EXercise to prevent AnthraCycline-based Cardio-Toxicity (EXACT 2.0)

in women with breast cancer

by

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Abstract

Background: Cardiotoxicity from breast cancer (BC) therapy, specifically anthracyclines, is a significant cause of morbidity and mortality in women with BC. Although aerobic exercise (AE) during anthracycline therapy has been shown to reduce side effects including fatigue, nausea, and pain, the cardioprotective benefits of exercise remain unclear. We investigated the effect of a 24-week home-based AE program on cardiac function in women with BC receiving anthracyclines using echocardiography, treadmill testing, and quality of life surveys.

Methods: Women with BC were randomized to either a control group (standard of care) or to standard of care with a 24-week home-based AE program. Based on our previous feasibility study in this patient population, the graduated exercise program consisted of 2 self-directed sessions per week (performed at 35-85% incremental heart rate reserve intensity) to achieve a minimum of 90 minutes of exercise weekly. Serial transthoracic echocardiography (TTE) was conducted to assess cardiovascular systolic and diastolic function, including strain parameters. Peak oxygen uptake (VO2 max) was estimated using predictive equations based on duration on Bruce protocol treadmill. Quality of life was measured using Functional Assessment of Cancer Therapy – Breast questionnaire. All outcome measurements were performed at baseline and at 24-weeks.

Results: A total of 15 women with BC (49 ± 10 years old) were recruited and randomized to either control (n=7) or AE (n=8). A total of 14 patients received adriamycin and cyclophosphamide for 8 weeks and 1 patient received fluorouracil, epirubicin, and cyclophosphamide for 9 weeks. Additionally, 13 patients received adjuvant radiation therapy. A total of 11 women had baseline

cardiovascular risk factors including hypertension (n=1), hyperlipidemia (n=2), smoking history (n=4), and family history of premature coronary artery disease (n=4). The characteristics of patients in the two groups were similar. Participants randomized to AE demonstrated an average of 92% adherence to the program. There were no significant differences between the two groups in the measured cardiovascular morphological or functional parameters. At baseline, mean LVEF was 62±2% in the control group and 63±2% in the AE group. At 24-weeks, mean LVEF was 62±3% and 58±8% in the control and exercise groups, respectively (p = NS). Additionally, at baseline, mean global longitudinal strain (GLS) was -19.5±1.5% in the control group and -19.0±1.2% in the AE group. At 24-weeks, mean GLS was -18.2±1.3% in the control group and -17.5±2.3% in the AE group (p = NS). Further, while VO2 max was 30.1 mL/kg/min for both groups at baseline, it was 33.6 mL/kg/min and 36.3 mL/kg/min at 24-weeks for control and exercise groups, respectively (p = NS). Finally, the FACT-B quality of life scores were not statistically different for both groups at both time points.

Conclusion: These findings indicate that although a 24-week home-based AE program was feasible, we were unable to demonstrate cardioprotection in women with BC receiving chemotherapy in comparison to standard of care.

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Table of Contents

List of Figures

List of Tables

Chapter 1: Introduction to Breast Cancer

1.1 Breast Cancer Epidemiology

Breast cancer is the second most commonly diagnosed cancer in the world and the most common malignancy in women.[1] According to the Canadian Cancer Society, there will be an estimated 27,700 new cases of breast cancer in 2020 which accounts for 25% of new diagnoses in females.[2] The incidence of breast cancer in men is relatively rare accounting for only 220 cases on an annual basis. [2] Among the 38,700 women that die from cancer every year, 13% of them will die from breast cancer. [2] As compared to 1984, the age-standardized mortality rate associated with breast cancer in 2015 had significantly decreased by 2.3%/year. [2] This has been credited to a combination of improved detection and treatment methods.[2]

1.2 Breast Cancer Risk Factors

The incidence of breast cancer is dependent on multiple different risk factors including age, genetic mutations, physical inactivity, hormone replacement therapy, alcohol use, and personal and family history of breast cancer.[3]

Age is the most important risk factor for breast cancer. There is a direct correlation with age and breast cancer incidence with nearly 40% of breast cancer cases being diagnosed in women between 30 and 59 years of age. [2] Genetic predisposition is another important risk factor and is thought to be mainly associated with mutations in BRCA1 and BRCA2 loci. BRCA1 and BRCA2 are tumor suppressor genes involved in DNA repair and mutations at these loci are associated with increased

risk of breast and other cancers. [4] Mutations in these genes are associated with an estimated 45-82% risk of breast cancer development during the course of a lifetime. [5,6]

Certain lifestyle choices may also increase the risk of developing breast cancer. Active tobacco smoking and passive exposure to second-hand smoke have been linked with a moderate increase in breast cancer risk.[7] Alcohol consumption is a known risk factor for breast cancer development in early and late adult life, even at levels as low as 3-6 drinks per week.[8] Of note, cumulative alcohol intake and binge drinking, not the frequency of drinking, seems to be most associated with increased breast cancer risk. [8]

Obesity is linked with an increased risk of breast cancer in post-menopausal women with a 5-kg increase in adult weight being linked with an 11% increased risk of breast cancer.[9] Obesity is also correlated with worse survival outcomes and increased risk of recurrence in breast cancer patients.[10] Interestingly, however, increased adiposity in childhood and adolescence is associated with a lifelong decrease in breast cancer risk.[11]

Physical activity and sedentary lifestyle may also impact the incidence of breast cancer. Meta-analysis studies revealed a 25% decreased risk of breast cancer in physically active women as compared to their non-active counterparts.[12] This relationship was most evident when exercise was done at regular intervals as well as at moderate to vigorous intensity. [12] Further, physical activity post-diagnosis has been linked with decreased breast-cancer related deaths in current patients.[13]

Also, increased time in sedentary behavior seems to be a risk factor for breast cancer independent of physical activity. [14]

1.3 Breast Cancer Diagnosis

Early diagnosis of breast cancer remains a critical component of improving breast cancer prognosis and survival. Detection of breast cancer can be done through a variety of methods including screening mammography (SM), digital breast tomosynthesis (DBT), screening ultrasounds, magnetic resonance imaging (MRI), and positron emission mammography (PEM).[15]

Through randomized control trials, it has been shown that screening mammography (SM) is able to reduce the risk of breast cancer mortality by over 20%.[16] According to the 2015 Guideline update from the American Cancer Society, it is recommended that average-risk women aged 45 to 54 years should be screened annually and then transition to screening biennially after the age of 55.[16] However, if women have higher risk of breast cancer, either due to BRCA1/2 mutations or a family history of breast cancer, screening at earlier ages may be recommended.[16] According to the National Mammography Database, SM detects an average of 3.43 cancers per every 1000 mammograms.[17] However, its sensitivity for women with dense breasts is a limitation as dense fibroglandular tissue can obstruct the detection of tumors in these women.[15]

In contrast, digital breast tomosynthesis (DBT) can often find cancers occult from SM. DBT reports higher detection rates ranging from 5.3 to 8.1 cancers detected per 1000 screens.[18] DBT

acquires images as the x-ray moves around the breast and this technique increases visibilities of possible malignancies as well as reduces false positives.[15,18]

The ASTOUND-2 clinical trial (2018) evaluated the additional cancer detection rate of adjunct imaging, specifically DBT and ultrasound, in women with dense breasts who received a negative SM.[19] The study found that DBT used in conjunction with 2D SM was able to detect an additional 2.8 cancers per 1000 examinations, while adjunct ultrasound was able to detect an additional 4.9 cancers per 1000 screens.[19] However, it must also be noted that while ultrasound had better detection rates than DBT, it also came with higher false-positive rates (1.0% vs 0.3% for DBT).[19]

In addition, breast MRI with the contrast-enhancement agent gadolinium has been found to have a sensitivity greater than 90% for breast cancer detection.[15] The pooled data from 8 clinical trials have shown that MRI has been found to have a detection rate of 31 cancers per 1000 high-risk women screened.[15] Despite its high detection and sensitivity, less than one-third of women considered high-risk actually receive a breast MRI. This may be attributed to its expense and the lack of widespread availability.[15] Finally, positron emission mammography and breast-specific gamma imaging are also promising modalities for breast cancer detection with sensitivities greater than 90%. However, larger scale studies are required regarding their screening utility prior to implementation in clinical practice.

1.4 Breast Cancer Staging

The prognosis and treatment for breast cancer are dependent on the stage of breast cancer. Over the past few decades, the staging of cancer has been based on the TNM system which is the size

of the primary tumor (T), the involvement of surrounding lymph nodes (N), and metastasis (M). The T stage can be staged as no tumor (T0), tumor less than 2 cm (T1), tumor more than 2 cm but less than 5 cm (T2), tumor greater than 5 cm (T3), and a tumor of any size that extends into skin or chest wall (T4).[20] The N stage ranges from N0 to N3 and is dependent on the involvement of the axillary, internal mammary, supraclavicular, and intramammary lymph nodes. [20] The M stage is divided into M0, where there is no metastasis (M0) or M1 meaning the primary cancer has spread to a distant secondary site (M1). The combination of TNM values are used to stage breast cancer into one of the following 9 stages: 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, or IV (Figure 1). [20] For both the TNM and stage values, higher numbers are indicative of more advanced cancer.[21]

The American Joint Committee on Cancer (AJCC) in 2017 made some significant changes in the guidelines for staging of breast cancer. Previously, the anatomical characteristics of cancer as dictated by the TNM system were the sole determinants of staging. In its 8th edition, the AJCC Breast Cancer Staging Manual has incorporated estrogen and progesterone receptor (ER, PR) status, human epidermal growth factor receptor 2 (HER2) status, and tumor grade into the staging to derive a more clinically accurate prognostic stage.[22]

Figure 1: Anatomical Stages of Breast Cancer. Adapted from AJCC 8th Edition (2017).[22]

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	**0**
T1	N0	M0	**IA**
T0	N1mi	M0	**IB**
T1	N1mi	M0	**IB**
T0	N1	M0	**IIA**
T1	N1	M0	**IIA**
T2	N0	M0	**IIA**
T2	N1	M0	**IIB**
T3	N0	M0	**IIB**
T0	N2	M0	**IIIA**
T1	N2	M0	**IIIA**
T2	N2	M0	**IIIA**
T3	N1	M0	**IIIA**
T3	N2	M0	**IIIA**
T4	N0	M0	**IIIB**
T4	N1	M0	**IIIB**
T4	N2	M0	**IIIB**
Any T	N3	M0	**IIIC**
Any T	Any N	M1	**IV**

Hormone receptor status is dependent on whether the cancer cells within the body express the receptor for either estrogen or progesterone. Immunohistochemistry is the diagnostic tool of choice to determine the hormone receptor status of breast cancer. If greater than 1% of cells within a tumor biopsy sample have a positive staining for ER or PR, it is considered to be ER/PR+ breast cancer. This indicates the growth of these cancer cells is dependent on the ER and/or PR hormones. [22] This is important for therapy as breast cancer patients who are hormone receptor positive will often receive endocrine therapy which lowers estrogen and/or block the actions of the estrogen receptors.[23] Higher levels of hormone receptor have a better response to endocrine therapy and thus often have a better prognosis than ER- and/or PR- breast cancers [22,24,25]. Further, hormone receptor positive cancers tend to be slowly progressing but have an increased chance of recurrence years after treatment.[23]

Conversely, HER2 positivity is associated with worse prognosis in breast cancer patients.[25] HER2+ breast cancers indicate the gene Erb-B2 Receptor Tyrosine Kinase 2 (*ERBB2*) which encodes the HER2 protein is amplified and overexpressed.[26] HER2 belongs to a family of epidermal growth factors which also include HER1, HER3, and HER4. [26] While HER2 does not yet have an elucidated ligand, it dimerizes with the other HERs to trigger a tyrosine kinase signalling cascade. [26] This pathway leads to increased cell migration, proliferation, and invasion. [26] As such, HER2+ breast cancers are often more aggressive than their HER2- counterparts. [26] Fortunately, the development of the monoclonal antibody trastuzumab and other anti-HER2 therapies have significantly improved outcomes for HER2+ breast cancer patients.[26]

In combination with the aforementioned staging characteristics, histological tumor grade is another tool used to understand prognosis. This is calculated according to the Nottingham Grading System which accounts for the degree of nuclear pleomorphism, tubular and glandular formation, and mitotic count [25,27,28]. Each of the 3 morphological features is given a score ranging from 1 to 3, with 1 resembling normal breast cells and 3 being most abnormal. Grade I tumor is assigned if the cumulative score for the features is 3-5, grade II if the score is 6 or 7, and grade III if the score is 8 or above.[25] Higher grade breast cancers have an increased likelihood of recurrence, earlier metastasis, and a decreased probability of survival compared to lower grade breast cancers.[28]

1.5 Breast Cancer Treatment

Breast cancer treatment involves the combination of surgery, radiation, chemotherapy, endocrine therapy, and targeted biological therapy. The specific treatments and their sequence are a carefully considered decision depending upon the characteristics of the cancer. [29]

The gold-standard for the treatment of breast cancer since the early 1900's was radical mastectomy, which includes the removal of the breast, underlying chest muscles, and the axillary lymph nodes.[29] However, Fisher et al. in 2002 showed through a large randomized control trial there was no improvement in outcomes in patients receiving simple mastectomy and radical mastectomy.[30] Further, this group in another randomized control trial also showed lumpectomy with chest irradiation was superior to mastectomy.[31] As such, this paved way for the current standard of care for breast cancer patients being breast-conserving surgery (lumpectomy) over mastectomy.[29]

In most cases, radiation is administered after surgery and chemotherapy.[29] Many trials have shown radiation therapy (RT) after mastectomy or breast-conserving therapy reduces the risk of a local regional recurrence by about 70%.[32] In the 1997 Danish 82-B conducted by Overgaard et al., it was shown that in addition to reducing recurrence, postoperative radiation improved 10-year survival from 45% to 54% in a cohort of premenopausal women with breast cancer.[33] Further studies have shown that while recurrence is lowered with RT, the combination of tamoxifen with RT was more effective in reducing local recurrence in several different breast cancer populations.[34–36] RT can include either external beam radiation or internal breast cancer radiation.[37] The external beam breast cancer radiation focuses on the cancerous area within the breast for two to three minutes.[37] This is repeated 5-6 times a week for five to six weeks. Conversely, the internal radiation, also referred to as brachytherapy, is a newer form of radiation that involves the insertion of a radioactive treatment into the affected area. [37] The appropriate method and radiation dose are decided by a radiation oncologist based on patient and tumor characteristics. [37] However, brachytherapy is not a standard form of radiation treatment for breast cancer patients.

Drug therapies in breast cancer can fall into one of the three categories including chemotherapy, endocrine therapy, and/or targeted therapy. In some patients, only one of these agents is required whereas, in other patients, all three may be required.[38] Drug therapy can be used alone to treat cancer, or it can be used in combination with surgical and radiation therapies. [38] The sequence of the therapies is also an essential consideration and is determined on a case-by-case basis. [38]

Neoadjuvant drug therapies refer to drug therapy used prior to the other treatment methods, which is often done to reduce the size of a tumor before removal by surgery. [38] Conversely, adjuvant drug therapy refers to the use of drugs after first-line therapy, in order to reduce the risk of cancer recurrence after surgery or radiation. [38] Drug therapy can also be concurrent which indicates it used at the same time as RT in order to increase the cancer cell sensitivity to radiation.[38]

There is a wide variety of chemotherapy drugs and regimens, of which the most commonly prescribed third-generation chemotherapy regimens are herein discussed. The regimens are frequently a combination of anthracyclines and taxane classes of anti-cancer agents.[39] Anthracyclines often used in breast cancer are doxorubicin (A; DOX), also referred to as Adriamycin, and Epirubicin (E) while Paclitaxel (T) and Docetaxel (D) are the most popular taxane drugs.[39]

Adriamycin (A; DOX) is combined with alkylating agent cyclophosphamide (C) and taxane Paclitaxel (T) in the AC-T regimen.[40] The routine dosage is 60 mg/m^2 for DOX, 600 mg/m^2 for C and 175 mg/m^2 for T.[40] The AC is given for the first four cycles of treatment followed by the Paclitaxel for the subsequent four cycles.[40] In the second-generation regimen, each cycle was 21 days.[39] However, in the third-generation dose-dense version of AC-T which is the current standard, each cycle is only 14 days apart.[39] The dose-dense AC-T schedule was shown by the C9741 trial by Citron et al. in 2003 to increase both disease-free and overall survival as it prevented cancer cells from recovering in between cycles.[41] However, to note, the benefits seen were only seen in ER- carcinomas and not seen in their ER+ counterparts. [41]

The other commonly used third-generation chemotherapy regimen is the combination of 5-fluorouracil (F), epirubicin (E), and cyclophosphamide (C) with docetaxel (D), referred to as FEC-D. [39] The routine dosage is 500 mg/m^2 for F, 100 mg/m^2 for E, 500 mg/m^2 for C, and 100 mg/m^2 for D. [39,42] In the PACS01 trial by Roche et al. in 2006, it was shown that the FEC-D regimen was associated with improved disease-free and overall survival compared to the second-generation FEC regimen without the subsequent docetaxel administration.[42] Hence, aside from the AC-T, FEC-D is the most popular anthracycline and taxane regimen that is prescribed by oncologists for breast cancer. The FEC-D regimen consists of 6 cycles of 21 days each, with the first 3 cycles being FEC and the last 3 cycles being the docetaxel.[39]

In addition to chemotherapy, hormone receptor breast cancer patients receive endocrine therapy.[43] Endocrine drug therapy can be designed to prevent estrogen production using aromatase inhibitors or alternatively, be used to block the action of estrogen on tumor cells using selective estrogen receptor modulators (SERM).[43] Aromatase is the enzyme responsible for catalyzing the conversion of androgen to estradiol and aromatase inhibition has been strongly supported for use in post-menopausal women with breast cancer.[43–45] Currently, the third-generation aromatase inhibitors Anastrozole, Letrozole, Vorozole, and Exemestane have been associated with greater inhibition and response rates as compared with first-generation aminoglutethimide and second-generation fadrozole. [46–48]

Historically, the use of aromatase inhibitors has been contraindicated for pre-menopausal women, and it was recommended that SERMs are used within this patient population instead.[43,46] More

recently, there has been evidence that aromatase inhibitors can have strong overall survival benefits in pre-menopausal women as well. Regardless, Tamoxifen is the most commonly prescribed SERM and has long been considered the gold standard of care for HR+ breast cancer. It serves as a competitive inhibitor to estrogen, preventing its binding to the estrogen receptor as well as has the additional effect of causing apoptosis in ER+ cells.[49,50] According to the 2005 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, Tamoxifen is recommended to be taken 20 mg daily for a total of 5 to 10 years.[51] The long-term use of Tamoxifen has been shown by various randomized clinical trials to reduce recurrence by over 40% and decreases the risk of death by 34% as compared to the non-Tamoxifen counterparts.[51] However, unlike the aromatase inhibitors, Tamoxifen can be used in both pre- and postmenopausal women.[43] While the benefits of these anti-estrogen therapies were only seen in 30% of ER+/PR- breast cancer patients, they were seen in 50-70% of breast cancer patients who were both ER+/PR+.[43]

Finally, in the setting of HER2+ breast cancers, the administration of monoclonal antibodies in addition to chemotherapy is now standard of practice. Trastuzumab (TRZ), or also referred to as Herceptin, was the first of the anti-HER2 monoclonal antibodies to be developed against the tyrosine kinase receptor encoded by the HER2 gene. In 2005, the HERA trial conducted by Cameron et al. showed TRZ with adjuvant chemotherapy can reduce cancer recurrence by 50% and improve survival by 30% as compared to HER2+ BC patients who did not receive TRZ.[52,53] In addition, the 11-year follow-up of the HERA trial participants showed administration of TRZ had an improved 10-year disease-free survival rate compared to the control group.[54] It further elucidated there was no additional benefit of administering TRZ over a 2-year period as compared

to 1-year. [54] Given the results of this trial and various other large randomized clinical trials, the administration of TRZ is now standard in women with HER2+ breast cancer, with an initial 8 mg/kg dose followed by 6 mg/kg dose once every 3 weeks for a year. [54,55]

Chapter 2: Cardio-Oncology – Are Today's Breast Cancer Patients, Tomorrow's Cardiac Patients?

Since 1994, the advancements in breast cancer treatment have led to a yearly decrease in mortality by 2.3%.[56] However, with the increased survivorship of breast cancer patients, the long-term side effects of these anti-neoplastic therapies have become more apparent. Particularly, anthracyclines and monoclonal antibodies have been associated with long-term cardiovascular complications including decreased left ventricular ejection fraction, cardiomyopathy, arrhythmias, and end stage heart failure.[57] These adverse cardiovascular side-effects are currently the leading cause of non-cancer death in breast cancer survivors.[58,59] While our laboratory has previously shown anthracycline and TRZ mediated cardiac dysfunction develops in 25% of the breast cancer population, some studies even cite this number being as high as 57%.[60,61]

While cardiotoxicity can be defined as a decline in cardiac function, the parameters for the decline does not have a universal definition. [60] However, the 2014 expert consensus of the American Society of Echocardiography and the European Association of Cardiovascular Imaging states a left ventricular ejection fraction (LVEF) decline of 10% from baseline or an absolute LVEF less than 53% is defined as cancer therapeutic-related cardiac dysfunction (CTRCD).[62] The guidelines also recommend confirmation of the observed decline by repeating an imaging study within 3 weeks from initial decline. [62]

This committee further differentiates CTRCD into Type I and Type II sub-categories (Table 1).[62] Type I CTRCD, which is seen with anthracycline agents, is a cumulative dose-dependent effect of the drug with the underlying damage being permanent and irreversible. [62] It is irreversible because these agents directly cause cell damage and apoptosis, and adult cardiomyocytes possess no effective capacity for regeneration.[62] In contrast, Type II CTRCD is defined as reversible, not dose related and most consistent with agents like TRZ.[62] However, this is complicated by the fact that in some settings, anthracyclines and TRZ are given concurrently or sequentially, meaning cell damage could be indirectly increased with TRZ administration.[62] Furthermore, recent evidence has shown anthracycline cardiotoxicity can be reversed if appropriate interventions are initiated and conversely, TRZ has the potential for irreversible cardiomyocyte damage.[63] In light of these new studies, it may be time for a reassessment of the Type I and Type II cardiotoxicity definitions.[63]

Anthracycline mediated cardiotoxicity can be further divided into acute and chronic subtypes.[60] Acute refers to cardiotoxicity that develops within 1 week of anthracycline administration, and is rare, seen in less than 5% of patients on anthracyclines.[60] This cardiac decline can present itself as changes on electrocardiography (ECG), dyspnea and often resembles acute toxic myocarditis with interstitial edema and inflammation.[60] Conversely, chronic anthracycline cardiotoxicity refers to any cardiotoxicity

Table 1: Differences between Type I and II Cardiotoxicity. Adapted from Ewer & Ewer (2010).[64]

Type of Drug	Prototype	Findings on Endomyocardial Biopsy	Cumulative Dose Relationship	Reversibility	Associated with increased cardiovascular mortality
Type I	Doxorobucin (anthracycline)	Vacuoles, sarcomere disruption, necrosis	Yes	No (might respond to very early treatment)	Yes
Type II	Trastuzumab (monoclonal antibody)	Benign ultrastructural appearance	No	Yes, in most cases	Np

that develops after week 1, and can be classified as early onset, if is within the first year of cancer treatment completion or as late onset chronic cardiotoxicity, thereafter.[60] Chronic cardiotoxicity can be characterized through loss of myofibrils, formation of vacuoles and necrosis as seen by histological analyses, which often precedes declines in LVEF as measured by echocardiographic or nuclear imaging.[60] Chronic cardiotoxicity can have many different clinical manifestations including LV systolic dysfunction, cardiomyopathy, and arrhythmias.[60]

It is understood the cardiotoxicity associated with anthracycline chemotherapy is cumulative.[65–67] A study with 630 cancer patients receiving doxorubicin chemotherapy showed congestive heart failure developed in 5% of the population at doses of 400 mg/m^2 but increased to 48% at doses of 700 mg/m^2.[67] Age also plays a factor as those over 65 years old have a disproportionately larger risk of adverse cardiac events compared to their younger counterparts for every cumulative dose larger than 400 mg/m^2.[67] In addition to age and cumulative dose, African American ancestry, pre-existing cardiovascular disease as well as concurrent radiotherapy are also risk factors for anthracycline mediated cardiotoxicity.[65,68] Traditional cardiovascular risk factors including obesity, hyperlipidemia and diabetes are also believed to increase the likelihood of chemotherapy mediated cardiac dysfunction.[68]

Anthracycline: Mechanism of Action and Cardiotoxicity

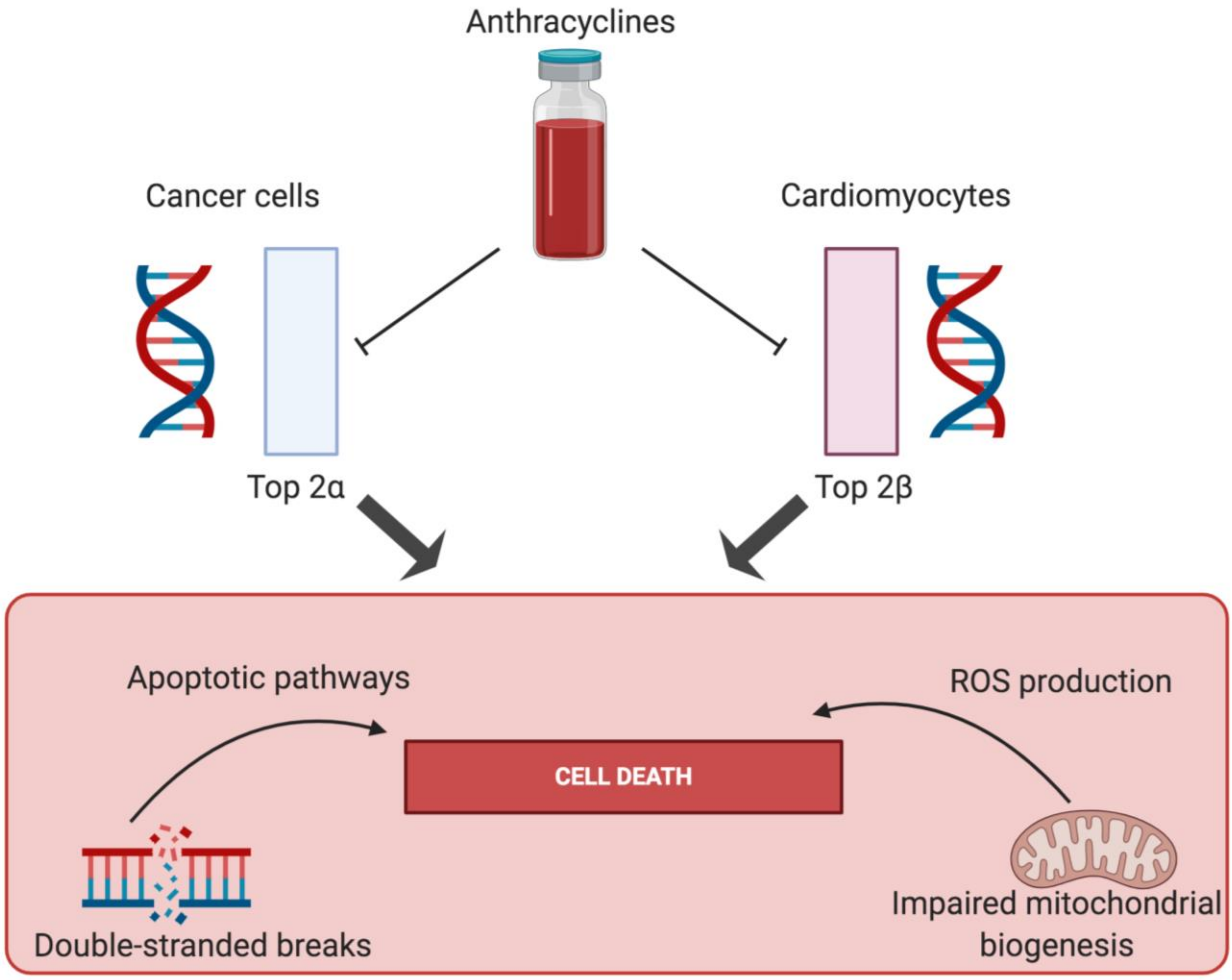
While the anthracyclines doxorubicin and epirubicin are two of the most efficacious anti-neoplastic agents used in the breast cancer setting, their mechanism of action is still a subject of controversy. There have been multiple proposed mechanisms, including topoisomerase inhibition,

oxidative damage through free radical generation, DNA binding, alkylation and cross-linking.[69] Among these, the most widely accepted pathway of cardiotoxicity in literature is DNA topoisomerase II inhibition. Of note, some of the other proposed mechanisms have only contributed to cardiotoxicity in doses that were higher than clinically relevant.[69]

Topoisomerase II (Top2) are ATP-dependent enzymes, that by introducing transient double strand DNA breaks and then re-annealing the DNA backbone, are able to remove DNA supercoils.[70] Top2 exists in the Top2α and Top2β isoforms in humans.[71] Top2α is found in highly proliferative cells such as cancer cells while Top2β is found in quiescent cells like adult cardiomyocytes.[72] In this context, anthracyclines like doxorubicin, work by forming a ternary complex with DNA and the Top2 isoenzyme.[72] When bound to Top2α, anthracyclines will prevent DNA replication and induces apoptosis in the proliferative cells which contributes to its anti-cancer mechanism of action (Figure 2).[72]

However, doxorubicin can also bind to Top2β, increasing the number of double-strand breaks activating cell death pathways in cardiomyocytes (Figure 2). In mice models, DOX administration increased expression of genes involved in the p-53 apoptotic proteins including *Trp53inp1*, *Apaf1*, *Bax*, and *Fas*.[73] Activation of this apoptotic pathway in cardiomyocytes is associated with mitochondrial dysfunction, as it is thought to suppress peroxisome proliferator-activated receptor gamma receptor co-activators (PPARδ), specifically PPARδ1a and PPARδ1b.[73] These

Figure 2: Anthracycline-mediated cell death pathways in cancer cells and cardiomyocytes. Adapted from Heriksen (2018).[65]



Anthracyclines lead to cell death in cancer cells through a topoisomerase 2-alpha mediated pathway while it leads to death in cardiomyocytes through a topoisomerase 2-beta mediated pathway. Anthracyclines, within each of these cell types, cause DNA double-stranded breaks and impaired mitochondria biogenesis which will activate apoptotic and oxidative stress pathways, respectively, ultimately leading to cell death.

coactivators are required for mitochondrial biogenesis, which is defined as the growth and replication of existing mitochondria.[73–75] With doxorubicin administration, there was also downregulation of *Ndufa3*, *Sdha* and *Atp5a1* transcripts, which are genes encoding proteins found in the electron transport chain indicating there is decrease in mitochondrial function as well. On electron microscopy, DOX leads to mitochondrial damage, vacuolization, and disarray and loss of myofibrils.[73,62] It has been shown that cardiomyocyte-specific Top2β deletion in mice models receiving anthracycline did not show decreases in LVEF and a lesser degree of mitochondrial dysfunction, further supporting that anthracycline-mediated cardiotoxicity occurs through a Top2β mechanism.[73]

Furthermore, it has been widely documented that anthracyclines can increase reactive oxygen species (ROS) production in the heart.[76] However, it is still debated whether the increased ROS is the primary cause of cardiomyocyte injury or the downstream effects of other cardiomyocyte damage pathways.[77] The changes in mitochondria observed by Zhang et al.'s study under doxorubicin administration suggests ROS formation occurs as a consequence of cardiomyocyte mitochondrial damage, rather than solely a result of redox cycling originating from DOX's quinone structure as suggested by some previous literature.[73,78]

Monitoring Chemotherapy Induced Cardiotoxicity

The current recommendation for monitoring cardiac function in patients receiving anthracycline chemotherapy is quantifying LVEF both prior to commencing chemotherapy as well as at the end of chemotherapy.[65] The European Society for Medical Oncology recommends additional testing

after patients receive a cumulative anthracycline dose of 250 mg/m^2 and for every subsequent 100 mg/m^2 increase.[65] For patients who develop cardiotoxicity during the course of chemotherapy, a long- term surveillance schedule should also be considered.[79]

There are multiple diagnostic tools that can be used for assessing cardiotoxicity.[79] Echocardiography is the current standard practice for measuring cardiac function, given its wide scale availability, ability to detect hemodynamic parameters and to assess cardiac structures without radiation.[79] 3D echocardiography is superior to 2D for measuring LVEF, but both are dependent on image quality and subject to inter-observer variability.[79] While 3D echocardiography has better reproducibility, it is still recommended that LVEF measurements are conducted by the same observer and equipment to reduce variability.[79] Furthermore, global longitudinal strain (GLS) has emerged as a tool for early detection of left ventricular systolic dysfunction.[62] A study by Sawaya et al. showed a GLS of higher than -19% after anthracycline chemotherapy was detected in all patients who later developed heart failure. [80] They also showed that a decrease of GLS of 10% from baseline levels to the end of chemotherapy to be predictive of subsequent cardiotoxicity and it is able to precede decreases in LVEF.[80] Additionally, our lab has previously shown GLS can be used as an early predictor in DOX+TRZ-mediated cardiotoxicity.[81] It was shown that GLS values increased as early as 3 months in the group that developed subsequent cardiotoxicity. In contrast, LVEF within this group that developed TRZ-cardiotoxicity only decreased at 6-months.[81] As such, LVEF declines are often preceded by increases in GLS %, making GLS using echocardiography an excellent early diagnostic tool for monitoring CTRCD.

Multigated radionuclide angiograph (MUGA) is another imaging modality for measuring LVEF which involves injection of a radioactive tracer that attaches to red blood cells and a gamma camera which captures the movement of these cells in the heart.[82] However, unlike echocardiography, it is unable to provide information regarding hemodynamics and cardiac structures.[79] Further, unlike echocardiography and cardiac magnetic resonance (CMR), a single MUGA scan exposes patient to 5 mSV of radiation, which is roughly equivalent to 50 chest X-rays.[83,84] Despite these limitations, MUGA has become part of monitoring protocols for breast cancer patients due to its excellent reproducibility.[79] CMR, serving as the gold-standard for cardiac imaging, also allows for a non-invasive diagnosis of cardiotoxicity.[79] CMR's superior image quality allows for exceptional accuracy and reproducibility and as such, is often used to clarify or confirm echocardiographic or nuclear imaging results.[79]

Cardiac biomarkers including troponin levels and natriuretic peptides can also be used as early markers for CTRCD. Troponins are thin-filament contractile proteins that are found in high concentration within the myocardium.[85] Elevated serum cardiac troponin-T (cTnT) levels were shown by Kilickap et al. in patients receiving anthracycline chemotherapy, to correlate with a decrease in E/A, a marker of diastolic dysfunction.[85] Several other studies have also validated this correlation between cTnT and anthracycline-mediated cardiomyopathy in both pre-clinical models and clinical trials.[86–90] Further, in a large clinical trial with 703 cancer patients, elevations in troponin I (TnI) over 0.08 ng/mL has been associated with an increased risk of adverse cardiac events and the severity of CTRCD.[85]

Similar to troponins, natriuretic peptides are produced in the myocardium, that are released as a result of increased pressure and volume overload.[91] Pro-brain natriuretic peptide is enzymatically cleaved giving rise to an amino-terminal inactive form, NT-pro BNP, as well as the carboxy-terminal active form, BNP.[91] Both of these cardiac biomarkers have been used to assess CTRCD; however, the literature on their clinical utility is conflicting.[62] Some studies showed patients receiving anthracyclines with persistently elevated BNP and/or NT-proBNP levels had an increased risk of developing heart failure.[92–94] In contrast, other studies do not show such a correlation between natriuretic peptide levels and cardiotoxicity in the cancer population.[95–97]

Other biomarkers including markers of inflammation such as C-reactive protein (CRP) have also shown some potential in identifying patients that may develop CTRCD. A study by Onitilo et al. investigated the role of BNP, cardiac TnI, and CRP as potential early markers for TRZ-mediated cardiotoxicity in a population of HER2+ BC patients.[98] Elevated levels of high-sensitivity CRP, defined as ≥ 3 mg/L, predicted a future decrease in LVEF with a sensitivity of 92% and a specificity of 45%, but no such relation was found with BNP nor TnI.[98]

Chapter 3: Pharmaceuticals and Nutraceutical Cardio-Protective Therapies

Given the need for protection from the cardiotoxic effects of anthracycline, recent research efforts have focused on developing pharmaceutical and nutraceutical agents to prevent CTRCD.

Dexrazoxane

Dexrazoxane remains the only clinically approved cardioprotective agent to prevent anthracycline-mediated cardiotoxicity.[68] While it was initially believed its cardioprotective benefits stemmed due to its iron chelation properties, other iron chelating agents such as deferasirox do not confer cardioprotection in this setting.[72] It is now understood that the pharmacological benefits of dexrazoxane derives from its competitive inhibition of the Top2β's ATP-binding site.[65] This leads to a conformation change which prevents Top2β from binding to anthracyclines and thus provides the basis for its cardioprotective benefits.[65] However, the current guidelines by the American Society of Clinical Oncology recommends the use of dexrazoxane only in the limited setting of metastatic breast cancer patients receiving more than 300 mg/m^2 of doxorubicin.[99,100] The clinical use of dexrazoxane has been restricted due to a report that it may negatively interfere with the anti-neoplastic efficacy of anthracyclines.[99,101]

Antioxidants

Due to the relative importance of ROS involvement in cardiotoxicity, the potential benefits of antioxidant supplementation have been an ongoing field of research in the breast cancer setting.

Our lab has previously investigated the cardioprotective roles of Probucol, N-acetylcysteine amide (NACA), and flaxseed due to their antioxidant abilities within this setting. We have shown that prophylactic administration of Probucol in a pre-clinical DOX+TRZ-induced cardiotoxicity model reduced mortality by 40% and partially attenuated the cardiotoxic side effect of these agents.[102] Similarly, prophylactic NACA administration, which is an analogue of N-acetyl cysteine with increased bioavailability, was able to reduce cardiac apoptosis, attenuate increases in oxidative stress and reduce cardiac remodelling in a murine model of DOX + TRZ mediated cardiotoxicity.[103] Within this same model, Asselin et al. (2020) recently showed prophylactic flaxseed, and its components alpha-linoleic acid and secoisolariciresinol-diglucoside (SDG), was able to attenuate LV systolic dysfunction as well as lower inflammation, apoptosis and mitochondrial dysfunction.[104] Currently, our lab is now investigating the role of flaxseed in conjunction with the angiotensin-converting-enzyme inhibitor Perindopril, in both the prevention and treatment of anthracycline-mediated cardiotoxicity in an *in vivo* murine model. [105]

While antioxidant supplementation seems to provide benefits in attenuating CTRCD, its utility in the clinical setting is a topic of debate. Recently, a clinical trial conducted by Ambrosone et al. in 2019 has shown that use of antioxidants before and during treatment, defined as use of either Vitamin A, C, E, carotenoids, and/or coenzyme Q10, was associated with an increased risk of breast cancer recurrence and to a lesser degree, associated with decreased overall survival.[106] This is congruent with a study completed by Jung et al. in 2019 which showed a worse prognosis for postmenopausal BC patients who use antioxidant supplementation during chemotherapy or radiotherapy.[107] It is believed this may be because chemotherapeutic agents, like anthracyclines,

exerts their antineoplastic effects through production of ROS and thus antioxidant supplementation may reduce its efficacy.[108] Therefore, the supplemental use of antioxidants as a cardioprotective agent during treatment in women with breast cancer warrants further investigation and should be taken with caution.

Renin-Angiotensin System Antagonism and Beta-Blockers

ACE inhibitors like Perindopril and Angiotensin receptor blockers (ARBs) such as Valsartan are two classes of renin-angiotensin system (RAS) antagonists which are traditionally used as blood pressure lowering medications.[109] Beta-blockers (β-Blocker), such as metoprolol, block the effects of the hormone epinephrine, and is often used in the setting of heart failure.[110] While ACE inhibitors, ARBs, and β-Blockers have all are currently used in the treatment of CTRCD, a number of recent clinical studies have evaluated the role of these heart failure medication in the *prevention* setting.

The PRADA trial (2016) compared the cardioprotective effects of the ARB Candesartan and the β-Blocker Metoprolol alone and synergistically in a randomized control trial with 120 breast cancer patients receiving FEC chemotherapy.[111] Metoprolol showed no significant attenuation of cardiac decline nor showed any synergistic interaction with candesartan.[111] In the placebo group that did not receive candesartan, there was a 2.6% decline of LVEF as assessed by magnetic resonance imaging (MRI) after chemotherapy. However, no significant decline was noted in the candesartan group, indicating this agent may be cardioprotective.[111] In contrast, a randomized

placebo-controlled clinical trial conducted by Boekhout et al. in 2016, showed no such cardioprotective benefits of candesartan in HER2+ BC patients receiving anthracyclines and TRZ.[112] As such, the use of ARB candesartan as a prophylactic agent against CTRCD warrants further investigation.

In the last decade, several landmark trials have also investigated the individual and synergistic cardioprotective role of β-Blockers and ACE inhibitors in the prevention of CTRCD. The OVERCOME trial (2013) examined a population of patients with hematological malignancy receiving intensive chemotherapy, and randomized women to either receive the β-Blocker carvedilol and the ACE inhibitor enalapril, or the control group that did not receive these medications.[113] The primary outcome measure was changes in LVEF. It was found the intervention group had no changes after chemotherapy whereas control group experienced a greater than 3% decline, suggesting the medications together may have a cardioprotective role in this population.[113] The MANTICORE trial (2017) further explored the role of β-Blockers and ACE inhibitors in the setting of TRZ-mediated cardiotoxicity within the same HER2+ BC patient population.[114] The research team, which included collaborators on our current EXACT 2.0 trial, evaluated LV remodelling defined as a change in indexed LV end diastolic volume as the primary outcome and LVEF by MRI as the secondary outcome in patients at baseline and after 1 year of TRZ use.[114] They showed neither β-Blocker bisoprolol nor ACE inhibitor perindopril prevented LV remodelling, but each were able to attenuate a decline in LVEF.[114] Similarly, the recent study conducted by Guglin et al. (2019) investigated another β-Blocker and ACE inhibitor, carvedilol

and lisinopril, also in the setting of TRZ-mediated cardiotoxicity.[115] In contrast to the findings of MANTICORE, this team showed there were no difference in LVEF in the treatment groups.[115] However, in a subgroup analysis of TRZ patients also receiving anthracyclines, both medications were found to increase cardiotoxicity-free survival.[115] The role of the β-Blocker carvedilol was further investigated in the CECCY randomized, placebo-controlled clinical trial (2018) of 200 HER2- BC patients receiving doxorubicin.[116] This study showed LVEF reduction by ≥10% occurred at the same incidence within both groups but that the carvedilol group showed lower incidence of diastolic dysfunction and levels of TnI.[116] As such, further studies are warranted to elucidate the true clinical utility of RAS antagonists and beta-blockade in the prevention of CTRCD.

Additionally, there are multiple ongoing clinical trials investigating the role of these cardioprotective pharmacological agents including: i) ICOS-ONE (NCT01968200), investigating the role of prophylactic enalapril; ii) PROACT (NCT03265574), investigating the role of enalapril in post-surgery BC patients receiving epirubicin; iii) CARDIAC CARE (ISRCTN24439460), assessing role of ARB and β-Blockers in BC patients receiving anthracyclines; iv) PRADA II (NCT03760588), investigating the role of heart failure medication sacubitril/valsartan in BC patients receiving anthracyclines; and iv) SWOG S1501 (NCT03418961) assessing the efficacy of carvedilol in a metastatic HER2+ BC setting.[68]

Statins

Statins are another emerging therapeutic agent that is being considered for a potential application in the Cardio-Oncology setting.[68] An observational, retrospective study by Seicean et al. (2012) investigated the use of statins in BC patients receiving anthracycline.[117] The authors showed the continuous use of statins over 3 years was associated with reduced likelihood of incident heart failure hospitalizations.[117] However, this study must be interpreted with caution, as 45% of the statin users were also using β-Blockers and another 39% were using ACE inhibitors.[117] Another recent retrospective study conducted by Calvillo-Argüelles et al. (2019) demonstrated statin usage before and during TRZ treatment in HER2+ BC patients prevented LVEF declines and was associated with a lower risk of cardiotoxicity.[118] While there has not been a randomized control trial for statin use in the setting of CTRCD as of yet, two trials are currently underway, including: i) PREVENT (NCT01988571), investigating the efficacy of the statin Atorvastatin in breast cancer and lymphoma patients receiving anthracyclines and; ii) STOP-CA (NCT02943590), investigating the role of statins in Non-Hodgkin's Lymphoma patients receiving chemotherapy.[68]

While the benefits of pharmaceutical and nutraceutical agents are important to be considered, by lowering blood pressure and heart rate, some of these medications may exacerbate the fatigue experienced from cancer therapy.[118] In such a context, the role of lifestyle modifications cannot be overlooked.[68] Specifically, physical exercise has been well known to be beneficial for the heart in a non-cancer setting, but in the next chapter, its potential therapeutic role in the setting CTRCD is discussed.

Chapter 4: Exercise as a Cardioprotective Measure for CTRCD

While diagnosis of cancer and chemotherapy-related fatigue can lead to a lack of physical activity in patients, research has shown that cancer patients who were able to maintain regular physical activity benefit from a lower incidence of cardiovascular events as compared to their non-active counterparts.[68] In this setting, pre-clinical animal models have been important in understanding the mechanism of cardioprotection conferred by aerobic exercise (AE) activities.[119] Clinical trials, on the other hand, are equally essential in showing the translatability of those findings and feasibility of implementing such activity in different breast cancer patient populations.[119] The findings of such pre-clinical and clinical studies have guided the American Heart Association (AHA) in 2019 to recommend individualized Cardio-Oncology rehabilitation to cancer patients at high-risk for developing cardiotoxicity from therapy.[120] The American Cancer Society and American College of Sport Medicine also recommends cancer patients complete a weekly prescription of 75 minutes of vigorous AE or 150 minutes of moderate intensity AE, or an intermediate duration of a combination of both. [121]

Acute and Chronic Basic Science Studies: Exercise's Mechanism of Cardioprotection

Several molecular mechanisms have been postulated in how exercise may protect against CTRCD, including: i) suppression of oxidative stress; ii) inhibition of energy metabolism alteration; iii) promotion of protein synthesis; iv) inhibition of apoptosis; and/or v) prevention of ultrastructural changes. Suppression of oxidative stress and apoptotic inhibition, being the most widely supported theories, are herein discussed in further detail.

i. Oxidative Stress

A study by Kavazis et al. (2010) showed exercise training prior to DOX therapy in a murine model had attenuated cardiac mitochondrial ROS production and oxidative protein damage in comparison to their sedentary counterparts.[122] It was also found that with exercise, there was an increase in the expression of cardiac antioxidant enzymes, including superoxidase dismutase (SOD) 1 and 2, catalase, and glutathione peroxidase 1 (GPX1).[122] This is supported by another preclinical study that also showed with exercise, there is an increase in mitochondrial antioxidant enzymes, including manganese SOD and copper zinc SOD.[123] These enzymes serve as primary antioxidant defences and convert ROS to H_2O_2 and oxygen.[123] As such, in the setting of CTRCD where ROS production is a clear contributor to the cardiotoxicity, this may serve as an essential cardioprotective mechanism.

Ascensao et al. (2005) went further and explored the roles of chronic exercise in mice receiving DOX.[124] The exercise program was a 14-week regimen which involved swimming for 1 hour a day and 5 times a week.[124] They demonstrated that in DOX treated mice, there were elevated levels of cardiac TnI, increased lipid peroxidation products and elevated oxidized glutathione.[124] In comparison, the DOX mice that exercised had attenuated levels of cardiac TnI and higher levels of total and reduced glutathione in their heart. This is relevant as glutathione is considered a powerful antioxidant and reduced glutathione (GSH), which is the active form, is capable of free radical scavenging.[125] Once GSH captures these free radicals, they become oxidized becoming the inactive form, oxidized glutathione.[125,126] Therefore, this study suggests it is through a glutathione-related mechanism that exercise confers its cardioprotective benefits. [124]

ii. Apoptosis

Increased oxidative stress has been also linked with activation of pro-apoptotic proteases, so the aforementioned antioxidant enzymes may be linked to downregulated protease activation and apoptosis.[127] Caspase 3 is a protease involved in mitochondrial apoptosis while calpain plays an essential role in cardiomyocyte apoptosis and necrosis.[122] While these proteins were activated in mice administered DOX, this activation was attenuated in mice that exercised prior to their DOX administration.[122] Apoptosis, as assessed by TUNEL-positive nuclei, was also significantly lower in the hearts of the exercised animals.[122] Chicco et al. (2006) found similar results for the role of exercise during the course of chronic DOX treatment in cardiomyocyte apoptosis.[128] The authors showed a low-intensity motorized treadmill exercise program in rats was able to attenuate the DOX-induced caspase-3 activation in the heart.[128]

This finding is further supported in a study by Shirinbayan and Roshan (2012) that showed a 3-week treadmill running regimen in rats increased 70-kDa heat shock protein (HSP_{70}) expression in the heart.[129] HSP_{70} is known for its role in protecting cells from apoptosis in the setting of oxidative stress, so it was postulated that the cardioprotective mechanism of exercise may be mediated through heat shock proteins (HSP). [129] Another study also showed this increase in HSP_{70} as well as showed an increase in apoptosis repressor in a caspase recruitment domain (ARC) in treadmill-exercised rats.[123] This is important as ARC is a key inhibitor of cytochrome *c*-mediated apoptosis within cardiomyocytes.[130] In contrast, Kavazis' study showed a cardioprotective phenotype was still present in the heart of these exercised animals, independent of HSP_{72} expression.[122] As such, the role of HSPs in the setting of CTRCD warrants further investigation.

Clinical Exercise Trials in Women with Breast Cancer

While there are several exercise clinical trial projects conducted within this patient population, previous studies have been primarily focused on their effects in breast cancer recurrence and tolerance of chemotherapy. However, even with the recent studies that have focused on the cardioprotective roles of exercise, there has been great variance in terms of type, timing, duration, intensity, as well as whether it was supervised or home-based. This has subsequently led to different results in terms of adherence to the program as well as observed benefit.

The PACES randomized clinical trial (2015) was one of the largest studies conducted in breast cancer patients and evaluated the effectiveness of: i) a low-intensity home-based exercise program (Onco-Move; OM); ii) a moderate-intensity supervised exercise program (On-Track; OT); and iii) usual care (UC).[131] The researchers randomly assigned 207 breast cancer patients receiving adjuvant chemotherapy into one of these three groups, with all exercise regimens starting during the first cycle of chemotherapy and continuing until 3 weeks after chemotherapy.[131] Outcome measurements, in the form of performance-based tests and questionnaires, were conducted at baseline, at the end of chemotherapy (abbreviated as T1) as well as at 6 months after chemotherapy (abbreviated as T2).[131] It was found that the OT group had significantly better cardiorespiratory fitness and less chemotherapy dose adjustments than both the OM and UC groups at T1.[131] Both the OT and OM group had longer mean endurance time, better physical function, less nausea, less vomiting and less pain than UC at T1.[131] However, these benefits became non-significant by T2.[131] The exercise groups also had better social functioning and return to work rates than UC at T2.[131] In regard to adherence, it was found that at least 75% of the exercise sessions were completed by

48% of the OT group and 55% of the OM group.[131] Overall, this study was able to show that a supervised moderate intensity exercise program had benefits in women with breast cancer undergoing chemotherapy.[131] While the home-based lower intensity exercise was slightly less effective, it had higher rate of adherence and may be more convenient for patients to follow during chemotherapy.[131] However, while the study did not investigate the cardioprotective benefits of exercise, it showed most of its other benefits were limited to the period of chemotherapy regimen, as by T2 they were not significantly different from UC.[131]

Within this same demographic of women with breast cancer, Vincent et al. (2013) conducted a 12-week home-based walking training program to assess its effects on cardiorespiratory fitness.[132] This pilot study with 39 breast cancer patients showed an average adherence of 73% with an average completion of 26 out of 36 planned sessions.[132] It showed this group had significant improvements in VO2 max, a measure of cardiorespiratory fitness and aerobic capacity.[132] An increase in cardiorespiratory fitness was also corroborated by several other clinical trials within this population.[131,132,133]

Furthermore, a clinical trial by Courneya et al. randomized 243 Canadian women with breast cancer into either supervised aerobic exercise, supervised resistance exercise or usual care groups.[134] It was found resistance exercise improved self-esteem, muscular strength and chemotherapy completion rates as compared to the usual care group.[134] Similarly, aerobic exercise improved self-esteem, aerobic fitness and percent body fat.[134] Additionally, neither caused lymphedema nor any other adverse side effects.[134] The team followed the patients for this study

for 8 years to assess the role of exercise in long-term breast cancer outcomes, the results of which was published in the START trial (2014).[135] It was found that 8-year disease free survival for the exercise group was 82.7% while it was 75.6% in the control group.[135] Further sub-group analyses showed further benefits on disease free survival with exercise in BC patients who were overweight, ER/HER2+ and/or receiving taxane as part of chemotherapy.[135] Finally, this same team initiated the CARE trial to further explore the roles of type and dose of exercise in improving physical functioning within the breast cancer population.[136] They compared between supervised 25-30 minutes of aerobic exercise, 50-60 minutes of aerobic exercise and 50-60 minutes of combined aerobic and resistance exercise session, with each group completing their respective sessions thrice weekly.[136] However, their study showed there was no changes in their primary outcome of physical functioning between the exercise groups as assessed by the Medical Outcomes Survey Short Form -36 physical functioning scale nor in body composition and chemotherapy completion rates.[136]

Clinical Trials in Setting of CTRCD

The aforementioned studies have given incredible insight into the tolerance and compliance of exercise in women with BC as well as the benefits as it relates to breast cancer outcomes, fitness and psychosocial functioning. However, there are only a limited number of clinical studies investigating the potential role of exercise in attenuating CTRCD.

In this setting, Jones et al. (2014) assessed the incidence of cardiovascular events in 2,973 nonmetastatic BC patients with varying exercise activities.[137] It was found that there was a decrease in CV events as there was an increase in metabolic-equivalent task (MET)-hours per week

activity.[137] Specifically, an adherence to the guidelines of completing ≥ 9 MET-h/week was associated with a 29% reduction in heart failure as compared to the group that did not meet this guideline.[137] Interestingly, the exercise-mediated reduction in cardiovascular events was not affected when adjusted for age, CVD risk factors or type of anti-cancer therapy.[137] Therefore, it was able to successfully show exercise can be beneficial in a variety of different demographics within the BC setting.

In a recent clinical trial, Kirkham et al. (2018) evaluated the role of an acute 30-minute vigorous intensity exercise before each DOX administration during BC patients' chemotherapy cycles.[138] It was shown that there were no changes in levels of TnT nor LV strain on echocardiography, indicating that acute exercise did not have any benefits against anthracycline-mediated cardiotoxicity.[138] Another clinical trial by Haykowsky et al. (2009) investigated the role of AE in TRZ-mediated cardiac dysfunction in 17 women with HER2+ BC.[139] This supervised exercise program consisted of 30-60-minute sessions for 3 days a week during the first 4 months of TRZ administration.[139] Results show participants completed an average of 59% of the exercise sessions at an average of 78% of their maximum heart rate.[139] However, similar to the Kirkham trial, the exercise program did not attenuate CRTCD.[139] The authors believe the low adherence to the program could have contributed to the lack of benefits seen by the exercise group.[139] The study was also limited in that it did not contain a non-exercise control for comparison. As such, there is an immediate need for chronic, long-term aerobic exercise studies investigating improving anthracycline-mediated cardiotoxicity in the setting of breast cancer.

EXercise to Prevent AnthrCycline-based Cardio-Toxicity (EXACT) in Individuals With Breast or Hematological Cancers: A Feasibility Study Protocol

As a first step in this endeavour, our colleagues conducted the "Exercise to prevent AnthraCycline based Cardio-Toxicity (EXACT)" feasibility study.[140] This trial investigated the cardioprotective role of a 12-week hospital-based AE program in women with breast cancer receiving AC treatment.[140] The results showed that the AE program was safe and an average participant attended 75% of the sessions.[140] However, the study's low recruitment (n=15) prevented conclusive evidence on the cardioprotective role of the AE regimen.[140] Of the initially approved 44 participants in the study, most cited the additional travel to the site of intervention as a significant barrier to their participation.[140] This prompted the transition to a home-based exercise program within this population for the current EXercise to prevent AnthraCycline-based Cardio-Toxicity (EXACT 2.0) in women with breast cancer project.

Chapter 5: Hypothesis, Objectives, and Study Rationale

Study Rationale

It has been well-established that aerobic exercise can provide cardiovascular benefits in a non-cancer setting.[141,142] However, recent studies have explored exercise as an effective strategy to counter the adverse side effects of AC treatment.[138,143–146] AE has been shown to attenuate declines in peak oxygen uptake usually found in AC-treated BC patients.[147] This is important as peak oxygen uptake and cardiovascular disease are inversely related.[148] Furthermore, evidence from animal studies have shown AE performed either prior to or during AC therapy can protect the heart without decreasing its anti-cancer potential.[149] However, to our knowledge, these cardioprotective benefits of AE have not been well defined in women receiving AC-based treatments. Thus, there is need for additional research to bridge the gap between animal studies and the clinical world.

Hypothesis

Our hypothesis is that home-based AE during the course of AC-based chemotherapy will reduce the cardiotoxic side effects of ACs in women with breast cancer.

Objectives

The primary objective of the study is to characterize the impact of the 24-week aerobic exercise intervention on: 1) preventing structural and functional changes in the heart; and 2) decreasing biological markers associated with cardiac injury. A secondary objective of the study is to determine the effect of the home-based AE intervention on cancer patient fatigue and perceived quality of life.

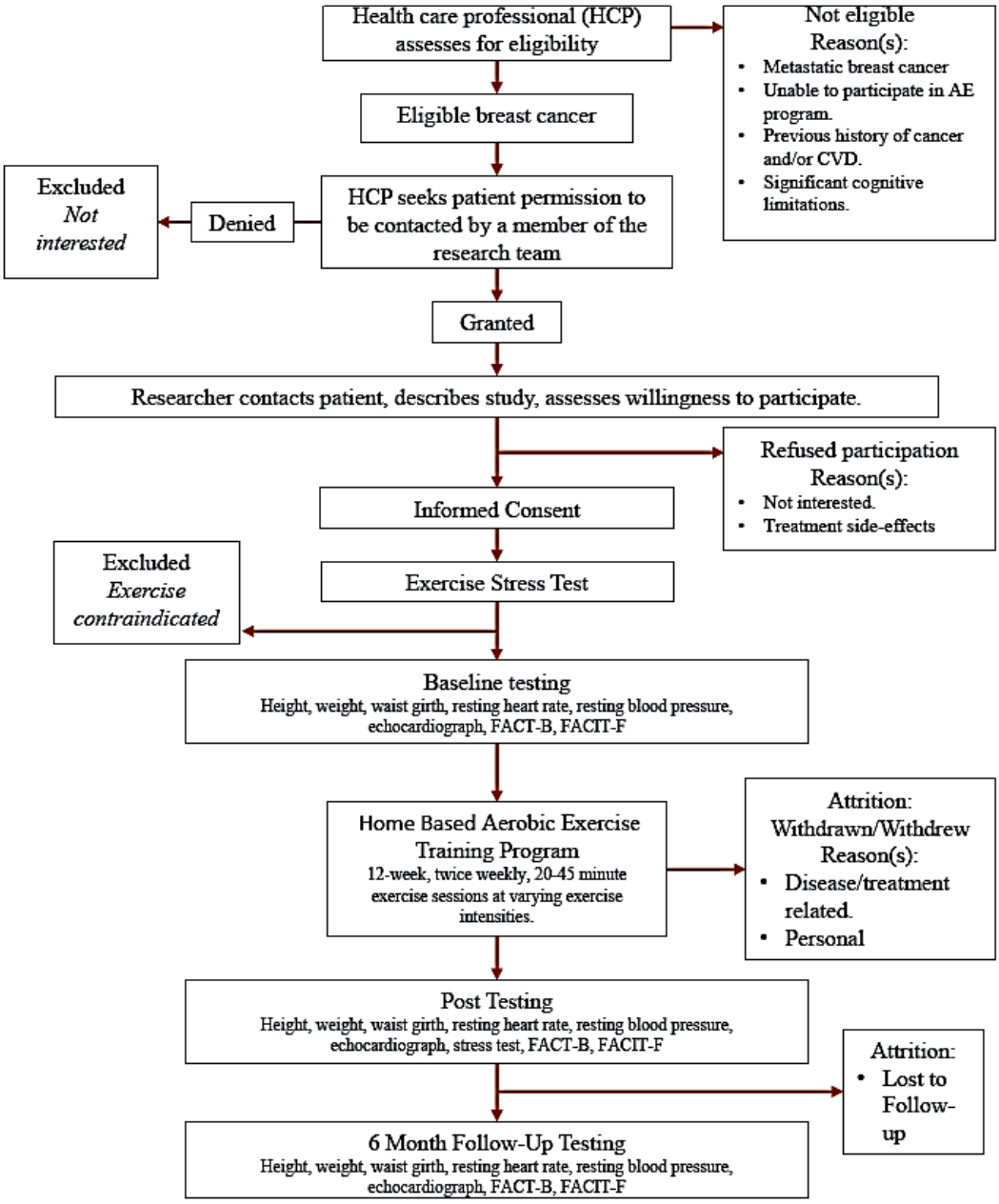
Chapter 6: Methodology

Recruitment and Randomization

A total 16 women with breast cancer was recruited from the two CancerCare Manitoba locations at St. Boniface Hospital and Health Sciences Centre (Figure 3) in Winnipeg, Manitoba, Canada. The inclusion criteria for recruitment included: 1) > 18 years of age; 2) diagnosed with breast cancer (stages I-III) and have not started therapy; 3) scheduled to receive AC-based chemotherapy (minimum dose of 240 mg/m^2 of DOX or 300 mg/m^2 of DAN); 4) able to undertake a 24-week home-based, progressive AE; and 5) have medical clearance from a cardiologist to participate in the study. Participants that met the inclusion criteria but had significant cognitive limitations and/or any pre-existing conditions that contraindicated aerobic exercise were excluded from the study. Any patient that was receiving beta-blocker medication were also excluded from the study as they would be unable to raise their heart rate as required for the exercise program. A similar recruitment practice was performed for the patients recruited from Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia by Dr. Scott Grandy and his research team. Each participant provided informed written consent prior to participating in the study.

All women with breast cancer were randomly assigned to either the control standard of care group (SOC; CTL) or the AE group (SOC + 24-week home-based AE program; AEX). The outcome measures (questionnaires, stress test, cardiac biomarkers, and transthoracic echocardiography) were performed for both groups at baseline and after the aerobic exercise regimen (6-month). At

Figure 3: Participant flow through the EXACT 2.0 study (Winnipeg site)



A total of 16 women with breast cancer starting on AC-based chemotherapy were recruited at two CancerCare Manitoba locations at St. Boniface Hospital and Health Sciences Centre in Winnipeg, Manitoba, Canada. Participants met all inclusion criteria to partake in the study. Participants were randomized to either standard of care control group (SOC) or the aerobic exercise group (SOC + 24-week home-based aerobic exercise program). Outcome measurements were made prior to participants starting AC therapy (week 0) and post-exercise intervention (week-24).

each appointment, height, weight, waist girth and medical history information was collected from the study participants. The study duration was 6 months for each participant, and participants could withdraw from participation at any point during the study. Due to delays associated with lumpectomy/mastectomy surgeries and the COVD-19 pandemic, participants were offered an additional 4 weeks from their originally proposed 6-month time point to schedule follow-up appointments, if necessary.

Exercise Intervention

Participants in the AEX group performed AE sessions on two non-consecutive days per week for a total of 24 weeks. Each session was preceded by a 5-minute warm-up and ended with a 10-minute cool down. The sessions varied in intensity: 1) low (35-45% heart rate reserve (HRR)); 2) low-moderate (46-55% HRR); 3) high-moderate (56-70% HRR); or 4) high (71-85% HRR) (Figure 4). Sessions also varied from 20 to 45 minutes in length, with higher intensities having shorter durations (Figure 5 and 6). Heart rate reserve is the difference between resting and maximal HRs as determined by stress testing (Formula 1, 2, and Sample Calculation 1). Participants were provided a Polar A370 Activity/HR monitor (Polar Canada) that allowed us to monitor HR remotely during training sessions. This data was uploaded automatically after each exercise by syncing with the Polar Flow web-based application and allowed for the tracking of adherence to the AE program. Participants had routine weekly ‘check-ins’ as well as was contacted immediately if abnormal or missing data was detected. Participants who missed 4 consecutive exercise sessions (two weeks of the program) were considered non-compliant and withdrawn from the study.

Formula 1:

Heart Rate Reserve = (maximum heart rate during stress test) – (resting heart rate)

Formula 2:

Heart Rate Target for Zone = Resting Heart Rate + (X%) * (Heart Rate Reserve)

Sample Calculation 1: Heart Rate Target for Low Intensity Exercise at 35% HRR

Participant has a resting heart rate of 88 and maximum heart rate of 150.

Heart Rate Reserve = 150 – 88

= 62

Heart Rate Target for Zone = 88 + (0.35) * (62)

= 88 + 22

= 110 bpm

Figure 4: Sample Heart Rate Zones for Exercise Group Participant

Resting Heart Rate	88	
Maximum Heart Rate	150	
	Lower	Upper
Zone 1 (35-44% HRR)	110	115
Zone 2 (45-54% HRR)	116	121
Zone 3 (55-69% HRR)	122	131
Zone 4 (70-85% HRR)	131	141

Each exercise group participant is prescribed an exercise program with four heart rate intensity range. Heart rate reserve values were used to determine the intensity of each zone. For a sample participant with a resting heart rate of 88 beats per minute (bpm) and a maximum heart rate of 150 bpm, the zones would be as follows: Zone 1 between 110 and 115 bpm, Zone 2 between 116 and 121 bpm, Zone 3 between 122 and 131 bpm, and Zone 4 between 131 and 141 bpm.

Figure 5: Sample Exercise Program for Weeks 1 to 12

Month	Week	Exercise Duration	Exercise Zone	Target Heart Rate (BPM)	
				Lower	Upper
1	1	20	z1	110	115
1	1	25	z1	110	115
1	2	35	z2	116	121
1	2	35	z1	110	115
1	3	35	z2	116	121
1	3	40	z2	116	121
1	4	25	z3	122	131
1	4	45	z1	110	115
2	1	20	z3	122	131
2	1	30	z2	116	121
2	2	35	z2	116	121
2	2	35	z2	116	121
2	3	35	z3	122	131
2	3	35	z2	116	121
2	4	40	z3	122	131
2	4	45	z2	116	121
3	1	25	z4	131	141
3	1	45	z1	110	115
3	2	30	z4	131	141
3	2	45	z1	110	115
3	3	30	z4	131	141
3	3	45	z1	110	115
3	4	20	z4	131	141
3	4	40	z1	110	115

The first 12 weeks of the graduated exercise program for a sample participant with a resting heart rate of 88 bpm and maximal heart rate of 150 bpm. The exercise regimen gradually increases in duration and intensity throughout the program. Exercise zone refers to one of the four heart rate intensity zones as explained in Figure 4.

Figure 6: Sample Exercise Program for Weeks 13 to 24

Month	Week	Exercise Duration	Exercise Zone	Target Heart Rate (BPM)	
				Lower	Upper
4	1	35	z2	116	121
4	1	40	z2	116	121
4	2	25	z3	122	131
4	2	45	z1	110	115
4	3	20	z3	122	131
4	3	30	z2	116	121
4	4	35	z2	116	121
4	4	35	z2	116	121
5	1	35	z3	122	131
5	1	35	z2	116	121
5	2	40	z3	122	131
5	2	45	z2	116	121
5	3	25	z4	131	141
5	3	45	z1	110	115
5	4	30	z4	131	141
5	4	45	z1	110	115
6	1	30	z4	131	141
6	1	45	z1	110	115
6	2	20	z4	131	141
6	2	40	z1	110	115
6	3	35	z2	116	121
6	3	35	z2	116	121
6	4	35	z3	122	131
6	4	35	z2	116	121

The last 12 weeks of the graduated exercise program for a sample participant with a resting heart rate of 88 bpm and maximal heart rate of 150 bpm. The exercise regimen gradually increases in duration and intensity throughout the program.

Transthoracic Echocardiography

Left ventricular (LV) function was assessed using transthoracic echocardiography (TTE) (Vivid IQ, GE Medical Systems, Milwaukee, WI; standard multi-frequency transducer). LV cavity dimensions and LV ejection fraction (LVEF) were determined from 2D parasternal and apical view images as per the American Society of Echocardiography (ASE) guidelines (Figures 7 and 8). [150] Two sonographers, blinded to group assignment, conducted all the baseline and follow-up heart image acquisition. LV volumes and LVEF calculations were conducted using the modified biplane Simpson's method as per the 2014 joint expert consensus by the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines (Figure 8).[151] Tissue velocity imaging (TVI), strain imaging (SI), and 2D based global longitudinal strain (GLS) were also conducted due to their ability to detect LV systolic dysfunction earlier than global LVEF (Figures 9-12).[152,153] Global longitudinal strain was calculated using automated function imaging (AFI) and using the apical long-axis, 4-chamber and 2- chamber views on GE Healthcare's EchoPAC software (Figure 11 and 12).

Cardiac Stress Tests

Participants performed a graded exercise stress test using a 12-lead ECG monitoring (GE Medical Systems, Milwaukee W, USA) following the Bruce Protocol until they reached volitional fatigue.[154,155] All stress tests were administered by the same stress testing specialist who placed the leads, and took blood pressure measurements at 2 minute intervals during the graded exercise. All stress tests were supervised by a cardiologist (Drs. Davinder Jassal, Umar Ismail, or Hilary Bews). Peak oxygen uptake was calculated using predictive equations based on total duration on stress test.[156]

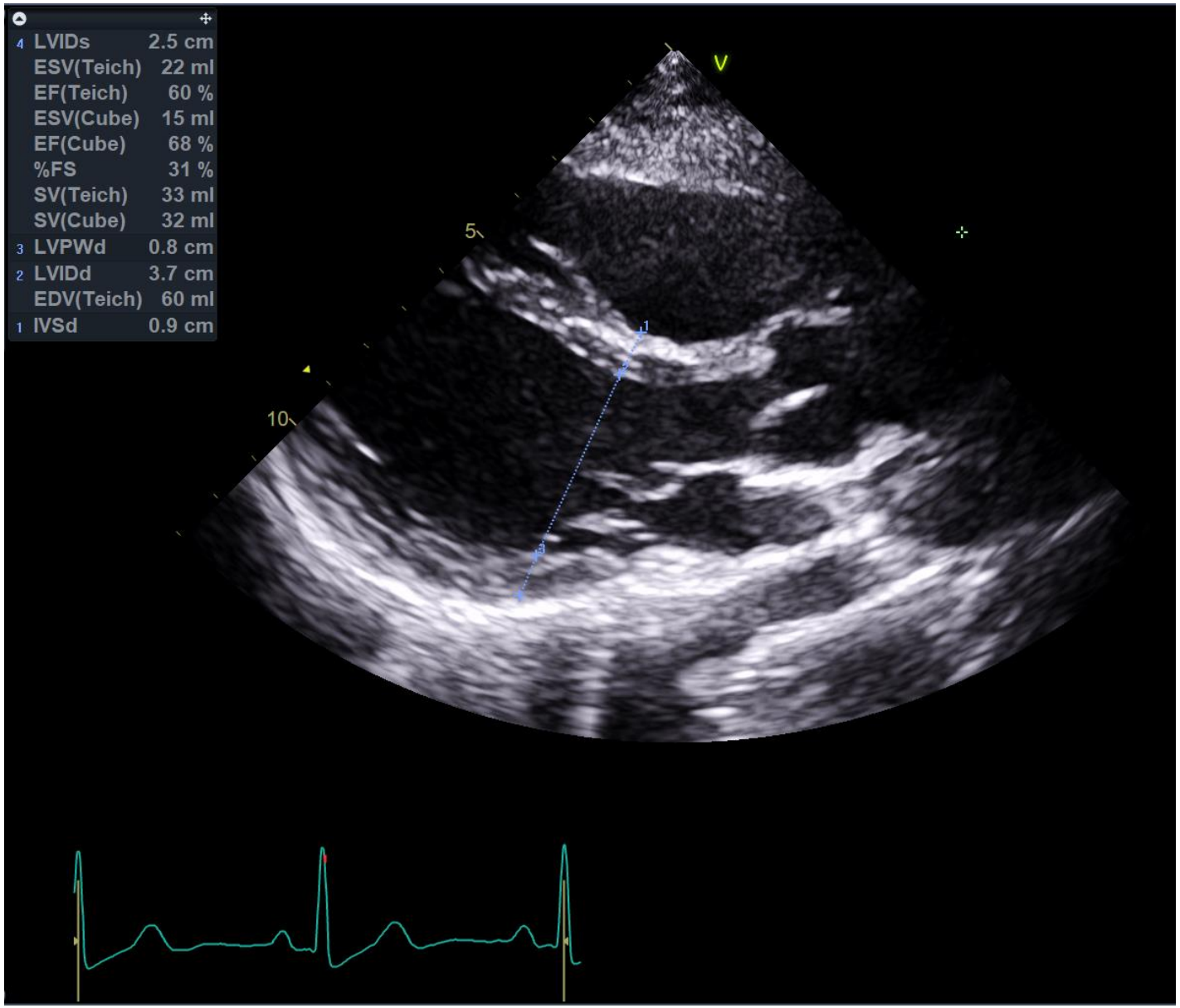
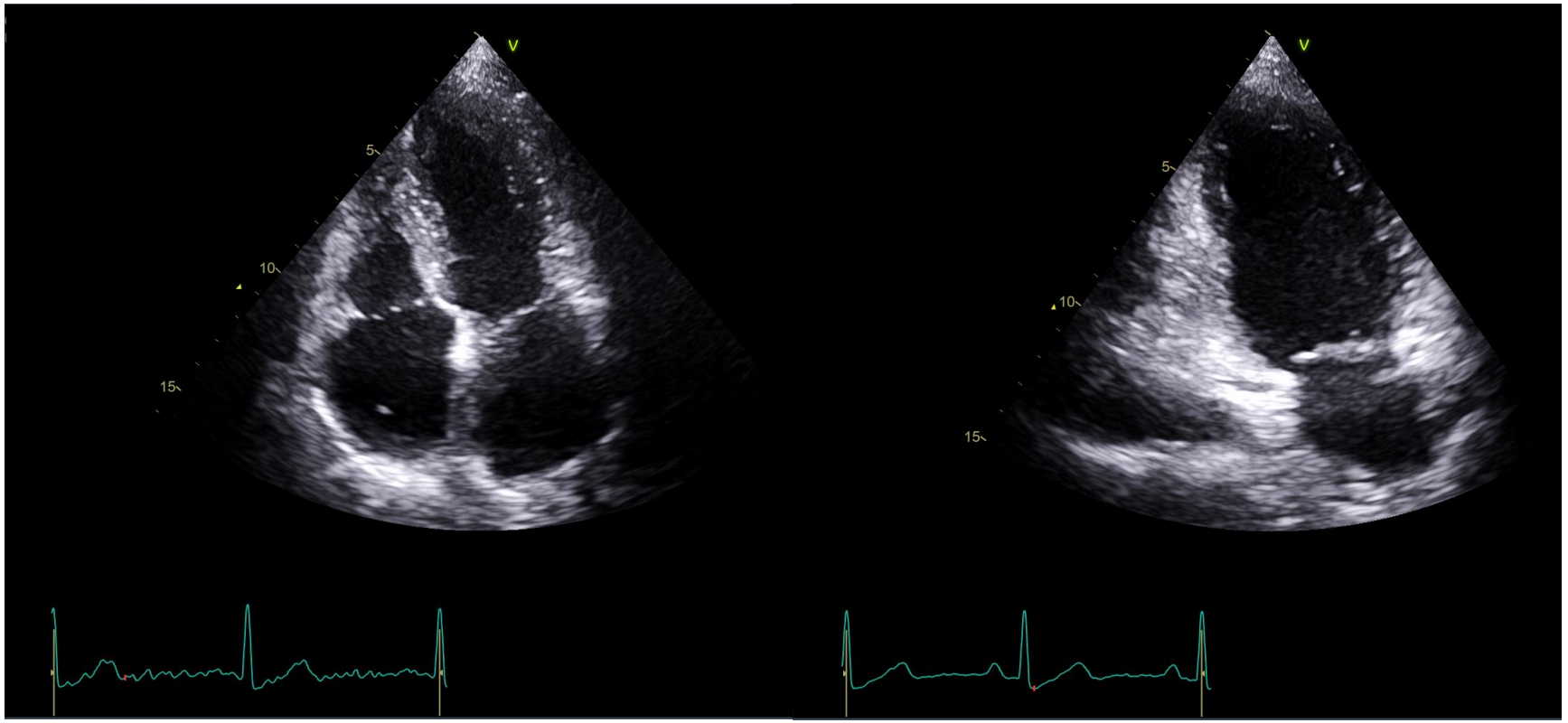


Figure 7: Parasternal Long Axis View on Transthoracic Echocardiography

(1) IVSd: Interventricular septum diameter at end diastole;
(2) LVIDd: Left ventricle internal diameter at end diastole;
(3) LVPWd: Left ventricle posterior wall thickness at end diastole;
(4) LVIDs: Left ventricle internal diameter at end systole

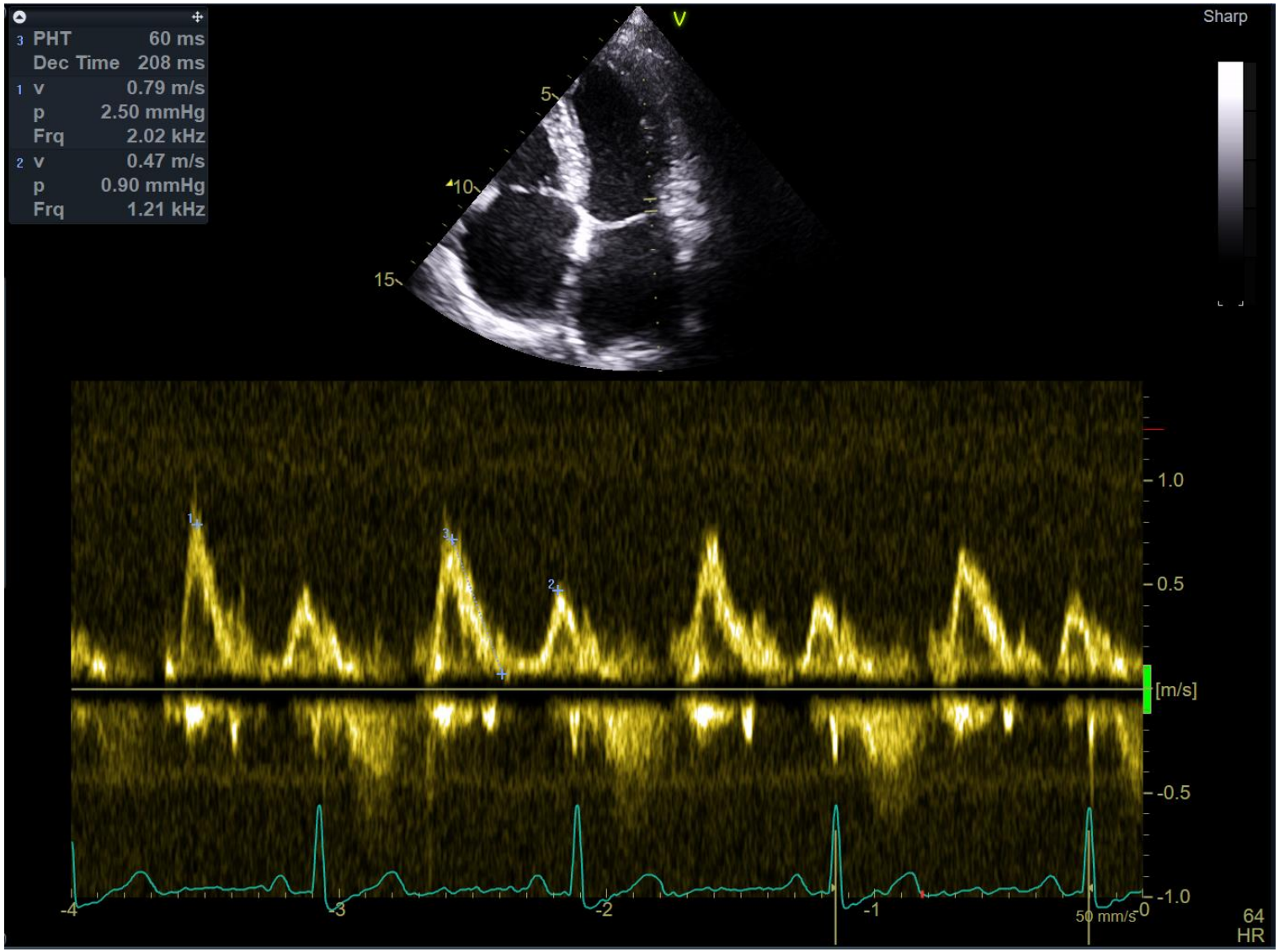
EDV: End Diastolic Volume; SV: Stroke Volume; %FS: Fractional shortening; EF: Ejection fraction; ESV: End systolic volume.

Figure 8: **Apical 4 Chamber and Apical 2 Chamber Views on Transthoracic Echocardiography**



The modified biplane Simpson's method calculates the left ventricle ejection fraction (LVEF) using the (A) apical 4-chamber and (B) apical 2-chamber views. LVEF is used to determine whether participants have normal or abnormal systolic function.

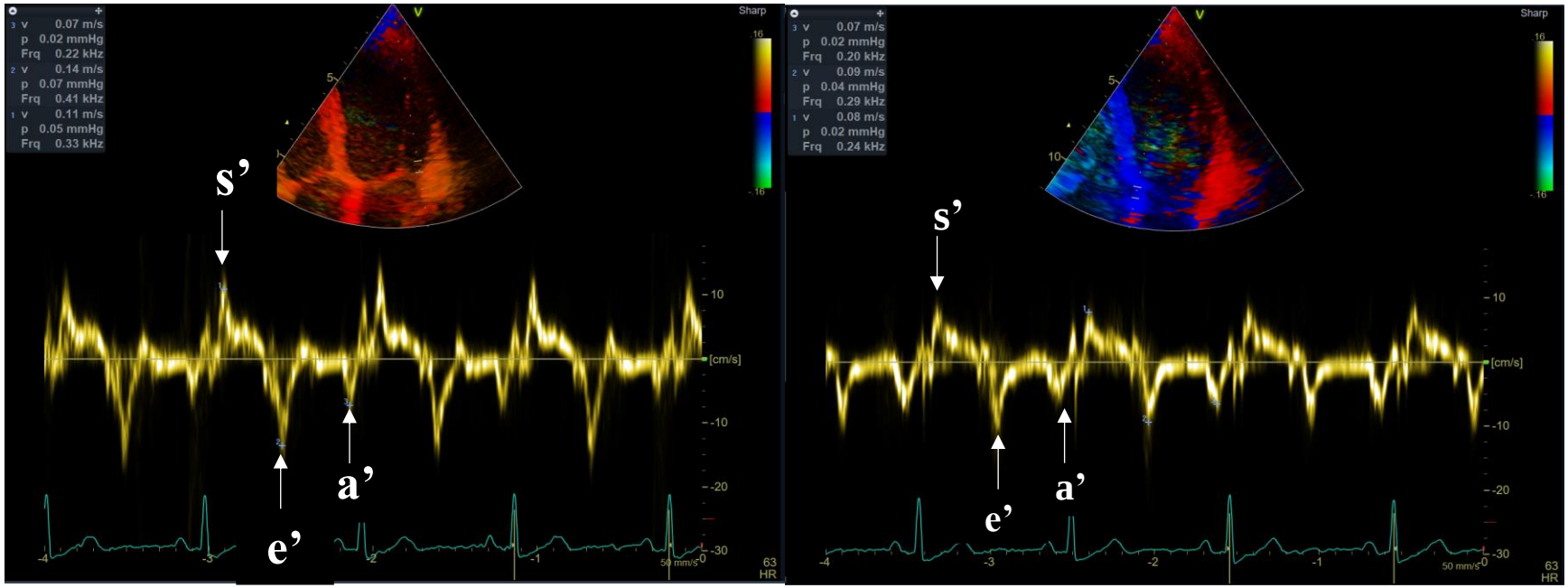
Figure 9: **Diastolic parameters on transthoracic echocardiography**



(1) E: Early Filling Velocity (m/s)
(2) A: Atrial Filling Velocity (m/s)
(3) Dec Time: Deceleration Time (ms)

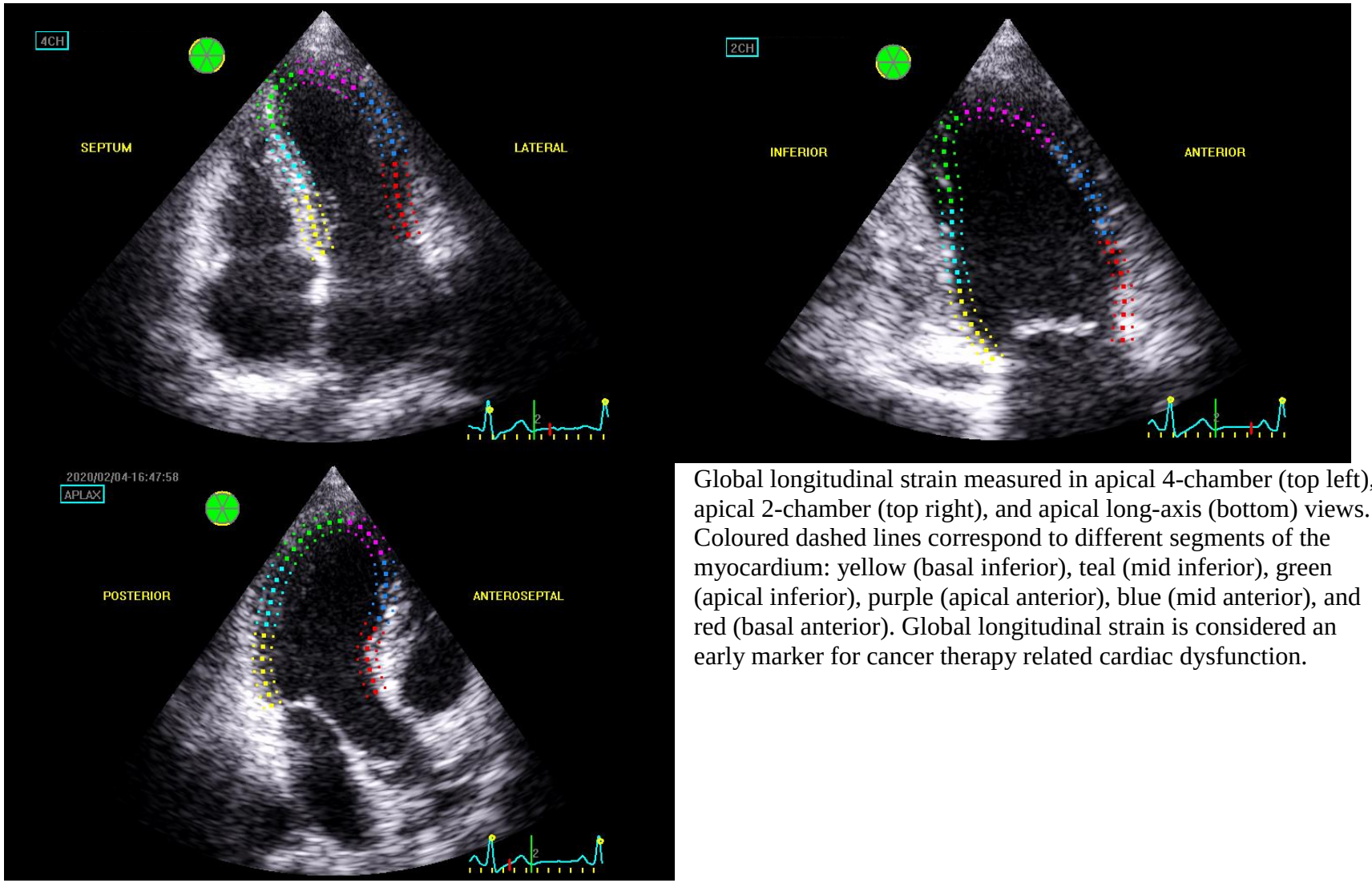
Abnormal values in diastolic parameters indicate impaired diastolic function in participants.

Figure 10: Lateral and Medial Mitral Annulus Velocity



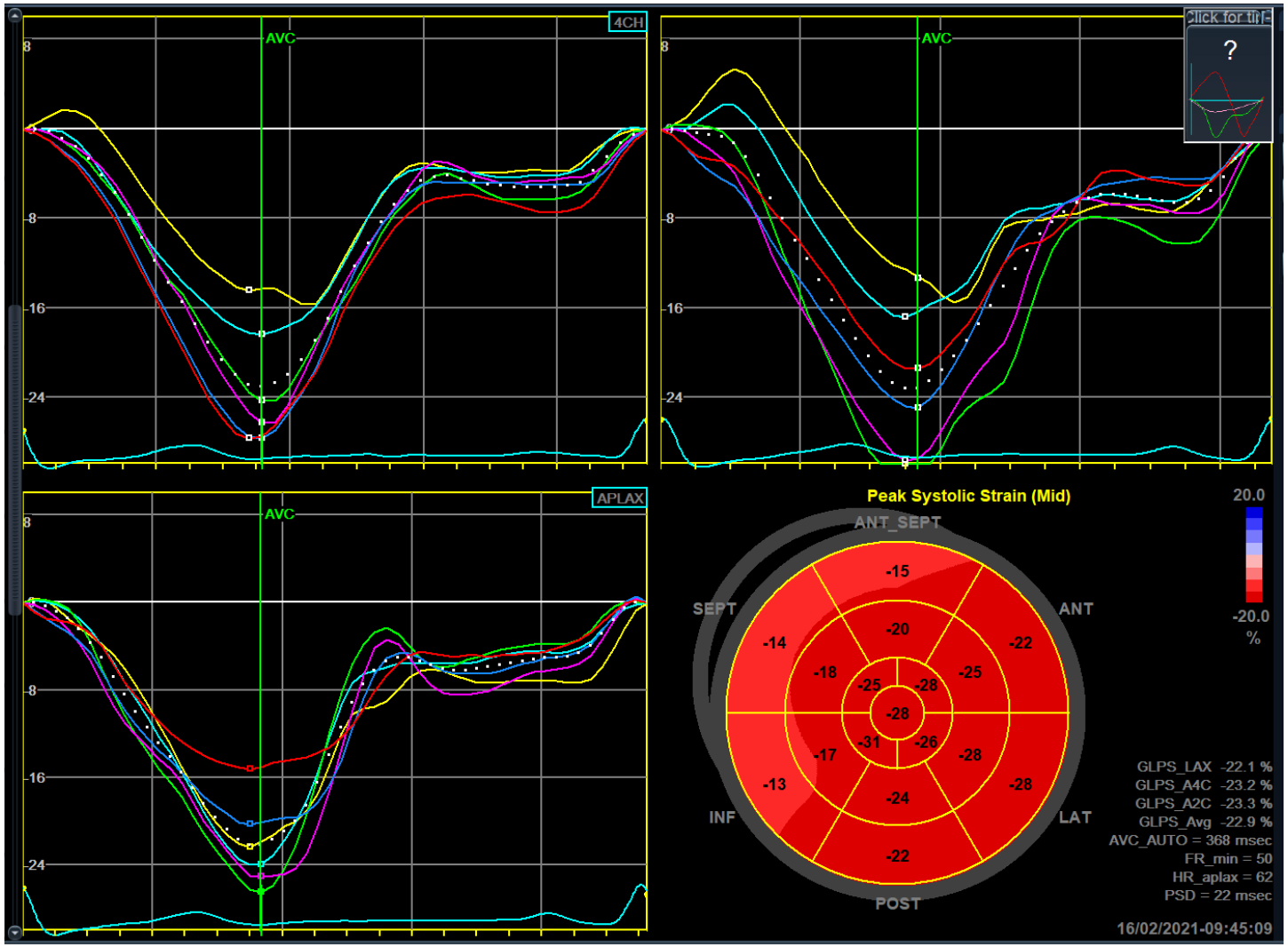
Lateral (left) and medial (right) mitral annulus velocity. s' velocity is a positive systolic wave representing myocardial contraction, e' velocity represents early diastolic myocardial relaxation, and a' velocity represents late diastolic atrial contraction.

Figure 11: **Global Longitudinal Strain (GLS)**



Global longitudinal strain measured in apical 4-chamber (top left), apical 2-chamber (top right), and apical long-axis (bottom) views. Coloured dashed lines correspond to different segments of the myocardium: yellow (basal inferior), teal (mid inferior), green (apical inferior), purple (apical anterior), blue (mid anterior), and red (basal anterior). Global longitudinal strain is considered an early marker for cancer therapy related cardiac dysfunction.

Figure 12: **Global Longitudinal Strain (GLS) Bullseye Plot**



Graphs resulting from GLS analysis of the myocardium in apical 4-chamber (top left), apical 2-chamber (top right), and apical long-axis (bottom right) views. Composite bullseye graph combining data from 3 different views (bottom right). More negative numbers (< -19%) indicate normal LV systolic function.

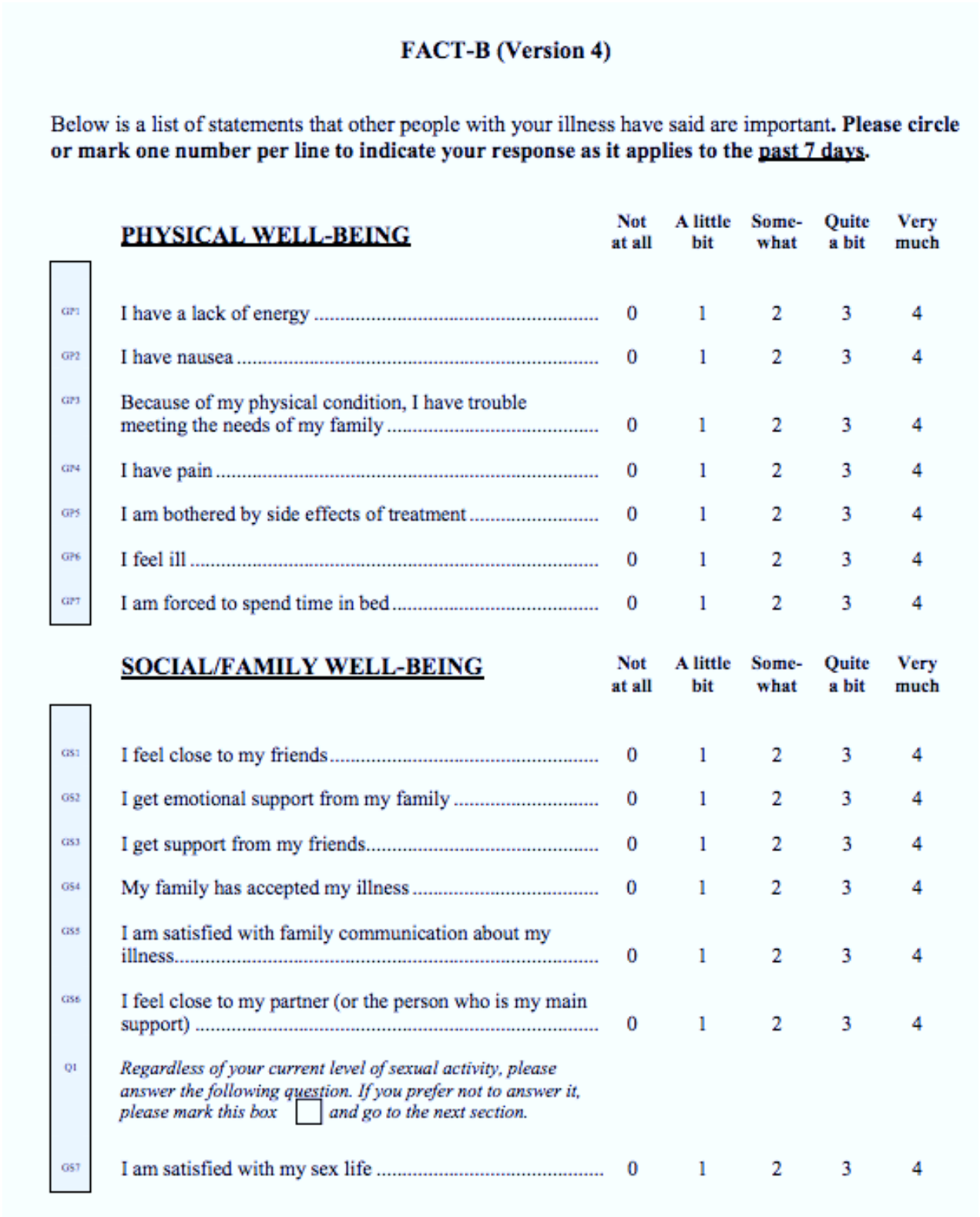
Quality of Life Factors

The Functional Assessment for Cancer Therapy survey for patients with breast cancer (FACT-B) was used to assess the quality of life. The FACT-B includes five subscales including: Physical Well-being (PWB), Social Well-being (SWB), Emotional Well-being (EWB), Functional Well-being (FWB), and the Breast Cancer Subscale (BCS).[157] Additionally, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) was used to assess cancer therapy related fatigue which was composed of 1 subscale.[157,158] Each of the FACT-B subscales and the FACIT-F subscale have a list of questions assessing quality of life pertaining to that specific category, with each question being given a rating from 0 to 4. A higher score for a question such as 3 and 4 is indicative of a better the quality of life. The PWB, SWB, and FWB subscales have 7 questions each, resulting in a score range of 0 to 28 within each respective category (Figure 13 & 14). The EWB subscale has six questions resulting in a score range of 0 to 24 (Figure 14). The BCS subscale had ten questions resulting in a score range of 0 to 40 (Figure 15). Finally, the FACIT-F subscale which assesses fatigue as a result of cancer therapy has thirteen questions resulting in a score of 0 to 52 (Figure 16).

In the case where individual questions within a subscale are skipped, subscale scores were prorated using the average of the other answers in the scale. As per Functional Assessment of Chronic Illness Therapy (https://www.facit.org/) guidelines, this can be done as long as 50% of questions within the specific subscale have been answered.

The total FACT-B score is a simple addition of the scores of the individual subscales and therefore, can range from 0 to 148. However, two guidelines need to be met prior to performing this

Figure 13: Functional Assessment for Cancer Therapy – Breast Cancer (FACT-B): Physical and Social Well-being Questions



FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	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

Figure 14: Functional Assessment for Cancer Therapy – Breast Cancer (FACT-B): Emotional and Functional Well-being Questions

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	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

Figure 15: Functional Assessment for Cancer Therapy – Breast Cancer (FACT-B): Breast Cancer Subscale

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Figure 16: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Subscale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		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

calculation. Firstly, all of the subscales must have a valid response for more than 50% of the questions within their individual category. Secondly, as a whole, more than 80% of the questions of the cumulative 37 questions needs to be answered. Since FACIT-F is a scale with only one set of questions, it requires 50% of the questions within its 13 questions to be valid for the calculation to be performed.

Baseline Data Collection

CancerCare Manitoba's medical record database (ARIA) was used to extract baseline data information regarding participants enrolled in the study. Data collected include: i) baseline demographics, including age, height, and weight; ii) cardiovascular risk factors, including hypertension, diabetes, hyperlipidemia, smoking history, and family history of CAD; iii) tumor parameters, including size of cancer, grade, ER, PR, and HER2 statuses; and, iv) cancer therapy regimens.

Data Analyses

A one-way ANOVA was used to compare mean differences between groups for all the outcome variables. Program adherence was calculated as a percentage of the total number of exercise session completed. Safety was determined by calculating the number of adverse events per participant hour. This was determined by dividing the total number of adverse events, if any, by total number of participant hours. GraphPad Prism Version 6.0c software was used for all data analyses. $P < 0.05$ was considered significant.

Chapter 7: Results

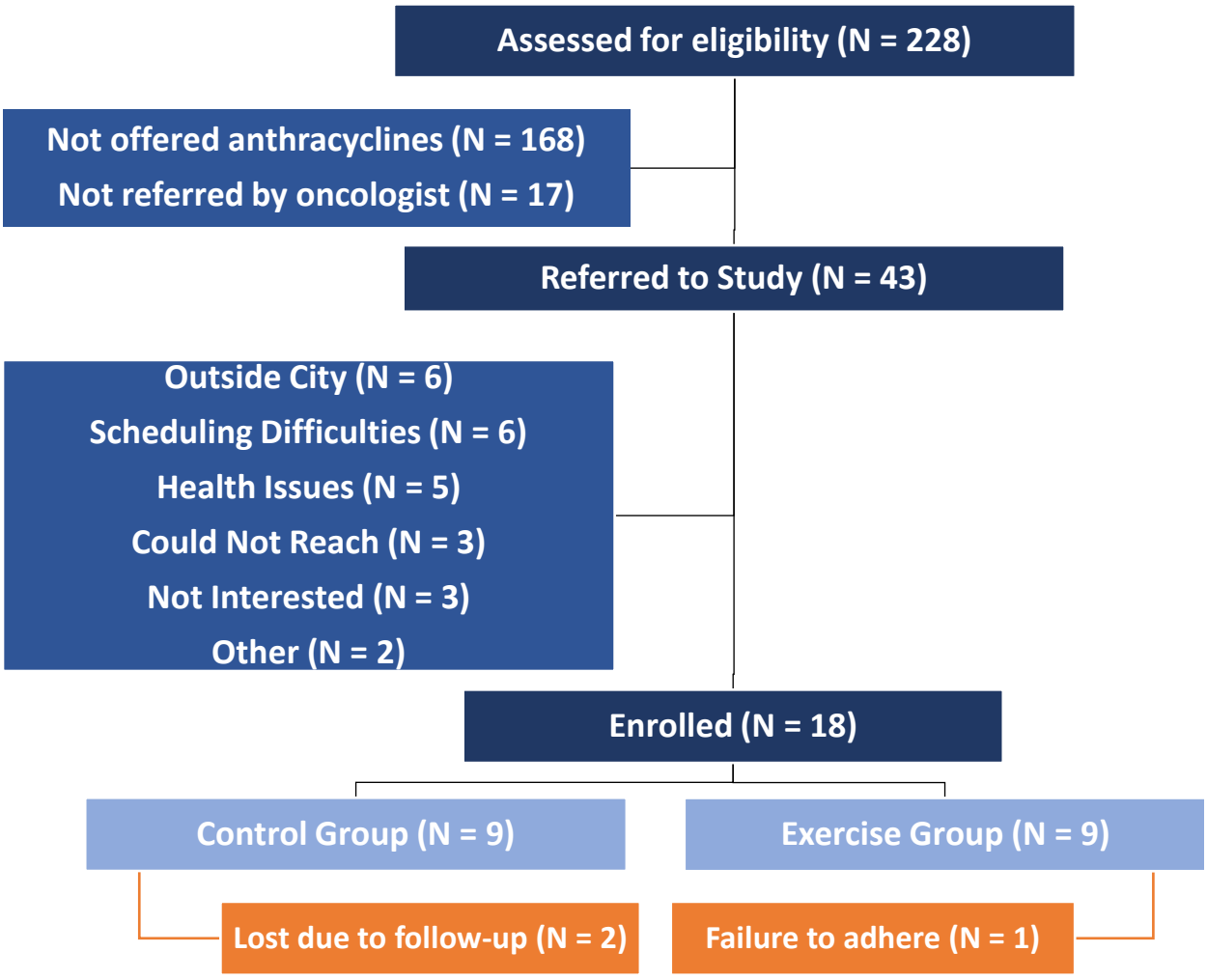
Patient Screening and Recruitment

From November 2019 to November 2020 inclusive, a total of 228 breast cancer patients were screened by CancerCare Manitoba, of which 43 participants met the inclusion criteria and were referred by oncologists (Figure 17). Among these 43 participants, 18 participants were recruited into the EXACT 2.0 study. The two most common reasons that referred participants did not participate in the study were living outside the city (n=6) and scheduling difficulties (n=6). These were challenges as there was usually a period of 1 week between an oncologist seeing a new patient and the start of chemotherapy. As such, baseline appointment had to be scheduled within this narrow window of time, which was not always conducive to patient availability, especially for those living outside Winnipeg. The COVID-19 pandemic halted patient recruitment into the study between March to August 2020 and mid-November 2020 onwards. Out of the 18 participants enrolled into the study, 9 were randomized to the control arm and 9 were randomized to the aerobic exercise (AEX) program. However, 2 participants from the control group were unable to complete the 6-month follow-up appointment and thus were removed from the data analysis. Additionally, as per original protocol, one participant within the exercise group was removed from the study for non-compliance as more than 4 consecutive exercise sessions were missed and hence, not included in exercise group data analysis.

Demographic Data

Demographic data was collected from study participants at baseline appointment and extracted from ARIA medical database. The average age was 54 ± 14 years old in the control group and 49

Figure 17: Patient screening and enrollment cumulative data from November 2019 to November 2020



± 6 years old in the exercise group (Table 2). A total of 14 patients received Adriamycin and Cyclophosphamide for 8 weeks and 1 patient received Fluorouracil, Epirubicin, and Cyclophosphamide for 9 weeks. Additionally, 13 patients received adjuvant radiation therapy. A total of 11 women had baseline cardiovascular risk factors including hypertension (n=1), hyperlipidemia (n=2), smoking history (n=4), and family history of premature coronary artery disease (n=4). Other patient characteristics, including tumor attributes and cancer therapies between the two groups were similar (Table 2).

Exercise Adherence

Among the exercise group participants, there was an average adherence of 92% to the exercise program (Figure 18). This equates to completing 44 of the 48 exercise sessions. The average weekly exercise duration within the control group was 57 ± 28 minutes compared to 90 ± 17 minutes within the AEX group. There were no reported adverse events or any exercise-related injuries in either group.

Echocardiographic Parameters

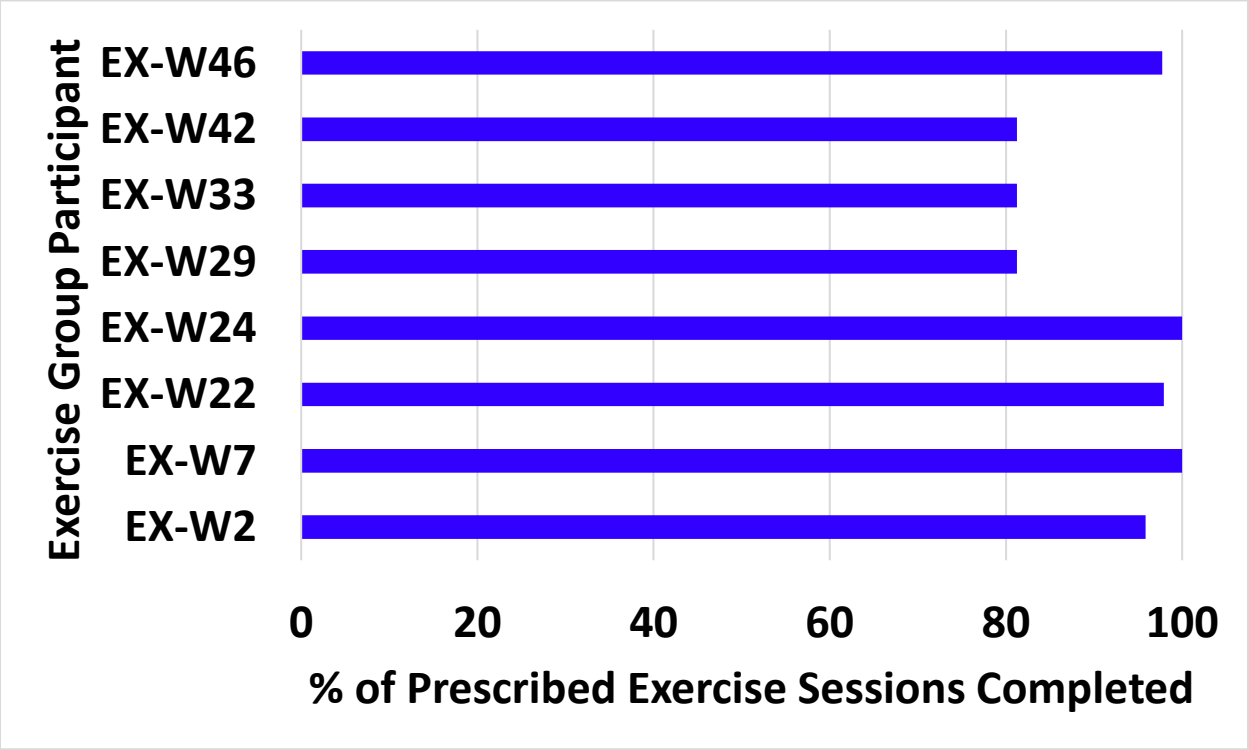
Firstly, the analysis of cavity dimension data acquired from parasternal long axis views showed no differences between control and exercise groups at both time points. In the control group at baseline, the values for LVEDD, LVESD, IVS, and PWT were 4.2 cm, 2.7 cm, 0.9 cm, and 0.9 cm, respectively. Within the control group at 6-months, the values for LVEDD, LVESD, IVS, and PWT were 4.3 cm, 2.9 cm, 0.9 cm, and 0.8 cm, respectively (Table 3). In the exercise group at baseline, the values for LVEDD, LVESD, IVS, and PWT were 4.4 cm, 2.9 cm, 0.9 cm, and 0.9 cm, respectively. Within the exercise group at 6-months, the values for LVEDD, LVESD, IVS, and PWT were 4.4 cm, 3.0 cm, 0.9 cm, and 0.9 cm, respectively (Table 3). Similarly, left atrium

Table 2: Demographic data of control and AEX participants enrolled in study.

	Control (n = 7)	Exercise (n = 8)
Age (years) (mean±SD)	54 ± 14	49 ± 6
BMI (kg/m^2) (mean±SD)	28 ± 7	28 ± 6
Hypertension (n, %)	1 (14)	0
Diabetes (n, %)	0	0
Hyperlipidemia (n,%)	2 (29)	0
Smoking history (n, %)	3 (43)	1 (13)
Family History of CAD (n, %)	2 (29)	2 (25)
Estrogen Receptor Positivity (n, %)	6 (86)	5 (63)
Progesterone Receptor Positivity (n, %)	4 (57)	4 (50)
HER2 Positivity (n, %)	2 (29)	4 (50)
Total Dose of Anthracycline (mg/m^2)	429	507
Trastuzumab (n, %)	2 (29)	4 (50)
Location of Cancer – left only (n, %)	5 (71)	6 (75)
Location of Cancer – right only (n, %)	2 (29)	2 (25)
Location of Cancer – bilateral (n, %)	0	0
Radiation (n, %)	5 (71)	8 (100)
Lymph Node + (n, %)	5 (71)	6 (75)
Chemotherapy – FEC (n, %)	0	1 (13)
Chemotherapy – AC (n, %)	7 (100)	7 (88)
Mastectomy (n, %)	4 (57)	3 (38)
Lumpectomy (n, %)	4 (57)	5 (63)

Baseline characteristics of control (n = 7) and exercise (n = 8) participants. AC, adriamycin, cyclophosphamide; BMI, body mass index; CAD, coronary artery disease; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; SD, standard deviation.

Figure 18: Adherence of Exercise Group Participants



Adherence of exercise group (n=8) to 24-week home-based aerobic exercise program. There were two sessions per week for 24-weeks, for a total of 48 sessions. Each session ranged from 20 to 45 minutes and ranged from 35 to 85% heart rate reserve intensity. Average adherence was 92%, which equates to completing 44 of 48 sessions.

Table 3: Echocardiographic parameters for control and exercise participants enrolled in study.

Echocardiographic Parameters	Control - Baseline	Control – 6 Months	Exercise - Baseline	Exercise – 6 Months
Parasternal Long Axis				
LVEDD (cm)	4.2 ± 0.2	4.3 ± 0.1	4.4 ± 0.2	4.4 ± 0.1
LVESD (cm)	2.7 ± 0.2	2.9 ± 0.1	2.9 ± 0.2	3.0 ± 0.3
IVS (cm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
PWT (cm)	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.0	0.9 ± 0.1
LA (s) (cm)	3.4 ± 0.3	3.4 ± 0.4	3.2 ± 0.4	3.0 ± 0.5
RV (d) (cm)	3.2 ± 0.2	3.2 ± 0.3	3.1 ± 0.2	3.1 ± 0.2
Simpsons' Modified Biplane				
LVEF (%)	62.38 ± 1.5	61.57 ± 2.6	63.00 ± 1.6	58.25 ± 8.1
Diastolic parameters				
E (m/s)	0.61 ± 0.06	0.63 ± 0.11	0.68 ± 0.07	0.75 ± 0.08
A (m/s)	0.56 ± 0.07	0.61 ± 0.12	0.46 ± 0.07	0.52 ± 0.09
Deceleration Time (ms)	207 ± 35	211 ± 31	233 ± 27	223 ± 18
Medial				
S'	0.08 ± 0.02	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
E'	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
A'	0.09 ± 0.02	0.09 ± 0.01	0.07 ± 0.01	0.08 ± 0.01
Lateral				
S'	0.10 ± 0.02	0.09 ± 0.02	0.09 ± 0.01	0.09 ± 0.01
E'	0.11 ± 0.02	0.10 ± 0.01	0.11 ± 0.02	0.10 ± 0.01
A'	0.10 ± 0.03	0.09 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
Global Longitudinal Strain				
Apical Long Axis	-19.94 ± 1.11	-18.91 ± 1.52	-19.36 ± 1.77	-17.68 ± 2.41
Apical 4-Chamber	-19.99 ± 1.07	-17.96 ± 1.59	-19.78 ± 2.53	-17.71 ± 3.15
Apical 2-Chamber	-20.69 ± 1.44	-18.47 ± 1.26	-19.69 ± 1.46	-17.19 ± 2.27
Total	-19.49 ± 1.45	-18.16 ± 1.29	-18.95 ± 1.23	-17.46 ± 2.27

Echocardiographic parameters measured in control (n = 7) and exercise (n = 8) participants for the parasternal long axis, apical 4-chamber, and apical 2-chamber views. Data are mean ± SD at baseline and at 24-week follow-up. LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; IVS, interventricular septal thickness; PWT, posterior wall thickness; LA, left atrium; RVEDD, right ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

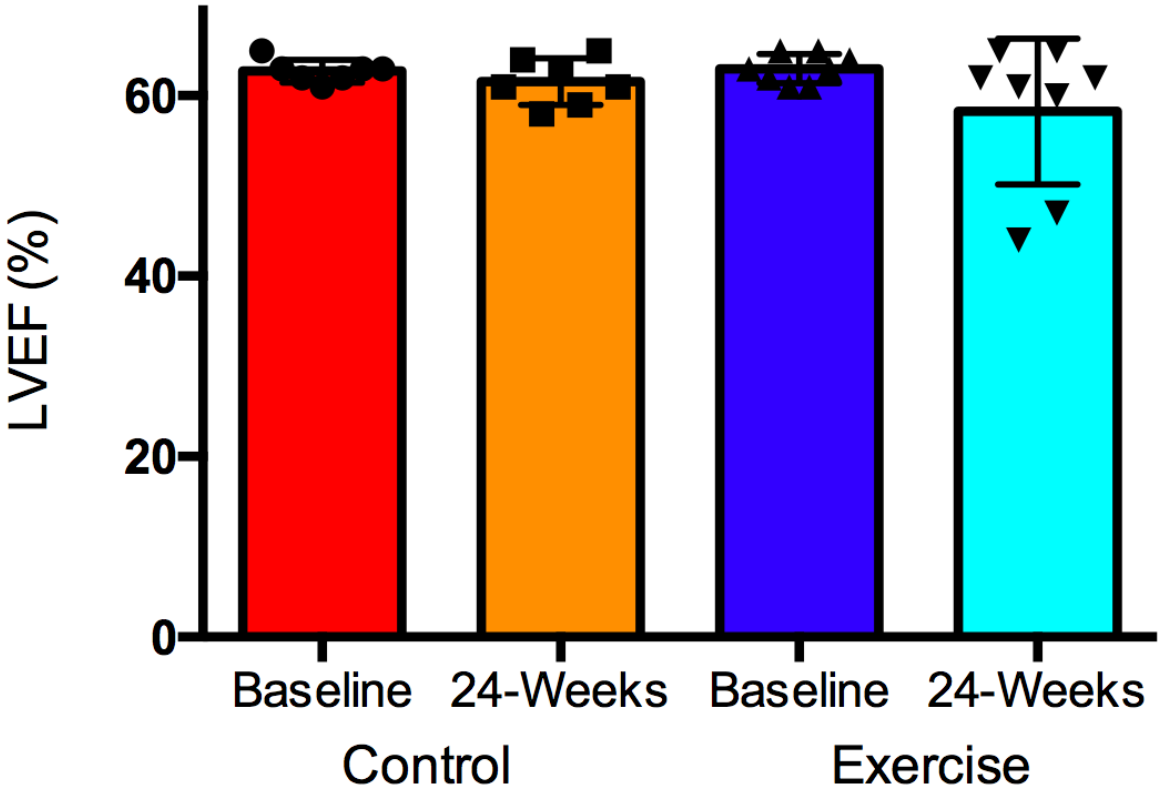
and right ventricle diameters were not different at baseline and at 6-months for both the control and the exercise groups (Table 3). Furthermore, diastolic function did not differ between both groups. For control group participants at baseline, the E, A, and deceleration time were 0.61 m/s, 0.56 m/s, and 207 ms, respectively. For control group participants at 6-months, the E, A, and deceleration time were .63 m/s, 0.61 m/s, and 211 ms, respectively (Table 3). Within the exercise group at baseline, the E, A, and deceleration time were 0.68 m/s, 0.46 m/s, and 233 ms, respectively. Within the exercise group at 6-months, the E, A, and deceleration time were 0.75 m/s, 0.52 m/s, and 223 ms, respectively (Table 3). Similarly, medial and lateral S', E', and A' values were not different in the control and exercise groups at both time points.

Finally, LVEF and GLS values were not significantly different between both groups at baseline and 6-months. In the control group, the mean LVEF was 62±2% at baseline and 62±3% at 6-months (Figure 19). In the AEX group, the mean LVEF was 63±2% at baseline and 58±8% at 6-months. Similarly, in the control group, the mean GLS was -19.5±1.5% at baseline and-18.2±1.3% at 6-months. In the AEX, the mean GLS was -19.0±1.2% at baseline and -17.5±2.3% at 6-months (Figure 20).

Cardiac Stress Test: VO2 Max

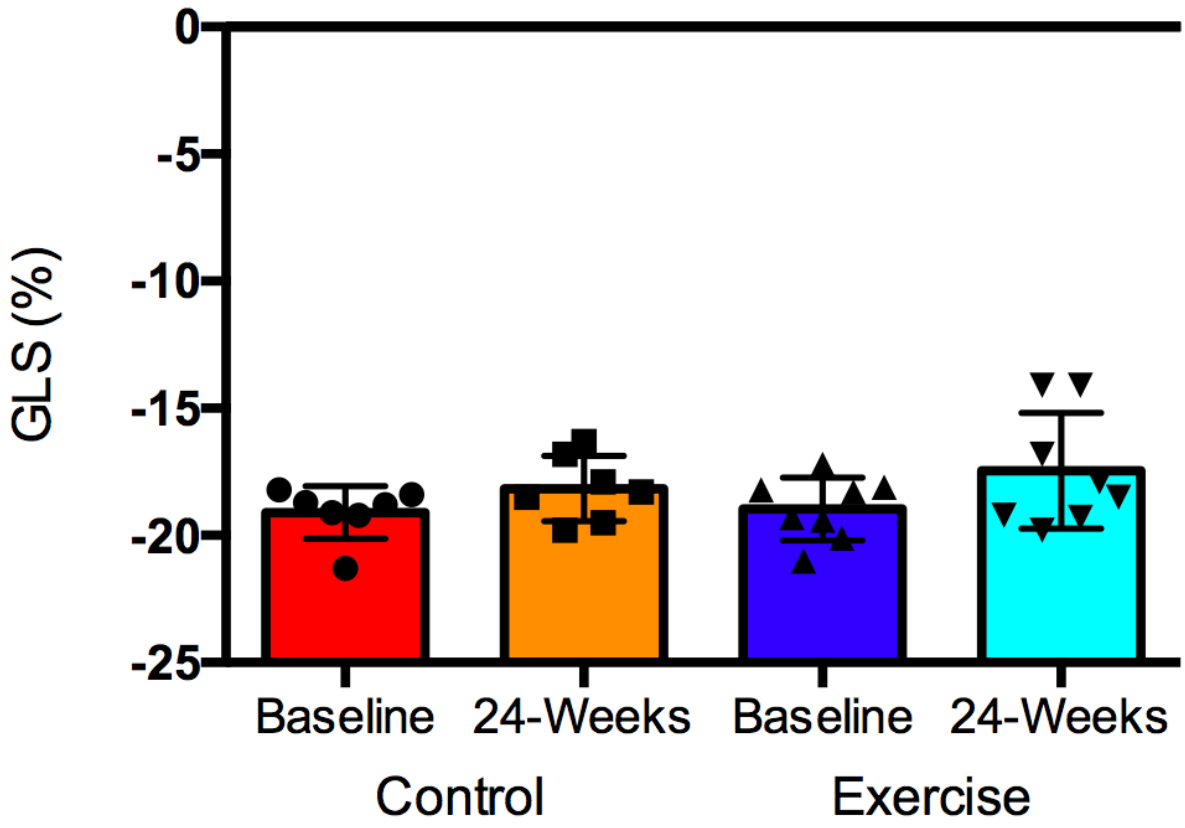
Maximal oxygen uptake (VO2 max) was calculated using duration on treadmill based on the Bruce Protocol (Formula 2). The estimated VO2 max on the treadmill for the control group was 30.1 ml/kg/min at baseline and 33.7 ml/kg/min minutes at 6-months. In the exercise group, the average duration was 30.1 ml/kg/min at baseline and 36.3 ml/kg/min at 6-month follow-up. While the predicted VO2 max was higher within the AEX group at 6-month, this trend was not significantly different ($p > 0.05$; Table 4 and Figure 21). Additionally, due to recent surgery or neuropathy

Figure 19: Left ventricle ejection fraction in control and exercise participants throughout study period.



Bars correspond to group averages. No significant differences between control (n = 7) and exercise (n=8) groups at baseline or 6-months. Data shown are the average ± SD and analyzed by a one-way ANOVA ($p > 0.05$). LVEF, left ventricular ejection fraction.

Figure 20: Global longitudinal strain in control and exercise participants throughout study period.

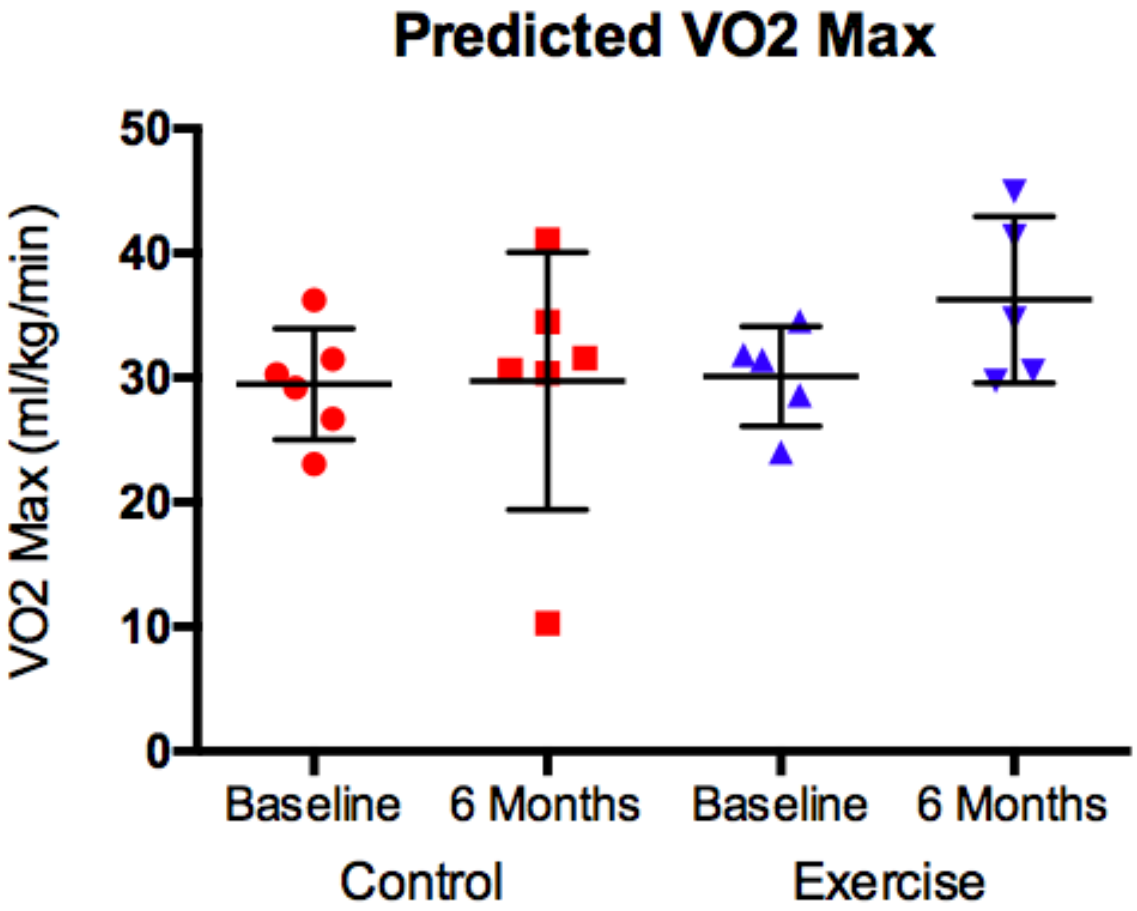


Bars correspond to group averages. No significant differences between control (n = 7) and exercise (n=8) groups at baseline or 6-months. Data shown are the average ± SD and analyzed by a one-way ANOVA ($p > 0.05$). GLS, global longitudinal strain.

Table 4: Average Duration on Treadmill on Bruce Protocol and Predicted VO2 Max in Control and Exercise groups.

VO2 Max	Control - Baseline	Control – 6 Months	Exercise - Baseline	Exercise – 6 Months
Average Duration (minutes)	7.8	8.6	7.8	9.2
VO2 Max (ml/kg/min)	30.1	33.6	30.1	36.3

Figure 21: Predicted VO2 Max within Control and Exercise Groups at Baseline and 6-Months



Dots correspond to individual participant scores. No significant differences between control (n = 7) and exercise (n=8) groups at baseline or 6-months. Data shown are the average ± SD and analyzed by a one-way ANOVA ($p > 0.05$).

concerns, 3 participants were unable to participate in the follow-up stress test. As such, the VO2 max reflects the data of 12 participants, six from both control and exercise groups.

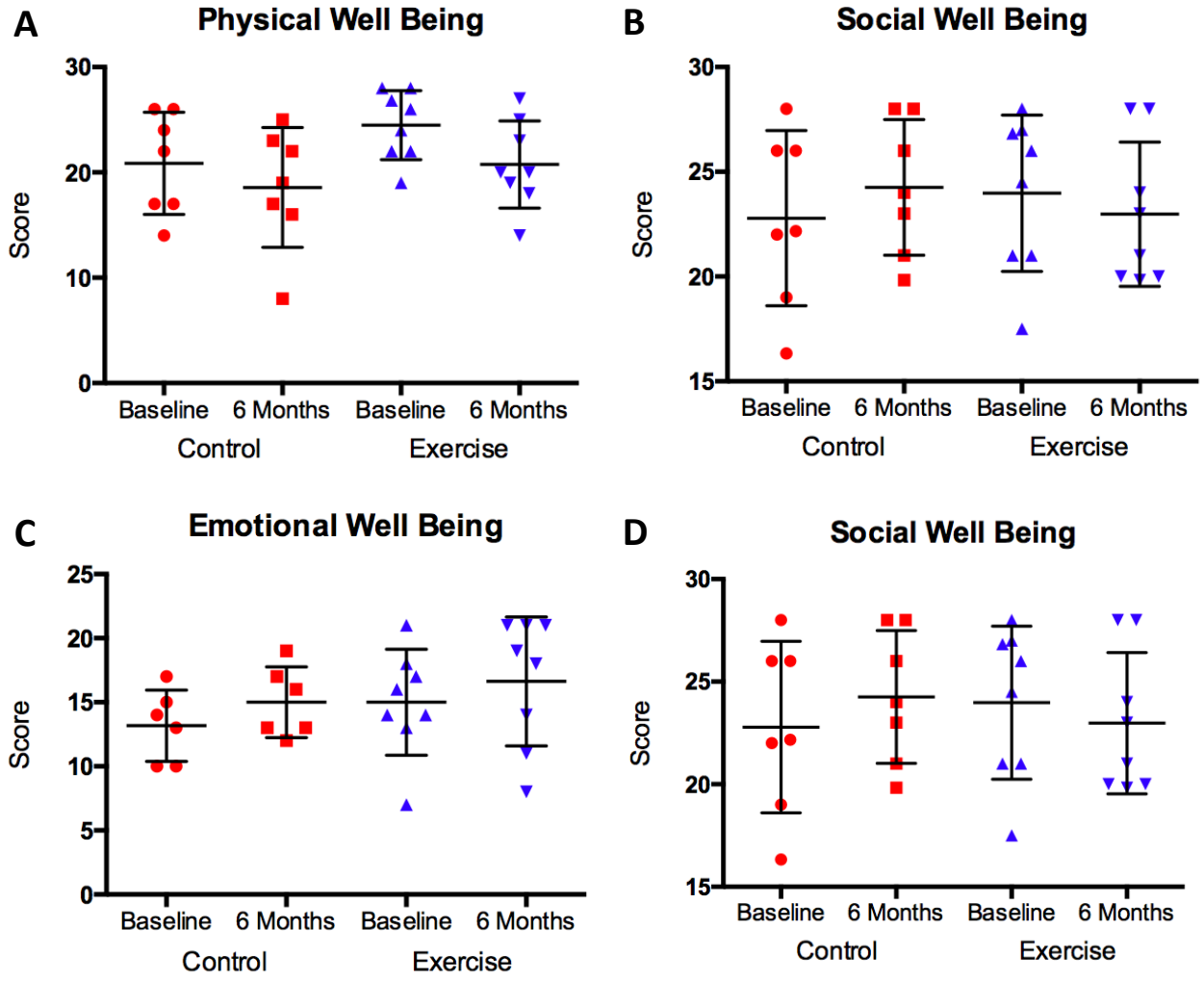
Formula 2:

$$VO2\ Max = 4.38\ x\ T - 3.9$$

Survey Answers

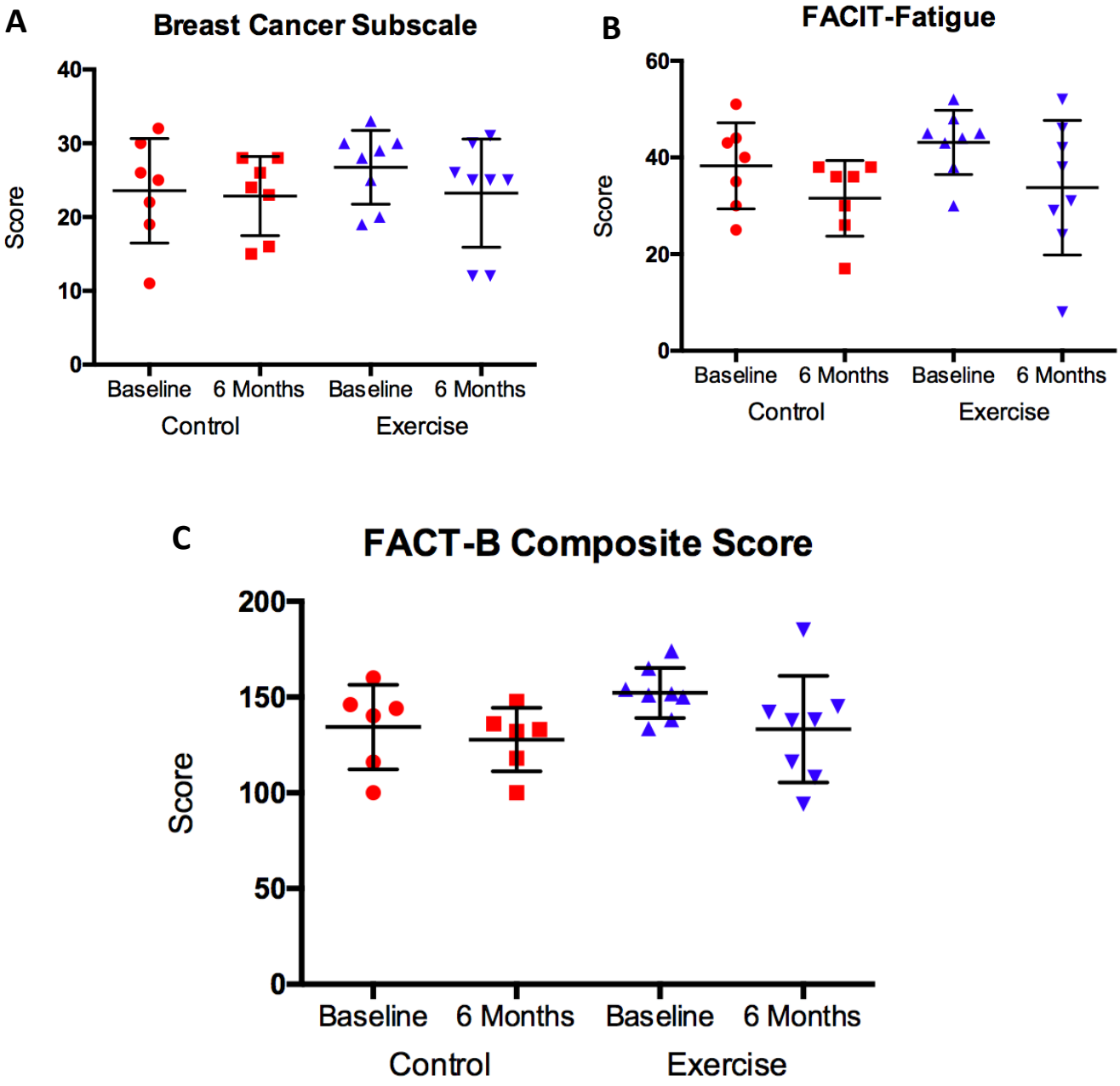
There were no significant differences between the control and exercise groups at baseline in the six quality of life subscales. Similarly, there were no significant differences between the two groups at the 6-month follow-up (Figure 22 and 23).

Figure 22: Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B) Subscale Results



Dots correspond to individual participant scores with higher scores being indicative of a better quality of life within the category. There was no significant difference between control (n = 7) and exercise (n=8) groups at baseline or 6-months in physical (A), social (B), emotional (C), and functional (D) well-being. Data shown are the average ± SD and analyzed by a one-way ANOVA ($p > 0.05$).

Figure 23: Breast Cancer, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Subscale, and FACT-B Composite Score Results



Dots correspond to individual participant scores with higher scores being indicative of less cancer therapy related fatigue. No significant differences in breast cancer subscale (A), fatigue subscale (B), and composite FACT-B scores were noted between control (n = 7) and exercise (n=8) groups at baseline and 6-months. Data shown are the average ± SD and analyzed by a one-way ANOVA ($p>0.05$).

Chapter 8: Discussion

Overall Summary

Cancer therapy related cardiac dysfunction remains a significant challenge in the breast cancer population. While pre-clinical models have shown that aerobic exercise within this setting is beneficial, there is a gap between basic science studies and the clinical world. As a first step toward bridging this divide, the EXACT 1.0 study investigated the benefits of a hospital-based exercise program within this patient population.[140] While they found the exercise program itself to be safe, the study suffered from low recruitment which prevented any conclusive results on the cardioprotective benefits of exercise in the breast cancer population.[140] The primary reason cited by women for preventing their participation in the study was the additional travel to the site of intervention.

In the current EXACT 2.0 study, we investigated the benefits of a 24-week home-based exercise program in women with early breast cancer. Our findings showed that our home-based exercise regimen was followed with a higher compliance. However, our data analyses did not show any significant differences in cardiovascular remodelling, VO2 max, nor quality of life measurements.

Exercise Adherence

Among some of the biggest challenges faced by exercise clinical trials is the adherence, or the lack thereof, of participants to the prescribed exercise regimen. In the PACES randomized clinical trial conducted by Waart et al. (2015), they investigated the effectiveness of two different forms of exercise interventions in cancer patients: i) a supervised moderate-intensity program; ii) and a lower intensity home-based program.[131] In the supervised program, approximately 48% of

participants met the target activity levels 75% of the time. [131] In comparison, 55% of participants in the home-based program met the target activity levels 75% of the time. In relation to the EXACT 2.0, 100% of our exercise group participants followed the prescribed exercise program 75% of the time. The difference in adherence between the PACES clinical trial and EXACT 2.0 can be attributed to the difference in study commitment. The home-based program in the PACES clinical trial called for 30 minutes a day for 5 days per week totalling at 150 minutes per week. In contrast, the EXACT 2.0 trial sessions ranged from 45 minutes to 85 minutes a week. Intensity of exercise sessions for the home-based groups were comparable for both studies.

In 2016, Cornette et al. investigated the benefits of a home-based program in breast cancer patients in improving peak oxygen consumption.[159] The program consisted of 2 aerobic exercise sessions and 1 resistance exercise session per week for 27 weeks. [159] The aerobic exercise sessions ranged from 20 to 40 minutes per session. The resistance sessions consisted of 2 sets working on one of five muscle groups (triceps, abdominal, glutes, hamstring, quadriceps) for 8-12 repetitions.[159] The study adherence was measured at an average of 88% for the complete program, with 109% average adherence to aerobic training targets and 46% average adherence to resistance training targets.[159] This study draws many parallels with our EXACT 2.0 study including the use of Polar HR monitors, weekly calls from study staff, and similar study duration and intensity. These similarities might play a role in a comparable exercise compliance between the two studies. However, there are two fundamental differences between the two studies. First, in the EXACT 2.0 study, if a participant completed more than the prescribed exercise sessions per week, they did not get a score above 100% adherence. However, in the Cornette et al. study, participants who went beyond the target duration for the week could get scores over 100% adherence which led to a range of

compliance of 9-202%, 0-96%, and 10-167% for the aerobic training component, resistance training component, and the whole program, respectively. If a similar data analysis had been implemented in the EXACT 2.0 study, average compliance within the study would have been higher as several exercise group participants completed more than the recommended sessions per week. Secondly, the EXACT 2.0 study did not have any prescribed resistance exercise sessions, although two participants did report adding routine strength training sessions to their 24-week aerobic program.

In a third study, Schmitz et al. (2019) conducted the Women in Steady Exercise Research (WISER) Survivor clinical trial investigating the benefits of home-based exercises in reducing lymphedema in breast cancer survivors.[160] The home-based program consisted of aerobic and resistance exercises over the course of 52 weeks.[160] Aerobic exercise consisted of a maximum of 180 minutes of walking per week.[160] Resistance exercise was performed twice weekly with each session consisting of 9 resistance exercises performed for 10 repetitions.[160] It was found that the 176 women randomized to the exercise group completed an average of 72% of the resistance exercises and 74% of the aerobic exercises.[160] Similar to the EXACT 2.0 study, the investigators conducted weekly check-ins with participants. However, a key difference in the patient demographic within the WISER Survivor group was that it only recruited women with a BMI over 25 that completed cancer therapy and had a previous history of breast cancer-related lymphedema. In comparison to the EXACT 2.0 study, the lower adherence seen within this study can be due to the longer duration (twice as long) as well as the increased number of exercise sessions per week.

Further, Ammitzboll et al. (2019) conducted Preventive Intervention against Lymphedema after Breast Cancer (LYCA) clinical trial, which also investigated the benefits of exercise in the setting of breast cancer therapy related lymphedema.[161] The progressive resistance training program consisted of two phases, with Phase 1 lasting 20 weeks and Phase 2 lasting 30 weeks.[161] In Phase 1, participants completed two supervised exercise programs at the study hospital and one exercise session at home per week.[161] In Phase 2, participants completed all three exercise sessions per week at home.[161] Each of the sessions involved 2-3 sets of 10-12 repetitions of an exercise targeting major muscle groups.[161] The weights used progressively got more challenging throughout the program, starting from a 25-repetition maximum load (the maximal weight that a woman could lift 25 times) to 12-repetition maximum load by the end of the program.[161] In a follow-up study by Ammitzboll et al. (2019), they analyzed the adherence statistics from this LYCA clinical trial.[162] They defined adherence as 'low to medium' if participants attended fewer than a 67% average of sessions per week and as 'high' if participants participated in more than 67% of the sessions.[162] It was shown that 73% of the 62 participants within the study had surpassed the high adherence threshold.[162] They conducted further analyses to determine any possible adherence differences between the supervised Phase 1 and home-based Phase 2 programs.[162] However, participants that were categorized as high adherence between Phase 1 and Phase 2 were comparable, at 57% and 56%, respectively.[162] Using this definition of 'high' adherence (completing greater than 67% of sessions) for the EXACT 2.0 study would lead to defining 100% of the exercise group participants within the high adherence category.

In our EXACT 2.0 study, exercise adherence was excellent with the 8 exercise group participants averaging a 92% adherance to the program. A higher exercise adherence to our program as

compared to other studies within the breast cancer population may be attributed to several different reasons. First, the home-based regimen may have led to a reduction in barriers that traditionally prevents exercise participation in women with breast cancer. This can include barriers such as lack of access to transportation to gyms, anxiety of acquiring infections from public gym spaces, and increased time spent commuting to the recreational facility. In the current COVID-19 era, some of these barriers may be heightened and highlights the important benefits of home-based exercises in cancer patients. Second, study staff contacted participants on a weekly to bi-weekly basis. This ensured that participants were engaged in the study and allowed opportunities to discuss any challenges in meeting exercise targets. Third, as compared to some of the other studies that have previously been conducted in this patient population, the EXACT 2.0 study has a shorter duration and a lower average intensity for each exercise session. As these women are often receiving multiple forms of cancer treatment, including chemotherapy, radiation, and surgery, the lower intensity and shorter durations may have been easier to follow. Finally, the Polar A370 Heart Rate wrist monitors, provided to all participants, may have encouraged more compliance to the program. The watch's ability to monitor heart rates and keep a log of the exercise sessions may have allowed for more participant engagement throughout the program. Additionally, the watch notified the participant with an alert stating 'Time to Move' if they have been sitting for an extended period of time which could have served as reminders to complete exercise sessions.

Cardiovascular Remodelling

To our understanding, there have not been any randomized control trials investigating the benefits of a home-based exercise program on cancer therapy related cardiac dysfunction (CTRCD) in women with breast cancer receiving anthracycline-based chemotherapy. As such, the EXACT 2.0 study stands as the first randomized control trial to investigate the benefits of an exclusively home-

based program in this clinical setting. However, outside of CTRCD, the potential benefits of exercise programs have been explored in other cardiac pathologies.

In a study by Wisloff et al. (2007), they investigated the benefits of exercise training in heart failure patients with reduced ejection fraction.[163] The researchers randomized participants into a moderate-intensity continuous training (MCT), high-intensity aerobic interval training (AIT), or control group.[163] The MCT group partook in uphill treadmill walking exercise at 70-75% of peak heart rate for 47 minutes per each exercise session.[163] The AIT group completed an exercise session walking at 90-95% of peak heart rate for 4 minutes interspersed with 3 minutes of walking at 50-70% of peak heart rate.[163] The AIT group walked for a total of 38 minutes per exercise session.[163] For both the MCT and AIT groups, they repeated their respective sessions three times a week for a total of 12 weeks.[163] In contrast, the control group participated in a 47-minute session at 70% of peak heart rate once every 3 weeks.[163]

The results of the study showed that the AIT group had significantly reduced LV cavity dilatation and preserved LV ejection fraction (LVEF) at follow-up as compared to the control participants.[163] Specifically in relation to LVEF, the AIT group showed a 10% increase at the end of the exercise program as compared to baseline values.[163] However, these improvements were not seen within the participants of the MCT group.[163] Hence, this study concluded that higher intensity interval training was superior to moderate continuous training in reversing LV remodelling.[163] In contrast to the Wisloff et al. study, the EXACT 2.0 study had four different heart rate zones throughout the study period which roughly ranged from 73% to 77% (Zone 1), 77-81% (Zone 2), 81-87% (Zone 3), and 87-94% (Zone 4) of peak heart rate in exercise intensity. Therefore, it can be postulated

the lack of benefits seen in cardiovascular remodelling within our patient population could be due to the majority of our exercises being performed at a lower intensity than necessary for inducing cardioprotection.

In a more recent study by Howden et al. (2019), they investigated the benefits of a combined aerobic and resistance exercise program in women with breast cancer receiving anthracyclines.[164] The exercise program consisted of three sessions per week, of which two were supervised and one was home-based.[164] Each of the supervised sessions consisted of 30 minutes of aerobic exercise and 30 minutes of resistance exercise.[164] The home-based session consisted of 30-60 minutes of aerobic exercise.[164] The study duration lasted as long as the individual patient's chemotherapy schedule so it was 8-weeks in length for 3 patients and 12-weeks in length for the other 11 participants.[164] Additionally, the program also varied in intensity throughout the course of chemotherapy, with a lowering of exercise intensity during treatment weeks to account for fatigue and increasing of intensity on non-treatment weeks.[164] The results of the study demonstrated that LVEF had a small but significant reduction throughout the course of chemotherapy within the usual-care group.[164] This LVEF reduction was also seen in the exercise group meaning that the exercise program was not able to reverse the cardiovascular remodelling.[164] The study further demonstrated exercise did not have any benefits on global longitudinal strain parameters (GLS) nor diastolic parameters.[164]

While the exercise programs within this study and EXACT 2.0 are different, they both did not see any changes in these echocardiographic parameters due to exercise. There are two potential reasons for this negative result. First, as the authors points out, this was a non-randomized study

where participants could choose to be placed in exercise or control groups. This led to a selection bias of younger women in the exercise group and women who were less fit and heavier within the control group.[164] This could have prevented significant results as often it is those who are not regularly active who are often most at-risk of developing CTRCD and have the most to benefit from enrolling in an exercise program.[165] Second, while the lowering of intensity during treatment weeks may have increased compliance, it may have decreased the efficacy of the exercise program. Particularly, for participants in the dose-dense 8-week chemotherapy schedule, four out of the eight weeks would have been completed at a lower intensity. Similar to the EXACT 2.0 study, the exercise programs being at a lower intensity for the majority of the program may not have been sufficient to acquire cardioprotective benefits.

As the effects of exercise training on cardiovascular remodelling is still not clear within this setting, further studies are warranted. To this extent, there are several trials which are currently active which hopes to better elucidate these benefits including ClinicalTrials.gov Identifiers NCT02842658, NCT03748550, NCT03850171, NCT03964142, and NCT02796365.[166]

Peak Oxygen Uptake

While the results of the estimated VO2 max showed no significant difference between control and exercise groups, there was a trend of an increased VO2 max within the exercise group at 6-month follow-up. With a larger sample size, this difference maybe shown to be statistically significant as found in other exercise programs within this patient population.[164]Additionally, it is important to note that in our EXACT 2.0 study, the VO2 max was determined using predictive equations based on time spent on treadmill following the Bruce Protocol. Ideally, VO2 max should be determined

through a cardiopulmonary exercise test (CPET) but due to a lack of resources to administer this test, we used the aforementioned formula to predict VO2 max.

In a large study by Klassen et al. (2014) with 222 breast cancer patients, it has been shown that VO2 max is significantly reduced during as well as after chemotherapy.[167]In order to see whether exercise training may be able to alleviate these declines in VO2 Max, a study by Giallauria et al., investigated the benefits of a 12-month moderate-intensity exercise program in breast cancer patients.[168] The exercise program consisted of three 30-minute sessions of cycling or running per week for 3-months at 60-70% of baseline VO2 max.[168] For the following 9 months, sessions were reduced to once per week at the same intensity.[168] It was found that this training program led to a significant increase in VO2 max within participants.[168] Again, while EXACT 2.0 showed a similar trend in increase of VO2 max with exercise, it was not statistically significant. This could be potentially due to the shorter duration of the EXACT 2.0 exercise program (24 weeks) as compared to the 52-week program in the Giallauria et al. study.[168]

In another clinical trial by Howden and colleagues, they investigated the changes to VO2 max through the use of a combined resistance and aerobic exercises in BC patients prescribed AC-based therapy.[164] They found that there was a larger proportion of the usual-care group participants that met the criteria for functional disability, defined as VO2 max lower than 18 mL/mg/min, after AC therapy.[164] While not significant, the EXACT 2.0 study also found that the only participant that met the functional disability criteria at follow-up belonged to the control group.

Quality of Life Measurements

While the Functional Assessment of Cancer Therapy - Breast (FACT-B) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) analyses showed no differences between the control and home based AEX groups in the current EXACT 2.0 study, it is important to address some of confounding variables which may have affected the results. With the COVID-19 pandemic, many of the participants in both control and exercise groups reported pandemic-related changes affected their survey answers. This might cause challenges particularly in the analysis of data from participants who completed their baseline appointments between December 2019 to March 2020 (pre-pandemic) and completed follow-up appointments during July-August 2020 (pandemic). Of note, participants reported the functional well-being subscale being the most affected by pandemic as it included the rating of statements like "I am able to work" and "I am enjoying the things I usually do for fun". This may be one potential reason the results of the EXACT 2.0 study does not corroborate other studies in the field which have investigated the role of exercise training in breast cancer patients.

In a study by Dieli-Conwright et al. (2018), they investigated the benefits of a supervised aerobic and resistance exercise program.[169] The exercise program consisted of two 80-minute sessions with one 50-minute aerobic exercise session per week for 16 weeks.[169] It was shown this exercise program led to significant improvements in the five FACT-B subscale scores as well as the composite FACT-B score at the post-intervention follow-up compared to the usual group.[169] Interestingly, these improvements were also seen at a 3-month follow-up point, meaning the benefits were apparent even during the course of chemotherapy.[169]

Another study by Murtezani et al. (2014) examined the effects of a moderate-intensity aerobic exercise program on quality-of-life parameters as assessed by the FACT-B scales in breast cancer survivors.[170] The exercise program consisted of three sessions per week for 10 weeks.[170] Each session ranged from 25 to 45 minutes in length and 50 to 75% HRR intensity.[170] It was found that this program was able to significantly improve the composite FACT-B score as well as the functional well-being subscale.[170]

Limitations and Future Directions

There are some limitations presented by the current EXACT 2.0 study which are important to note. First, the sample size of 15 participants within the study were not sufficient to reach the appropriate statistical power of 80% (alpha = 0.05). In order to show a significant difference in LVEF and GLS, a total of nearly 100 participants are required for the study. As such, accounting for study attrition, the original goal of the study was to recruit 100 participants into the study between the two recruitment sites (Winnipeg, MB and Halifax, NS). However, this recruitment target was unattainable due to COVID-19-related delays. While our Winnipeg site was able to enroll the 18 participants into the study, our sister site in Halifax was unable to enroll any participants.

Second, as seen by the average exercise durations of both the control and exercise participants, it can be seen there was only a difference of 33 minutes per week of activity between the groups. This could have served as a potential reason for the lack of differences seen in the outcomes measured as the activity level of the exercise group was not much more than that of the usual care group. However, this may be an inherent challenge with exercise studies which attract individuals who are more motivated to be physically active. Nonetheless, for future studies, it would be

important to understand the baseline levels of activity in average cancer patients to prescribe a more appropriate exercise intervention.

Third, some exercise studies have shown that higher intensity aerobic workouts are more beneficial compared to lower intensity sessions.[131] Hence, the benefits in this study may only become evident if the participants were participating in a more strenuous exercise program. However, it is important to consider that this may lead to a lower adherence by breast cancer patients who might find a higher intensity program too challenging to follow during cancer therapy.

Finally, the EXACT 2.0 study was exclusively an aerobic exercise program and did not include any resistance training components. According to the guidelines by American College of Sports Medicine, in addition to aerobic exercise, it is recommended that cancer patients complete two strength training exercises per week that target all the major muscle groups.[171] As such, similar to some of the aforementioned exercise studies, adding a resistance training component may provide a more holistic training program that can lead to enhanced cardioprotective effects.

Conclusion

The EXACT 2.0 study demonstrates that a 24-week home-based aerobic exercise program is safe and can be followed with a high degree of compliance in women with early breast cancer receiving anthracycline-based chemotherapy. However, participating in the exercise program did not improve cardiovascular mechanics, cardiorespiratory fitness nor quality of life parameters. Future randomized control trials with a larger sample size may be required to show statistically significant differences.

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