiographic strain and its association with mortality in cancer patients. *J Am Soc Echocardiogr*. 2015;28:667–73.
33. Chaosuwannakit N, D'Agostino R Jr, Hamilton CA, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. *J Clin Oncol*. 2010;28:166–72.
34. Grover S, Lou PW, Bradbrook C, et al. Early and late changes in markers of aortic stiffness with breast cancer therapy. *Intern Med J*. 2015;45:140–7.
35. Nethononda RM, Lewandowski AJ, Stewart R, et al. Gender specific patterns of age-related decline in aortic stiffness: a cardiovascular magnetic resonance study including normal ranges. *J Cardiovasc Magn Reson*. 2015;17:20.
36. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2000;2:271–8.