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# Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients

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## Abstract

**Background:** Anthracycline chemotherapy may be associated with decreased cardiac function and functional capacity measured as the peak oxygen uptake during exercise ($\dot{V}O_2$ peak). We sought to determine (a) whether a structured exercise training program would attenuate reductions in $\dot{V}O_2$ peak and (b) whether exercise cardiac imaging is a more sensitive marker of cardiac injury than the current standard of care resting left ventricular ejection fraction (LVEF).

**Methods:** Twenty-eight patients with early stage breast cancer undergoing anthracycline chemotherapy were able to choose between exercise training (mean ± SD age 47 ± 9 years, $n = 14$) or usual care (mean ± SD age 53 ± 9 years, $n = 14$). Measurements performed before and after anthracycline chemotherapy included cardiopulmonary exercise testing to determine $\dot{V}O_2$ peak and functional disability ($\dot{V}O_2$ peak < 18 ml/min/kg), resting echocardiography (LVEF and global longitudinal strain), cardiac biomarkers (troponin and B-type natriuretic peptide) and exercise cardiac magnetic resonance imaging to determine stroke volume and peak cardiac output. The exercise training group completed 2 × 60 minute supervised exercise sessions per week.

**Results:** Decreases in $\dot{V}O_2$ peak during chemotherapy were attenuated with exercise training (15 vs. 4% reduction, $P = 0.010$) and fewer participants in the exercise training group met the functional disability criteria after anthracycline chemotherapy compared with those in the usual care group (7 vs. 50%, $P = 0.01$). Compared with the baseline, the peak exercise heart rate was higher and the stroke volume was lower after chemotherapy ($P = 0.003$ and $P = 0.06$, respectively). There was a reduction in resting LVEF (from 63 ± 5 to 60 ± 5%, $P = 0.002$) and an increase in troponin (from 2.9 ± 1.3 to 28.5 ± 22.4 ng/mL, $P < 0.0001$), but no difference was observed between the usual care and exercise training group. The baseline peak cardiac output was the strongest predictor of functional capacity after anthracycline chemotherapy in a model containing age and resting cardiac function (LVEF and global longitudinal strain).

**Conclusions:** The peak exercise cardiac output can identify patients at risk of chemotherapy-induced functional disability, whereas current clinical standards are unhelpful. Functional disability can be prevented with exercise training.

## Keywords

Exercise, survivorship, heart failure, cardiorespiratory fitness, cardiotoxicity

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## Introduction

Survival from breast cancer has improved progressively over the past 25 years as a result of earlier detection and advances in cancer care.[1] Despite improved breast cancer outcomes, however, survivors are faced with an increased risk of developing cardiovascular disease due to the potential for anticancer therapies to exacerbate underlying comorbid conditions, accelerate cardiovascular aging, and directly impair cardiovascular function.[2]

Anthracycline chemotherapy is a mainstay of treatment for higher risk patients with early-stage breast cancer, but treatment has been associated with dose-dependent left ventricular dysfunction, termed cardiotoxicitiy.[3] Although only a small percentage of patients develop acute cardiac complications during treatment, a significant proportion develop heart failure in the longer term and, overall, cardiovascular conditions are the dominant cause of mortality in women with early stage breast cancer.[4,5] The early and accurate identification of cardiotoxicity is crucial to enable the targeted use of cardioprotective interventions and prevent morbidity from chemotherapy-induced heart failure.[6,7] However, the current standard of care relies on the evaluation of resting left ventricular function as quantified by the left ventricular ejection fraction (LVEF) or tissue deformation as the global longitudinal strain (GLS).[8] These measures have only modest reproducibility and can only identify cardiac dysfunction at a relatively advanced stage. Although clinical weight is placed on changes in the LVEF within the normal range (>45–50%), these have not been shown to correlate with prognosis, cardiovascular reserve or risk of heart failure.[9,10] Furthermore, right ventricular function may be a crucial determinant of heart failure[11] and there is no data documenting the impact of anthracycline-based chemotherapy on the right ventricle.

Current diagnostic techniques for the identification of cardiotoxicity rely on resting measures of left ventricular function and therefore do not assess the heart's functional capacity or reserve. The LVEF may be normal despite the patient having limited ability to increase cardiovascular function in response to physical activity or illness. Some studies have suggested that an assessment of exercise cardiac reserve may be a better measure of global cardiovascular capacity, a more sensitive and accurate marker of early cardiac injury, and a predictor of future events.[2]

Peak oxygen uptake during exercise ($\dot{V}O_2$ peak) is a holistic measure of functional capacity and a low $\dot{V}O_2$ peak is associated with heart failure and increased mortality.[12–14] Importantly, $\dot{V}O_2$ peak is modifiable by the relatively inexpensive, yet effective, intervention of exercise training. There is good evidence demonstrating the favorable effects of exercise training on cardiovascular function in both the general population[15] and those with existing cardiovascular disease.[16] Exercise training during chemotherapy has been demonstrated to reduce fatigue[17] and is considered to be safe and effective in improving physical fitness.[18] There is currently only limited data on whether the benefits of exercise also include protection from anthracycline-induced cardiac injury. It may be hypothesized that the combination of global and specific measures of cardiac function during exercise ($\dot{V}O_2$ peak and peak cardiac output, respectively) may identify patients at risk of heart failure with the greatest accuracy.

We tested the hypothesis that (a) a structured exercise training program will prevent a decrease in $\dot{V}O_2$ peak and (b) measurements of cardiac reserve are a more sensitive marker of early cardiac injury than the standard of care measurement of resting LVEF.

## Methods

### *Participant population and study design*

This study was a prospective, non-randomized controlled trial. Women with early stage breast cancer were recruited from local hospitals in the Melbourne metropolitan area. Patients self-selected to participate in either exercise training or usual care before starting anthracycline-based chemotherapy. After obtaining informed consent, all participants were screened for eligibility to participate in the study. The exclusion criteria included known structural heart disease, arrhythmias, or a contraindication to cardiac magnetic resonance imaging (CMR). The experimental procedures were explained to all participants, with informed consent obtained as approved by the institutional review boards of the Alfred Health Research Ethics Committee and registered with Australia and New Zealand Clinical Trials Registry (ACTRN12616001602415). All procedures conformed to the standards set by the Declaration of Helsinki.

### *Interventions*

*Exercise intervention.* A periodized exercise training program incorporating aerobic and resistance exercises was designed to synchronize with the participant's individual chemotherapy schedule and was started after the first treatment. For those participants who received the dose-dense protocol ($n = 3$), the intervention was about 8 weeks long, whereas all other patients received a 12-week intervention. Participants performed two supervised exercise sessions per week (each consisting of 30 minutes of aerobic training and 30 minutes of resistance training). Participants were also prescribed one unsupervised 30–60 minute home-based aerobic

exercise session per week. Each exercise program was individually prescribed based on the baseline maximal exercise test and regular submaximal incremental exercise tests performed throughout the intervention. This periodization plan followed a modified version of the 2:1 step paradigm (2 weeks of loading, 1 week unloading), which is similar to an athletic-style mesocycle. The periodization plan incorporated a 2–10% increase in exercise intensity per non-treatment week, whereas during the treatment week the exercise intensity was reduced by 2–10% with no change in training volume. Importantly, this model accounted for the accumulation of fatigue with the inclusion of an unloading week, which corresponded to the week following chemotherapy treatment. Total minutes of weekly unsupervised exercise was monitored by a logbook method and reported to the study exercise physiologist weekly.

*Usual care group.* The usual care group received standard medical care throughout the trial. These participants were not provided with any specific exercise recommendations, but were not precluded from exercising independently of the study.

## Measurements

All participants underwent a battery of testing before starting and three weeks after completing anthracycline chemotherapy.

*Patient history.* The medical history, reported physical activity levels, and resting blood pressure of the participants were recorded.

*Exercise capacity.* Exercise tests were performed on an electronically braked cycle ergometer (Lode, Gronigen, the Netherlands) for the measurements of $\dot{V}O_2$ peak. Briefly, all participants performed an incremental ramp protocol, which began at 10–25 W and progressively increased at 10–30 W/min until volitional exhaustion. Respiratory gas analysis was measured continuously throughout the test using a calibrated metabolic cart (True One 2400, Parvomedics, Sandy, UT, USA). $\dot{V}O_2$ peak was defined as a 30 s rolling average of the six highest 5 s oxygen consumption values.

*Echocardiography.* A comprehensive resting echocardiography study (Vivid E95, General Electric Medical Systems, Milwaukee, WI, USA) was performed and images were saved in a digital format for offline analysis (Echopac v13.0.00, GE, Norway). A full-volume, three-dimensional dataset was acquired. Left ventricular end-diastolic and end-systolic volumes were measured according to standard recommendations.[19] Two-dimensional global left ventricular strain was quantified from three apical views at a temporal resolution of 60–90 frames/s. The average negative value on the strain curve was reported as GLS. Left ventricular inflow was assessed by pulsed-wave Doppler from the apical four-chamber view with the sample volume located between the tips of mitral leaflets and included peak early ($E$) and late diastolic flow velocity ($A$), and the deceleration time of the E-wave. Pulsed-wave tissue Doppler was used to measure the peak early diastolic tissue velocity ($e'$) at the septal and lateral portions of the mitral annulus. The ratio of early diastolic mitral inflow to mitral annular velocity ($E/e'$) and the ratio of early diastolic inflow to late diastolic inflow ($E/A$) were used as measures of diastolic function.

*CMR imaging.* The real-time CMR protocol used in this study has been described in detail previously and validated against invasive measures.[20] In brief, imaging was performed with a Siemens MAGNETOM Prisma 3.0T CMR instrument with a five-element phased array coil. Ungated, real-time, steady-state, free-precision cine imaging was performed without cardiac or respiratory gating. Forty to 75 consecutive frames were acquired every 36–38 ms at each of the 13–18 contiguous 8 mm slices in the SAX plane, and 50 consecutive frames were acquired at about the same temporal resolution for 11–15 contiguous 8 mm slices in the HLA plane. Using this technique, our group has demonstrated excellent inter-observer ($R = 0.98$ and $R = 0.97$ for left ventricular and right ventricular stroke volume, respectively) and inter-study reproducibility ($R = 0.98$ for cardiac output).

After resting images were obtained, the participants cycled on a magnetic resonance imaging compatible ergometer (MR Ergometer Pedal, Lode, Groningen, the Netherlands) at an intensity equal to 20, 40, and 60% of the maximal power output obtained during the upright incremental cycle exercise test. These workloads will subsequently be referred to as rest and low, moderate, and high intensity. We have previously determined that 66% of the maximal power during upright cycling approximates the maximal exercise capacity in a supine position.[20] Each stage of exercise was maintained for about 3 min 30 s to achieve a physiological steady state and 2.5 min for image acquisition.

The images were analyzed on a software program developed in-house (RightVol – Right Volume Leuven, Leuven, Belgium) in which the physiological data (respiratory movement and electrocardiogram) were synchronized to the images so that contouring could be performed at the same point in the respiratory

cycle, thereby greatly minimizing the cardiac translation error. Left and right ventricular endocardial contours were then manually traced on the SAX image and the points of transection with the HLA plane were indicated, thus enabling constant referencing of the atrioventricular valve plane. Trabeculations and the papillary muscle were considered to be part of the ventricular blood pools and the volumes were calculated by a summation of disks. Stroke volume was measured as the difference between the end-diastolic and end-systolic volumes, whereas cardiac output ($Q_c$) was calculated as (RVSV+LVSV/2) × heart rate. Cardiac reserve was defined as the ability to augment $Q_c$ during exercise (peak $Q_c$). Peripheral muscle arterio-venous oxygen extraction was calculated indirectly according to the Fick principle,[21] using $\dot{V}O_2$ peak and peak $Q_c$ measured by exercise CMR.

*Biochemistry.* Peripheral venous blood samples were collected to measure B-type natriuretic peptide and troponin I. Hemoglobin values were obtained from the participants' medical records.

*Definition of functional disability.* The assessment of change in $\dot{V}O_2$ peak was used to quantify the number of participants who fell below the $\dot{V}O_2$ peak cut-off point suggested by the American Heart Association Scientific Statement as that required for functional independence (i.e., 18 ml/kg/min) at the follow-up visit.[22]

*Statistical analysis.* Continuous variables were checked for normal distribution via the Kolmogorov–Smirnov test and are expressed as mean ± standard deviation (SD) values and categorical variables are expressed as *n* (%). The primary analysis included all participants who completed follow-up testing after the completion of anthracycline-based chemotherapy. Continuous variables were compared by ANCOVA (for variables from the upright exercise test) or repeated measures ANOVA analyses. The repeated measures models included a repeated factor for study visits and an interaction term for the time × exercise response. To determine whether exercise training modified any of the variables the group × time and group × time × exercise response were also assessed where appropriate. Age, LVEF, GLS, biomarkers, and anthracycline dose were assessed as univariate predictors of functional disability. According to the per-stated hypothesis, a logistic regression analysis was performed in which cardiac reserve (peak cardiac output) was added to the model after age and LVEF had been entered to determine whether cardiac reserve had added independent predictive value. Two-sided $P < 0.05$ was considered statistically significant.

## Results

### Participant characteristics

Thirty women with early stage breast cancer were recruited to participate in this non-randomized study between November 2015 and March 2017. The participants were able to choose between either usual care or exercise training for the duration of their anthracycline chemotherapy. Two participants withdrew from the study before completing the baseline testing due to changes in their personal circumstances and geographical constraints. The participant characteristics are summarized in Table 1. The usual care group were older and, although the groups reported a similar

**Table 1.** Characteristics of participants.

| | Usual care ($n = 14$) | Exercise training ($n = 14$) | *P* |
|---|---|---|---|
| Age (years) | 52 ± 12 | 42 ± 9 | 0.10 |
| Weight (kg) | 74.9 ± 16.4 | 67.4 ± 20.7 | 0.29 |
| Body mass index (kg/m$^2$) | 27.8 ± 6.2 | 25.2 ± 7.6 | 0.33 |
| $VO_2$peak (ml/kg/min) | 22.0 ± 5.9 | 27.4 ± 5.7 | 0.021 |
| Systolic blood pressure (mmHg) | 125 ± 17 | 121 ± 15 | 0.49 |
| Diastolic blood pressure (mmHg) | 80 ± 11 | 73 ± 1.8 | 0.07 |
| Family history of breast cancer | 7 (50) | 5 (36) | 0.44 |
| Physical activity (sessions/week) | 3.3 ± 2.8 | 4.5 ± 2.6 | 0.29 |
| Physical activity duration (min) | 35 ± 24 | 52 ± 22 | 0.08 |
| Breast cancer diagnosis | | | |
| HER2+ | 4 (29) | 2 (14) | 0.85 |
| Triple negative | 3 (21) | 8 (57) | 0.053 |
| ER and/or PR positive | 7 (50) | 4 (29) | 0.25 |
| Treatment | | | |
| Anthracycline (doxorubicin/ cyclophosphamide)[a] | 11 (79) | 9 (64) | 0.60 |
| Dose-dense, 2-weekly anthracycline[a] | 2 (14) | 3 (21) | 0.62 |
| FEC-D (fluouracil, epirubicin, cyclophosphamide, docetaxel) | 1 (7) | 2 (14) | 0.54 |

ER: estrogen-receptor positive; HER2+: human epidermal growth factor receptor 2; PR: progesterone-receptor positive.
Continuous variables are presented as mean ± SD values and categorical variables as *n* (%).
[a]With or without subsequent taxane therapy.

level of physical activity before starting treatment, they were less fit and heavier than the exercise group. One patient in the usual care group reported a history of hypertension and two reported a history of hyperlipidemia. There was no reported cardiovascular risk factor in the exercise training group. The primary breast cancer diagnosis was similar between groups, as were the prescribed chemotherapy regimen and dose of chemotherapy received (Table 1). The adherence to the exercise intervention was modest, with half of the participants completing 80% of the 24 prescribed sessions (group average 76%, range 38–88%). In addition, the exercise training group reported performing $76 \pm 8$ min/week of unsupervised exercise.

## Exercise capacity

The effect of anthracycline therapy on exercise capacity is summarized in Table 2 and Figure 1(a). Following treatment, there was a greater reduction in $\dot{V}O_2$ peak and peak power output in the usual care group (15 and 14%, respectively) compared with the exercise intervention (about 4 and 1%; group × time interactions $P = 0.01$ and $P = 0.013$, respectively).

## Resting cardiac function, morphology, and cardiac biomarkers

Conventional echocardiographic measurements of resting cardiac function are summarized in Table 3. There was a small, but statistically significant, reduction in resting LVEF measured by echocardiography after anthracycline treatment. Five participants (17.8%) had a >10% change in LVEF during the course of treatment (from $69 \pm 3$ to $55 \pm 3$%), but the LVEF did not fall to <50% in any patient. The GLS was unchanged, as were indices of diastolic function (Table 3). Exercise training had no effect on resting measures of cardiac function. Anthracycline chemotherapy was associated with a significant increase in troponin (time $P < 0.0001$), which tended to be lower in the exercise-trained group (group × time, $P = 0.10$) whereas there was no change in B-type natriuretic peptide levels (visit $P = 0.95$, group × time $P = 0.99$). Hemoglobin levels were reduced similarly in both groups (Time $P < 0.0001$, Group × Time $P = 0.50$).

## Cardiac reserve

The central hemodynamic response to exercise is summarized in Figure 2 and Table 4. In contrast to our hypothesis, exercise training did not significantly affect measures of cardiac reserve after the completion

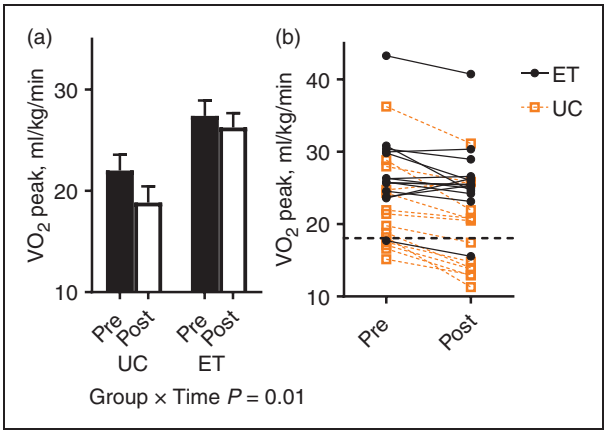


**Figure 1.** Effect of usual care and exercise training on $VO_2$ peak. (a) The $VO_2$ peak is significantly reduced with chemotherapy in the usual care group, but the effect is blunted in the exercise-trained group. (b) Individual responses in $VO_2$ peak relative to the threshold for independent living (18 ml/kg/min) (signified by the dashed line).

**Table 2.** Peak exercise parameters during upright cycle exercise.

| | Usual care | | Exercise trained | | *P* (group × time) |
|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | |
| Peak power (W) | $134 \pm 55$ | $117 \pm 54$ | $145 \pm 36$ | $149 \pm 35$ | 0.003 |
| $VO_2$ peak (L/min) | $1.62 \pm 0.43$ | $1.38 \pm 0.47$ | $1.79 \pm 0.34$ | $1.69 \pm 0.29$ | 0.054 |
| Peak heart rate (bpm) | $172 \pm 14$ | $176 \pm 14$ | $173 \pm 6$ | $174 \pm 10$ | 0.84 |
| Respiratory exchange ratio | $1.20 \pm 0.11$ | $1.25 \pm 0.14$ | $1.27 \pm 0.09$ | $1.29 \pm 0.12$ | 0.40 |
| Peak stroke volume (mL) | $92 \pm 6$ | $89 \pm 9$ | $97 \pm 13$ | $97 \pm 10$ | 0.20 |
| Peak cardiac output (L/min)* | $15.9 \pm 1.9$ | $15.7 \pm 2.2$ | $16.7 \pm 2.4$ | $16.8 \pm 2.1$ | 0.51 |
| Arterio-venous $O_2$ difference (%)[a] | $10.2 \pm 2.2$ | $8.7 \pm 2.1$ | $10.8 \pm 2.1$ | $10.1 \pm 1.9$ | 0.035 |

[a]Calculated from peak stroke volume measured during CMR.
Data are presented as mean±SD values.

**Table 3.** Resting echocardiographic measures of cardiac function and biochemical measures.

| | Usual care | | Exercise trained | | | |
|---|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment e | Post-treatment | *P* (time) | *P* (group × time) |
| LVEF (%) | 62.8 ± 4.9 | 59.1 ± 4.1 | 64.1 ± 5.0 | 60.6 ± 5.4 | 0.003 | 0.95 |
| GLS (%) | −20.4 ± 2.1 | −19.5 ± 2.0 | −19.7 ± 2.0 | −19.6 ± 2.0 | 0.17 | 0.28 |
| *E/A* | 1.09 ± 0.46 | 1.03 ± 0.46 | 1.31 ± 0.29 | 1.23 ± 0.24 | 0.35 | 0.94 |
| *E/e′* | 7.76 ± 2.38 | 6.99 ± 2.05 | 7.28 ± 2.09 | 7.21 ± 2.15 | 0.33 | 0.42 |
| DT (cm/s) | 212 ± 31 | 218 ± 45 | 210 ± 35 | 219 ± 33 | 0.37 | 0.87 |
| LAVI (ml/m$^2$) | 28.7 ± 7.4 | 28.6 ± 9.4 | 30.8 ± 6.7 | 33.5 ± 5.9 | 0.37 | 0.33 |
| LVMI (g/m$^2$) | 61 ± 14 | 64 ± 17 | 62 ± 9 | 62 ± 11 | 0.53 | 0.50 |
| BNP (ng/L) | 35.8 ± 39.6 | 36.2 ± 19.7 | 39.6 ± 31.6 | 40.2 ± 23.4 | 0.95 | 0.99 |
| Troponin I (ng/L) | 2.6 ± 1.0 | 35.6 ± 27.2 | 3.2 ± 1.5 | 21.4 ± 16.0 | <0.001 | 0.10 |
| Hemoglobin (g/dL) | 13.3 ± 1.8 | 11.1 ± 0.9 | 12.9 ± 1.3 | 11.1 ± 1.7 | <0.001 | 0.50 |

Data are mean ± SD values.
BNP: B-type natriuretic peptide; DT: deceleration time; *E/A* ratio: ratio of peak early to late mitral inflow velocities; *E/e′* ratio: ratio of peak early mitral inflow to peak early mitral annular velocity; GLS: global longitudinal strain; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index.

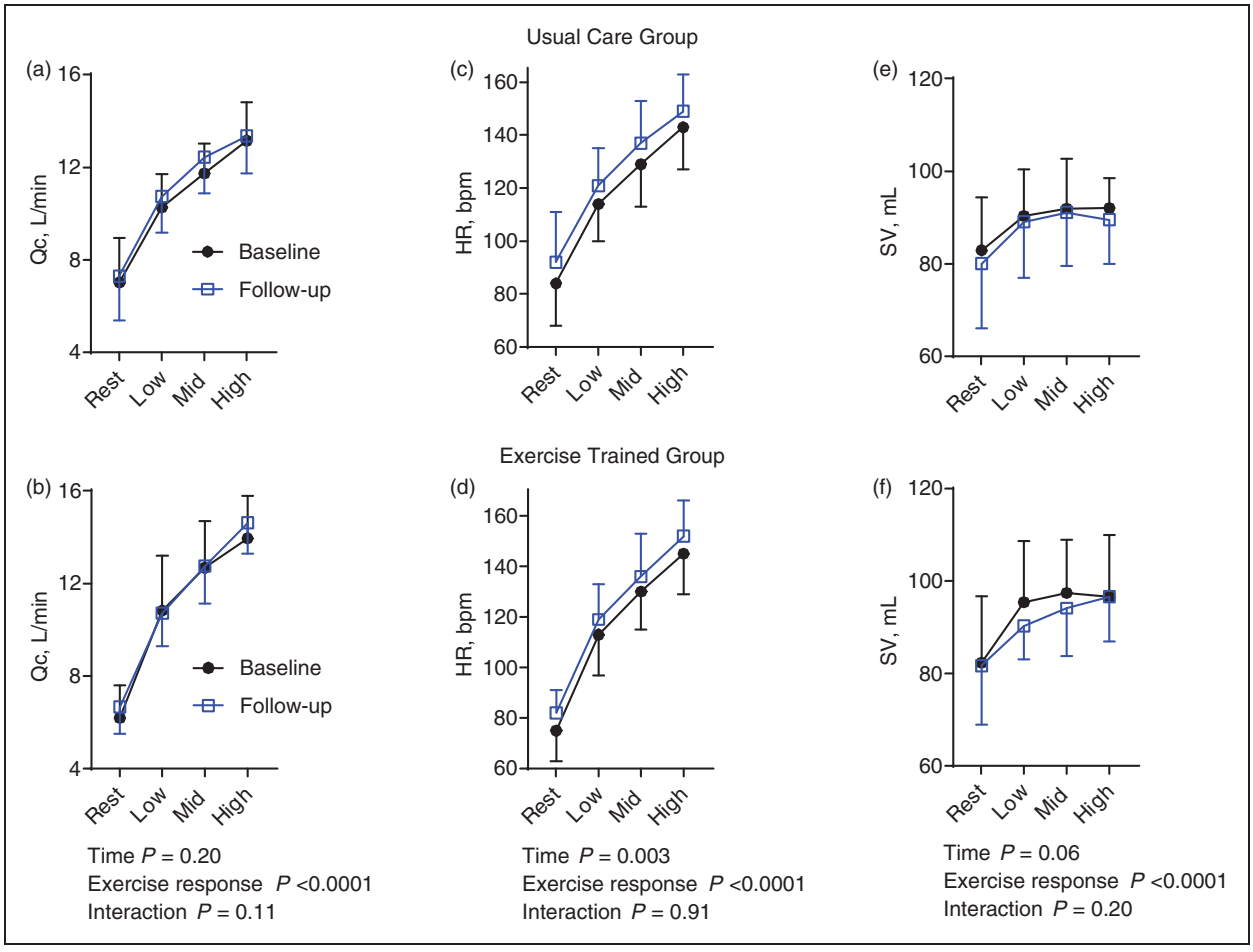


**Figure 2.** Effect of usual care and exercise training on response in cardiac reserve before and after chemotherapy. Cardiac output ($Q_c$) was unchanged with chemotherapy in (a) the usual care group and (b) the exercise-trained group. (c, d) Heart rate was significantly increased in both groups, although there was a trend (e, f) toward a reduction in stroke volume during exercise.

**Table 4.** Effect of chemotherapy on the biventricular response to exercise.

| | Rest | Light | Moderate | High | *P* (time) | *P* (group × time) |
|---|---|---|---|---|---|---|
| Pre-treatment LVEDV (mL) | 125 ± 21 | 130 ± 18 | 131 ± 17 | 131 ± 19 | 0.43 | 0.99 |
| Post-treatment LVEDV (mL) | 131 ± 21 | 135 ± 20 | 133 ± 19 | 134 ± 16 | | |
| Pre-treatment LVESV (mL) | 40 ± 11 | 35 ± 10 | 33 ± 11 | 34 ± 11 | 0.21 | 0.28 |
| Post-treatment LVESV (mL) | 41 ± 11 | 37 ± 11 | 36 ± 12 | 35 ± 11 | | |
| Pre-treatment RVEDV (mL) | 131 ± 21 | 135 ± 20 | 133 ± 19 | 134 ± 16 | 0.31 | 0.49 |
| Post-treatment RVEDV (mL) | 129 ± 21 | 130 ± 18 | 133 ± 20 | 132 ± 16 | | |
| Pre-treatment RVESV (mL) | 50 ± 12 | 44 ± 12 | 41 ± 12 | 42 ± 10 | 0.70 | 0.75 |
| Post-treatment RVESV (mL) | 50 ± 12 | 43 ± 12 | 41 ± 13 | 40 ± 10 | | |
| Pre-treatment LVEF (%) | 67 ± 6 | 72 ± 5 | 73 ± 6 | 73 ± 6 | 0.72 | 0.54 |
| Post-treatment LVEF (%) | 67 ± 6 | 72 ± 6 | 73 ± 7 | 74 ± 6 | | |
| Pre-treatment RVEF (%) | 63 ± 5 | 70 ± 7 | 72 ± 6 | 71 ± 5 | 0.06 | 0.72 |
| Post-treatment RVEF (%) | 61 ± 6 | 68 ± 6 | 70 ± 6 | 70 ± 6 | | |

Data are presented as mean±SD values.
LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; RVEF: right ventricular ejection fraction; RVEDV: right ventricular end-diastolic volume; RVESV: right ventricular end-systolic volume.

of anthracycline chemotherapy. Cardiac output increased similarly in response to exercise at both visits (time $P = 0.20$, interaction $P = 0.11$). After anthracycline therapy, the heart rate response to exercise at a given workload was significantly higher for both groups (Figure 2(c) and 2(d), time $P = 0.003$, interaction $P = 0.91$), and consequently stroke volume tended to be lower (Figure 2(e) and 2(f), time $P = 0.06$, interaction $P = 0.20$). All other measures of cardiac function responded similarly after treatment (Table 4), excluding right ventricular ejection fraction, which tended to be lower at follow-up, both at rest and during exercise.

### *Predictors of functional disability*

Following anthracycline therapy, a greater proportion of the usual care group met the criteria for functional disability ($\dot{V}O_2$ peak <18 ml/kg/min) than the exercise group (7 of 14 (50%) vs. 1 of 14 (7%), $P = 0.01$, respectively; Figure 1(b)). Age, anthracycline dose and measures of cardiac function performed at baseline (before chemotherapy) were assessed as predictors of functional disability at the completion of chemotherapy. Baseline cardiac reserve (estimated from peak cardiac output) was independently associated with functional disability ($R^2 = 0.23$, $P = 0.012$), whereas age, LVEF and GLS were not. There was no association between the change in LVEF or GLS and the change in $VO_2$peak ($R^2 = 0.00$ and $R^2 = 0.04$, respectively), nor was there any association between the change in biomarkers and $\dot{V}O_2$ peak (troponin $R^2 = 0.02$ and B-type natriuretic peptide $R^2 = 0.00$).

## Discussion

We were able to confirm the value of exercise testing and exercise therapy in breast cancer patients treated with anthracycline chemotherapy. We demonstrated that (a) exercise measures of cardiac function predicted the patients who developed significant functional impairment during cancer treatment and (b) a supervised exercise training program markedly attenuated functional decline. Importantly, resting measures of cardiac function, representing the current standard of care for identifying those at risk of cardiotoxicity, did not predict a decrease in functional capacity and the minor changes that occurred during chemotherapy were independent of changes in $\dot{V}O_2$ peak.

There is a strong relationship between cardiorespiratory fitness and risk of heart failure, cardiovascular events, and overall mortality.[23,24] Reductions in fitness are related to poorer prognoses and outcomes in both the general population[25,26] and cancer survivors.[27,28] In the usual care group, we observed a 15% reduction in $\dot{V}O_2$ peak during a 4-month period of anthracycline-based chemotherapy. This decrease approximates the change that would normally be expected with 15 years of aging.[27] Functional disability represents an important clinical outcome[22] because it defines a population in need of assistance to perform the activities of daily living,[29] is associated with a seven-fold increase in heart failure risk,[23] and a two-fold increase in all-cause mortality in breast cancer patients.[27] Neither age nor current standard of care echocardiographic measures of resting left ventricular function were related to dropping below the threshold of

independent living. Cardiac reserve was the only early indicator of those at risk of functional disability and thus may be used in risk stratification before chemotherapy.

Compared with the marked reductions in $\dot{V}O_2$ peak observed in the usual care group, the changes in standard resting measures of cardiac function were modest. There was no change in GLS and only a 5.5% relative reduction in the LVEF. Furthermore, the LVEF did not fall to <50% in any of the participants and the magnitude of change in the LVEF did not correlate with reductions in cardiopulmonary fitness. Cardiac troponin, but not B-type natriuretic peptide, increased significantly after chemotherapy, although the increase did not correlate with any meaningful clinical outcome. The GLS did not fall significantly (relative reduction >15%) in any participant and chemotherapy had no effect on the average GLS values. This is surprising given that GLS has been demonstrated to be more reproducible and sensitive to subtle changes in myocardial function, resulting in optimism that it may be a favorable tool for the assessment of cardiotoxicity.[30] However, our findings are consistent with recent studies that have observed no change[31] or only very modest changes in GLS[32] associated with anthracycline use in breast cancer patients. Thus the marked changes in cardiopulmonary fitness and the accompanying increase in risk would not be identified using the types of cardiovascular assessment that are currently used as part of typical chemotherapy risk surveillance programs.

Contrary to expectation, anthracycline chemotherapy did not cause a marked reduction in cardiac reserve. Rather, the change in $\dot{V}O_2$ peak in the usual care group appears to be driven mostly by reductions in skeletal muscle oxidative metabolism. Specifically, estimated peripheral oxygen extraction fell by 11%. Thus neither the change in cardiac reserve nor peripheral oxygen consumption was able to fully explain the substantial reductions in $\dot{V}O_2$ peak, nor the difference in the groups. Our methodology may have contributed to this observation and it is possible that we did not identify a subtle decrease in exercise cardiac function. Despite a significant reduction in peak power during the follow-up testing, we prescribed the workload for the magnetic resonance imaging ergometer according to the baseline $\dot{V}O_2$ peak testing. Thus the same power output was performed for both tests, implying that this would have represented a greater relative level of exertion on the post-chemotherapy testing for many participants. This is supported by the fact that the heart rate was higher throughout testing after chemotherapy (Figure 2(c) and 2(d)). Interestingly, the stroke volume tended to be lower ($P = 0.06$) throughout exercise on follow-up testing and this finding is suggestive of anthracycline-induced cardiac injury and reduced cardiac reserve. Furthermore, there is data to suggest that right ventricular function may be a more sensitive indicator of cardiac dysfunction during exercise[11] and it may be significant that, although the LVEF augmented to a similar extent before and after chemotherapy, the right ventricular ejection fraction was consistently 2% (absolute) lower after chemotherapy, at rest and throughout exercise ($P = 0.06$, Figure 3(b)). The effect of chemotherapy on right ventricular function and its relationship to overall cardiovascular capacity requires further study.

According to the Fick principle, the finding of reduced $\dot{V}O_2$ peak and preserved cardiac output implies a reduction in oxygen extraction at the skeletal muscle level. Although anthracycline-induced skeletal muscle damage has been well described,[33] it has tended to be overlooked as a cause of chemotherapy-associated fatigue and exercise intolerance. It is not surprising that greater attention has focused on myocardial injury given the more direct relationship with heart failure, although it should be noted that heart failure is a complex syndrome in which abnormalities along the whole of the oxygen utilization cascade can contribute to symptoms.[34] We speculate that the reduction in $\dot{V}O_2$ peak can be partially attributed to abnormalities in microvascular function and consequently impaired oxygen diffusive conductance within the skeletal muscle. Thus our data suggest that future evaluations of heart failure risk in patients undergoing chemotherapy should not focus solely on cardiac function.

Exercise constitutes a holistic therapy and improves functional capacity through a combination of enhanced

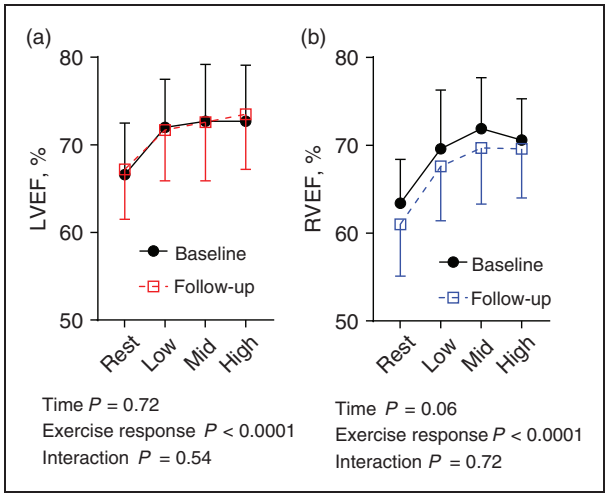


**Figure 3.** Effect of anthracycline chemotherapy on left and right ventricular ejection fraction during exercise. (a) The left ventricular ejection fraction response to exercise was unchanged after chemotherapy, whereas (b) the right ventricular ejection fraction was blunted.

cardiovascular, skeletal muscle, and metabolic processes. It has the potential to attenuate chemotherapy-induced injury due to any, or all, of these factors. All patients allocated to the supervised exercise training group completed the study without adverse effects related to training, consistent with previous studies that have reported good safety and moderate adherence to exercise programs during chemotherapy.[35] Although there was an overall reduction in $\dot{V}O_2$ peak over the 4-month period of adjuvant chemotherapy, the extent of the decrease was significantly less for the exercise group than the usual care group. Some studies have reported improvements in $\dot{V}O_2$ peak associated with exercise training,[36] although most exercise interventions have been performed after chemotherapy was complete. We were unable to achieve an improvement in $\dot{V}O_2$ peak in the present study, although the exercise intervention preserved function and thus reduced the adverse impact of chemotherapy in this relatively young cohort of average baseline fitness. As demonstrated in Figure 1(b), there was significant variability in the individual responses, but in all but two participants there was a slight reduction in $\dot{V}O_2$ peak. By contrast, $\dot{V}O_2$ peak decreased in every participant undergoing usual care, despite receiving recommendations to maintain physical activity levels.

The greatest limitation in the interpretation of our data is the non-randomized nature of the trial. We were unable to randomize the participants due to geographical constraints. All exercise training was performed in the Baker Heart and Diabetes physical rehabilitation center, the location of which was inconvenient for many participants for twice weekly sessions. Although these transport factors seemed to be the major factor influencing involvement in the supervised training sessions, it is also likely that participants who were more motivated to exercise chose to undergo training. This represents a likely explanation for the higher level of baseline fitness and lower body mass index in the exercise training group. It is not possible to exclude the fact that this selection bias may have influenced the observed differences in functional capacity. A literal interpretation that incorporates the potential confounding of selection suggests that those who volunteered to participate in a supervised exercise program will have better functional outcomes than those who do not. In a pragmatic sense, this represents a real-world experience in which patients may be recommended exercise therapy, but the motivation to adhere is an important determinant of outcome. Additional limitations that may influence our findings include the relatively small sample size and lack of follow-up information on physical activity behavior in the two groups.

This study represents the first stage of a potential paradigm shift away from resting measures of cardiac function that are insensitive markers to changes in cardiovascular function. We demonstrate that reduced augmentation of cardiac function during exercise is the strongest predictor of functional disability associated with chemotherapy. Exercise training during chemotherapy can almost completely alleviate the substantial reductions in functional capacity associated with chemotherapy for breast cancer. In short, exercise can be used to identify those at risk and can prevent functional disability.

## Author contribution

EH, RB, SF, SS, SL, MH, and ALG contributed to the conception or design of the work. EH and ALG drafted the manuscript; all authors critically revised the manuscript and gave final approval.

## Declaration of conflicting interests

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