Exercise to Prevent Anthracycline-Induced Cardiotoxicity (EXACT2.0) in Females with Breast Cancer

by

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Dalhousie University is located in Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

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ABSTRACT

The cardioprotective effects of aerobic exercise (AE) in mitigating anthracycline (AC)-induced cardiotoxicity in females with breast cancer (BC) remain unclear. This study investigated the impact of a 24-week home-based AE program on cardiac function, VO2peak, fatigue, and health-related quality of life (HRQoL) in females with BC receiving AC. Participants (N=20; 52±10 years-old) were randomized to standard of care (SOC; n=10) or SOC+24-week home-based AE program (AEX; n=10). The exercise program consisted of two self-directed sessions per week (35-85% incremental heart rate reserve) to achieve 90-minutes of exercise weekly. Cardiac function [left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS)], were assessed using serial transthoracic echocardiography at baseline and at 24-weeks. Total time exercising during the Bruce treadmill exercise stress test performed at baseline and 24-week follow-up was used to calculate VO2peak. At baseline, mean LVEF was 62.2±1.4% and 63.1±1.6% in the SOC and AEX group, respectively (p=0.247; r=-0.27). After 24-weeks, mean LVEF was 61.9±2.7% and 58.9±7.3% in the SOC and AEX groups, respectively (p=0.905; r=0.04). At baseline, the GLS was -18.9±1.6% and -19.1±1.2% in the SOC and AEX groups, respectively. After 24-weeks, the GLS was -18.3±1.2% and -17.3±2.2% in the SOC and AEX groups, respectively. There was no significant Group × Time interaction effect for GLS (p=0.241; η_p^2=0.080). At baseline, the mean VO2peak was 23.4±3.29 mL/kg/min and 28.9±9.23 mL/kg/min in the SOC and AEX groups, respectively (p=0.232; r=-0.33). At 24- weeks, mean VO2peak was 23.3±8.2 mL/kg/min and 32.2±7.8mL/kg/min in the SOC and AEX groups, respectively (p=0.049). At baseline, the mean HRQoL was 104.3±16.5 and 110.8±6.9 in the SOC and AEX groups, respectively. At 24- weeks, mean HRQoL was 109.6±14.4 and 112.1±11.2 in the SOC and AEX groups, respectively. There was no significant Group × Time interaction effect for HRQoL (p=0.351; η_p^2=0.051). At baseline, the mean fatigue was 39.8±8.3 and 41.1±5.4 in the SOC and AEX groups, respectively. At 24- weeks, mean fatigue was 34.2±9.2 and 33±12.4 in the SOC and AEX groups, respectively. There was no significant Group × Time interaction effect at follow-up compared to baseline for fatigue (p=0.651; η_p^2=0.012). The findings of this study demonstrated that the 24-week aerobic exercise program deployed by EXACT2.0 was insufficient at mitigating decreases in indices of cardiotoxicity (i.e., LVEF, GLS), VO2peak, and patient reported levels of HRQoL and fatigue. It is possible that shortcomings in patient recruitment (e.g., underpowered), exercise prescription, and protocol design, each ultimately limited due to a global pandemic, contributed to the results reported herein.

List of Abbreviations Used

AC – Anthracycline
ACSM – American College of Sports Medicine
AE – Aerobic exercise
AEX – Aerobic exercise program
ANOVA – Analysis of variance
BCS – Breast cancer survivor
BC – Breast cancer
BMI – Body-mass index
CHMP – Committee for Medicinal Products for Human Use
CRF – Cardiorespiratory fitness
CRP – C-reactive protein
CVD – Cardiovascular disease
DNA – Deoxyribonucleic acid
DOX – Doxorubicin
ECG - Electrocardiogram
EXACT – EXercise to prevent Anthracycline-based CardioToxicity in females with breast cancer
FACIT-F – Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-B – Functional Assessment of Cancer Therapy - Breast
GLS – Global longitudinal strain
HIIT – High intensity interval training
HER2+ – Human epidermal growth factor receptor 2
HRQoL- Health-related quality of life
HRR – Heart rate reserve
Hs-TNT – high sensitivity troponin
IPAQ – International Physical Activity Questionnaire
LV – Left ventricle
LVEF – Left ventricular ejection fraction
NS – Nova Scotia
NSHA – Nova Scotia Health Authority
NT-proBNP – N-terminal pro-brain natriuretic peptide
PGC-1a/b - Peroxisome proliferator-activated receptor-gamma coactivator
QEII – Queen Elizabeth II
SOC – Standard of care
ROS – Reactive oxygenase species
TOP2a/b – Topoisomerase II alpha/beta
TTE – Transthoracic echocardiography
TVI – Tissue velocity imaging
US DHHS – United States Department of Health and Human Services
UK – United Kingdom
2D – 2-dimensional

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Chapter 1: INTRODUCTION

1.1 Cancer: Definition and Statistics

Cancer can be defined as a malignant growth or tumour caused by abnormal, uncontrolled growth or spread of deleterious cells. With more than 100 known types of cancer, the proliferation of malignant cells can occur anywhere in the body. With a mortality rate of 30%, cancer is the leading cause of death in Canada. It is expected that nearly 50% of Canadians (i.e., ~220 400) will develop cancer during their lifetime, and approximately 25% (i.e., ~82 100) will die due to the disease[1,2]. Among Canadian females, breast cancer (BC) is the most common type of cancer and the second leading cause of death in women with cancer. It is estimated that in 2020, 1 in 4 (i.e., ~27 400) cancer diagnoses in Canadian females will be breast cancer and that breast cancer will claim the lives of 13% (i.e., ~5100) of all female Canadians diagnosed with cancer[1]. There is an inverse relationship that exists between a Canadian's risk of dying due to cancer vs. their risk of receiving a cancer diagnosis during their life. This means, the number of deaths due to cancer is declining in Canada, however, the number of new cases of cancer is rising[1,2]. In addition to the increase in total population within the country, this rise in the number of cancer cases has been primarily attributed to the aging population seen in Canada, along with improved screening practices (e.g., increased mammogram frequency) and the implementation of more effective treatment strategies (e.g., anthracyclines; ACs)[1,2].

The 5-year net survival for breast cancer sits just below 90%, indicating that ~9/10 Canadian females diagnosed with cancer will live at least 5-years post diagnosis[1]. Consequently, with the improved survival seen following a breast cancer BC diagnosis in Canada, the long-term treatment-related side-effects of breast cancer are becoming more apparent. Specifically, treatment with AC-chemotherapy, while extremely effective in halting tumour growth and preventing advancements in the cancer trajectory, it is often accompanied by corresponding

cardiotoxicity, defined as any heart damage brought on by cancer treatment, which eventually leads to heart failure and premature death. Therefore, adjuvant therapies must be explored that could aid in alleviating the cardiotoxic effects of AC chemotherapy on the hearts of females diagnosed with BC. To combat the manifestation of cardiotoxicity, dexrazoxane was previously prescribed as a cardio-protectant[3,4]; however, the drug has recent reports of adverse side effects (i.e., decrease chemotherapy efficacy, increase risk of mortality and secondary primary malignancies)[5] limiting its clinical utility[5,6]. There is plenty of preclinical evidence which suggests aerobic exercise (AE) can serve as an adjuvant therapy to AC treatment and has revealed many pathways of cardio-protection[7–10]. However, there is little clinical data regarding the use of AE as an adjuvant therapy to attenuate AC-induced cardiotoxicity. Thus, there is an immediate need to perform more clinical trials.

1.2 EXACT2.0: Purpose and Study Objectives

The previous iteration of this study sought to add to the current clinical literature and was coined the "EXercise to prevent Anthracycline-based CardioToxicity (EXACT1.0)" trial[11,12]. The purpose of this pilot study was to examine the feasibility and potential efficacy of a facility-based 12-week, individualized aerobic exercise program designed to mitigate cardiotoxicity and patient-reported outcomes associated with AC-based chemotherapy in Halifax, NS[11]. This pilot study demonstrated that an individualized aerobic exercise plan is a safe, effective, and feasible option and can be used to explore the effects of exercise on chemotherapy-induced cardiac damage[11]. However, the trial was under-powered to detect changes in cardiovascular remodelling. A major barrier existed in the recruitment of participants for this trial, particularly relating to travel to the in-person exercise facility, in addition to parking and other difficulties arriving at the exercise site[12]. EXACT1.0 reported approximately 15 recruits annually, below the average recruitment noted in similar studies in the field[12].

Additionally, EXACT1.0 struggled with study retention, reporting a relatively low retention rate of 67%, well below the mean of similar studies in the cancer space (i.e., 84% retention; range: 65-100%)[12]. Therefore, the current iteration of the EXACT study, EXACT2.0, addressed this barrier by offering a home-based approach to exercise, in addition to increasing the length of the exercise intervention. The primary objectives of the study were to characterize the impact of a 24-week AE intervention on: 1) ventricular function via echocardiography; and 2) aerobic fitness. Secondary objectives of the study consisted of the analysis of self-reported levels of health-related quality of life (HRQoL), and fatigue.

Chapter 2: LITERATURE REVIEW

2.1 Breast Cancer Treatment: Anthracycline-Based Chemotherapy and Cardiotoxicity

The gold-standard treatment for breast cancer includes a combination of various treatment modalities, consisting of radiotherapy, surgical intervention and drug therapies[13]. Radiation therapy is generally prescribed following surgical and drug therapies. Surgical therapy for BC was originally radical mastectomy of the affected breast[14]. A mastectomy involves the full removal of the breast, along with all chest muscles and axillary lymph nodes. This recommendation was later amended to favor simple mastectomy over radical mastectomy[14]. This meant that the axillary lymph nodes are left untouched during surgery. Most recently however, standard practice has evolved to perform a lumpectomy coupled with chest irradiation. A lumpectomy involves the removal of the malignant growth and a small portion of healthy tissue surrounding it. This procedure is favoured due to the ability to conserve the maximum amount of breast tissue[15]. Drug therapies include chemotherapy, targeted therapy, and endocrine therapy. Examples of these include ACs, monoclonal antibodies, and selective estrogen receptor modulators respectively[13]. Many patients will need administration of more than one drug therapy (i.e., human epidermal growth factor receptor 2+ (HER2+) BC), while others may only be prescribed one drug therapy. Nonetheless, each drug therapy is accompanied by its own respective risk factors or side effects, both acute and long-lasting[13]. Consequences of these side-effects can be specific to localized organ systems (e.g., structural cardiac damage), or they may pose a more systemic interruption (e.g., increased systemic inflammation)[16].

The class of chemotherapy drugs known as AC are mostly dominated by its doxorubicin (DOX) derivative. However, this specific class of anti-neoplastic drugs contains several other effective agents such as epirubicin, daunorubicin, and idarubicin[17]. Since the discovery of AC in the 1960s, it has proven very efficacious, and therefore has been used to treat breast cancer for

over 30 years[18]. This is due to the ability of anthracycline-based regimens to decrease cancer growth and mortality in females with breast cancer by up to 38%[19]. In addition to carcinoma (i.e., BC), other cancers are also responsive to AC-chemotherapy such as leukemia, lymphoma and sarcoma[20]. However, the overall utility of ACs in cancer care comes at a cost as these drugs also have significant cardiotoxic side-effects[17,21].

The most important determinant of AC-mediated cardiotoxicity is the cumulative dose of AC administered. Cumulative dose is positively associated with cardiovascular complications and can be defined as the total amount of anthracycline administered in an individual's lifetime[22,23]. It was reported that the prevalence of heart failure in a sample of 630 patients rose exponentially from 5 to 48% at cumulative doses of an AC (i.e., doxorubicin) ranging from 400-700 mg/m^2 respectively[24]. This exponential increase in cardiotoxic risk with cumulative dose limits the clinical use of AC to treat cancer[25]. Importantly, while ironclad recommendations have been established to alleviate potential cardiotoxic risk (i.e., maximum cumulative dose of 500mg/m^2), no accepted dose is without risk[21,26]. This is exemplified by reports of cardiotoxicity manifesting following doses as low as 100 mg/m^2 [21,26,27]. However, reports of cardiotoxicity at these lower doses have varied greatly, in large part due to differing patient populations consisting of varying periods of follow-up and inconsistent definitions of cardiotoxicity[21,26,27]. Other risk factors also exist in the development of AC-induced cardiotoxicity such as administration schedule, concomitant use of other cardiotoxic therapies (i.e., trastuzumab), genetic predisposition (i.e., HER2+), cardiac disease history and mediastinal irradiation (Figure 1)[16]. All of which creates an obstacle in the management of breast cancer. Therefore, uncovering methods to prevent or mitigate the cardiotoxicity of anthracyclines remains an important avenue of scientific and clinical inquiry.

2.2 Cardiotoxicity: Detection, Manifestation, Prevention and Risk Factors

The detection of cardiotoxicity has been outlined in detail by The American Society of Echocardiography and the European Association of Cardiovascular Imaging[28]. Early detection of asymptomatic cardiotoxicity has received a recent increase in scientific exploration due to the importance of detecting cardiotoxicity before it manifests as an irreversible condition. This was sparked by increased interest to uncover new methods to avoid significant cardiovascular damage as a result of cancer treatment[29]. The aforementioned agencies have established a consensus to define cardiotoxicity as a decrease in left ventricular ejection fraction (LVEF) of >10 percentage points, to a value <53% as determined by two-dimensional (2D) echocardiography[28]. After a period following the initial 2D echocardiogram (e.g., 2-3 weeks), findings should be confirmed with an additional echocardiographic study[28]. The degree of cardiotoxicity can be further classified as reversible, partially reversible, and irreversible, depending on the degree of LVEF recovery from the lowest observed value[28]. However, recent reports of LVEF's ability to detect cardiac damage prior to becoming irreversible has been questioned[30]. It has been postulated that by the time LVEF decreases to the established criteria indicating cardiotoxicity, cardiac damage is already at an irreversible stage[30].

Therefore, the novel use of global longitudinal strain (GLS) is considered an additional, more sensitive indicator of early left ventricular (LV) dysfunction and has also been shown to provide information regarding the reversibility of LV dysfunction among patients receiving AC therapy[30]. GLS is a simple parameter that expresses longitudinal contractile shortening of the heart as a percentage (i.e., change in length as a proportion to baseline length) and is derived from speckle tracking and analyzed by post-processing of apical images of the LV[31]. GLS is used in clinical practice aimed at the earlier detection of asymptomatic changes in myocardial contractile function[32]. The American Society of Echocardiography and the European Association

of Cardiovascular Imaging have agreed that deformity changes precede ventricular dysfunction. Therefore, the addition of GLS alongside LVEF is necessary to confer subclinical changes in the cardiac physiology. A > 15% reduction in GLS immediately after or during anthracycline treatment, was a strong predictor of cardiotoxicity. If the reduction in GLS remains < 8%, a diagnosis of cardiotoxicity should be excluded[33]. Ultimately, LVEF and GLS are two valid and reliable measures that can be used to detect cardiotoxicity early enough to intervene with mitigation strategies that target anthracycline-based cardiotoxicity[31–33].

To combat this apparent manifestation of cardiotoxicity, dexrazoxane was previously prescribed as a cardio-protectant via the drug's ability to chelate iron, however, more recent reports propose that dexrazoxane's ability to confer cardioprotection is due to its ability to prevent an anthracycline from binding to topoisomerase IIβ[3,4]. That said, the drug has reports of adverse side effects limiting its clinical utility. For example, in the UK, dexrazoxane was previously contraindicated for use in *all* childhood and adolescent cancer patients as well as adult patients presenting without advanced/metastatic disease due to the drug's potential adverse side-effects (i.e., decrease chemotherapy efficacy, increase risk of mortality and secondary primary malignancies)[5]. This recommendation was made by the Committee for Medicinal Products for Human Use (CHMP), however, due to the convoluted and inconsistent nature of the clinical literature surrounding its use in clinical practice, dexrazoxane's contraindication was eventually challenged, and amended[5]. In 2017, the CHMP limited the contraindication for dexrazoxane to children aged 0-18 years who are expected to receive a cumulative dose of < 300 mg/m^2 of anthracycline. There was no amendment regarding its clinical use in adult patients, meaning dexrazoxane's clinical use in this patient population mirrors that of the American Society of

Clinical Oncology[6] wherein dexrazoxane is *still* contraindicated in those patients without advanced/metastatic disease[5,6].

Regardless of the lack of corroborating evidence supporting such claims, the clinical use of dexrazoxane has been restricted due to reports of adverse side-effects ((i.e., decrease chemotherapy efficacy, increase risk of mortality and secondary primary malignancies)[5,6]. Therefore, it is of vital importance that additional adjuvant therapies, such as aerobic exercise, are explored to offer additional cardioprotection during chemotherapy in breast cancer patients receiving an anthracycline.

As mentioned previously, cardiotoxicity can manifest as reversible, partially reversible, and irreversible and can vary in severity, ranging from asymptomatic declines in LV function to symptomatic heart failure with observable clinical signs[20]. More specifically, there is an increased risk of several cardiovascular complications including: 1) cardiomyopathy, 2) arrhythmia, 3) valvular disease, and/or 4) heart failure, eventually leading to premature death[21,34–37]. Age, adjuvant chemotherapy, and traditional cardiac risk factors such as a family history of coronary artery disease, smoking, and hypertension all increase the likelihood of developing cardiotoxicity from anthracycline chemotherapy[38,39]. It has been reported that the risk of CVD is up to 77% higher in BC survivors and that between 26-40% of females with early-stage breast cancer die of CVD[40]. A review consisting of 43 338 patients with stage I-III breast cancer aged 66-70 years reported a 26% higher risk of developing congestive heart failure compared to those treated with non-AC chemotherapy[41]. This is exemplified by evidence from long-term follow-up of childhood cancer survivors (i.e., long-term survivors) that received AC are more susceptible and are at an elevated risk of developing heart failure decades after cancer remission[42]. Of note, the magnitude of CVD risk for long-term survivors may exceed the risk of

a secondary malignancy, which is a known complication of primary cancer therapy[42–46]. Thus, the long-term cardiotoxic effects of cancer therapy is a significant concern for breast cancer survivors. Despite this limitation, given its anti-neoplastic efficacy, there is no plan in the near future to omit ACs from chemotherapy regimens[47]. Thus, there is a need to develop therapies that can be used concurrently with AC treatment to protect the heart from AC toxicity while not detracting from its overall effectiveness.

2.2 Mechanisms of Anthracycline-Induced Cardiotoxicity

It is widely accepted that AC induces cardiotoxicity through two proposed physiological mechanisms: 1) deoxyribonucleic acid (DNA) topoisomerase II (Top2) inhibition[48,49], and 2) oxidative damage and free radical generation[21, 50]. Until recently, oxidative damage and free radical generation was the most universally accepted hypothesis for AC-induced cardiotoxicity. More recently, Top2 inhibition has become dominantly recognized as the key mediator pathway of AC-induced cardiotoxicity[48,49,51] (Figure 1). In humans, there are two isoforms of the DNA Top2, Top2α and Top2β[51]. Top2α is found in highly proliferative cells such as tumours and normal proliferating cells[51]. Within these proliferative malignant cells, doxorubicin, one of the most widely prescribed AC's, binds to Top2α causing double stranded DNA breaks, prevents DNA replication and arrests the malignant cells, eventually leading to programmed cell death (i.e., apoptosis)[52–54]. Therefore, Top2α is recognized as the primary target of ACs antitumor mechanism[49,50]. In contrast, cardiomyocytes exclusively express the Top2β isoform of Top2[52,54,55] and in unison, AC administration causes Top2β inhibition within the heart, an action which mirrors that of Top2α inhibition, leading to double-strand DNA breaks resulting in premature cardiomyocyte death[4,49]. Cardiomyocyte death is significant as these cells do not regenerate, meaning that once these heart cells are lost, function may be impaired indefinitely;

consequentially making Top2β inhibition the major Top2 isoform responsible for AC-induced cardiotoxicity[50, 52].

The generation of free radicals, reactive oxygen species (ROS) and their corresponding oxidative stress have been previously thought to be the primary contributor to the pathogenesis of anthracycline-induced cardiotoxicity[56–58]. Levels of ROS have been shown to dramatically increase in AC-treated cells as compared to controls[56]. Structurally, AC consists of a tetracyclic aglycone linked with an amino sugar[49]. A one-electron reduction of the tetracyclic ring of AC leads to the formation of an intermediate free radical[49]. When introduced to oxygen, an unpaired electron of the free radical can be transferred to the oxygen molecule to form a superoxide radical. Superoxide radicals are very active electron donors that can undergo dismutation spontaneously or through the activity of the superoxide dismutase enzyme to become hydrogen peroxide (H_2O_2), a low-toxicity ROS molecule, and oxygen (O_2)[49]. Hydrogen peroxide, while a relatively stable compound on its own, can then potentially initiate a chemical reaction if in the presence of superoxide radicals, generating toxic hydroxyl radicals[49]. This demonstrates that a relatively large amount of ROS can be introduced from a small amount of AC. ROS is also produced via the binding of AC to iron (Fe^{3+}), forming an AC-Fe^{3+} complex[49]. In the presence of reducing agents, redox cycling between AC-Fe^{2+} and AC-Fe^{3+} can also generate significant amounts of a superoxide radical[49]. Elevated concentrations of free radicals and ROS result in irreversible damage to cell membranes, DNA, and other cellular structures by oxidizing lipids, nucleic acids, and proteins, respectively[58,59]. Sub-cytotoxic concentrations of DNA-damaging agents including free radicals and ROS leads to expedited cellular senescence resulting in early vascular and cardiac aging[57]. While natural defences such as endogenous antioxidants including glutathione peroxidase and superoxide dismutase are present in cardiomyocytes, these defences

are not capable of ameliorating the redox imbalance and exaggerated oxidative stress resulting from anthracyclines[60,61]. Interestingly however, although *in vivo* and *in vitro* studies have confirmed increased free radicals (i.e., ROS) in cardiomyocytes after AC-chemotherapy, neither antioxidant nor iron chelation therapy prevented cardiotoxicity – conferring the hypothesis that an alternate mechanism must be driving the manifestation of AC-induced cardiotoxicity[3,62,63].

2.2.1 The Mitochondria and Topoisomerase 2 Inhibition

The heart muscle exhibits relatively high mitochondrial concentrations compared to other organs and tissues in the body. AC has deleterious effects on Top2-mediated mitochondrial function. Combined, this may explain why mitochondrial dysfunction is considered a central pathway leading to early cardiomyocyte death and the development of AC-mediated cardiotoxicity[64]. AC has been associated with impairing mitochondrial function through the downregulation of essential proteins responsible for ensuring proper organelle function, found within the electron transport chain[51]. As a result, when mitochondria are exposed to ACs, cardiomyocytes experience decreased markers of mitochondrial function[65,66], reduced mitochondrial antioxidant capacity[65,67], and impaired mitochondrial electron transport chain activity[68,69], ultimately leading to cellular apoptosis and myocardial dysfunction[64,65,70].

Mitochondrial dysfunction can lead to ROS production and pro-apoptotic signalling (e.g., cytochrome c, apoptosis-inducing factor) via Top2 inhibition. Brought on by resulting oxidative stress, this further supports the hypothesis underpinning Top2 as a key factor leading to AC-mediated myocardial cell death[16, 49]. To corroborate the hypothesis that Top2 is the primary driver underpinning AC-induced cardiotoxicity, a study by Lyu *et al* (2007)[4] demonstrated that mouse embryonic fibroblasts lacking Top2β were protected from doxorubicin-induced cytotoxicity. Impressively, Top2β mice (knockout) also had a 60% reduction of DNA double-strand breaks. An accumulation of DNA double-strand breaks is an antecedent of permanent

DNA damage and triggers the p-53 mediated apoptotic pathway[20]. Activation of this pathway also leads to the suppression of peroxisome proliferator-activated receptor-gamma receptor co-activators (PGCs), specifically PGC-1α and PGC-1β[51]. These coactivators are important for mitochondrial biogenesis pathways, and processes responsible for the growth and replication of existing mitochondria[71]. Consequently, DNA Top2β poisoning leading to transcriptome alterations within the mitochondria has been suggested as one of the key contributors involved in anthracycline-mediated cardiotoxicity[51]. Zhang et al. (2012), a study of mice models with a cardiomyocyte-specific deletion of Top2β further corroborates findings reported by Lyu and collogues, reporting 70% fewer apoptotic nuclei observed in the hearts of Top2β mice (knockout) as compared with those of wild-type mice[51]. These mice also display less mitochondrial impairment, fewer double-strand breaks and preserved LVEF[51]. Taken together, these results suggest that Top2 inhibition, specifically the Top2β isoform, is the major mediator of doxorubicin-induced DNA damage, mitochondrial dysfunction and premature cardiac cell death leading to cardiotoxicity[4]. Thus, finding therapies that reverse these effects of ACs on mitochondria may be beneficial in preventing AC-mediated cardiotoxicity.

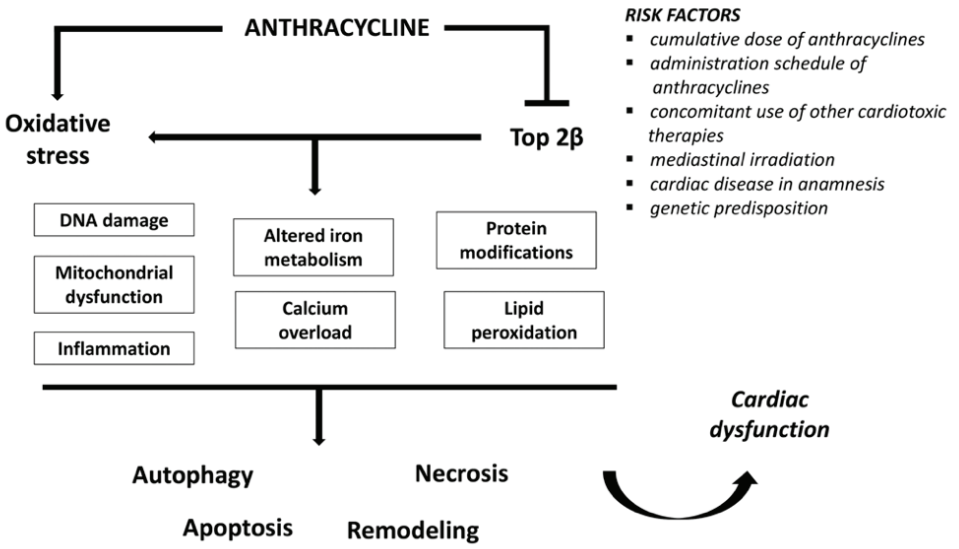


Figure 1. **A high-level overview of the mechanisms responsible for anthracycline (AC)-induced cardiac dysfunction. AC administration leads to oxidative stress both independently via the drug's metabolism in the body, or via its concurrent Topoisomerase 2β inhibition. Both of which contribute to a myriad of physiological responses in which each contributes to cardiac dysfunction via autophagy, necrosis, remodelling and/or cellular apoptosis**[16]

2.3 Cardiotoxicity Mitigated by Aerobic Exercise – Pre-clinical and Clinical

2.3.1 Pre-clinical

AC-induced increases in markers of cardiotoxicity (i.e., oxidative stress and Top2 inhibition-mediated cardiomyocyte apoptosis) have repeatedly demonstrated their attenuation in response to aerobic exercise in preclinical populations, alluding to enhanced cardioprotection. Several pre-clinical exercise studies have exemplified these benefits in models of AC-induced cardiotoxicity. For example, an acute exercise study by Wonders et al. investigated the effectiveness of a single 60-minute bout of treadmill running performed 24 hours prior to an AC (DOX)- injection in rats at an intensity of 25m/min (i.e., maximal speed) with a 5% grade. This study reported that in response to acute exercise training, there was a 45% reduction in levels of oxidative stress (i.e., myocardial lipid peroxidation) ($p<0.05$) and significantly improved cardiac function (i.e., end-systolic pressure, left ventricular developed pressure and maximal rate of left

ventricular pressure development) after DOX injection[7]. In addition to acute training protocols, these findings are also supported by chronic exercise (i.e., treadmill running for 25-39 min/day at 15-17 m/min, 5 days/week for 3 weeks[72,73]) studies which report statistically significant improvements in markers of oxidative stress (i.e., increased [heat shock protein$_{70}$]; ~21mg/gram → ~27mg/gram of protein[72] and ~16ng/mg → ~30ng/mg of protein or ~5.4 → 41%[73]) and increases in antioxidant capacity (i.e., superoxide dismutase; ~75 mg/gram → 100mg/gram of protein[72] and ~12 → 31%[73]) in rats that ran on treadmills or wheels prior to AC treatment compared to their sedentary counterparts[72–74]. Further corroborating these findings, Hydock et al. (2012)[75] looked to investigate the effects of 10-weeks of voluntary exercise during and after treatment with an AC (DOX). Cardiac function was assessed via echocardiography (i.e., left ventricular developed pressure) pre and post intervention. The report found that rats expressed lower activity levels as treatment progressed, expressing significantly lowered distances at 2 weeks (DOX: ~30,000m; saline: ~50,000m; $p < 0.05$), 6 weeks (DOX: ~20,000m; saline: ~50,000m; $p < 0.05$) and 10 weeks (DOX: ~10,000m; saline: ~40,000m; $p < 0.05$). Regardless, 10-weeks of voluntary exercise performed following both daily and weekly DOX injections was still able to protect against significant decreases in cardiac function. The authors postulate that given the significant distance drop off as treatment progressed, it may be concluded that low-intensity endurance training may be an effective rehabilitative approach to attenuating AC-induced cardiotoxicity[75].

Exercise-induced reductions in oxidative stress are thought to be in part due to an increase in antioxidant expression. A recent report conducted by Phungphong et al. (2020)[8] investigated the impact of aerobic exercise on protein carbonylation, a marker of oxidative stress, in response to DOX injection. This investigation demonstrated that a 10-week exercise program

performed at 21m/min for 30 minutes twice on 5 days/week led to the attenuation of AC-induced increases in oxidative stress via augmented levels of serum protein carbonylation[8]. Furthermore, Ascensao et al. investigated the benefits of a 14-week endurance swim protocol (i.e., 1hour/day for 5 days/week) in DOX-treated mice. Specifically, this study showed endurance swimming for 14 weeks led to increases in antioxidant glutathione and heat shock protein$_{60}$ expression in hearts of DOX-treated mice[10]. Building on this, Ascensao et al. later investigated the benefits of a 14-week motorized treadmill running program (i.e., 30m/min for 50min 5 days/week) in DOX-treated mice[65]. They found that exercise training was able to increase the antioxidant enzyme superoxide dismutase[65]. Other pre-clinical studies have also reported similar findings[72,73,76]. These studies demonstrated exercise training increases the expression of antioxidant enzymes (i.e., catalase and glutathione peroxidase) in DOX-treated animals[76]. Ascensao et al. also report exercise training was able to attenuate DOX-induced increases of pro-apoptotic proteins including Bax and cleaved caspase 3[65], which has also been observed in chronic exercise settings[8,77]. The reductions of these pro-apoptotic proteins indicate exercise can decrease cardiomyocyte apoptosis in the setting of AC (i.e., DOX) leading to preserved heart structure and function. These exercise studies varied regarding the length of training program; nevertheless, each report similar results in reducing pro-apoptotic markers[8,65,77].

2.3.2 Clinical

A variety of clinical populations, including BC survivors after treatment with an AC, exhibit a strong relationship between cardiorespiratory fitness and the risk of cardiovascular events and mortality[78]. In fact, BC survivors are at a higher risk of cardiovascular disease mortality compared to BC-related mortality[79,80]. The administration of AC-based chemotherapy has significant implication on cardiorespiratory fitness (CRF) in this patient population - affecting respiratory, cardiovascular, and skeletal muscle functions[78,81]. Poor CRF has direct

consequences on the ability to complete activities of daily living, and thus impacts patients' overall quality of life[81]. The most appropriate way to assess CRF in response to aerobic training is to use indices of aerobic capacity. Aerobic capacity can be thought of as the body's dual ability to: 1) supply oxygen-rich blood to the various tissues of the body (i.e., skeletal muscle), and 2) the ability of the body's tissues to extract this oxygen from the bloodstream to make energy that the body can use[82]. CRF is best quantified with the measure of peak oxygen consumption (i.e., VO2peak) and is expressed as an absolute (i.e., L/min) or relative (adjusted for body weight (kg); mL/kg/min) rate, the latter being the most relevant as it allows for comparisons to be made between individuals[82]. A study consisting of 222 BC patients, published by Klassen et al. found that BC patients have significantly impaired cardiopulmonary function (VO2peak) during and after chemotherapy[78]. Specifically, VO2peak has been shown to decline between 5 and 27% during exposure to anthracycline regimens[78], and many patients do not recover to their baseline cardiorespiratory fitness after treatment completion[83]. The authors note that chemotherapy appears to impair CRF primarily by influencing the oxygen delivery system[78].

To combat this reported impairment in CRF, Giallauria et al. examined whether exercise training improves cardiopulmonary and endothelial function in women with BC[84]. Fifty-one females with a history of BC were recruited for the study and asked to cycle on a stationary bike 3 times per week at 60-70% VO2peak for 12 months. Cardiopulmonary (i.e., VO2peak) and endothelial function (i.e., reactive hyperemia index) were assessed at baseline and 1-year follow-up. At baseline, the training and control groups had mean baseline VO2peak values of 12.6 and 12.8ml/kg/min respectively. At 1-year follow-up, the training and control groups mean VO2peak scores were 14.5 and 12.6ml/kg/min respectively. This data translates to a statistically significant between group difference ($p<0.001$). Regarding the reactive hyperemia index, at baseline, the

training and control group observed mean indices of 2.1 and 2.0 respectively. At follow-up, these indices were observed to be 2.5 and 1.9 in the training and control groups respectively. This data also translates to a statistically significant between group difference ($p<0.001$) [84]. Overall, the author concludes that cardiopulmonary and endothelial function can be improved, or reductions can be mitigated in response to exercise training in BC patients receiving an AC. It is clear cardiorespiratory fitness is lost following administration of AC-chemotherapy and that AE training can help attenuate losses seen in VO2peak – decreasing the risk of cardiac dysfunction and cardiovascular mortality[11,78,82,84].

It has been postulated that exercise training should be initiated prior to, or shortly after chemotherapy treatment to effectively intervene in the corresponding premature destruction of cardiomyocytes. Therefore, Kirkham et al. investigated the acute cardiovascular changes that occur in BC survivors who were randomized to exercise prior to DOX chemotherapy (i.e., 24 hours prior to a single dose and 24 hours prior to every dose of DOX)[85,86]. Results showed that the first DOX treatment is associated with a transient increase in N-terminal pro-b-type natriuretic peptide (NT-proBNP) levels, undesirable echocardiographic parameters of myocardial relaxation, LV volume overload, and changes in longitudinal strain, all of which are indicative of cardiotoxicity[85,86]. These indices were attenuated by exercise sessions performed 24 h prior to a single dose of treatment. However, exercise performed prior to each dose over a course of a total treatment regimen did not mitigate decreases in subclinical markers [i.e., 10% reduction in LVEF and GLS, presence of cardiac biomarkers (i.e., troponins)] of cardiotoxicity[85,86]. Although future investigations are needed to corroborate these findings in larger randomized control trials, it offers evidence supporting the feasibility of using AE in BC populations.

It is clear that AE may be a viable strategy to improve cardiorespiratory fitness and mitigate treatment-induced cardiotoxicity in BC patients receiving chemotherapy[11,78,84–86], however, many of these trials focused primarily on continuous low-moderate intensity AE (e.g., <55% HR_{max}), performed at contrasting frequencies and durations. Consequently, these studies did not assess the potential cardioprotective effects of higher intensity exercise (e.g., >80% HR_{max}). This makes it difficult to establish a consensus regarding the optimal type, duration, and intensity of exercise interventions among these patients. To further characterize the optimal prescription of AE, Lee et al. initiated a pilot study to determine whether higher-intensity training elicits favourable cardiac adaptations in BC survivors[87]. To achieve this, N=30 females were randomly allocated to an 8-week high-intensity interval training (HIIT) program or control to test the feasibility of the proposed exercise strategy for women with BC. Each HIIT training session included 7 times of a 1-min interval performed at 90% peak power output followed by a 2-min interval performed at 10% peak power output. The researchers hypothesized that HIIT could induce preferred cardiovascular adaptions in BC patients. While the study did not have sufficient power to determine the program's overall effectiveness on health outcomes, they found that HIIT for BC patients receiving chemotherapy is feasible with a session attendance rate of 82.3% and a retention rate of 100%[87]. Lee et al. reported no significant differences in the observed adherence and retention rates compared to that of moderate-intensity continuous exercise[87].

To confer the ability of HIIT to mitigate AC-induced cardiac damage, a larger study cohort involving a longer follow-up is needed. Therefore, Ansund et al. published a 2021 study using data from the OptiTrain randomized control trial[88] to determine if high-intensity exercise during breast AC-chemotherapy has a positive effect on cardiorespiratory fitness (i.e., VO2peak)

and plasma biomarker levels of myocardial damage (i.e., cTnT and NT-proBNP)[88]. To do this, N=88 females starting chemotherapy were randomized to 16-weeks of either resistance and high-intensity interval training (RT-HIIT), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), or usual care (UC). Outcome measures were assessed at baseline, post-intervention, and at 1- and 2-years. Plasma cTnT and NT-proBNP was not different at baseline but increased in all groups post-intervention with no differences between groups. However, at 1-year follow-up, NT-proBNP was lower in the exercise groups compared to UC. Regarding VO2peak, at 16-weeks VO2peak significantly differed between the groups. Specifically, RT-HIIT and AT-HIIT maintained cardiorespiratory fitness, while there was a decline in the UC group. Interestingly, at 2-years, there was a drop in VO2peak for patients with high cTnT and NT-proBNP, regardless of group assignment[88]. Taken together with the attenuated decreases in cardiopulmonary function in participants with low levels of plasma biomarkers, indicates a long-term cardioprotective effect of higher intensity exercise. From these investigations, additional studies are needed to corroborate the feasibility and effectiveness of higher intensity exercise in BC patients.

2.4 Safety and Feasibility of Home-Based Aerobic Exercise in Breast Cancer Patients

To enhance the clarity regarding exercise guidelines in this patient population, the United States Department of Health and Human Services (US DHHS) compiled the literature on the benefits of exercise in breast cancer survivors[89]. Evidence showed that there do not appear to be significant risks to breast cancer patients engaging in aerobic exercise given sufficient screening for exercise contraindications and proper prescription practices are adhered to[89]. More specifically, the ACSM International Multidisciplinary Roundtable recommends 3 moderate-intensity aerobic training sessions a week with a minimum duration of 30 minutes each for at least 8-12 weeks[90]. However, the US DHHS Physical Activity Guidelines recommends that if

cancer survivors are unable to meet these aerobic exercise targets, patients should do as much physical activity as their abilities and conditions allow and should also limit inactivity as much as possible[89]. The ACSM International Multidisciplinary Roundtable report also showed that physical activity in normal weight, overweight, obese, pre-menopausal and post-menopausal BC survivors are associated with dose-dependent lower risks of both BC-associated mortality as well as all-cause mortality[90]. Patient fatigue is a commonly reported concern that cancer patients receiving chemotherapy experience[90] and therefore, it has been questioned if participation in regular structured aerobic exercise would be difficult. However, evidence shows that structured exercise therapy in a cancer patient population, receiving chemotherapy treatment, is a viable and feasible intervention[11,89,90]. Several exercise intervention studies conducted in cancer patients have shown relatively high adherence rates (i.e., 66-85% adherence) with low adverse event rates to exercise[91–97]. The feasibility of an aerobic exercise program in cancer patients receiving ACs in a smaller Canadian city (i.e., Halifax) was assessed in the previous pilot iteration of the EXACT2.0 study (i.e., EXACT1.0)[11]. Specifically, EXACT1.0 published a feasibility study outlining a 12-week, progressive, AE program that ranged from the light-moderate intensity and was administered during and after chemotherapy treatment[11]. This pilot study demonstrated that an individualized aerobic exercise plan is safe (e.g., lack of adverse events), and feasible (e.g., program adherence) program and can be used to explore the effects of exercise on chemotherapy-induced cardiotoxicity[11]. However, due to barriers imposed by the facility-based intervention, sufficient participant recruitment was not achieved, resulting in under-powered data, limiting any conclusions to be drawn. Moreover, it is possible that the exercise intervention lacked adequate duration (i.e., 12-week intervention). Thus, in the current iteration of this work (i.e., EXACT2.0), we look to address this barrier to exercise, along with the current COVID-19

pandemic climate, by offering a 24-week home-based, virtually supervised exercise intervention, in a hope that the program will have a greater participant outreach.

Home-based exercise offers a unique opportunity for researchers to alleviate barriers to exercise participation arising from traditional, facility- or- hospital-based programs. For example, it can be difficult for the research team, particularly in a clinical cohort such as cancer patients, to offer training sessions that align with all interested participants' schedules. Furthermore, a facility- or- hospital-based program also introduces barriers related to travel to the exercise location, which oftentimes can be a debilitating and fatiguing task for many cancer patients on active treatment[11]. A home-based program may alleviate these barriers that prevent patients from seeking participation in exercise programs while maintaining the effectiveness of the programs on physiological measures of health and fitness (i.e., VO2peak [98], muscle strength[98], fatigue[98,99], etc.). Nevertheless, home-based exercise programs are often thought to be subject to non-adherence bias[100, 101], limiting the statistical integrity of the resulting data leading to its under-utilization. This bias can be limited, or adequately controlled in clinical investigations that look to utilize home-based exercise as its primary means of exercise prescription by adopting an adequate research design. For example, virtually monitoring participant activity data via the incorporation of live tracking physical activity monitors (i.e., Polar), as well as routine follow-up calls with the research team[100,101]. The incorporation of live-tracking activity monitors is vital as this will allow the researchers to control for self-reported response bias. In addition, the research staff are aware of the adherence of each participant relating to the frequency and intensity of their prescribed exercise sessions, as well the adherence of the participant wearing the activity monitor as described in the study protocol and during the consenting process. Moreover, including routine (i.e., weekly) participant follow-ups allow the

research staff to address any non-adherence with the participants, provide motivational support and answer any questions or concerns the participant may have regarding their exercise prescription.

2.5 Summary and Purpose

It was quickly learned that anthracyclines' overall utility in cancer care is hindered due to their cardiotoxic side-effects following treatment[17,21]. This corresponding cardiotoxicity may lead to an increased risk of several cardiovascular complications including: 1) cardiomyopathy, 2) arrhythmia, 3) valvular disease, and/or 4) heart failure, eventually leading to premature death[21,34–37]. Early detection of asymptomatic cardiotoxicity has received a recent increase in scientific exploration due to the importance of detecting cardiotoxicity before it manifests as irreversible. Determining indices of cardiotoxicity prior to the onset of symptomatic cardiotoxicity is important to prevent irreversible cardiac damage. LVEF and GLS are two valid and reliable measures that can be used to detect cardiotoxicity early enough to intervene with mitigation strategies that target anthracycline-based cardiotoxicity. It is widely accepted that AC induces cardiotoxicity through two proposed physiological mechanisms: 1) DNA topoisomerase II (Top2) inhibition[48,49], and 2) oxidative damage and free radical generation[21, 50]. Until recently, oxidative damage and free radical generation was the most universally accepted hypothesis for AC-induced cardiotoxicity. More currently, however, Top2 inhibition is most dominantly recognized as the key mediator pathway of AC-induced cardiotoxicity[48,49,51] (Figure 1). Although there do exist strategies to counteract the cardiotoxic effects of AC treatment (i.e., Dexrazoxane), current management strategies cannot fully manage this cardiotoxicity. Preclinical evidence suggests AE can serve as an adjuvant therapy to AC treatment and has revealed many pathways of cardio-protection. However, there is little clinical data regarding the use of AE as an adjuvant

therapy to attenuate AC-induced cardiotoxicity. Thus, there is an immediate need to perform more clinical trials.

The current iteration of the EXACT study, EXACT2.0, looked to address this by offering clinical evidence that a home-based approach to exercise can realize cardioprotective benefits in BC survivors. Specifically, the purpose of EXACT2.0 was to explore the cardioprotective benefits of a 24-week *home-based* AE program in BCS receiving AC-based chemotherapy. Primary and secondary study outcome measures were used to assess the efficacy of the AE intervention. The primary objectives of the study were to characterize the impact of the AE program on: 1) ventricular function via 2-D echocardiography (i.e., LVEF and GLS); and 2) aerobic fitness (i.e., VO2peak). Secondary objectives of the study consisted of the analysis of self-reported levels of HRQoL and fatigue. Findings from EXACT2.0 will support future work in the pursuit of uncovering evidence that AE, adjuvant therapy to AC treatment, can be successfully used to attenuate AC-induced cardiotoxicity while maintaining the anti-cancer potential of current treatment strategies.

Chapter 3: METHODOLOGY

3.1 Experimental Overview

3.1.1 Study Design

EXACT2.0 was approved by the Nova Scotia Health (NSH) Research Ethics Board (REB file: NSH ROMEO file #: 1024489) and is a registered trial at ClinicalTrials.gov (# NCT03748550). EXACT2.0 is a randomized control clinical trial with repeated measures where breast cancer survivors (BCS) were the target population. BCS were screened for eligibility by their attending nurse or oncologist (i.e., healthcare professional) and confirmed permission to be contacted by the study coordinator for detailed information regarding participation in the study, ensuring informed consent was obtained before enrolment (Appendix A). Informed consent was obtained digitally via e-consent using NSH's secure REDCap database.

BCS were required to come to the (Queen Elizabeth (QEII) Health Sciences Centre, Halifax, twice during their participation in the study – once at baseline and once at follow-up with each visit mirroring one another. At the initial visit, BCS underwent cardiac stress testing at the Queen Elizabeth (QEII) Health Sciences Centre, Halifax, under the supervision of a cardiologist to confirm exercise was not contraindicated, as well to individualize exercise program prescription. Thereafter, BCS were randomly assigned to either the standard of care – control (SOC) or the AE group (SOC + 24-week home-based AE program; AEX) and completed remaining baseline testing (i.e., echocardiogram). SOC for BC patients varies depending on stage and relevant comorbidities, the reader is directed here[102] for more information. Following the participants initial visit to the QEII, the research staff administered the baseline study questionnaire package digitally via REDCap. The questionnaire package consisted of the International Physical Activity Questionnaire (IPAQ), Functional Assessment for Cancer Therapy – Breast (ver. 4) (FACT-B) and the Functional Assessment for Chronic Illness – Fatigue (ver. 4) FACIT-F.

BCS randomized to the AE group were prescribed a 24-week home-based aerobic exercise program designed to promote cardiac adaptations in response to aerobic training. Primary and secondary study outcome measures were used to assess the efficacy of the AE intervention. The primary outcome measure for the study was cardiac function as determined by left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) assessed via 2D-echocardiography and aerobic fitness assessed via cardiac stress test or predictive equations (i.e., VO2peak). Secondary outcome measures included patient-reported outcomes, including levels of HRQoL and fatigue. Participant descriptive statistics (e.g., anthropometrics) were used to define the study population. Each experimental measure was assessed prior to the participants starting AE (week-0) and post-exercise intervention (week-24). For an EXACT2.0 study flow overview, the reader is directed to Figure 2.

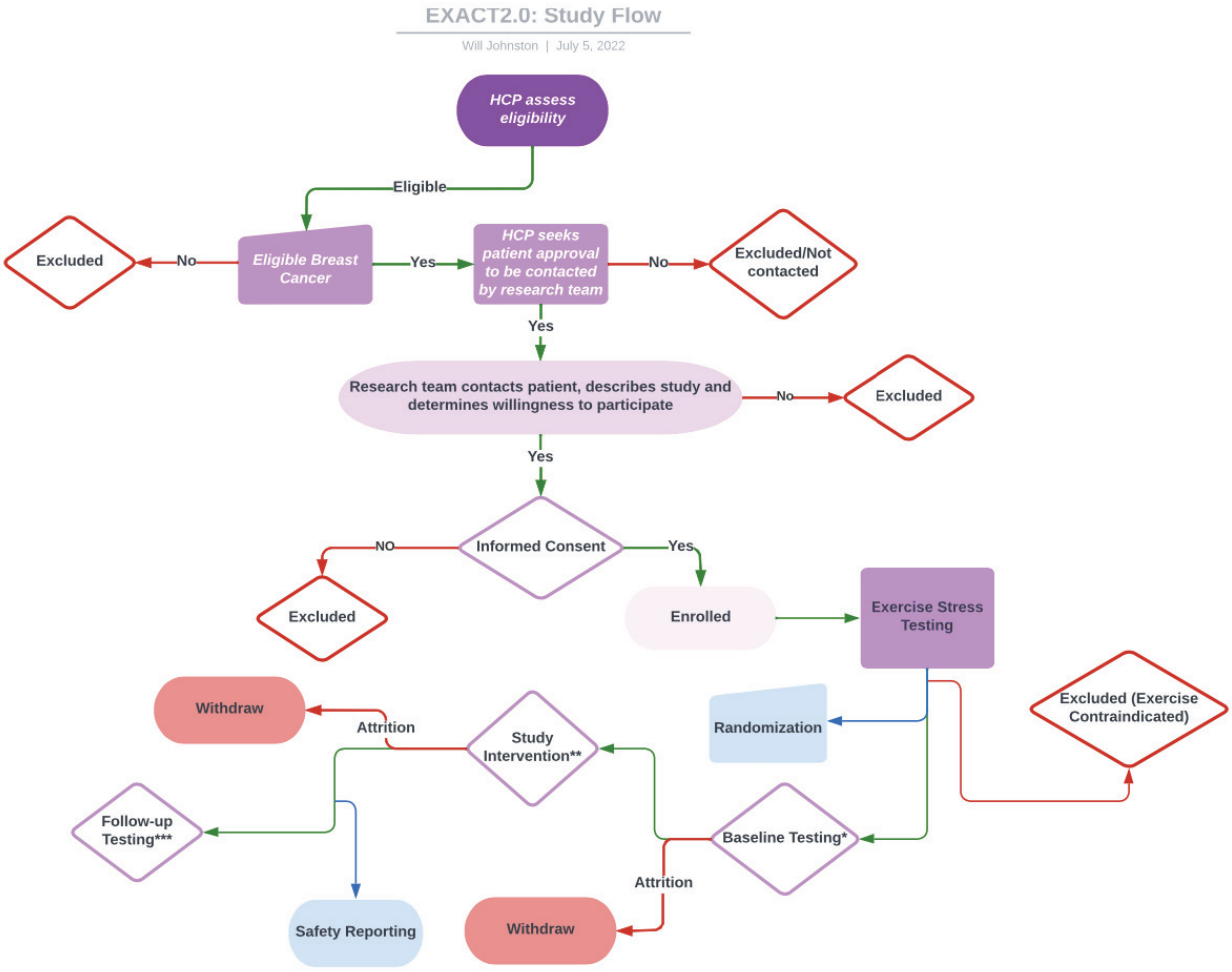


Figure 2. Chart displaying the flow through EXACT2.0 for participants randomized to the intervention group from assessment of eligibility to post-intervention testing.

3.1.2 Study Sample and Recruitment

EXACT2.0 recruited BCSs from cancer clinics in two urban centres (QEII Health Sciences Centre, Halifax, NS; St. Boniface Hospital, Winnipeg, MB). Both the QEII and St. Boniface are tertiary care centres that represent similar size urban and rural communities. Study protocols mirrored one another, maintaining standard study procedures across sites to ensure adequate data quality. Potential participants were identified by their medical oncologist and/or clinic nurse based on the following inclusion criteria: 1) must be 18 years of age or older 2) diagnosed with breast cancer (stages I-III) and not have started therapy; 3) must be scheduled to

receive AC-based chemotherapy (i.e., a minimum dose of 100 mg/m^2 of doxorubicin or 120 mg/m^2 of daunorubicin or 150 mg/m^2 of epirubicin[21,26,27]); 4) can undertake a 24-week home-based, progressive AE; and 5) have medical clearance from a cardiologist (e.g., based on stress test results) to participate in the study. Any BCS that met the inclusion criteria but presents with: 1) significant cognitive limitations; and/or 2) any pre-existing medical condition that would otherwise contraindicate AE was excluded from the study.

Upon enrollment, participant demographics (e.g., age, BMI, waist girth, tumor location, VO2peak, total dose of AC administered, smoking history, family history of CVD, baseline PA behaviour (min/week), history of hypertension, hyperlipidemia, smoking, or underwent chest radiation) were collected via accessing the participants respective health records (Table 1).

3.1.3 Exercise Intervention

All BCSs randomized to the AEX group continued to receive SOC as well as prescribed a structured 24-week, home-based progressive AE program (Appendix B). This program is based on core training principles (Figure 3), has been shown to decrease fatigue associated with higher intensity exercise, and consists of a nonlinear and progressive training approach (Figure 4) and was used to optimize training adaptations in the various physiological systems involved in the cardiopulmonary response[103]. Further, it has been previously shown that a 6-month exercise program vs. a traditional 3-month exercise program is similar or provided additional benefits[104]. This bodes well since the COVID-19 pandemic forced EXACT2.0 to pivot from a 3-month program to a longer 6-month program.

Figure 3. Successful exercise prescription relies upon four important core training principals. These include specificity, individualization, progressive overload, and recovery. Specificity: The exercise prescription uses modalities which disrupts the physiological equilibrium of a target system, stimulating specific adaptation. Individualization: The exercise prescription bases the dose (i.e., frequency, intensity, and duration) on the current fitness status of the individual. Progressive overload: the specific dose of exercise progresses throughout the program as to prevent chronic adaptation to future stressors. Recovery: Exercise is prescribed with appropriate days of rest and recovery to leave time for the necessary growth and development of target tissues[103].

Each BCS was asked to perform AE sessions (e.g., walking) twice per week, on non-consecutive days. Exercise was prescribed on non-consecutive days to promote physiological adaptation between exercising sessions. Exercise performed 2x/week has been shown to favour perceptions of fatigue and promotes study adherence and retention[103]. The AE sessions varied between low (35-45% heart rate reserve (HRR)), low-moderate (45-55% HRR), moderate-high (55-70% HRR) and high (70-85% HRR) intensity. HRR were calculated for each BCS based on the resting and maximal HRs, as seen in Appendix B, obtained during their stress test. When cardiac stress testing was not available (e.g., No stress test tech due to COVID-19; N=5), age-related predictive equations were used[105]. All exercise sessions began with a 5-minute warm-up and ended with a 10 min cool-down. Since the duration of each session was inversely related to AE intensity, sessions ranged from 20 minutes (high intensity) to 45 minutes (low intensity), in addition to warm-up and cool-down.

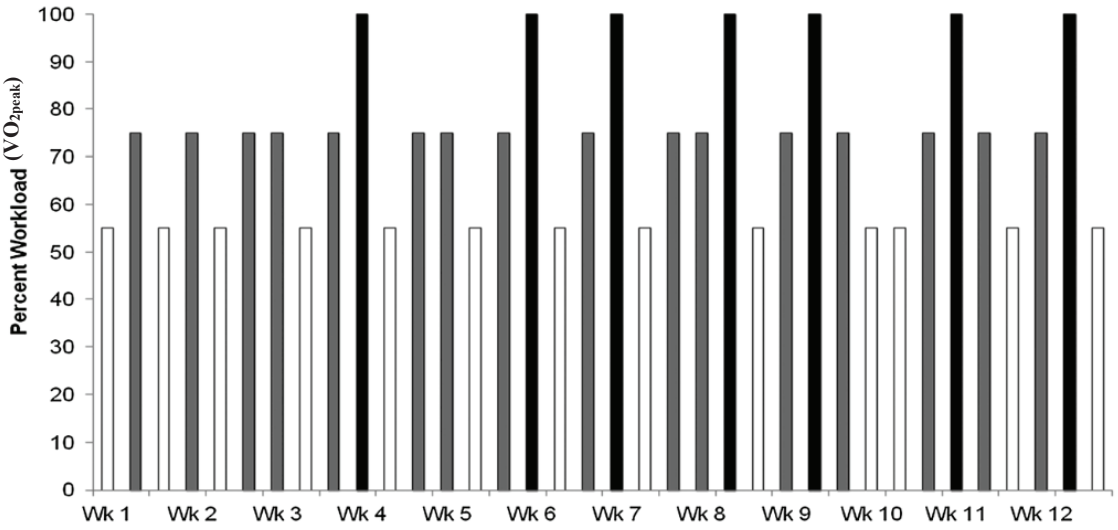


Figure 4. Example of a non-linear, progressive approach tailored to an individual's current fitness status. Intensity is individually prescribed based on cardiopulmonary exercise testing or exercise tolerance testing. The overall goal of the individualized approach is to specifically address a particular outcome. To target the various physiological systems involved in the cardiopulmonary response to exercise, training duration and frequency progress over the course of the prescribed program and vary between low intensity (e.g., 55% VO2peak; white bars), moderate (e.g., 75%; grey bars) and high intensity (e.g., 100% VO2peak; black bars) training. To ensure adequate recovery between training, sessions involving high relative intensity workloads are conducted in shorter bouts and are less frequent. VO2peak, peak rate of oxygen consumption[103].

3.1.4 Protocol Adherence, Safety and Monitoring

To maintain the integrity of the research and limit the potential for self-report bias, each participant was given a Polar A370 Activity/HR monitor (Polar Canada). This was to ensure that BCSs were: 1) wearing their activity trackers during exercise, 2) training at the appropriate frequency (i.e., two days/week), and 3) keeping exercising intensity and duration within the prescribed target HR zone for the prescribed amount of time. The A370 is a wrist-worn monitor that utilizes a proprietary 2-LED optical tracking method for the continuous measurement of heart rate (HR). These monitors were specifically chosen as they do not require a chest strap to be worn, which could be uncomfortable or not possible for some BCSs to wear. The Polar monitors has been previously validated against electrocardiography by members of my lab (data not published), as well, the monitors been shown to be very accurate when compared to other

validated methods of monitoring heart rate[106]. BCS were taught before the study how to use these functions and were required to upload their total exercising time to a secure site (e.g., REDCap) at the end of each week. Participants were contacted bi-weekly, as a routine "check-in" to allow the researchers to track each participant's program adherence, progress, as well as offer a chance to address any adverse events or concerns the participant may have regarding their participation in the study. For example, if a participant did not upload their data or their data suggested there was an issue with their AE program, they were contacted immediately. Safety was simultaneously monitored by examining the total number of adverse events, if any, that occur over the duration of the 24-week AE program. The total number of adverse events over the course of the study were divided by the total number of participant hours to determine the number of adverse events per participant hour.

3.2 Data Collection: Experimental Outcome Measures

3.2.1 Primary Outcome Measures

3.2.1.1 Echocardiography

Due to their respective abilities to detect subclinical changes in cardiac damage (e.g., decrease in LVEF of >10 percentage points, to a value <53%), serial transthoracic echocardiography (TTE), in addition to tissue velocity imaging (TVI) and strain imaging (SI) was used to assess LV structure and function[107,108]. Serial TTE and TVI were performed using a GE Vivid 7 platform (General Electric, Milwaukee, WI). Images from parasternal and apical views were obtained using a standard multi-frequency transducer (Figure 5A, B & C).

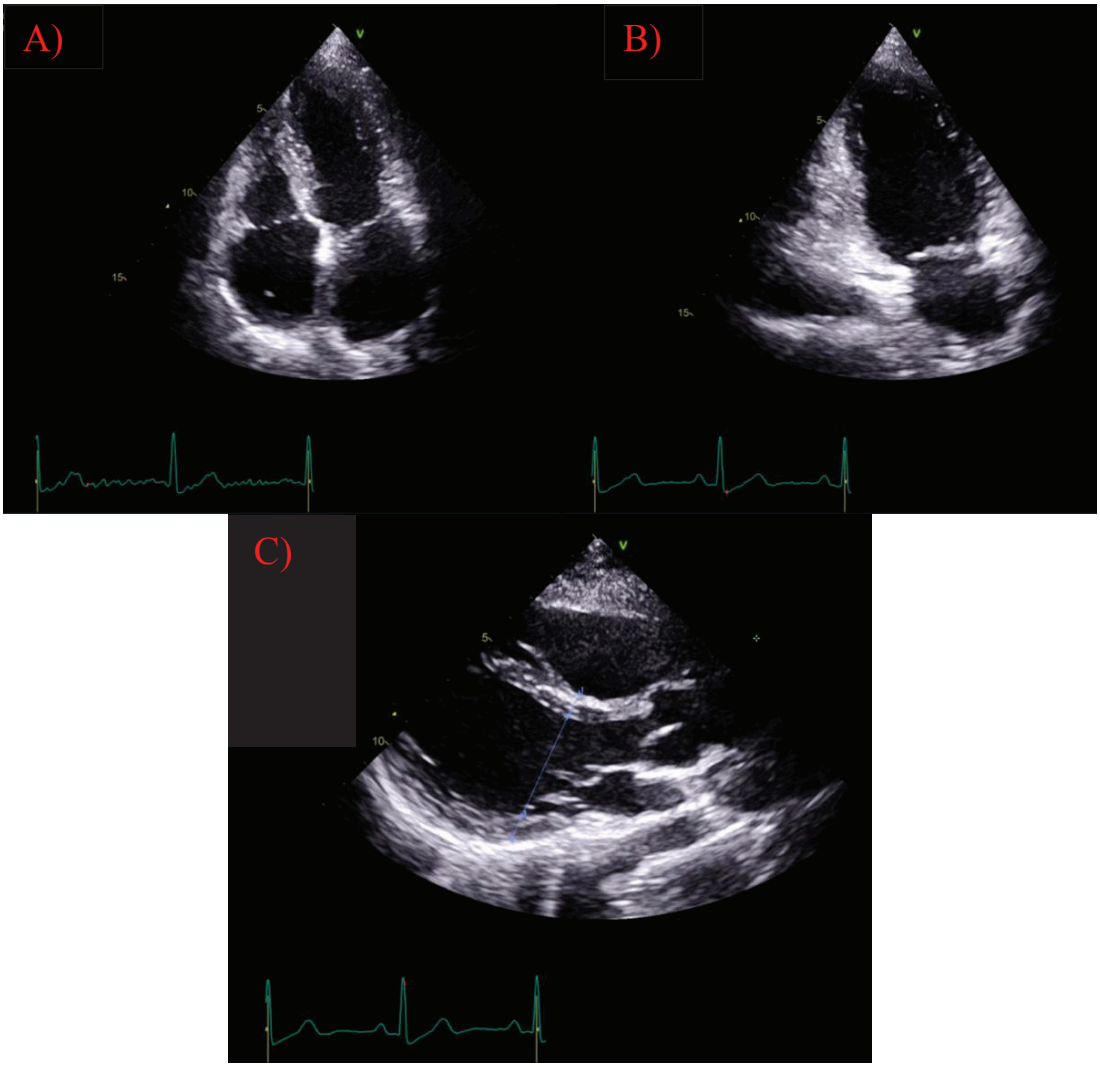
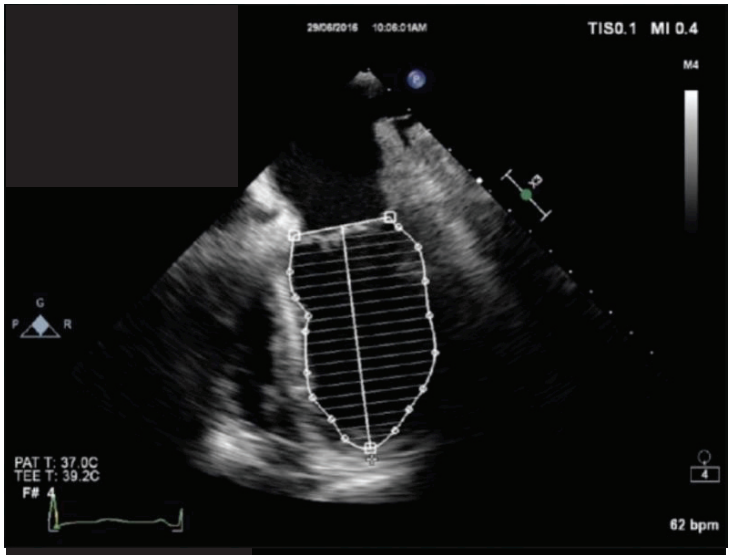


Figure 5. A) Apical 4 chamber, B) Apical 2 chamber and C) Apical parasternal long axis as assessed via serial transthoracic 2-D echocardiogram planes of view.

LV cavity dimensions and LVEF were determined using the modified biplane Simpsons' method from the acquired 2D images according to established criteria[109] (Figure 6A & B).

A)



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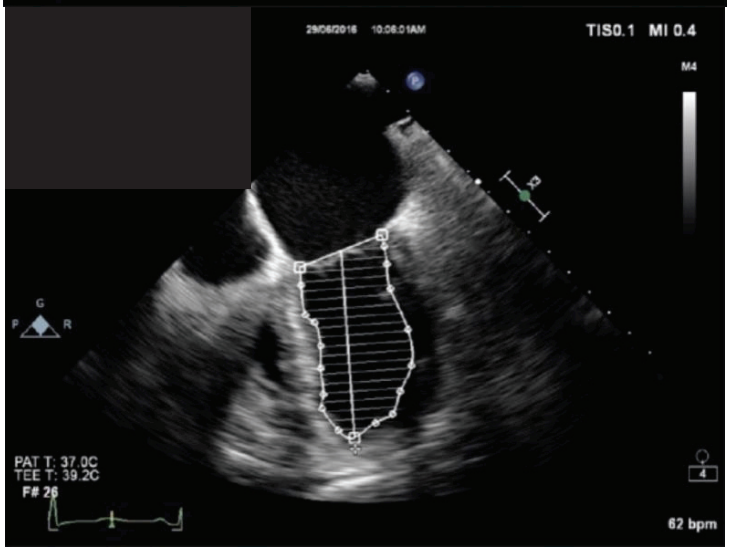


Figure 6. Modified Biplane Simpson's Method as assessed via 2-D serial transthoracic echocardiography; A) End-diastolic volume measurement; B) End-systolic volume measurement[110].

Tissue Doppler-derived indexes were recorded at the base of the lateral mitral annuli to determine longitudinal endocardial velocities[107]. The indexes that were assessed are systolic (S'), early diastolic (e') and late diastolic (a') velocities (Figure 7).

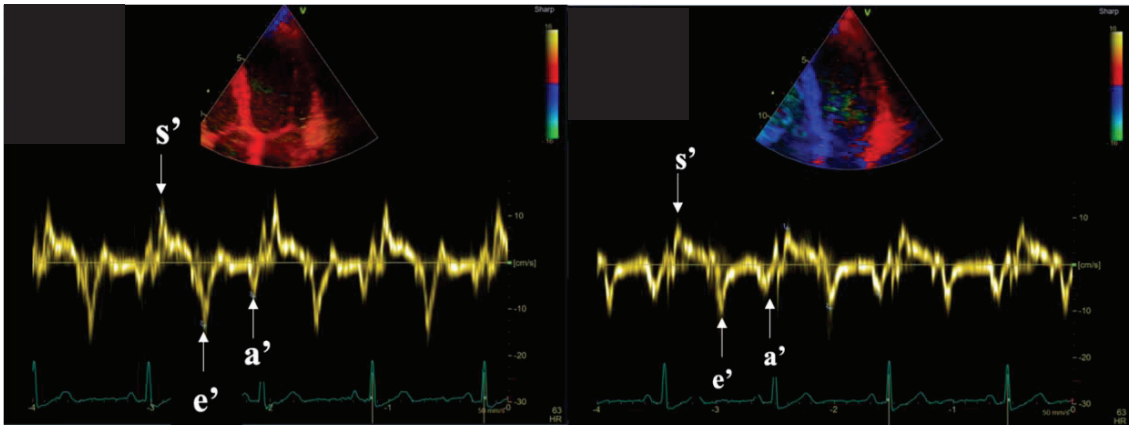
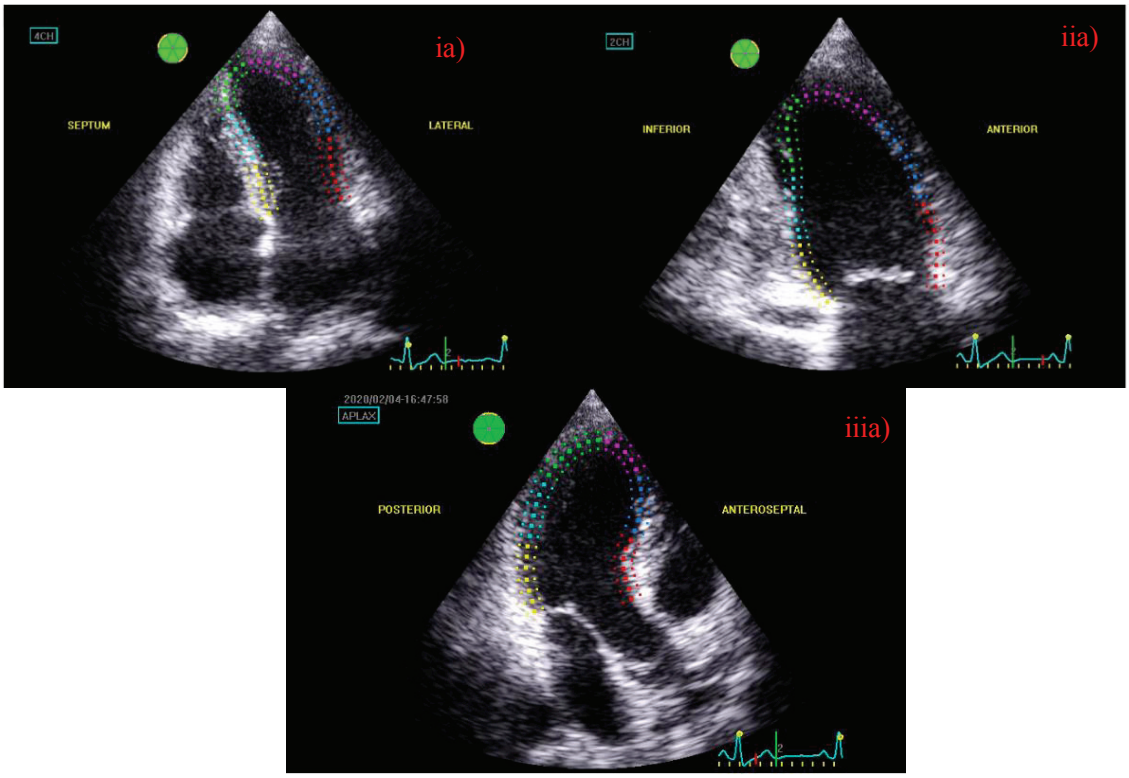


Figure 7. Lateral (left) and medial (right) mitral annulus velocity. s' velocity is a positive systolic wave representing myocardial contraction, e' velocity represents early diastolic myocardial relaxation, and a' velocity represents late diastolic atrial contraction.

Doppler-independent strain was performed using parasternal and apical views to determine global longitudinal strain (Figure 8). Assessments were made offline using semi-automated speckle tracking techniques[108].

A)



B)

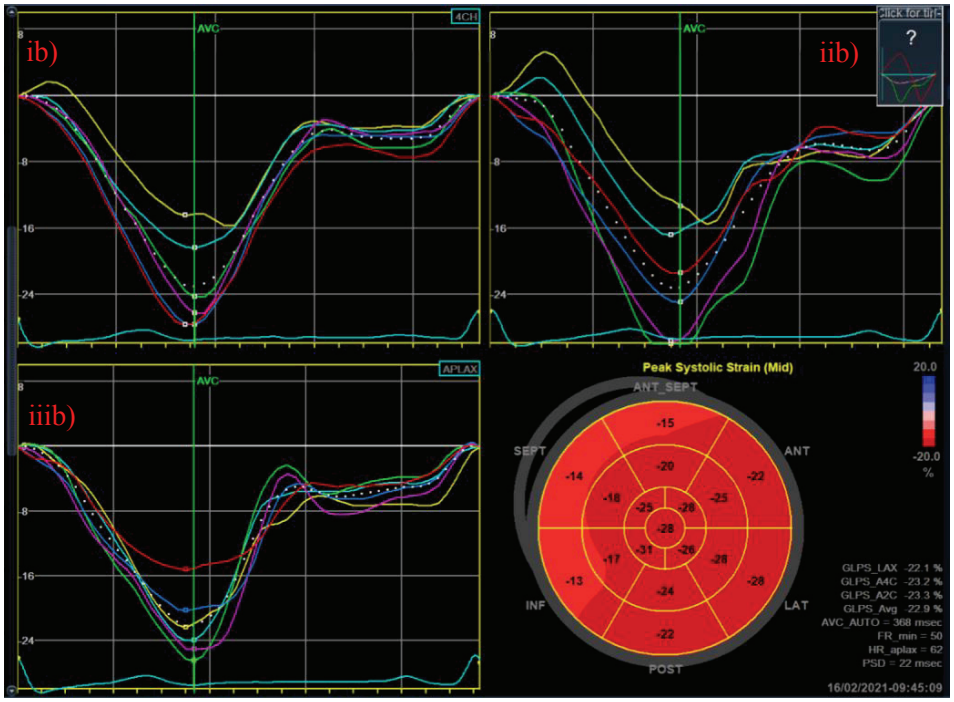


Figure 8. A) Left ventricular global longitudinal strain (GLS) assessment with two- dimensional speckle tracking echocardiography. The figure demonstrates analysis of left ventricular GLS from the apical 4 chamber (ia; 4CH) two – chamber (iia; 2CH) and long axis (iiia; APLAX) views; B) with their respective time to strain curves and polar map with the regional values from the 17 segments which is within the normal value[111].

Echocardiograms were conducted at the QEII Health Sciences Centre (Halifax) and St. Boniface Hospital (Winnipeg). Analysis/ interpretation for the research study was performed at St. Boniface Hospital (Winnipeg) by a team cardiologist that has been blinded to BCS group assignment.

3.2.1.2 Aerobic Fitness – Cardiac Stress Tests

Cardiac stress tests were used to examine cardiac electrical activity (e.g., electrocardiogram; ECG) as well as determine peak oxygen consumption (VO2peak. Specifically, BCSs performed a graded exercise test until they reached volitional fatigue, or until the test was terminated due to adverse physiological changes[112]. Cardiac electrical activity (P-wave, T-wave, QRS complex, PR interval, QT interval and HR variability) were monitored using

a 12 lead ECG (General Electric Case System). Predictive equations were used to predict the BCS's VO2peak based on the total duration (seconds) of the treadmill test.

3.2.2 Secondary Outcome Measures

3.2.2.1 Patient-Reported Health-Related Quality of Life and Fatigue

To assess HRQoL, the FACT-B questionnaire was used [113]. The FACT-B includes 5 independent sub-scales for assessing physical, social/family, emotional, functional well-being as well as additional BC concerns (Appendix C). Cancer-related fatigue was assessed using the FACIT-F questionnaire. The FACIT-F is a 13 item questionnaire that was used to assess fatigue in the patient population (Appendix D)[114].

3.2.2.2 Supporting Measures

Baseline physical activity (PA) behaviour was assessed in both groups upon participant enrollment. To assess PA behaviour, participants were asked about their normal weekly PA behaviour using a self-report questionnaire (i.e., IPAQ). The questionnaire is designed to capture PA behaviour relating to employment, transportation, housework, both indoor and outdoor, as well as leisure time PA (Appendix E). Intra-study mean weekly exercise time was assessed in both groups post-intervention via uploaded Polar HR monitor data.

3.3 Statistical Data Analysis

Participant descriptive characteristics were used to define the population and compared via independent samples t-tests where appropriate. All data were assessed for normality (e.g., Shapiro-Wilk test), and non-normalized data, where appropriate, were compared using non-parametric statistical models. For all normal data (i.e., GLS, HRQoL, fatigue), a two-factor (i.e., treatment and time) repeated measures ANOVA was used to compare differences between groups. The variance of differences (i.e., assumption of sphericity) was assessed using Mauchly's test and when violated, the Greenhouse-Geisser correction to the degrees of freedom was applied. Bonferroni *post hoc* testing was conducted for any statistically significant

ANOVAs. ANOVA effect sizes were calculated for main effects and *post hoc* analyses as Partial Eta Squared (η_p^2). Effect sizes were determined as follows: 1) 0.01- 0.06 indicates a small effect, 2) 0.06-0.14 indicates a medium effect, and 3) ≥0.14 indicates a large effect.

All non-normal data (i.e., LVEF, VO2peak, baseline self-report PA, intra-study exercise) were compared via a Mann-Whitney U (i.e., between subject effects) and a Wilcoxon Signed Rank (i.e., within subject effects) test (i.e., LVEF and VO2peak) or non-parametric t-tests (i.e., baseline self-report PA, intra-study exercise) to assess significance both between groups. R values were used to calculate effect sizes (i.e., $r=Z/\sqrt{N}$) for non-parametric within- and- between-group effects. Effect sizes were determined as follows: 1) 0.10-0.30 indicates a small effect, 2) 0.30-0.50 indicates a medium effect, and 3) ≥0.50 indicates a large effect.

Program adherence was calculated as the percentage of the total number of exercise sessions completed, the percentage of exercise sessions completed at the prescribed intensity and duration, as well as the percentage of sessions the exercise monitor was worn for (based on uploaded data from the A370 monitor).

Safety was determined by examining the total number of adverse events, if any, that occur over the duration of the 24-week AE program. The total number of adverse events over the course of the study were divided by the total number of participant hours to determine the number of adverse events per participant hour. All statistics were completed in SPSS Version 27.0 (IBM, NY). Statistical significance is accepted as $p < 0.05$. All data are presented as means ± SD.

Chapter 4: RESULTS

4.1 Participant Group Demographics and Cardiac Anatomy

Overall, N=20 participants were recruited and enrolled into the study with an even distribution in each group. Ten participants (n=10) completed a 24-week individualized home-based aerobic exercise program (AEX). Participant demographics were collected upon enrollment into the study, group characteristics are displayed in Table 1. Specifically, the SOC and AEX groups were similar in age, BMI, waist girth, VO2peak, total dose of AC administered, smoking history, and family history of CVD ($p>0.05$), while baseline PA behaviour (min/week) in the SOC group was significantly higher compared to AEX ($p=0.016$). There was n=3 participants enrolled in the study with hypertension (SOC: n=2). Three participants enrolled in the study presented with hyperlipidemia (SOC: n=3), 5 had a history of smoking (SOC: n=3), 4 had family history of CVD (SOC: n=2), and 7 underwent chest radiation (SOC: n=4).

Table 1. Participant Demographics for participants enrolled in the study separated by SOC and AEX group randomization

Measure	SOC (n = 10)	AEX (n = 10)	T-Test
Age (years) (mean ± SD)	51 ± 12	49 ± 6	>.05
BMI (kg/m^2) (mean ± SD)	30.2 ± 6.8	27.6 ± 6.1	>.05
Waist Girth (cm) (mean ± SD)	101.27 ± 16.3	102.33 ± 26.7	>.05
*Baseline PA Behaviour (min/week) (mean ± SD)	1220 ± 548	652 ± 657	.0016
VO2peak (mL/kg/min (mean ± SD)	23.4 ± 3.29	28.9 ± 9.23	>.05
Hypertension (n, %)	(2, 10)	(1, 5)	-
Diabetes (n, %)	0	0	-
Hyperlipidemia (n, %)	(3, 15)	0	-
Smoking History (n, %)	(3, 15)	(2, 10)	-
Family History of CAD (n, %)	(2, 10)	(2, 10)	-
Total dose of Anthracycline (mg/m^2)	407.1 ± 181.5	467.4 ± 128.1	>.05
Chest Radiation (n, %)	(4, 20)	(3, 15)	-
Location of Cancer: Left only (n, %)	(6, 30)	(7, 35)	-
Location of Cancer: Right only (n, %)	(4, 20)	(3, 15)	-
Location of Cancer: Bilateral (n, %)	0	0	-

SOC: standard of care; AEX: aerobic exercise program; BMI: body mass index; CAD: coronary artery disease; SD: standard deviation; PA: physical activity; mg: milligrams; m: meters; data displayed as mean ± SD; *significance at $p<0.05$.

Cardiac anatomy data obtained from echocardiography assessments are outlined in Table 2. Left ventricle inner-dimension diameter at systole (LVID(s)) did not reflect a significant Group × Time interaction effect (p=0.900). Each of the following: interventricular septum (IVS), left ventricle inner-dimension diameter at diastole and diastole (LVID(d)); posterior wall thickness (PWT), left atrium diameter (posterior-anterior; LA), and right ventricle diameter did not significantly differ at baseline between groups, nor at 6-month follow-up (Table 2). Additionally, each of the echocardiography parameters mentioned previously did not significantly differ within the AEX or SOC groups when compared between timepoints (Table 2).

Table 2. Echocardiographic parameters for participants enrolled in the study separated by SOC and AEX group randomization

Echocardiographic Parameter	SOC		AEX		Interaction (P-value)	Baseline (b/w)	AEX (within)
	Baseline	6-Month	Baseline	6-Month		6-month (b/w)	SOC (within)
Anatomy (Parasternal Long Axis)							
IVS (cm)	0.93 ± 0.10	0.91 ± 0.09	0.95 ± 0.12	0.92 ± 0.08	-	.842	.380
						.968	.577
LVID (d) (cm)	4.21 ± 0.20	4.33 ± 0.19	4.32 ± 0.24	4.42 ± 0.18	-	.243	.305
						.315	.077
LVID (s) (cm)	2.83 ± 0.23	2.96 ± 0.21	2.95 ± 0.21	3.06 ± 0.26	.900	-	-
PWT (cm)	0.91 ± 0.12	0.84 ± 0.11	0.90 ± 0.08	0.88 ± 0.09	-	.968	.480
						.497	.202
LA (cm)	3.34 ± 0.33	3.21 ± 0.58	3.19 ± 0.46	3.21 ± 0.52	-	.400	.833
						.905	.777
RV (cm)	3.19 ± 0.21	3.14 ± 0.26	3.04 ± 0.25	3.15 ± 0.19	-	.156	.076
						1.000	.670
Modified Biplane Simpson's							
*LVEF (%)	62.2 ± 1.4	61.9 ± 2.7	63.1 ± 1.6	58.9 ± 7.3	-	.247	.042
						.905	.369
Global Longitudinal Strain							
*†LAX (%)	-19.5 ± 1.4	-18.2 ± 1.9	-19.6 ± 1.8	-14.2 ± 11.0	-	.968	.041
						.315	.038
A4C (%)	-19.2 ± 1.0	-18.6 ± 2.4	-19.3 ± 2.5	-13.9 ± 11.4	-	.400	.050
						.211	.441
*A2C (%)	-20.1 ± 1.7	-14.3 ± 12.7	-20.0 ± 1.42	-17.2 ± 2.3	-	.905	.021
						.400	.051
Total (%)	-18.9 ± 1.6	-18.3 ± 1.4	-19.1 ± 1.2	-17.3 ± 2.2	.241	-	-

SOC: standard of care group; AEX: aerobic exercise group; b/w: between group comparison; IVS: interventricular septum; LVID(d): left ventricular inner-dimension - diastole; LVID(s): left ventricular inner-dimension - systole; PWT: posterior wall thickness; LA: left atrium diameter (anterior-posterior); RV: right ventricle diameter; LVEF: left ventricular ejection fraction; LAX: parasternal long axis; A4C: apical 4-chamber; A2C: apical 2-chamber; cm: centimeter; data displayed as mean ± SD; *significance within AEX at $p<0.05$; †significance within SOC at $p<0.05$

4.2 Left Ventricular Function and Global Longitudinal Strain

Levels of left ventricular function were assessed using echocardiographic measurements of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). LVEF was observed to be non-normally distributed at follow-up in the AEX group (p=0.002). Therefore, a Mann-Whitney U was used to assess between subject effects and a Wilcoxon Signed Rank test was used to assess within subject effects. At baseline, mean LVEF was 62.2±1.4% and 63.1±1.6% in the SOC and AEX groups respectively. At follow-up, mean LVEF was 61.9±2.7% and 58.9±7.3% in the SOC and AEX groups respectively (Table 2). LVEF did not significantly differ between groups at baseline (p=0.247; r=-0.27) or at follow-up (p=0.905; r=0.04) nor was significance detected within group regarding SOC (p=0.369; r=-0.21). However, there was a statistically significant decrease within group regarding the AEX cohort (p=0.042; r=-0.46). An overview of LVEF data is displayed in Figure 9A.

A similar trend as seen in LVEF was also seen with GLS; however, GLS was observed to be normally distributed in both study cohorts at each timepoint. Therefore, a two-factor (i.e., treatment and time) repeated measures ANOVA was used to compare mean differences between groups. At baseline, mean GLS was -18.9±1.6% and -19.1±1.2% in the SOC and AEX groups respectively. At follow-up, mean GLS was -18.3±1.2% and -17.3±2.2% in the SOC and AEX groups respectively (Table 2). There was no significant Group × Time interaction effect at follow-up compared to baseline (p=0.241; η_p^2=0.080). However, there was a statistically significant effect of time (p=0.03), but no significant effect of group was detected (p=0.456). An overview of GLS data is displayed in Figure 9B.

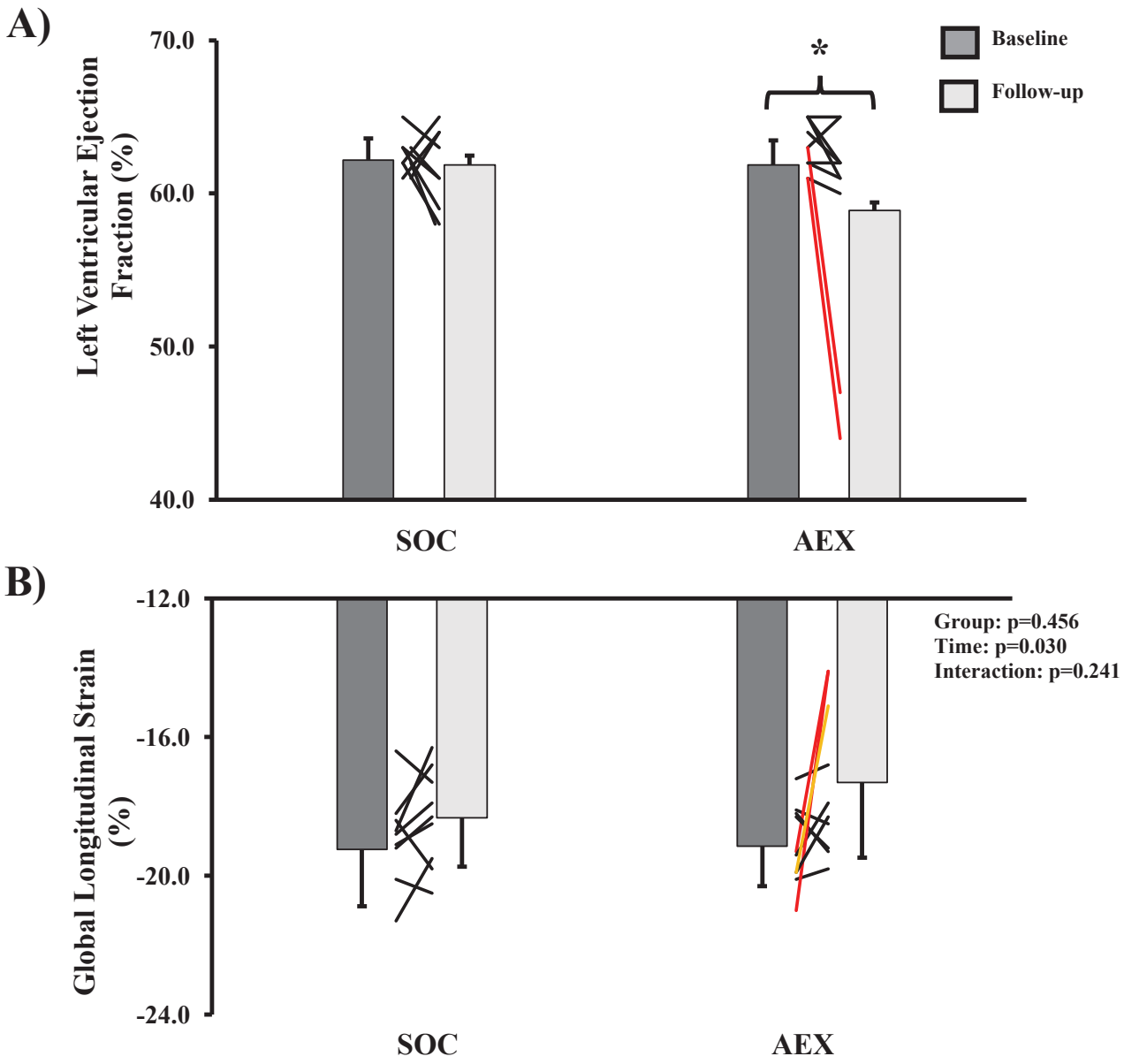


Figure 9. A) Left ventricular ejection fraction expressed as a percentage based on data obtained from baseline and follow-up 2-D serial transthoracic echocardiographic assessments B) Left-ventricular global longitudinal strain expressed as a percentage based on data obtained from baseline and follow-up echocardiographic assessments. Baseline data are expressed by dark grey bars, follow-up data expressed by light grey bars. Individual data for SOC (n=9) and AEX (n=10) are expressed between the group mean bars. Red lines indicate decreases in LVEF or GLS to cardiotoxic levels. Orange bars indicate decreases approaching cardiotoxic levels. A) Non-parametric hypothesis testing was used to determine between group (Mann Whitney U) and within group (Wilcoxon signed ranked test) differences at each timepoint. *, P<0.05 within groups between timepoints. B) Group × Time interaction effects were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post-hoc* pairwise comparisons to determine within and between group differences.

4.3 Aerobic Fitness

Aerobic fitness was assessed using VO2peak as predicted using data derived from a hospital-based cardiac stress test and a corresponding predictive equation (i.e., VO2=4.38T – 3.9; where T=total time exercising during treadmill stress test). VO2peak was observed to be non-normally distributed at baseline in the AEX group (p=0.005). Therefore, a Mann-Whitney U was used to assess between subject effects and a Wilcoxon Signed Rank test was used to assess within subject effects. At baseline, mean VO2peak was 23.4±3.29 mL/kg/min and 28.9±9.23 mL/kg/min in the SOC and AEX groups respectively. At follow-up, mean VO2peak was 23.3±8.2 mL/kg/min and 32.2±7.8mL/kg/min in the SOC and AEX groups respectively. VO2peak did not significantly differ between groups at baseline (p=0.232; r=-0.33) however there was a significant difference detected at follow-up (p=0.049; r=-0.48). Significance was not detected within group regarding both SOC (p=0.889; r=0.04) and AEX (p=0.237; r=0.32). An overview of VO2peak data is displayed in Figure 10.

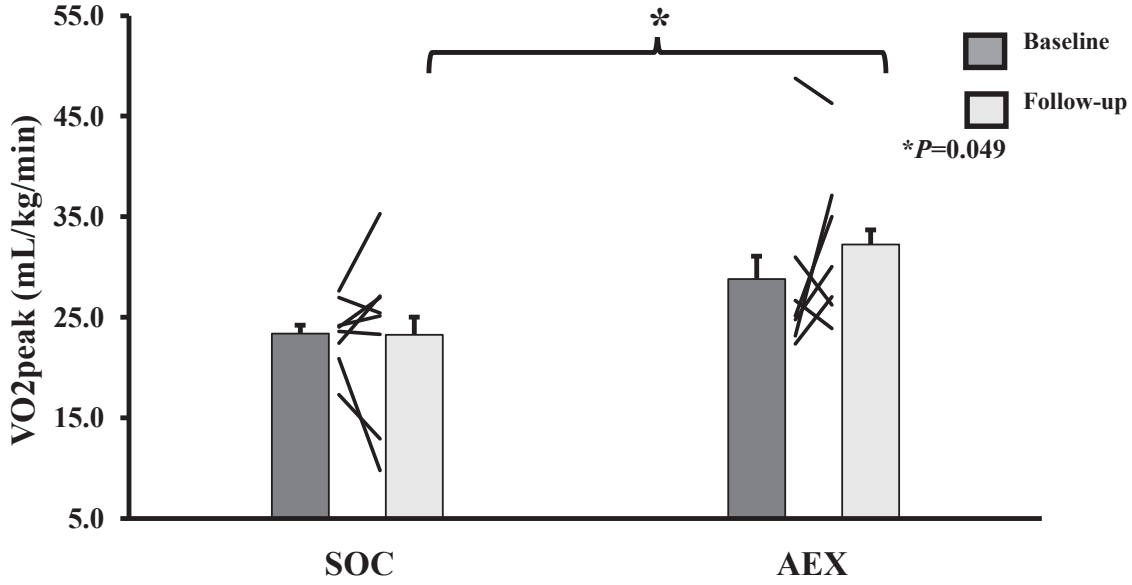


Figure 10. Relative VO2peak expressed as ml/kg/min based on data obtained from baseline and follow-up cardiac stress test assessments. Baseline data are expressed by dark grey bars, follow-up data expressed by light grey bars. Individual data for SOC (n=8) and AEX (n=7) are expressed between the group mean bars. Data compared using non-parametric hypothesis testing to determine between group (Mann Whitney U) and within group (Wilcoxon signed ranked test) differences at each timepoint. *, P<0.05 between groups at the same time point.

4.4 Health-Related Quality of Life and Fatigue

4.4.1 Health Related Quality of Life

HRQoL was assessed using the FACT-B (Appendix C). HRQoL was observed to be normally distributed in both study cohorts at each timepoint. Therefore, a two-factor (i.e., treatment and time) repeated measures ANOVA was used to compare mean differences between groups. At baseline, mean HRQoL was 104.3±16.5 and 110.8±6.9 in the SOC and AEX groups respectively. At follow-up, mean HRQoL was 109.6±14.4 and 112.1±11.2 in the SOC and AEX groups respectively. There was no significant Group × Time interaction effect at follow-up compared to baseline ($p=0.351$; $\eta_p^2=0.051$). However, there was an overall effect of time ($p=0.018$), but no significant group effect was detected ($p=0.418$). An overview of HRQoL data is displayed in Figure 11.

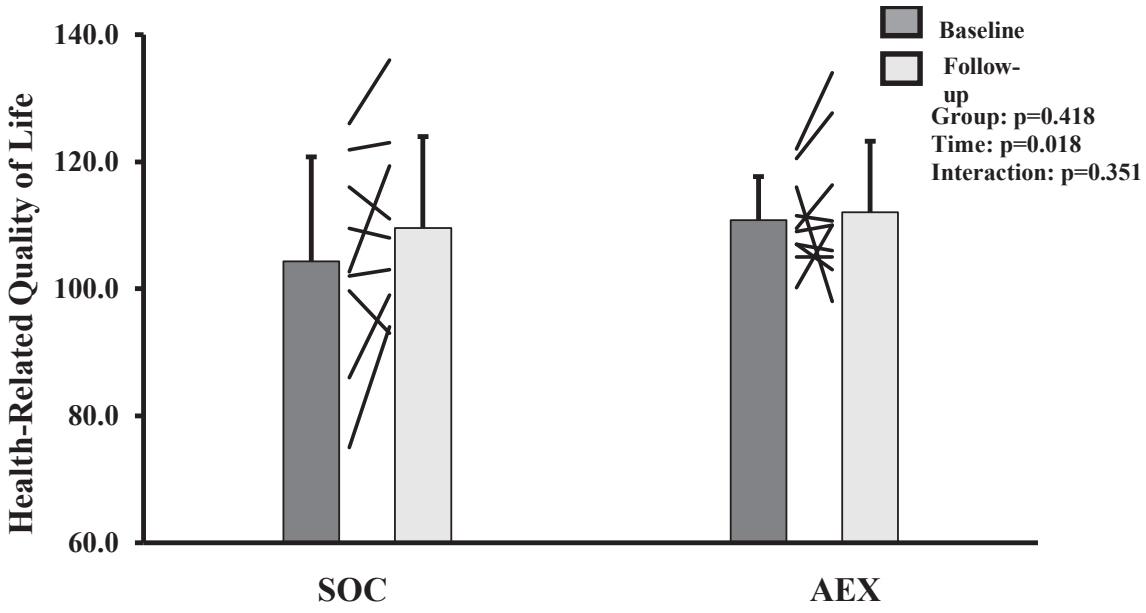


Figure 11. HRQoL based on data obtained from baseline and follow-up FACT-B questionnaire assessments. Baseline data are expressed by dark grey bars, follow-up data expressed by light grey bars. Individual data for SOC (n=9) and AEX (n=10) are expressed between the group mean bars. Data compared by Group × Time interaction effects and were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post-hoc* pairwise comparisons to determine within and between group differences.

4.4.2 Fatigue

Fatigue was assessed using the FACIT-F (Appendix D). Fatigue was observed to be normally distributed in both study cohorts at each timepoint. Therefore, a two-factor (i.e., treatment and time) repeated measures ANOVA was used to compare mean differences between groups. At baseline, mean fatigue was 39.8±8.3 and 41.1±5.4 in the SOC and AEX groups respectively. At follow-up, mean fatigue was 34.2±9.2 and 33±12.4 in the SOC and AEX groups respectively. There was no significant Group × Time interaction effect at follow-up compared to baseline ($p=0.651$; $\eta_p^2=0.012$). However, there was a statistically significant effect of time

(p=0.024), but no significant group effect was detected (p=0.988). An overview of fatigue data is displayed in Figure 12.

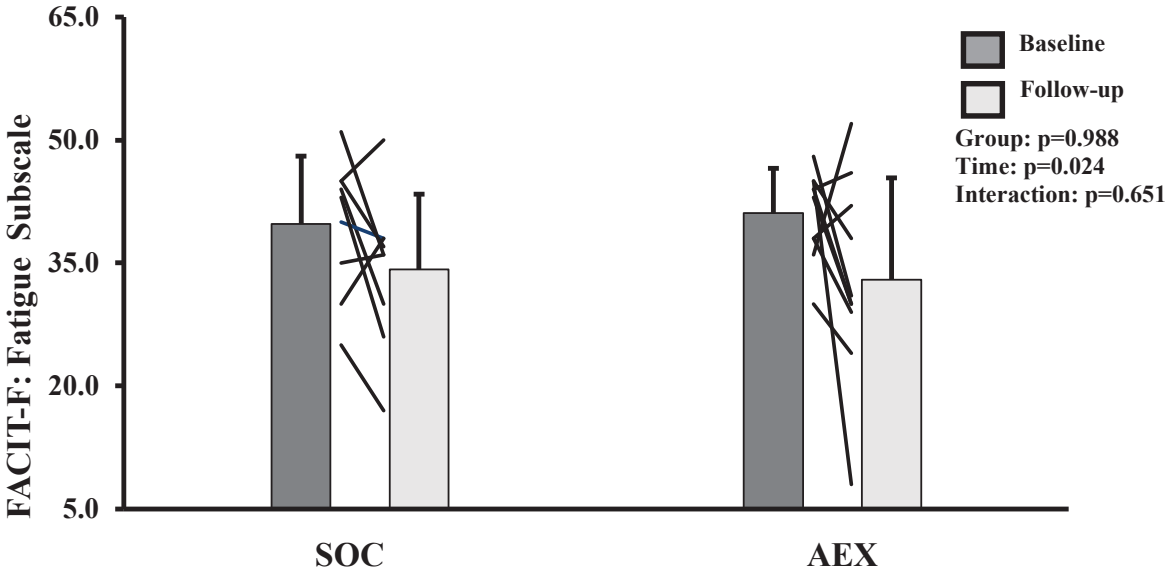


Figure 12. Fatigue based on data obtained from baseline and follow-up FACIT-F questionnaire assessments. Baseline data are expressed by dark grey bars, follow-up data expressed by light grey bars. Individual data for SOC (n=9) and AEX (n=10) are expressed between the group mean bars. Data compared by Group × Time interaction effects and were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post-hoc* pairwise comparisons to determine within and between group differences.

4.5 Supporting Measures

4.5.1 Baseline Physical Activity Behaviour

At baseline, mean physical activity behaviour was 1220.56 ±548.74 min/week and 652.22±657.2 min/week in the SOC and AEX groups respectively. The SOC and AEX groups were significantly different at baseline (p=0.016). An overview of baseline PA behaviour data is displayed in Figure 13.

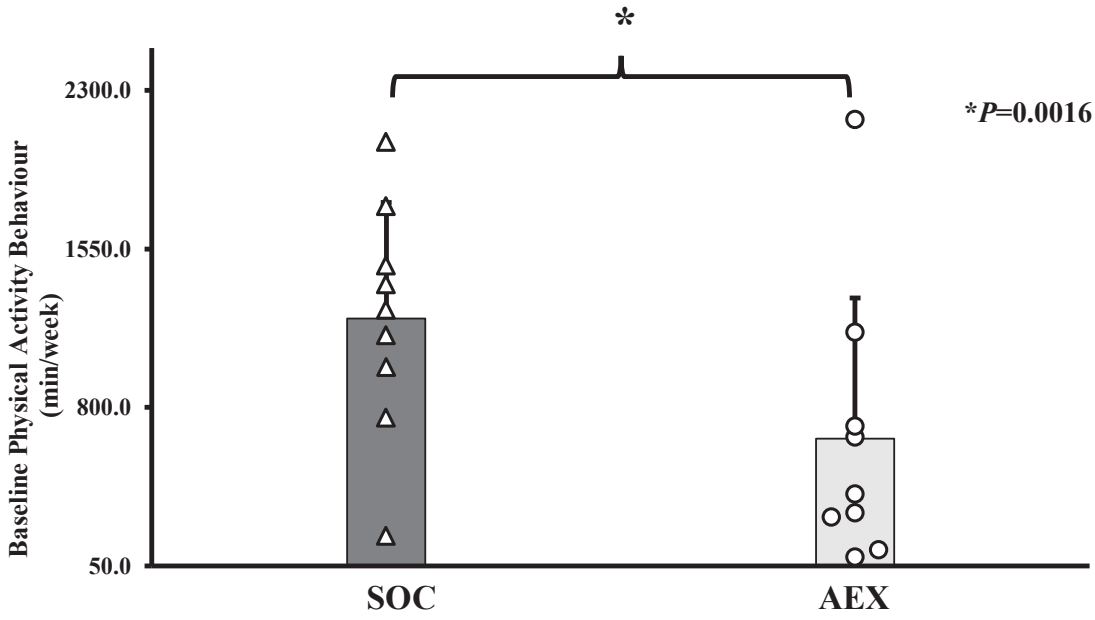


Figure 13. Baseline PA behaviour obtained from self-report questionnaires administered upon enrollment. SOC group is expressed via a dark grey bas while the AEX group is expressed via a light grey bar. Individual SOC data expressed by white triangles while individual AEX data are expressed as white circles. Data compared using non-parametric hypothesis testing to determine between group (Mann Whitney U) comparisons. *, P<0.05 between groups at the same time point.

4.5.2 Intra-study Average Weekly Exercise Time

Mean intra-study mean weekly exercise time was 65.9±30.3 min/week and 96.4±30.5 min/week in the SOC and AEX groups respectively. The SOC and AEX groups were not significantly different (p=0.05) regarding mean weekly exercise time during the study period. Intra-study mean weekly exercise time data is displayed in Figure 14.

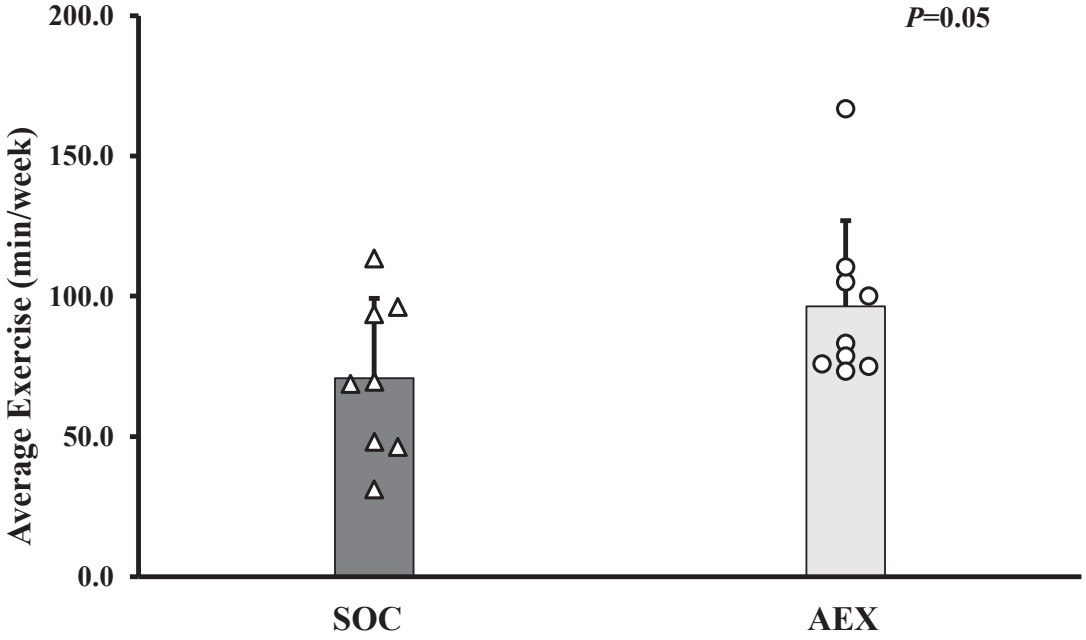


Figure 14. Average Exercise (minutes/week) obtained via the Polar exercise tracker worn by each participant. SOC group is expressed via a dark grey bas while the AEX group is expressed via a light grey bar. Individual SOC data expressed by white triangles while individual AEX data are expressed as white circles. Data compared using non-parametric hypothesis testing to determine between group (Mann Whitney U) comparisons.

4.6 Exercise and Protocol Adherence

Based on exercise monitor data (i.e., wrist-bound Polar monitor) observations of adherence revealed that overall, 100% of the participants enrolled, SOC and AEX, wore the exercising monitor for at least 90% of the exercising bouts lasting at least 10 minutes or more (Figure 15A). Considering the AEX group exclusively, it was observed that 100% of exercising participants completed at least 85% of the exercise sessions (Figure 15B). Moreover, it was confirmed that 90% of exercisers completed 80% of their exercise sessions at the prescribed intensity and duration (Figure 15C).

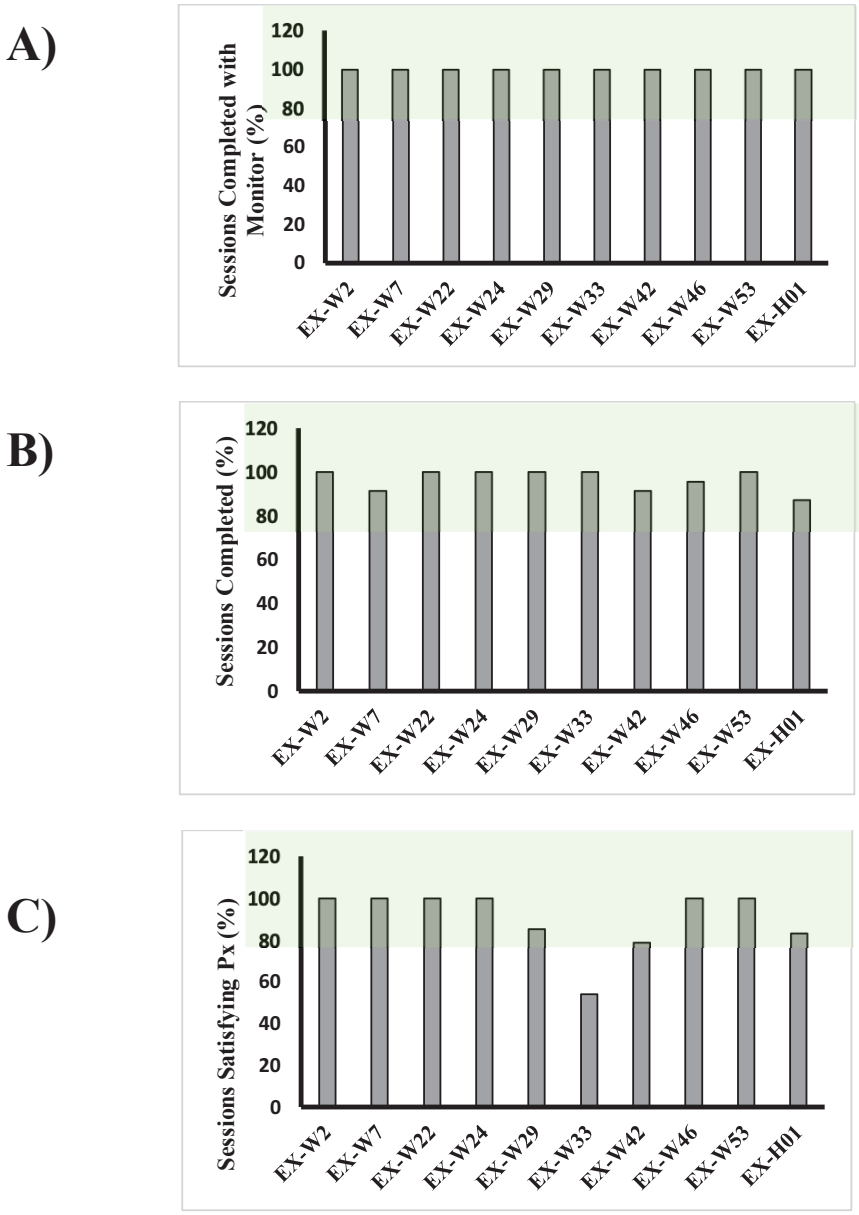


Figure 15. Individual adherence data. A) Adherence data obtained from the Polar exercise tracker. Grey bars represent the percent of exercising sessions completed while wearing the wrist-worn monitor. B) Adherence data regarding the percent of the prescribed exercise sessions completed during the study expressed by grey bars. C) Adherence data regarding the percent of completed exercising sessions which satisfied the individually prescribed intensity and duration expressed by grey bars.

Chapter 5: DISCUSSION

5.1 General Overview

The purpose of EXACT2.0 was to explore the cardioprotective benefits of a 24-week *home-based* AE program in BCS receiving AC-based chemotherapy. Primary and secondary study outcome measures were used to assess the efficacy of the AE intervention. The primary objectives of the study were to characterize the impact of the AE program on 1) left ventricular function; and 2) aerobic fitness. Secondary objectives of the study included self-reported levels of HRQoL and fatigue. Based on previous preclinical research[74,75,115,116], it was expected that an aerobic exercise program (AEX), such as deployed in EXACT2.0, could improve or attenuate decreases in left ventricular function and cardiorespiratory fitness when compared to standard of care (SOC). Furthermore, based on previous clinical cancer literature , it was anticipated that patient reported levels of HRQoL and fatigue would be improved following participation in an exercise program[117,118] when compared to SOC.

The results of EXACT2.0 provide one of the first longitudinal clinical investigations into the impact of aerobic training on indices of cardiotoxicity in a cohort of female's diagnosed with breast cancer. Inconsistent with the previous pre-clinical work [74,75,115,116], this investigation found that the AEX program deployed herein did not significantly improve or attenuate decreases in the targets of cardiotoxicity previously outlined when compared to SOC. Similarly, in contrast to previous reports[117,119], the AEX program did not improve levels of HRQoL and fatigue compared to SOC.

5.2 Echocardiographic Parameters

Contrary to evidence previously established in preclinical work indicating that aerobic exercise can significantly improve, or attenuate decreases in left ventricular function following treatment with AC[75], this investigation was unable to translate such findings to a clinical setting. Specifically, this study found that following a home-based, 24-week individualized aerobic

exercise program, changes in LVEF and GLS were not different between study groups and time-points (Figure 9A&B). In fact, the study reports decrease in LVEF and GLS at follow-up compared to baseline within the AEX group with no changes occurring in the SOC group.

The mean decrease in reported echocardiographic measures seen in the AEX group, in addition to the absence of between group differences may be explained by a few study-related factors. First, at baseline, the SOC cohort had significantly higher levels of physical activity (Figure 13). It has been previously shown that exercise preconditioning can have a cardioprotective effect in response to treatment with an AC[120]. Second, throughout the intervention, it was found that the SOC and AEX study groups participated in similar amounts of structured exercise (Figure 14). Third, there were 2 participants who had met cardiotoxic criteria regarding their individual changes in LVEF and GLS between baseline and follow-up, and both were randomized to the AEX group. These observations, when coupled with a small study sample size (N=20, 10 AEX), may have exacerbated and/or skewed statistical comparisons, both between and within group. Consequently, it remains uncertain whether changes observed within the AEX group were meaningful observations, or if such differences occurred due to other factors such as study design.

It is possible that the follow-up period deployed in EXACT2.0 was not long enough to: 1) adequately detect decreases in LVEF and GLS to cardiotoxic thresholds in both study groups, and 2) appropriately capture physiological adaptations relating to cardiac remodelling in response to aerobic exercise training. To compound the latter, it has been documented that higher-intensity exercise in this patient population is safe, well tolerated, and offers favourable outcomes regarding indices of cardiotoxicity (i.e., LVEF and GLS)[121]. Given the exercise program deployed by EXACT2.0 has a significant focus on low and moderate intensity exercise

(i.e., 45-65% HRR), it is possible that participants in the AEX group may have responded more favourably to a program consistent with higher intensity exercise[121]. To address the former, it is well-documented in the literature that anthracycline-induced cardiotoxicity can be expressed days to weeks post first infusion (i.e., acute cardiotoxicity), all the way up to years and decades following treatment (i.e., long-term cardiotoxicity)[122,123]. Therefore, up-and-coming clinical trials investigating AC-related cardiotoxicity, such as the ATOPE trial[124], are beginning to deploy exceedingly longer follow-up periods such as 1- and 3-years post-intervention to better represent the demographic in which the research is intended. Ergo, the cardioprotection relating to AC-induced cardiotoxicity may not be as evident unless the targeted physiological parameters (i.e., LVEF and GLS) have had enough time to show signs of impairment, clinically or sub clinically.

As a result, including a longer follow-up period, with an increased focus on high intensity exercise (i.e., 70-85% HRR), and a larger study sample would: 1) make for a more appropriate time-lapse between treatment, study intervention and follow-up analysis to allow treatment-related side-effects to become more apparent, and 2) offer increased confidence that the results of the study were not simply due to the study design.

5.3 Cardiorespiratory Fitness

Previous research in BC patients demonstrates that females with BC have impaired CRF, as assessed by VO_2peak, compared to healthy controls before[125], and after[78,125] cancer treatment. VO_2peak is a good indicator of overall cardiovascular and cardiopulmonary health, as well as oxygen transport and utilization. Low VO_2peak is linked to cardiovascular morbidity, all-cause mortality[126] and cancer survival[83], and therefore findings consistent with impaired VO2peak are concerning for BC survivors.

Consistent with previous findings, EXACT2.0's total study cohort mean baseline VO2peak (25.9 ml/kg/min; data not shown) was comparable to reports by Peel et al. (2014)[125] which

indicated BC patients at 50 years old, had similar cardiovascular health profiles as 60-year-old sedentary females without BC. Moreover, a 2016 investigation by Giallauria et al. reported that in a cohort of BC survivors, a 12-week aerobic exercise program performed at 60-70% baseline VO2peak, 3 times per week significantly improved VO2peak at follow-up compared to non-exercising controls[127]. Findings from EXACT2.0, although not able to detect significant Group × Time differences, demonstrate that the exercise program was able to significantly detect changes within the AEX group between baseline and post-intervention regarding VO2peak (Figure 10). It is possible that given that EXACT2.0's control group was similarly active throughout the intervention compared to the intervention group (Figure 14), between group comparisons were skewed in a statistically insignificant direction. Additionally, the way in which exercise was prescribed by Giallauria and colleagues (i.e., 60-70% VO2peak 3x/week)[127] differed from what was deployed by EXACT2.0 (45-85% heart rate reserve 2x/week; Appendix B). The contrasts in study protocols and control group exercise behaviours may explain differences seen between results reported by Giallauria et al (2016)[127] and herein.

It has been reported that CRF (i.e., VO2peak) may be more acutely impacted by cancer treatment than central cardiac function and conversely, more acutely responsive to aerobic exercise than echocardiographic parameters of cardiotoxicity (i.e., LVEF and GLS)[125]. This was made evident by reports of impaired VO2peak in a population of BC patients who also presented with normal measures of cardiac function (i.e., LVEF)[83,125]. Therefore, it has been postulated that acute-onset cardiotoxicity may be dominated by other insults to oxygen (O2) transport/utilization mechanisms such as O_2 extraction (i.e., endothelial function), O2 carrying capacity (i.e., haemoglobin concentration), and skeletal muscle mass, as opposed to cardiac structure and function[83,97,125,128–130].

When taken together, the investigations mentioned above offers sound rationale regarding why EXACT2.0 was able to detect significant within group (AEX) improvements in VO2peak while simultaneously detecting significant within group (AEX) decreases in left ventricular function. This offers additional evidence that EXACT2.0 may have benefitted from an extended follow-up period with increased assessments of CRF (i.e., VO2peak) and left ventricular function (i.e., LVEF and GLS) throughout both the intervention and follow-up periods.

5.4 Patient Reported Outcomes

Health related quality of life (HRQoL) and fatigue have previously demonstrated mixed results in response to exercise training in cancer research[117,119]. This is likely due to the lack of a clear consensus on the optimal prescription of exercise (i.e., frequency, intensity, time, and type; *FITT*) in the literature[119]. Therefore, reports exist that are consistent with exercise providing improvements in HRQoL and fatigue[118], while other investigations report no differences with exercise programming[117]. The results reported herein are consistent with the latter, finding no Group × Time significance between study cohorts for either HRQoL (Figure 11) or fatigue (Figure 12). It should also be noted that EXACT2.0 did detect a significant effect of time regarding fatigue, in addition to satisfying criteria (i.e., 3-4 point change[131]) for a minimally important difference in both study cohorts, indicating that when all participants are considered together, fatigue scores at follow-up indicate significantly more fatigue when compared to baseline. Note, a minimally important difference was not satisfied regarding HRQoL, in either study cohort, when compared to established criteria (i.e., 7-8 point change[131]).

Previous literature reports heterogeneity in the type of exercise that should be utilized when targeting HRQoL and fatigue. Originally, it was thought that aerobic exercise was the favourable type of exercise to modify these measures[119], however more recent reports speak to the contrary, reporting resistance exercise as the favourable type of exercise to modify fatigue

and HRQoL[118]. To further confuse the issue, it has been postulated in the literature that HRQoL and fatigue are shown to benefit from other psychosocial and behavioural support other than exercise[118,132,133]. For example, fatigue is associated with psychological and depressive symptoms[134,135], and thus any means of social support (i.e., patient group) could influence perceptions of fatigue and quality of life[118,132–135]. Consequently, it makes it harder to decipher whether such changes across time are more dominated by adaptations associated with exercise training or from confounding psychosocial factors[118].

When taken together, it is possible that the inability of EXACT2.0 to confer significant improvements in HRQoL and fatigue between groups is due to: 1) the modality/prescription of exercise training failed to incorporate a key type of exercise (i.e., resistance training) that has been previously shown to provide additional benefits regarding HRQoL and fatigue[118]; or 2) the inability to distinguish between physiological and psychosocial adaptations relating the program contributed to the findings reported herein[118,132,133].

5.5 Adherence and Safety

Compared with what has been previously documented in the literature regarding exercise programming in BC patients[136–139], the intervention deployed by EXACT2.0 was similarly, or more tolerated and adhered to. Specifically, investigations by both Kirkham et al (2018)[137] and Witlox et al. (2019)[139] reported overall adherence (i.e., percentage of sessions attended) to their respective high-intensity exercise programs of 60% and 83% respectively. Overall adherence reported herein (e.g., 85%) falls just above what was found by Witlox et al. (2019) but much greater than what was found by Kirkham et al. (2018). In addition, Kirkham et al. (2018) and Witlox et al. (2019) report a 64% and 50% adherence to the prescribed exercise intensity respectively. However, another exercise program in BC patients, this time a home-based program[136], reported a much lower adherence (i.e., 23.7%) to higher intensity exercise (i.e., 60-

90% VO2max), but also reporting high overall adherence at 87.6%. The adherence to the exercise prescription found by EXACT2.0's home-based program was much more tolerated at an 80% adherence rate with a comparable overall adherence rate of 85% (Figure 15B & C).

The contrasting adherence rates in the above-mentioned can be explained by the deployment of: 1) center-based protocols, and 2) varying exercising prescription (i.e., FITT). Both Kirkham et al. (2018) and Witlox et al. (2019) utilize center-based approaches, including higher intensity aerobic exercise, with the addition of resistance training days (i.e., 2-3 days/week totalling 90-120 minutes). When compared to EXACT2.0's prescription of twice weekly home-based aerobic training at 45-85%HRR totalling 90 minutes, the overall time-and-energy-commitment burden is much higher (e.g., the increased duration and intensity of exercising sessions may be less tolerated in the interventions described by Kirkham et al. (2018) and Witlox et al. (2019)).

The high adherence and tolerance rates reported in this study (i.e., EXACT2.0) can be attributed to several factors. A previous review conducted by Ormel et al. (2018)[138] outlined factors predicting high adherence to exercise. These included physical, physiological, and behavioral factors (i.e., family support and feedback by trainers, as well as having a high motivation to exercise)[138]. The study protocol deployed by EXACT2.0 incorporated many of these characteristics which predicted high adherence to the exercise intervention. For example, the physical and physiological characteristics of participants is captured during the baseline assessment phase of the study (i.e., cardiac stress test, echocardiography). Moreover, EXACT2.0's intervention is consistent with behavioural factors predicting high adherence such as the inclusion of bi-weekly support from study representatives. These assessments ensured: 1) participants were medically cleared to engage in low-high intensity exercise, 2) exercise intensity

was individually prescribed based on level of physical fitness and 3) created a sense of safety, comfortability, and accountability to continue exercising.

The time commitment involved in the participation in an exercise program is significant and is often a major reason for discontinuation of training within a supervised center-based program[138,140,141]. Consequently, travel distance is also thought to be a predictor of low adherence to a supervised exercise intervention in other clinical settings as well[138,142]. Home-based exercise interventions, in which patients can exercise individually, can offer a convenient solution, and may be preferred by certain groups of patients (e.g., participants from rural areas)[143,144]. A home-based approach was successful in the deployment of EXACT2.0, conferring with previous reports by Sturgeon et al. (2022) that home-based interventions are well tolerated and report high exercise adherence rates in a cohort of newly diagnosed BC patients[136]. Additionally, the use of activity trackers for intervention monitoring was successfully utilized and well adhered to (Figure 15A) as also reported by Sturgeon et al (2022)[136]. Last, the intervention did not bring about any adverse events in any of the enrolled participants, confirming that the participation in the program is safe for newly diagnosed BC patients.

5.6 Limitations

To the author's knowledge, EXACT2.0 is one of the first longitudinal studies investigating the influence of a 24-week aerobic exercise on markers of cardiotoxicity in females diagnosed with BC. To detect a significant difference in study outcome measures and achieve 80% power (α=0.05), 88 participants (44 CTL, 44 AEX) are required for the study upon recruitment termination (G*Power 3.1.9.2). To account for attrition the goal is to recruit a total of 100 participants (Halifax 25 SOC, 25 AEX; Winnipeg 25 SOC, 25 AEX). Since EXACT2.0 is an ongoing clinical trial, the report herein is consistent with an interim report on the data and includes a decreased study sample. Therefore, it is possible that the expectations regarding the

response to aerobic exercise on markers of cardiotoxicity were not met due to the study sample size not being appropriately powered.

The COVID-19 pandemic had a significant impact on several EXACT2.0 related areas. First, the recruitment rate during peak pandemic years (i.e., 2020, and 2021) was significantly halted in a response to increasing case numbers, an overwhelmed health care system here in Nova Scotia, in addition to a nullified frequency in which AC was prescribed within our recruiting cancer care clinic. Given that exercise interventions in BC patients have been previously shown to struggle with recruitment and retention[138,145,146], the addition of a global pandemic only compounded this effect in the case of EXACT2.0. The route of administration for AC is intravenous infusions over several hours on multiple hospital visits. Thus, to limit person-to-person contact, prescription of other forms of chemotherapy (i.e., capecitabine and cyclophosphamide) that could be self-administered at home took precedent. Second, the COVID-19 pandemic hit Nova Scotia while recruitment was well under-way, with several participants having already completed baseline measures and begun their exercise training at home. It is possible, although not measured by EXACT2.0, that a significant change in motivation during baseline assessments was present in those recruited mid-pandemic due to the possibility of participants being uncomfortable and the associated anxiety accompanied with an in-person research setting during such an unprecedented time. This change in motivation may have prevented true maximal exercise intensity to be achieved during baseline and follow-up cardiac stress testing in many participants.

To further compound limitations surrounding cardiac stress testing and exercise prescription, due to the COVID-19 pandemic, the cardiac stress test technician at the Winnipeg recruitment site was unable to continue with the study, preventing several participants (n=5)

from undergoing baseline and follow-up cardiac stress testing which had an impact on exercise prescription as it had to be reliant on predictive equations[105]. Moreover, motivation during cardiac stress testing, could have prevented individuals from obtaining a true maximal intensity. Limitations in cardiac stress testing introduces implications regarding the prescription of exercise (i.e., lower HR targets during training), consequently influencing group comparisons of VO2peak, impacting the ability of the intervention to confer adaptations in cardiac function.

It has been well established in the literature that cardiotoxicity may be acute (i.e., present soon after treatment), or long lasting (i.e., present years to decades post treatment)[122,123]. Therefore, it is possible that the lack of follow-up period deployed in EXACT2.0 prevented observations of cardiotoxicity to be equally expressed in both study groups. Consequently, it has been reported that indices of cardiac function (i.e., LVEF and GLS) in response to aerobic exercise training, may not be detectable immediately following aerobic exercise training[83,125]. Additionally, it was found that both study groups herein report similar level of weekly structured exercise. This is a common limitation expressed in many exercise trials, and unfortunately, EXACT2.0 was not immune to this potential recruitment bias (e.g., individuals who already engage in regular PA are likely to agree to participation in an exercise study). Therefore, it is possible that the similar levels of structured exercise, performed weekly, limited the ability of the intervention to confer significant differences between groups in all outcome measures.

5.7 Conclusion

The findings of this study demonstrated that the 24-week aerobic exercise program deployed by EXACT2.0 was insufficient at mitigating decreases in indices of cardiotoxicity (i.e., LVEF, GLS), CRF (i.e., VO2peak), and patient reported levels of HRQoL and fatigue. It is possible that shortcomings in patient recruitment, exercise prescription, and protocol design, each ultimately limited due to a global pandemic, contributed to the results reported herein.

EXACT2.0 provides a basis to improve on in the search for an optimal 1) research protocol design consistent with longer follow-up assessments, and 2) exercise type and dosage that will most effectively confer the attenuation of cancer treatment-related cardiac damage, while not detracting from AC's anti-tumour potential.

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Appendix

APPENDIX A: Informed Consent Form Interventional Studies

STUDY TITLE:	**EX**ercise to prevent **A**nthraCycline-based **C**ardio-**T**oxicity (EXACT 2.0) in individuals with breast cancer
CLINICAL STUDY REGISTRATION NUMBER:	NCT03748550
PRINCIPAL INVESTIGATOR:	Scott A. Grandy, Ph.D. School of Health and Human Performance Dalhousie University, NSHA Affiliate Scientist, Division of Cardiology (902) 494-4303
FUNDER:	Canadian Cancer Society Canadian Institutes of Health Research

1. Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study. You may take as much time as you wish to decide whether or not to participate. Feel free to discuss it with your friends and family, or your family doctor.

Please ask the research team or the principal investigator to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

- Discuss the study with you;
- Answer your questions;
- Be available during the study to deal with problems and answer questions.

You are being asked to consider participating in this study because you have been diagnosed with breast cancer and will be treated with a type of chemotherapy called anthracyclines.

If you decide not to take part or if you leave the study early, your cancer treatment and your usual health care will not be affected.

2. Why is there a need for this study?

With improvements in cancer treatments, more people diagnosed with cancer are becoming long-term survivors. However, studies have shown that the damage caused by the treatments responsible for this success can lead to other health problems. One of the most concerning problems associated with a cancer drug known as anthracyclines (type of chemotherapy) is its damaging effect on the heart, leading to an increased risk of heart disease.

Aerobic exercise (e.g., riding a bike, walking, or swimming) has been shown to be very safe and beneficial for those with cancer. Cancer patients are often encouraged to increase their levels of physical activity to help improve their fitness, health, and overall quality of life. While exercise has been shown to be beneficial for individuals receiving cancer treatments, very little is known about how exercise may protect the heart of those receiving anthracyclines. It also is not clear whether exercise performed at home leads to the same health benefits as those seen in individuals performing exercise in a supervised program. Therefore, the purpose of this study will be to collect information on the benefits of a 12-week home-based exercise program on heart health in those individuals receiving anthracycline-based chemotherapy.

3. What is being tested?

Research studies have shown that performing aerobic exercise before or during anthracycline therapy helps to prevent damage to heart as well as maintain heart function. However, these research studies have mostly been conducted on animals and it is not clear whether exercise has the same protective effects on the heart in humans. Thus, this study will examine the benefits of a home-based aerobic exercise program on heart health in patients receiving anthracycline therapy.

4. How long will I be in the study?

The first part of this study is 14 weeks long. If you decide to participate you will be invited to complete a 12-week home-based aerobic (e.g., walking, cycling) exercise program. You will be asked to complete two exercise sessions per week which is expected last between 30 to 60 minutes (for a total of 24 training sessions over 12 weeks). In addition to the exercise program, you will also be asked to complete two testing sessions. The first will take place about one week before starting the exercise training. The second will take place following the completion of the 12-week program. Each assessment will take approximately 1-2 hours to complete. Your total time commitment for the first part of the study would be about 28 hours.

To help us better understand the potential long-term protective effects of exercise on your heart we would like to ask your permission to contact you in the future regarding new follow-up studies. These studies will be designed to assess your health through in person visits and/or reviewing your healthcare file. At time of contact you will be provided with the specific details of the study and will have the option to participate or decline. The additional studies will take

place over the next 10 years. If you indicate, you are interested in learning more about these new studies you will not be contacted more than 1-2 times per year.

5. How many people will take part in this study?

It is anticipated that about 100 people will participate in this study, 50 people the Queen Elizabeth II Health Sciences Centre (Halifax, NS) and 50 people from St. Boniface Hospital (Winnipeg, MB).

6. How is the study being done?

Adult female breast cancer patients that are receiving a specific type of chemotherapy known as anthracyclines will be invited from breast cancer clinics at the QEII Health Sciences Centre (Halifax, NS) and St. Boniface Hospital (Winnipeg, MB). Participants in this study will be randomly (by chance) placed in one of two study groups: 1) control or 2) exercise. All participants will undergo testing prior to starting the study and then will undergo the same testing again at the end of the study. Participants randomized to the control group will receive the standard treatment for their cancer. Participants randomized to the exercise group will receive standard treatment plus a 12-week home based aerobic exercise program. All data will be analyzed in Halifax, Nova Scotia, except for the heart ultrasound (echocardiogram), which will be analyzed by the team cardiologist (JS) in Winnipeg, Manitoba.

The study will involve you coming to the hospital for 1 or 2 appointments for the baseline testing and 1 or 2 appointments for the post-study testing. Each appointment will last 1-2 hours.

7. What will happen if I take part in this study?

If you agree to take part in the study, you will be asked to complete the following:

BASELINE ASSESSMENT
During the baseline assessment you will be asked to complete a survey and provide some basic information about yourself (e.g., age, sex, occupation, household income, lifestyle behaviors, quality of life, etc.). It will take you approximately 20-25 minutes to complete the survey. You may skip any questions that you are uncomfortable answering. We will also measure your height, weight, and waist size. A picture of your heart will be taken using an ultrasound machine. This procedure is described in more detail below. You will also be asked to complete an exercise stress test and provide a blood sample (about 2 tablespoons of blood). The exercise stress test is described in more detail below. The blood sample will be drawn by a trained research nurse. The collection of the blood sample and completion of the stress test and ultrasound is necessary for study participation. All blood samples will be taken to Dr. Scott Grandy's secure research lab (Dalhousie University) where it will be stored in a secured freezer until it is analyzed. Approximately 1 tablespoon of blood will be sent to Winnipeg for analysis and 1 tablespoon of blood will be analyzed in Halifax.

Echocardiogram
An echocardiogram uses sound waves to produce an image of your heart. This image allows us to see your heart beating and pumping blood. For this procedure the technician will place gel on a transducer which looks like an electric shaver. The technician will then press the transducer against your chest over your heart in order to get the picture. The technician may have to try different positions in order to get the best picture. This procedure takes place in a private room. This procedure is not likely to cause any discomfort, but if it does please let the technician know immediately. Echocardiograms will be sent to Winnipeg for analysis. All files will be deidentified scans and sent via secure file transfer.

Exercise Stress Test
The exercise stress test will be supervised by a cardiologist. Prior to beginning the test, electrocardiograph (ECG) or heart monitoring stickers will be placed on your chest (a private room will be available for the application the stickers). The electrode stickers will then be attached to cables which link to an ECG machine (allowing us to monitor your heart while exercising). You will then be asked to perform a graded exercise test by walking on a treadmill. You will begin at a very slow pace. The speed and incline (slope) of the treadmill will increase every three minutes until you feel that you are no longer able to continue. If you feel unwell during the test, you will be asked to tell the doctor and technician at once. The test will be stopped if you feel severe chest pain or become very tired or short of breath.

12 WEEK EXERCISE PROGRAM
The aerobic exercise training program will be developed by a specially trained member of the research team, a certified exercise physiologist (CEP). The intensity (i.e., how hard you will work) of the exercise program will be determined by an assessment of your current fitness level and abilities. This will be determined using the results from your baseline stress test. To ensure that you are not working too hard, we will provide you with a heart rate monitor (worn around your wrist) so that we can monitor how hard you are exercising. At the end of your baseline assessment you will be given your 12-week home-based exercise program. The CEP will explain how to perform the program as well as how to use the heart rate monitor. The CEP or a member of the research team will follow-up with you on a weekly basis to see if you have any questions or if your exercise program needs to be adjusted. You will also be given a number that you can call at any time if you have questions about your exercise program.

POST TRAINING ASSESSMENT
Following the completion of the exercise program, you will be asked to complete a survey assessing your lifestyle behaviors and overall quality of life. We will repeat the measures of weight and waist girth. You will also be asked to complete another exercise stress test and provide a final blood sample as well as the ultrasound of your heart.

6-MONTH FOLLOW-UP ASSESSMENT
Six months after the completion of the exercise program, you will be asked to return to complete a survey assessing your lifestyle behaviors and overall quality of life. We will repeat the measures of weight and waist girth. You will also be asked to complete another exercise stress test and provide a final blood sample as well as the ultrasound of your heart.

OPTIONAL FOLLOW-UP
If you agree, we will follow your health for up to 10 years. The bulk of this follow-up will be done "behind the scenes" by accessing your hospital records and other health databases. However, you may also be contacted in the future to provide additional information on your health and lifestyle behaviors (e.g., physical activity) or to return to our assessment center to provide additional health data (e.g., blood samples, fitness assessments, heart scans). You may indicate your consent for long-term follow-up on the signature page.

ADDITIONAL RESPONSIBILITIES
Throughout your participation in the study, it is important that you tell the research team about any new treatment therapies, drugs or medicines you are taking or wish to take. You must also tell the research team about anything unusual that is happening with your health. This includes any medical problems that seem to be getting worse. If you have to see another doctor or have to go to a hospital, you should let the doctors know that you are in a research study. You should also tell your own doctor as quickly as possible, for your safety.

NOTE: You may decide not to take part in any of these activities and to stop participating in the study at any time by contacting the research team.

8. Are there risks to the study?

As with any physical activity program or study there are some risks. To give you the most complete information available, we have listed the *possible* risks, which may appear alarming. We do not want to alarm you, but we do want to make sure that you have had a chance to think about all the risks carefully before you choose to participate. Please also be aware that there may be risks in participating in this study that we do not know about yet.

Physical activity studies have shown that a very common side-effect of training for both those with and without cancer is mild fatigue, shortness of breath, increased body temperature, muscle soreness and/or stiffness. These symptoms will vary depending on your level of fitness. For example, if you have not exercised for a long time, it is likely that you will experience greater muscle stiffness at the beginning of the program than at the end. These side-effects typically go away within 1-2 days. However, if they last longer or you are concerned you can contact one of the members of the research team to discuss your concerns. Study staff will check in with you on a weekly basis to ensure that you are doing your exercise correctly and not doing too much exercise. This will decrease your risk of experiencing unnecessary fatigue or muscle soreness. If you experience an injury during training, please seek the necessary medical treatment and then report the injury to the research team. We also ask that you to report any other injuries or illnesses that occur during the time of the study.

Exercise stress testing has been shown to be a safe procedure with the risk of a serious adverse event occurring (e.g., life threatening complication) is very rare (i.e., less than 5 per 100,000 tests). Given that many cancer patients receive treatments that may impact exercise tolerance, the risk of an adverse event may be elevated. A cardiologist will be present for all testing and we will closely monitor your response to the test to maximize your safety.

In addition to the exercise program, you will be asked to complete two surveys (one at each assessment) and provide two blood samples. These surveys will ask you questions about your lifestyle behaviors and overall quality of life. If you are uncomfortable in responding to any of these questions you can leave them blank or you are free to withdraw from the study at any time without penalty. There is a possibility of pain, bruising, swelling or infection related to giving blood. These discomforts are minimal and brief.

To protect your information, we will not keep your name or other information that may identify you with the sample; only a code number. Files that link your name to the code number will be kept in a secure place. Although no one can absolutely guarantee confidentiality, using a code number makes the chance much smaller that someone other than the research staff or other authorized groups or persons (discussed later in the consent form) will ever be able to link your name to your sample or to any test results.

The effects or discomforts of tests/procedures that are part of this study but are also part of your normal clinical care (e.g., heart scan, additional blood tests) will be reviewed by your treating physician. In order to ensure your safety, a copy of this consent form, outlining the study details and contact information, will be sent to your primary oncologist.

You will be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the research team.

9. Are there benefits of participating in this study?

You may or may not benefit directly from participating in this study. However, possible benefits include improved fitness and quality of life. Your participation may or may not help other people with cancer receiving treatment in the future.

10. Are there other choices?

You are free to seek other opinions or choices if you wish. You do not have to participate in this trial to begin an exercise program or to become more physically active. You may choose to speak with your physician, oncologist, or a qualified fitness expert about physical activity.

11. What happens at the end of the study?

If you would like a summary of the results, please notify the research team and a summary will be mailed or emailed to you upon completion of the study. Should you be interested in learning more about the physical activity options in your area, we encourage you to speak to your physician, oncologist, or the research team CEP.

12. What are my responsibilities?

As a study participant you will be expected to:

- Read and sign the consent form;
- Follow the directions of the research team;
- Complete the 12-week, home based, biweekly exercise program;
- Complete the testing at the beginning and end of the study;
- Report any problems that you experience that you think might be related to participating in the study; and
- Report any changes to your health during the time of the study (even those occurring outside of the study).

13. Can my participation in this study end early?

The Nova Scotia Health Authority Research Ethics Board and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

The principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- There is new information that shows being in this study is not in your best interest;
- You are experiencing side-effects that are harmful to your health or well-being;
- You are not following the directions of the Principal Investigator or research team;
- The Principle Investigator or Nova Scotia Health Authority Research Ethics Board decides to stop the study.

If you are withdrawn from this study, a member of the research team will discuss the reasons with you and plans will be made for your continued care outside of the study.

You can also choose to end your participation at any time. If you choose to withdraw from this study by providing notice to the research team, your decision will have no effect on your current or future medical treatment and healthcare.

If you withdraw your consent, the information about you, including all completed assessments (e.g., exercise stress test, questionnaires, blood samples) that were collected before you left the study will still be used. No new information about you will be collected (and no further testing of your blood samples will be done without your permission). If you wish to withdraw from the study, please inform the study staff.

14. What will happen to my sample after the study is over?

After this study is over, we will dispose of all the samples we collected as part of the study by burning them.

15. What about new information?

It is possible that new information may become available while you are in the study that might affect your health, welfare, or willingness to stay in the study. You will be told about the new information and then asked whether you wish to continue taking part in the study or not.

16. Will it cost me anything?

Compensation

Participating in this study will involve several additional visits to the QEII and may result in added transportation and parking costs. Unfortunately, we are not able to reimburse you for these costs.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate in the study. In no way does this waive your legal rights nor release the principal investigator, the research team, the study sponsor or involved institutions from their legal and professional responsibilities.

17. What about my privacy and confidentiality?

Protecting your privacy is an important part of this study and every effort to protect your privacy will be made. However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records. Also, as your physician/oncologist has reviewed your medical history to ensure your fit with this study he/she will be aware that you are taking part in the study.

If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

If you decide to participate in this study, the research team will collect personal health information from you and your health record. The research team will collect and use only the information they need for this study and to judge the safety and usefulness of the study.

"Personal health information" is health information about you that could identify you because it includes information such as your;

- Name,
- Information from the study surveys;
- New and existing medical records; or
- The types, dates and results of various tests and procedures.

Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- The Nova Scotia Health Authority Research Ethics Board and people working for or with the Nova Scotia Health Authority Research Ethics Board because they oversee the ethical conduct of research studies at the QEII in Halifax.

These people will view your study records at this institution and will not take identifying information away with them.

Use of Your Study Information

To protect your information, we will not keep your name or other information that may identify you with any of the study measurements; only a code number. Files that link your name to the code number will be kept separately from any of the measurements, samples or other information about you. Although no one can absolutely guarantee confidentiality, using a code number makes the chance much smaller that someone other than the research staff or other authorized groups or persons will ever be able to link your name to your sample or to any test results.

Information collected for this study will be kept for 25 years. Information will be stored in a databank at Nova Scotia Health Authority in Halifax. Information may be shared with other researchers for the purposes of health research. Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your Access to Records

You may ask the study researchers to see the information that has been collected about you.

18. Declaration of Financial Interest

The Canadian Cancer Society and Canadian Institutes of Health Research are reimbursing the principal investigator and/or the principal investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study.

19. What About Questions or Problems?

For further information about the study you may call the principal investigator who is the person in charge of this study:

The principal investigator is Dr. Scott Grandy.
Telephone: 902-494-4303
Email: Scott.Grandy@dal.ca

If you experience any symptoms or possible side effects or other medical problems, please let the principal investigator or research coordinator know as soon as possible.

If you can't reach the principal investigator or research coordinator, or it is after regular business hours, speak to the physician on call. The after hour's number is **(902) 473-2222.**

This doctor may not be the one you usually see while in this study. Please call the principal investigator or research coordinator the next business day to tell them about the possible side effects or other medical problems you experienced.

20. What Are My Rights?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study. You have the right to withdraw your consent at any time.

If you have questions about your rights as a research participant, and/or concerns or complaints about this research study, you can contact the Nova Scotia Health Authority Research Ethics Board manager at 902-473-8426 or Patient Relations at (902) 473-2133 or 1-855-799-0990 or healthcareexperience@nshealth.ca.

In the next part you will be asked if you agree (consent) to join this study. If the answer is "yes", please sign the form.

21. Consent Form Signature Page

I have reviewed all of the information in this consent form related to the study called:

EXercise to prevent **A**nthraCycline-based **C**ardio-**T**oxicity (EXACT 2.0)
in individuals with breast cancer

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I authorize access to my personal health information, and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

☐ I **agree** to permit the researchers to re-contact me to consider participation in future related research studies. (If yes, please provide contact information: _____)
☐ I **do not agree** to permit the researchers to re-contact me to consider participation in future related research studies.

_____	_____	____ / _____ / ___
Signature of Participant	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Signature of Person Conducting Consent Discussion	Name (Printed)	Year Month Day*
_____	_____	____ / _____ / ___
Signature of Investigator	Name (Printed)	Year Month Day*

Note: Please fill in the dates personally

I will be given a signed copy of this consent form.
Thank you for your time and patience!

APPENDIX B: Overview of the Aerobic Exercise Training Program

WEEK	DAY	ZONE	DURATION
1	1	1	20
	2	1	25
2	1	2	35
	2	1	35
3	1	2	35
	2	2	40
4	1	3	25
	2	1	45
5	1	3	20
	2	2	30
6	1	2	35
	2	2	35
7	1	3	35
	2	2	35
8	1	3	40
	2	2	45
9	1	4	25
	2	1	45
10	1	4	30
	2	1	45
11	1	4	30
	2	1	45
12	1	4	20
	2	1	40
13	1	2	35
	2	2	40
14	1	3	25
	2	1	45
15	1	3	20
	2	2	30
16	1	2	35
	2	2	35
17	1	3	35
	2	2	35
18	1	3	40
	2	2	45
19	1	4	25
	2	1	45
20	1	4	30
	2	1	45
21	1	4	30
	2	1	45
22	1	4	20
	2	1	40
23	1	2	35
	2	2	35

Legend	
Exercising Zone	**Heart Rate Reserve Percent (HRR%)**
1	35-45
2	45-55
3	55-70
4	70-85

*Target HR = [(HRmax - RHR) * HRR%] + RHR;
where HRmax = Max heart rate, RHR = resting heart rate, and HRR% = target percent of heart rate reserve

APPENDIX C: Functional Assessment for Cancer Therapy – Breast

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX C: Functional Assessment for Cancer Therapy – Breast

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

APPENDIX C: Functional Assessment for Cancer Therapy – Breast

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX D: Functional Assessment of Chronic Illness Therapy-Fatigue

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

PARTICIPANT QUESTIONNAIRE

EXACT 2.0 STUDY

Exercise to prevent AnthraCycline-based Cardio-Toxicity

GENERAL INSTRUCTIONS

We need your help to make our study a success. Your candid answers to the items in this survey are very important to us. This will not take too long to complete.

REMEMBER…

- We want to know what **you** think and how **you** feel.
- There are no right or wrong answers.
- Everything you tell us will be kept strictly confidential.

AND PLEASE

- Try and answer all questions.
- Provide only one answer for each item.

If, at any time, you have questions as you complete this questionnaire, or regarding your participation in this study, please call:

Dr. Scott Grandy
School of Health & Human Performance
Dalhousie University
Phone: 902-494-4303

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

GETTING TO KNOW YOU

The information within this section is needed to help understand the characteristics of the people participating in this study. For this reason, it is very important information. **Be assured that it will remain confidential.**

1. Your date of birth: DD _____ MM _____ YYYY _____

2. Sex (tick the box): □ Female □ Male

3. What is your marital status? (tick the box that best describes you):
□ Never married □ Divorced □ Living common law □ Married □ Separated □ Widowed

4. Ethnicity: (tick the box that best describes you):
□ White □ Korean □ Latin American
□ Black □ Filipino □ Aboriginal people of North America
□ Chinese □ Arab □ Japanese
□ South Asian □ Other: _____

5. What is the highest level of education that you have completed?
□ Elementary school
□ High school
□ Trade, technical or vocational school
□ Diploma from a community college or non-university certificate
□ University certificate below Bachelor's level
□ Bachelor's degree
□ Graduate degree (MSc, MBA, MD, PhD, etc.)
□ None

6. What is your employment status? (tick the box that best describes you):
□ Full-time □ Unemployed □ Retired □ Part-time □ Homemaker
□ Presently on disability leave □ Doing unpaid or volunteer work □ Student

7. The next question asks about your household income. We understand that this information is very private, but the question is important as it helps us to understand whether the study includes a wide variety of participants. All answers will be kept anonymous and strictly confidential. Which category best describes the total income of all household members, before taxes, for last year?

□ Less than $10,000
□ $10,000-$24,999
□ $25,000-$49,999
□ $50,000-$74,999
□ $75,000-$99,999
□ $100,000-$149,999
□ $150,000-$199,999
□ $200,000 or more
□ Don't know
□ Prefer not to answer

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

HEALTH STATUS AND HABITS

General Health

1. How would you rate your general health?
□ Excellent □ Very good □ Good □ Fair □ Poor

Sleep Habits

2. Over the ***past 4 weeks,*** on average, how many ***hours per day*** do you usually sleep, including naps? *A day refers to a 24 hour period. Please think of the total amount of unbroken sleep.*
_____ Hours AND _____ Minutes □ Don't know

3. Over the ***past 4 weeks***, how often have you had trouble going to sleep or staying asleep?
□ Never □ Little of the time □ Some of the time □ Most of the time □ All of the time □ Don't know

Alcohol Use

4. Have you ever consumed alcohol?
□ Yes □ No *(skip to question #7)* □ Don't know *(skip to question #7)*

5. On average, ***over the last year (12 months)***, how often did you drink alcoholic beverages?
□ Never *(skip to question #7)*
□ Less than monthly *(skip to question #7)*
□ About once a month *(skip to question #7)*
□ 2 to 3 times a month *(skip to question #7)*
□ Once a week
□ 2 to 3 times a week
□ 4 to 5 times a week
□ 6 to 7 times a week

6. On average, on the days that you drank, how many drinks do you have in a typical week? *A standard drink means one glass of wine or a wine cooler (142ml or 5 ounces), one bottle or can of beer or a glass of draft (341ml or 12 ounces), one straight or mixed drink with 1.5 ounces (43ml) of liquor.*

Red wine	_____ drinks per week	□ None	□ Don't know
White wine	_____ drinks per week	□ None	□ Don't know
Beer	_____ drinks per week	□ None	□ Don't know
Liquor/spirits	_____ drinks per week	□ None	□ Don't know
Other alcohol	_____ drinks per week	□ None	□ Don't know

Tobacco Use

7. Have you smoked at least 100 cigarettes in your life? (about 4-5 packs)?
□ Yes □ No □ Don't know

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

8. At what age did you smoke your ***first*** whole cigarette?
_____ Age

9. At ***the present time***, do you smoke cigarettes daily, occasionally, or not at all?
□ Daily (at least one cigarette every day for the past 30 days) *(go to question #10)*
□ Occasionally (at least one cigarette in the past 30 days, but not everyday) *(skip to question #13)*
□ Not at all (you did not smoke at all in the past 30 days) *(skip to question #15)*

10. Age what age did you begin smoking daily?
_____ Age

11. How many cigarettes do you smoke each day now?
□ 1-5 cigarettes
□ 6-10 cigarettes
□ 11-15 cigarettes
□ 16-20 cigarettes
□ 21-25 cigarettes
□ 26+ cigarettes (If +26, how many? _____)

12. During the total years that you have smoked daily, about how many cigarettes have you usually smoked? *(If your smoking pattern has changed over the years, make your best guess of the average number of cigarettes you have smoked per day.)*
□ 1-5 cigarettes
□ 6-10 cigarettes
□ 11-15 cigarettes
□ 16-20 cigarettes
□ 21-25 cigarettes
□ 26+ cigarettes (If +26, how many? _____)

<u>If you currently smoke daily SKIP to PHYSICAL ACTIVITY questions beginning on page 6.</u>

13. On how many of the last 30 days did you smoke at least one cigarette?
□ 1-5 days
□ 6-10 days
□ 11-20 days
□ 21-29 days

14. On the days that you smoked, how many cigarettes did you usually smoke?
□ 1-5 cigarettes
□ 6-10 cigarettes
□ 11-15 cigarettes
□ 16-20 cigarettes
□ 21-25 cigarettes
□ 26+ cigarettes (If +26, how many? _____)

15. Have you ever smoked cigarettes daily? (*At least one cigarette a day for 30 days in a row)*
□ Yes □ No □ Don't Know

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

16. Age what age did you begin smoking daily?
_____ Age

17. When you smoked daily, how many cigarettes did you usually smoke each day?
□ 1-5 cigarettes
□ 6-10 cigarettes
□ 11-15 cigarettes
□ 16-20 cigarettes
□ 21-25 cigarettes
□ 26+ cigarettes (If +26, how many? _____)

18. For how many total years did you smoke daily?
_____ Years

19. When did you stop smoking cigarettes daily?
□ Less than 1 year ago
□1 to 2 years ago
□ 3 to 5 years ago
□ More than 5 years ago
□ Don't know

PHYSICAL ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the ***last 7 days***.

- Please answer each question even if you do not consider yourself to be an active person.
- Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the ***last 7 days***.

- **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.
- **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY
The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. *Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family.* These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

The next questions are about all the physical activity you did in the ***last 7 days*** as part of your paid or unpaid work. This does not include traveling to and from work.

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

2. During the ***last 7 days,*** on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for ***at least 10 minutes at a time.***

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for ***at least 10 minutes at a time***. During the ***last 7 days,*** on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the ***last 7 days***, on how many days did you **walk** for ***at least 10 minutes at a time*** **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the ***last 7 days***, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the ***last 7 days***, on how many days did you **bicycle** for ***at least 10 minutes at a time*** to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the ***last 7 days***, on how many days did you **walk** for ***at least 10 minutes at a time*** to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the ***last 7 days*** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the ***last 7 days***, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for ***at least 10 minutes at a time***. During the ***last 7 days***, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for ***at least 10 minutes at a time***. During the ***last 7 days***, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the ***last 7 days*** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the ***last 7 days***, on how many days did you **walk** for ***at least 10 minutes at a time*** **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

22. Think about only those physical activities that you did for ***at least 10 minutes at a time***. During the ***last 7 days***, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for ***at least 10 minutes at a time***. During the ***last 7 days***, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the ***last 7 days***, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the ***last 7 days***, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

APPENDIX E: Physical Activity Questionnaire

Participant ID: _____
Date: _____

for taking the time to complete this survey.