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# Exercise Capacity Is Reduced in Cancer Survivors Previously Treated With Anthracycline-Based Chemotherapy Despite a Preserved Cardiac Output Response

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We measured peak exercise capacity ($VO_{2\ peak}$) and resting and 20-s immediately post-exercise (IPE) measures of left ventricular (LV) volumes and cardiac output in 14 (5 men and 9 women) anthracycline-treated cancer survivors (ATS) ≥12 months removed from their treatment, and 14 age-, gender-, and body mass index–matched subjects (CON) without cancer. Our intent was to determine if peak exercise capacity and exercise-associated cardiac output were reduced in ATS relative to CON participants.

The Institutional Review Board of the Wake Forest University School of Medicine approved this study, and all participants provided informed consent. ATSs were recruited consecutively over 6 months. The CON had no history of cancer. Participants in both the ATS and CON groups were excluded if they had: 1) contraindications for cardiovascular magnetic resonance (CMR) or cardiopulmonary treadmill exercise testing (CPET) testing; 2) prior myocardial infarction, angina, arrhythmia, or valvular heart disease; 3) inability to provide informed consent; or 4) an acute illness (e.g., a concurrent upper respiratory viral syndrome) or injury (orthopedic problems) that might impair exercise.

Each participant underwent the following: 1) physical activity assessments (via the Godin Leisure Time Physical Activity Questionnaire) (1); and 2) CMR before and after CPET. Participants transitioned rapidly between the treadmill and the magnetic resonance scanner

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to achieve the short interval between exercise and imaging, according to previously described methods (2). Results pertaining to intramuscular fat content on these subjects were recently reported (3). CMR images were collected before and immediately post-exercise (IPE ≤20 s) on a Siemens 1.5-T Avanto scanner (Tarrytown, New York) to calculate LV stroke volume (using a modified Simpson's rule) (3,4) and derived measures of cardiac index (LV stroke volume × heart rate/body surface area). An image analyst blinded to both study groups processed all images offline using Medis software (Leiden, the Netherlands) (4).

Baseline characteristics and CMR measures of LV and exercise-derived variables were compared between ATS and CON using 2-sample *t*-tests or Fisher exact tests for continuous and categorical variables, respectively. General linear models were fit comparing the ATS and CON groups adjusting for age, gender, and body mass index (BMI), to increase precision of the estimates (Table 1).

There were no differences in age, sex, weight, height, or BMI between ATS and CON subjects. Self-reported strenuous activity (days/week) was greater ($p = 0.006$) in the CON compared with the ATS group. Within the 14 ATS participants, an average of 327 ± 139 mg/m$^2$ of doxorubicin was received 5.1 ± 2.7 years earlier. Seven, 0, and 6 patients received concomitant cyclophosphamide, trastuzumab, or radiation treatment, respectively. Four ATSs and 4 CONs were taking cardioactive medications (an angiotensin-converting enzyme inhibitor or receptor blocker, beta blocker, and/or a diuretic) for hypertension. One CON subject also had diabetes.

Accounting for age, gender, and BMI, exercise capacity was 22% lower in the ATS compared with CONs ($VO_{2\ peak}$ 26.9 ± 6.4 ml/kg/min vs. 34.3 6.3 ml/kg/min, $p = 0.0048$, respectively). Resting LV ejection fraction averaged 58% and 53%, but trended lower ($p = 0.09$) in the ATS versus CON groups, respectively. IPE cardiac index was not significantly different in ATSs versus CONs (5.7 ± 1.3 l/min/m$^2$ vs. 5.9 ± 1.3 l/min/m$^2$, respectively, $p = 0.62$). When we examined the change in IPE cardiac index from baseline to post-exercise we found that the changes were not (3.13 ± 1.6l/min/m$^2$ vs. 3.10 ± 1.4 l/min/m$^2$, respectively, $p = 0.95$). The LV mass index was 122 ± 23 g/m$^2$ in the ATSs and was 128 ± 15 g/m$^2$ in the CONs ($p = 0.40$). We did not find an association between anthracycline dose and change in exercise-associated LV ejection fraction or cardiac index, however, we recognize with the modest sample size($n = 14$) that this lack of association could be related to sample size and could be examined in the future with larger studies.

Performing CMR before and after CPET in this casecontrol study identified a 22% lower $VO_{2\ peak}$ for anthracycline-treated subjects, confirming previous research (5). We newly report that this reduction in $VO_{2\ peak}$ occurred concomitantly with a preserved exercise-associated augmentation of cardiac index. These results indicate that factors other than LV dysfunction that reduce exercise-associated cardiac index, including those that impact peak exercise arterio-venous oxygen extraction, may contribute to exercise intolerance among ATSs. Further studies are needed to determine the differential effect of cancer versus its treatment on $VO_{2\ peak}$.

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**TABLE 1**

Assessments in ATS and CON

| | CON (n = 14) | | ATS (n = 14) | |
|---|---|---|---|---|
| Demographics | | | | |
| Age (yrs) | 54 ± 15 | | 54 ± 17 | |
| Weight (lbs) | 162 ± 35 | | 171 ± 42 | |
| Height (inches) | 66 ± 4 | | 66 ± 5 | |
| Body mass index (kg/m$^2$) | 26 ± 4 | | 27 ± 4 | |
| White | 14 | | 13 | |
| African American | 0 | | 1 | |
| Female | 9 | | 9 | |
| Functional Assessment of Cancer Therapy - Fatigue | 48 ± 3 | | 46 ± 6 | |
| Godin Physical Activity Questionnaire | | | | |
| Days/weeks of strenuous activity | 3.8 ± 2.0 | | 1.5 ± 1.9* | |
| Days/weeks of moderate activity | 2.0 ± 1.8 | | 3.4 ± 2.4 | |
| Days/weeks of mild activity | 3.4 ± 3.0 | | 3.5 ± 2.5 | |
| Cardiopulmonary exercise testing | Rest | Peak Exercise | Rest | Peak Exercise |
| HR (beats/min) | 72 ± 9 | 163 ± 18 | 79 ± 10* | 170 ± 27 |
| Systolic blood pressure (mm Hg) | 126 ± 17 | 163 ± 20 | 122 ± 14 | 156 ± 13 |
| Diastolic blood pressure (mm Hg) | 82 ± 15 | 79 ± 12 | 81 ± 13 | 81 ± 15 |
| $VO_2$ (ml/kg/min) | 3.7 ± 0.5 | 34.0 ± 10.3 | 3.5 ± 1.1 | 25.7 ± 7.0* |
| Respiratory exchange ratio | 0.79 ± .09 | 1.10 ± 0.10 | 0.82 ± .07 | 1.11 ± .06 |
| Minute ventilation (l/min) | 10.8 ± 4.2 | 88.9 ± 34.4 | 10.5 ± 4.0 | 67.9 ± 21.9* |
| Estimated peak metabolic equivalent | —— | 9.0 ± 3.0 | —— | 7.4 ± 2.0* |
| Magnetic resonance imaging | Pre-Exercise | Immediately Post-Exercise | Pre-Exercise | Immediately Post-Exercise |
| $LVEDV_i$ (ml/m$^2$) | 76.3 ± 12.3 | 78.6 ± 15.7 | 69.9 ± 14.0 | 71.3 ± 16.0 |
| $LVESV_i$ (ml/m$^2$) | 32.4 ± 7.3 | 26.1 ± 7.8 | 33.3 ± 8.5 | 27.9 ± 10.6 |
| $SV_i$ (ml/m$^2$) | 43.8 ± 9.0 | 52.6 ± 12.3 | 36.5 ± 7.1* | 43.4 ± 11.7* |
| EF% | 57 ± 7 | 67 ± 9 | 53 ± 6 | 61 ± 9 |

| | CON (n = 14) | | ATS (n = 14) | |
|---|---|---|---|---|
| $Q_i$ (l/min/m$^2$) | 2.7 ± 0.5 | 5.8 ± 1.5 | 2.3 ± 0.5 * | 5.5 ± 1.6 |

Values are mean ± SD or n.

* $p < 0.05$ difference between groups after adjusting for age, sex, and body mass index.

ATS = anthracycline-treated cancer survivors; CON = matched comparator subjects without cancer; $LVEDV_i$ = left ventricle end diastolic volume indexed for body surface area; $LVESV_i$ = left ventricle end systolic volume indexed for body surface area; $Q_i$ = cardiac output indexed for body surface area; $SV_i$ = left ventricular stroke volume indexed for body surface area; $VO_2$ = oxygen consumption.