EXERCISE CARDIO-PROTECTION FROM CHEMOTHERAPY FOR BREAST CANCER

by

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Abstract

One in nine women in Canada will be diagnosed with breast cancer during their lifetime, yet 88% will live for at least five years after diagnosis. Cardiovascular disease has become the most common cause of death of older breast cancer survivors, and breast cancer survivors are more likely to die of cardiovascular disease than women who have not had breast cancer. One of the contributing factors to the increased cardiovascular morbidity and mortality is anthracycline chemotherapy-related cardiotoxicity, or damage to the myocardium. The need for balance of oncological efficacy with cardiotoxicity of anthracycline chemotherapy has driven the active investigation of cardio-protective strategies. Exercise, an accessible and inexpensive intervention with numerous other health benefits, has demonstrated efficacy for attenuating cardiotoxicity in numerous preclinical (i.e. animal model) studies; a finding yet to be confirmed by clinical research. This dissertation investigated the potential for exercise cardio-protection from anthracycline chemotherapy in women diagnosed with breast cancer in three studies. The primary findings are: 1) during anthracycline treatment, adherence to supervised exercise training following the guidelines for cancer survivors varies widely; 2) the primary reason for withdrawal, missed exercise sessions, and non-adherence to prescribed intensity and/or duration was treatment-related symptoms; 3) despite low and variable adherence, women who enrolled in an exercise training program during anthracycline chemotherapy for breast cancer did not experience a clinically relevant deterioration of echocardiography-derived systolic global longitudinal strain or strain rate, which are both established predictive markers of cardiotoxicity; 4) global longitudinal strain has excellent intra-observer reliability and is consistently measurable in breast cancer patients, making it an excellent option for an outcome measure to assess cardio-protection; 5)
performance of a single vigorous intensity aerobic exercise bout performed 24 hours prior to anthracycline treatment attenuates the acute NT-proBNP myocardial injury marker response to the first treatment, and alters hemodynamic regulation and cardiac structure after completion of treatment, but has no effect on longitudinal strain or strain rate or treatment symptoms. Overall this dissertation provides proof-of-principal for exercise cardio-protection, and contributes novel findings regarding exercise prescription and outcome measure assessment for future exercise cardio-protection studies during anthracycline treatment for breast cancer.
**Preface**

Design and implementation of the research projects are my original work in consultation with my committee members, K. Campbell, D. McKenzie, N. Eves, and K. Gelmon.

Portions of Chapter 2 text and Table 2.1 have been previously published with M. Davis as a co-author, where I performed the writing and Dr. Davis provided oversight on concept and revisions: Kirkham AA & Davis MK. Exercise prevention of cardiovascular disease in breast cancer survivors. Journal of Oncology 2015:Article ID 917606.

The exercise training program in Chapter 3 and 4 was a part of a larger parent study, of which K. Campbell and C. Van Patten were the principal investigators. I was a co-investigator in this study and the primary graduate student involved. A number of paid staff and volunteers helped with implementation of the exercise program and collection of the adherence data, but I conceived of, and designed the exercise prescription and data collection methods to capture data relevant to the exercise prescription, as well as trained all involved individuals in delivery of the exercise prescription and related data collection. I developed the study concepts and designs for Chapter 3 and 4. I performed the data collection for the sub-study visits in Chapter 3 and 4. The British Columbia Cancer Agency Research Ethics Board approved these studies (Implementation of physician-referred exercise and healthy eating intervention as supportive care in breast cancer survivors; certificate number, H12-02504).

The study in Chapter 5 was conceived of, designed and implemented by myself. The University of British Columbia Clinical Research Ethics Board approved this study (The
effects of exercise before doxorubicin chemotherapy on cardiac function; certificate number, H13-03090).

A certified sonographer was paid to perform the echocardiography in Chapters 4 and 5, and a nurse was paid to perform the venipunctures for Chapter 5. I was trained in recognizing the echocardiography images and actively participated in the collection of images. I was also responsible for processing and storing some of the blood samples in Chapter 5. A clinical laboratory analyzed the blood samples in Chapter 5. I performed all echocardiographic image analysis and statistical data analysis for all projects.
Table of contents

Abstract.............................................................................................................................................. ii
Preface ................................................................................................................................................ iv
Table of contents .............................................................................................................................. vi
List of tables ....................................................................................................................................... vii
List of figures ..................................................................................................................................... viii
List of abbreviations ......................................................................................................................... xi
Acknowledgements .......................................................................................................................... xv

Chapter 1: Introduction ..................................................................................................................... 1

Chapter 2: Literature review ............................................................................................................. 7
  2.1 Chemotherapy cytotoxic mechanisms ...................................................................................... 7
  2.2 Anthracycline -induced cardiotoxicity .................................................................................... 8
    2.2.1 Characteristics .................................................................................................................. 8
    2.2.2 Risk factors ..................................................................................................................... 9
    2.2.3 Incidence ......................................................................................................................... 9
    2.2.4 Combination therapy ....................................................................................................... 11
    2.2.5 Mechanisms ................................................................................................................... 12
  2.3 Prevention and treatment of cardiotoxicity .......................................................................... 15
    2.3.1 Delivery and pharmacology .......................................................................................... 15
    2.3.2 Exercise ........................................................................................................................ 17
    2.3.3 Potential mechanisms for exercise cardio-protection from anthracyclines .................... 17
    2.3.4 Evidence for exercise cardio-protection from anthracyclines and/or breast cancer treatment ...................................................................................................................... 21
  2.4 Translation of preclinical exercise cardio-protection findings to clinical studies ............. 26
    2.4.1 Exercise intervention design ........................................................................................ 27
    2.4.2 Outcome measures ......................................................................................................... 31
  2.5 Chapter 2 tables ....................................................................................................................... 58

Chapter 3: Adherence and effectiveness of the recommended exercise prescription during anthracycline chemotherapy for breast cancer .............................................. 85
  3.1 Introduction ............................................................................................................................. 85
  3.2 Methods ................................................................................................................................... 89
    3.2.1 Ethics .............................................................................................................................. 89
    3.2.2 Design and participants ............................................................................................... 89
    3.2.3 Intervention ................................................................................................................... 91
    3.2.4 Outcome measures ........................................................................................................ 93
    3.2.5 Statistical analyses ......................................................................................................... 97
  3.3 Results ..................................................................................................................................... 98
    3.3.1 Recruitment and participants ...................................................................................... 98
    3.3.2 Exercise program adherence ....................................................................................... 99
  3.4 Discussion ............................................................................................................................... 104
    3.4.1 Adherence to prescribed frequency .......................................................................... 105
    3.4.2 Adherence to prescribed intensity and duration ........................................................ 107
    3.4.3 Prescription adjustments ............................................................................................. 111
Chapter 4 - Responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy for breast cancer ................................................................. 128

4.1 Introduction .................................................................................................................. 128
4.2 Methods ....................................................................................................................... 131
  4.2.1 Participants .............................................................................................................. 131
  4.2.2 Intervention ........................................................................................................... 131
  4.2.3 Outcome measures ............................................................................................... 132
  4.2.4 Statistical analysis ................................................................................................. 138
4.3 Results .......................................................................................................................... 140
  4.3.1 Recruitment and withdrawal ............................................................................... 140
  4.3.2 Participants ............................................................................................................ 141
  4.3.3 Descriptive variables ......................................................................................... 141
  4.3.4 Exercise adherence ............................................................................................ 142
  4.3.5 Myocardial mechanics reliability ..................................................................... 142
  4.3.6 Myocardial mechanics response to exercise training ........................................... 143
  4.3.7 Clinical and other echocardiographic parameters of cardiac function ............... 143
  4.3.8 GLS and exercise dose ....................................................................................... 144
  4.3.9 GLS and VO\textsubscript{2}peak ................................................................................ 144
4.4 Discussion ...................................................................................................................... 144

4.5 Conclusion .................................................................................................................... 153
4.6 Chapter 4 tables .......................................................................................................... 155

Chapter 5 - The effects of a single exercise bout 24 hours prior to anthracycline chemotherapy for breast cancer on myocardial mechanics and cardiac biomarkers ................................................................................. 161

5.1 Introduction .................................................................................................................... 161
5.2 Methods ....................................................................................................................... 163
  5.2.1 Design and participants ....................................................................................... 163
  5.2.2 Intervention ........................................................................................................ 166
  5.2.3 Outcome measures ............................................................................................ 167
  5.2.4 Statistical analyses ............................................................................................ 171
5.3 Results .......................................................................................................................... 174
  5.3.1 Recruitment ........................................................................................................... 174
  5.3.2 Participants .......................................................................................................... 175
  5.3.3 Exercise ................................................................................................................ 175
  5.3.4 Resting heart rate and blood pressures – 24 hours .............................................. 177
  5.3.5 LV Volumes – 24 hours ....................................................................................... 177
  5.3.6 LV dimensions and wall thicknesses – 24 hours ................................................. 177
  5.3.7 LV diastolic function – 24 hours ....................................................................... 178
  5.3.8 LV myocardial mechanics – 24 hours ................................................................ 178
  5.3.9 Cardiac biomarkers – 24 hours .......................................................................... 178
  5.3.10 Resting heart rate and blood pressures – post AC ........................................... 179
  5.3.11 LV volumes – post AC .................................................................................... 179
  5.3.12 LV dimensions and wall thicknesses – post AC .............................................. 180
5.3.13 LV diastolic function – post AC ................................................................. 181
5.3.14 LV myocardial mechanics – post AC ......................................................... 181
5.3.15 Cardiac biomarkers – post AC ................................................................. 181
5.3.16 Patient-reported symptoms ...................................................................... 182

5.4 Discussion ..................................................................................................... 182
5.4.1 24 hours after first AC treatment .............................................................. 183
5.4.2 Post last AC treatment .............................................................................. 186
5.4.3 Timing of exercise ..................................................................................... 190
5.4.4 Strengths, limitations, and considerations .............................................. 191

5.5 Conclusion .................................................................................................... 192
5.6 Chapter 5 tables and figures ........................................................................ 194

Chapter 6 - Conclusion ..................................................................................... 204

6.1 Adherence and effectiveness of the recommended exercise prescription during anthracycline chemotherapy for breast cancer (Chapter 3) ........................................ 204
6.2 Responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy for breast cancer (Chapter 4) ........................................ 207
6.3 The effects of a single exercise bout 24 hours prior to anthracycline chemotherapy for breast cancer on myocardial mechanics and cardiac biomarkers (Chapter 5) .... 210
6.4 Overall .......................................................................................................... 216
   6.4.1 Strengths and limitations ....................................................................... 216
   6.4.2 Significance ............................................................................................. 218
   6.4.3 Conclusion ............................................................................................. 219

References ........................................................................................................... 221
List of tables

Table 2.1: Evidence for potential mechanisms for exercise cardio-protection from doxorubicin ................................................................................................................................. 57

Table 2.2: Studies investigating the role of aerobic exercise cardio-protection from doxorubicin .................................................................................................................................. 60

Table 2.3: Studies measuring myocardial mechanics in breast cancer before and after anthracycline treatment .................................................................................................. 66

Table 2.4: Studies measuring myocardial mechanics in non-breast or mixed cancer before and after anthracycline treatment ............................................................................................. 70

Table 2.5: Prognostic associations with cardiac mechanic parameters ................................................................................................................................. 76

Table 2.6: Studies measuring cardiac biomarker responses to anthracycline treatment .......... 79

Table 2.7: Summary of studies implementing a supervised, aerobic exercise intervention during chemotherapy treatment for breast cancer ............................................................................. 83

Table 3.1: Aerobic exercise prescription ............................................................................................... 119

Table 3.2: Study participant demographics and cancer diagnosis and treatment characteristics. ........................................................................................................................................ 120

Table 3.3: Baseline physical variables .................................................................................................. 121

Table 3.4: Mean adherence to frequency, intensity, and duration, and required intensity adjustments across participants .................................................................................................. 121

Table 3.5: Reasons for missed supervised sessions and non-adherence to prescription ........... 122

Table 3.6: Exercise test and hematological data .................................................................................. 123

Table 4.1: Physical activity and weight changes (n=22) .................................................................. 155

Table 4.2: Supervised exercise adherence data (n=22) ................................................................... 155
Table 4.3: Intra-class correlation and coefficient of variation for intra-observer reliability of myocardial mechanics in women with breast cancer ................................................................. 156

Table 4.4: Myocardial mechanics data ................................................................................. 156

Table 4.5: Clinical and traditional echocardiographic data (n=22) ....................................... 157

Table 5.1: Study participant demographics and cancer diagnosis and treatment characteristics. ................................................................................................................................. 194

Table 5.2: Body size and physical activity ............................................................................. 195

Table 5.3: Resting heart rate and blood pressure ................................................................... 196

Table 5.4: Standard LV volumetric and diastolic measures .................................................. 197

Table 5.5: LV dimensions and wall thicknesses and serum biomarkers ............................... 198

Table 5.6: Myocardial mechanics ......................................................................................... 199
List of figures

Figure 3.1: Study design and recruitment flow through study .......................................................... 124
Figure 3.2: Flow through the study .................................................................................................. 125
Figure 3.3: Adherence to prescribed intensity (A) and duration (B) by each week of the
prescription; with prescription displayed by bars and secondary axes ............................................ 126
Figure 3.4: Attendance and adherence to intensity and/or duration prescription as a
percentage of total prescribed sessions, divided by treatment cycle .............................................. 127
Figure 4.1: Representative examples of strain rate (A) and strain (B) curves where the 2D
Strain Analysis Tool chose X as the peak value, and the operator adjusted the peak value to
the checkmark. X-axis is duration of aortic valve opening ............................................................. 158
Figure 4.2: Individual changes in myocardial mechanics ................................................................. 159
Figure 4.3: Relationship between percent change in GLS and various measures of exercise
dose .................................................................................................................................................. 160
Figure 5.1: Participant flow through study ......................................................................................... 201
Figure 5.2: Mean change from baseline to 24 hours for both groups in end-diastolic volume,
cardiac output, stroke volume, heart rate, mean arterial pressure and NT-proBNP ...................... 202
Figure 5.3: Mean change from baseline to post AC treatment for both groups in end-diastolic
volume, cardiac output, stroke volume, heart rate, mean arterial pressure and cardiac troponin T ....................................................................................................................................... 203
List of abbreviations

2D = two-dimensional

2DSTE = two-dimensional speckle tracking echocardiography

ACTG = chemotherapy protocol involving concurrent doxorubicin and cyclophosphamide, before or after paclitaxel, administered on a dose-dense schedule

ACT = chemotherapy protocol involving concurrent doxorubicin and cyclophosphamide, before or after paclitaxel

AC = referring to the concurrent doxorubicin and cyclophosphamide aspect of chemotherapy only

BCCA = British Columbia Cancer Agency

BNP = B-type natriuretic peptide

CO = cardiac output

CSR = circumferential strain rate

cTnI = cardiac troponin I

cTnT = cardiac troponin T

CV = coefficient of variation

DT = deceleration time

DC = docetaxel and cyclophosphamide chemotherapy protocol

ECG = electrocardiography

GCS = global circumferential strain

GLS = global longitudinal strain

GRS = global radial strain

HDL = high-density lipoprotein
HER2 = human epidermal growth factor receptor 2
HR = hazard ratio
HSP = heat shock protein
ICC = intra-class correlation
IVRT = isovolumic relaxation time
kg = kilogram
LDL = low density lipoprotein
LSR = longitudinal strain rate
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
m = meter
MET = metabolic equivalent
mg = milligrams
MHC = myosin heavy chain
MVPA = moderate to vigorous intensity physical activity
ml = milliliter
NO = nitric oxide
NT-proBNP = the amino-terminal fragment precursor of B-type natriuretic peptide
OR = odds ratio
PGC-1α = peroxisome proliferator-activated receptor-γ coactivator
RCT = randomized controlled trial
ROS = reactive oxygen species
RSR = radial strain rate
SERCA2a = sarcoplasmic reticulum Ca\(^{2+}\) ATPase 2a

SV = stroke volume

TDI = tissue Doppler imaging

VO\(_{2}\)peak = peak oxygen consumption

\(\mu g\) = micrograms
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Chapter 1: Introduction

Breast cancer is the most frequently diagnosed cancer in Canadian women, accounting for 26% of newly diagnosed cancers, and 14% of deaths due to cancer each year.\textsuperscript{1} One in nine women in Canada will be diagnosed with breast cancer during their lifetime,\textsuperscript{2} yet 88% will live for at least five years after diagnosis,\textsuperscript{3} many for much longer. The breast cancer mortality rate has decreased by 40% since its peak in 1986 at 32.5 per 100,000.\textsuperscript{1} This decrease is attributed to increased mammography screening to detect cancer at an earlier stage, and use of more effective adjuvant therapies.\textsuperscript{1} Treatment for breast cancer is commonly multi-modal and may consist of some or all of the following: surgery, and radiotherapy to control local recurrence, and systemic therapies with chemotherapy, targeted therapies, or endocrine therapy directed at controlling distant disease. Successful treatment provides a benefit regardless of recurrence risk, and this benefit is long lasting, as a further reduction in the risk of recurrence occurs each year in the 10 years following completion of treatment.\textsuperscript{4} It follows that with an increase in treatment efficacy, new competing risks for morbidity and mortality will be realized in women who have completed treatment for breast cancer, termed breast cancer survivor in this dissertation. The term breast cancer patient will be used in this dissertation to describe women who are currently receiving chemotherapy or radiation treatment for breast cancer.

Cardiovascular disease is the only cause of death claiming the lives of more Canadian women than cancer.\textsuperscript{5} Breast cancer, in particular, and cardiovascular disease appear to be linked, as breast cancer survivors are at elevated risk of cardiovascular disease,\textsuperscript{6} and are more likely to die of cardiovascular disease than women who have not had breast cancer.\textsuperscript{7} It was recently recognized that cardiovascular disease has marginally surpassed breast cancer as the
most common cause of death of older breast cancer survivors.\textsuperscript{8} There are a number of direct and indirect proposed contributing factors to the elevated risk of cardiovascular disease morbidity and mortality amongst breast cancer survivors. Firstly, at the time of a breast cancer diagnosis, 13\% of these women who are over the age of 65 already have cardiovascular disease,\textsuperscript{8} and 93\% of women over age 55 years diagnosed with breast cancer have at least one comorbid condition.\textsuperscript{9} Secondly, a reduction in physical activity, and an increase in body weight and waist circumference are known to be common following breast cancer treatment,\textsuperscript{10-12} and are also significant independent risk factors for cardiovascular disease.\textsuperscript{13-15} Thirdly, peak oxygen consumption, a strong independent predictor of presence of cardiovascular disease risk factors,\textsuperscript{16} and future cardiac events in individuals with and without previous history of cardiovascular disease,\textsuperscript{17} is also known to decrease with breast cancer treatment and remain lower than healthy sedentary controls following treatment.\textsuperscript{18,19} Fourthly, chemotherapy for breast cancer will induce menopause early in up to one-half of women,\textsuperscript{20} and the occurrence of menopause is a determinant of the increased risk of cardiovascular disease in women with age.\textsuperscript{21} Fifthly, the increased life expectancy due to increased effectiveness of anticancer therapy increases breast cancer survivors’ risk of cardiovascular disease independent of breast cancer treatment.\textsuperscript{22} The final potential reason for the increased risk of cardiovascular disease morbidity and mortality amongst breast cancer survivors is the direct adverse effects of chemotherapy, radiotherapy (especially left-sided), and targeted therapy for breast cancer on the cardiovascular system.\textsuperscript{23} Further, risk for cardiotoxicity may be increased in certain individuals due to pharmacogenetics.\textsuperscript{24}

Chemotherapy as a single breast cancer treatment modality is estimated to reduce the breast cancer mortality rate by 36\%.\textsuperscript{25} Unfortunately it is associated with numerous short and
long-term side effects including hair loss, fatigue, nausea, vomiting, myelosuppression, weight gain, emotional problems, and cardiotoxicity. Cardiotoxicity, generally defined as damage to the myocardium, is a classically described complication of a specific class of breast cancer chemotherapeutic agents referred to as anthracyclines, and is the focus of this dissertation.

Anthracyclines emerged as a novel antineoplastic agent in the 1960s, and since the 1980s, the anthracycline agents, doxorubicin and epirubicin, have been included in the primary class of combination regimens for treatment of early and advanced breast cancer. Anthracyclines are among the most effective and toxic treatments ever developed for breast cancer. For the purposes of this document, the term anthracyclines will be used to refer to the general class of drugs, or when multiple different anthracycline agents are used within a study. When the specific anthracycline agent name (e.g. doxorubicin or epirubicin) is used, the statement can be attributed directly to that agent.

Current polychemotherapy treatment protocols for early and locally advanced breast cancer in British Columbia typically consist of cyclophosphamide, and a taxane agent, with or without an anthracycline agent. Cyclophosphamide is used in polychemotherapy protocols for breast cancer, especially in combination with anthracyclines. The taxanes, paclitaxel and docetaxel, are very commonly used to treat breast cancer in British Columbia. Taxane-containing protocols offer improved overall survival and disease free survival in early breast cancer compared with non-taxane chemotherapy regimes.

Currently, the two most common protocols given at the Vancouver Centre of the British Columbia Cancer Agency (BCCA) include doxorubicin combined with cyclophosphamide followed by paclitaxel (ACT), or docetaxel combined with
cyclophosphamide (DC). ACT is typically administered as four treatment cycles of 60 mg/m\(^2\) of doxorubicin and 600 mg/m\(^2\) of cyclophosphamide, followed by four treatment cycles of 175 mg/m\(^2\) of paclitaxel, each three weeks apart, or in a dose-dense schedule with a granulocyte colony-stimulating factor, two weeks apart (ACTG).\(^{33}\) Trastuzumab is added to the paclitaxel dosing every one or three weeks for human epidermal growth factor receptor 2 (HER2) positive tumors. The protocols and doses used at the BCCA are the same whether given before (neoadjuvant) or after (adjuvant) surgery, with the exception of ACTG chemotherapy given for HER2-negative tumors in the neoadjuvant setting, which is administered in two week cycles starting with the four treatment cycles of paclitaxel, followed by four treatment cycles of doxorubicin and cyclophosphamide since November 1, 2014.\(^{34}\)

The use of anthracycline-containing chemotherapy for breast cancer results in morbidity and mortality associated with cardiotoxicity, and in turn, can reduce the ability of patients to receive the optimal treatment, resulting in morbidity and mortality from their malignancy.\(^{35}\) The balance of oncological efficacy with cardiotoxicity of anthracycline chemotherapy for breast cancer patients has driven the active investigation into cardio-protective strategies that would allow for the continued used of anthracycline treatment. Modifications of drug administration and pharmacological intervention have been the primary strategies investigated. However, exercise, an accessible and inexpensive intervention with numerous other health benefits, has demonstrated efficacy for attenuating cardiotoxicity in numerous preclinical (i.e. involving animal models) studies. These preclinical findings have yet to be confirmed by clinical research.
The theme of this dissertation is to investigate the potential for exercise cardio-protection from anthracycline-containing chemotherapy in human breast cancer patients. Chapter 2 of this dissertation is a thorough literature review of anthracycline-related cardiotoxicity, prevention and treatment of cardiotoxicity including available evidence for the potential of exercise cardio-protection, and requirements for translation of the preclinical exercise cardio-protection findings to clinical studies.

The studies in Chapters 3 to 5 take place across the duration of chemotherapy treatment with doxorubicin concurrent with cyclophosphamide (AC). Most study participants will have received the four AC treatments either before or after paclitaxel as described above, but this is not included in the timeline of the studies. In the first research chapter, adherence and effectiveness of an exercise program with an exercise prescription consistent with cancer-specific exercise guidelines will be assessed during AC treatment for breast cancer. In particular, the components of adherence assessed include adherence to the prescribed frequency, intensity, and duration, as well as retention of participants. The effectiveness of the exercise program will be assessed by change in peak oxygen consumption between the pre-AC baseline and post-AC follow-up. It was hypothesized that implementation of an exercise program consistent with the recommended exercise guidelines for cancer survivors would result in ≥70% adherence to frequency, ≥80% adherence to intensity and duration, and ≥80% retention of participants; and the typical decline in peak oxygen consumption observed with AC treatment will be attenuated by better adherence.

In Chapter 4, a promising outcome measure for noninvasively investigating exercise cardio-protection in humans, echocardiography-derived myocardial mechanics, will be
assessed for responsiveness to exercise training in breast cancer patients receiving AC treatment. The responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy will be assessed by the percent change from pre to post AC treatment. The primary hypothesis is that there will be no clinically relevant change in global longitudinal strain with exercise training during AC treatment.

Chapter 5, the third and final research chapter, is a translational research study based on two preclinical studies demonstrating cardio-protection with a single exercise session 24 hours prior to AC treatment. This randomized controlled trial (RCT) utilizes myocardial mechanics, the outcome investigated in chapter 4, and cardiac biomarkers to determine whether a single exercise session protects the heart when performed 24 hours prior to the first AC treatment relative to no exercise (primary aim), and attempts to extend this finding to performance of the single exercise session 24 hours prior to each AC treatment (secondary aim). As an exploratory aim, this study compares the effect of the single exercise session relative to no exercise prior to each treatment on patient-reported symptoms. It is hypothesized that the exercise sessions 24 hours prior to AC treatment will attenuate the negative response in myocardial mechanics and cardiac biomarkers, and reduce patient-reported symptoms relative to the non-exercise control group.

Lastly, the final dissertation chapter will summarize and describe the overall contribution to the field, comment on the significance, strengths and limitations of the work, and discuss potential applications and future research directions.
Chapter 2: Literature review

2.1 Chemotherapy cytotoxic mechanisms

The individual chemotherapeutic agents in the ACT protocol that is commonly used to treat breast cancer exert their cytotoxicity via different mechanisms. The cytotoxicity of anthracyclines stems from generation of free radicals, typically reactive oxygen species (ROS). Specifically, the quinone chemical structure of anthracyclines allows them to accept electrons in oxo-reductive reactions, resulting in a semiquinone free radical intermediate, which rapidly reoxidizes via electron acceptors like oxygen, thereby generating the superoxide anion free radical, or with further reductions to hydrogen peroxide and the presence of iron catalyst, the highly reactive hydroxyl free radical. Anthracycline-mediated generation of free radicals results in degradation of DNA, but this may only occur at higher supraclinical concentrations of anthracyclines, whereas at lower, more clinically relevant concentrations of anthracyclines, DNA degradation and subsequent apoptosis appear to be associated with inhibition of topoisomerase II, a critical enzyme for DNA unwinding for replication and synthesis.

Cyclophosphamide is a non-hormonal chemotherapy agent classified as a nitrogen mustard alkylating agent. Cyclophosphamide is activated by hydroxylation in the liver to a 4-hydroxycyclophosphamide metabolite, which quickly equilibrates with its tautomer aldophosphamide. Aldophosphamide and 4-hydroxycyclophosphamide enter cells readily, and aldophosphamide spontaneously produces phosphoramid mustard, a reactive alkylating agent. The primary antineoplastic mechanism for nitrogen mustards like phosphoramid mustard, is induction of interstrand cross-linking of DNA, which prevents DNA replication and promotes cell death.
Taxanes exert their cytotoxic effects by inhibiting microtubule dynamics, a key feature to microtubule functions including morphogenesis, migration, intracellular transport and cell division.\textsuperscript{39} During mitosis, taxanes stabilize the microtubules, inhibiting disassembly, the completion of metaphase, and progression of mitosis. Mitosis may then be permanently blocked, thus activating the mitotic checkpoint and induction of apoptosis, or the checkpoint may be overridden and an aberrant mitotic exit into G1 cell phase with multiple nuclei occurs, whereby apoptosis is then induced by a DNA damage checkpoint.\textsuperscript{39} The taxane agents, paclitaxel and docetaxel, are very similar in mechanism of action and clinical activity.\textsuperscript{40}

2.2 Anthracycline -induced cardiotoxicity

2.2.1 Characteristics

Although anthracycline-containing regimens have a higher antitumor effectiveness than other chemotherapeutic substances, they are significantly more cardiotoxic.\textsuperscript{41} Anthracyclines are associated with dose-dependent, cumulative, progressive cardiac dysfunction, that can manifest subclinically, increasing susceptibility to progressive dysfunction associated with aging, infections and other diseases, or overtly as congestive heart failure.\textsuperscript{23,27,42} Acute manifestations of anthracycline-induced cardiotoxicity may present as myocardial electrical rhythm disturbances,\textsuperscript{43,44} elevated cardiac biomarkers,\textsuperscript{45} or depressed myocardial mechanics.\textsuperscript{46} In rare instances, more serious cardiac issues such as pericarditis, myocarditis or even myocardial infarction can occur acutely.\textsuperscript{43} Early-onset of cardiotoxicity in the first year after treatment can present as a chronic progressive dilated cardiomyopathy, whereas asymptomatic diastolic and systolic dysfunction, cardiomyopathy and arrhythmias have been reported to occur in late-onset cardiotoxicity, years to decades after treatment.\textsuperscript{43} With adequate monitoring, the median time of onset of asymptomatic cardiotoxicity in breast
cancer patients receiving low to moderate doses of anthracyclines has been reported as one to 3.5 months, and the range of onset including during treatment to three years later; yet up to 98% of cases may occur within the first year after completion of treatment.\textsuperscript{47,48}

### 2.2.2 Risk factors

The incidence of cardiotoxicity increases exponentially over a cumulative dosage of 500 mg/m\(^2\) of doxorubicin and 950 mg/m\(^2\) of epirubicin, and is higher amongst those with preexisting risk factors such as valvular, coronary or myocardial heart disease, and a longstanding history of hypertension, even at doses under 500 mg/m\(^2\).\textsuperscript{49} Other reported risk factors include female gender, older age, black race, chromosomal abnormalities, liver disease, mediastinal radiation, and combination therapy with other pharmacological agents.\textsuperscript{43} A retrospective cohort study of over 43,000 older (over age 65 years) breast cancer survivors demonstrated that anthracycline chemotherapy treatment increased the risk of development of congestive heart failure by 26% relative to non-anthracycline containing chemotherapy in women aged 66 to 70.\textsuperscript{50}

### 2.2.3 Incidence

Left ventricular ejection fraction (LVEF) is the parameter used to diagnose cardiotoxicity in clinical management of oncology patients and in virtually all clinical trials investigating the cardiac safety of anticancer therapies.\textsuperscript{51} It is calculated as the difference between the left ventricular (LV) end-diastolic volume and end-systolic volume, divided by the end-diastolic volume, and is expressed as a percentage. The most recent expert consensus defines cardiac dysfunction related to cancer therapy, or cardiotoxicity, as a decrease in LVEF of >10 percentage points to a value <53%.\textsuperscript{52} However prior to the publication of this 2014 consensus document, several other definitions were used, such as either a LVEF
decline of 20 percentage points from baseline, a LVEF decline of 10 percentage points to a value below 50%, a LVEF decline to equal to or below a value of 45%, or clinical presentation of congestive heart failure. Using the latter group of three possible definitions, pooled results from three multicenter studies of 630 individuals treated with doxorubicin for breast cancer or small cell lung cancer demonstrated an overall incidence of congestive heart failure of 5%. Cumulative incidence rates of congestive heart failure of 16%, 32% and 65% at doses of 300, 400, and 550 mg/m² occurred. Rates of a LVEF drop of 10 percentage points or more shortly after completion of four cycles of low dose doxorubicin and cyclophosphamide, have been reported to range from 13 to 23% in breast cancer patients, and LVEF at completion of anthracycline treatment, but not LVEF prior to treatment is predictive of later development of cardiotoxicity. Results from a recent 10-year follow-up of breast cancer patients treated with more modern anthracycline-containing chemotherapy protocols reported that 16% of patients experience ≥20% relative LVEF reduction, and that the consistent increase in cumulative frequency of congestive heart failure over time throughout the follow-up period may indicate continued and indefinite long-term risk.

Due to the incredible reserve capacity of the heart, subclinical damage to the myocardium is not reflected by a change in LVEF until substantial cardiomyocyte damage has occurred to the point where the heart’s ability to compensate is exceeded. Therefore, rates of subclinical damage not detected by LVEF are suspected to be much higher than the rates of LVEF-defined cardiotoxicity or a >10 percentage point LVEF drop, but remain unknown. Witteles et al. postulate that the subtle signs of acute cardiac injury occurring early in anthracycline treatment can follow one of three paths. If the injury is small and occurs in the absence of risk factors for development of cardiac dysfunction, the injury will
likely recover without progression to overt heart failure. If the acute injury is large enough, and concomitant risk factors are present, symptomatic heart failure or serious arrhythmias could occur immediately. Lastly, with a moderate sized or repetitive injury, which occurs with multiple anthracycline treatment cycles and/or co-administration of other cardiotoxic therapies, the left ventricle will gradually start to remodel due to the injury and a delayed presentation of heart failure may occur months or years later.\textsuperscript{35}

2.2.4 Combination therapy

Doxorubicin treatment with doses under the threshold of 500mg/m\textsuperscript{2} in combination with the taxane paclitaxel produces very high rates of tumor response, but increases the incidence of congestive heart failure beyond that typical of doxorubicin alone.\textsuperscript{49} It appears that paclitaxel modulates anthracycline pharmacokinetics and metabolism, resulting in increased doxorubicin uptake into the heart, reduced elimination of doxorubicin, and increased conversion of doxorubicin to toxic intermediates.\textsuperscript{49} As a result, paclitaxel is now typically administered following the completion of anthracycline therapy, or prior to anthracycline therapy.\textsuperscript{34,57}

High-dose cyclophosphamide is associated with acute cardiotoxicity within 10 days of administration, with symptomatic presentation in 22-25% of individuals and fatal cardiotoxicity in 11-12%.\textsuperscript{58} However, doses lower than 1550 mg/m\textsuperscript{2} per day are associated with an incidence of symptomatic cardiotoxicity of 3% with no fatalities.\textsuperscript{58} Cyclophosphamide doses for early breast cancer can range from 75 to 830 mg/m\textsuperscript{2}, but the most common anthracycline combination protocols include a cyclophosphamide dose of either 500 or 600 mg/m\textsuperscript{2}.\textsuperscript{33,57} The mechanism of cyclophosphamide-induced cardiotoxicity is
not clear, but may involve direct endothelial damage and leakage of plasma proteins and red blood cells.\textsuperscript{59}

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of HER2, a transmembrane tyrosine kinase receptor that is overexpressed in one quarter of breast cancers, leading to negatively altered cell signaling. A demonstrated incidence rate of congestive heart failure of 7\% with single agent trastuzumab, dramatically increased to 28\% when combined with anthracyclines in an early study.\textsuperscript{49} The enhanced cardiotoxicity of anthracyclines by trastuzumab is related to downstream antibody-receptor interactions.\textsuperscript{49} Trastuzumab inhibits the release of neuregulin-1β, an important protein in minimizing cardiac myofilament disarray induced by anthracyclines, resulting in aggravated myofilament damage.\textsuperscript{49} Current guidelines recommend against concurrent administration of trastuzumab and anthracyclines.\textsuperscript{57}

\textbf{2.2.5 Mechanisms}

The exact mechanism for anthracycline-induced cardiotoxicity remains unclear, but is most likely multifactorial with summative effects and feedback from diverse processes. Some of the hypothesized mechanisms are described below.

\textbf{Iron and free radical formation:} It is well accepted that the mechanism for cardiotoxicity associated with anthracyclines involves the generation of ROS.\textsuperscript{36} ROS generation may occur via redox cycling, or via mediation by the affinity of anthracyclines for the inner mitochondrial membrane phospholipid cardiolipin, which when bound to anthracyclines will be reduced by NADH dehydrogenase, leading to formation of a superoxide anion radical.\textsuperscript{37} This particular pathway for free radical formation is specific to cardiotoxicity, as NADH dehydrogenase is preferentially expressed in heart mitochondria.\textsuperscript{60}
A non-enzymatic pathway involving metal ions exists for production of free radicals in the heart as well. Doxorubicin also has a strong affinity for iron, which when bound, the complex can catalyze the production of free radicals. Free radicals formed by any of these mechanisms will damage cell membrane lipids (lipid peroxidation), proteins and nucleic acids, ultimately leading to apoptosis of these damaged cells.

It is generally accepted that iron plays a pivotal role in anthracycline-induced cardiotoxicity, likely due to its ability to convert $\text{O}_2^-$ and $\text{H}_2\text{O}_2$ into the pro-apoptotic $\text{OH}^-$. However iron homeostasis dysregulation must occur first to create a source of free iron within the cell to catalyze this reaction. One theorized source of free iron is from the semiquinone anthracycline intermediate and $\text{O}_2^-$, which indirectly causes release of iron from intracellular stores of ferritin. A larger and potentially more toxic source of iron to cardiomyocytes comes from the reaction of secondary alcohol metabolites of anthracyclines (formed by two-electron reduction of anthracyclines) with the iron-containing protein cytoplasmic aconitase.

**Apoptosis:** In addition to ROS-induced apoptosis, there is evidence suggesting that anthracyclines may directly trigger apoptosis. A proposed explanation for the susceptibility of cardiomyocytes to cytotoxic effects of anthracyclines is that cardiomyocytes have low levels of catalase and readily allow inactivation of GSH-peroxidase-1 (both are involved in cellular defense against $\text{H}_2\text{O}_2$), therefore allowing initiation of the mitochondrial apoptosis pathway. Other potential mechanisms for anthracycline-induced cardiomyocyte mitochondria apoptosis include through the p38 mitogen-activated protein kinases signaling pathway, down-regulation of the cardiac progenitor cell transcription factor GATA-4, and a $\text{Ca}^{2+}$ channel coupled increase in the permeability of the mitochondrial membranes.
Anthracyclines also decrease myocyte defense against apoptosis by decreasing the expression of neuregulin-1β, a required activator of the PI3K-Akt pathway that protects against anthracycline apoptosis.37

**Immune system activation of cardiac inflammation**: Doxorubicin stimulates a number of important components of immune responses.62 Toll-like receptors are involved in the cardiac stress reaction by triggering an inflammatory response and extracellular matrix degradation, and have been causally linked to heart failure development.62 Toll-like receptor activity is positively associated with GATA-4 activity, a key regulator of heart development and potential target of anthracycline-induced cardiotoxicity.62

**Genetic expression**: The wide range of effects on cardiac-specific gene expression associated with anthracyclines may help to explain the wide variation in experience of cardiotoxicity between individuals.37 Associations with cardiotoxicity were identified among six single-nucleotide polymorphisms in five different genes.37 Mechanisms for anthracycline-induced genetic expression modulation include direct binding of anthracyclines to DNA and thereby modifying DNA structure and nucleic acid alteration by free radical generation.60 Potential targets of modified genes include regulators of apoptosis, mitochondrial function, glycolysis, and fatty acid metabolism.62 Progressive doxorubicin dosage is associated with upregulated expression of natriuretic peptide, cardiac troponin, encoding proteins for cardiac Ca$^{2+}$ homeostasis, and several enzymes implicated in cardiac dysfunction.62 Doxorubicin is also known to down-regulate expression of cardiac muscle contractile proteins, which may explain the myofibrillar loss and resulting decreased contractility associated with anthracycline-induced cardiotoxicity.63
Ubiquitin-proteosome system activation: The ubiquitin-proteasome system maintains protein function and quality control by modulating protein activity by ubiquitination or degrading the protein with proteasomes.\textsuperscript{62} Doxorubicin activates proteolysis via this system, which modulates specific proteins that result in myofibrillar loss, decreased cardiomyocyte survival factors, increased proapoptotic factors and impaired sarcomeric structure.\textsuperscript{62}

Inhibition of progenitor cells: There is preliminary evidence that doxorubicin may decrease levels of cardiac, bone marrow, and endothelial progenitor cells and block the associated repair processes.\textsuperscript{62}

2.3 Prevention and treatment of cardiotoxicity

2.3.1 Delivery and pharmacology

Strategies to protect the heart from anthracycline-induced cardiotoxicity include limiting or adjusting the total dose, development of an analog without this toxic effect, finding alternative routes of administration to minimize toxicity, or finding therapies to prevent, slow or reverse the toxicity.\textsuperscript{64,65} First, limiting the total cumulative dose is the most common strategy used to prevent cardiotoxicity,\textsuperscript{65} but this method may have untoward effects on recurrence or cancer-related mortality.\textsuperscript{66} Likewise, dose discontinuation upon discovery of cardiotoxicity during treatment could have implications for survival, as RCTs suggest a reduced oncological benefit of chemotherapy at lower doses.\textsuperscript{67} Second, two thousand analogs of the original anthracycline agents (doxorubicin and daunorubicin) have been synthesized and evaluated,\textsuperscript{64} but the only one to achieve widespread use for treatment of breast cancer is epirubicin. The risk of cardiotoxicity occurs at a higher dose of epirubicin than with doxorubicin, but the typical dose required is also higher, which may mitigate the
reduction in cardiotoxicity. Even low doses (i.e. 268 mg/m²) of epirubicin have been reported to result in a 35% prevalence of LVEF drop ≥10 percentage points to <55% immediately after treatment completion in breast cancer patients without cardiovascular risk factors. Third, some modifications to agent delivery such as longer infusion time, weekly delivery, and liposome encapsulation have been associated with reduced heart failure incidence, but due to practical disadvantages, these practices have not been widely adopted. Finally, a number of pharmacological therapies have been evaluated for prevention or treatment of anthracycline-related cardiotoxicity. The iron-chelator dexrazoxane is the only proven pharmacological cardio-protective agent for cardiotoxicity associated with doxorubicin and epirubicin. However, due to a possible association with secondary cancers, the United States Food and Drug Administration restricts the use of dexrazoxane to adults with metastatic breast cancer after cumulative doses of 300 mg/m² of doxorubicin or 540 mg/m² of epirubicin. In addition, angiotensin-converting enzyme (ACE)-inhibitors and β-blockers may slow progression of subclinical dysfunction to heart failure and reverse LV dysfunction when initiated early enough. However, only 11% of adults treated with ACE-inhibitors alone or in combination with a β-blockers for anthracycline-related cardiotoxicity experience a return of LVEF to baseline, while a partial response where LVEF is returned to a value of >50% is common. The use of ACE-inhibitors and β-blockers for cancer therapy-related cardiotoxicity is recommend by the American College of Cardiology, but is not common practice. Additionally, pharmacological interventions may be associated with additional side effects and cost, and thus may not represent an ideal prevention or treatment strategy.
2.3.2 Exercise

A growing body of work using animal models suggest that exercise is a promising non-pharmacological therapy to attenuate doxorubicin-induced cardiac damage. The effect of exercise on the heart has not been investigated with any other anthracycline analog. In non-cancer populations, physical activity, or more specifically moderate intensity aerobic exercise training, is an effective primary and secondary prevention strategy for cardiovascular disease and cardiovascular disease-related mortality. Within breast cancer populations, exercise training has been established as a safe and effective strategy for improving numerous health outcomes that are affected by cancer treatment, including cardiorespiratory fitness, muscular strength, body composition, fatigue, anxiety, depression and pain. Furthermore, cancer survivorship guidelines now include a recommendation of 150 minutes per week of aerobic exercise training, plus strength training two or more times per week. However, the effect of exercise on cardiac function or outcomes during or after anthracycline treatment for breast cancer is not well established in humans.

2.3.3 Potential mechanisms for exercise cardio-protection from anthracyclines

The vast majority of the studies investigating exercise prevention of direct cardiotoxicity are in rodent models with a sedentary doxorubicin-treated group to compare against an aerobic exercise-trained doxorubicin-treated group. The discussion of mechanisms and preclinical evidence refers to studies with this design unless otherwise noted. The exercise protocol utilized varies widely between studies, and while the length, frequency, duration, and type of aerobic training are easy to quantify and describe, the intensity of exercise is not typically described and is difficult to quantify objectively for rodents. Further, the intensity can be difficult to compare between different studies due to differing aerobic
capacities of rodents with species (i.e. rats vs. mice), strain, age, and gender, as well as differing modes of exercise such as treadmill running, swimming, and voluntary wheel running. This is a limitation in the ability to translate these findings to humans, and the intensity of the preclinical exercise protocols utilized will only be described where possible.

The mechanism underlying the cardio-protective effects of aerobic exercise before or during treatment with doxorubicin has not been fully elucidated, but due to the pleotropic effects of exercise, is likely to be multifactorial. Potential mechanisms by which exercise may act in opposition to the negative effects of doxorubicin to protect the heart and vasculature are listed in Table 2.1. There is available evidence from animal models for exercise protection mechanisms related to inhibition of ROS, interruption of topoisomerase-mediated pathways, cardiomyocyte contractile protein isoform shifts, and up regulation of heat shock proteins (HSP), endothelial nitric oxide (NO), and endothelial progenitor cells.

The most widely supported mechanism by which exercise may prevent anthracycline cardiotoxicity is through its antioxidative effects. As previously mentioned, production of ROS is one of the possible mechanisms for anthracycline cardiotoxicity. Although cells are equipped with an endogenous antioxidant system to protect against ROS, cardiomyocytes have only one fourth of the antioxidative capacity of the liver and other tissues, making them particularly vulnerable to oxidative stress. Exercise-induced enhancement of cardiomyocyte antioxidant capacity may prevent ROS-induced damage associated with anthracycline treatment. Compared with untrained animals, aerobic exercise-trained rodents have increased levels of antioxidant activity and reduced levels of oxidative stress markers following doxorubicin exposure. Reduced levels of protein turnover via the ubiquitin-proteosome pathway, an important mechanism for degradation of cellular proteins with
oxidative damage, have been demonstrated in exercise-trained rodents compared to sedentary rodents. This finding provides further support for exercise protection via reduced oxidative stress.

Anthracycline-induced ROS cause lipid peroxidation and down regulate expression of the sarcoplasmic reticulum calcium pump, SERCA2a. Decreased calcium uptake by SERCA2a then leads to an increase in cytosolic calcium. These two changes result in opening of the mitochondrial permeability transition pore, allowing release of calcium from the mitochondrial matrix, down regulation of mitochondrial respiration, and leaking of proapoptotic mitochondrial proteins into the cytosol. A single vigorous intensity treadmill exercise session completed 24 hours prior to doxorubicin treatment prevented opening of the mitochondria permeability transition pore, mitigating the downstream effects. This hypothesis is supported indirectly by several other studies demonstrating attenuation of doxorubicin-associated increases in the proapoptotic proteins caspase-9 and 3 in exercise trained rodents. These findings may be related to modulation of defense systems including stress chaperones like HSPs, or antioxidants, but thus far appear to not be related to exercise-induced up regulation of SERCA2a.

There is emerging evidence implicating topoisomerase 2β, an enzyme regulating DNA unwinding, in doxorubicin-induced cardiomyocyte mitochondrial dysfunction, secondary to down regulation of peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, a transcriptional coactivator of mitochondrial biogenesis. Exercise training up regulates expression of PGC-1α in skeletal muscle, although a similar response in healthy cardiomyocytes has not been observed. Two recent preclinical studies investigating the role of PGC-1α in exercise cardio-protection for doxorubicin reported differing findings
regarding the effects of doxorubicin and exercise training on cardiac PGC-1α in rodents. Neither a large bolus dose, or a sub-chronic weekly dosing of doxorubicin changed heart levels of PGC-1α, while five consecutive days and 12 weeks of five days per week of moderate-to-vigorous intensity treadmill running, as well as voluntary wheel running all resulted in an increase in PGC-1α in the non-treated group. Based on these initial findings it may seem there is no interaction between doxorubicin and exercise training with respect to PGC-1α in cardiomyocytes, but this potential mechanism as well as the direct role of topoisomerase 2β requires further investigation before it can be dismissed.

In the rodent heart, doxorubicin causes disruption of cardiac bioenergetics and an associated shift from the α isoform of the contractile protein, myosin heavy chain (MHC), to the β isoform, which has reduced contractile power. Exercise training before and during doxorubicin treatment conserves the α isoform in rats. However, healthy human hearts express 7% of the α isoform on average, while this is the predominant isoform expressed in the rat heart. Therefore the extent, and subsequent impact of a doxorubicin-induced shift in MHC isoform distribution may be smaller for human myocardium. Clinical research is required to clarify the role of prevention of MHC isoform shifts in exercise cardio-protection.

HSPs control protein folding and unfolding, and are up regulated in cardiomyocytes during times of oxidative stress. An exercise-induced increase in HSP expression is hypothesized to play a role in cardio-protection against doxorubicin by preserving the integrity and activity of mitochondrial respiratory complexes and thereby attenuating mitochondrial dysfunction. Although there is some evidence supporting HSP-mediated cardio-protection, there are also conflicting results, with no apparent difference related to exercise intensity.
2.3.4 Evidence for exercise cardio-protection from anthracyclines and/or breast cancer treatment

2.3.4.1 Impact of acute exercise before or after doxorubicin exposure in animal models

In animal models, doxorubicin-related cardiotoxicity can be attenuated by a single exercise session in close proximity to time of exposure. In the seminal study in this area, a 30-minute swimming session completed half an hour after high dose doxorubicin exposure reduced mortality. These findings were extended to demonstrate that an exhaustive treadmill exercise session immediately after doxorubicin exposure attenuated markers of cardiomyocyte mitochondrial dysfunction (state 3 and 4 respiration in succinate substrate). More recently, convincing evidence for the beneficial effect of exercise performed prior to doxorubicin exposure has emerged. Sixty minutes of vigorous intensity treadmill exercise performed 24 hours prior to doxorubicin prevented or attenuated LV systolic and diastolic dysfunction, cardiomyocyte mitochondrial apoptosis and dysfunction, and lipid peroxidation at five days post-treatment in rodents.

2.3.4.2 Impact of exercise training prior to doxorubicin exposure in animal models

In animals receiving high-dose bolus doxorubicin, exercise preconditioning, ranging from 3 to 14 weeks of voluntary wheel running, or five days a week of progressive treadmill running or swimming prevents or attenuates acute increases in cardiac troponin I, markers of oxidative stress, cardiac mitochondrial dysfunction, cardiomyocyte morphological and histological damage, markers of apoptosis, and decreases in HSP expression and LV systolic function typically measured at 24 hours after doxorubicin exposure. Similar findings have been reported in studies that extended the follow-up time to 5-10 days after doxorubicin exposure without further exercise training after
doxorubicin. New findings reported by these studies with longer follow-up include attenuation of deficits in coronary flow, transmitral and transaortic flow, as well as transformation to the β-MHC isoform. Even at four weeks after doxorubicin exposure, the beneficial effects of exercise preconditioning on β-MHC transformation, LV wall thickness, mass and systolic function, and transmitral/transaortic flow were still apparent.

2.3.4.3 Impact of exercise training concurrent with doxorubicin exposure in animal models

Exercise training ranging from 2 to 21 weeks of voluntary wheel running or five days per week of progressive treadmill running or swimming, concurrent to chronic doxorubicin treatment in rodents has been associated with attenuation of LV systolic and diastolic dysfunction, cardiomyocyte apoptosis, transformation to β-MHC, reductions in LV wall thickness and heart mass, and deficits in coronary, transmitral and transaortic flow.

2.3.4.4 Impact of exercise training after doxorubicin exposure in animal models

Few studies have implemented exercise after completion of doxorubicin treatment. Two weeks of exercise training initiated two weeks after low dose (3 mg/kg) doxorubicin exposure reduced markers of cardiomyocyte apoptosis and oxidative stress in young rodents. Six weeks of exercise training in rats with established doxorubicin-induced heart failure reduced mortality rates by 50% and improved endothelial-dependent vasodilation in mesenteric vascular beds. The effect of exercise on cardiac function was not assessed in this study.

In summary, acute and chronic exercise before, during or after doxorubicin treatment in rodents consistently results in prevention or attenuation of doxorubicin-induced
deleterious effects to cardiomyocyte morphology and biochemistry, as well as cardiac
function.

2.3.4.5 Impact of acute exercise or exercise training on anthracycline treatment in humans

To date, no studies have examined the impact of acute exercise bouts in close
proximity either before or after doxorubicin treatment or exercise preconditioning on
markers of cardiotoxicity in humans. One small RCT has assessed the effect of aerobic
exercise training on cardiac function for the duration of AC treatment delivered every three
weeks in breast cancer patients, but full details of the study have not been reported as the
related publications are a conference abstract and brief mention in a review paper.\textsuperscript{112,115} The
exercise prescription is unknown and the only cardiac function parameter reported, LVEF,
did not change in either the usual care or aerobic exercise group.\textsuperscript{112,115}

A single-arm study investigated the effects of four months of exercise training during
the first four months of trastuzumab therapy in 17 breast cancer patients, 9 of which had
recently completed doxorubicin-containing chemotherapy treatment.\textsuperscript{116} Despite aerobic
exercise training, prescribed at moderate to high intensity (60-90\% peak oxygen
consumption) three days per week for 30 to 60 minutes, trastuzumab treatment was
associated with LV dilatation and reduced LVEF.\textsuperscript{116} However the authors suggested that the
exercise training stimulus received may have been insufficient, as average attendance of
prescribed sessions was only 59±32\%.

These preliminary clinical studies of the effects of exercise training on cardiac
function in humans undergoing breast cancer treatment have provided limited insight. More
sensitive measures of cardiac function and a higher exercise dose are likely required in order
to demonstrate a cardio-protective benefit in clinical studies.
2.3.4.6 Impact of exercise training on cardiovascular risk factors in human breast cancer survivors

The predominant evidence for the benefits of exercise for cardiovascular health of human breast cancer survivors is on cardiovascular risk factors rather than direct measures of cardiac function. The measurement of traditional cardiovascular risk factors can provide an avenue to monitor and manage risk of cardiotoxicity in human breast cancer patients who receive cardiotoxic cancer therapies to prevent additional injury. In general, moderate intensity aerobic exercise is known to favorably improve a number of cardiovascular risk factors including hypertension, raised cholesterol/lipids, overweight and obesity, raised blood glucose or diabetes, and cardiorespiratory fitness. Thus evidence of the effect of exercise training on cardiovascular risk factors in breast cancer populations provides indirect evidence for exercise cardio-protection in humans. It should be noted that the majority of studies reporting the prevalence of cardiovascular risk factors or the effect of exercise on cardiovascular risk factors in breast cancer survivors do not exclusively include those treated with anthracyclines. Therefore this section is a general discussion of exercise prevention of cardiovascular disease in breast cancer survivors, not anthracycline-related cardiotoxicity.

Hypertension is more than twice as prevalent among breast cancer survivors age 55 and older as it is among the general age-matched population, and may be caused by chemotherapy agents used to treat breast cancer including cyclophosphamide, cisplatin and carboplatin. Chemotherapy for breast cancer is also associated with elevations in triglyceride levels, while tamoxifen treatment may reduce levels of protective high density lipoprotein (HDL). Prior to treatment, breast cancer survivors may already have a suboptimal lipid profile including higher total cholesterol, triglyceride, and LDL levels, and
lower HDL levels than healthy controls.\textsuperscript{123-127} A similar pattern occurs with overweight or obesity, known risk factors for development of breast cancer\textsuperscript{128} that are often an issue prior to treatment, and chemotherapy treatment perpetuates the problem via its association with weight gain in the year following diagnosis.\textsuperscript{129} Almost half of Canadian breast cancer survivors are overweight or obese.\textsuperscript{130} Treatment also has lasting adverse effects on peak oxygen consumption (VO\textsubscript{2}peak), the gold standard measurement of cardiorespiratory fitness.\textsuperscript{131} Chemotherapy causes a 5-10\% reduction in VO\textsubscript{2}peak,\textsuperscript{18,115} and following breast cancer treatment completion, remains an average of 22\% lower than that of healthy sedentary controls.\textsuperscript{19} Furthermore, the level of cardiorespiratory fitness amongst breast cancer survivors appears to mediate the incidence of cardiovascular disease and risk factors.\textsuperscript{132} Lastly, breast cancer survivors are at an increased risk for diabetes from 2 to 10 years following diagnosis,\textsuperscript{133} and its presence increases the risk of mortality in this population.\textsuperscript{9} In early stage breast cancer survivors, high blood insulin levels, indicative of insulin resistance, are associated with obesity, poor lipid profiles,\textsuperscript{134} distant recurrence and death.\textsuperscript{135}

A number of exercise intervention studies in human breast cancer survivors have included cardiovascular risk factors as outcome measures. Moderate intensity aerobic exercise interventions, with or without resistance training in breast cancer survivors have consistently reported decreases in systolic blood pressure of 3-5 mmHg both during and after\textsuperscript{136-138} treatment. Reported effects on blood lipids following an exercise intervention with or without dietary intervention include significant positive effects on triglycerides,\textsuperscript{140,143} and HDL,\textsuperscript{143} or no effect.\textsuperscript{142,144,145} Numerous exercise interventions have measured weight or body composition change with mixed results, showing either no effect or weight reduction.\textsuperscript{76} Small feasibility studies have demonstrated that the combination of exercise with a diet
intervention could be more effective in reducing weight in breast cancer survivors.\textsuperscript{144,145}

Aerobic exercise training during chemotherapy or radiation treatment for breast cancer can prevent the deterioration that occurs in usual care controls\textsuperscript{18} or improve\textsuperscript{112,115,146-148} VO\textsubscript{2peak}. Aerobic exercise training following breast cancer treatment improves VO\textsubscript{2peak}.\textsuperscript{144,149,150}

Only one\textsuperscript{143} of six RCTs to examine the effect of an aerobic exercise intervention with or without resistance on insulin and/or insulin resistance demonstrated statistically significant changes.\textsuperscript{142,145,151-153} This same study also reported improvements in fasting blood glucose.\textsuperscript{143}

In summary, aerobic exercise interventions with or without a resistance exercise component appear to have clinically meaningful effects on blood pressure and VO\textsubscript{2peak}, whereas the effects on blood lipids, weight and insulin/glucose and potential development of diabetes are less clear. The strong established relationships between both blood pressure and VO\textsubscript{2peak} and cardiovascular disease development and mortality in non-cancer populations\textsuperscript{21,154-156} provide convincing support for the role of exercise prevention of cardiovascular disease in human breast cancer survivors.

2.4 Translation of preclinical exercise cardio-protection findings to clinical studies

Substantial preclinical evidence supports the role of exercise in the prevention of cardiovascular toxicity, and there is some evidence for modification of cardiovascular risk factors in clinical trials. Further clinical research is warranted to determine whether exercise is a feasible and effective method for the reduction of cardiovascular morbidity, and ultimately mortality in breast cancer survivors. Requirements for the translation of preclinical findings to humans include use of sensitive and relatively non-invasive outcome measures and identification of the required exercise dose.
2.4.1 Exercise intervention design

An important factor in the effective translation of the preclinical findings to humans is the exercise intervention design. The timing of the intervention relative to treatment delivery, length of the exercise intervention, and the exercise prescription are the primary variables that need to be defined.

2.4.1.1 Timing relative to treatment delivery and length of exercise intervention

The potential of a single exercise session to provide cardio-protection is particularly appealing, as high adherence to the prescription of regular, supervised exercise training during chemotherapy may not be feasible for all patients due to distance from home to exercise centres, difficulty with treatment symptoms, and scheduling conflicts with work or family obligations.\(^7^4\)

The feasibility of exercise preconditioning (i.e. exercise training before receipt of treatment) in humans has been questioned, as the interval between breast cancer diagnosis and treatment is shorter than the length of most preconditioning exercise protocols that have been studied in animals (8 to 14 weeks of training)\(^7^4\). The duration of time between diagnosis and either initiation of chemotherapy in the case of neoadjuvant regimens, or between recovery from surgery and initiation of chemotherapy for adjuvant regimens, could be a few days to several weeks. However, cardio-protective effects have been reported after as little as five days to three weeks of training in rodents\(^8^5,8^7,1^0^8\). It should be noted that administered doxorubicin doses in these animal studies were higher than comparable human doses. A 10-25 mg/kg dose in a rodent is equivalent to 410-1020 mg/m\(^2\) for the average woman,\(^1^5^7\) whereas typical modern protocols for early breast cancer are 240 mg/m\(^2\).\(^3^3\) It is unclear whether similar benefits would be seen in patients receiving standard treatment doses.
Sturgeon et al. administered 4 mg/kg of doxorubicin to mice (equivalent to 164 mg/m² in an average woman) and reported that two weeks of very low intensity exercise five days/week for 45 minutes did not preserve LV volumes or mass measured non-invasively via echocardiography nor histologic cardiomyocyte fibrosis.\textsuperscript{157}

The remaining preclinical studies and the single clinical study that have measured the effect of exercise on cardiac function have implemented the intervention for the duration of ongoing doxorubicin treatment. Exercise training in humans during and after chemotherapy treatment for breast cancer has been shown to be safe and effective for improving numerous health outcomes,\textsuperscript{76} so exploring the potential of exercise training during chemotherapy for cardio-protection is also warranted.

2.4.1.2 Exercise prescription parameters

There are four parameters commonly used to describe the exercise prescription for an intervention or program. These include frequency of exercise bouts per week, intensity of each exercise bout, duration of each exercise bout, and type of activity, such as aerobic or resistance exercise.

Most preclinical anthracycline cardio-protection studies have employed a rather strenuous exercise prescription of five days a week, moderate to high intensity aerobic exercise for 20-90 minutes (most commonly 60 minutes), that would likely not be tolerable for humans undergoing chemotherapy treatment\textsuperscript{158} due to treatment side effects, or feasible due to the number of medical appointments on top of normal family or work obligations for women undergoing chemotherapy treatment for breast cancer. Additionally, many of these studies utilized a supraclinical dose of doxorubicin, which may complicate the interpretation of the exercise dose and protection response. However, one study by Chicco et al. in rodents
implemented a more feasible and practical exercise prescription, in addition to a chronic, low-dose doxorubicin treatment protocol that is more clinically relevant. The exercise prescription involved 20 minutes of low intensity aerobic exercise, performed five days per week for two weeks during chronic low dose (2.5 mg/kg three times per week for two weeks) doxorubicin exposure initiated on the first day of training. The lower exercise dose was protective against LV systolic and diastolic dysfunction measured via an isolated perfused preparation, as well as markers of cardiomyocyte apoptosis. Of note, this doxorubicin dose was greater than that of Sturgeon et al. described earlier; the difference in findings of cardioprotective benefit between the two studies administering low doses of exercise could be related to difference in doxorubicin dose and methods of assessing cardiac function.

In other populations, preclinical and clinical experimental studies demonstrate that high or vigorous intensity aerobic exercise results in greater cardiac benefits than moderate or low intensity exercise. However, a meta-analysis of exercise interventions in heart failure patients, reported that moderate intensity exercise performed three days per week can improve systolic function. The applicability of these findings from populations with a different pathophysiological etiology of cardiac dysfunction to individuals with anthracycline-related cardiotoxicity is unknown. Therefore, based on this evidence taken from preclinical models and other clinical populations, the required exercise dose for cardio-protection likely involves three to five days per week of moderate to high intensity aerobic exercise of at least 20 minutes in duration, but greater benefits will likely occur with higher doses.

Although the dose of exercise required for cardiac benefits in cancer patients is not known, there are exercise prescription recommendations for general health benefits for
For cancer survivors not already meeting the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors in the previous month, the initial recommended prescription entails three 20-minute walking sessions per week at a moderate intensity. The prescription should be progressed, as tolerated, up to five 30-minute sessions per week. It is suggested that intensity be prescribed via the heart rate reserve method at 50-75%, or using a rating of perceived exertion of 11 to 14.

There are three large high-quality RCTs (n≥230) that have established the efficacy of prescriptions similar to these exercise guidelines in interventions during adjuvant chemotherapy for women with early breast cancer. Reported average attendance for the 451 women randomly assigned to a supervised moderate intensity aerobic exercise group (with or without resistance exercise) ranged from 70 to 73% for the three large RCTs (Table 2.7). Several other smaller RCTs have implemented a supervised aerobic exercise intervention during adjuvant chemotherapy for breast cancer, but have also included individuals receiving radiotherapy or hormonal therapy either in combination with chemotherapy or alone (Table 2.7). Attendance for these studies ranges from 70 to 83%, or is not reported. Adherence to the desired exercise prescription is often not reported in exercise interventions involving women with breast cancer including with the aforementioned studies. In the few studies to report adherence data, just an overall percent adherence, with no breakdown of adherence to different aspects of the prescription (i.e. adherence to prescribed intensity, duration, or progressions to the exercise prescription) was reported.

Furthermore, treatment side effects differ amongst the different treatment protocols, yet previous studies, including those discussed above, tend to combine all chemotherapy
protocols in analyses of attendance and adherence. Anthracyclines are considered to be among the most toxic drugs ever developed, and their associated side effects could realistically affect exercise intervention tolerance and the resulting adherence to a particular exercise prescription. A small study by Hornsby et al. of 10 women receiving neoadjuvant doxorubicin and cyclophosphamide reported 82% attendance of one-on-one scheduled exercise sessions, and 77% adherence to the prescribed minimum intensity and duration. To date, there is a very limited description of adherence to the recommended exercise prescription during group-based or adjuvant anthracycline-containing chemotherapy treatment, and a lack of understanding of barriers to adherence. The optimal prescription requires a balance of patient tolerance with health benefit efficacy, and further understanding of exercise adherence is required in order to delineate such a prescription.

2.4.2 Outcome measures

Demonstration of the cardio-protective benefits of exercise in rodents has typically required euthanasia. One of the greatest barriers to translation of this research to humans is identification of a minimally or non-invasive outcome measure that is sensitive to early signs of cardiac dysfunction or damage with anthracycline chemotherapy.

Earlier initiation of heart failure therapy following detection of anthracycline-induced cardiotoxicity via LVEF is associated with improvement of cardiac function with a ceiling effect at six months following chemotherapy. Therefore, early detection of anthracycline-induced cardiotoxicity with techniques that are more sensitive than LVEF would allow for earlier intervention and likely have an even greater effect in the prevention and reversal of occult heart failure. The gold standard for early evidence of subclinical cardiac damage, endomyocardial biopsy, is not feasible for routine clinical practice due to its invasive
nature. As previously mentioned, LVEF does not change until substantial, potentially irreversible myocardial injury has occurred. The use of LVEF as a therapeutic target for interventional research does not allow for identification of cardio-protective strategies for the early stages of cardiotoxicity development, due to the insensitivity to early dysfunction. Therefore techniques for early detection of subclinical (i.e. before LVEF drop or presentation of symptoms) anthracycline-induced cardiac cardiotoxicity and prediction of later cardiotoxicity are an area of active investigation. Echocardiographic measurement of myocardial mechanics and serum levels of cardiac biomarkers are the most promising techniques for detection of subclinical cardiotoxicity, and may therefore also be suitable outcome measures to assess the effect of exercise training on cardiac function during anthracycline chemotherapy in human breast cancer patients.

Unfortunately improvement in surrogate markers, or improvement in consequences of altered physiology linked to disease outcomes (e.g. ischemia as a marker of heart failure) often does not translate to improved clinical outcomes. To increase the chances of successful translation of therapies to meaningful clinical benefit, Marti et al. have proposed a set of four requirements that should be met when utilizing a novel therapeutic target, or outcome measure for a phase II or III clinical trial. For example, if myocardial mechanics and/ or cardiac biomarkers as early markers of anthracycline-related cardiotoxicity meet these requirements, this increases the chances that therapies that improve these measures, such as exercise, will translate to improved cardiovascular morbidity and mortality. This section will: 1) describe the available observational evidence demonstrating the ability of myocardial mechanics and biomarkers to detect early anthracycline-related cardiac dysfunction; 2) discuss the extent that available evidence demonstrates that these measures
fulfill the requirements proposed by Marti et al. will be discussed; and 3) identify knowledge gaps requiring further investigation.

2.4.2.1 Myocardial mechanics

Cardiac myofiber geometry is intimately linked to myocardial mechanics. Myofiber orientation in the LV wall transitions from a right-handed helix in the subendocardium, the innermost tissue layer, to a left-handed helix with roughly longitudinal orientation in the subepicardium, the outermost tissue layer, whereas the midwall myofibers are predominantly circumferentially oriented. Contraction of the different layers will cause rotation of the base and apex in the opposite directions, however due to the increased torque afforded by the larger radius of rotation, the outer epicardial layer dominates the direction of rotation. The large torque of the subepicardium’s left-handed helix orientation of myofibers is coupled transmurally to the midwall and subendocardium causing a global counterclockwise rotation near the apex and clockwise rotation near the base during systole. Translation of the torque to the midwall causes circumferential shortening, whereas it causes shearing of subendocardial fibers toward the LV cavity, LV wall thickening and thereby shortening of the LV longitudinal axis. Both shortening in the longitudinal and circumferential directions and myofiber shearing contribute to thickening of the LV wall in the radial direction. Shearing forces of the subendocardium result in storage of potential energy, which is subsequently released during isovolumic relaxation and early diastole with torsional recoil or untwist contributing to diastolic suction. Echocardiography allows non-invasive dynamic imaging of the heart, making it ideally suited for the assessment of myocardial mechanics including strain and LV rotation imaging.
LV strain is a measurement of myocardial deformation expressed as a fractional change in length of a myocardial segment.\textsuperscript{176} It is a unitless parameter expressed as a percentage. Strain rate is the rate of change in strain expressed as sec\textsuperscript{-1}. Strain and strain rate are vectors in that they have a direction along the anatomic coordinates of the cardiac chambers – longitudinal, radial and circumferential.\textsuperscript{176} Furthermore, each of the directional strains can be expressed for each of the theoretical vascular distribution areas of the myocardium (i.e. segmental strain) or as an average value for all segments (i.e. global strain).\textsuperscript{176} LV global longitudinal strain (GLS) is controlled predominantly by subendocardial myofibers, whereas global circumferential strain (GCS) is related to the midwall, and global radial strain (GRS) is measured across all three layers of the LV wall, but occurs to the greatest extent in the subendocardium.\textsuperscript{175,176}

Echocardiography can be used to assess strain by tissue Doppler imaging (TDI) or 2D speckle tracking echocardiography (2DSTE).\textsuperscript{178} 2DSTE is preferred however as it offers an extra dimension of deformation measurement, semi-automated processing, a more accurate global strain assessment, is less influenced by artifacts, and is angle independent.\textsuperscript{178,179} Good image quality is a requirement to achieve accurate results with 2DSTE.\textsuperscript{176} 2DSTE has been validated as a noninvasive method to determine myocardial deformation against sonomicrometry and cardiac magnetic resonance imaging.\textsuperscript{180} 2DSTE involves off-line analysis of B-mode (2D) images with dedicated software that uses a temporally stable and unique speckle pattern of natural acoustic markers viewed as bright and dark pixels on the image. The speckle pattern results from interference of the reflected ultrasound wavelets from the cardiac tissue.\textsuperscript{181} In the speckle tracking technique, a region of interest is defined, wherein the unique speckle pattern is tracked with a search algorithm to recognize the most
similar speckle pattern from one frame to another. The geometric displacement of each speckle represents local tissue deformation. In contrast, TDI derives strain rate from colour Doppler data indicating the tissue velocity relative to the transducer for a defined region of interest. The strain rate calculation involves the difference in velocities between two points within the region of interest divided by the distance between these two points. Strain is then calculated from the temporal integral of strain rate.

LV rotation refers to rotation of the myocardium around the long axis of the LV and is expressed in degrees. During systole, the LV rotates counterclockwise when viewed from the apex, and clockwise when viewed from the base. The net absolute apex to base difference in rotation is referred to as the net LV twist angle and is expressed in degrees. In contrast, during isovolumic relaxation of early diastole, untwisting of the LV occurs in the opposite directions as during systole. The maximum velocity at which twist or untwist occurs is the twisting or untwisting rate (degrees per second). Torsion refers to the gradient in rotation (degrees per cm) along the long axis of the left ventricle. LV torsion reflects subepicardial function predominantly. LV rotation imaging can also be done by 2DSTE or TDI.

Response of myocardial mechanics to anthracycline treatment

There is a considerable body of work demonstrating that LV strain and strain rate measurements by echocardiography are able to detect anthracycline-induced cardiotoxicity much earlier than LVEF. Specific to breast cancer, there are 12 original studies that have examined the change in various parameters of myocardial mechanics with anthracycline treatment (Table 2.3). Overall these studies all demonstrate the ability of strain parameters to identify early anthracycline-induced changes in myocardial function. However,
there are a number of factors that complicate the interpretation of the combined findings including lack of reported data, inconsistency in assessment of similar parameters and in use of echocardiography assessment techniques and software, and different anthracycline analog use.

Fallah-Rad et al.\(^{186}\) measured, but did not report data for post-anthracycline assessment of myocardial deformation parameters. However, at three months into trastuzumab therapy following anthracyclines, the study demonstrated the ability of GRS and GLS to distinguish those who later developed cardiomyopathy from those who did not (GLS: -19.8±1.8 to -16.4±1.1\% vs. no change; GRS: 41.4±10.5 to 34.5±15.2\% vs. no change).

Tan et al.\(^{195}\) also did not include an echocardiography assessment after completion of anthracyclines in their study of HER2-positive breast cancer patients receiving anthracyclines and sequential trastuzumab, but provide a relatively rare glimpse at the durability of chemotherapy-related strain alterations.\(^{197}\) GLS and LSR significantly decreased from pre anthracycline chemotherapy to post completion of trastuzumab (-20.0±2.5 to -17.6±2.5\%, and -1.26±0.23 to -1.09±0.14 /sec) and this decrease was sustained 12 months later.\(^{195}\) However, because there was no assessment of strain after completion of anthracyclines and before initiation of trastuzumab, it is unknown whether this persistent decrease in myocardial function is due to the anthracyclines, or the additive effect of trastuzumab on top of anthracyclines.\(^{197}\) Another recent study offers some insight in this regard. Lange et al.\(^{189}\) measured global and regional longitudinal strain before and after anthracycline chemotherapy, and every three months throughout trastuzumab. GLS decreased significantly after anthracycline treatment (from -21.1±0.5 to -18.9±0.5\%) with no further progression (or improvement) throughout trastuzumab.\(^{189}\) This deterioration in GLS
with anthracycline chemotherapy was concurrent to a decrease in standard systolic and diastolic function parameters. In contrast, another study reporting a significant decrease in GLS following completion of anthracycline chemotherapy in HER2-negative breast cancer patients, demonstrated that GLS returned to baseline by 12 months after the initiation of chemotherapy.\textsuperscript{193}

Zhang et al.\textsuperscript{196} measured peak systolic longitudinal strain rate (LSR) at baseline prior to chemotherapy and 7 days after cumulative epirubicin doses of 100, 200, 300, 400 mg/m\textsuperscript{2}. After 100 mg/m\textsuperscript{2} of epirubicin, there were no significant differences from baseline, but the change from baseline to after 200 mg/m\textsuperscript{2} was significant (1.69±0.64 to 1.35±0.36 /sec). However, Jiang et al.\textsuperscript{187} demonstrated that peak diastolic LSR decreased even earlier than peak systolic LSR. Although this article was published in Chinese, with only limited details of methodology, and no data available, the English abstract reported that diastolic LSR significantly decreased after two cycles of epirubicin, while systolic LSR was significantly decreased after three cycles of epirubicin.

Jurcut et al.\textsuperscript{188} reported a significant decrease from pre chemotherapy baseline to 7-14 days after the third cycle of pegylated doxorubicin (90 mg/m\textsuperscript{2}) in peak systolic GRS (50.1±11.6 to 37.7±10.2\%) and radial strain rate (RSR) (4.57±1.18 to 3.64±1.52 /sec), but no change in peak systolic GLS and LSR until 7-14 days after the sixth cycle (180 mg/m\textsuperscript{2}) (-22.7±2.8 to -18.8±2.8\%, and -1.54±0.19 to -1.36±0.23 /sec, respectively) in 16 older (65-74 years) women. However the pegylated formulation of doxorubicin is given at a lower dose and is associated with a lower rate of heart failure due to less myocardial accumulation, so this study may not be generalizable to the standard anthracycline formulations.
Sawaya et al.\textsuperscript{191} assessed all three directions of strain at baseline (which was prior to doxorubicin or epirubicin treatment in 33 women, and post anthracyclines in 10), three and six months later. Peak systolic GLS and GCS had significantly decreased by three months (-20.5±2.2 to -19.3±2.4\% and -18±4 to -15±4\%, respectively), preceding the significant decline in LVEF at six months (65±6 to 59±5\%). The change in peak systolic GRS by three months (55±12 to 52±12\%) was not significant for the entire group, but was a significant predictor of LVEF-defined cardiotoxicity by six months from baseline including trastuzumab treatment subsequent to anthracyclines. Similarly, the change in GLS at three months was also a predictor of later cardiotoxicity. In a similar study, Sawaya et al.\textsuperscript{190} measured the three strain coordinates before and after doxorubicin or epirubicin treatment in 81 women. In this study the three directions of peak systolic strain decreased to a similar extent as the previous study (GLS: -21±2 to -19±2\%; GRS: 53±15 to 50±17\%, GCS: -18±4 to -16±4\%) but were all significant changes at three months. The mean 2-percentage point decline in LVEF at three months (64±5 to 62±5\%) was significant. However, only peak systolic GLS was a significant predictor of LVEF-defined cardiotoxicity occurrence up to 12 months following anthracycline completion.

Stoodley et al.\textsuperscript{192} measured all three directions of global peak systolic strain and strain rate in 52 women before and after doxorubicin or epirubicin treatment. The change in peak systolic GLS (-17.8±2.1 to -16.3±2.0\%) and GRS (40.5±11.4 to 34.5±11.4\%) were significant, but the change in GCS (-20.3±2.6 to -20.3±3.3\%) was not. It should be noted that baseline values of GLS, GRS, and LVEF were lower than usual, likely due to inclusion of participants with a history of coronary artery disease, mild valvular stenosis, or regurgitation. This may also explain the parallel significant decreases in strain parameters and LVEF.
following completion of anthracyclines. No significant differences occurred in global strain rates from before to after anthracycline treatments. In a separate analysis of the same cohort, Stoodley et al.\textsuperscript{194} reported a significant change in global early diastolic LSR (1.00±0.24 to 0.90±0.22 /sec) but not global late diastolic LSR (0.63±0.16 /sec, no change) or peak diastolic GLS (10.9±2.5 to 10.4±2.0%) with anthracycline treatment.

Florescu et al.\textsuperscript{69} were the first to measure changes in rotation, twist and untwist rate in breast cancer patients receiving anthracyclines. The authors performed echocardiography at baseline, 24 hours after the third and sixth cycle of low dose (268±22 mg/m\textsuperscript{2}) epirubicin in 40 women. GLS was the only parameter to change significantly after the third cycle in the group as a whole (-23.1±1.7 to -19.8±2.7%). When the participants were divided by later development of cardiotoxicity (defined as ≥10% LVEF drop from baseline to a LVEF of <55% at completion of treatment), the group who developed cardiotoxicity had a significantly larger drop in GLS by the third cycle (-23.8±1.9 to -19.0±2.1% vs. -22.4±1.5 to -20.4±3.0%), which was maintained after the sixth cycle (-19.1±2.0%), whereas the group without cardiotoxicity had a slight recovery in GLS by the sixth cycle (-21.3±2.1%). The significant decrease in systolic LSR in the whole group after the sixth cycle (-1.5±0.2 to 1.3±0.4 /sec) was explained by the significant drop in the cardiotoxicity group only, whereas the group without cardiotoxicity did not experience a change. A similar pattern emerged in GRS, LV twist, apical rotation, and untwist rate, where significant decreases occurred by the sixth cycle in the whole group (GRS: 47.5±5.5 to 43.2±5.1%; LV twist: 12.0±0.8 to 10.1±0.9°; apical rotation: 7.7±3.5 to 6.2±1.1°; untwist rate: 85.5±12.8 to 71.4±16.5°/sec), with no differences in the change between the two groups. There were no changes in GCS,
CSR, RSR, or basal rotation. The change in GLS and systolic LSR from baseline to post third cycle demonstrated a strong ability to predict decrease in LVEF >10%.

Dogru et al.\textsuperscript{185} measured GLS in the apical 2- and 4-chamber views as well as GLS calculated as the average across all three views before and one month after low dose (150-200 mg/m\textsuperscript{2}) doxorubicin in 35 breast cancer patients. Only GLS in the apical 4-chamber view demonstrated a significant decrease after chemotherapy (-17.9±3.6 to -16.4±3.2), and there was no change in LVEF. Although 40% of these study participants had hypertension, the reported baseline and change values following anthracycline chemotherapy did not differ from the aforementioned studies.

Additionally, strain parameters have been used in long-term follow-up to distinguish between anthracycline-treated breast cancer survivors and either no chemotherapy or healthy controls in four studies.\textsuperscript{198-201} Bi et al.\textsuperscript{198} demonstrated the ability of peak systolic GLS to distinguish between 42 women treated with \geq 360 mg/m\textsuperscript{2} of epirubicin and 36 no chemotherapy controls for all 18 LV segments. In the same study, a group of 38 women treated with 120-340 mg/m\textsuperscript{2} of epirubicin were distinguishable from both the controls and the higher dose group on 11 longitudinal segments. Ho et al.\textsuperscript{199} compared peak systolic regional and global longitudinal and radial strain between 70 breast cancer survivors treated with anthracyclines up to six years earlier and 50 healthy controls. GLS and several regional longitudinal strain segments were significantly lower in the survivors compared to the controls, and the magnitude of the difference was not affected by anthracycline dose or time since last treatment. Global and regional radial strain were not different between the two groups. Khouri et al.\textsuperscript{200} reported that the change in GLS from rest to peak exercise is significantly different between 38 doxorubicin-treated survivors 35±20 months following
treatment and 11 healthy controls. Bulten et al.\textsuperscript{201} compared all directions of strain and strain rate between 57 breast cancer survivors 12.6 months post completion of doxorubicin treatment and previously published norms for the same age category. Mean strain did not differ between the study population and previously published norms, but mean strain rates (LSR, RSR, CSR inclusive) were all significantly lower.

Approximately 11 other studies have examined strain parameters before and after anthracycline treatment for other cancer types, and 4 studies in rodents injected with doxorubicin. These studies are summarized in Table 2.4. The three studies\textsuperscript{184,185,202} using 2DSTE to measure strain in adult patients demonstrated significant and progressive deterioration of GLS, whereas it did not change in the three studies\textsuperscript{203-205} using TDI to measure strain. These latter studies, all from the same group of researchers, did however consistently demonstrate a deterioration of systolic LSR after just 200 mg/m\textsuperscript{2} of epirubicin.\textsuperscript{203-205}

Two recent studies\textsuperscript{184,202} have investigated the use of LV rotation imaging for early identification of anthracycline-induced cardiotoxicity and demonstrated that it may be a better marker of early cardiotoxicity than strain imaging (Table 2.4). Motoki et al.\textsuperscript{184} measured peak systolic net LV twist angle and twisting rate, peak early diastolic untwisting rate, GLS and GCS before anthracycline treatment in 25 predominantly (72\%) non-Hodgkin’s lymphoma patients and at one month (mean dose 98±59 mg/m\textsuperscript{2}) and three months (mean dose 170±87 mg/m\textsuperscript{3}) into treatment. Throughout the study, there were no change in any standard echocardiographic parameters or tissue Doppler imaging parameters other than an increase in isovolumic relaxation time at three months, yet LV torsion, twisting and untwisting rates and GLS were significantly lower at one month and three months into
treatment compared to baseline. In addition, these myocardial mechanics parameters were significantly inversely correlated with anthracycline dose. Three patients in this study had received anthracyclines two years or more earlier and showed impaired torsion at baseline and progression of impairment with further treatment.

Mornos et al.\textsuperscript{202} measured cardiac rotation parameters and GLS and GRS before, at 6 weeks (mean dose $118 \pm 43 \text{ mg/m}^2$) and 12 weeks (mean dose $178 \pm 58 \text{ mg/m}^2$) after starting anthracycline treatment in 74 patients with mixed adult cancer types (45\% breast). At baseline, all cardiac mechanic parameters were not significantly different in the patient group compared to a healthy control group. By 6 weeks into anthracycline treatment, LV apical rotation, LV twist, GLS, and GRS, as well as a new combined parameter of GLS multiplied by LV twist were all significantly lower than baseline ($8.1 \pm 1.4$ to $6.8 \pm 1.3^\circ$; $13.8 \pm 1.7$ to $12.3 \pm 1.7^\circ$; $-21.2 \pm 2.5$ to $-19.0 \pm 2.4\%$; $47.8 \pm 5.3$ to $41.1 \pm 5.4\%$; $-297 \pm 68$ to $-238 \pm 57\%^\circ$, respectively). A dose response relationship was exhibited between anthracycline dose and all of these parameters by a further significant deterioration between 6 and 12 weeks. No differences over the course of the study were identified in LV basal rotation and LV untwist rate.

In studies measuring strain during anthracycline treatment in children, GLS, GRS, LSR and RSR deteriorated during\textsuperscript{206} and after\textsuperscript{207-209} treatment. A few long-term follow-up studies to anthracycline treatment in childhood cancer survivors have reported that LV rotation mechanics differ among treated and healthy controls, particularly in the apical rotation, twisting and untwisting rate.\textsuperscript{210,211} Four studies have measured strain parameters in rodents before, during and after chronic anthracycline injection.\textsuperscript{212-215} The time detection threshold (i.e. earliest time for detection) for strain parameters was similar to standard
echocardiography parameters including LVEF and fractional shortening, likely due to their use of supraclinical doses of doxorubicin known to cause severe cardiotoxicity.

Requirement: Biological plausibility for cause-effect relationship

The first requirement proposed by Marti et al.\textsuperscript{174} that candidate outcome measures for clinical trials should meet is that there is biological plausibility for cause and effect between the disease process and the measure. There are proposed mechanisms for how anthracycline-induced cardiotoxicity causes changes in myocardial mechanics at both structural and cellular levels. The subendocardium is the most vulnerable tissue layer to diseases of the myocardium including myocardial ischemia, due to its higher metabolic demands or lower blood supply.\textsuperscript{216} Due to the predominantly longitudinal orientation of the subendocardium, this will result in decreased longitudinal strain but circumferential strain and the net LV twist angle may remain preserved.\textsuperscript{176,217} However, anthracycline-induced cardiotoxicity does not result in a similar pattern. The fact that anthracycline treatment is associated with reduced longitudinal, radial, and circumferential strain\textsuperscript{190} in addition to twist mechanics\textsuperscript{184} indicates that anthracyclines likely affect all layers of the heart.\textsuperscript{176,188,217} This is a plausible explanation due to the systemic nature of chemotherapy treatment. Morphological evidence indicates that although myocyte damage occurs intramurally, the highest concentration of myocyte damage occurs in the subendocardium.\textsuperscript{218} This morphological finding matches that of a recent systematic review that reported that during or immediately after anthracycline treatment, the most common and largest size of change is in GLS, with changes in GRS and GCS being smaller and occurring less frequently.\textsuperscript{46}

At a cellular level, the cardiomyocyte oxidative stress associated with anthracyclines leads to calcium overload and increased calpain activity. The proteolytic action of calpains
lead to degradation and disarray of titan, a myofilament protein that plays a central role in sarcomere formation and myocardial mechanics. Calpain activation and subsequent titan degradation are early events occurring in cardiomyocytes after anthracycline treatment. It is hypothesized that these events underlie the early decrease in LV strain and torsion seen with anthracycline treatment. Other significant relationships identified between myocardial mechanics parameters and pulse wave velocity, ROS, IL-6 and antioxidants support the hypothesis that the decrease in mechanical function may be related to ROS-mediated damage.

Requirement: Measurability

The second requirement that candidate outcome measures for clinical trials should fulfill is that they are measurable. Measurement of myocardial mechanics parameters is feasible. Most modern cardiac ultrasound machines have the ability to do TDI or 2DSTE and capture the images required for offline processing. A special software package is required for analysis, and there are some issues between different software vendors in that a proprietary format may be used that cannot be used in other vendor’s software, although a solution to this issue is currently being investigated. A trained sonographer has the skills and experience to do the imaging and can learn the analysis techniques.

Measurement of myocardial mechanics parameters is reliable, and reliability is highest when a single observer does the analysis. Reported intra-observer reliability for peak GLS (ICC=0.94, CV=3.5%) and GRS (ICC=0.91, CV=3.2%) are very good in anthracycline-treated breast cancer patients. Intra-observer reliability for LV net twist angle in anthracycline-treated adults with mixed cancer types is very good (ICC=0.93, CV=3.1%). Inter-observer reliability for peak GLS (ICC=0.90, CV=5.2%) and GRS (ICC=0.82,
CV=5.4%) are very good for anthracycline-treated breast cancer patients.\textsuperscript{186} Inter-observer reliability for LV net twist angle is very good (ICC=0.89, CV=4.8%).\textsuperscript{202} Test-retest reliability has been reported as \( \pm 7.2\% \) for GLS, \( \pm 2.9\% \) for LSR, \( \pm 9.5\% \) for GRS, \( \pm 8.5\% \) for RSR, \( \pm 8.9\% \) for GCS, \( \pm 7.2\% \) for CSR, \( \pm 8.6\% \) for twist, and \( \pm 10.5\% \) for untwist rate.\textsuperscript{69}

However, the requirement of high quality images for the speckle tracking echocardiography techniques used to measure myocardial mechanics may limit their ability to be consistently measured within a breast cancer population. Scar tissue related to left-sided mastectomy, expanders and/or silicone implants, and chest pain\textsuperscript{191,194} higher subcutaneous fat, and older age, are factors that may impede the acquisition of high quality echocardiographic images in breast cancer patients. Global strain parameters, especially GLS, seem to have been the most consistently measured and show the most consistent results in terms of capturing anthracycline-related changes in cardiac function in adult cancer patients. Previous longitudinal studies have reported paired GLS measurements (i.e. both time points within a given participant) before and after anthracycline chemotherapy being analyzable in 87-88\% of breast cancer patients,\textsuperscript{193,194} whereas paired measurements of GRS and GCS were only available in 76-79\% of patients.\textsuperscript{191,192} Another study with a single time point one year post completion of anthracyclines, reported insufficient image quality for successful acquisition of GLS in 4\% and GRS and GSC in only 28\% of breast cancer survivors.\textsuperscript{201} All of the aforementioned studies appear to have acquired the scans specifically for research purposes and utilized practices to maximize image analyzability for myocardial mechanics. The use of clinical scans may further reduce these rates.
 Requirement: Established clinical relevance

The third requirement that candidate outcome measures for clinical trials must fulfill is that it has a consistent and credible observational association with outcomes. The prognostic value of strain parameters for cardiovascular events is not known for the cancer population, but this has been investigated in a number of studies in other populations as shown in Table 2.5. GLS was predictive of all-cause mortality for a number of cardiac conditions ranging from 546 individuals with known or suspected LV dysfunction,222 to 849 individuals who experienced a recent myocardial infarction and were awaiting coronary angioplasty.223 In some of these studies, GLS was a stronger predictor than LVEF.222,224

Several studies have identified early changes in myocardial mechanics parameters as significant predictors of cardiotoxicity from one month up to one year after completion of anthracycline treatment.69,186,190,191 GLS and GRS were significant prognosticators in relation to trastuzumab-related cardiotoxicity.186,190,191 Decreases in GLS and LSR from baseline to halfway through anthracycline treatment greater than 9% and 12% respectively, were significant and sensitive predictors of a >10% LVEF decrement by completion of treatment in breast cancer patients.69 Mornos et al.202 also demonstrated the prognostic value of GLS for anthracycline-related cardiotoxicity in mixed cancer types, and additionally reported that GLS multiplied by LV net twist angle, LV apical rotation, LV net twist angle alone, and LV torsion were significant predictors. In a selected population of patients with normal to low-normal LVEF (i.e. 50 to 59%), GLS, but not LVEF prior to anthracycline treatment was predictive of major adverse cardiac events.73 However the prognostic value of an anthracycline-related decrease in myocardial mechanics or LVEF for mortality and cardiovascular events is not known.
Reduced GLS has been reported over two decades after anthracycline treatment in Hodgkin’s lymphoma survivors compared to healthy controls and non-anthracycline treated survivors suggesting that the anthracycline-induced changes in strain are not transient. Further research is needed to elucidate the association between myocardial mechanics parameters and CV events and mortality in anthracycline-treated cancer survivors.

Requirement: Amenability to intervention

The fourth and final requirement that candidate outcome measures for clinical trials must fulfill is that it is amenable to intervention, or in other words, responsive to treatment. There is some initial evidence regarding the effect of interventions on myocardial mechanics. In a RCT of the cardio-protective effects of Telmisartan, an angiotensin II receptor blocker, LSR was able to differentiate between the placebo and treatment groups after 300 mg/m² of epirubicin up to the final follow-up measure taken at 18 months in adult mixed cancer types. The antioxidant Salidroside, also had a significant effect on LSR relative to placebo after the third and fourth cycles (300 mg/m² and 400 mg/m²) of epirubicin in breast cancer patients. Negishi et al. performed an observational study of mixed diagnoses adult cancer patients who received anthracyclines alone, trastuzumab alone, or both, and also experienced a decline in GLS ≥11% at 6 months post initiation of treatment. Those who were non-randomly prescribed β-blockers due to the decline in GLS experienced a significant improvement in GLS, whereas there was no change in those who did not receive treatment. In mice, the antihyperlipedemic, Probucol, attenuated the marked doxorubicin-induced reduction in RSR demonstrated in the placebo animals.
A few studies have evaluated the response of myocardial mechanics to exercise training in healthy and in non-cancer clinical populations, but the results are conflicting. In a study of 20 competitive rowers, 90 days of organized athletics significantly increased all segments of regional longitudinal, radial and circumferential strain. However, in another study of 10 young healthy men who completed 24 weeks of aerobic exercise training, peak systolic GLS and LSR, peak early diastolic and late diastolic strain rates did not significantly change, despite the occurrence of the typical eccentric hypertrophy associated with endurance training. Two studies have demonstrated nominal but statistically significant changes in longitudinal, radial and circumferential strain with 6-12 months of high volume endurance training in previously untrained, healthy, young individuals. However the direction of the changes was conflicting for apical circumferential and radial strain, and apical rotation. There was no change in TDI-derived regional longitudinal strain and strain rate in just two selected segments following 16 weeks of three times per week moderate intensity aerobic and resistance exercise training in symptomatic but medicated heart failure patients.

The effect of exercise training on myocardial mechanics has not been previously assessed in a cancer population who has received cardiotoxic cancer therapy. The cardiac adaptations to exercise could arguably be different amongst young, athletic individuals with normal heart function, older individuals with established cardiac pathology, and individuals with normal heart function exposed to an event known to cause negative cardiac function changes (i.e. breast cancer patients treated with anthracyclines). This is to say that exercise-induced prevention of negative cardiac changes could be a different physiological process than exercise-induced improvements in baseline cardiac function. There are examples of the
former that more closely parallel exercise-induced cardio-protection from chemotherapy-related changes. For example, exercise cardio-protection from aging-related decline in cardiac function has been demonstrated by cross-sectional studies of masters athletes compared to age-matched, less active, or sedentary controls. Competitive Masters athletes and committed lifelong exercisers have significantly higher systolic function and diastolic filling and relaxation relative to sedentary or casual exercisers.\textsuperscript{233} Scott et al. provide another example of exercise-induced cardio-protection from a negative event, where aerobic and resistance training prevented head-down tilt bed rest-induced myocardial dysfunction.\textsuperscript{234} The decline in LV twist, GLS, and GRS that occurred in the control group following 70 days of head-down tilt bed rest was completely prevented by exercise training. Overall there is evidence that myocardial mechanics parameters are amenable to pharmacological and exercise intervention, yet there appears to be a differential response amongst the different variables (i.e. strain vs. strain rates of the different coordinates) depending on the intervention.

Summary

In summary, the literature demonstrates a consistent relationship between anthracycline treatment for breast and other cancer types and negative changes in echocardiography-derived myocardial mechanics parameters. Upon further examination of a proposed schema for evaluation of an outcome measure for a phase II or III clinical trial,\textsuperscript{174} thus far, myocardial mechanics parameters appear to be suitable outcome measures. Biological plausibility exists for anthracycline-induced decreases in myocardial strain; myocardial mechanics appear to be measurable and reliable, at least for purposes of clinical assessment; consistent associations with outcomes are established; and lastly, some
myocardial mechanics parameters have been shown to be amenable to pharmacological interventions in animal models and cancer populations, and exercise intervention in healthy populations. However, further investigation of the reliability of ascertaining the different parameters in breast cancer populations for purposes of assessing an intervention (i.e. repeated measurements in a longitudinal study), and response to exercise training during cardiotoxic therapies are required.

2.4.2.2 Cardiac biomarkers

Cardiac troponin is a protein complex that regulates the contraction of cardiac muscle.\textsuperscript{235} There are three isoforms of cardiac troponin that play different roles in the regulation of cardiac muscle contraction. Cardiac troponin C binds calcium, cardiac troponin T (cTnT) attaches to tropomyosin on thin filaments of myofibrils, and cardiac troponin I (cTnI) inhibits actomyosin ATPase.\textsuperscript{235} cTnT and cTnI have unique N-terminal amino acid sequences that can be identified by assays and therefore allow for detection of elevated levels in circulating blood.\textsuperscript{235} Increased levels of circulating cardiac troponins is a highly sensitive diagnostic tool indicating presence of myocardial infarction.\textsuperscript{235} Both cTnI and cTnT have demonstrated diagnostic utility and the sensitivity of assays is continuously improving, such that even a minor increase in troponin can be detected.\textsuperscript{235}

Cardiac natriuretic peptides are released from the heart in response to increased hemodynamic stress such as chamber overload and increased wall tension and also in response to angiotensin II, endothelin, cytokines, insulin, thyroid hormones and estrogens.\textsuperscript{236} Their release is associated with systemic arterial dilatation and modulation of blood volume.\textsuperscript{236} Atrial natriuretic peptide is synthesized and released from the atria, whereas B-type natriuretic peptide (BNP) and the amino-terminal fragment of its precursor (NT-
proBNP, are synthesized and secreted by the ventricles.\textsuperscript{236} Like cardiac troponins, assays have been developed to measure circulating cardiac natriuretic peptide levels in the bloodstream.

Response of cardiac biomarkers to anthracycline treatment

The use of cardiac biomarkers for stratification of heart failure patients into risk categories is well established.\textsuperscript{51} There is now accumulating evidence that cardiac biomarkers serve as early indicators of future cardiotoxicity,\textsuperscript{45} and may be a valid minimally-invasive diagnostic and monitoring tool for cancer-related cardiotoxicity.\textsuperscript{237} Table 2.6 summarizes the cardiac biomarker response during and after anthracycline treatment in numerous studies. Even after the first cycle of anthracycline treatment, elevation of biomarkers often occurs. Several studies have reported an elevation in cTnI following the first cycle of anthracyclines in approximately one third of patients,\textsuperscript{238-241} and following completion of anthracyclines,\textsuperscript{190,191,242} whereas others have reported no change.\textsuperscript{205,243-245} The kinetics of cTnI response following a single treatment seem to be variable, and several measurement time points may be necessary to capture the peak response.\textsuperscript{239} cTnT does not appear to increase in a high percentage of individuals following the first dose of anthracyclines, nor following the completion of treatment in most studies.\textsuperscript{186,246-249}

NT-proBNP is the cardiac biomarker with the most evidence for a statistically significant response,\textsuperscript{247,250,251} and response in a high percentage of patients\textsuperscript{245,248,252} following the first cycle of anthracyclines. Analysis of the kinetics of NT-proBNP following a single cycle of anthracyclines indicates that 24 hours following infusion is the optimal time to catch the peak response.\textsuperscript{245,247,251,252} NT-proBNP also appears to be elevated following completion of anthracycline treatment.\textsuperscript{245,253-255}
There is not strong evidence regarding the response of atrial natriuretic peptide, BNP and creatine kinase MB to anthracyclines. The response of atrial natriuretic peptide to anthracyclines has not been frequently assessed, but appears to increase significantly both during and following treatment.\textsuperscript{247,255,256} There is mixed evidence regarding the BNP response following anthracycline therapy on the other hand, as increases\textsuperscript{241,243,256} and no change\textsuperscript{205,242} have been reported, and no studies have investigated the response to single cycles, likely due to its short 20-minute half-life.\textsuperscript{236} There appears to be no response of creatine kinase MB, an enzymatic marker of muscular damage now replaced by the more specific cardiac troponins, to anthracycline treatment.\textsuperscript{205,247,249,251,253,254}

**Requirement: Biological plausibility for cause-effect relationship**

Although there is a strong biological plausibility for the cause-effect relationship between cardiac dysfunction in general and elevated cardiac biomarkers in the circulation, there is not a strong understanding of the specific mechanism for anthracycline-induced elevations in circulating cardiac biomarkers. For example, there is a strong established relationship between increased circulating cardiac troponins and myocardial infarction, but the origin of cardiac troponins following chemotherapy does not seem to be related to ischemia.\textsuperscript{45} An animal model of anthracycline-induced cardiotoxicity demonstrated a strong relationship between reduced LV contractility and increased cTnT levels.\textsuperscript{257} Elevated troponin levels indicate myocardial injury, but do not indicate the mechanism of injury, as several other etiologies of elevated troponin levels have been reported including silent myocardial necrosis, pathological LV hypertrophy, LV systolic dysfunction, increased cardiac preload, microvascular disease, and endothelial dysfunction secondary to oxidative stress.\textsuperscript{258} However, it has been argued that the accumulated evidence of the relationship
between cardiac dysfunction and cTnI response provides a rationale for the measurement of cTnI in all patients undergoing chemotherapy, regardless of the mechanism of myocardial injury underlying the cardiotoxic effect of cancer therapies.\textsuperscript{237}

The natriuretic peptides are released into the circulation in response to mechanical stimulation or in response to neuroendocrine agents, triggering systemic arterial dilatation via increased excretion of sodium and urine.\textsuperscript{236} Plasma BNP levels increase within four hours of an acute ventricular overload.\textsuperscript{259} A relationship exists between elevation of natriuretic peptides and anthracycline-related cardiac damage,\textsuperscript{236} but it is less clear which trigger causes this response. It has been hypothesized that elevations of BNP and NT-proBNP in the context of cardiotoxic cancer therapy demonstrate a pathologic overload cardiomyopathy.\textsuperscript{45} Early investigations of BNP response to anthracyclines supported this hypothesis by a positive correlation with LV end-diastolic diameter,\textsuperscript{260} but a more recent, larger study utilizing more modern chemotherapy protocols did not report a relationship between natriuretic peptides and diastolic dysfunction.\textsuperscript{261}

Requirement: Measurability

In contrast to echocardiography, the interpretation of cardiac biomarker measurement results does not rely on the expertise of the operator, which eliminates error introduced by inter-observer variability.\textsuperscript{237} Although this factor improves the reliability of cardiac biomarkers, there are a number of limitations to the measurement of both cardiac troponins and natriuretic peptides for the assessment of anthracycline-related cardiotoxicity. The variability in assay sensitivity and subsequent inability to compare absolute concentrations of cardiac troponins limits their measurability.\textsuperscript{235} The measurement of natriuretic peptides for monitoring cancer treatment related cardiac dysfunction is limited by
day-to-day variability and confounding variables such as age, gender, renal function, body weight, and presence of metabolic or endocrine diseases.\textsuperscript{236} As discussed above, the timing of the blood sample following anthracycline administration is critical to the detection of a positive cardiac biomarker response. For example, peak values of cTnI following high dose chemotherapy treatment occurred after 12 hours in 22\%, after 24 hours in 8\%, after 36 hours in 24\%, and after 72 hours in 13\% of cases,\textsuperscript{239} indicating substantial inter-individual variability in kinetics. The requirement for three to four venipunctures following each chemotherapy treatment reduces the feasibility of cTnI for clinical or research assessment of cardiotoxicity. NT-proBNP, on the other hand, seems to produce a reliable response at 24 hours after a treatment.\textsuperscript{245,247,251,252}

Requirement: Established clinical relevance

A large epidemiological study of more than 11,000 individuals reported a significant risk of cardiovascular disease mortality within the 10 years of follow-up after a cTnT measurement $>14$ ng/L (HR=7.34) and NT-proBNP measurement $>159$ pg/ml (HR=7.48) compared to those in the lowest quintile for these biomarkers, even after adjustment for other cardiovascular disease risk factors.\textsuperscript{262} NT-proBNP $>159$ pg/ml was also significantly associated with risk of cancer mortality (HR=1.41), with no differentiation on cancer type or treatment available.\textsuperscript{262} In non-Hodgkin’s lymphoma patients, a NT-proBNP level over 900 pg/ml prior to chemotherapy was significantly associated with mortality (HR=14.7) within 13 months of follow-up.\textsuperscript{263}

There is evidence for the cardiac event prognostic value of cardiac biomarkers. cTnI is predictive of major adverse cardiac events within 20 months of follow-up to high-dose chemotherapy in mixed cancer types.\textsuperscript{239} Cardinale et al. reported that 1\% of 495 patients
without an increase in cTnI following treatment experienced a cardiac event, compared to 37% of 145 patients with an early (i.e. within 3 days after a chemotherapy treatment) cTnI increase that was not sustained, and 84% of 63 patients with early and late (i.e. within one month of completion of chemotherapy) cTnI increases.\textsuperscript{239}

A number of studies have reported associations between cardiac biomarkers and anthracycline-induced decreases in LVEF. In 201 women treated with high-dose chemotherapy for breast cancer, LVEF significantly decreased by one month after treatment in individuals who experienced an cTnI $\geq$0.05 ng/ml during treatment, whereas those without cTnI elevations did not experience a change in LVEF.\textsuperscript{238} Thirty-two percent of mixed cancer types treated with high-dose chemotherapy presented with an elevated cTnI above the 99\textsuperscript{th} percentile of healthy controls (0.07 $\mu$g/L) and a concomitant 18% decrease in LVEF compared to a 2.5% decrease in patients with cTnI below the cut-off.\textsuperscript{240} In 43 epirubicin or doxorubicin-treated breast cancer patients, cTnI >0.015 $\mu$g/L at three months after initiating treatment was significantly predictive of development of LVEF-defined cardiotoxicity within six months of initiating chemotherapy (OR=9.0, 1.8-50).\textsuperscript{191} In a group of 33 doxorubicin-treated breast cancer patients, the change in NT-proBNP was significantly higher in individuals who also experienced a decrease in LVEF.\textsuperscript{253} NT-proBNP and proANP following epirubicin treatment for breast cancer were significantly associated with a decrease in LVEF ($r=0.7$, $r=0.8$, respectively), and marked elevations occurred in 100% of the women who experience a LVEF of at least 10 percentage points.\textsuperscript{255} NT-proBNP elevation seems to be exclusive to anthracycline treatment, as increases were not reported for non-anthracycline-treated breast cancer patients.\textsuperscript{255} The level of post-epirubicin increase in NT-proBNP is
comparable to women with New York Heart Association classification of II-IV heart failure.\textsuperscript{255}

Requirement: Amenability to intervention

There are a few RCTs utilizing cardiac biomarkers as an outcome to assess the effect of a cardio-protective agent during anthracycline treatment in humans or rodents. One RCT investigated the effect of the ACE-inhibitor, enalapril, in adult cancer patients who experienced an elevation in cTnI within 72 hours of high-dose chemotherapy treatments.\textsuperscript{264} cTnI levels were significantly lower, and a lower percentage of participants in the treatment group had cTnI elevations as early as 2 months after enalapril was initiated. Furthermore, 2% of participants in the treatment group who had reduced levels of cTnI, experienced major adverse cardiac events relative to 52% in the non-treatment group whose cTnI levels remained elevated.\textsuperscript{264} Colombo & Cardinale\textsuperscript{265} reported that since completion of the latter study in 2006, they have screened >1300 cancer patients for cTnI elevations, and that enalapril has prevented significant decreases in LVEF over 1 to 5 years of follow-up. cTnT was similarly amenable to the iron-chelating cardio-protective agent dexrazoxane in childhood cancer patients receiving doxorubicin.\textsuperscript{266} There were significantly less patients with elevated levels of cTnT starting at 2 months post treatment in the group receiving dexrazoxane than the group receiving doxorubicin alone.\textsuperscript{266}

Rodent studies have reported an amenability of cTnI or cTnT to pharmacological intervention by dexrazoxane, erythropoietin, and the copper-chelator tetrathiomolybdate.\textsuperscript{267-269} Three rodent studies have demonstrated that 14 weeks of exercise preconditioning attenuates the doxorubicin-related increase in cTnI.\textsuperscript{80-82} Few studies have examined the effect of submaximal moderate duration exercise on cardiac biomarkers in non-athletic human
In cardiac populations, a single aerobic exercise bout can raise the level of NT-proBNP, but aerobic exercise training or cardiac rehabilitation does not improve baseline levels of NT-proBNP, despite an improved exercise capacity.

**Summary**

In summary, cardiac biomarkers are an active and promising area of investigation as early markers of anthracycline-related cardiotoxicity. Although the pathophysiology of the elevated response in cardiac troponins or natriuretic peptides following anthracycline treatment is not well understood, it is clear that it represents an indication of early myocardial injury. The measurement of cardiac biomarkers has the potential to be easy, minimally invasive and cost effective, but a number of factors can influence the results and further investigation is needed to determine the optimal timing for measurement. There is strong evidence supporting the clinical relevance of an elevation in cardiac troponins or natriuretic peptides in numerous populations, including cancer. These biomarkers are strong predictors of later development of cardiotoxicity and can be used to guide therapy that results in improved cardiac outcomes. Further, cardiac biomarkers have demonstrated amenability to pharmacological and exercise cardio-protection strategies. Therefore, cardiac biomarkers, specifically cardiac troponins and B-type natriuretic peptides, appear to be suitable outcome measures for phase II or III clinical trials.
### 2.5 Chapter 2 tables

Table 2.1: Evidence for potential mechanisms for exercise cardio-protection from doxorubicin

<table>
<thead>
<tr>
<th>Myocardial target</th>
<th>Role of target</th>
<th>Direction of exercise-induced change*</th>
<th>Direction of doxorubicin-induced change*</th>
<th>Evidence of exercise prevention of doxorubicin-induced change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant to oxidative stress ratio</td>
<td>Prevention of oxidative damage</td>
<td>↑ 79</td>
<td>↓ 36</td>
<td>✓ 81-85,274</td>
</tr>
<tr>
<td>Expression of α:β myosin heavy chain isoform in rodents</td>
<td>Motor protein required for muscular contraction; in a healthy rodent heart there is a much higher concentration of the α isoform</td>
<td>↑ 275</td>
<td>↓ 276</td>
<td>✓ 92,98-100</td>
</tr>
<tr>
<td>Caspase 3 and 9 activity</td>
<td>Markers for apoptotic signaling</td>
<td>↓ 277</td>
<td>↑ 49</td>
<td>✓ 82,87,88,90</td>
</tr>
<tr>
<td>HSP 60 expression</td>
<td>Controls protein folding and unfolding in response to stress</td>
<td>↑ 82</td>
<td>↑ 83</td>
<td>✓ 81,83</td>
</tr>
<tr>
<td>Mitochondrial permeability transition pore opening</td>
<td>Regulation of calcium handling and apoptosis</td>
<td>↓ 278</td>
<td>↑ 279</td>
<td>✓ 88</td>
</tr>
<tr>
<td>Ubiquitin-proteosome activation</td>
<td>Maintains protein function and quality control</td>
<td>↓ 280</td>
<td>↑ 62</td>
<td>✓ 87</td>
</tr>
<tr>
<td>Endothelial progenitor cell level</td>
<td>Physiologic and pathologic vessel formation</td>
<td>↑ 281</td>
<td>↓ 282</td>
<td>✓ 283</td>
</tr>
<tr>
<td>HSP72 expression</td>
<td>Controls protein folding and unfolding in response to stress</td>
<td>↑ 82,284 = 285</td>
<td>✓ 90</td>
<td>× 87,103</td>
</tr>
<tr>
<td>SERCA2a expression</td>
<td>Calcium recycling from the cytosol into the sarcoplasmic reticulum</td>
<td>↑ 286</td>
<td>↓ 287</td>
<td>✓ 288</td>
</tr>
</tbody>
</table>

### Mechanisms with evidence against their role in exercise cardio-protection

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP 70 expression</td>
<td>Controls protein folding and unfolding in response to stress</td>
<td>↑ 289</td>
</tr>
<tr>
<td>AMPK activation</td>
<td>Senses and regulates energy homeostasis</td>
<td>↑ 291</td>
</tr>
<tr>
<td>Myocardial target</td>
<td>Role of target</td>
<td>Direction of exercise-induced change*</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Cardiac progenitor cell level/ heart mass</td>
<td>Physiological turnover of cardiomyocytes</td>
<td>↑293</td>
</tr>
<tr>
<td>Expression of PGC-1α</td>
<td>Transcription coactivator that regulates mitochondrial biogenesis and angiogenesis</td>
<td>=95,96</td>
</tr>
</tbody>
</table>

**Potential mechanisms for exercise cardio-protection lacking investigation**

| Neuregulin-1/ErbB4 signaling          | Cardiac cell survival growth factor         | ↑296                                  | ↓297                                    | Ø                                                         |
| Expression of GATA-4                  | Transcription factor involved in cardiac survival, hypertrophic growth of the heart | ↑298                                  | ↓299                                    | Ø                                                         |

*Note: where possible reference cited provides evidence for the cardiomyocyte response, which may differ from other cell types

Abbreviations: HSP = heat shock protein; SERCA = sarcoplasmic reticulum calcium pump; AMPK = AMP-activated protein kinase; PGC = peroxisome proliferator-activated receptor-γ coactivator; ↑ = increase; ↓ = decrease; = = no change; ✓ = evidence available in favor of this mechanism; × = evidence available against this mechanism; Ø = no evidence available;
Table 2.2: Studies investigating the role of aerobic exercise cardio-protection from doxorubicin

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal model</th>
<th>Drug dosage &amp; timing</th>
<th>Exercise</th>
<th>Timing of outcome measurements</th>
<th>Outcomes in treated exercise training groups relative to treated sedentary group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascensão et al., 2011</td>
<td>Rats</td>
<td>Bolus 20 mg·kg⁻¹ DOX 24 hr after ex session</td>
<td>60 min of acute treadmill running ex before tx</td>
<td>5 days after DOX</td>
<td>Attenuated negative changes in markers of antioxidant defense in cardiac mitochondria, markers of apoptosis, cardiac mitochondrial function, and activity of oxidative phosphorylation respiratory complexes</td>
</tr>
<tr>
<td>Combs et al., 1979</td>
<td>Mice</td>
<td>Bolus 18 or 23 mg·kg⁻¹ DOX 30 min before ex</td>
<td>30 min of acute swimming ex after tx</td>
<td>Monitored for 30 days</td>
<td>Improved survival rate</td>
</tr>
<tr>
<td>Ji and Mitchell, 1994</td>
<td>Rats</td>
<td>2 x bolus 4 mg·kg⁻¹ DOX 24 hr and 30 min before ex</td>
<td>~25 min of acute exhaustive treadmill ex after tx</td>
<td>Immediately after ex or after 30 min recovery</td>
<td>Attenuation of some markers of cardiac mitochondrial respiration dysfunction</td>
</tr>
<tr>
<td>Wonders et al., 2008</td>
<td>Rats</td>
<td>Bolus 15 mg·kg⁻¹ DOX 24 hr after ex session</td>
<td>60 min of acute treadmill running ex before tx</td>
<td>5 days after DOX</td>
<td>Attenuated negative changes in LVESP, LVDP, rates of pressure development and decline, and lipid peroxidation</td>
</tr>
</tbody>
</table>

**Exercise training before treatment**

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal model</th>
<th>Drug dosage &amp; timing</th>
<th>Exercise</th>
<th>Timing of outcome measurements</th>
<th>Outcomes in treated exercise training groups relative to treated sedentary group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascensão et al., 2005</td>
<td>Mice</td>
<td>Bolus 20 mg·kg⁻¹ DOX 24 hr after last ex session</td>
<td>Swimming 60–90 min/d, 5 d/wk for 14 wks</td>
<td>24 hrs after DOX</td>
<td>Attenuated negative changes in cardiac troponin I, lipid peroxidation and other markers of oxidative stress in cardiac mitochondria, HSP60 expression, and improved markers of antioxidant defense</td>
</tr>
<tr>
<td>Ascensão et al., 2005</td>
<td>Mice</td>
<td>Bolus 20 mg·kg⁻¹ DOX 24 hr after last ex session</td>
<td>Treadmill running 60–90 min/d, 5 d/wk for 14 wks</td>
<td>24 hrs after DOX</td>
<td>Attenuated negative changes in cardiac troponin I, mitochondrial calcium control, cardiac mitochondrial function, and activity of oxidative phosphorylation respiratory complexes, markers of oxidative stress and apoptosis, and cardiomyocyte ultrastructural abnormalities, and improved antioxidant enzyme activity</td>
</tr>
<tr>
<td>Author</td>
<td>Animal model</td>
<td>Drug dosage &amp; timing</td>
<td>Exercise</td>
<td>Timing of outcome measurements</td>
<td>Outcomes in treated exercise training groups relative to treated sedentary group</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>----------------------</td>
<td>---------------------------------</td>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ascensão et al., 2006&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 20 mg·kg&lt;sup&gt;–1&lt;/sup&gt; DOX 24 hr after last ex session</td>
<td>Treadmill running 30 min/d, 5 d/wk, for 14 wks</td>
<td>24 hrs after DOX</td>
<td>Attenuated negative changes in markers of oxidative stress, antioxidant defense, respiratory chain dysfunction, and HSP60, and protected heart mitochondria against an oxidative stress-mediated deleterious stimulus</td>
</tr>
<tr>
<td>Ascensão et al., 2006&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Mice</td>
<td>Bolus 20 mg·kg&lt;sup&gt;–1&lt;/sup&gt; DOX 24 hrs after last ex session</td>
<td>Swimming 60 min/d, 5 d/wk for 24 hr after DOX</td>
<td>24 hr after DOX</td>
<td>Improved heart mass and skeletal muscle oxidative capacity, attenuated negative changes in vacuolar morphology, mitochondrial and sarcoplasmic reticulum structural damage</td>
</tr>
<tr>
<td>Ashrafi et al., 2012&lt;sup&gt;84&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 10 or 20 mg·kg&lt;sup&gt;–1&lt;/sup&gt; DOX 24 hr after last ex session</td>
<td>Treadmill running 25-54 min/d, 5 d/wk for 6 wks</td>
<td>24 hr after DOX</td>
<td>Attenuated negative changes in markers of oxidative stress and antioxidant defense</td>
</tr>
<tr>
<td>Ashrafi et al., 2012&lt;sup&gt;85&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 10 or 20 mg·kg&lt;sup&gt;–1&lt;/sup&gt; DOX 24 hr after last ex session</td>
<td>Treadmill running 25-39 min/d, 5 d/wk for 3 wks</td>
<td>24 hr after DOX</td>
<td>Attenuated negative changes in markers of oxidative stress and antioxidant defense</td>
</tr>
<tr>
<td>Chicco et al., 2005&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Rats</td>
<td>60 min cardiac perfusion with 10-µM DOX after last day of ex</td>
<td>Voluntary wheel running for 8 wks</td>
<td>During (cardiac function) or after (biochemical analyses) perfusion</td>
<td>Attenuated negative changes in LVDP, rates of pressure development and decline, HSP72, and lipid peroxidation</td>
</tr>
<tr>
<td>Chicco et al., 2006&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 15 mg·kg&lt;sup&gt;–1&lt;/sup&gt; DOX 24 hr after last ex session</td>
<td>Progressive treadmill running 20–60 min/d, 5 d/wk for 12 wks</td>
<td>5 days after DOX</td>
<td>Attenuated negative changes in coronary blood flow, mortality rate, LVDP, rates of pressure development and decline, and lipid peroxidation, and improved HSP72 expression</td>
</tr>
<tr>
<td>Author</td>
<td>Animal model</td>
<td>Drug dosage &amp; timing</td>
<td>Exercise</td>
<td>Timing of outcome measurements</td>
<td>Outcomes in treated exercise training groups relative to treated sedentary group</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>----------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hydock et al., 2008&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 10 mg·kg&lt;sup&gt;-1&lt;/sup&gt; DOX 24 hrs after last ex session</td>
<td>Progressive treadmill running 5 d/wk or voluntary wheel running for 10 wks</td>
<td>5 and 10 days after DOX</td>
<td>Attenuated negative changes in LV mass, LV circumferential shortening, aortic and mitral flow velocities, and LVDP, rates of pressure development and decline and maintained α-MHC expression</td>
</tr>
<tr>
<td>Hydock et al., 2011&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Rats</td>
<td>1 mg·kg&lt;sup&gt;-1&lt;/sup&gt;·d&lt;sup&gt;-1&lt;/sup&gt; DOX for 10 days 24 hrs after last ex session</td>
<td>Progressive treadmill running 5 d/wk or voluntary wheel running for 10 wks</td>
<td>4 sedentary weeks after exercise</td>
<td>Attenuated negative changes in survival rate, septal wall thickness in systole and diastole, relative wall thickness, LV mass, LVDP, rate of pressure development, aortic and mitral flow velocities, but not posterior wall thickness, or SERCA2a levels, and maintained α-MHC expression</td>
</tr>
<tr>
<td>Jensen, 2013&lt;sup&gt;109&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 10 mg·kg&lt;sup&gt;-1&lt;/sup&gt; DOX 24 hr after last ex session</td>
<td>Progressive treadmill running 20-60 min, 5 d/wk or voluntary wheel running for 10 wks</td>
<td>1, 3, 5, 7, and 9 days after DOX</td>
<td>Treadmill and wheel running attenuated negative changes in cardiac DOX accumulation and clearance, aortic and mitral flow velocities, fractional shortening, LVDP, LVESP, but not rates of pressure development and decline</td>
</tr>
<tr>
<td>Kavazis et al., 2010&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 20 mg·kg&lt;sup&gt;-1&lt;/sup&gt; DOX immediately after last ex session</td>
<td>Treadmill running 60 min for 5 consecutive d</td>
<td>24 hr after DOX</td>
<td>Attenuated negative changes in cardiac mitochondrial function, markers of cardiac mitochondrial oxidative stress and damage, and markers of cardiomyocyte apoptosis</td>
</tr>
<tr>
<td>Smuder et al., 2013&lt;sup&gt;300&lt;/sup&gt;</td>
<td>Rats</td>
<td>Bolus 20 mg·kg&lt;sup&gt;-1&lt;/sup&gt; DOX immediately after last ex session</td>
<td>Treadmill running 60 min for 5 consecutive d</td>
<td>24 hr after DOX</td>
<td>Prevented increased markers of cardiac autophagy signaling</td>
</tr>
<tr>
<td>Author</td>
<td>Animal model</td>
<td>Drug dosage &amp; timing</td>
<td>Exercise</td>
<td>Timing of outcome measurements</td>
<td>Outcomes in treated exercise training groups relative to treated sedentary group</td>
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<tr>
<td>Werner et al., 2008</td>
<td>Rats</td>
<td>Bolus 22.5 mg·kg⁻¹ DOX</td>
<td>Voluntary wheel running for 3 wks</td>
<td>24 hr after DOX</td>
<td>Attenuated negative changes in LV p53 expression, an important protein in DNA damage checkpoints, and markers of cardiomyocyte apoptosis</td>
</tr>
<tr>
<td>Wonders et al., 2009</td>
<td>Rats</td>
<td>Bolus 10 mg·kg⁻¹ DOX and 30 mg·kg⁻¹ HER2-inhibitor 24 hrs after last ex session</td>
<td>Progressive treadmill running 20-60 min, 5 d/wk for 10 wks</td>
<td>2, 5 or 10 days after DOX</td>
<td>Attenuated negative changes in LVDP, rates of pressure development and decline, oxidative stress, apoptosis</td>
</tr>
<tr>
<td>Chicco et al., 2006</td>
<td>Rats</td>
<td>2.5 mg·kg⁻¹·d⁻¹ for 2 wks starting on 1st ex session day</td>
<td>Treadmill running 20 min/d, and final ex session</td>
<td>5 days after DOX</td>
<td>Improved coronary blood flow, attenuated negative changes in LVDP, rates of pressure development and decline, HSP72, and myocardial apoptosis,</td>
</tr>
<tr>
<td>Dolinsky et al., 2013</td>
<td>Mice</td>
<td>8 mg·kg⁻¹·d⁻¹ for 8 wks starting at 1st ex session</td>
<td>Treadmill running 45 min/d, 5 d/wk for 8 wks</td>
<td>48 hrs after final ex session</td>
<td>Attenuated negative changes in LVESV and LVEF, and improved time and distance ran to fatigue</td>
</tr>
<tr>
<td>Hayward et al., 2012</td>
<td>Rats</td>
<td>2 mg·kg⁻¹·d⁻¹ DOX for 7 days, 1st injection before 1st day of ex</td>
<td>Voluntary wheel running for 10 wks</td>
<td>After final day of ex training</td>
<td>Attenuated negative changes in IVRT, aortic and mitral flow velocities, LVDP, rates of pressure development and decline</td>
</tr>
<tr>
<td>Hydock et al., 2009</td>
<td>Rats</td>
<td>2.5 mg·kg⁻¹ DOX 1 d/wk for 6 wks starting 1 wk after wheel running</td>
<td>Voluntary wheel running for 7 wks</td>
<td>7 days after last DOX</td>
<td>Maintained α-MHC expression</td>
</tr>
<tr>
<td>Author</td>
<td>Animal model</td>
<td>Drug dosage &amp; timing</td>
<td>Exercise</td>
<td>Timing of outcome measurements</td>
<td>Outcomes in treated exercise training groups relative to treated sedentary group</td>
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<tr>
<td>Hydock et al., 2011</td>
<td>Rats</td>
<td>15 mg·kg(^{-1})·d(^{-1}) DOX over 10 d and 2 x 3.6 mg LHRH agonist 24 hrs before 1(^{st}) ex session</td>
<td>Progressive treadmill running 5 d/wk for 8 wks</td>
<td>24 hrs after last ex session</td>
<td>Attenuated negative changes in septal wall thickness at end systole, aortic and mitral flow velocities, LVDP, rates of pressure development and decline, but not septal wall thickness at end diastole, posterior walk thicknesses or LV dimensions</td>
</tr>
<tr>
<td>Hydock et al., 2012</td>
<td>Rats</td>
<td>1 mg·kg(^{-1})·d(^{-1}) DOX over 15 d, 1(^{st}) injection before 1(^{st}) day of ex 2.5 mg·kg(^{-1})·wk(^{-1}) for 6 wks, 1(^{st}) injection before 1(^{st}) day of ex</td>
<td>Voluntary wheel running for 10 wks</td>
<td>After final day of ex training</td>
<td>Improved LVDd, attenuated negative change in aortic and mitral flow velocities, LVEDP, LVESP, LVDP, rates of pressure development and decline, maintained α-MHC expression</td>
</tr>
<tr>
<td>Jones et al., 2011</td>
<td>Mice</td>
<td>8 mg·kg(^{-1}) DOX 1 d/wk for 4 wks</td>
<td>Treadmill running 45 min, 5 NR d/wk for 8 wks</td>
<td>NR</td>
<td>Attenuated negative changes in LV systolic volume, fractional shortening, LVEF, markers of oxidative phosphorylation, aerobic capacity</td>
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<tr>
<td>Humans</td>
<td></td>
<td>60 mg·m(^{-1}) DOX</td>
<td>Aerobic exercise 60 min, 3 d/wk for 12 wks</td>
<td>Post-intervention</td>
<td>Improved VO(_2) peak and endothelial function, but did not attenuate negative change in hemoglobin</td>
</tr>
<tr>
<td>Kanter et al., 1985</td>
<td>Rats</td>
<td>40 mg·kg(^{-1}) DOX over 7 wks starting after 9 wks of ex training</td>
<td>Swimming 15-55 min, 5 d/wk for 21 wks</td>
<td>24 hr after last ex session</td>
<td>Improved antioxidant enzyme activity, and attenuated negative changes in cardiomyocyte morphology</td>
</tr>
</tbody>
</table>

**Note:** DOX refers to doxorubicin, LHRH is luteinizing hormone-releasing hormone, LVDP is left ventricular developed pressure, LVEDP is left ventricular end-diastolic pressure, LVESP is left ventricular end-systolic pressure.
<table>
<thead>
<tr>
<th>Author</th>
<th>Animal model</th>
<th>Drug dosage &amp; timing</th>
<th>Exercise</th>
<th>Timing of outcome measurements</th>
<th>Outcomes in treated exercise training groups relative to treated sedentary group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marques-Aleixo et al., 2015</td>
<td>Rats</td>
<td>2 mg·kg(^{-1}) DOX weekly over 7 wks, starting after 5 wks of ex training</td>
<td>Treadmill running 60 min, 5d/wk or voluntary wheel running, both for 12 wks</td>
<td>48 hr after last ex session</td>
<td>Both treadmill and voluntary running prevented negative changes in heart mass, mitochondrial density, mitochondrial respiration, mitochondrial damage, oxidative stress</td>
</tr>
<tr>
<td>Heon et al., 2003(^{13})</td>
<td>Rats</td>
<td>Bolus 3 mg·kg(^{-1}) DOX 2 wks before first ex session</td>
<td>Swimming 10-45 min/d, for 2 wks</td>
<td>After completion of ex training period</td>
<td>Reduced markers of cardiomyocyte apoptosis and oxidative stress and reduced expression of a cardiac-specific transcription factor</td>
</tr>
<tr>
<td>Matsuura et al., 2010(^{14})</td>
<td>Rats</td>
<td>10 mg·kg(^{-1}) DOX over 10 d 4 wks before first ex session</td>
<td>Treadmill running 60 min/d, 5 d/wk for 6 wks</td>
<td>Immediately after last ex session</td>
<td>Attenuated negative changes in mortality rate in rodents with confirmed cardiotoxicity</td>
</tr>
</tbody>
</table>

Abbreviations: DOX = doxorubicin; d = days; ex = exercise; HSP = heat shock protein; LHRH = luteinizing hormone-releasing hormone; LVDd = left ventricular dimension at end diastole, LVDP = left ventricular developed pressure; LVEDP = left ventricular end-diastolic pressure, LVESP = end-systolic pressure; LV = left ventricle; MHC = myosin heavy chain; min = minutes; NR = not reported; TZB = trastuzumab; tx = treatment; VO\(_2\)peak = peak oxygen consumption; wk(s) = week(s);
Table 2.3: Studies measuring left ventricular myocardial mechanics in breast cancer before and after anthracycline treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>n, age (yrs)</th>
<th>Agent, dose (mg/m²)</th>
<th>Time points (#, timing)</th>
<th>Conventional systolic and diastolic parameters</th>
<th>Myocardial mechanics imaging technique</th>
<th>Myocardial mechanics parameters</th>
<th>Myocardial velocity parameters</th>
<th>Biomarkers</th>
<th>Myocardial mechanics statistically significant findings</th>
<th>Other statistically significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogru et al., 2013¹⁸⁵</td>
<td>35, 49±10</td>
<td>DOX, 150-200</td>
<td>2; pre-CT, 1 mo post</td>
<td>LVEF, FS, MPI2DSTE</td>
<td>GLS</td>
<td>E', E/E' ratio</td>
<td></td>
<td></td>
<td>↓ GLS</td>
<td>↑ MPI; ↓ E'</td>
</tr>
<tr>
<td>Fallah-Rad et al., 2011¹⁸⁶</td>
<td>42, 47±9</td>
<td>EPI, ≤600 or DOX, ≤240</td>
<td>6; pre-CT, 3 wks post-CT/pre trastuzumab (data NR), 3, 6, 9, 12 mo post-CT</td>
<td>LVEF</td>
<td>2DSTE</td>
<td>GLS, GRS</td>
<td>E', A', S'</td>
<td>cTnT, CRP, NT-proBNP</td>
<td>Data NR for post anthracyclines; ↓ GLS &amp; GRS by 3 mo into trastuzumab tx in the 25% who developed LVEF-defined cardiotoxicity within 1 yr post-CT, progressive decline throughout tx to 12 mo</td>
<td>↓ S' by 3 mo post initiation of trastuzumab in those who later developed cardiotoxicity, persistent to 12 mo; ↓ LVEF by 6 mo post trastuzumab initiation in those who developed cardiotoxicity, persistent to 12 mo</td>
</tr>
<tr>
<td>Florescu et al, 2014⁶⁹</td>
<td>51±8</td>
<td>EPI, 268±22</td>
<td>3; pre-CT, 24 hr post 3⁰ cycle; 24 hr post 6⁰ cycle</td>
<td>LVEF, FS, E/A ratio, AVRD</td>
<td>2DSTE</td>
<td>GLS, LSR, GCS, CSR, GRS, RSR, basal &amp; apical Rot; LV twist; LV untwist rate</td>
<td>S'+Ss, E/E' ratio</td>
<td></td>
<td>↓ GLS after 3⁰ and 6⁰ cycles; ↓ GRS, LSR, LV twist, apical rotation, untwist rate after 6⁰ cycle</td>
<td>↓ LVEF, LVESV after 6⁰ cycle; ↓ E/A ratio, S'+Ss, AVRD after 3⁰ &amp; 6⁰ cycles; ↓ DLSR in every segment after 2⁰ cycle, ↓ Dm in the lateral, anterior &amp; inferior walls after 2⁰ cycle after the 3⁰ cycle of EPI</td>
</tr>
<tr>
<td>Jiang et al., 2013¹⁸⁷ ³⁰</td>
<td>NR dosage [Chinese]</td>
<td>EPI, NR</td>
<td>3; pre-CT, after 2⁰ cycle, after 3⁰ cycle</td>
<td>TDI</td>
<td>regional LS, LSR, &amp; DLSR</td>
<td>S', Ss, Dm</td>
<td></td>
<td></td>
<td>↓ DLSR in every segment after 2⁰ cycle of EPI; ↓ LSR in every segment</td>
<td>↓ Dm in the lateral, anterior &amp; inferior walls after 2⁰ cycle after the 3⁰ cycle of EPI</td>
</tr>
<tr>
<td>Author</td>
<td>n, age (yrs)</td>
<td>Agent, dose (mg/m²)</td>
<td>Time points (#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
<td>Myocardial mechanics parameters</td>
<td>Myocardial velocity parameters</td>
<td>Bio-markers</td>
<td>Myocardial mechanics statistically significant findings</td>
<td>Other statistically significant findings</td>
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<tr>
<td>Jurcut et al., 2008&lt;sup&gt;88&lt;/sup&gt;</td>
<td>16, 70±3</td>
<td>PL-DOX, 180</td>
<td>3; pre-CT, 7-14 d after 3&lt;sup&gt;rd&lt;/sup&gt;, 6&lt;sup&gt;th&lt;/sup&gt; CT cycles</td>
<td>LVEF, LV volumes, diameters, wall thickness &amp; mass index, E, A, E/A ratio, DT, IVRT, SV, AVRD, ACR, ACRT, Sp, Dp</td>
<td>GLS &amp; LSR, IFW RS &amp; RSR</td>
<td>E', A', S', Es, As, Ss</td>
<td>↓ RS &amp; RSR after 3 cycles &amp; again after 6 cycles; ↓ LS &amp; LSR after 6 cycles</td>
<td></td>
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<tr>
<td>Lange et al., 2015&lt;sup&gt;89&lt;/sup&gt;</td>
<td>27, 56 (SD NR)</td>
<td>EPI, 519 or DOX, 300</td>
<td>2; pre-CT, post-CT</td>
<td>LVEF, FS, SV, E, A, E/A ratio, DT, IVRT, Dp, Sp</td>
<td>GLS, regional E', A', S', Es, As, Ss</td>
<td>↓ GLS, septal, anterior, anterolateral LS</td>
<td>↓ LVEF, E, E/A ratio; ↑ LVESV &amp; LVEDV;</td>
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<tr>
<td>Sawaya et al., 2011&lt;sup&gt;90&lt;/sup&gt;</td>
<td>43, 48±10</td>
<td>EPI, 300 or DOX, 240</td>
<td>3; baseline/pre-CT, 3, 6 mo of tx</td>
<td>LVEF, LV volumes, diameters &amp; wall thickness, LA volume, E, A, E/A ratio</td>
<td>2DSTE GLS, GRS, GCS</td>
<td>E', E/E' ratio, cTnI, NT-proBNP</td>
<td>↓ GLS &amp; GCS by 3 mo; ↓ GRS by 6 months.</td>
<td>↑ LVESV &amp; ↓ LVEF by 6 mo; ↓ E' by 3 mo;</td>
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<tr>
<td>Sawaya et al., 2012&lt;sup&gt;91&lt;/sup&gt;</td>
<td>81, 50±10</td>
<td>EPI 300 mg/m² or DOX 240 mg/m²</td>
<td>2; pre chemo, post chemo</td>
<td>LVEF</td>
<td>2DSTE GLS, GRS, GCS</td>
<td>cTnI, NT-proBNP, ST2</td>
<td>↓ GLS, GRS, GCS post chemo</td>
<td>↓ LVEF post chemo; ↑ cTnI with ultra sensitive assay post chemo</td>
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<tr>
<td>Author</td>
<td>n, age (yrs)</td>
<td>Agent, dose (mg/m²)</td>
<td>Time points (#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
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<tr>
<td>Stoodley et al., 2012¹⁹²</td>
<td>49±9</td>
<td>DOX, 236±33 or EPI, 408±110</td>
<td>2; pre-CT, post-CT</td>
<td>LVEF</td>
<td>2DSTE</td>
<td>regional LS, RS &amp; CS; GLS &amp; LSR, GRS &amp; RSR, GCS &amp; CSR</td>
<td></td>
<td></td>
<td>↓ GLS &amp; GRS post-CT; ↓ regional LS in the basal, mid &amp; apical septum, as well as the mid &amp; basal lateral wall; ↓ LVEF post-CT</td>
<td>regional RS in the anterior septum, inferior &amp; septal walls; ↓ regional CS in septal wall</td>
</tr>
<tr>
<td>Stoodley et al., 2013¹⁹⁴ [same cohort as above]</td>
<td>52, 49±9</td>
<td>DOX, 236±33 or EPI, 408±110</td>
<td>2; pre-CT, post-CT</td>
<td>LVEF, LA max/min volume, LAF, SF, E, A, E/A ratio, ACRT, VTIs, VTId</td>
<td>2DSTE</td>
<td>GLS, DLS, ELSR, ALSR Es, As, E/Es</td>
<td></td>
<td></td>
<td>↓ ELSR post-CT</td>
<td>↑ A, LAF, SF post-CT; ↑ E/A ratio post-CT</td>
</tr>
<tr>
<td>Stoodley et al., 2013¹⁹³</td>
<td>52±10</td>
<td>DOX, 238 or EPI 392</td>
<td>4; pre-CT, 7 days post-CT, 6 &amp; 12 mo post baseline</td>
<td>LVEF, LV dimensions</td>
<td>2DSTE</td>
<td>GLS</td>
<td>Ss</td>
<td></td>
<td>↓ GLS 7 days post-CT &amp; 6 mo post baseline but recovered by 12 mo post baseline</td>
<td>↓ Ss 6 mo post baseline only</td>
</tr>
<tr>
<td>Tan et al., 2015¹⁹⁵</td>
<td>29, 50±10</td>
<td>DOX, 240 or EPI 300</td>
<td>3; pre-CT, post trastuzumab, &gt;12 post trastuzumab</td>
<td>LVEF, LV mass, LV dimensions, LVESV, LVEDV</td>
<td>2DSTE</td>
<td>GLS, LSR</td>
<td></td>
<td></td>
<td>No echo for post anthracyclines; ↓ GLS, LSR at end of trastuzumab persisting &gt;12 later</td>
<td>↓ LVEF, ↑ LV mass, LVEDV, LVESV at end of trastuzumab persisting &gt;12 later</td>
</tr>
<tr>
<td>Zhang et al., 2012¹⁹⁶</td>
<td>52±6</td>
<td>EPI, 440±40</td>
<td>5; pre-EPI, 1 wk after 100, 200, 300, 400</td>
<td>LVEF</td>
<td>TDI</td>
<td>IVS LSR</td>
<td></td>
<td></td>
<td>↓ LSR after 200 mg/m², persistent to 400 mg/m²</td>
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</tbody>
</table>
Abbreviations: 2DSTE = two-dimensional speckle tracking echo; A = mitral flow peak atrial filling velocity; ACR = peak reversal velocity during atrial contraction; ACRT = duration of atrial contraction reversal; Ad = late diastolic mitral annular velocity; ALSR = peak late diastolic longitudinal strain rate; As = late diastole interventricular septum myocardial velocity; AVRD = atrioventricular ring displacement; BNP = brain natriuretic peptide; CRP = C reactive protein; CS = peak systolic circumferential strain; cTnI = cardiac Troponin I; cTnT = cardiac Troponin T; d = day; DLS = diastolic longitudinal strain; DLSR = peak diastolic longitudinal strain rate; Dm = peak diastolic myocardial velocity; DOX = doxorubicin; Dp = pulmonary venous peak diastolic velocity; DT = mitral flow early deceleration time; E = mitral flow early phase filling velocity; ELSR = peak early diastolic longitudinal strain rate; Es = early diastole interventricular myocardial septum velocity; EPI = epirubicin; E' = early diastolic lateral mitral annulus velocity; GCS = peak systolic global circumferential strain; GLS = peak systolic global longitudinal strain; GRS = peak systolic global radial strain; IFW = inferolateral wall (radial axis); IVS = interventricular septum (longitudinal axis); LAF = left atrial fraction; LSR = longitudinal strain rate; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; mo = month; MPI = myocardial performance index; NR = not reported; PL-DOX = pegylated doxorubicin; RS = peak systolic radial strain; SF = systolic fraction; Ss = peak systolic interventricular septum myocardial velocity; Sp = pulmonary venous peak systolic velocity; SV = stroke volume; S' = systolic lateral mitral annulus velocity; TDI = tissue Doppler imaging; VTI = velocity time integral; wk = week
Table 2.4: Studies measuring myocardial mechanics in non-breast or mixed cancer before and after anthracycline treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>n, cancer type, age (yrs)</th>
<th>Agent, dose (mg/m²)</th>
<th>Time points (#, timing)</th>
<th>Conventional systolic and diastolic parameters</th>
<th>Myocardial mechanics imaging technique</th>
<th>Myocardial mechanics parameters</th>
<th>Myocardial velocity parameters</th>
<th>Bio-marker</th>
<th>Myocardial mechanics statistically significant findings</th>
<th>Other statistically significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dessi et al., 2013¹⁰³</td>
<td>24, Mixed adult cancers, ≤400±53±10</td>
<td>EPI, ≤400±30</td>
<td>7; pre-CT, 1 wk after EPI, doses of 100, atrial, 200, 300, 400 diameters, E, mg/m², 12 mo, 18 mo</td>
<td>LVEF, LV diameters, E, A, E/A ratio, DT, IVRT</td>
<td>TDI</td>
<td>IVS LS &amp; LSR</td>
<td>Ss, Es, As</td>
<td>TNF-α, IL-6, ROS, GPx, SOD</td>
<td>↓ LSR after 200 mg/m² with persistent decreased function to 18-month FU; ↓ E/A ratio after 300 &amp; 400 mg/m², then returned to baseline; ↑ IL-6 after 300 &amp; 400 mg/m² EPI; returned to baseline at 3 months FU; ↑ ROS after 200 &amp; 300 mg/m², then returned to baseline after 400 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Dogru et al., 2013¹⁸⁵</td>
<td>15, Lymphoma, 41±7</td>
<td>DOX, 300-400 mg/m²</td>
<td>2; pre-CT, 1 mo post-CT</td>
<td>LVEF, FS, MPI</td>
<td>2DSTE</td>
<td>GLS</td>
<td>E', E/E' ratio</td>
<td>↓ GLS</td>
<td>↓ LVEF, FS</td>
<td></td>
</tr>
<tr>
<td>Drafts et al., 2013²⁴²</td>
<td>53, Mixed adult cancers, 50±2</td>
<td>ANTH, 50-375</td>
<td>4; pre-CT, 1, 3, 6 mo post-CT start</td>
<td>LVEF, LV volumes</td>
<td>cMRI</td>
<td>middle papillary mid-wall CS</td>
<td>TnI, BNP ↓ CS at 6 mo</td>
<td>↑ LVESV, ↓ LVEF at 6 mo</td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>n, cancer type, age (yrs)</td>
<td>Agent, dose (mg/m²)(#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
<td>Myocardial mechanics parameters</td>
<td>Myocardial velocity parameters</td>
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<td>Myocardial mechanics statistically significant findings</td>
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<tr>
<td>Mantovani et al., 2008&lt;sup&gt;204&lt;/sup&gt;</td>
<td>31, Mixed adult cancers, 59±14</td>
<td>EPI, 300-400 mg/m²</td>
<td>9; pre-CT, 7 d after EPI doses of 100, 200, 300, 400 LVEF, E, A, E/A ratio, DT 12, 18 months post-CT start</td>
<td>TDI</td>
<td>IVS LS &amp; LSR</td>
<td>Ss, Es, As</td>
<td>IL-6, sIL-6R, TNF-α, sTNF-αR1, IL-1β, ROS, GPx, SOD</td>
<td>↓ E/A ratio after 300 &amp; 400 mg/m², then again at 6 mo FU; ↓ Es after 400 mg/m² &amp; 3-mo FU; ↓ Es/As ratio after 200 &amp; 3-mo FU; ↓ LSR after 200 mg/m², persistent until 6 mo FU; ↓ Ss at 18 mo FU; ↓ IL-6 after 200 mg/m², persistent to 400 mg/m²; ↓ sIL-6R after 100 mg/m², persistent until 3-mo FU; ↓ ROS at 200 mg/m²</td>
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<td>Mercuro et al., 2007&lt;sup&gt;205&lt;/sup&gt;</td>
<td>16, Mixed adult cancers, 56±3</td>
<td>EPI, 300-400 mg/m²</td>
<td>5; pre-CT, 7 d post EPI doses of 100, 200, 300, 400 LVEF, E, A, E/A ratio, DT</td>
<td>TDI</td>
<td>IVS LS &amp; LSR</td>
<td>Ss, Es, As</td>
<td>BNP, TnI, Myo, CK-MB, ↓ LSR after 200 ↓ E/A ratio, Es, IL-6, sIL-6R mg/m², EPI, persistent until 300 &amp; 400 mg/m²; ↑ GPx α, sTNF-αR1, IL-1α, ROS, GPx, SOD</td>
<td>Es/As ratio after 300 &amp; 400 mg/m²; ↑ GPx &amp; ↑ IL-6 &amp; sIL-6R after 200 mg/m²</td>
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<td>Author</td>
<td>n, cancer type, age (yrs)</td>
<td>Agent, dose (mg/m²)(#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
<td>Myocardial mechanics parameters</td>
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<tr>
<td>Mornos et al., 2013²⁰²</td>
<td>74, Mixed adult cancers, 51±11</td>
<td>DOX, 259±52 wks post-CT start</td>
<td>LVEF, E, A, E/A ratio, IVRT, IVRT</td>
<td>2DSTE</td>
<td>basal &amp; apical Rot; LV twist; LV untwist rate; GLS; GRS; LV twist x GLS</td>
<td>Ss, Es, As, E/Es ratio</td>
<td>TnT, NT-proBNP</td>
<td>↓ GRM, GLS, apical Rot, LV twist &amp; LV untwist rate &amp; GLS at 6 wks &amp; again between 6 &amp; 12 wks</td>
<td>↑ IVRT at 6 wks &amp; between 6 &amp; 12 wks; ↓ Ss at 6 wks &amp; between 6 &amp; 12 wks; ↑ E/Es ratio by 12 wks; ↑ cTnT by 6 wks, persistent at 12 wks</td>
<td></td>
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<tr>
<td>Motoki et al., 2012²⁰⁴</td>
<td>25, Adult hematologica cancers, 58±11</td>
<td>ANTH, 170±78 mo, 3 mo post-CT start</td>
<td>LVEF, LV volumes, dimensions, LA dimensions, E, A, IVRT, DT, Tei index, Sp, Dp</td>
<td>2DSTE</td>
<td>twist; twist &amp; untwist rate; GLS; GCS</td>
<td>Ss, Es, As</td>
<td>↓ twist, twist &amp; untwist rates, GLS</td>
<td>↓ IVRT at 3 mo</td>
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<tr>
<td>Al-Bitagi et al., 2012²⁰⁷</td>
<td>25, ALL, 9±3 DOX, 120</td>
<td>2; before and after CT (timing NR)</td>
<td>LVEF, LV dimensions, FS, E, A, E/A ratio, IVRT, IVCT</td>
<td>TDI</td>
<td>GLS</td>
<td>Ss, Es, As</td>
<td>cTnI, CKMB</td>
<td>↓ GLS post treatment</td>
<td>↓ FS, IVCT after treatment; ↑ cTnI, IVRT after treatment</td>
<td></td>
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<tr>
<td>Ganame et al., 2007²⁰⁶</td>
<td>13, Mixed childhood cancers, 11±4</td>
<td>ANTH, 45-225 hrs post cycle 1, 2, 3</td>
<td>LVEF, wall thickness &amp; thickening, E, A, E/A ratio, DT, IVRT, FS, AVRD, Sp, Dp, ACR, ACRT, MPI</td>
<td>TDI</td>
<td>IVS GLS &amp; LSR; IFW RS &amp; RSR</td>
<td>Ss, Es, As, E/Es</td>
<td>↓ GLS, LSR, RS, RSR after cycle 1; ↓ RS again between cycle 1 and 3</td>
<td>↓ LVEF after cycle 1 &amp; between cycle 1 and 3; ↓ wall thickening, AVRD, E, A, E/A ratio after cycle 1; ↑ IVRT, MPI after cycle 1</td>
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<tr>
<td>Author</td>
<td>n, cancer type, age (yrs)</td>
<td>Agent, dose (mg/m²)(#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
<td>Myocardial mechanics parameters</td>
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<tr>
<td>Mavinkurve-Groothuis et al., 2013</td>
<td>60, ALL, 6 (2 ANTH, ≤300 to 15)</td>
<td>3; pre-CT, 10 wks, 1 year post-CT start</td>
<td>LV mass, FS, IVRT, E/A ratio, E/E' ratio</td>
<td>2DSTE</td>
<td>GLS &amp; LSR; GRS &amp; RSR; GCS &amp; CSR</td>
<td>cTnT, NT-proBNP</td>
<td>↓ LSR, GRS, GCS by end of study</td>
<td>↓ IVRT, FS by 10 wks; ↓ z-scores of LV mass &amp; dimensions by end of study</td>
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<tr>
<td>Poterucha et al., 2012</td>
<td>19, Mixed childhood cancers, 15±33</td>
<td>ANTH, 3; pre-CT, 4, 8 mo post-CT start</td>
<td>LVEF, LV dimensions, wall thickness &amp; mass, E, A, E/A ratio</td>
<td>2DSTE</td>
<td>regional &amp; GLS</td>
<td>E', S'</td>
<td>↓ GLS at 4 mo, persistent to 8 mo</td>
<td>↓ ED IVS wall thickness, at 8 mo; ↑ A &amp; ↓ E/A ratio at 4 mo, persistent to 8 mo; ↓ E' &amp; S' at 8 mo</td>
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<tr>
<td>Jassal et al., 2009</td>
<td>10, Mice, NR</td>
<td>DOX, 20 (mg/kg) bolus</td>
<td>6; pre DOX, days 1-5 post volumes and dimensions, FS</td>
<td>TDI</td>
<td>papillary RSR</td>
<td>endocardial Ss</td>
<td>↓ RSR after 1 d, progressive to d 5</td>
<td>↓ LVEF, LVEDD, FS at day 5; ↓ Ss after d 1, progressive ↓ d 5; ↑ apoptosis markers after d 5 (not measured before)</td>
<td></td>
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<tr>
<td>Kim et al., 2012</td>
<td>29, Rats, 11 wks</td>
<td>DOX 206; pre DOX, (mg/kg) 1, 2, 4, 6, 8 wks initiation and volumes, FS,</td>
<td>LVEF, LV dimensions over 1 mo of DOX</td>
<td>2DSTE</td>
<td>GLS &amp; LSR; GRS &amp; RSR; GCS &amp; CSR</td>
<td>FS,</td>
<td>↓ GLS by 2 wks; ↓ LSR by 2 wks by 4 wks; ↓ GCS by 4 wks by 6 wks; ↓ CSR by 6 wks; ↓ GRS, RSR by 8 wks</td>
<td>↓ LVEF by 4 wks; ↓ FS by 6 wks</td>
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<tr>
<td>Author</td>
<td>n, cancer type, age (yrs)</td>
<td>Agent, dose (mg/m²)(#, timing)</td>
<td>Conventional systolic and diastolic parameters</td>
<td>Myocardial mechanics imaging technique</td>
<td>Myocardial mechanics parameters</td>
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<tr>
<td>Migrino et al., 2008²¹⁴</td>
<td>14, Rats, NR</td>
<td>DOX 2.5mg/kg/week pre DOX, 4; 8, 10 and 12 wks post-CT start</td>
<td>FS</td>
<td>2DSTE</td>
<td>GRS</td>
<td>capase-3</td>
<td>▼ GR at wks 8-12</td>
<td></td>
<td>▼ FS by 10-12 wks; ▲ capase-3 activity at wks 8-12; ▼ cardiac mass, ▲ fibrosis (measured by histology)</td>
<td></td>
</tr>
<tr>
<td>Neilan et al., 2006²⁰⁶</td>
<td>10/20, Mice, NR</td>
<td>DOX 206; pre DOX, 1, 2, 3, 4, 5 d post DOX</td>
<td>LVEF, LV volumes, dimensions &amp; wall thicknesses, FS</td>
<td>papillary RSR</td>
<td>endocardial Ss</td>
<td>▼ RSR after 2 d LVEF &amp; FS after 5 d</td>
<td></td>
<td>▼ Ss after 1 d; ▼ Ss after 6 wks; ▼ Ss after 6 wks; ▼ LVEF &amp; FS after 12 wks</td>
<td></td>
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<tr>
<td>Piegari et al., 2008²¹⁵</td>
<td>26, Rats, 3 mo</td>
<td>DOX 20 mg/kg over 4 wks post DOX</td>
<td>LVEF, LV dimensions &amp; wall thicknesses</td>
<td>posterior myocardial RS &amp; RSR</td>
<td>radial myocardial velocity</td>
<td>▼ RS, RSR than baseline &amp; controls at 2-4 wks</td>
<td></td>
<td>▼ LVEDD, ▼ LVEF at 4 wks</td>
<td></td>
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<tr>
<td>Walker et al., 2011²²⁷</td>
<td>25, Mice, NR</td>
<td>DOX 202; pre DOX, 10 days post DOX</td>
<td>LVEF, LV volumes, dimensions &amp; wall thicknesses, FS</td>
<td>papillary RS</td>
<td>endocardial Ss</td>
<td>▼ RSR</td>
<td></td>
<td>▼ LVEDD, ▼ FS &amp; endocardial Ss</td>
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</tbody>
</table>

Abbreviations: 2DSTE = two-dimensional speckle tracking echo; A = mitral flow peak atrial filling velocity; ACR = peak reversal velocity during atrial contraction; ACRT = duration of atrial contraction reversal; ALL = acute myeloid leukemia; As = late diastole interventricular septum myocardial velocity; ANTH = ratio-adjusted anthracycline using: DOX = 1.0, daunorubicin = 0.5, and idarubicin = 1.6; AVRD = atrioventricular ring displacement; BNP = brain natriuretic peptide; CKMB = creatine kinase MB; CS = peak systolic
circumferential strain; cTnI = cardiac Troponin I; cTnT = cardiac Troponin T; d = day; DOX = doxorubicin; Dp = pulmonary venous peak diastolic velocity; DT = mitral flow early deceleration time; E = mitral flow early phase filling velocity; Es = early diastole interventricular myocardial septum velocity; EPI = epirubicin; FS = fractional shortening; E' = early diastole lateral mitral annulus velocity; FU = follow-up; GCS = peak systolic global circumferential strain; GLS = peak systolic global longitudinal strain; GPx = glutathione peroxidase; GRS = peak systolic global radial strain; IFW = inferolateral wall (radial axis); IVCT = isovolumic contraction time; IVS = interventricular septum (longitudinal axis); LSR = longitudinal strain rate; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; mo = month; MPI = myocardial performance index; NR = not reported; ROS = reactive oxygen species; Rot = rotation; RS = peak systolic radial strain; Ss = peak systole interventricular septum myocardial velocity; SOD = superoxide dismutase; Sp = pulmonary venous peak systolic velocity; S' = systolic lateral mitral annulus velocity; TDI = tissue Doppler imaging; TNF = tumor necrosis factor; wk = week
Table 2.5: Prognostic associations with myocardial mechanic parameters

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Population</th>
<th>Statistically significant relationships (effect sizes reported when available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertini et al., 2012</td>
<td>1060</td>
<td>Patients with chronic ischemic cardiomyopathy</td>
<td>GLS was an independent predictor of all-cause mortality during 31 month FU (HR=1.69)</td>
</tr>
<tr>
<td>Cho et al., 2009</td>
<td>201</td>
<td>Patients hospitalized for acute HF</td>
<td>GLS (HR=1.10) &amp; GCS (HR=1.13) were predictors of cardiac death or readmission for HF 3+ yrs later;</td>
</tr>
<tr>
<td>Ersboll et al., 2013</td>
<td>849</td>
<td>Patients with a MI and LVEFs &gt;40% within 48 h of admission for coronary angiography</td>
<td>GLS was an independent predictor of all-cause mortality and hospitalization for HF in 30 mo FU (HR=1.20)</td>
</tr>
<tr>
<td>Iacoviello et al., 2013</td>
<td>308</td>
<td>Clinically stable CHF patients with LVEF ≤45%</td>
<td>GLS was a significant predictor of all-cause mortality (HR=1.15), cardiovascular disease death (HR=1.24), heart transplantation (HR=1.24), acute HF hospitalizations (HR=1.15), &amp; arrhythmic events (HR=1.17) in 26 mo FU</td>
</tr>
<tr>
<td>Liu et al., 2013</td>
<td>88</td>
<td>Stable hemodialysis patients</td>
<td>GLS was an independent predictor of all-cause mortality in 26 mo FU (HR=3.57)</td>
</tr>
<tr>
<td>Mousavi et al., 2015</td>
<td>158</td>
<td>Cancer patients with baseline LVEF of 50-59% who received anthracyclines</td>
<td>Baseline (pre-CT) GLS was predictive of mortality (HR=1.13 per unit decrease) in 1.8 yr FU</td>
</tr>
<tr>
<td>Neilan et al., 2006</td>
<td>10</td>
<td>Male mice injected with DOX</td>
<td>ΔRSR from pre DOX to 6 wks post DOX correlated with ↓ in FS at 12 wks; a 33% ↓ RSR from pre DOX to 6 wks post DOX correlated with DOX-induced mortality</td>
</tr>
<tr>
<td>Stanton et al., 2009</td>
<td>546</td>
<td>Individuals with known or suspected LV dysfunction</td>
<td>GLS predicted mortality within a 5.2 yr FU ($X^2$=34.9)</td>
</tr>
<tr>
<td>Yingchoncharoen et al.,</td>
<td>79</td>
<td>Patients with severe aortic stenosis with LVEF&gt;50%</td>
<td>GLS predicted death &amp; AV valve replacement in 23 month FU (HR=1.14)</td>
</tr>
<tr>
<td>Author</td>
<td>n</td>
<td>Population</td>
<td>Statistically significant relationships (effect sizes reported when available)</td>
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<tr>
<td><strong>Cardiovascular associations</strong></td>
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<tr>
<td>Fallah-Rad et al., 2011</td>
<td>42</td>
<td>Breast cancer patients receiving ANTH followed by trastuzumab</td>
<td>ΔGLS &amp; ΔGRS at 3 mo post ANTH &amp; trastuzumab start were predictors of LVEF-defined cardiotoxicity within 1 yr FU</td>
</tr>
<tr>
<td>Florescu et al., 2015</td>
<td>40</td>
<td>Breast cancer patients receiving ANTH</td>
<td>ΔGLS at CT halfway predicted LVEF-defined cardiotoxicity at end of CT</td>
</tr>
<tr>
<td>Hwang et al., 2012</td>
<td>70</td>
<td>Hypertensives with LVEF &gt; 55%</td>
<td>Peak systolic GLS (r=0.300, early diastolic SR (r=-0.479), basal Rot (r=-0.301), and twist (r=-0.256) correlated with PWV</td>
</tr>
<tr>
<td>Mornos et al., 2013</td>
<td>74</td>
<td>Adult mixed cancer types treated with ANTH</td>
<td>ΔGLS (OR=3.98), ΔLV apical Rot (OR=7.25), ΔLV twist (OR=2.54), ΔLV untwist rate (OR=0.7), and ΔGLSxLV twist (OR=1.1) from pre-CT to 6 wks post-CT start predicted LVEF-defined cardiotoxicity within 1 yr FU</td>
</tr>
<tr>
<td>Mousavi et al., 2015</td>
<td>158</td>
<td>Cancer patients with baseline LVEF of 50-59% who received anthracyclines</td>
<td>Baseline (pre-CT) GLS was predictive of major adverse cardiac events (HR=1.36 per unit decrease) in 1.8 yr FU</td>
</tr>
<tr>
<td>Sawaya et al., 2011</td>
<td>43</td>
<td>77% breast cancer patients receiving ANTH &amp; 23% post-ANTH, all received trastuzumab post ANTH</td>
<td>↓ GLS &amp; GRS &amp; ↑ cTnI at 3 mo post ANTH start were predictors of LVEF-defined cardiotoxicity 6 mo post ANTH start</td>
</tr>
<tr>
<td>Sawaya et al., 2012</td>
<td>811</td>
<td>Breast cancer patients receiving ANTH, followed by taxanes and trastuzumab</td>
<td>GLS post ANTH was predictive of LVEF-defined cardiotoxicity in 12 mo post ANTH FU</td>
</tr>
<tr>
<td>Yoneyama et al., 2008</td>
<td>137</td>
<td>Patients with suspected congestive HF</td>
<td>GLS was an independent predictor of plasma log BNP levels (r=0.75)</td>
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<td><strong>ROS and antioxidant association</strong></td>
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<tr>
<td>Cadeddu et al., 2010</td>
<td>24</td>
<td>Adults with solid tumors being treated with ANTH</td>
<td>ΔIVS LSR from pre-CT to after 200 mg/m2 EPI correlated with ↑ IL-6 (r=0.58) and ROS (r=0.51)</td>
</tr>
<tr>
<td>Author et al., 2007&lt;sup&gt;205&lt;/sup&gt;</td>
<td>n</td>
<td>Population</td>
<td>Statistically significant relationships (effect sizes reported when available)</td>
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<tr>
<td>Mercuro et al.</td>
<td>16</td>
<td>Adult mixed cancer types being treated with EPI</td>
<td>ΔIVS LSR from pre-CT to after 200 mg/m2 EPI correlated with ↑ IL-6 (r=-0.98) &amp; ROS (r=-0.94), &amp; ↓ GPx (r=0.55)</td>
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<td>Mavinkurve et al., 2013&lt;sup&gt;208&lt;/sup&gt;</td>
<td>60</td>
<td>Children with ALL being treated with ANTH</td>
<td>GRS, GLS &amp; LSR correlated with ANTH dose</td>
</tr>
<tr>
<td>Mornos et al., 2013&lt;sup&gt;202&lt;/sup&gt;</td>
<td>74</td>
<td>Adult mixed cancer types treated with ANTH</td>
<td>ΔGLS (r=0.58), ΔLV twist (r=-0.31), ΔGRS (r=-0.29), and ΔGLSxLV twist (r=0.61) from pre-CT to 6 wks post-CT start correlated with ANTH dose</td>
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<tr>
<td>Motoki et al., 2012&lt;sup&gt;184&lt;/sup&gt;</td>
<td>25</td>
<td>Adults with hematological cancers</td>
<td>LV twist (r=-0.524), twist rate (r=-0.419), untwist rate (r=-0.379), &amp; GLS (r=-0.313) correlate with ANTH dose</td>
</tr>
<tr>
<td>Lafitte et al., 2009&lt;sup&gt;308&lt;/sup&gt;</td>
<td>65</td>
<td>Asymptomatic aortic stenosis patients</td>
<td>↓ GLS in pts with abnormal exercise response</td>
</tr>
<tr>
<td>Stoodley et al., 2013&lt;sup&gt;194&lt;/sup&gt;</td>
<td>52</td>
<td>Breast cancer pts being treated with DOX or EPI</td>
<td>Post ANTH early diastolic LSR correlated with age (r=0.54)</td>
</tr>
</tbody>
</table>

**Anthracryline dose-response relationship**

**Other**

Abbreviations: ANTH = ratio-adjusted anthracycline using: DOX = 1.0, daunorubicin = 0.5, and idarubicin = 1.6; AV = atrioventricular; CHF = chronic heart failure; EPI = epirubicin; FU = follow-up; GLS = global longitudinal strain; GPx = glutathione peroxidase; GRS = global longitudinal strain; HF = heart failure; HR = hazard ratio; IVS = interventricular septum; LSR = longitudinal strain rate; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PWV = pulse wave velocity; ROS = reactive oxygen species; Rot = rotation; SR = strain rate; wks = weeks; yr = year;
Table 2.6: Summary of studies measuring cardiac biomarker responses to anthracycline treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Cancer type</th>
<th>Age</th>
<th>Agent</th>
<th>Biomarker</th>
<th>Timing</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auner et al., 2003</td>
<td>78</td>
<td>Hematological cancers</td>
<td>Median 58 (28-78)</td>
<td>ANTH dose NR</td>
<td>cTnT</td>
<td>Within 48 h of start of each cycle and every 48 h thereafter</td>
<td>15% had increase &gt;0.03 ng/ml; 6% of them were after 1st cycle; median of 2 cycles until increase</td>
</tr>
<tr>
<td>Broeyer et al., 2008</td>
<td>12</td>
<td>Mixed</td>
<td>48±3</td>
<td>DOX 440±138 mg/m2</td>
<td>NT-proBNP, cTnT, CK-MB, ANP</td>
<td>Before, 4 &amp; 24 hr post the first 4 CT cycles</td>
<td>269% (169-400%) ↑ in NT-proBNP 24 hr after 1st cycle; similar ↑ after cycles 2-4; mean of 44% (4-101%) ↑ in ANP &amp; 26% (4-52%) ↑ in CK-MB at 24 hr after all courses</td>
</tr>
<tr>
<td>Cardinale et al., 2002</td>
<td>136</td>
<td>Breast</td>
<td>46±11</td>
<td>EPI 200 mg/m2</td>
<td>cTnI</td>
<td>Before, immediately after, and 12, 24, 36, and 72 h after end of each cycle</td>
<td>TnI &gt;0.05 ng/ml in 39% after at least 1 cycle</td>
</tr>
<tr>
<td>Cardinale et al., 2004</td>
<td>700</td>
<td>Mixed</td>
<td>47±12</td>
<td>Mixed, high dose</td>
<td>cTnI</td>
<td>Before and 12, 24, 36, and 72 h after each cycle; 1 mo after last cycle</td>
<td>30% had an increase &gt;0.08 ng/mL from 0-72 post cycle</td>
</tr>
<tr>
<td>Cil et al., 2009</td>
<td>33</td>
<td>Breast cancer</td>
<td>45 (27-66)</td>
<td>DOX 240 mg/m2</td>
<td>NT-proBNP, cTnI, CK-MB</td>
<td>Pre-CT, post-CT</td>
<td>30% had ↓ LVEF &amp; ↑ NT-proBNP</td>
</tr>
<tr>
<td>Dodos et al., 2008</td>
<td>98</td>
<td>Mixed</td>
<td>46±1 (20-70)</td>
<td>ANTH 226±8 mg/m2</td>
<td>cTnT, NT-proBNP</td>
<td>Before and 3-5 d after first cycle; 24-72 h, 1, 6, and 12 mo after last cycle</td>
<td>3.6% had TnT &gt;0.01 ng/ml 72 hr post last cycle; 15% had an increase above limit of NT-proBNP post 1st cycle</td>
</tr>
</tbody>
</table>

Footnotes:

1. ANTH: Anthracyclines
2. NR: Not reported
3. DOX: Doxorubicin
4. EPI: Epirubicin
5. NT-proBNP: N-Terminal pro-B-type natriuretic peptide
6. cTnI: Cardiac troponin I
7. cTnT: Cardiac troponin T
8. CK-MB: Creatine kinase-MB
9. LVEF: Left ventricular ejection fraction
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Cancer type</th>
<th>Age</th>
<th>Agent</th>
<th>Biomarker</th>
<th>Timing</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drafts et al., 2013&lt;sup&gt;242&lt;/sup&gt;</td>
<td>53</td>
<td>Mixed types</td>
<td>50±2</td>
<td>50 to 375 mg/m&lt;sup&gt;2&lt;/sup&gt; doxorubicin</td>
<td>BNP, cTnI</td>
<td>Pre-CT, 1, 3, &amp; 6 mo post initiation of CT</td>
<td>26% had TnI &gt;0.06 ng/mL before final cycle</td>
</tr>
<tr>
<td>Ekstein et al., 2007&lt;sup&gt;250&lt;/sup&gt;</td>
<td>23</td>
<td>Mixed childhood cancers</td>
<td>10 (0.67 to 23)</td>
<td>ANTH 30 – 300 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-proBNP</td>
<td>Before and after every cycle</td>
<td>↑ from baseline to after 1&lt;sup&gt;st&lt;/sup&gt; cycle when doses ≥25 mg/m&lt;sup&gt;2&lt;/sup&gt;; peak level occurred after first dose in 61%</td>
</tr>
<tr>
<td>Erdim et al., 2009&lt;sup&gt;309&lt;/sup&gt;</td>
<td>45</td>
<td>Breast</td>
<td>48±8</td>
<td>EPI 360-450 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>cTnT</td>
<td>Before and 72 hours after every cycle</td>
<td>63% pts had TnT &gt; 0.01 ng/ml at least one cycle</td>
</tr>
<tr>
<td>Erkus et al., 2007&lt;sup&gt;243&lt;/sup&gt;</td>
<td>29</td>
<td>ALL</td>
<td>7±0.6 (1–16)</td>
<td>ANTH 181.6±64.9 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>BNP, cTnI</td>
<td>Pre-CT, 1 mo post completion</td>
<td>↑ BNP following ANTH</td>
</tr>
<tr>
<td>Fallah-Rad et al., 2011&lt;sup&gt;186&lt;/sup&gt;</td>
<td>42</td>
<td>Breast</td>
<td>47±9</td>
<td>EPI ≤600 mg/m&lt;sup&gt;2&lt;/sup&gt; or DOX ≤240 mg/m&lt;sup&gt;2&lt;/sup&gt;, followed by trastuzumab</td>
<td>cTnT, NT-proBNP</td>
<td>Pre-CT, post-CT, 3 mo post-CT &amp; initiation of trastuzumab</td>
<td>No change</td>
</tr>
<tr>
<td>Feola et al., 2011&lt;sup&gt;241&lt;/sup&gt;</td>
<td>53</td>
<td>Breast</td>
<td>Median 55 (28-73)</td>
<td>EPI 540 m/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>cTnI, BNP</td>
<td>Pre-CT, 1 mo, 1 yr, 2 yr post-CT</td>
<td>↑ cTnI &amp; BNP at 1 mo</td>
</tr>
<tr>
<td>Horacek et al., 2007&lt;sup&gt;251&lt;/sup&gt;</td>
<td>26</td>
<td>ALL</td>
<td>46±12</td>
<td>ANTH 464 ± 118 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-proBNP, CK-MB</td>
<td>Pre-CT, 24 hr post 1&lt;sup&gt;st&lt;/sup&gt; CT cycle; 24 hr post last CT cycle; 6 mo post-CT completion</td>
<td>↑ NT-proBNP 24 hr post 1&lt;sup&gt;st&lt;/sup&gt; cycle; 89% were over normal limit for NT-proBNP</td>
</tr>
<tr>
<td>Kılıçkap et al., 2005&lt;sup&gt;310&lt;/sup&gt;</td>
<td>41</td>
<td>Mixed</td>
<td>44.3±15.4 (17–69)</td>
<td>ANTH 228 ± 127 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>cTnT</td>
<td>Before and 3-5 d after first cycle; after last cycle</td>
<td>5% had TnT &gt;0.01 ng/ml after 1&lt;sup&gt;st&lt;/sup&gt; cycle &amp; 34% after therapy in 34%</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Cancer type</td>
<td>Age</td>
<td>Agent</td>
<td>Biomarker</td>
<td>Timing</td>
<td>Significant findings</td>
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<tr>
<td>Kittiwarawut et al., 2012&lt;sup&gt;254&lt;/sup&gt;</td>
<td>52</td>
<td>Breast</td>
<td>50±10</td>
<td>DOX 237±12 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-proBNP, cTnT, CK-MB</td>
<td>Pre-CT, before 2&lt;sup&gt;nd&lt;/sup&gt; CT cycle, 3 wks post last cycle</td>
<td>↑ NT-proBNP at 3 wks post in 21% who developed echo changes</td>
</tr>
<tr>
<td>Kouloubinis et al., 2007&lt;sup&gt;255&lt;/sup&gt;</td>
<td>26</td>
<td>Breast</td>
<td>53 ± 12</td>
<td>EPI 480-540 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-proBNP, ANP</td>
<td>Pre-CT, post-CT</td>
<td>↑ NT-proBNP &amp; ANP</td>
</tr>
<tr>
<td>Meinardi et al., 2001&lt;sup&gt;256&lt;/sup&gt;</td>
<td>40</td>
<td>Breast</td>
<td>Median 46 (28-55)</td>
<td>EPI 360-450 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-ANP, BNP</td>
<td>Pre-CT, 1 mo, 1 yr post-CT completion</td>
<td>↑ BNP &amp; NT-ANP after 1 mo &amp; 1 yr</td>
</tr>
<tr>
<td>Mercuro et al., 2007&lt;sup&gt;205&lt;/sup&gt;</td>
<td>16</td>
<td>Mixed adult cancers</td>
<td>56±3</td>
<td>EPI 300-400 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>BNP, cTnI, Myo, CK-MB</td>
<td>Pre-CT, 7 d post EPI doses of 100, 200, 300, 400 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No changes</td>
</tr>
<tr>
<td>Nisticco et al., 2007&lt;sup&gt;249&lt;/sup&gt;</td>
<td>20</td>
<td>Breast</td>
<td>Median 56 (34-75)</td>
<td>EPI 600 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>cTnT, CK-MB, myo</td>
<td>Before &amp; 4 hr post each weekly EPI</td>
<td>No increase over upper limit of normal</td>
</tr>
<tr>
<td>Polena et al., &lt;sup&gt;244&lt;/sup&gt;</td>
<td>31</td>
<td>Mixed</td>
<td>68 (42-71)</td>
<td>DOX 520 mg/m&lt;sup&gt;2&lt;/sup&gt; (450-650)</td>
<td>cTnI</td>
<td>Before &amp; 48-72 h after each cycle</td>
<td>Only 1 pt with cTnI &gt; 2.0 ng/mL after third cycle</td>
</tr>
<tr>
<td>Romano et al., 2011&lt;sup&gt;245&lt;/sup&gt;</td>
<td>71</td>
<td>Breast cancer</td>
<td>54±12</td>
<td>PL-DOX 240-300 mg/m&lt;sup&gt;2&lt;/sup&gt; or EPI 540 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT-proBNP, cTnI</td>
<td>Before &amp; 24 h after each cycle</td>
<td>↑ NT-proBNP at 24 hr in 38%; 30% had persistently elevated NT-proBNP; cTnI &gt;0.08ng/ml in 6%</td>
</tr>
<tr>
<td>Sandri et al., 2003&lt;sup&gt;240&lt;/sup&gt;</td>
<td>179</td>
<td>Mixed</td>
<td>47±11</td>
<td>Mixed, high dose, EPI 200 mg/m&lt;sup&gt;2&lt;/sup&gt; in 43%, Idarubicin 45 g/m&lt;sup&gt;2&lt;/sup&gt; in 27%</td>
<td>cTnI</td>
<td>Before, immediately after, 12, 24, 36, &amp; 72 h after end of each cycle</td>
<td>cTnI &gt;0.08 µg/L in 32% at some point</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Cancer type</td>
<td>Age</td>
<td>Agent</td>
<td>Biomarker</td>
<td>Timing</td>
<td>Significant findings</td>
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<tr>
<td>Sandri et al., 2005&lt;sup&gt;252&lt;/sup&gt;</td>
<td>52</td>
<td>Mixed</td>
<td>47±11</td>
<td>Mixed, high dose</td>
<td>NT-proBNP</td>
<td>Before, immediately after, and 12, 24, 36, and 72 h after end of each cycle</td>
<td>↑ NT-proBNP post cycle for up to 72 hr in 33%; ↑ at 12-36 hr but then decreased toward 72 hr in 37%; ↓ in 31% from pre to post cycle</td>
</tr>
<tr>
<td>Sawaya et al., 2011&lt;sup&gt;191&lt;/sup&gt;</td>
<td>43</td>
<td>Breast</td>
<td>48±10</td>
<td>EPI 300 mg/m2 or DOX 240 mg/m2, followed by trastuzumab</td>
<td>uscTnI, NT-proBNP</td>
<td>Before, 3 &amp; 6 mo after CT initiation</td>
<td>uscTnI &gt;0.015 µg/L at 3 mo in 28%</td>
</tr>
<tr>
<td>Sawaya et al., 2012&lt;sup&gt;190&lt;/sup&gt;</td>
<td>81</td>
<td>Breast</td>
<td>50±10</td>
<td>EPI 300 mg/m2 or DOX 240 mg/m2, followed by trastuzumab</td>
<td>uscTnI, NT-proBNP, ST2</td>
<td>Pre-CT, post-CT</td>
<td>↑ uscTnI post-CT</td>
</tr>
<tr>
<td>Tanindi et al., 2011&lt;sup&gt;311&lt;/sup&gt;</td>
<td>37</td>
<td>Breast</td>
<td>42±5</td>
<td>DOX 360 mg/m2</td>
<td>NT-proBNP</td>
<td>Before CT, 24 hr post 1&lt;sup&gt;st&lt;/sup&gt; CT cycle, 24 hr post 2&lt;sup&gt;nd&lt;/sup&gt; CT cycle</td>
<td>↑ NT-proBNP after 2&lt;sup&gt;nd&lt;/sup&gt; cycle</td>
</tr>
</tbody>
</table>

Abbreviations: ALL = acute myeloid leukemia; ANP = atrial natriuretic peptide; ANTH = ratio-adjusted anthracycline using: DOX = 1.0, daunorubicin = 0.5, and idarubicin = 1.6; BNP = B-type natriuretic peptide; CT = chemotherapy; cTnI = cardiac troponin I; cTnT = cardiac troponin T; d = day; DOX = doxorubicin; EPI = epirubicin; hr = hour; mo = month; Myo = myoglobin; uscTnI = ultra sensitive cardiac troponin I;
Table 2.7. Summary of studies implementing a supervised, aerobic exercise intervention during chemotherapy treatment for breast cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Exercise arm</th>
<th>Concurrent treatment type</th>
<th>Timing of intervention</th>
<th>Intervention delivery</th>
<th>Aerobic prescription</th>
<th>Adherence (mean±SD)†</th>
<th>Change in relative $\text{VO}_2\text{peak}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al., 2005</td>
<td>RCT</td>
<td>Aerobic &amp; resistance=12</td>
<td>Adjunct CT or radiation CT type NR</td>
<td>2-3rd CT cycle (or 2-3 w of radiation) for 12 w total</td>
<td>Group-based</td>
<td>F: 2x/week I: 60-75% HRpeak T: 10-20 min</td>
<td>F: 70±20 I: NR T: NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Courneya et al., 2007</td>
<td>RCT</td>
<td>Aerobic=78</td>
<td>Adjunct CT 86% ANTH 27% AC only</td>
<td>1-2 w after CT start to 3 w post CT finish; 17±4 weeks total</td>
<td>Group-based</td>
<td>F: 3x/week I: 60-80% BL VO$_2$peak T: 15-45 min</td>
<td>F: 72±30 I/T: &gt;95%</td>
<td>+1%</td>
</tr>
<tr>
<td>Courneya et al., 2013</td>
<td>RCT</td>
<td>Aerobic &amp; resistance=104</td>
<td>Adjunct CT 69% ANTH 6% AC only</td>
<td>1-2 w after CT start to 3-4 w post CT finish; 16.3±3.2 weeks total</td>
<td>Group-based</td>
<td>F: 3x/week I: 55-75% BL VO$_2$peak T: 15-30 min</td>
<td>F: 71±23% I/T: &gt;90% (including resistance sessions)</td>
<td>-13%</td>
</tr>
<tr>
<td>Hornsby et al., 2014</td>
<td>RCT</td>
<td>Aerobic=10</td>
<td>Neoadjuvant CT 100% AC only</td>
<td>1st CT cycle to 3 w post CT; 12 w total</td>
<td>One-on-one</td>
<td>F: 3x/week I: 60-70% BL Wpeak* T: 15-45 min</td>
<td>F: 82% I/T: 77%</td>
<td>+13%</td>
</tr>
<tr>
<td>Kim et al., 2006</td>
<td>RCT</td>
<td>Aerobic=22</td>
<td>Adjunct CT and/or radiation CT type NR</td>
<td>1st month of CT or 1-2 w radiation for 8 w total</td>
<td>One-on-one</td>
<td>F: 3x/week I: 60-70% HRR T: 30 min</td>
<td>F/I/T: 78±20%</td>
<td>+8% Absolute</td>
</tr>
<tr>
<td>MacVicar et al., 1989</td>
<td>RCT</td>
<td>Aerobic=18</td>
<td>Adjunct CT or HT No ANTH</td>
<td>Timing NR, length was 10 w</td>
<td>One-on-one</td>
<td>F: 3x/week I: 60-85% HRR† T: NR</td>
<td>F: NR# I: NR T: NR</td>
<td>+40%</td>
</tr>
<tr>
<td>Mutrie et al., 2007</td>
<td>RCT</td>
<td>Aerobic and resistance=101</td>
<td>Adjunct CT and/or RT CT type NR</td>
<td>Timing NR, length was 12 w</td>
<td>Group-based</td>
<td>F: 2x/week I: 50-75% HRpeak T: 20 min</td>
<td>F: NR I: NR T: NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Segal et al., 2001</td>
<td>RCT</td>
<td>Aerobic=42</td>
<td>Adjunct CT, RT, or HT 62% ANTH 21% AC</td>
<td>1st 2 w of CT/RT/HT for 26 w total</td>
<td>Group-based</td>
<td>F: 3x/week I: 50-60% predicted VO$_2$peak T: NR</td>
<td>F: 72% I: NR T: NR</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Study design</td>
<td>Exercise arm</td>
<td>Concurrent treatment type</td>
<td>Timing of intervention</td>
<td>Intervention delivery</td>
<td>Aerobic prescription</td>
<td>Adherence (mean±SD)†</td>
<td>Change in relative VO$_2$peak</td>
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<tr>
<td>Travier et al., 2015$^{168}$</td>
<td>RCT</td>
<td>Aerobic &amp; resistance=102</td>
<td>Adjuvant CT &amp; radiation</td>
<td>Before/after CT (timing NR) for 18 w total</td>
<td>One-on-one</td>
<td>F: 2x/week</td>
<td>F: 83%</td>
<td>-12%</td>
</tr>
<tr>
<td>van Waart et al. 2015$^{77}$</td>
<td>RCT</td>
<td>Aerobic &amp; resistance=76</td>
<td>Adjuvant CT &amp; radiation</td>
<td>1st CT cycle to 3 w post CT</td>
<td>One-on-one</td>
<td>F: 2x/week</td>
<td>F: 71%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: Data only reported for study arms including supervised aerobic exercise.

*This study also incorporated one weekly session at ventilatory threshold in weeks 5-9, and 10-15 intervals of 30 seconds at 100% BL Wpeak, followed by 60 seconds active recovery for one workout per week in weeks 10-12.

†Adherence values reported without SD are percent completion for the whole study arm rather than mean of adherence for each participant

‡ This prescription consisted of intervals of unknown length and unknown intensity for easy interval

# It was reported that make-up sessions were scheduled for missed sessions, so attendance may have been 100%, but several participants also withdrew and no data is reported for them

Abbreviations: BL = baseline; CT = chemotherapy; F = frequency; HRpeak = peak heart rate; HRR = heart rate reserve; I = intensity; HT = hormonal therapy; NR = not reported; RCT = randomized controlled trial; T = time/duration; VO$_2$peak = peak oxygen consumption; VT = ventilator threshold; w = weeks; Wpeak = peak workload;
Chapter 3: Adherence and effectiveness of the recommended exercise prescription
during anthracycline chemotherapy for breast cancer

3.1 Introduction

In the past 10-15 years it has been demonstrated that exercise training is safe and
effective for improving numerous health outcomes in early stage breast cancer survivors both
during and after chemotherapy, with the majority of studies to date introducing exercise
following the completion of primary adjuvant treatment. The ACSM first published a
roundtable consensus document on exercise guidelines for cancer survivors in 2010. The
guidelines suggest that individuals with breast cancer should avoid inactivity, and continue
with normal exercise as much as possible during and after treatment. The aerobic exercise
training recommendations are the same as the physical activity guidelines for Americans,
which also match the Canadian physical activity guidelines. These guidelines state
that adults can achieve substantial health benefits by performing 150 minutes per week of
moderate intensity, or 75 minutes per week of vigorous intensity aerobic exercise, performed
in bouts of at least 10 minutes at a time, and resistance training for major muscle groups at
least two days per week, with additional benefits gained by greater amounts of exercise.
Courneya et al., and Jones et al. have published more detailed aerobic exercise prescription
recommendations for cancer survivors including suggested starting points and
progressions. Based on these more detailed exercise recommendations, the initial
recommended prescription is three 20-minute walking sessions per week at a moderate
intensity for cancer survivors not already meeting the ACSM guidelines for exercise in the
previous month. The prescription should be progressed, as tolerated, up to five 30-minute
sessions per week. These guidelines also recommend that intensity should be prescribed
via the heart rate reserve method at 50-75%, or using a rating of perceived exertion of 11 to 14.\textsuperscript{162}

As acceptance of the general safety and efficacy of exercise during cancer treatment has grown in both research and clinical settings, interest in gaining a better understanding of the potential of more targeted exercise prescriptions focused on particular cancer-related side effects has emerged. However, Campbell et al. have identified that the majority of exercise interventions for breast cancer populations published to date have not applied the principles of exercise training, and have incompletely reported both the exercise prescription components themselves, as well as the adherence to the exercise prescription components.\textsuperscript{169} As a result, it is difficult to interpret and compare exercise prescriptions employed in different studies in order to be able to tailor an exercise prescription for timing of cancer treatment (i.e. during chemotherapy, radiation, or following treatment), or to utilize a specific prescription to achieve a specific outcome (i.e. to improve fitness, or to improve heart function).\textsuperscript{169}

Accurate assessment of adherence is required in order to ensure that health outcomes can be attributed to a treatment, including exercise.\textsuperscript{315} The World Health Organization defines adherence as the extent to which the behaviour of an individual corresponds with recommendations.\textsuperscript{315} Adherence to an exercise prescription can be objectively assessed as the number of exercise sessions that were attended out of the total planned sessions (i.e. attendance), and the number of sessions where the exercise performed met the prescribed intensity or duration (i.e. adherence to duration and intensity). Adherence to an exercise program for a particular study sample or group of individuals can also be described by the percentage of participants who completed the program, or retention rate.
Although several RCTs have demonstrated the efficacy of supervised exercise training during chemotherapy for breast cancer for numerous health benefits, adherence to the exercise prescription has either not been well documented, or reported as attendance only.\textsuperscript{169} To date there have been three large (n≥230) RCTs of supervised exercise in breast cancer patients during adjuvant chemotherapy (START,\textsuperscript{18} CARE,\textsuperscript{164} and PACES\textsuperscript{77}) that provide high quality evidence of the efficacy of exercise in attenuating the negative effects of chemotherapy on VO$_{2}$peak, muscular strength, and quality of life. These studies have reported average attendance for aerobic or combined aerobic and resistance exercise interventions as 72±31\textsuperscript{170} and 73±24\textsuperscript{171} for a three times per week intervention, and 71\% (standard deviation not reported)\textsuperscript{77} for a twice weekly intervention, respectively. Courneya et al. published an analysis of barriers to adherence to exercise frequency in the START trial,\textsuperscript{316} which provides additional insight into the issues related to exercise adherence during adjuvant chemotherapy for breast cancer. Half of all missed sessions were due to treatment-related symptoms or appointments.\textsuperscript{316} Adherence to the prescribed intensity and duration of exercise sessions performed was not reported or incompletely reported in these three studies; and have been reported in very few of the other published exercise interventions performed in breast cancer populations.\textsuperscript{169}

In addition, previous studies tend to combine all chemotherapy protocols when reporting attendance and adherence. This is problematic due to the difference in related side effects, the time between cycles, and total length of treatment for different treatment protocols. Of particular relevance to breast cancer, understanding the exercise training tolerance and resulting adherence to a particular exercise prescription during anthracycline-containing protocols is key as they are considered to be among the most toxic drugs ever
Furthermore the more modern anthracycline protocols may affect adherence to exercise, as they are administered every two weeks, leaving less time for recovery between cycles, and are administered with granulocyte-colony stimulating factor, which causes additional side effects.

Another key element in understanding the most appropriate exercise prescription approach for interventions during breast cancer treatments is how this can be translated into clinical programming. Effectiveness of an intervention is the ability to produce a similar effect under real-world conditions. Efficacy and effectiveness trials exist along a continuum as to the extent that they operate under ideal or real-world circumstances. Very little is known about adherence to supervised exercise during chemotherapy for breast cancer or the effectiveness on outcomes when implemented outside a RCT, under less stringent conditions.

The purpose of this chapter is to critically and objectively describe adherence to a supervised exercise program during anthracycline treatment for breast cancer that is consistent with the recommended exercise prescription for cancer survivors, and to describe the effectiveness of this program in light of the described adherence. The sample was partially drawn from the parent trial, a pragmatic single-arm study, the Nutrition and Exercise during adjuvant Therapy (NExT) study, that aimed to test a model of an oncologist-referred exercise program within a large clinical cancer centre for all women newly diagnosed with breast cancer who were scheduled to receive adjuvant chemotherapy of any type. The NExT study exercise program was consistent with the recommended exercise guidelines and aerobic exercise prescription described above. The first study objective was to assess adherence to the exercise program. The components of adherence to the exercise
program were: 1) adherence to prescribed exercise frequency (i.e., attendance) of three times per week; 2) adherence to prescribed exercise intensity starting at 50% of age-predicted heart rate reserve and progressing to 70%; 3) adherence to the prescribed exercise duration starting at 20 minutes and progressing to 30 minutes; and 4) retention of participants. Reasons for non-adherence and number of required prescription adjustments were collected to describe barriers to adherence. It was hypothesized that implementation of the recommended exercise prescription in a pragmatic single-arm exercise program format would result in $\geq 70\%$ adherence to frequency, $\geq 80\%$ adherence to intensity and duration, and $\geq 80\%$ retention of participants.

The second study objective was to assess the effectiveness of the exercise prescription as change in aerobic fitness (peak oxygen consumption, \(\text{VO}_2\text{peak}\)), the most typical parameter by which to assess the effect of an exercise prescription. The hypothesis was that higher adherence to the recommended exercise prescription will attenuate the decline \(\text{VO}_2\text{peak}\) commonly observed during adjuvant chemotherapy, relative to lower adherence to the exercise prescription.

3.2 Methods

3.2.1 Ethics

The British Columbia Cancer Agency Research Ethics Board approved this study. All participants signed an informed consent form prior to beginning the study.

3.2.2 Design and participants

This study was a sub-analysis of the NExT study, a feasibility study of implementation of an oncologist-referred lifestyle intervention by a research team in conjunction with the Vancouver Centre of the British Columbia Cancer Agency. There were
two streams of recruitment used to generate the sample reported in this chapter, both using convenience samples, as shown in Figure 3.1. In stream 1, participants were recruited via oncologist referral for the NExT study between August 6, 2013 and October 31, 2015. Participants in NExT who received an anthracycline-containing chemotherapy protocol were included in the assessment of adherence to the exercise program (first study objective) reported in this Chapter. The inclusion criteria to participate in NExT included female sex, diagnosis of histologically confirmed stage I-IIIA breast cancer, age 19 years or older, referral prior to or within the first half of adjuvant chemotherapy treatment, body mass index <40 kg/m², deemed safe to exercise by their treating oncologist, and able to understand and communicate in English.

Starting on February 1, 2014, participants referred to NExT were also assessed for eligibility and interest in participation in an optional sub-study. Those who enrolled in the sub-study formed the participants for the assessment of exercise prescription effectiveness (second study objective) in this chapter and the assessment of cardiac function in Chapter 4. Eligibility criteria to participate in the sub-study included being willing and able to participate in the baseline sub-study visit prior to starting anthracycline treatment, and approval from the treating oncologist for participation in a maximal exercise test. Exclusion criteria for the sub-study consisted of medical history factors that may affect exercise capacity or response including prior diagnosis of cardiovascular or respiratory disease, uncontrolled hypertension or diabetes, prior treatment with anthracyclines, trastuzumab, or mediastinal radiation, current smoking status, or concurrent participation in an ongoing pharmacological cardio-protection trial.
Following closure of recruitment for NExT on October 31, 2014, recruitment for this study was continued via stream 2, where oncologists referred directly to the sub-study. Only those who met the inclusion and exclusion criteria for the sub-study were enrolled via stream 2. Participants recruited via stream 2 performed the same intervention as those in NExT for the duration of their anthracycline-containing treatments plus two weeks. Exercise program attendance and adherence of these participants recruited via stream 2 was also included in the adherence assessment for this study.

3.2.3 Intervention

All participants recruited via either stream were invited to participate in an aerobic and resistance exercise training program and a nutrition information session. The exercise program took place at a private gym used exclusively for breast cancer research, located at 614 W 8th Ave (co-directors, Drs. Karen Gelmon, Don McKenzie and Kristin Campbell). The exercise program started up to two weeks prior to the first chemotherapy treatment, depending on timing of referral, and the participant’s availability. The exercise program consisted of supervised aerobic and resistance exercise three times per week, with home aerobic exercise once per week encouraged starting in week three of the program, and twice per week starting in week six. The gym was open Mondays, Wednesdays, and Fridays during normal business hours except for statutory holidays, and the week between Christmas Eve and New Year’s Eve. Participants were encouraged to schedule a consistent time to attend the gym each day, but were allowed flexibility around the time of day for sessions to accommodate schedule conflicts. No make up sessions on alternate days were provided. Missed sessions were followed by a phone call, email, or in-person discussion at the next gym session, at the discretion of the gym staff based on participant preference and regular
attendance pattern. For example, a participant that does not regularly attend, might be called after three missed sessions, whereas a regularly attending or new participant would be called after one missed session. Additionally some participants expressed a preference for not being called. The gym staff included a paid research coordinator, graduate students with a minimum of a Master’s of Science in Exercise Physiology (completed or in progress), Kinesiology undergraduate students, and volunteers. The exercise program was individualized to each participant, but was performed in a group-based environment with other participants. A ratio of one staff member to four participants was maintained at all times.

The prescription was progressive throughout treatment, but was designed to be both flexible and feasible during chemotherapy for all levels of fitness and prior exercise experience. The aerobic exercise prescription is described in Table 3.1. Generally, it consisted of a 5-minute warm-up, 20-30 minutes at 50-75% heart rate reserve (HRR), and a 5-minute cool down for supervised sessions; and a 5-minute warm-up, 15-30 minutes at a Borg scale rating of perceived exertion (RPE) of 12-13, and a 5-minute cool-down for home sessions. The standard aerobic exercise prescription was designed for those who are not very experienced with exercise, or who had reduced their exercise levels recently following their breast surgery. The advanced exercise prescription was used for those participants who reported performing moderate intensity aerobic exercise for at least 30 minutes three times per week in the previous month. Available modes of aerobic exercise were treadmill, elliptical, upright and recumbent cycle ergometer.

Age-predicted maximal heart rates and weekly measured resting heart rate were used to calculate heart rate reserve and determine heart rate targets for the supervised exercise.
Resting heart rate was measured approximately once a week as the lowest heart rate during the last 30 seconds of a five-minute period of quiet, seated rest, in hard-backed chair with back flat against the chair and feet flat on the floor, arms and legs uncrossed, and arms supported by arm rests. Each time a new resting heart rate was measured, that participant’s target heart rate range was recalculated using the new resting heart rate. This method was used to account for the wide variations in resting heart rate noted (but not reported) in a previous exercise study in a similar population of early stage breast cancer survivors undergoing adjuvant chemotherapy by members of the NExT research team. Age-predicted maximal heart rate was calculated using the equation developed by Gulati et al. from a cohort of over 5000 asymptomatic women: peak heart rate = 206 – 0.88*age.

The resistance exercise prescription consisted of two sets of 10 to 12 repetitions at 50-60% of predicted one repetition maximum for leg press and chest press, and a similar RPE for leg curls, calf raises, seated row, biceps curls, and triceps extensions, plus two core strengthening exercises. Due to the focus on aerobic exercise of this dissertation, data on adherence to the resistance program will not be reported. The nutrition class was a single 90-minute group information session with a registered dietician specializing in breast cancer.

3.2.4 Outcome measures

3.2.4.1 Adherence

Exercise adherence variables for each participant were collected throughout the intervention period for supervised sessions only. To determine adherence to frequency (i.e., attendance) and reasons for non-adherence for each participant, missed supervised exercise sessions were recorded and a reason was collected from the participant by phone, email or in person at their next visit. Attendance for each participant was calculated as the number of
attended exercise sessions divided by the total prescribed sessions (i.e., sum of missed and attended sessions). The prescribed number of sessions was counted starting on the first Monday, Wednesday, or Friday after enrollment in the study, until two weeks after the last anthracycline-containing chemotherapy treatment. Statutory holidays falling on a Monday, Wednesday, or Friday, where the gym was closed were not counted as missed sessions. To determine adherence to the duration and intensity, the duration and average heart rate of the aerobic exercise session were recorded at each session, and a reason was collected if that session’s prescription was not met. Reasons were not collected separately for missing the specific intensity and specific duration prescription target, but rather either element of the prescription for any given exercise session. Total adherence, or adherence to all three exercise prescription components combined was calculated as the total number of exercise sessions that were attended at which the participant adhered to both the intensity and duration prescription, divided by the total number of prescribed sessions for each participant. Total adherence was calculated as an exploratory adherence variable as this is not normally reported by studies.

To accommodate for the dynamic nature of cyclical chemotherapy treatments, a standardized prescription adjustment method was implemented for the days where participants felt particularly unwell. If upon arrival to the gym, a participant told gym staff that they were feeling particularly unwell, staff preemptively reduced their prescribed aerobic exercise intensity for that session by 10 percentage points. For example, if their prescribed intensity was intended to be 60 to 65 %HRR, they were instead given a target heart rate range of 50 to 55% HRR. These preemptive reductions in aerobic exercise intensity were recorded, along with the required reason for the reduction. Intensity reductions were also
made for participants on cardiac medications such as β-blockers, or for asthma symptoms exacerbated by exercise intensity that were maintained for the remainder of the program. If participants met the reduced prescription, this was counted as meeting the prescription for that day. The percent adherence to intensity and duration were calculated as the number of sessions where the average heart rate met or exceeded the lower limit of the target heart rate range, and the target duration was completed or exceeded, respectively. Adherence to exercise intensity was calculated, and is reported, with and without the prescription adjustments.

Retention of participants was calculated as the percentage of participants who did not withdraw from the intervention, out of the total who enrolled in the study. A program withdrawal was considered either a specific request by the participant for study withdrawal after signing the study consent form, or failure to attend any sessions in the last three weeks of the eligible intervention period (i.e., up to two weeks after completion of the last anthracycline-containing treatment). Participants who withdrew were included in assessment of adherence. They were asked for a primary reason for the withdrawal and this was recorded as the reason for the remainder of missed sessions until the planned program completion data for that participant.

3.2.4.2 Exercise capacity

Those who met the eligibility criteria and agreed to participate in the sub-study performed a maximal incremental cardiopulmonary treadmill test 0-14 days before initiation, and 7-14 days after completion of anthracycline-containing chemotherapy. Prior to each test, participants were asked to not drink caffeine or alcohol, or take non-vital drugs for at least three hours; refrain from eating for at least one, and up to three hours if possible; and to
refrain from strenuous exercise for 24 hours. The sessions took place at the Exercise
Physiology Laboratory of the Allan McGavin Sports Medicine Centre (Principal investigator:
Dr. Don McKenzie; 3055 Wesbrook Mall) until it closed in June 2015; then the sessions took
place at the Clinical Exercise Physiology Laboratory located in the University of British
Columbia Hospital (Principal investigator: Dr. Kristin Campbell; 2177 Wesbrook Mall).

The cardiopulmonary exercise tests were performed to volitional exhaustion on a
treadmill using a modified Balke protocol. Heart rate and gas analysis were recorded
continuously by a Parvo Medics TrueOne 2400 metabolic measurement system
(ParvoMedics, Sandy, UT), which was calibrated according to manufacturer instructions
prior to each test. RPE was collected via the Borg 6-20 scale at the end of each test stage,
and at VO₂peak. The test was stopped when the participant indicated her desire to stop, or
occurrence of other standard termination criteria. VO₂peak was defined as the highest 30-
second average VO₂ during the test, whereas peak heart rate was taken as the highest 5-
second average. Oxygen pulse was calculated for every 30-second average as absolute VO₂
divided by heart rate, and reported as the peak 30 seconds. Criteria for achieving VO₂peak
included a respiratory exchange ratio ≥1.10, peak heart rate within five beats per minute
(bpm) of age-predicted peak heart rate using the same Gulati equation, and RPE≥18.

3.2.4.3 Descriptive variables

A number of other variables were collected at baseline for descriptive purposes.
Demographics, information about diagnosis and treatment were collected at baseline with a
short questionnaire for all participants. Height and weight were measured at baseline for all
participants. Participants were asked to remove their shoes and were measured in one-layer
of light clothing. Height was measured with a standiometer at the end of a normal expiration
to the nearest half a centimeter. Weight was measured with a digital scale to the nearest tenth of a kilogram. Weight was also measured again at the follow-up exercise test to calculate relative VO$_2$peak. A modified version of the Minnesota Leisure Time Physical Activity Questionnaire$^{326}$ was administered by interview at baseline for all participants to describe baseline physical activity. Participants were asked whether they had performed a specific list of activities within the previous six months; if they had performed the activity, they were asked for the average number of times per month, average minutes per time, and a description of the intensity. The description of intensity was used to choose a metabolic equivalent (MET) score from the Compendium of Physical Activities.$^{327}$ All activities with a MET score $\geq$3.0 were considered moderate or vigorous intensity. Data are reported as average moderate-to-vigorous minutes of physical activity (MVPA). Change in hemoglobin and hematocrit from pre chemotherapy to post completion of anthracycline-containing chemotherapy was extracted from British Columbia Cancer Agency medical records for all participants to use as a potential confounding variable for change in VO$_2$peak.

3.2.5 Statistical analyses

Descriptive statistics were used to characterize the study participants at baseline for height, weight, body mass index, demographics, menopausal status, cancer diagnosis and treatment details, comorbid conditions, and self-reported MVPA over the previous six months. Adherence outcomes were described using counts and frequencies. All average resting heart rate measurements taken during each treatment cycle were averaged across all participants and reported with the adherence to intensity data to illustrate the need to adjust the target heart rate calculated via the HRR method used in this study. The change in VO$_2$peak was analyzed initially by a two-tailed paired t-test for the whole group between
follow-up and baseline exercise tests. Then individual linear regressions were performed to determine the relative influence of known moderators of an exercise training effect as a method to choose the best variable to use to divide the groups for comparison of VO$_2$peak. The independent variables assessed included baseline VO$_2$peak, program length, adherence to frequency, intensity and duration prescription,\textsuperscript{319} adherence to all three exercise prescription components (i.e. total adherence), and percent change in hemoglobin. Percentage change in absolute VO$_2$peak was the dependent variable. Multiple regression was not performed due to the small sample size available. The strongest predictor of the change in VO$_2$peak, total adherence, was used to divide those who completed the follow-up test into high and low adherence groups, above and below the median. One-tailed independent t-tests were used to compare the two groups. P-values were set at 0.05 for all analyses.

3.3 Results

3.3.1 Recruitment and participants

Of the 109 patients referred to the main study, 16 were ineligible, and 20 of the remaining 93 (22%) declined or did not respond regarding study enrollment (Figure 3.2). Twenty-two of the 73 participants who enrolled in the main study were not receiving anthracycline chemotherapy during their exercise program enrollment and were subsequently excluded from this analysis. Twenty-eight of the 51 participants receiving anthracyclines who enrolled in the main study were referred after the start of the sub-study on February 1, 2014 and were subsequently screened for the sub-study. Two women declined participation in the main study but were screened for the sub-study. Fourteen women were referred directly to the sub-study. Of the 44 screened for the sub-study, 16 were ineligible, 3 declined, and 25 (57%) agreed to participate. Eleven of these participants in the sub-study were not
enrolled in the main study but performed the same exercise program for the duration of anthracycline treatment. All together, 64 women are included in the exercise program adherence analysis (first study objective) and 25 in the effectiveness analysis (second study objective).

The baseline demographics, diagnosis, treatment, and physical variables are reported for the participants included in the adherence and effectiveness analyses in Tables 3.2 and 3.3. All participants received a chemotherapy protocol that included four cycles of 60 mg/m^2 of doxorubicin combined with 600 mg/m^2 of cyclophosphamide (AC), either two or three weeks apart. Some participants then received paclitaxel and trastuzumab, but this was after completion of the intervention period. The length of the program, calculated as the number of weeks between the first exercise session and two weeks after the last AC treatment where the program would end, was 8.6±2.5 weeks, with a range of 2.3 to 13.0 weeks. On average, participants were at least mildly anemic (hemoglobin <120 g/L) for 2.8±1.4 of 4 cycles of AC, and the average decrease in hemoglobin was 18±8% from pre-chemotherapy to post last cycle of AC.

Including the withdrawals, 36% of participants completed their first exercise session prior to starting chemotherapy treatment, while 39% started after their first treatment, 9% after their second, and 5% after their third. On average, the first session was 4±14 days after the first chemotherapy treatment.

**3.3.2 Exercise program adherence**

The retention rate was 77%, as 15 of the 64 participants enrolled in the exercise program either requested withdrawal or did not attend any sessions in the last three weeks of the program. Seven of these participants enrolled in the study and then did not attend a single
exercise session, while the remaining eight participants who withdrew attended between 2 and 14 exercise sessions. Reasons for withdrawal were treatment-related illness (n=5), living too far away (n=4), working during treatment (n=2), family obligations (n=2), and non-treatment-related illness (n=2). The results for the additional adherence components are reported for all participants combined including the withdrawals, unless otherwise stated.

For adherence to frequency (attendance), in total, 964 exercise sessions were completed and 626 sessions were missed, for an overall attendance of 61% of prescribed sessions. Attendance as a mean of each participant’s attendance was 59±30% (Table 3.4). When the withdrawals were removed, average attendance was 72±19%. Forty-five percent of participants achieved attendance ≥70%, and average attendance per week for those who attended at least one session was 2.0±0.7 sessions. No serious adverse events occurred during the exercise sessions.

For the determination of adherence to exercise intensity and duration, six participants (9%) qualified for the advanced exercise prescription of intensity and duration, and the remaining participants performed the standard exercise prescription. The presented results are combined for both prescriptions. For the adherence to intensity criteria, the mean adherence to the lower limit of the target heart rate range for intensity was 75±25% when calculated as strict adherence to the prescription without including the prescription adjustments, and 80±22 when including the prescription adjustments (Table 3.4). Fifty-four percent of participants met the intensity prescription for ≥80% of sessions, not including the prescription adjustments. The average resting heart rates for pre-chemotherapy, cycle one, cycle two, cycle three, and cycle four were 70±7, 77±11, 79±9, 82±10, and 83±10 beats per minute. Adherence to the duration prescription was 89±15% (Table 3.4). Eighty-one percent
of participants adhered to the duration prescription for ≥80% of sessions. Figure 3.3 shows the percentage of sessions where the intensity and duration prescriptions were met for each of the first eight weeks of the standard prescription group. For the six participants in the advanced program, achievement of the duration was met 90-100% of the time each week, while achievement of the prescribed heart rate was met 75-100% of the time each week (data not shown).

The overall total adherence to the full exercise dose, namely the percentage of sessions that were attended where the prescribed intensity and duration were adhered to, was 43±27%. Seventeen percent of participants had an overall adherence ≥70%. Figure 3.4 shows the percentage of sessions with total adherence for each treatment cycle separately. For sessions performed before the first treatment and sessions performed after the first and second treatments, adherence to all three components of the exercise prescription occurred for approximately 50% of sessions, and this decreased to less than 40% for the third and fourth treatments.

Reasons were successfully obtained for 98% of instances of non-adherence to frequency (i.e. missed supervised session) and 95% of instances of non-adherence to intensity or duration prescriptions (Table 3.5). One-third of missed sessions were attributed to treatment-related illness. Non-treatment related illness, appointments conflicting with gym times, and transportation to the gym were the next most common reasons for missed sessions, accounting for 12-16% of missed sessions each. Ten percent of the total missed sessions were attributed to work conflicting with gym times, while 8% of the sessions were due to vacation or being out of town. Overall, the least most common reasons were obligations to family or friends (e.g. taking care of kids, elders, visitors in town) (3%) and hospitalizations
(1%). After treatment-related illness, the rank of the reasons for missed sessions differed amongst the completers and withdrawals. In the withdrawals, transportation to the gym and work were the second and third most common reasons for missed sessions (25% and 18%, respectively), while these were some of the least common for the completers (1% and 3%, respectively).

Of the 262 instances of non-adherence to intensity or duration prescriptions, the most common reason was treatment symptoms (27%). While this reason includes reported symptoms such as nausea, fatigue, and pain, specific treatment symptoms were not collected individually. The next most common reason was that the prescription felt too difficult, but not directly because of treatment symptoms (25%). Different types of human or equipment error, such as incorrect use of the heart rate monitor, accounted for the next most common reasons, which occurred in 89 sessions (9% of all exercise sessions). In total, there were intensity adjustments in 58 (6%) exercise sessions, which were due to treatment symptoms (69%), cardiac medications (14%), and asthma symptoms (17%). All adjustments occurred for completers’ exercise sessions and there were no adjustments for the withdrawals.

3.3.3 Effectiveness of exercise prescription

Follow-up exercise tests were completed in 19 of 25 (76%) of participants who enrolled in the sub-study. Two participants were too overwhelmed and stressed to complete the test, two were too ill from treatment to perform the test, and two were experiencing severe and frequent migraines. One other participant unexpectedly did not receive her fourth AC treatment and started her first paclitaxel treatment instead, and was hospitalized shortly thereafter. Her exercise test was performed 20 days after her first paclitaxel treatment, but
before her second paclitaxel treatment. No adverse events occurred with maximal exercise testing.

For those completing both exercise tests, the peak respiratory exchange ratio equaled or exceeded 1.10 and the peak heart rate was within five bpm of age-predicted peak heart rate for all tests. The average peak RPE was 18.8±1.2, and peak RPE was 17 (less than criteria of 18) in five participants. In the 19 participants who completed the follow-up exercise test, there was an average decrease in relative VO$_2$peak of 10±8% (p<0.01), and a decrease in test length of 1.0±1.6 minutes (-6±11%, p=0.02) (Table 3.6). There was no change in peak heart rate, but peak oxygen pulse decreased by 11% on average. Hemoglobin and hematocrit decreased by 18±9 and 19±9% in those who completed the test (both p<0.01).

Individual linear regressions were then performed to determine the variable explaining the most variability in percentage change in absolute VO$_2$peak. The variables explaining a statistically significant amount of the variability in the change in VO$_2$peak were total adherence (R$^2$=49%, p<0.01), attendance (R$^2$=41%, p<0.01), and adherence to duration (R$^2$=32%, p=0.01) and intensity (R$^2$=23%, p=0.04) prescriptions. Percent hemoglobin decrease (R$^2$=12%, p=0.15), program length (R$^2$=10%, p=0.20), and baseline absolute VO$_2$peak (R$^2$=1%, p=0.67) were not significant predictor variables.

The median total adherence to the prescribed frequency, intensity, and duration (45%) was used as an arbitrary cut-point to divide the participants into a high adherence (mean 68±15%) and low adherence (mean 30±18%, p<0.01 for difference) groups. The mean percentage decrease in VO$_2$peak from baseline to follow-up was more than 50% lower in the high adherence than low adherence group (absolute: -7±9% vs. -16±5%, p<0.01; relative: -5±10% vs. -14±3%, p=0.01).
3.4 Discussion

The main findings of this study are that adherence to an exercise program consistent with the recommended exercise prescription for cancer survivors, was lower than hypothesized for women with breast cancer during anthracycline treatment, but was deemed to be effective in those with better adherence to the prescription during anthracycline chemotherapy for early breast cancer. The primary reason for non-adherence to the exercise prescription and withdrawal was treatment symptoms.

Regarding adherence, with the withdrawals included in the analysis, only one of four hypothesized adherence components was met. On average, participants adhered to the prescribed duration in 89% of sessions, exceeding the hypothesis of 80% adherence. Adherence to the prescribed frequency and intensity, and retention were lower than hypothesized. The hypothesis that attendance would be 70% or greater was based on previous RCTs implementing similar exercise prescriptions during chemotherapy treatment for breast cancer. However the attendance in the current study, which was a single arm feasibility intervention with a less stringent explicit expectation regarding attendance due to the study design was substantially lower at 59%, but did exceed 70% when the 15 withdrawals were excluded. Adherence to the prescribed intensity was 75%, while retention was 77%, which were both slightly lower than the hypothesized values of 80% for both measures. In the sub-group who performed maximal exercise tests before and after anthracycline treatment, there was an overall significant 10% decrease in relative VO$_2$peak. However total adherence to all components of the exercise prescription explained nearly half of the variability in the percentage change in VO$_2$peak. Also when the group was divided by the median total adherence, the size of the decrease was significantly smaller in those with
higher adherence. Therefore higher levels of adherence to the recommended exercise prescription were effective in attenuating the decline in VO$_2$peak.

3.4.1 Adherence to prescribed frequency

Specific to the prior large, high quality RCTs of exercise interventions during adjuvant chemotherapy in women with early stage breast cancer (START, CARE, PACES), two of the trials, START and CARE prescribed similar exercise interventions to that of the NExT study, with three times per week, supervised, group-based exercise initiated within the first couple weeks of adjuvant chemotherapy until 3-4 weeks after completion of chemotherapy in early stage breast cancer patients.\(^{18,164}\) The exercise prescription of the NExT study was most similar to the combined aerobic and resistance arm of the CARE trial.\(^{164}\) Attendance for the combined aerobic and resistance arm in CARE trial was 71±23%\(^{164,171}\) In the START trial, attendance was 72±30% in the aerobic group and 68±28% in the resistance group\(^{316,328}\). Despite a reduced weekly frequency prescription (two vs. three sessions per week in START and CARE), the supervised aerobic and resistance arm of the PACES trial was reported by van Waart et al. to have a similar attendance of 71% of all prescribed sessions (mean across participants not reported)\(^{77}\).

A detailed analysis of the reasons for missed sessions for the aerobic and resistance arms of the START trial was published\(^{316}\). Similar to the current study, the top two reasons in the START trial for missed sessions were ‘feeling sick’ and fatigue, likely both related to treatment, accounting for 23% of the reasons for missed sessions\(^{316}\). Additional content analysis determined that the reasons for missed sessions fell into three major themes, namely disease or treatment-related reasons, life-related barriers, and motivation. Disease or treatment-related reasons including symptoms and treatment-related appointments accounted
for 53% of the missed sessions, which is similar to the current study at 49% of total reasons for missed sessions.

It is difficult to envision a strategy to address these reasons for missed sessions in order to increase exercise adherence, and this represents a major barrier to delivering a specific prescribed dose of exercise during anthracycline chemotherapy. Life-related barriers including vacation or planned absences, taking care of family members, visitors, work, transportation issues, cold or flu, and accounted for 34% of missed sessions in the START trial. In the current study, combining non-treatment-related illness, transportation, family obligations, vacation, and work accounted for approximately 50% of the missed sessions. The final theme identified by Courneya et al. related to motivation, included lack of time, performing home exercise, lost interest, miscommunication, and forgetting were largely not reported by participants in the current study, perhaps due to the shorter program duration and loss of interest or other motivational factors were not specifically asked about.

Courneya et al. did not analyze whether differences exist in adherers and non-adherers in the START trial, and the current study identified that those who withdrew from the program differed in their reasons for missed sessions from those who completed the program. Both groups reported treatment symptoms as the largest reason, but the withdrawals cited transportation to the gym and conflict with work hours as the next most common reasons for missed sessions. Therefore screening for participants who have reliable transportation and live close to the gym, or expanding gym hours to accommodate those women who plan to work during treatment, and allowing make-up sessions could help to improve adherence in a supervised exercise program. In addition, developing creative
distance-based interventions to complement supervised programming may help to address this element of adherence.

Several other smaller RCTs of exercise during chemotherapy for early breast cancer have been published. An RCT of a three times per week supervised aerobic exercise during neoadjuvant chemotherapy reported an overall attendance of 82% of prescribed sessions for 10 participants receiving AC every three weeks, but did not report mean attendance across participants.\textsuperscript{172} It is important to note that exercise sessions were individually scheduled with an exercise trainer in this study, which would be expected to increase attendance. Reported attendance in other RCTs during adjuvant therapy which included some participants only receiving radiation treatment, attendance to a two or three times per week intervention during chemotherapy and/or radiation ranged from 70-83%,\textsuperscript{138,165,167,168} and are less relevant for comparison purposes to the current study as adherence may differ during radiation.

3.4.2 Adherence to prescribed intensity and duration

Adherence to the prescribed intensity and duration occurred for 95% of all exercise sessions in the aerobic and resistance arms combined of the START trial,\textsuperscript{170} and 90% of all aerobic and resistance exercise sessions combined in the CARE trial.\textsuperscript{171} An ad hoc analysis of the START trial reported that adherence to the prescribed intensity and duration for the aerobic arm only were 63±30 and 69±30%, respectively.\textsuperscript{329} Unfortunately more detailed analysis including separate statistics for aerobic and resistance sessions, and for achievement of duration and intensity for aerobic workouts were not reported for the CARE trial combined arm that most closely matches the program implemented in the current study. In a small RCT of aerobic exercise during neoadjuvant chemotherapy, Hornsby et al. reported adherence to the minimum prescribed intensity or duration for 77% of sessions.\textsuperscript{172} However
this value included adherence to sessions prescribed at the ventilatory threshold as well as high intensity interval sessions, so this might be expected to be lower than adherence to a moderate intensity prescription. Unfortunately the format of combining adherence to both intensity and duration into a single adherence variable, and combining adherence to both aerobic and resistance workouts in the majority of published studies makes it difficult to compare to the results of the current study. Furthermore, to the author’s knowledge no data has been reported for adherence to each progression in exercise intensity or duration throughout the program.

There are a number of novel findings that can be drawn from the analysis of adherence to intensity and duration in the current study. There was higher adherence to prescribed duration than intensity. The prescribed duration initially started at 20 minutes for the first week and nearly all sessions were performed for this prescribed duration (Figure 3.3). Whereas the first major decline in achievement of prescribed duration was in week four of the program when the prescription increased to 30 minutes, and only 80% of sessions were performed at this prescription. However, between weeks five to seven, while the prescription remained at 30 minutes, the percent of sessions where the prescribed duration was achieved steadily increased, so that nearly all session were being performed for the prescribed duration. This observation indicates that 20 minutes is a feasible initial duration, and that 30 minutes is feasible with appropriate progression, but perhaps an extra week or two would be helpful in the rate of progression from 20 to 30 minutes.

The prescribed intensity for the first two weeks of the program was 50-55 %HRR and the average heart rate for the exercise session was at or above the lower limit of this target range was achieved for approximately 80% of sessions. Generally, the target heart rate was
reached for approximately 80% of sessions with each intensity level thereafter, with a tendency for a slight decrease in adherence in first week of an increased intensity prescription. Unfortunately, due to the short duration of the current study’s program (based on length of treatment protocol), not enough data were available to provide an unbiased analysis of adherence to the highest level of intensity prescribed, 70-75 %HRR. Based on the high percentage of adherence to both intensity and duration by the six participants who were eligible for the advanced stream of the exercise prescription, this prescription and method of assessing eligibility for either prescription also appears to be feasible.

There is not a strong consensus as to the best method for prescribing exercise intensity in cancer survivors, especially during chemotherapy. The author has previously performed a cross-sectional analysis of the accuracy of four different methods of prescribing intensity: HRR, direct heart rate and oxygen consumption relationship, ACSM metabolic equation for treadmill walking, and RPE. In a similar group of breast cancer patients who had completed adjuvant chemotherapy within the previous two to three weeks, the HRR method was the most accurate in achieving 60% of oxygen consumption reserve. Resting heart rate was measured that day, and peak heart rate was measured 2-14 days earlier on a maximal exercise test. However, as the current study reported, resting heart rate changes during chemotherapy treatment. The method for adjusting the prescription to account for the weekly change in the resting heart rate that was employed in the current study requires empirical testing to confirm that the change in HRR matches the change in oxygen consumption reserve.

Hornsby et al. reported a list of the major reasons for non-adherence to the prescribed intensity and duration including nausea, fatigue, and not feeling well. In agreement with
Hornsby et al., the primary reason for non-adherence in the current study was treatment symptoms. The next most common reason for non-adherence was that the prescription felt too difficult. This was not one of the originally planned reasons, but was added to the list after participants reported difficulty in meeting the heart rate target or duration in absence of any particular treatment symptom. A potential reason for the prescription being too difficult for some participants, especially those who consistently did not meet their target heart rate, is that the use of age-predicted peak heart rate overestimated that participant’s actual peak heart rate, which would cause their target heart rate to be higher than the planned relative intensity. Use of measured maximal heart rate in calculation of target heart rates may have increased adherence to the intensity prescription.

The next three most common reasons, all related to error of implementing the prescription, either via calculation or update of prescription, equipment (i.e. heart rate monitor) error or imprecision, accounted for 35% of all reasons for non-adherence to the prescription. The most common of these errors, an accidental miss of the target heart rate by 1-3 bpm occurs either because the heart rate monitor watch used did not display ongoing average heart rate throughout the session, or because the participant was distracted and let their heart rate fall below the lower limit for a few minutes. An easy way to reduce non-adherence related to error, is to utilize watches that provide an ongoing average heart rate throughout the workout, so that participants will know if they had let their heart rate fall below the lower limit and make up for this later in the session. A heart rate monitor error occurred when the heart rate monitor either stopped receiving the chest strap signal, the measured heart rate was abnormal (displaying zero or >200 sporadically) typically due to low strap battery, or the average heart rate was lost from the watch or not recorded. Errors
due to heart rate monitor or strap low battery could be averted with low battery indicator lights that were checked regularly. The last reason for missed prescription that was due to error was that the gym staff members either calculated the target heart rate range incorrectly, or forgot to provide the next progression in the prescription to a participant. The total number of errors would likely be greatly reduced if the intervention was implemented in a one-on-one setting with each session provided undivided attention from an experienced trainer, but this format would increase intervention cost and reduce the feasibility of implementing a similar program, and also reduce the benefits of group-based exercise, which includes social support from other participants.

It is encouraging to note that non-cancer related injuries such as orthopedic or athletic injuries (i.e. plantar fasciitis, knee injuries) only accounted for 2% of reasons for non-adherence. The lack of injuries impeding completion of the exercise prescription could be attributed to the conservative prescription at the start of the intervention and slow progression of the program, in addition to use of a warm-up and cool-down period, intended to help reduce injuries. However, the length of the exercise program was a mean of 8.6 weeks, so it could be expected that this would become a larger issue with a longer program.

3.4.3 Prescription adjustments

Participants only required preemptive decreases in the prescribed intensity for 5% of all exercise sessions completed, yet still failed to meet the heart rate target for 20% of exercise sessions on average, and often reported treatment symptoms as the reason. This appears to indicate that many participants did not take advantage of this preemptive intensity reduction option for accommodating treatment symptoms. Courneya and et al. reported that the exercise trainers in the CARE trial modified the exercise prescription or progression
based on the participant’s individual experience with exercise or treatment symptoms, but did not offer further details,\textsuperscript{171} so this may not have been a standardized approach, such as what was used in the current study. To the author’s knowledge, this is the first study to report a standardized approach to modifying an exercise prescription for “bad days” during chemotherapy treatment.

3.4.4 Retention and recruitment timing

Retention was operationally defined in the START and CARE trials as participants completing ≥66% of prescribed exercise sessions, and was 72% for the aerobic and 68% for the resistance exercise group in START, and 56% for the combined aerobic and resistance group in CARE.\textsuperscript{18} Using this definition for retention, 52% of participants in the current study were retained.

Even though participants were eligible to start the exercise program up to two weeks prior to starting chemotherapy, only 36% completed their first exercise session prior to their first treatment, due to either the participant’s personal schedule, or timing of the referral from their oncologist. Although referral prior to starting chemotherapy was encouraged, the oncologists reported that the flexibility to refer within the first 50% of treatment increased their rate of referral, as some patients were too emotional or overwhelmed prior to starting treatment to consider enrolling in the program. Beginning the exercise program even a short time prior to the first treatment may be an important component required for exercise cardio-protection, as the first treatment of anthracyclines is thought to cause damage to the myocardium,\textsuperscript{70} and ‘exercise pre-conditioning’ has been shown to be an effective cardio-protection strategy in preclinical studies (Table 2.2). However, the findings from the current study suggest that this may be a challenge unless more emphasis is placed on the importance
of ‘exercise preconditioning’ for cardio-protection and making this a priority. The risk for cardiotoxicity increases with dose,\textsuperscript{53} and unfortunately exercise adherence decreased with number of treatment cycles (Figure 3.4). This may also introduce a limitation to implementation of exercise training for cardio-protection in humans, in that exercise adherence is worst when their myocardium may be most at risk for damage.

Although the majority (69\%) of women in the CARE trial combined arm received an anthracycline-containing protocol, most either received epirubicin or an AC protocol combined with a taxane agent in a much longer protocol; only 6\% received an AC protocol similar to the current study participants. One quarter of the 78 participants in the aerobic exercise arm of the START trial received an AC protocol, however at the time of the study, AC was likely delivered every three weeks for all patients, whereas the majority (69\%) in the current study received the dose dense protocol delivered every two weeks with granulocyte colony-stimulating factor. This difference in treatment protocols could likely affect adherence as the two week protocol allows less time for recovery in between treatments and is associated with a higher relative risk of non-hematological (i.e. other than neutropenia) side effects.\textsuperscript{331}

\textbf{3.4.5 Effectiveness of exercise prescription}

While 24\% of the participants did not complete the follow-up exercise test, and this likely introduced some bias in our analysis, the maximal exercise tests for those who did complete the test were of high quality, with all tests exceeding the respiratory exchange ratio and peak heart rate criteria for maximal effort. In comparison, another study reported that 13\% of early breast cancer patients did not fulfill this criteria due to poor compliance.\textsuperscript{332} The finding of an average 10\% decrease in relative VO\textsubscript{2}peak was likely conservative considering
that the six participants who did not complete the follow-up exercise test also had very low adherence (mean, 14±13%, range, 0-35% total adherence for non-completers of the exercise test). Further, the AC treatments included in this study were only half of the total chemotherapy protocol, which was followed by a similar duration of paclitaxel for most participants, so VO_{2peak} may decrease even more during the second half of treatment with paclitaxel. Both the regression and two group comparison analyses used to identify influences on the change in VO_{2peak} demonstrated a critical role for exercise adherence, predominantly explained by attendance.

For the START and CARE trials, age, baseline BMI and VO_{2peak} were similar to those of the current study, but the chemotherapy protocols and timing of VO_{2peak} assessment differed. The baseline maximal treadmill exercise test was performed up to two weeks after starting treatment, while the follow-up was performed three to four weeks following treatment completion, which could potentially cause a lower baseline and higher follow-up (due to greater recovery time) VO_{2peak} relative to that of the current study. Due to the different treatment protocols, the length of the intervention was a mean of 16.4 weeks, almost double that of the current study. Despite these differences, there was a comparable 13% mean decrease in relative VO_{2peak} in the combined aerobic and resistance group of the CARE trial. In the START trial there was no change in relative VO_{2peak} in the aerobic group, a 5% decrease in the resistance group, and a 6% decrease in the usual care group.\(^1\)\(^8\) The greater decrease in VO_{2peak} with all exercise groups in the CARE trial than the decrease in the control group in the START could be attributed to changes in chemotherapy protocol.\(^1\)\(^6\)\(^4\) However, Hornsby et al. reported a 13% improvement in VO_{2peak} in a recent pilot RCT during neoadjuvant treatment with 10 women in the exercise group, perhaps due
to their higher adherence and incorporation of training sessions at ventilatory threshold and high-intensity intervals.\textsuperscript{172} Although this study reported that the prescription was safe with one-on-one supervision, further research will be needed to determine the tolerability and efficacy of this prescription in a wider group of participants, as well as with a two-week chemotherapy protocol. Travier et al. also implemented an interval training approach above and below the ventilatory threshold.\textsuperscript{168} Despite 18 weeks of training, the aerobic and resistance training group experienced a mean decrease in VO\textsubscript{2}peak of 12%. Lastly, Kim et al. implemented an exercise prescription and program length similar to the current study but with much higher total adherence that resulted in an 8% improvement in VO\textsubscript{2}peak.\textsuperscript{138} However it should be noted that the study population was not comparable to the current study, as 32% of participants were receiving radiation only and chemotherapy protocols were not reported for the remainder. Regardless, this study highlights the importance of adherence to the exercise prescription with regards to the efficacy of the intervention, as measured by changes in aerobic fitness.

\textbf{3.4.6 Strengths and limitations}

To the author’s knowledge, this study was the first comprehensive assessment of adherence to an exercise program implementing an exercise prescription consistent with the recommended exercise guidelines for cancer survivors during chemotherapy for breast cancer in a setting more closely resembling a clinical program than a RCT. Further strengths include inclusion of participants on a single, commonly used chemotherapy protocol containing one of the most effective yet most toxic chemotherapeutic agents used for both neoadjuvant and adjuvant treatment of early breast cancer. The current study completed collection of frequency, intensity and duration adherence data for 964 exercise sessions,
along with reasons for 613 missed sessions. A potential limitation to the study in the context of application for cardio-protection was that the exercise intervention also included resistance training, which may have influenced adherence to the aerobic exercise prescription due to overall session length and energy required for the combined session. In the CARE trial, although the group that performed aerobic exercise only had higher attendance than the group that performed a combined aerobic and resistance exercise prescription, the change in VO$_{2\text{peak}}$ was similar.\textsuperscript{164} A limitation to the assessment of adherence to exercise intensity is the use of age-predicted peak heart rate to calculate target heart rates, rather than measured peak heart rate from a maximal exercise test. However, because the parent study, NExT, was focused on testing a model of a program that would be implemented within a cancer centre, submaximal exercise testing was used at entry into the program as maximal exercise testing is not a standard of care currently. A maximal exercise test was only performed for those enrolled in the sub-study. For consistency, age-predicted peak heart rate was used for prescribing exercise intensity for all participants. The equation used to predict peak heart rate was developed from a cohort of over 5000 women which may improve specificity for the study population over the generic equations, but this equation still has a standard deviation of 12 bpm.\textsuperscript{322}

A limitation of the study design includes lack of a control group and small sample size for the effectiveness analysis, however the range of adherence in the exercise group allowed for division into high and low adherence groups to examine the effectiveness of adhering to the exercise prescription. The effectiveness analysis is also limited by 24\% of the participants refusing to complete the follow-up assessment due to treatment-related illness or stress. These participants were also some of the lowest adherers, which introduced some bias.
in the assessment of change. Future studies with larger sample sizes will be needed to more definitively identify the effect of adherence to different exercise prescriptions on VO$_2$peak, including categorization into more than two levels of adherence and assessment of non-linear exercise prescriptions during treatment.$^{333}$ It is important to note that adherence to exercise was assessed in this study for a supervised, group-based program in a private research facility in a large urban city, and these results may not be generalizable to one-on-one supervised exercise, home-based exercise, nor community-based or fee-for-service programming.

3.5 Conclusion

In summary, adherence to exercise consistent with the current recommended exercise prescription for cancer survivors administered in a model of a clinical care program was lower than previous RCTs during anthracycline-containing chemotherapy treatment for breast cancer patients. Overall mean adherence to a three times per week frequency, a progressive intensity of 50-70% of age-predicted heart rate reserve, and a progressive duration of 20-30 minutes, was 59%, 75%, 89%, respectively, and a total adherence to all three of 43%. Less than half of all participants attended 70% or more of all prescribed sessions during chemotherapy and in sessions that were attended, only slightly more than half adhered to the prescribed intensity for 80% or more of the time, and 73% adhered to the prescribed duration 80% or more of the time. The primary reason for missed sessions and missing prescription targets was treatment symptoms, while conflicting appointments and other life-related reasons were also common reasons for non-adherence. However, in assessment of the effectiveness of the prescription, adherence to all three prescription
components for 45% or more of sessions, significantly attenuated the reduction in VO$_2$peak that is common with chemotherapy treatment. Taken together, these results suggest that it is a challenge for many early breast cancer patients to adhere to the recommended exercise prescription for cancer survivors during anthracycline chemotherapy treatment for a variety of reasons, but there is a greater benefit for those who achieve greater adherence. The low rates of supervised exercise adherence may indicate a potential issue for studies aiming to implement exercise programming to target specific side effects of anthracycline-containing chemotherapy treatment in a clinical setting, such as cardiotoxicity. Development of strategies to address key barriers to exercise adherence or determination of a minimal effective exercise dose may be an important consideration in order to improve specific side effects of cancer treatment, such as for cardio-protection from anthracycline chemotherapy.
### Table 3.1: Aerobic exercise prescription

<table>
<thead>
<tr>
<th>Week of program</th>
<th>Supervised gym exercise prescription</th>
<th>Home exercise prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly frequency</td>
<td>Duration (minutes)</td>
</tr>
<tr>
<td>1</td>
<td>Standard stream:</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Advanced stream:</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Standard stream:</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Advanced stream:</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Standard stream:</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Advanced stream:</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Standard stream:</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Advanced stream:</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: HRR, heart rate reserve; RPE, rating of perceived exertion;
| Table 3.2: Study participant demographics and cancer diagnosis and treatment characteristics |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                  | Total n=64        | Completers n=49  | Withdrawals n=15 | Effectiveness analysis n=25 |
| Age (years) (mean±SD)           | 49±9             | 49±9             | 46±4             | 51±8             |
| Menopausal status n (%)         |                  |                  |                  |                  |
| Pre-menopausal                  | 26 (41%)         | 22 (44%)         | 4 (29%)          | 8 (32%)          |
| Post-menopausal                 | 24 (38%)         | 21 (42%)         | 3 (21%)          | 10 (40%)         |
| Peri-menopausal                 | 14 (22%)         | 7 (14%)          | 7 (50%)          | 7 (28%)          |
| Ethnicity (n %)                 |                  |                  |                  |                  |
| White                           | 37 (58%)         | 29 (58%)         | 9 (64%)          | 14 (56%)         |
| Asian                           | 22 (34%)         | 19 (38%)         | 3 (21%)          | 10 (40%)         |
| Other                           | 5 (8%)           | 2 (4%)           | 2 (14%)          | 1 (4%)           |
| Marital status (n %)            |                  |                  |                  |                  |
| Married/common-law              | 47 (73%)         | 37 (74%)         | 10 (71%)         | 19 (76%)         |
| Divorced/separated/widowed      | 4 (6%)           | 3 (6%)           | 1 (7%)           | 3 (12%)          |
| Single                          | 9 (14%)          | 9 (18%)          | 0                | 3 (12%)          |
| Missing response                | 4 (6%)           | 1 (2%)           | 3 (21%)          | 0                |
| Education (n %)                 |                  |                  |                  |                  |
| Bachelor’s degree or above      | 35 (55%)         | 30 (60%)         | 5 (36%)          | 13 (52%)         |
| Below Bachelor’s degree         | 24 (38%)         | 19 (38%)         | 5 (36%)          | 11 (44%)         |
| Missing response                | 5 (8%)           | 1 (2%)           | 4 (29%)          | 1 (4%)           |
| Personal income before tax (n %) |                  |                  |                  |                  |
| ≥$80,000                        | 20 (31%)         | 16 (32%)         | 4 (29%)          | 9 (36%)          |
| $50,000-79,999                   | 12 (19%)         | 9 (18%)          | 3 (21%)          | 4 (16%)          |
| $30,000-49,999                   | 18 (28%)         | 17 (34%)         | 1 (7%)           | 9 (36%)          |
| <$30,000                         | 7 (11%)          | 5 (10%)          | 2 (14%)          | 2 (8%)           |
| Missing response                | 6 (9%)           | 2 (4%)           | 4 (29%)          | 1 (4%)           |
| Comorbid conditions (n %)       |                  |                  |                  |                  |
| Heart disease/angina            | 1 (2%)           | 0                | 1 (7%)           | 1 (4%)           |
| Diabetes                        | 1 (2%)           | 1 (2%)           | 0                | 0                |
| Asthma/ lung disease            | 2 (3%)           | 2 (4%)           | 0                | 0                |
| Arthritis                       | 11 (17%)         | 9 (18%)          | 2 (14%)          | 7 (28%)          |
| Fibromyalgia                    | 2 (3%)           | 2 (4%)           | 0                | 0                |
| Joint replacement               | 1 (2%)           | 1 (2%)           | 0                | 1 (4%)           |
| Osteoporosis/ osteopenia        | 4 (6%)           | 4 (8%)           | 0                | 1 (4%)           |
| Stage (n %)                     |                  |                  |                  |                  |
| I                               | 9 (14%)          | 9 (18%)          | 0                | 5 (20%)          |
| II                              | 46 (72%)         | 34 (68%)         | 12 (86%)         | 17 (68%)         |
| III                             | 9 (14%)          | 7 (14%)          | 2 (14%)          | 3 (12%)          |
| Surgery (n %)                   |                  |                  |                  |                  |
| Lumpectomy                      | 48 (75%)         | 36 (72%)         | 12 (86%)         | 23 (92%)         |
| Mastectomy                      | 16 (25%)         | 14 (28%)         | 2 (14%)          | 2 (8%)           |
| Weeks between cycles (n %)      |                  |                  |                  |                  |
| Two weeks                       | 44 (69%)         | 33 (66%)         | 11 (79%)         | 18 (72%)         |
| Three weeks                     | 20 (31%)         | 17 (34%)         | 3 (21%)          | 7 (28%)          |
| Time since surgery* (weeks): (mean±SD) | 6.5±7.6        | 6.5±8.1          | 6.6±2.6          | 6.8±1.6          |

* Calculated as time between surgery and first exercise session
Table 3.3: Baseline physical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adherence analysis</th>
<th>Effectiveness analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n=64</td>
<td>Completers n=49</td>
</tr>
<tr>
<td>Weight (kilograms)</td>
<td>70.5±18.0</td>
<td>72.1±18.9</td>
</tr>
<tr>
<td>Height (meters)</td>
<td>163.4±6.6</td>
<td>163.6±6.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3±5.9</td>
<td>26.8±6.1</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>71±9</td>
<td>71±9</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mmHg)</td>
<td>111±14</td>
<td>111±13</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mmHg)</td>
<td>75±11</td>
<td>75±9</td>
</tr>
<tr>
<td>MVPA (weekly minutes)</td>
<td>163±129</td>
<td>169±127</td>
</tr>
</tbody>
</table>

Data are mean±SD.
Abbreviations: BMI, body mass index; bpm, beats per minute; mmHg, millimeters of mercury; MVPA, moderate-to-vigorous physical activity; SD, standard deviation;

Table 3.4: Mean adherence to frequency, intensity, and duration, and required intensity adjustments across participants

<table>
<thead>
<tr>
<th>Exercise prescription parameter</th>
<th>Total n=64</th>
<th>Completers n=49</th>
<th>Withdrawals n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise sessions attended (n)</td>
<td>15.1±8.9 (0, 32)</td>
<td>18.4±7.0 (4, 32)</td>
<td>4.2±4.9 (0, 14)</td>
</tr>
<tr>
<td>Missed sessions (n)</td>
<td>9.8±7.1 (0, 31)</td>
<td>7.0±4.5 (0, 18)</td>
<td>18.7±6.6 (9, 31)</td>
</tr>
<tr>
<td>Attendance (%)</td>
<td>59±30 (0, 100)</td>
<td>72±19 (27, 100)</td>
<td>16±19 (0, 45)</td>
</tr>
<tr>
<td>Adherence to intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not including adjustments (%)</td>
<td>75±25 (0,100)</td>
<td>75±24 (6, 100)</td>
<td>73±35 (0, 100)</td>
</tr>
<tr>
<td>Including adjustments (%)</td>
<td>80±22 (0, 100)</td>
<td>82±19 (19, 100)</td>
<td>73±35 (0, 100)</td>
</tr>
<tr>
<td>Adherence to duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting or exceeding duration target (%)</td>
<td>89±15 (41, 100)</td>
<td>89±15 (41, 100)</td>
<td>93±13 (63, 100)</td>
</tr>
<tr>
<td>Total adherence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended and met intensity and duration target (%)</td>
<td>43±27 (0, 96)</td>
<td>53±23 (0, 96)</td>
<td>12±15 (0, 39)</td>
</tr>
<tr>
<td>Adjustments to intensity prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessions with adjustments (n)</td>
<td>1.0±2.0 (1, 10)</td>
<td>1.2±2.1 (1, 10)</td>
<td>0</td>
</tr>
<tr>
<td>Sessions with adjustments (%)</td>
<td>6±13 (0, 53)</td>
<td>7±13 (0, 53)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation (minimum, maximum).
Table 3.5: Reasons for missed sessions and non-adherence to prescription

<table>
<thead>
<tr>
<th></th>
<th>Total (n=64)</th>
<th>Completers (n=49)</th>
<th>Withdrawals (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Missed sessions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed sessions (n)</td>
<td>626</td>
<td>345</td>
<td>281</td>
</tr>
<tr>
<td>Reasons collected (n (%))</td>
<td>613 (98%)</td>
<td>335 (97%)</td>
<td>278 (99%)</td>
</tr>
<tr>
<td><strong>Reasons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related illness</td>
<td>207 (33%)</td>
<td>130 (38%)</td>
<td>77 (27%)</td>
</tr>
<tr>
<td>Non-treatment-related illness</td>
<td>103 (16%)</td>
<td>61 (18%)</td>
<td>42 (15%)</td>
</tr>
<tr>
<td>Conflicting appointment</td>
<td>89 (14%)</td>
<td>73 (21%)</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>Issue with transportation to gym</td>
<td>74 (12%)</td>
<td>5 (1%)</td>
<td>69 (25%)</td>
</tr>
<tr>
<td>Work</td>
<td>62 (10%)</td>
<td>12 (3%)</td>
<td>50 (18%)</td>
</tr>
<tr>
<td>Vacation or planned absence</td>
<td>49 (8%)</td>
<td>46 (13%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Family and/or friend obligations</td>
<td>19 (3%)</td>
<td>5 (1%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>7 (1%)</td>
<td>3 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td><strong>Missed intensity/duration prescription</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessions with missed prescription (n)</td>
<td>262</td>
<td>245</td>
<td>17</td>
</tr>
<tr>
<td>Reasons collected (n (%))</td>
<td>250 (95%)</td>
<td>236 (96%)</td>
<td>14 (82%)</td>
</tr>
<tr>
<td><strong>Reasons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment symptoms</td>
<td>71 (27%)</td>
<td>69 (28%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Prescription too difficult</td>
<td>65 (25%)</td>
<td>63 (26%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Accidental miss of target heart rate</td>
<td>40 (15%)</td>
<td>35 (14%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Staff error in providing prescription</td>
<td>32 (12%)</td>
<td>29 (12%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Heart rate monitor error</td>
<td>17 (6%)</td>
<td>16 (7%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Left early for conflicting appointment</td>
<td>18 (7%)</td>
<td>17 (7%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Non-cancer-related injury</td>
<td>5 (2%)</td>
<td>5 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3.6: Exercise test and hematological data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Baseline n=25</th>
<th>Non-completers Baseline n=6</th>
<th>Completers Baseline n=19</th>
<th>Completers Follow-up n=19</th>
<th>Completers % change n=19</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2}peak (L/min)</td>
<td>1.81±0.44</td>
<td>1.69±0.27</td>
<td>1.85±0.48</td>
<td>1.63±0.43</td>
<td>-12±9</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>VO\textsubscript{2}peak (mL/kg/min)</td>
<td>27.4±4.5</td>
<td>25.0±2.4</td>
<td>28.1±4.8</td>
<td>25.3±4.4</td>
<td>-10±8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Peak heart rate (bpm)</td>
<td>173±11</td>
<td>171±12</td>
<td>174±11</td>
<td>173±11</td>
<td>0±4</td>
<td>0.87</td>
</tr>
<tr>
<td>Peak O\textsubscript{2} pulse (mL)</td>
<td>11.9±3.1</td>
<td>11.8±3.8</td>
<td>11.9±3.1</td>
<td>10.4±3.2</td>
<td>-11±21</td>
<td>0.05*</td>
</tr>
<tr>
<td>O\textsubscript{2}/beat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.22±0.08</td>
<td>1.23±0.06</td>
<td>1.22±0.08</td>
<td>1.24±0.09</td>
<td>2±7</td>
<td>0.30</td>
</tr>
<tr>
<td>Peak VE (L/min)</td>
<td>54.9±11.5</td>
<td>51.4±5.7</td>
<td>56.9±12.6</td>
<td>54.9±12.0</td>
<td>-3±12</td>
<td>0.23</td>
</tr>
<tr>
<td>Test length (min)</td>
<td>14.5±3.0</td>
<td>15.3±2.9</td>
<td>15.5±3.1</td>
<td>14.5±3.1</td>
<td>-6±11</td>
<td>0.02*</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>133±8</td>
<td>135±12</td>
<td>132±6</td>
<td>107±11</td>
<td>-18±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>0.41±0.02</td>
<td>0.41±0.04</td>
<td>0.40±0.02</td>
<td>0.33±0.03</td>
<td>-19±9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*p≤0.05

Data are mean±SD.

Abbreviations: min = minute; O\textsubscript{2} = oxygen; RER = respiratory exchange ratio; VE = ventilation; VO\textsubscript{2}peak = peak oxygen consumption;
Women, ≥19 years, stage I-IIIA breast cancer

**Stream 1**

Screened for exercise intervention:
- <50% of adjuvant chemotherapy
- Body mass index <40 kg/m²
- Deemed safe to exercise
- Understand English

Those on non-anthracycline chemotherapy excluded

Enrolled in supervised exercise program

**Adherence** to exercise during anthracycline chemotherapy:
- Frequency
- Intensity
- Duration
- Retention rate

**Stream 2**

Screened for sub-study:
- Willing/able to do pre anthracycline visit
- Body mass index < 35 kg/m²
- No history of cardiovascular disease, respiratory disease, uncontrolled diabetes, hypertension
- Non-smoker
- No previous treatment with anthracyclines, radiation, or trastuzumab

Maximal exercise test 0-14 days pre anthracyclines

Maximal exercise test 7-14 days post anthracyclines

**Effectiveness** of exercise during anthracycline chemotherapy:
- Change in peak oxygen consumption
Figure 3.2: Flow through the study

**Ineligible for main study**
- n=16
  - past first half of tx n=3
  - BMI> 40kg/m² n=1
  - no adjuvant chemotherapy n=8
  - does not speak English n=3
  - med hx too complex n=1

**Decline/ no response main study**
- n=20
  - lives too far away n=8
  - working during tx n=4
  - family obligations n=2
  - already exercising n=2
  - too overwhelmed/busy n=1
  - no response n=3

**Excluded NExT participants**
- n=22
  - non-AC protocol n=21
  - completed AC n=1

**Declined sub-study**
- n=3
  - too overwhelmed/busy n=3

**Ineligible for sub-study**
- n=16
  - no anthracyclines n=1
  - not able/willing to do pre chemo visit n=11
  - BMI> 35 kg/m² n=2
  - Joined pharmacological cardio-protection study n=2

**Referrals to main study**
- n=109

**Screened for main study**
- n=109

**Enrolled in main study**
- n=73

**Main study participants on AC**
- n=51

**Referred after Feb 2014**
- n=28

**Screened for sub-study**
- n=44

**Included in exercise program**
- n=64

**Completed exercise program**
- n=50
  - Reasons for withdrawal:
    - tx-related illness n=5
    - transportation/commute n=4
    - family obligations n=2
    - work n=2
    - non-tx-related illness n=1

**Completed follow-up exercise test**
- n=21
  - Reasons for non-completion:
    - too sick due to tx n=2
    - too overwhelmed n=2

**Enrolled in sub-study**
- n=25

**Abbreviations:**
- tx = treatment
- hx = history
- AC = anthracycline-containing chemotherapy

* Patients who were referred to and declined the main study but joined the sub-study
Figure 3.3: Adherence to prescribed intensity (A) and duration (B) by each week of the prescription; with prescription displayed by bars and secondary axes.
Figure 3.4: Attendance and adherence to intensity and/or duration prescription as a percentage of total prescribed sessions, divided by treatment cycle.

- **Attended and adhered to intensity and duration**
- **Attended but did not adhere to intensity and/or duration**
- **Did not attend**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Attendance and Adherence</th>
<th>Did not Attend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-cycle 1</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>40%</td>
<td>60%</td>
</tr>
</tbody>
</table>
Chapter 4 - Responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy for breast cancer

4.1 Introduction

Women diagnosed with breast cancer may be at a heightened risk for cardiovascular diseases, due in part to the direct toxic effects of adjuvant treatment on the heart. Dose-dependent, cumulative, progressive cardiotoxicity is a well-recognized complication of anthracyclines, the most common and effective class of chemotherapeutic agents used to treat breast cancer. Investigation of effective interventions to stop, slow or reverse early cardiotoxicity are actively being pursued, including administration of dexrazoxane and traditional heart failure medications, including β-blockers and ACE inhibitors, and attempts to develop a less cardiotoxic anthracycline analog with similar antitumor efficacy.

Exercise is a promising non-pharmacological intervention that attenuates anthracycline-induced cardiotoxicity in rodents. Exercise can induce favourable cardiac remodeling in heart failure patients, but the effect on human cardiac function in the context of anthracycline-related cardiotoxicity is unknown. A requirement for translation of these preclinical findings to humans is determination of an effective exercise dose for cardio-protection that is also tolerable for humans during anthracycline-containing chemotherapy. The animal studies demonstrating exercise cardio-protection typically use a fairly strenuous exercise prescription of five days a week, moderate to high intensity, 20–90 minutes duration, that may not be tolerable in humans due to treatment symptoms, or feasible due to the high amounts of medical appointments on top of normal family or work obligations for women undergoing chemotherapy treatment for breast cancer. In the absence of evidence around the required exercise dose for cardio-protection from...
anthracyclines in humans, a logical first step is to examine the effect on cardiac function of an exercise intervention consistent with the currently recommended exercise guidelines for cancer survivors from the ACSM\textsuperscript{76} and other experts in the field of exercise prescription of cancer survivors.\textsuperscript{162,163}

A second requirement for the translation of these preclinical findings to human models is selection of a sensitive noninvasive outcome measure to measure the effect in humans.\textsuperscript{74} Early detection of cardiotoxicity is associated with improved prognosis.\textsuperscript{335} The primary parameter used to identify cardiotoxicity in oncological clinical care and research, LVEF is not sensitive to early cardiac dysfunction,\textsuperscript{51} limiting its effectiveness as a primary outcome in investigation of analogs and interventions that could mitigate early anthracycline-induced cardiotoxicity and prevent late cardiotoxicity. However, several parameters of myocardial mechanics,\textsuperscript{191,202} including left ventricular strain and strain rates have been identified as candidate markers of early anthracycline-induced cardiotoxicity.

Echocardiographic quantification of myocardial mechanics – the motion or forces producing motion of the heart, is a promising technique for measuring sensitive cardiac function changes during chemotherapy and potentially during exercise training. As described in Chapter 2, and in Tables 2.3 and 2.4, there is a consistent observed deterioration of certain myocardial mechanics parameters during anthracycline treatment for breast and other adult cancer types that can also predict later development of cardiotoxicity defined by a drop in LVEF. The combination of this observational evidence and biological plausibility of cause and effect\textsuperscript{184} are strong indications that myocardial mechanics can identify early anthracycline-induced changes in cardiac function, and therefore may be a promising outcome measure for investigating the cardio-protective benefit of exercise during chemotherapy.
Two further requirements that should be fulfilled by novel therapeutic targets to be considered for phase II/III clinical trials include reliability and responsiveness to intervention.\textsuperscript{174} The requirement of high quality images for the speckle tracking echocardiography techniques used to measure myocardial mechanics may limit their reliability within a breast cancer population. Left-sided mastectomy and/or silicone implants,\textsuperscript{194} higher subcutaneous fat, and older age, are factors that may impede the acquisition of high quality echocardiographic images in breast cancer patients. Although there is some limited evidence that myocardial mechanics are responsive to exercise training in other populations,\textsuperscript{228-232} and that exercise training can prevent bed rest-induced deficits in myocardial mechanics,\textsuperscript{234} it is not known whether exercise training can prevent the chemotherapy-related deficit in myocardial mechanics. Global longitudinal strain (GLS) is the most reproducible myocardial mechanics parameter\textsuperscript{336} and has the most consistently demonstrated relationship with anthracycline treatment, and therefore was selected as a primary outcome for the proposed study.\textsuperscript{46}

The purpose of this study was to determine the responsiveness of myocardial mechanics to exercise training following the recommended exercise guidelines for cancer survivors during anthracycline chemotherapy for breast cancer. Responsiveness to exercise training will be assessed by percent change in GLS (primary outcome), and the other myocardial mechanics parameters (secondary outcomes) with enrollment in the exercise program studied in Chapter 3 during adjuvant AC treatment. The exploratory aims of this study were to explore the relationships between GLS and exercise dose, as well as GLS and VO\textsubscript{2}peak during anthracycline treatment for breast cancer.

It was hypothesized that exercise training would prevent a clinically relevant deterioration in GLS and the other myocardial mechanics parameters during anthracycline
treatment for breast cancer. Exploratory hypotheses include that a dose response relationship will exist between change in GLS and amount of exercise; and that the change in VO$_2$peak over the course of anthracyclines will be associated with the change in GLS.

4.2 Methods

This study was a single-arm pilot study. The study received ethical approval through the British Columbia Cancer Agency Research Ethics Board. All study participants signed an informed consent form prior to beginning the study.

4.2.1 Participants

The participants in this study are the same as those in Chapter 3 who participated in the maximal exercise test. All participants in this study met the sub-study eligibility criteria for Chapter 3. Briefly, this included a diagnosis of stage I-IIIA breast cancer, scheduled to receive, but not yet started adjuvant anthracycline-containing chemotherapy treatment and able to attend the baseline assessment prior to their first treatment. Exclusion criteria included conditions that may cause abnormal baseline cardiac function or potential acceleration of cardiac side effects with anthracycline treatment, including uncontrolled hypertension or diabetes, history of cardiovascular disease or respiratory disease, current smoking status, BMI >35 kg/m$^2$, and previous receipt of anthracyclines, trastuzumab, or thoracic radiation.

4.2.2 Intervention

The intervention was identical to that described in Chapter 3 and Table 3.1. Briefly, the aerobic exercise prescription consisted of a 5-minute warm-up, 20-30 minutes at 50-75% HRR, and a 5-minute cool down for supervised sessions three times per week. The intervention started up to two weeks prior to chemotherapy, depending on the timing of participant referral and their
availability. Participants were invited to attend gym sessions until the study follow-up assessment, 7 to 14 days after their last anthracycline treatment. Participants also completed resistance training during the intervention period as a part of the main study (NExT).

4.2.3 Outcome measures

Outcome measures were collected 0 to 14 days prior to the first cycle of anthracyclines, and 7 to 14 days after the last cycle of anthracyclines. This timing of follow-up matches that of the majority of observational studies of myocardial mechanics during anthracyclines (Tables 2.3 and 2.4). Additionally, the majority of participants were receiving their first paclitaxel treatment 14 days after the last anthracycline treatment, and the goal was to perform the follow-up before this new treatment type was received. The study visit consisted of collection of demographics, diagnosis and treatment information via a brief questionnaire, the modified Minnesota Leisure Time Physical Activity Questionnaire, height and weight, and a maximal exercise test as described in Chapter 3. The assessment also included a resting echocardiogram and measurement of seated resting heart rate and blood pressure. During the intervention period, exercise adherence variables were collected throughout the intervention period for each participant as described in Chapter 3. The number of possible sessions for the calculation of percent attendance and adherence was calculated as the number of open gym days between the baseline and follow-up assessments for each participant.

4.2.3.1 Physical activity questionnaire

At baseline, the Physical Activity Questionnaire was administered for the previous six months, whereas at follow-up, participants were asked about the physical activity they had performed since the baseline assessment including supervised exercise sessions as a part of this study. Only aerobic activities with a metabolic equivalent score of 3.0 or greater (considered
moderate intensity) were included in calculation of MVPA reported at both time points, whereas all reported physical activities were included in total MET-hours to give an indication of overall physical activity levels including light activity and non-aerobic activity.

4.2.3.2 Resting heart rate and blood pressure

Seated resting heart rate was measured as the lowest heart rate on a FT1 heart rate monitor (Polar, Lachine, Quebec) during five minutes of quiet, seated rest, in a hard-backed chair with back flat against the chair and feet flat on the floor, arms and legs uncrossed, and arms supported by arm rests. Resting blood pressure was measured at the end of the 5-minute resting period on the non-surgical side with a Littman Classic II stethoscope (3M, St. Paul, Minnesota) and an Aneroid Durashock sphygmomanometer (Welch Allyn, Mississauga, Ontario). Blood pressure was measured a second time after 60 seconds, and was recorded as the average of the two measurements. Supine blood pressure was also measured at the end of the echocardiogram (typically lasting 20-25 minutes) using the same protocol. Mean arterial pressure was calculated for the seated and supine postures as: diastolic blood pressure + 1/3 * (systolic – diastolic blood pressure). The rate pressure product was calculated as: resting heart rate * systolic blood pressure.

4.2.3.3 Echocardiogram and image analysis

A single portable Vivid I ultrasound unit with a 3S-RS cardiac probe with a frequency range of 2.0 to 3.6 MHz (GE Healthcare, Mississauga, ON) was used to acquire the echocardiogram images. A certified sonographer, blinded to exercise program attendance, performed all scans. It was not possible to blind the sonographer to time point due to the participant’s hair loss at the follow-up assessment. Two certified sonographers acquired the
images; the first completed study scans from February 2014 to August 2014, and the second from August 2014 for the rest of the study.

Transthoracic echocardiograms were performed on participants in the left lateral decubitus position. Images were acquired in the parasternal long-axis, parasternal short axis at the mid-papillary, mitral valve and apical levels, the apical 4-, 3-, and 2-chamber view. A modified Simpson’s Biplane method was used to calculate the end diastolic, end systolic volumes, stroke volume, and LVEF from the apical 4- and 2-chamber views. Cardiac output was calculated as the Biplane stroke volume multiplied by the heart rate during the three cardiac cycles used to measure the 4-chamber volumes (called supine heart rate). Systemic vascular resistance was calculated as: 80 * (supine mean arterial blood pressure / cardiac output). Peak early (E) and atrial (A) filling velocities, and deceleration time (DT) were measured using pulsed wave Doppler with the sample volume placed at the LV-inflow at the tips of the mitral valve leaflets. Correct positioning of the sample volume was confirmed by use of colour Doppler. Isovolumic relaxation time (IVRT) was captured from continuous wave Doppler with the sample volume placed between the tips of the mitral leaflets, and was defined as the time from aortic valve closure to mitral valve opening. Left ventricle dimensions and wall thicknesses were acquired from the parasternal long axis view according to American Society of Echocardiography recommendations. To estimate a measure of LV afterload (generally approximated as (end-systolic pressure * end-systolic radius) / end-systolic wall thickness), LV end-systolic wall stress was calculated using the equation by Reichek et al.: (0.334 * systolic blood pressure * end-systolic dimension)/(end-systolic posterior wall thickness * (1 + end-systolic posterior wall thickness/ LV end-systolic dimension)). The linear method was used to calculate LV mass using end-diastolic measures as: 0.8*1.04[(IVS thickness + LV dimension +
posterior wall thickness)\(^3\) – LV dimension\] +0.6.\(^{337}\) Relative wall thickness was calculated using end-diastolic measures as: \((2 \times \text{posterior wall thickness})/\text{LV dimension}\).\(^{337}\) GLS and LSR were captured from the apical 4-chamber view only, as this view has been reported to be more sensitive to change with anthracycline treatment in breast cancer patients than in the 2- and 3-chamber view,\(^{185}\) and the 4-chamber view has better inter-observer and intra-observer reliability than the 2-chamber view.\(^{339}\) Radial and circumferential strain and strain rate were captured from the parasternal short axis view at the level of the full thickness of the papillary muscle, where the mitral leaflets were no longer visible.

As mentioned, high quality images are a critical requirement for speckle tracking echocardiography.\(^{336}\) Therefore a number of technical considerations were implemented in image acquisition, including optimizing the gain, maximizing image depth for the length of the LV in the longitudinal view, and maximizing circularity of the LV in the short axis views, employing breath holds where necessary to avoid breathing artifacts, and use of a high frame rate (80 frames per second used for all images).\(^{336}\) Additionally, the frame rate, depth, and focal point were standardized for each image across all time points within a given participant. Several loops of three cardiac cycles were captured for each image.

All images were stored off-line and transferred to a computer station with Echopac Version 112 (GE Healthcare, Mississauga, ON) for analysis. Upon import of images to Echopac, the best quality three-cycle loop for each image in the baseline assessment was chosen for analysis, and the image from the follow-up assessment for that participant that best matched the image chosen from their baseline assessment was chosen for analysis. Next, the identifying information for each assessment was removed and replaced with a random four-digit number, and analyses were performed in sequential order of the random numbers, so that all
echocardiography analyses were blinded to study participant and time point. All values were averaged over three cardiac cycles if possible. On the rare occasion that three consecutive good quality cardiac cycles were not available, then the best quality cycles from two different stored three-cycle loops were utilized, or only one or two cycles were used for that parameter.

The speckle tracking echocardiography analysis was semi-automated, with input from the operator (i.e. the author). First, the operator verified the proper ECG gating of each cardiac cycle by the software. In the case of inaccurate gating by the program or an irregular ECG, the starting and ending frames were manually adjusted. The cardiac cycle was visually inspected first at slow speed to ascertain a visualization of the endomyocardial border. The software paused the cardiac cycle at the end systolic frame, where the endomyocardial border was manually traced. The software selected a region of interest to approximate the myocardium, and this was adjusted by the operator to fit the myocardial thickness, with care taken to not include the pericardium. The software then automatically divided the myocardium up into six segments, consisting of basal, mid, and apical portions of the LV free wall and interventricular septum for the apical 4-chamber view, and anterior septal, inferior septal anterior, lateral, posterior, inferior for short-axis views.

Within each segment, the software selects suitable speckles for tracking, and searches for them in the following frame via a differences algorithm for an entire cardiac cycle. The cardiac cycle loop was visually inspected at a reduced frame rate to ensure that each segment of the myocardium was being tracked by the software accurately. Slight adjustments to the placement of the endomyocardial border tracing and region of interest width were made if either the software or visual inspection indicated that the tracking quality was not adequate. The software provides ‘approval’ for the tracking quality within each of the six myocardial segments. The
software’s assessment of quality was used as a guide, but visual assessment of adequate tracking quality was used to override the software for inclusion or exclusion of each segment in the global measurement. Once the operator was satisfied with the tracking, any segments lacking adequate tracking were recorded, and the operator approved all segments, and strain and strain rate traces with frame-by-frame data were exported.

Custom-made software called 2D Strain Analysis Tool (Eric Stöhr, Cardiff, Wales) was used to adjust for intra and inter-individual variability of heart rate, by normalizing to the percentage of systolic and diastolic duration. Cubic spline interpolation was used to produce 600 data points for both the systolic and diastolic periods. Within the tool, the non-tracking segments were excluded. The tool displays the average and/or individual segment curves for each cardiac cycle with the parameter units on the Y-axis (i.e. percentage for strain, sec\(^{-1}\) for strain rate) and percentage of duration of aortic valve closure (set at 100%) on the X-axis. The tool automatically chooses the highest occurring value within the curve as the peak value for that parameter, regardless of location within the curve. Adjustments to the peak values were made at the discretion of the operator if, for example, a strain curve had more than one peak, or the second diastolic peak was chosen for strain rate. Figure 4.1 shows representative examples of both of these scenarios.

The tool averages all available cardiac cycles for each parameter and exports a single value for each parameter. Global strain and strain rates were calculated as the average of all tracking segments from a single cardiac cycle. At least 4 out of 6 adequately tracked segments were required to calculate global strain. During systole, the LV will shorten in the longitudinal and circumferential coordinates, but thickens in the radial coordinate, so are expressed as negative and positive values, respectively. Peak systolic strain and systolic strain rate were
defined as the peak negative values during the cardiac cycle (peak positive values for radial strain), whereas peak early diastolic strain rate were defined as the second-to last peak positive value (negative for radial strain rate).

4.2.4 Statistical analysis

All clinical and cardiac function variables are reported as mean ± standard deviation. The data reported in the tables does not include those who did not complete the follow-up assessment in the baseline mean. An independent t-test with unequal variances was used to assess baseline differences between those who completed and did not complete the follow-up assessment. Data was tested for normal distribution with the Shapiro-Wilk test. The change in myocardial mechanics parameters was assessed with a two one-sided test of equivalence for paired samples (TOST-P). In a test of equivalence, the null and alternative hypotheses are the reverse of those in a traditional test of difference, such as a t-test. The null hypothesis for equivalence testing states that the difference falls outside a predetermined relevant difference threshold, while the alternative hypothesis states that there is no meaningful difference (i.e. the difference is less than the selected difference threshold). This is the recommended approach when the research question is to assess similarities, as statistical hypothesis testing can only prove the alternative hypothesis by rejecting the null hypothesis, and does not prove the null hypothesis.

The TOST-P essentially applies two paired t-tests, one with the value of the chosen difference threshold, called the ‘equivalence interval’, added to the mean difference, and the second with the value of the equivalence interval subtracted from the mean difference. The null hypothesis is rejected if the p-values of both t-tests are less than the chosen alpha level. A recently published expert consensus on cardiac imaging in cancer survivors concluded that during chemotherapy, reductions in GLS of <8% are not likely clinically meaningful. Therefore
the equivalence interval for this study was set at 8%. A meaningful change has not been established for the other myocardial mechanics parameters, so 8% was also used for the assessment of change in the secondary outcomes. For those outcomes where the equivalence test null hypothesis is accepted (i.e. the difference is ≥±8%), a paired t-test was performed to assess whether the change is statistically significant. Paired t-tests were the only method of assessment for the other clinical and traditional echocardiographic data that were not primary or secondary outcomes.

To explore the influence of exercise dose on GLS, five different measures of exercise dose were utilized: 1) percentage total adherence to the exercise prescription; 2) percentage attendance; 3) total number of supervised exercise sessions 4) self-reported average weekly MVPA during the intervention period; and 5) self-reported average weekly total MET-hours. The latter two variables were calculated from the Minnesota Leisure Time Physical Activity Questionnaire completed at the follow-up assessment in reference to the time since the baseline assessment. MVPA included only aerobic activities with a MET score greater than 3.0, and total MET-hours included all aerobic activity. An univariate general linear model was fit using percentage change in GLS as the dependent variable and each exercise dose variable as an independent variable. Model fit was assessed by visual inspection of the residual plot for each model and by p-value ≤0.05. The relationship between GLS and VO2peak was assessed by Pearson correlation. Significant relationships were then further explored via individual linear regression.

To determine reliability of the myocardial mechanics parameters, the number of participants where speckle tracking echocardiography could be performed on at least four LV wall segments for both the baseline and follow-up echocardiograms was divided by the total
participants with both echocardiograms completed for GLS and for short axis (i.e. radial and circumferential both measured from the same parasternal short-axis image) global strain. The intra-observer reliability was determined by assessment of 10 randomly selected echocardiography examinations (five from the baseline and five from follow-up) with adequate tracking quality of three consecutive cardiac cycles for both the apical 4-chamber and parasternal short axis at the level of the mid-papillary muscles images. Each echocardiography examination was analyzed twice by the same investigator, separated by at least one week. The intra-class correlation and mean coefficient of variation were used to compare the data acquired from each analysis. The two-way mixed intra-class correlation for a single rater (ICC 3,1) was calculated, with 95% confidence intervals. The coefficient of variation was calculated as the standard deviation of the two measurements of a single examination divided by the mean of the two measurements of the same single examination. The mean coefficient of variation is reported for each variable.

For all analyses, there were no adjustments for multiple comparisons and alpha levels were set at 0.05. SPSS Version 20.0 (IBM Corporation, Armonk, New York) was used for the general linear model analysis and Python 2.7.10 (available at http://www.python.org) was used for all other analyses.

4.3 Results

4.3.1 Recruitment and withdrawal

Twenty-five participants enrolled in this study. The flow through the study is the same as Figure 3.2 in Chapter 3. Briefly, n=44 potentially eligible women were screened for the sub-study, n=3 declined participation, n=16 were ineligible (predominantly due to inability to attend
baseline visit prior to starting anthracycline treatment, n=11), and n=25 enrolled in the sub-study. While six participants did not complete the follow-up maximal exercise test in Chapter 3, three of these participants completed the other follow-up measures, including the echocardiogram. Therefore, 22 participants completed the follow-up echocardiogram. Two participants who did not complete any follow-up measures reported treatment symptoms and associated stress as the reason, while one participant reported treatment symptoms combined with unexpected oncology appointments as the reason. Two participants unexpectedly did not receive their fourth AC treatment and the echocardiogram was performed after their first paclitaxel treatment. The time between the baseline and follow-up assessment was 10±2 weeks on average.

4.3.2 Participants

The baseline demographics of all participants who enrolled in the sub-study are reported in the last column of Table 3.2 and 3.3 in Chapter 3. On average, participants were 51±8 years old. Baseline relative VO$_2$peak and hemoglobin were significantly lower in the three participants who did not complete the follow-up assessment than those with both assessments completed; all other variables did not differ (data not shown). All participants were prescribed four cycles of 60 mg/m$^2$ of doxorubicin and 600 mg/m$^2$ of cyclophosphamide, for a cumulative doxorubicin dose of 240 mg/m$^2$. Six participants received dose reductions due to nausea/vomiting (n=3), mucositis (n=2), and fatigue (n=1), and the mean dose received was 232±20 mg/m$^2$.

4.3.3 Descriptive variables

Table 4.1 reports weight, BMI, and self-reported physical activity at baseline and follow-up for those who completed the follow-up assessment. Total MET-hours was not normally distributed according to the Shapiro-Wilk test so was assessed via the paired samples Wilcoxon signed rank test. The other variables were normally distributed and were assessed via paired t-
tests. There was no significant change in average weekly aerobic physical activity between the 6-months prior to the baseline assessment and the time between the baseline and follow-up assessment. There was a significant mean weight loss of 1.4 kg, and reduction in BMI of 0.5 kg/m².

4.3.4 Exercise adherence

Table 4.2 reports the adherence for the sub-study participants. Mean attendance was 57±29%, mean adherence to intensity and duration prescriptions were 77±26 and 89±19%, respectively, while total adherence was 42±28%. These values were similar to those reported in Chapter 3 for the larger group.

4.3.5 Myocardial mechanics reliability

For the 22 participants with both assessments completed there was adequate tracking quality on at least 4 out of 6 segments to allow for accurate measurement of GLS at both time points in 100% of participants. There was adequate tracking quality to allow for accurate measurement of GCS and GRS at both time points in 77% of participants. The intra-class correlation and coefficient of variation for intra-observer intra-measurement reliability are reported for the myocardial mechanics parameters in Table 4.3. The intra-class correlation (ICC) and coefficient of variation (CV) were the strongest for GLS (CV=3.3%, ICC=0.88). Reliability was also excellent for early diastolic LSR (ICC=0.86, CV=6.6%), GRS (ICC=0.86, CV=7.2%), and GCS (ICC=0.82, CV=7.6%). Systolic LSR had a good coefficient of variation relative to the other measures (CV=7.3%), but a lower intra-class correlation (ICC=0.64). Systolic and early diastolic RSR and CSR were not reliable, with CV’s ≥15% and ICC’s <0.80.
4.3.6 Myocardial mechanics response to exercise training

Table 4.4 reports the baseline and follow-up data for myocardial mechanics parameters. All variables were normally distributed according to the Shapiro-Wilk test except for percentage change in GCS, thus parametric TOST-P and paired t-tests were used. Figure 4.2 shows the individual changes in myocardial mechanics parameters. The equivalence test was significant for GLS, indicating that the change was less than the clinically relevant 8% equivalence interval. Systolic LSR was also significant for the equivalence test. The equivalence test null hypothesis of a difference >8% was accepted for the rest of the myocardial mechanics parameters, and were subjected to paired t-tests. There was a significant decrease in diastolic LSR and systolic CSR, while the change in the remaining parameters was not significant.

4.3.7 Clinical and other echocardiographic parameters of cardiac function

There were two participants where the quality of the apical 2-chamber image was not conducive to volume measurement at one of their examinations, so LV volumes were measured from the apical 4-chamber image only for both time points for these participants. Overall, there was a significant increase in seated resting heart rate, but the supine measurement of heart rate taken during the 4-chamber image did not change. A significant decrease occurred in seated resting systolic, diastolic, and mean arterial blood pressure, as well as supine mean arterial blood pressure. Systemic vascular resistance also significantly decreased. There was no change in rate pressure product, end-systolic wall stress, LVEF, LV volumes, cardiac output, mitral deceleration time, E, A, or IVRT. There was a trend toward a significant decrease in E/A ratio. LV wall thicknesses did not change. LV dimensions in end-diastole and end-systole both significantly increased, while there was no change in fractional shortening, relative wall
thickness or LV mass. No participants had reductions in LVEF ≥10 percentage points. At follow-up two participants had an LVEF <53% but these values were not changed from their baseline.

4.3.8 GLS and exercise dose

There was no relationship between percentage change of GLS and any of the exercise dose variables as evidenced by the general linear model findings (percentage attendance (β=0.02, p=0.81), percentage total adherence (β=-0.02, p=0.85), total number of sessions (β=0, p=0.99), average weekly minutes of MVPA (β=0, p=0.74), nor average total MET-hours per week (β=0, p=0.40)) and heteroscedasticity exhibited by the residual plots of all models (not shown). The lack of relationship between the variables is exhibited in scatterplots in Figure 4.3.

As an exploratory further analysis to investigate the associations between effect of exercise and GLS, the group was divided by percent change in GLS below or above the clinically relevant 8% deterioration. Exercise dose was compared between groups with two-tailed independent t-tests. Exercise dose variables were nearly identical with no significant differences between those with deterioration in GLS and those without (data not shown).

4.3.9 GLS and VO2peak

There was no relationship between percent change in GLS and percent change in absolute or relative VO2peak (r=0.03, p=0.90 for both). It was also determined that there was also no relationship between GLS and absolute (r=0.15, p=0.47) or relative (r=-0.14, p=0.52) VO2peak at baseline. Based on the lack of associations, no further analysis was performed.

4.4 Discussion

The primary finding of this study is that women with breast cancer who enrolled in an exercise intervention during anthracycline treatment did not experience the deterioration in the
primary outcome, GLS, that is well established to occur with anthracycline treatment in similar populations as described in a recent systematic review.\(^{46}\) This lack of deterioration occurred with only moderate adherence to an exercise program consistent with the recommended exercise guidelines for cancer survivors to achieve general health benefits, and the dose of exercise received did not appear to be associated with the change in GLS. Furthermore, the speckle tracking quality was adequate to measure GLS in 100% of examinations, and the intra-observer ICC and CV were both considered excellent and were lower than for the other myocardial mechanics parameters.

In the current study, there was an overall mean reduction in GLS of 2.8%, whereas other studies that have measured the change in GLS with anthracycline treatment in similar populations in the absence of an intervention have reported a significant reduction in mean GLS from pre to post anthracyclines of 8.4%,\(^{185}\) 8.6%,\(^{193}\) 9.5%,\(^{190}\) 10.3%,\(^{192}\) 10.4%,\(^{189}\) 10.8%,\(^{69}\) 12.0%,\(^{195}\) and 17.2%.\(^{188}\) A recently published expert consensus on cardiac imaging in cancer survivors concluded that during chemotherapy, reductions in GLS of <8% are not likely clinically meaningful, while reductions >15% are very likely to be of clinical significance.\(^{52}\) The change in GLS in the current study was statistically less than an 8% change using an equivalence test. Furthermore, only 32% of participants (n=7) experienced a reduction in GLS >8%, and of these, 43% (n=3 or 14% of the total) experienced a reduction >15%. In comparison, Stoodley et al. reported that 48% of women who received low dose anthracyclines experienced a decrease of GLS of 10% or greater at one week after treatment completion, relative to pre-treatment.\(^{192}\) Two of these three participants in the current study with GLS reductions >15% had absolute reductions in LVEF of 3 and 7 percentage points respectively, and both had become quite ill during treatment resulting in attendance of 43 and 9%, respectively. The third participant, who
had an absolute LVEF reduction of 3 percentage points, had an attendance of 77%. This participant had received non-anthracycline chemotherapy treatment less than a year earlier, and whether this predisposes individuals to greater changes in myocardial mechanics with anthracycline treatment is not known.

Furthermore, women with breast cancer who enrolled in an exercise intervention during anthracycline treatment also did not experience deterioration in systolic LSR. The change in systolic LSR in the current study was statistically less than the 8% equivalence threshold. Florescu et al. reported an overall significant decrease in systolic LSR, and that a >9% reduction in this parameter was the best predictor of a later decrease ≥10% in LVEF in breast cancer patients treated with low dose epirubicin. Systolic LSR measured with TDI was also significantly reduced after the second or third treatments of epirubicin in two other studies in breast cancer, and three others in mixed adult cancer types. However, Stoodley et al. reported that no change in systolic LSR occurred with anthracycline treatment of breast cancer, despite significant reductions in GLS, GRS, and GSC, however, baseline values of all myocardial mechanics parameters were lower than typical in that study.

Interestingly, in adult mixed cancer types being treated with anthracyclines, an increase in circulating levels of ROS from pre-chemotherapy to after two treatments was predictive of a reduction in systolic LSR; and a reduction in systolic LSR also correlated with an increase in serum levels of the pro-inflammatory cytokine interleukin-6, and a decrease in serum levels of glutathione peroxidase, an antioxidant enzyme. The primary mechanism thought to be responsible for the protective benefit of aerobic exercise training in the rodent studies is through upregulation of antioxidants and reductions in oxidative stress. Therefore the lack of change in systolic LSR in the current study provides indirect support for this mechanism in humans.
The only significant changes in myocardial mechanics parameters in the current study were in early diastolic LSR and systolic CSR. Due to the large CV for systolic CSR, this change may not be relevant. Stoodley et al. also reported a significant reduction in early diastolic LSR following anthracycline treatment in breast cancer patients of similar relative magnitude to the current study, although the baseline was lower than the current study. Likewise, Jiang et al. reported a statistically significant reduction in early diastolic strain rate after two epirubicin treatments in breast cancer patients, but did not report values in the English abstract of this Chinese manuscript. Early diastolic LSR has been reported to correlate significantly with the invasively measured maximal rate of LV pressure decline during diastole. This finding suggests reduced LV relaxation, yet the reduction in E/A ratio was not significant (p=0.08). The maximal rate of LV pressure decline was preserved by exercise training during doxorubicin treatment in several preclinical cardio-protection studies, including those with a low intensity and volume of exercise. The reason for the discrepancy in the findings on the effect of exercise on diastolic function in rodents and humans is not known, but could be related to limited assessment of non-invasive measurement of diastolic parameters in the current study.

Diastolic dysfunction, or reduced LV relaxation may precede systolic dysfunction in the ischemic cascade of events. The possibility that the exercise program in the current study preserved systolic, but not diastolic function is therefore clinically relevant. However the current study did not include the thorough assessment of diastolic function required to investigate this possible outcome. Therefore future studies may want to consider measuring diastolic myocardial velocities, pulmonary venous flow velocities, and left atrial function with exercise training during anthracycline chemotherapy in order to further investigate the effect of exercise training during anthracycline treatment in diastolic function.
The literature is less consistent on the effect of anthracycline treatment on GRS and GCS parameters. Jurcut et al.\textsuperscript{188} reported a 35.5\% decrease in GRS, and that the change in GRS occurred sooner than the change in GLS. However the women with breast cancer in this study were considerably older (mean age = 70±3 years) than other studies, including the current study, and they received a pegylated liposomal formulation of doxorubicin. These factors could potentially be associated with an abnormal myocardial mechanics response, as age over 70 years is a known cardiotoxicity risk factor,\textsuperscript{27} and pegylated liposomal doxorubicin has much lower concentrations in myocardial tissue than for conventional doxorubicin.\textsuperscript{346} Others have reported much smaller decreases in GRS with anthracycline treatment in breast cancer patients, ranging from 5.7 to 14.8\%.\textsuperscript{69,190,192} In these same studies, GCS has been reported to not change,\textsuperscript{69,192} or to decrease by 11\%.\textsuperscript{190} In the current study, the change between the baseline and follow-up means for GRS and GCS were an increase of 4 and 1\%.

Interestingly, although there was no clinically relevant reduction in GLS in the current study, there was no relationship between exercise dose and change in GLS. One limitation to this analysis was the study’s sample size and it could be that this study was underpowered to establish a dose response relationship. But this could potentially be attributed to the fact that while a wide range of exercise dose was delivered; half of the participants experienced an absolute change in GLS of 5\% or less. So while there was a wide range of exercise dose delivered, there was not a varied response. If this were indeed a true observation that there was no relationship between exercise dose and change in GLS, then a possible interpretation is that a small amount of exercise is beneficial. By virtue of recruiting participants to participate in an exercise study, there was likely selection bias in the study sample, and it could be assumed that these individuals were interested in exercise and may have performed more total physical
activity than is typical during chemotherapy treatment. The Physical Activity Questionnaire performed at the follow-up assessment was intended to capture all exercise performed during the intervention period, including that completed outside of the supervised sessions. However this self-reported measured of MVPA or total MET-hours also did not have a relationship with change in GLS, further supporting the contention that the protective effect of exercise is not dose-dependent. A more objective method of measuring total physical activity that could be employed to test this hypothesis in future studies is accelerometry.

An exploratory hypothesis was that the change in GLS would be related to the change in VO$_2$peak. Although a cross-sectional study of childhood cancer survivors who received anthracycline treatment at least two years earlier failed to find a relationship between GLS and VO$_2$peak, a number of recent cross-sectional studies have reported significant relationships between GLS and VO$_2$peak in other populations, and were the basis for this hypothesis. Additionally, Smart et al. reported that the change in VO$_2$peak at the end of a 16-week aerobic exercise training intervention in heart failure patients was significantly predicted by baseline GLS and change in GLS at eight weeks. However there was no relationship between change in VO$_2$peak and change in GLS in the current study, which again may be due the lack of variation in change in GLS, but it is also possible that the anthracycline-related change in GLS may not be related to functional capacity.

The mean 8 mmHg reduction in systolic blood pressure and 7 mmHg reduction in diastolic blood pressure were much larger than expected for a 10-week combined exercise intervention, especially considering the low mean baseline of 106/72 mmHg. A recent systematic review and meta-analysis reported no change in systolic and diastolic blood pressure in those with normal blood pressure at baseline with either aerobic or combined aerobic and resistance
training interventions lasting 4 to 52 weeks. In breast cancer patients during treatment, exercise-induced reductions in systolic blood pressure have typically ranged from 3 to 5 mmHg, while reductions in diastolic blood pressure are minimal.

Mean cardiac output and systemic vascular resistance determine arterial blood pressure. As there was no change in cardiac output in the current study, the reduction in mean arterial blood pressure was likely due to the significant decrease in systemic vascular resistance. Hematocrit was reported in Chapter 3 to significantly decrease in this study sample. Hematocrit is the most powerful determinant of blood viscosity, which is in turn a determinant of systemic vascular resistance. Chemotherapy reduces hematocrit by way of myelosuppression, which one would expect to result in a decrease in systemic vascular resistance. However previous observational studies have reported an increase in blood pressure following anthracycline chemotherapy, or no change, indicating that there is a response to maintain blood pressure with decreased blood viscosity. While the nervous system is primarily responsible for responding to acute changes in mean arterial blood pressure, the kidneys play the primary role in long-term control of blood pressure by blood volume control, and would respond markedly to a small decrease in mean arterial pressure by retaining water and salt. It is not known whether blood volume changes in the normal course of chemotherapy treatment, but in the current study with exercise training, there does not appear to have been a change in blood volume as end-diastolic volume did not change and mean arterial pressure was markedly decreased by a greater amount than would be expected with eight weeks of exercise training. One of the key activators of kidney regulation of blood volume is the sympathetic nervous system. Because exercise training is known to reduce sympathetic nerve activity, this could explain a potential attenuated response to the marked decrease in mean arterial pressure in the current study. However the
cause of blood pressure changes requires further investigation via direct measurements of blood volume and autonomic balance to clarify this issue.

Regardless of the source, these large changes in blood pressure could potentially play a role in the attenuation of changes in GLS relative to the observational studies that have measured GLS during anthracycline treatment. Burns et al. investigated the effect of vasodilation on mechanics in humans by administering the vasodilator nitroglycerine to cause a decrease in end-systolic pressure, which resulted in no change in GLS, but was accompanied by a significant decrease in end-diastolic volume, end-systolic wall stress, and an increase in LVEF, which all did not change in the current study.\textsuperscript{356} In a porcine model, the application of a low level of aortic banding to stimulate increased afterload significantly reduces GLS, with no significant change in GRS; while with release of the banding, GLS then returns toward baseline.\textsuperscript{357} In addition, hypertensive individuals have significantly reduced GLS relative to individuals with normal blood pressure in the general population.\textsuperscript{349} Therefore, it could be hypothesized that the reduced mean arterial blood pressure (resulting from a reduction in systemic vascular resistance) was a contributing cause of the attenuation of the typical reduction in GLS with anthracycline treatment. Ultimately there is no prior evidence to clarify the relationship between GLS and blood pressure that occurred in the current study in the absence of LV volume and global function changes, with low baseline blood pressure.

It should be highlighted that while the effect of exercise appears favourable on resting systolic cardiac function, the author has previously reported in a systematic review that cardiac imaging during myocardial stress (including exercise) is known to uncover LV dysfunction and myocardial perfusion defects that are not apparent during resting imaging.\textsuperscript{358} Therefore it is possible that the effect of the exercise delivered in the current study was to preserve resting
function, and there may be reduced reserve capacity from rest to maximal function at peak exercise. Therefore, future studies may want to consider utilizing stress echocardiography.

In one of the only other studies to measure change in cardiac function with exercise training in individuals with cancer, Haykowsky et al. reported that a similar level of adherence to a similar aerobic exercise prescription as the current study did not prevent a reduction in LVEF (due to increases in both end-diastolic and end-systolic volumes) in women receiving trastuzumab for breast cancer. The authors hypothesized that the low adherence could be an explanation for the lack of protective effect. Although this study did not measure GLS, the change in LVEF is a telling sign that perhaps the role of exercise is different in anthracycline and trastuzumab-related cardiotoxicity, as the cardiotoxic mechanism for the two treatments are different.

This study has several strengths and limitations. This study was the first to report the effects of exercise training during cardiotoxic chemotherapy on sensitive parameters of cardiac function. Although the findings of this study are limited by the single group design, the size and consistentecy of the literature describing the myocardial mechanics response to anthracyclines provide a strong basis for the expected results in the absence of an intervention. This study is the first to measure GLS and report no clinically relevant mean change amongst breast cancer or any adult cancer type. This study provides proof-of-principle of exercise protection from anthracycline chemotherapy in humans, at least for systolic myocardial mechanics, with the caveat that no control group is available for comparison. Furthermore, the study sample was relatively homogeneous with respect to treatment type, disease stage and medical history.

Incomplete follow-up is a limitation to interpretation of these findings as the three participants who failed to complete the follow-up echocardiogram also had low adherence to the
exercise program and may also have had larger-than-average reductions in cardiac function. And although exercise adherence for those who completed the follow-up echocardiogram was not related to change in GLS, it is not known whether changes in other parameters of cardiac function affects adherence to exercise, so this cannot be ruled out. This study is also limited by a small sample size and selection bias in recruitment. Finally, the results of this study are only generalizable to a relatively young breast cancer population that is generally otherwise healthy.

This study is a positive first step toward identification of potential cardio-protection benefits during anthracycline chemotherapy and helps to establish longitudinal strain parameters as useful outcome measures in the assessment of this effect. The mechanism for the perseverance of systolic GLS and LSR in the current study is unknown and assessment of potential mechanisms is limited to the measurements completed in the current study. Based on findings in this study, future studies should include more comprehensive measures of diastolic function, vascular function and structure, and blood volume and red cell mass. This information would be helpful to elucidate the mechanisms responsible for maintenance of GLS and systolic LSR, and the reduction in VO$_2$peak. Although this study demonstrates that high adherence to exercise may not be a requirement for cardio-protection, future studies will need to empirically test the efficacy of different doses of exercise to establish the minimum effective dose.

4.5 Conclusion

This study assessed the responsiveness of myocardial mechanics to exercise training during anthracycline treatment for breast cancer. The primary findings are that women who enrolled in an exercise training program during anthracycline chemotherapy for breast cancer did not experience a clinically relevant deterioration of GLS or systolic LSR, which are both established predictive markers of cardiotoxicity. However, early diastolic LSR significantly
decreased, and this may be an earlier marker of dysfunction than systolic parameters. There was a wide range of adherence to the exercise program by the study participants, but there did not appear to be a relationship between the exercise dose received and change in GLS. The mechanism for maintenance of GLS may be related to the large reductions in blood pressure that occurred. Overall this study found that GLS is a reliable measure that could be employed in future cardio-protection trials.
### Table 4.1: Physical activity and weight changes (n=22)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Paired t-test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly MVPA (minutes)</td>
<td>162±117</td>
<td>176±80</td>
<td>3.3±11.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Total MET-hours</td>
<td>18±13</td>
<td>21±9</td>
<td>13±123</td>
<td>0.09#</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.9±14.3</td>
<td>65.7±14.7</td>
<td>-1.4±2.1</td>
<td>0.02*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8±4.7</td>
<td>24.3±4.9</td>
<td>-0.5±0.8</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

#P-value is for paired-sample Wilcoxon signed rank as change in total MET-hours did not have a normal distribution.

Data are mean ± standard deviation.

### Table 4.2: Supervised exercise adherence data (n=22)

#### Adherence to frequency
- Exercise sessions attended (n) 15.6±8.5 (0, 27)
- Missed sessions (n) 12.2±9.0 (1, 31)
- Possible sessions (n) 27.9±4.5 (23, 36)
- Attendance (%) 57±29 (0, 96)

#### Adherence to intensity
- Average lower limit target heart rate including adjustments (%) 77±26 (0, 100)
- Adherence to lower limit target heart rate not including adjustments (%) 77±30 (0, 100)

#### Adherence to duration
- Meeting or exceeding duration target (%) 89±19 (25, 100)

#### Total adherence
- Sessions meeting total prescription (n) 10.8±7.7 (0, 24)
- Sessions meeting total prescription (%) 42±28 (0, 96)

Data are mean ± standard deviation (minimum, maximum)
Table 4.3: Intra-class correlation and coefficient of variation for intra-observer reliability of myocardial mechanics in women with breast cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial #1</th>
<th>Trial #2</th>
<th>ICC (95% CI)</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>-19.8±2.5</td>
<td>-20.0±2.0</td>
<td>0.88 (0.58, 0.97)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Systolic LSR (sec(^{-1}))</td>
<td>-1.02±0.12</td>
<td>-1.05±0.13</td>
<td>0.64 (0.07, 0.90)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Diastolic LSR (sec(^{-1}))</td>
<td>1.37±0.38</td>
<td>1.40±0.30</td>
<td>0.86 (0.54, 0.96)</td>
<td>6.6%</td>
</tr>
<tr>
<td>GRS (%)</td>
<td>41.8±11.5</td>
<td>41.3±8.7</td>
<td>0.86 (0.53, 0.96)</td>
<td>7.2%</td>
</tr>
<tr>
<td>Systolic RSR (sec(^{-1}))</td>
<td>2.16±0.48</td>
<td>1.97±0.54</td>
<td>0.26 (-0.40, 0.75)</td>
<td>18.2%</td>
</tr>
<tr>
<td>Diastolic RSR (sec(^{-1}))</td>
<td>-3.09±1.32</td>
<td>-2.86±1.02</td>
<td>0.71 (0.19, 0.92)</td>
<td>16.8%</td>
</tr>
<tr>
<td>GCS (%)</td>
<td>-17.4±4.3</td>
<td>-17.5±3.6</td>
<td>0.82 (0.44, 0.95)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Systolic CSR (sec(^{-1}))</td>
<td>-0.92±0.26</td>
<td>-1.06±0.15</td>
<td>0.70 (0.16, 0.92)</td>
<td>14.6%</td>
</tr>
<tr>
<td>Diastolic CSR (sec(^{-1}))</td>
<td>1.07±0.59</td>
<td>1.19±0.52</td>
<td>0.79 (0.37, 0.95)</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

Abbreviations: GLS = global longitudinal strain; LSR = global longitudinal strain rate; GRS = global radial strain; RSR = global radial strain rate; GCS = global circumferential strain; CSR = global circumferential strain rate; ICC = intra-class correlation; CV = coefficient of variation;

Table 4.4: Myocardial mechanics data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Equivalence test p-value</th>
<th>Paired t-test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>22</td>
<td>-20.3±2.5</td>
<td>-19.6±2.9</td>
<td>0.6±2.0 (-3%)</td>
<td>0.01*</td>
<td>NR</td>
</tr>
<tr>
<td>Systolic LSR (sec(^{-1}))</td>
<td>22</td>
<td>-1.09±0.18</td>
<td>-1.09±0.15</td>
<td>-0.01±0.16 (2%)</td>
<td>0.04*</td>
<td>NR</td>
</tr>
<tr>
<td>Diastolic LSR (sec(^{-1}))</td>
<td>22</td>
<td>1.43±0.36</td>
<td>1.26±0.28</td>
<td>-0.17±0.33 (-9%)</td>
<td>0.42</td>
<td>0.03*</td>
</tr>
<tr>
<td>GRS (%)</td>
<td>17</td>
<td>38.9±9.3</td>
<td>39.9±7.4</td>
<td>1.1±11.3 (8%)</td>
<td>0.48</td>
<td>0.70</td>
</tr>
<tr>
<td>Systolic RSR (sec(^{-1}))</td>
<td>17</td>
<td>2.11±0.49</td>
<td>2.29±0.52</td>
<td>0.18±0.67 (13%)</td>
<td>0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic RSR (sec(^{-1}))</td>
<td>17</td>
<td>-2.77±1.16</td>
<td>-2.81±0.69</td>
<td>0.04±1.21 (16%)</td>
<td>0.26</td>
<td>0.89</td>
</tr>
<tr>
<td>GCS (%)</td>
<td>17</td>
<td>-16.2±5.2</td>
<td>16.2±3.2</td>
<td>0±4.0 (9%)</td>
<td>0.45</td>
<td>0.99</td>
</tr>
<tr>
<td>Systolic CSR (sec(^{-1}))</td>
<td>17</td>
<td>-1.01±0.21</td>
<td>-0.87±0.19</td>
<td>0.14±0.27 (-10%)</td>
<td>0.36</td>
<td>0.05*</td>
</tr>
<tr>
<td>Diastolic CSR (sec(^{-1}))</td>
<td>17</td>
<td>1.07±0.48</td>
<td>0.96±0.35</td>
<td>-0.11±0.50 (4%)</td>
<td>0.38</td>
<td>0.38</td>
</tr>
</tbody>
</table>

* Significant p≤0.05; NR = not reported due to significant equivalence test

Abbreviations: GLS = global longitudinal strain; LSR = global longitudinal strain rate; GRS = global radial strain; RSR = global radial strain rate; GCS = global circumferential strain; CSR = global circumferential strain rate.
Table 4.5: Clinical and traditional echocardiographic data (n=22)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Paired t-test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seated resting heart rate (bpm)</td>
<td>69±7</td>
<td>76±9</td>
<td>7±8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Seated systolic blood pressure (mmHg)</td>
<td>106±14</td>
<td>99±12</td>
<td>-7±14</td>
<td>0.02*</td>
</tr>
<tr>
<td>Seated diastolic blood pressure (mmHg)</td>
<td>72±10</td>
<td>67±9</td>
<td>-6±8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Seated mean arterial blood pressure (mmHg)</td>
<td>84±11</td>
<td>78±9</td>
<td>-6±9</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Seated rate pressure product (mmHg·bpm)</td>
<td>7359±1116</td>
<td>7513±1277</td>
<td>154±1072</td>
<td>0.51</td>
</tr>
<tr>
<td>Supine heart rate</td>
<td>69±9</td>
<td>73±9</td>
<td>3±12</td>
<td>0.22</td>
</tr>
<tr>
<td>Supine mean arterial blood pressure (mmHg)</td>
<td>81±13</td>
<td>74±10</td>
<td>-7±8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes·sec·cm⁻⁵)</td>
<td>2334±589</td>
<td>2080±473</td>
<td>-253±536</td>
<td>0.04*</td>
</tr>
<tr>
<td>End-systolic wall stress (x10³ dyn·cm⁻²)</td>
<td>56±33</td>
<td>54±23</td>
<td>-2±37</td>
<td>0.77</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57±5</td>
<td>56±4</td>
<td>-1±5</td>
<td>0.25</td>
</tr>
<tr>
<td>End-diastolic volume (mL)</td>
<td>74±14</td>
<td>74±14</td>
<td>0±10</td>
<td>0.93</td>
</tr>
<tr>
<td>End-systolic volume (mL)</td>
<td>32±9</td>
<td>32±7</td>
<td>1±7</td>
<td>0.72</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>42±7</td>
<td>42±8</td>
<td>-1±5</td>
<td>0.54</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.9±0.6</td>
<td>3.0±0.6</td>
<td>0.1±0.6</td>
<td>0.57</td>
</tr>
<tr>
<td>Mitral E wave (m/s)</td>
<td>0.70±0.17</td>
<td>0.67±0.13</td>
<td>-0.03±0.14</td>
<td>0.29</td>
</tr>
<tr>
<td>Mitral A wave (m/s)</td>
<td>0.55±0.16</td>
<td>0.57±0.15</td>
<td>0.02±0.08</td>
<td>0.17</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.32±0.33</td>
<td>1.21±0.27</td>
<td>-0.11±0.28</td>
<td>0.08</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>81±18</td>
<td>81±13</td>
<td>0±21</td>
<td>0.93</td>
</tr>
<tr>
<td>Mitral E wave DT (ms)</td>
<td>225±31</td>
<td>219±38</td>
<td>-5±42</td>
<td>0.55</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>408±48</td>
<td>427±50</td>
<td>19±25</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>End-systolic diameter (mm)</td>
<td>283±45</td>
<td>303±47</td>
<td>20±41</td>
<td>0.04*</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>30±8</td>
<td>29±8</td>
<td>-1±8</td>
<td>0.56</td>
</tr>
<tr>
<td>End-diastolic IVS thickness (mm)</td>
<td>91±14</td>
<td>88±13</td>
<td>-3±13</td>
<td>0.36</td>
</tr>
<tr>
<td>End-systolic IVS thickness (mm)</td>
<td>125±22</td>
<td>117±16</td>
<td>8±18</td>
<td>0.05*</td>
</tr>
<tr>
<td>End-diastolic posterior wall thickness (mm)</td>
<td>89±18</td>
<td>87±13</td>
<td>2±19</td>
<td>0.65</td>
</tr>
<tr>
<td>End-systolic posterior wall thickness (mm)</td>
<td>135±28</td>
<td>134±25</td>
<td>0±31</td>
<td>0.79</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.44±0.09</td>
<td>0.41±0.07</td>
<td>-0.03±0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>LV mass</td>
<td>115±37</td>
<td>119±33</td>
<td>4±21</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Significant for p≤0.05

Abbreviations: A = late filling; bpm = beats per minute; cm = centimeter; DT = deceleration time; E = early filling; IVRT, isovolumic relaxation time; IVS = interventricular septum; mm = millimeters; mmHg = millimeters of mercury; m/s = meters per second; sec = second;
Figure 4.1: Representative examples of strain rate (A) and strain (B) curves where the 2D Strain Analysis Tool chose X as the peak value, and the operator adjusted the peak value to the checkmark. X-axis is duration of aortic valve opening.
Figure 4.2: Individual changes in myocardial mechanics
Figure 4.3: Relationship between percent change in GLS and various measures of exercise dose
Chapter 5 - The effects of a single exercise bout 24 hours prior to anthracycline chemotherapy for breast cancer on myocardial mechanics and cardiac biomarkers

5.1 Introduction

Myocardial damage incurred by anthracyclines may present acutely,\(^70\) and is cumulative with repetitive doses.\(^51\) Anthracycline-induced cardiotoxicity that manifests acutely during active chemotherapy is captured as electrocardiographic abnormalities,\(^43\) increased cardiac biomarkers,\(^45\) or depressed cardiac mechanics.\(^46\) Cardiotoxicity may also present as progressive cardiomyopathy at early-onset (i.e., post chemotherapy up to one year), or late (i.e., after one year post chemotherapy).\(^43\) The relationship between acute toxicity and the subsequent development of delayed cardiotoxicity is not entirely clear, but echocardiographic quantification of cardiac mechanics and cardiac biomarkers measured during and immediately following chemotherapy have prognostic value in predicting future clinical presentation of cardiotoxicity.\(^184,191,239,359\) While evidence for effective pharmacological treatment for anthracycline-induced cardiotoxicity is still limited at this time, it appears to be more effective at improving cardiac function the sooner it is initiated after completion of anthracycline treatment.\(^72\) Therefore prevention and treatment of early anthracycline-related myocardial damage could be a key strategy for cardio-protection.

Oxidative stress and related apoptosis of cardiomyocyte mitochondria are primary mechanisms of anthracycline-induced cardiotoxicity.\(^88\) Exercise training improves myocardial tolerance to oxidative stress, and there is evidence that even a single exercise bout can protect the myocardium in other models of acute insult.\(^88\) Recently, Wonders et al. and Ascensão et al. have reported that an acute exercise bout performed 24 hours prior to a doxorubicin injection in
rodents provided a cardio-protective benefit.\textsuperscript{88,106} The single acute bout of exercise prevented or attenuated some of the anthracycline-induced negative effects on cardiomyocytes including oxidative stress, apoptosis, mitochondrial dysfunction, as well as systolic dysfunction.\textsuperscript{88,106}

There are no studies to date that have investigated the effects of an acute bout of exercise in close proximity to anthracycline infusion on cardiac, or other outcomes in humans. To translate the preclinical model to humans, ideally the exercise bout that patients performed would result in an increase in antioxidant capacity and decrease in oxidative stress within the following 24 hours post exercise, to coincide with the receipt of an anthracycline treatment. The choice of exercise prescription for the exercise bout must also consider the feasibility of the prescription such that potentially untrained women would be able to complete the bout during ongoing chemotherapy treatment.

A single submaximal exercise session performed in close proximity to each anthracycline treatment is an optimal intervention for those who are unable to commit to joining a more frequent supervised exercise program (i.e., three days per week during treatment), or who are unable to adhere to regular training due to treatment side effects. Furthermore, while aerobic exercise training is recommended throughout chemotherapy treatment,\textsuperscript{76} there are no guidelines in place in terms of the timing of exercise in relation to receipt of chemotherapy infusions. If this timing of exercise provides cardiac and other benefits on treatment side effects, it would be a helpful addition to exercise guidelines for cancer survivors.

This study was a RCT comparing the effects on cardiac function of a single vigorous intensity exercise session completed 24 hours prior to each of four treatments with doxorubicin and cyclophosphamide (AC) to no vigorous intensity exercise prior, in women with early stage breast cancer. The primary aim of the study was to compare the \textit{acute} effect of performing
exercise 24 hours prior to the first AC treatment compared to no exercise on markers of cardiotoxicity, including myocardial mechanics and the cardiac biomarkers, NT-proBNP and cardiac troponin T (cTnT). The secondary aim was to compare the chronic effect of performing exercise 24 hours prior to every AC treatment compared to no exercise on markers of cardiotoxicity. The exploratory aim was to determine whether exercise 24 hours prior to each AC treatment reduces patient-reported symptoms of treatment relative to no exercise for each treatment. The hypotheses for all three aims were that the group who performed vigorous exercise 24 hours prior to each AC treatment would result in favourable benefits relative to the group who did not perform vigorous exercise prior to the treatment.

5.2 Methods

5.2.1 Design and participants

All participants signed an informed consent prior to performing any study measurements, and the Clinical Research Ethics Board of the University of British Columbia approved this study. This study was a two-arm randomized control trial. A permutated block design, with random block sizes of four and six, with stratification by age equal to/above or below 50 years was used with a 1:1 allocation ratio. Participants were randomized to one of two conditions: 1) an acute bout of supervised vigorous intensity exercise completed approximately 24 hours prior to each AC treatment, and asked not to perform vigorous intensity exercise otherwise for 72 hours prior to each cycle of anthracyclines; or 2) asked not to perform vigorous intensity aerobic exercise for 72 hours prior to each cycle of anthracyclines. Vigorous intensity exercise was described to the participants as “higher intensity aerobic exercise where your heart is beating rapidly, you are sweating a fair amount, and are breathing hard.” The window of 72 hours prior
to treatment was chosen based on a time-course analysis of the cardio-protective effect of submaximal exercise (mediated by increased antioxidant activity) prior to ischemia-reperfusion injury that reported that exercise was still beneficial up to 60, but not at 72 hours prior. Both groups were also asked not to perform vigorous intensity exercise for 48 hours after each treatment to isolate the effect of exercise prior to treatment, as some initial preclinical evidence exists for cardio-protective benefit of exercise performed 24 hours after treatment. Participants were free to perform light or moderate intensity exercise at any time throughout the study in agreement with the ACSM guidelines for cancer survivors.

Women aged 18 or older, with newly diagnosed histologically confirmed stage I-III breast cancer who were scheduled to receive neoadjuvant or adjuvant doxorubicin-containing chemotherapy were eligible to participate. Additionally, potential participants had to have their oncologist’s approval to exercise, be willing and able to complete the first study assessment prior to their first chemotherapy treatment, be able to understand and provide written informed consent in English or Chinese, and be willing to accept random assignment to the exercise or control group. Potential participants were excluded if they were concurrently enrolled in an aerobic exercise training study or a formal, structured aerobic exercise program, were concurrently enrolled in a pharmacological cardio-protection trial, were current smokers, have orthopedic limitations to exercise, a body mass index greater than 35 kg/m², pre-existing cardiovascular disease, uncontrolled hypertension (blood pressure $\geq 140/90$ mmHg), uncontrolled diabetes or respiratory disease, or had previously received anthracycline-containing chemotherapy, trastuzumab treatment, or thoracic radiotherapy. During the study, the BCCA changed their chemotherapy protocol for HER2-negative patients receiving neoadjuvant AC treatment such that they received the four cycles of paclitaxel prior to their four cycles of AC. It was decided to
include patients on this new protocol since it was now standard of care for this sub-group of patients and because paclitaxel is not known to cause cardiotoxicity when given subsequently to AC.

Participants were primarily recruited through oncologist referral and posters at the Vancouver BCCA Centre. Oncologists at the Lions Gate Hospital, Richmond Hospital, and Burnaby General Hospital BCCA Community Chemotherapy Centres were also asked to refer potential participants. Recruitment posters were also posted at these Community Chemotherapy Centres, and at the Mount St. Joseph’s Rapid Access Breast Clinic. Recruitment also occurred via social media (i.e., monthly Facebook and Twitter blurbs poster by Canadian Breast Cancer Foundation BC/Yukon) and word of mouth from past participants and other studies involving breast cancer patients.

Referred patients were screened over the phone for eligibility, interest and availability for participation. Randomization was explicitly explained in the phone screening, and participants were asked whether they would be willing to accept assignment to the exercise or control group. If they agreed, they were emailed a copy of the consent form and were asked to read the consent and re-confirm that they would like to participate. Non-English speaking potential participants were screened by a translator and provided with a consent form in their native dialect (i.e. simplified or traditional Chinese). Participants were randomized after reading the consent form and confirming their interest in participation and within two weeks of their scheduled first treatment. Prior to completion of any study exercise sessions, the oncologist of the participant was contacted via email for approval that their patient was medically fit to participate in submaximal exercise. Randomization was performed prior to the baseline assessment to allow for scheduling of the first assessment and first exercise session together for those in the exercise
group. This was done to reduce participant burden and to increase recruitment as potential participants could be referred a few days prior to their first treatment.

5.2.2 Intervention

For those randomized to the exercise group, the exercise sessions were performed on a treadmill in a private gym used exclusively for breast cancer research, located at 614 W 8th Ave (co-directors, Drs. Karen Gelmon, Donald McKenzie and Kristin Campbell). Both preclinical studies serving as the model for this study utilized an exercise prescription including a 10-minute warm-up, followed by 50 minutes of running at approximately 75-80% VO\textsubscript{2}peak.\textsuperscript{88,106} The preclinical studies were used for guidance in choosing the exercise prescription for this study, but with adjustment to allow for potentially untrained women to be able to complete it during chemotherapy treatment. The exercise prescription for the session in this study was chosen as a 10-minute gradual warm-up to allow for acclimatization to the treadmill, and also increase total volume of the session. Following the warm-up, 30 minutes were performed at 70% of age-predicted HRR, which corresponds to a vigorous intensity,\textsuperscript{323} followed by a 5-minute cool-down. The Gulati et al. age-predicted peak heart rate prediction equation (206 – 0.88*age),\textsuperscript{322} and the same protocol for measuring resting heart rate were used as in Chapter 3. Resting heart rate was measured immediately prior to each exercise session a new target heart rate was calculated based on that day’s heart rate. Participants were asked to refrain from caffeine, alcohol and unnecessary drugs for 3 hours, and food for at least one hour prior to the exercise session, to minimize the effect of these on heart rate.

During the warm-up, treadmill speed was gradually increased to a comfortable walking speed, and then treadmill grade was increased, with the goal of attaining the target heart rate by the end of the 10-minute warm-up. The FT1 heart rate monitor (Polar, Lachine, Quebec) was
used to record and average the heart rate during the 30-minutes. During the 30-minute session, the heart rate response was closely monitored and treadmill speed or grade was adjusted when the participant’s heart rate deviated from the target heart rate by more than three beats per minute. Every five minutes throughout the session, the participant was asked to report their RPE on the Borg 6-20 scale. At the end of the session, the participant was asked to report an overall average RPE for the whole session, and was reminded that they are asked not to exercise at a vigorous intensity for 48 hours after their treatment.

The exercise session was scheduled once the participant had received confirmation of their treatment date and time from the BCCA, which occurred anywhere from seven to less than one day prior to the treatment. During the scheduling process, the exercise group participants were reminded that they are asked not to perform vigorous intensity exercise other than the study session in the 72 hours prior to their treatment. The preference was to schedule the session to start 25 hours in advance of the participant’s scheduled start time for the treatment, so that it would end approximately 24 hours before the treatment. However, a window of two hours on either side of that time was allowed to accommodate the participant’s schedule. When the exercise session was completed 24.5 hours or more prior, or 23.5 hours or less prior to the scheduled treatment time, a reason for difference was recorded to describe issues related to feasibility of implementation of this intervention.

5.2.3 Outcome measures

There were three study assessments for both groups. All sessions took place in the area of the Vancouver BCCA Centre, and were scheduled around other appointments that participants had in the area if possible, and also around the availability of the sonographer and nurse required
for data collection. Participants were provided up to $5 to cover the cost of these visits and the exercise session visits.

5.2.3.1 Baseline assessment

The baseline study visit took place up to two weeks before the first AC treatment and was scheduled immediately prior to the first exercise session for those in the exercise group if possible. For those who received paclitaxel treatment prior to the AC treatment, the baseline visit was scheduled after the last paclitaxel and before the first AC treatment, as close to the AC treatment as possible to maximize the time since the last paclitaxel treatment.

5.2.3.2 24-hour assessment

The second visit was intended to capture the acute effect of the first AC treatment, and was performed 24 to 48 hours after the first AC treatment. A 24-hour window was allowed to accommodate for the difficulty in scheduling the participant, the sonographer and nurse at the same time, but the preference was for as close to 24 hours as possible.

5.2.3.3 Post AC assessment

The third and final study assessment was performed 7 to 14 days after the last AC treatment to be comparable to the timing of previous observational studies measuring myocardial mechanics, 188,193,196,203-205 and to capture the chronic effect of the intervention for the duration of AC treatment.

Height and weight were measured with shoes removed at baseline and the post AC assessment. A brief questionnaire was administered to collect demographic, diagnosis, and treatment characteristics. The physical measures at each assessment included a resting echocardiogram, a venipuncture, and measurement of resting heart rate and blood pressure. The
procedures for measurement of seated resting heart rate and blood pressure, and the echocardiogram were identical to those reported in Chapter 4.

5.2.3.4 Resting heart rate and blood pressure

Briefly, seated resting heart rate was measured with a heart rate monitor as the lowest heart rate during five minutes of quiet seated rest. Seated blood pressure was measured at the end of the five minutes of quiet seated rest manually with a stethoscope and sphygmomanometer as the average of two measurements separated by 60 seconds. Supine blood pressure was measured following the same protocol at the end of the echocardiogram. Supine heart rate was measured from the electrocardiogram integrated into the ultrasound as the average of the three cardiac cycles used to measure 4-chamber volumes.

5.2.3.5 Echocardiography

A certified sonographer who was blinded to group assignment completed the echocardiograms. The primary outcome was GLS, and the other myocardial mechanics parameters including twist mechanics were secondary outcomes. Standard images in the apical 4- and 2-chamber, parasternal long axis, and parasternal short-axis were taken as described in Chapter 4. There were two additional images taken in the echocardiogram assessment for this study from the parasternal short axis to assess myocardial twist mechanics. Basal rotation was measured at the level of the mitral leaflets. Apical rotation was measured one to two rib spaces below the parasternal short axis view to align with the apical axis such that the papillary muscle is no longer visible in the LV cavity and the myocardial wall was as circular as possible. Anticlockwise rotation is assigned a positive value by convention, whereas clockwise rotation is negative. LV twist and twist velocity were calculated by subtracting the basal rotation and rotation velocity data from the corresponding apical rotation and rotation velocity data. The
2DSTE analysis was as described in Chapter 4. Also as with Chapter 4, standard LV volumes, dimensions, diastolic parameters were measured, and the other related variables described in Chapter 4 were calculated.

5.2.3.6 Cardiac biomarkers

NT-proBNP and cTnT were secondary outcomes. Blood was collected by venipuncture performed by a trained nurse at the Vancouver Coastal Health Research Institute Clinical Research Unit. The samples were spun and serum was extracted and stored for batch analysis at the end of the study. NT-proBNP and cTnT were measured by the proBNP II and Troponin T high sensitive short turn around time electrochemiluminescence sandwich immunoassays, respectively on a Roche E601 Cobas analyzer (Roche Diagnostics, Laval, Quebec). Both assays have a detection limit of 5 pg/mL.

5.2.3.7 Patient-reported symptoms

The Rotterdam Symptom Checklist was used to measure patient-reported side effects. It is a valid and reliable instrument that is sensitive to differences in physical distress. It asks the participant about experience and severity of a list of physical and psychological symptoms, and provides standardized physical and psychological distress scores. It was administered at the baseline and follow-up sessions in reference to the symptoms experienced in the past week, and time since the last chemotherapy treatment, respectively. The Rotterdam Symptom Checklist was also administered prior to the 2nd, 3rd, and 4th treatments. For participants in the exercise group, administration coincided with the study visit for the exercise session. For participants in the control group, each participant was provided with three copies of the Rotterdam Symptom Checklist at the baseline assessment to take home. Control participants were emailed three to four days in advance of their 2nd, 3rd, and 4th scheduled treatments and asked about scheduling a
time on the day before their treatment for a short phone call. In this email they were also reminded that they are asked not to exercise vigorously for 72 hours prior to, and 48 hours after their treatment. During the phone call the day prior to their treatment, they were reminded to complete the Rotterdam Symptom Checklist. These questionnaires were collected at the final study assessment.

5.2.3.8 Self-reported physical activity

A modified version of the Minnesota Leisure Time Physical Activity Questionnaire was administered at baseline as described in Chapter 3 to provide a measure of average baseline self-reported physical activity levels over the previous six months.

To quantify the amount of total moderate-vigorous intensity exercise each group performed during the intervention period, the Godin Leisure Time Exercise Questionnaire, a brief questionnaire that asks about frequency and intensity of moderate and vigorous exercise performed in the prior seven days, was verbally administered in person at the exercise sessions for the exercise group or during the phone call for the control group. The Godin was administered twice at each instance, first in reference to the past seven days, and a second time regarding the seven days following their last treatment. Those participants receiving treatment every three weeks were not asked about the middle week. For the non-English speaking participants, a translator verbally translated all questionnaires to the participant either over the phone or in-person and recorded their responses.

5.2.4 Statistical analyses

Age, height, weight and body mass index were compared between groups at baseline, and weight and body mass index between groups at post AC with independent t-tests. The Mann Whitney U test was used to compare the Minnesota Leisure Time Physical Activity
Questionnaire, and the Godin Leisure Time Exercise Questionnaire for each week of the study between groups as this data was not normally distributed due to a high occurrence of zeros. Python 2.7.10 (available at http://www.python.org) was used for these analyses and all data exploration, cleaning, and figures. For the assessment of differences between groups and time points, repeated measures analysis of variance was not an optimal choice for this small data set as it drops any cases with a missing data point. Furthermore, the physiological data in the study does not always follow normal distribution and does not have equal variances between groups or across time points. These properties of the data violate assumptions of the general linear model for normality and equal variances. A generalized linear model on the other hand, utilizes a “link function” to define the relationship between the systematic component of the data and the dependent variable such that normality and equal variances are not required.\textsuperscript{364} In a standard generalized linear equation however, the assumption of independence of observations is still required to be met.\textsuperscript{364} Failure to incorporate correlation of responses can lead to incorrect parameter estimation. Generalized estimating equations (GEE) are an extension of generalized linear models that account for correlation of responses within subjects in longitudinal data sets.\textsuperscript{365} The GEE estimate regression coefficients can be used to test main effects and interactions.

For the outcome measures, the GEE procedure was used in SPSS Version 20.0 (IBM Corporation, Armonk, New York) to assess the change between baseline and 24 hours (primary aim), and a separate GEE procedure was used to assess change between baseline and post AC (secondary aim). For both analyses, an identity link function that involves no transformation of the data was used. There is an option to specify a specific correlation matrix for the model or to have the model estimate a working correlation matrix to correct for correlation within subjects that matches the expected correlation structure within the subject though multiple iterations until
the extent of change in parameter estimates is minimized by the model, called a robust estimator. A model-based estimator was used rather than the robust estimator due to potential for biased estimates with a small sample size. An exchangeable working correlation matrix was used which assumes homogeneous correlations between time points. This model was fit with a maximum likelihood estimate and type III sums of squares. The time point of the study assessment was used as the repeated term, and the model included time and group as main effects and a group by time interaction. Because the group by time interaction was hypothesized, the main effects were only interpreted if the interaction was not significant. In case of an interaction effect, pairwise differences were investigated using contrasts for hypothesized differences only. Namely, for the physical data, contrasts were performed for baseline versus follow-up for each group, and the follow-up was compared between groups. If the interaction was not significant, the main effects are reported. However, it is recommended that non-significant interaction actions should not preclude pairwise comparisons between treatment and control groups, especially when there is biological relevance of the potential difference. As a compromise to minimize multiple comparisons but not miss potential real effects, the chosen approach was to only perform pairwise comparisons on non-significant interactions for variables that are potentially explanatory for other significant effects noted.

For the Rotterdam Symptom Checklist data, a similar GEE procedure was used, with the difference that all five time points (i.e. baseline, and 1st to 4th treatments) are included in one analysis, and pairwise contrasts performed to assess for differences between the groups at each time point only. For all interaction effects, main effects, and pairwise analyses, the effect was considered significant at the p<0.05 level. The significant contrasts for interaction effects are reported in the text with the estimated marginal mean ± standard error, whereas the p-value for
the interaction effect and main effect of time is reported with the raw mean ± standard deviation in tables.

5.3 Results

5.3.1 Recruitment

Figure 5.1 shows the flow through the study. Seventy-eight participants were referred to the study total, from oncologists (n=67), recruitment posters (n=5), and word of mouth (n=4). There was no response from four participants, and 19 declined participation due to: having too many appointments (n=5), not wanting to commute (n=5), feeling overwhelmed (n=3), family obligations (n=3), being too busy (n=2), or no reason given (n=1). Twenty-eight participants were not eligible for participation due to: not being willing or able to complete baseline study visits prior to first treatment (n=8), enrollment in another exercise study or pharmacological cardio-protection study (n=7), not receiving anthracyclines (n=3), medical history (n=3), current smoker status (n=3), BMI over 35 kg/m2 (n=2), stage IV breast cancer diagnosis (n=1), and mobility issues (n=1).

Twenty participants enrolled in the study, and n=11 were randomized to the exercise group, and n=9 were randomized to the control group. One participant randomized to the exercise group dropped out after the baseline study visit and refused to complete her first exercise session, so her baseline data is not included in the tables or analyses. One participant in the control group did not want to have the echocardiogram at the 24-hour assessment, but completed all other measures at that visit, and completed all measures at the post AC assessment; all of her completed data was included. One participant had not completed her post AC
assessment at the time of this analysis but her data were included for baseline and the 24-hour assessment.

5.3.2 Participants

Table 5.1 reports the baseline descriptive statistics for the two groups. Overall the participants were 49±9 years old and the groups did not differ in age. Participants were predominantly Caucasian, married, and educated. The most commonly reported co-morbid conditions were asthma and arthritis, both reported in 21% of participants. One participant in each group reported a history of hypertension that was controlled at the time of enrollment, and were taking a statin plus either a calcium channel blocker or beta-blocker medication for at least 10 years. One of these participants was also taking metformin for the previous year. Three participants were taking a thyroid replacement medication long-term. There were no differences between groups in MVPA, body weight or body mass index at baseline, and no differences in body weight or body mass index post AC (Table 5.2). The 24-hour assessment was performed 27.6±7.0 hours after the scheduled start time of the first treatment, and the post AC assessment was performed 10.3±2.2 days after the final AC treatment.

5.3.3 Exercise

All exercise sessions were completed as planned, and were a mean of 23.9±1.1 hours prior to the participant’s scheduled chemotherapy treatment time. Of 37 sessions, 13 (35%) were completed a half hour or more away from the 24-hour window; six due to the participant’s schedule, three due to participant medical appointments, two due to the participant being late, one due to a conflict with the study team’s schedule, and one due to the baseline study visit taking longer than anticipated prior to the first exercise session.
The average intensity of the aerobic exercise sessions was 71±4% of age-predicted HRR thereby meeting the goal of vigorous intensity aerobic exercise. Participants reported a mean RPE of 13±1. There was some variability in the subjective intensity of the exercise session, as the minimum RPE reported was 10 and the maximum was 15. Only one session was performed at less than 65% HRR, and the intensity was reduced on this session as the participant had been hospitalized for an extended period and was deconditioned. She reported a RPE of 13 for the reduced intensity. This participant also required a five-minute break during the session, but otherwise the full duration of all sessions was completed.

A bout of vigorous intensity exercise was self-reported on the Godin questionnaire nine times across all time points and all participants in the study. All of these vigorous sessions took place in the seven days prior to a treatment, and only one of these was reported within the 72-hour window (at 48 hours) where participants were asked not to perform vigorous intensity exercise prior to their treatment. No vigorous intensity sessions were reported in the seven days after a treatment. There was also no significant difference between the MVPA reported by either group for any week of the study (Table 5.2). Therefore compliance to this aspect of the protocol, albeit self-reported, was excellent.

Figure 5.2 shows the mean changes from baseline to 24 hours in key variables for both groups, while Figure 5.3 shows the mean changes from baseline to post AC in key variables for both groups. The data for the physical measures are presented in the text with estimated marginal means, standard error, and significant pairwise contrast p-values from the GEE model only. The data for the physical measures in the tables represent the unadjusted means and standard deviations.
5.3.4 Resting heart rate and blood pressures – 24 hours

Regardless of group, there was a significant decrease in seated resting systolic (105±3 to 102±3 mmHg, p=0.03), diastolic (69±2 to 62±2 mmHg, p<0.01) and mean arterial blood pressure (81±2 to 75±2 mmHg, p<0.01) (Table 5.3). In the exercise group only, there was a trend toward a significant decrease in seated resting heart rate (74±3 to 68±3 bpm, p=0.07), and a significant decrease in rate pressure product (8123±499 to 7148±512 mmHg·bpm, p=0.01).

In the supine position, there was no difference between groups. Supine resting heart rate and systolic blood pressure did not change, but diastolic blood pressure significantly decreased (63±2 to 58±3 mmHg, p=0.02), and there was a trend toward an overall decrease in mean arterial blood pressure (76±3 to 72±3 mmHg, p=0.07). There was an overall significant decrease in systemic vascular resistance (1984±94 to 1635±97 dynes·sec·cm⁻⁵, p<0.01), and no significant interaction or main effects in supine rate pressure product.

5.3.5 LV Volumes – 24 hours

End-diastolic volume (79±3 to 87±3 mL, p<0.01), stroke volume (46±2 to 52±2 mL, p<0.01), and cardiac output (3.2±0.1 to 3.6±0.1 L/min, p<0.01) increased significantly regardless of group (Table 5.4). There were no significant interaction or main effects for LVEF, but there was a trend toward an overall increase over time (58±1 to 60±1 %, p=0.10).

5.3.6 LV dimensions and wall thicknesses – 24 hours

There was an overall increase in end-diastolic dimension (429±10 to 444±10, p<0.01) and no change in end-systolic dimension or fractional shortening (Table 5.5). The only change in wall thicknesses was an overall increase in end-systolic IVS thickness (130±5 to 139±6, p=0.05), while end-diastolic IVS thickness and posterior wall thicknesses did not change. LV mass
increased overall (123±6 to 133±6, p=0.01). There were no interaction or main effects for relative wall thickness or end-systolic wall stress.

5.3.7 LV diastolic function – 24 hours

There were no group differences in diastolic function (Table 5.4). There was an overall significant increase in mitral E wave (0.69±0.03 to 0.85±0.03 m/s, p<0.01), and E/A ratio (1.18±0.07 to 1.36±0.08, p<0.01) and no significant changes in mitral A wave, IVRT, or mitral E wave deceleration time. There were trends toward overall decreases in IVRT (85±4 to 74±4 ms, p=0.09) and deceleration time (239±8 to 223±8 ms, p=0.10).

5.3.8 LV myocardial mechanics – 24 hours

There were no differences between groups in longitudinal strain or twist parameters (Table 5.6). However, there was an overall significant increase in GLS (-19.4±0.4 to -21.4±0.4%, p<0.01), systolic LSR (-1.02±0.03 to -1.09±0.03 /sec, p<0.01), and early diastolic LSR (1.23±0.08 to 1.41±0.08 /sec, p<0.01). Early diastolic RSR increased overall (-2.25±0.18 to -2.81±0.18 /sec, p=0.05), but systolic RSR increased in the exercise group only (1.95±0.21 to 2.95±0.20 /sec, p<0.01), and was significantly higher than the control group (2.31±0.22 /sec, p=0.04).

There was an overall significant increase in twist (16.0±1.3 to 19.0±1.3°, p=0.05) and apical rotation (9.5±0.9 to 11.8±0.9°, p=0.01), whereas basal rotation did not change. There were no interaction or main effects for systolic twist or untwist velocity.

5.3.9 Cardiac biomarkers – 24 hours

There was a significant increase in NT-proBNP in both groups (control: 59±28 to 310±28 pg/mL; exercise: 40±26 to 184±26 pg/mL, both p<0.01), and NT-proBNP was significantly lower in the exercise group (p<0.01) (Table 5.5). There were no significant interaction or main
effects for cTnT, but there was a trend toward an increase over time (1.3±0.5 to 2.0±0.5 pg/mL, p=0.10).

5.3.10 Resting heart rate and blood pressures – post AC

There was an overall increase in seated resting heart rate (70±2 to 77±2 bpm, p<0.01) and supine resting heart rate (70±2 to 74±2 bpm, p=0.03) (Table 5.3). There was an overall significant decrease in all blood pressures, in the seated position [systolic (105±3 to 97±3 mmHg, p<0.01), diastolic (69±2 to 61±2 mmHg, p<0.01), mean arterial (81±2 to 73±2 mmHg, p<0.01)], and supine position [systolic (101±3 to 93±3 mmHg, p<0.01), diastolic (63±2 to 59±2 mmHg, p=0.02), mean arterial (76±2 to 70±2 mmHg, p<0.01)]. There was a significant interaction effect for seated rate pressure product, but none of the hypothesized contrasts were significant and there was no overall effect of time. Supine rate pressure product did not change. There was an overall significant decrease in systemic vascular resistance (1984±85 to 1685±86 dynes·sec·cm⁻⁵, p<0.01).

5.3.11 LV volumes – post AC

There were no significant changes in end-diastolic, end-systolic or stroke volumes, nor LVEF. There was a significant increase in cardiac output in the control group only (3.0±0.2 to 3.5±0.2 L/min, p<0.01) (Table 5.4). Because cardiac output is calculated as stroke volume multiplied by heart rate, and it is interdependent with mean arterial pressure and systemic vascular resistance, the pairwise contrasts were calculated for these variables despite non-significant interaction effects to help explain the increase in cardiac output in the control group alone. All pairwise contrasts for stroke volume were not significant, and the decrease in supine mean arterial pressure was significant for both groups. Pairwise contrasts for supine heart rate and systemic vascular resistance revealed that a significant change existed only in the control
group (heart rate: 69±3 to 75±3 bpm, p=0.03; systemic vascular resistance: 2065±123 to
1623±123 dynes·sec·cm⁻⁵, p<0.01), and not the exercise group (heart rate: 71±3 to 74±3 bpm,
p=0.40; systemic vascular resistance: 1903±116 to 1747±121 dynes·sec·cm⁻⁵, p=0.16). This
group effect was also evident for seated resting heart rate upon further inspection as well
(control: 66±4 to 76±4, p<0.01 bpm; exercise: 74±3 to 78±3 bpm, p=0.19). Therefore the
increase in cardiac output in the control group was attributable to a higher resting heart rate.

5.3.12 LV dimensions and wall thicknesses – post AC

There was no change in end-diastolic dimension, and an overall increase in end-systolic
dimension (296±10 to 314±10 mm, p=0.03) (Table 5.5). There was an overall significant
decrease in fractional shortening (31±1 to 29±1%, p=0.05). There was a trend toward a decrease
in end-diastolic, and a significant decrease in end-systolic IVS thickness in the exercise group
only (end-diastolic: 99±6 to 89±6 mm, p=0.06; end-systolic: 133±6 to 117±6 mm, p<0.01). The
end-systolic IVS thickness was significantly greater in the control group than the exercise group
(135±1 vs. 117±1 mm, p=0.05). There was no change in end-diastolic posterior wall thickness,
but end-systolic posterior wall thickness significantly increased in the exercise group only
(122±5 to 135±5 mm, p=0.02). End-systolic wall stress and relative wall thickness did not
change.

Based on the apparent group effect on wall thicknesses and the direct relationship
between wall thickness and end-systolic wall stress, the pairwise contrasts for this parameter
were examined. There was no change in end-systolic wall stress in the control group (55±5 to
56±5 x10³ dyn·cm⁻², p=0.83), but the decrease in end-systolic wall stress in the exercise group
did not reach significance (59±5 to 51±5 x10³ dyn·cm⁻², p=0.16). Pairwise contrasts were also
examined for the other parameter that affects wall stress, end-systolic dimension. The increase in
end-systolic dimension was significant in the control group only (296±15 to 319±15 mm, p=0.05), while the change in the exercise group was not (295±14 to 309±14 mm, p=0.26). Fractional shortening was also only decreased in the control group (33±2 to 29±2%, p=0.02), while there was no change in the exercise group (30±2 to 29±2%, p=0.68).

5.3.13 LV diastolic function – post AC

There were no changes in mitral valve E or A waves or the E/A ratio (Table 5.4). There was an overall significant decrease in mitral valve E wave deceleration time (238±7 to 217±7 ms, p<0.01) and IVRT (85±4 to 74±4 ms, p=0.04).

5.3.14 LV myocardial mechanics – post AC

There was no change in GLS, but both systolic (-1.02±0.03 to -1.13±0.03 /sec, p=0.02) and early diastolic LSR (1.2±0.07 to 1.4±0.07 /sec, p=0.05) increased significantly overall (Table 5.6). There was no change in GRS, systolic and early diastolic RSR, GCS, and early diastolic CSR. There was a significant increase in systolic CSR in the control group only (-0.76±0.08 to -1.03±0.08 /sec, p=0.02).

There was no change in twist or twist velocity. There was an overall significant increase in untwist velocity (-99±9 to -117±9 °/sec, p=0.02). There was no change in apical rotation and while there was a significant interaction effect for basal rotation, the pairwise contrasts were not significant, nor was the main effect for time.

5.3.15 Cardiac biomarkers – post AC

Regardless of group, there was an overall significant increase in NT-proBNP (50±12 to 86±12 pg/mL, p=0.01) and cTnT (1.3±1.7 to 13.2±1.8 pg/mL, p<0.01) (Table 5.5).
5.3.16 Patient-reported symptoms

There were no significant differences between the exercise and control groups in the standardized scores of physical distress or psychological distress following any of the treatments.

5.4 Discussion

This study investigated the acute effect of a single vigorous intensity exercise session completed 24 hours prior to the first AC treatment relative to no vigorous exercise, and the chronic effect of a vigorous intensity exercise session performed 24 hours to each AC treatment for breast cancer on known markers of cardiotoxicity including myocardial mechanics and cardiac biomarkers. There was no effect of the exercise session 24 hours prior to AC treatment on GLS, or the other myocardial mechanics parameters at either time point. The differential response in RSR and CSR reported are not likely to be of biological relevance due to the variability in these measures, as reported in Chapter 4, and due to the lack of consistent changes in other related parameters. Exercise attenuated the NT-proBNP response at 24 hours after the first treatment, and there was no acute effect of exercise otherwise. There were a number of significant changes in both central and peripheral hemodynamics, and myocardial strain, strain rate and twist mechanics that occurred as an acute response to the AC treatment for all participants with no difference between groups that have not been previously reported. At post AC the exercise group differed in central and peripheral hemodynamics and cardiac geometry relative to the control group. However, the exercise sessions did not have an effect on physical and psychological patient-reported symptoms after any of the AC treatments.
5.4.1 24 hours after first AC treatment

The goal of the 24 hour assessment was to assess the acute effect of a single exercise session 24 hours before the first AC treatment on markers of cardiotoxicity. The optimal timing of this assessment is dependent on the timing of the response that will be captured by the chosen outcome measures. No studies that have measured myocardial mechanics in adults being treated with anthracycline chemotherapy have reported on an acute effect. However, in children, Ganame et al. reported significant deteriorations in GLS and GRS within two hours of the first anthracycline treatment. In a preclinical model, Jassal et al. performed a time-course analysis of the acute effect of a high dose (20 mg/kg) of doxorubicin on mouse RSR and reported a significant decrease from baseline at 24 hours that progressively decreased for the following four days. This finding was corroborated in another preclinical study reporting a 75-fold increase in cardiomyocyte apoptosis at 24 hours after doxorubicin injection.

In the current study, there was an unexpected significant increase in GLS, systolic and early diastolic LSR, twist and apical rotation at 24 hours with no differences between groups. Anthracyclines are consistently reported to induce deterioration in all of these parameters as outlined in Tables 2.3 and 2.4, even when measured 24 hours after the third and sixth treatments of epirubicin treatment for breast cancer. In the work of Florescu et al, at 24 hours after the third cycle, GLS had significantly decreased with no other changes, while at 24 hours after the sixth cycle, end-systolic volume, LVEF, systolic LSR, twist, apical rotation and untwist rate had also significantly decreased. The response of myocardial mechanics at 24 hours in the current study is likely related to the concurrent changes in loading conditions noted, as strain and twist are load-dependent parameters. However the majority of literature around blood pressure and mechanics involves hypertension or acute vasodilation, and little is known about the effect
of sustained low blood pressure. The reason for the lack of change in these parameters at post AC, even in the control group, is unknown. Participants in the Florescu et al. study were quite similar in diagnosis, age, BMI, baseline diastolic blood pressure, and presence of cardiovascular risk factors, other than smoking status (30% smokers) and baseline systolic blood pressure (mean of 124 mmHg) relative to the current study’s participants. Whether a low systolic blood pressure or resultant low pulse pressure (systolic – diastolic) at baseline affords a protective mechanism against anthracycline-related deterioration in myocardial mechanics, and whether this translates into reduced risk for cardiotoxicity should be further explored.

The primary acute effect of a single vigorous intensity exercise bout performed 24 hours prior to the first AC treatment in women with breast cancer was an attenuation of the NT-proBNP response relative to the control group, when measured at 24 hours after the treatment. Elevations of NT-proBNP in the context of cardiotoxic cancer therapy may demonstrate a pathologic overload cardiomyopathy.\textsuperscript{45} NT-proBNP is the amino-terminal fragment of the BNP precursor that is synthesized and secreted by the ventricles in response to increased hemodynamic stress such as chamber overload and increased wall tension and also in response to angiotensin II, endothelin, cytokines, insulin, thyroid hormones and estrogens.\textsuperscript{236} Its release is associated with systemic arterial dilatation and modulation of blood volume.\textsuperscript{236} While end-systolic wall stress did not change, end-diastolic volume increased, and systemic arterial dilation was evident by decreased mean arterial blood pressure and systemic vascular resistance, with no differences between groups. Whether the increased LV volume represents a pathological change or an acute or temporary hemodynamic response to fluid shifts caused by chemotherapy is not known.
The most important mechanism for cardiac release of NT-proBNP is stretch of cardiomyocytes, and the current study results appear to indicate NT-proBNP release was lower despite a seemingly similar stretch (i.e. increase in end-diastolic volume) in the exercise group relative to the control group. There is an acute effect of a single exercise session that could be hypothesized to help explain this differential response. End-diastolic volume will increase from rest with submaximal, upright exercise due to increased venous return as a result of the pumping action of the leg muscles. This exercise-related increase in end-diastolic volume could perceivably sensitize the cardiomyocytes to stretch, resulting in a lower stimulus when stretched again by hemodynamic changes resulting from the chemotherapy treatment.

Given the decrease in mean arterial pressure and increase in end-diastolic volume in both groups, it is plausible that there was an increase in blood volume in response to the decreased mean arterial blood pressure at 24 hours. Renal response to an acute hemodynamic change occurs within a few hours to days after an acute change in arterial pressure. When arterial pressure falls below normal, the kidneys retain water and salt, increasing blood volume until the pressure returns to normal. Both groups utilized the Frank-Starling mechanism (length-dependent activation of cardiomyocytes) to augment stroke volume. The increase in cardiac output appeared to be entirely due to the increased stroke volume as no change in supine heart rate occurred at 24 hours in either group. Normally, an increase in cardiac output will increase arterial pressure. The increase in cardiac output with a paradoxical decrease in mean arterial pressure at 24 hours after the first chemotherapy treatment in the current study could potentially be a result of a change in sympathetic nervous control of the vasculature. An exercising dog model can be used to demonstrate the relationship between these components of hemodynamics. A sympathectomized dog relative to a dog with intact nervous system had the same decrease in
systemic vascular resistance due to vasodilation initiated by local factors in the muscles, but was unable to maintain mean arterial pressure, which dropped with the drop in systemic vascular resistance, while the normal dogs had a (sympathetically-mediated) significant increase in mean arterial pressure. The sympathectomized dogs are still able to increase cardiac output by way of increased venous return, though markedly less so than the normal dog. This example provides an extreme example of the role of the sympathetic nervous system in blood pressure control, and the level of sympathetic dysregulation that would occur with chemotherapy treatment in humans is considerably less. However sympathetic dysregulation could be a plausible explanation for the changes that occurred in both groups at 24 hours, and measures of sympathetic nervous control of the vasculature should be included in future studies.

In both groups, there was a lack of change in systolic blood pressure in the supine position, while there was a significant decrease in the seated position at 24 hours. Autonomic balances differs with body position, where in vertical postures such as standing or sitting, sympathetic nervous control predominates, and while in supine or recumbent positions, vagal tone predominates. There was no change in resting heart rate in either position however. This suggests a decrease in sympathetic nervous control of arterial blood pressure, and may be a possible mechanism for the hemodynamic changes that occurred at 24 hours.

5.4.2 Post last AC treatment

The secondary aim of the study was to assess the chronic effect of performing the exercise bout 24 hours prior to every AC treatment. This aim was assessed by comparing the baseline assessment performed prior to the first AC, to the post AC assessment performed 7-14 days after the last AC treatment. There were no differences between groups in myocardial mechanics including GLS, or cardiac biomarkers. GLS had not significantly deteriorated from
baseline as all previous studies have reported. One important consideration in interpreting the results of this study including this lack of change in GLS is that although the control group in the current study did not receive an exercise intervention, they were willing to enroll in an exercise study, indicating that they were interested in exercise, and likely performed more exercise on their own throughout the intervention period than in observational studies reporting the effects of doxorubicin on cardiac function. The study sample’s self-reported physical activity levels for the previous six months indicate that they were moderately active prior to joining the study, and their low blood pressure and resting heart rate at baseline indicate that they were generally in good cardiovascular health. These factors likely explain some of the discrepancies in differences reported in the current study relative to other published observational studies.

A concerning finding was that regardless of the effect of exercise, all individuals in the study had elevated levels of cTnT at post AC. Elevated troponin levels indicate myocardial injury, but do not indicate the mechanism of injury, as several other etiologies of elevated troponin levels have been reported including silent myocardial necrosis, pathological LV hypertrophy, LV systolic dysfunction, increased cardiac preload, microvascular disease, and endothelial dysfunction secondary to oxidative stress.\textsuperscript{258} Even minor elevations of cTnT offer prognostic value; Auner et al. reported that patients who experienced an elevation of cTnT elevation over 3 pg/mL during anthracycline treatment later had a significantly reduced LVEF relative to those without an elevation.\textsuperscript{246} All participants in the current study had cTnT levels above this concentration at post AC; however the assay sensitivity has likely dramatically improved over the previous decade since the publication of Auner et al.’s results. NT-proBNP was also increased from baseline with no differences between groups, but the size of the increase is not likely clinical relevant.
Similar to 24 hours, mean arterial blood pressure was not different between groups, but was significantly decreased. Cardiac output and systemic vascular resistance regulate mean arterial blood pressure. Cardiac output was significantly increased relative to baseline in the control group only, explained by an elevated heart rate, while cardiac output and heart rate had not changed from baseline in the exercise group. There were no group differences at 24 hours however, likely due to differing baseline values. Likewise, systemic vascular resistance (calculated as mean arterial pressure divided by cardiac output), was significantly decreased in the control group, with no change in the exercise group. LV volumes and LVEF did not change in either group. These results suggest that the exercise and control groups had differing mechanisms for the decrease in mean arterial pressure. In individuals with conditions resulting in longer-term reduced systemic vascular resistance (i.e. anemia, arteriovenous shunts), cardiac output is chronically increased to the same magnitude as the reduction in systemic vascular resistance to maintain mean arterial pressure at normal levels by kidney-mediated control of blood volume. A potential explanation is that cardiac output in the control group was increased in response to the reduced systemic vascular resistance in attempts to maintain mean arterial pressure, albeit at a lower level than baseline.

The source of the decreased mean arterial pressure in the exercise group is less clear, but appears to have a different origin than that of the control group. Autonomic dysfunction, or an imbalance between sympathetic and parasympathetic nervous system activations, is an emerging potential risk factor for developing cardiovascular disease in breast cancer survivors associated with anthracycline treatment. Autonomic balance is a key regulatory mechanism in the control of cardiac output, vascular tone and blood pressure. At post AC in the current study, resting heart rate increased in the control group, but not the exercise group, which is a clinical marker of
autonomic dysfunction.\textsuperscript{372} Furthermore the acute effect of the exercise session at 24 hours after the first AC was a trend toward a decrease in resting heart rate in the exercise group. A reduction in sympathetic activity could be a potential mechanism for the reduced mean arterial blood pressure in the exercise group.

End-systolic wall stress was not measured directly, but was calculated using an equation, that while developed and validated against an invasive approach, assumes that brachial systolic blood pressure correlates well with LV end-systolic pressure, and also makes assumptions for geometric shape of the ventricle.\textsuperscript{338} Nonetheless if the relationship between brachial systolic blood pressure and LV end-systolic pressure is assumed, then this provides an alternative explanation for the mechanistic differences between groups for the change in blood pressure. At post AC, systolic blood pressure had significantly decreased and end-systolic wall stress had not changed, with no differences between groups. The groups differed however in how they regulated the load on the myocardium in end-systole (i.e. end-systolic wall stress) in response to the decrease in systolic blood pressure. End-systolic wall stress was calculated in the current study using supine systolic blood pressure, and LV end-systolic dimension and posterior wall thickness, and did not significantly change in either group. In the exercise group, there was an increase in end-systolic posterior wall thickness and a non-significant increase in end-systolic diameter, while in the control group there was an increased end-systolic dimension, but no change in wall thickness. A potential mechanism for the differential response in both systemic vascular resistance and hypertrophy of the posterior wall at post AC could be extrapolated from the differential acute response in NT-proBNP at 24 hours between groups.

One role of NT-proBNP is to act as regulatory system for the renin-angiotensin aldosterone system (RAAS) by reducing renin release, thereby reducing circulating levels of
angiotensin and aldosterone and down-regulating this pathway. \(^{373}\) RAAS stimulates cardiac hypertrophy and vasoconstriction. In addition to inhibiting RAAS-mediated vasoconstriction, NT-proBNP can also act locally on smooth muscle receptors to induce vasodilation. \(^{373}\) If the acute response of a higher NT-proBNP level occurred across each AC treatment in the control group, causing a greater inhibition of RAAS every treatment, this could help to explain the sustained reduction in systemic vascular resistance and lack of hypertrophy relative to the exercise group at post AC. However, the acute response was only measured after the first AC treatment in this study, so whether this is a plausible mechanism is unknown. Based on this theory, it would helpful to evaluate the acute response to the exercise session after each AC treatment in future studies.

This theory of down-regulation of the RAAS occurring to a greater extent in the control than exercise group is at odds with the changes in resting heart rate. However, sympathetic nervous system activity is only one control mechanism for heart rate; resting heart rate is also determined by the intrinsic firing frequency of the sinoatrial node, and parasympathetic nervous system activity. \(^{374}\) Additionally, changes in catecholamine concentration, neurotransmitter reuptake, \(\beta\)-adrenergic receptor number and sensitivity can influence resting heart rate. \(^{374}\) It is not known what mechanisms mediate the increase in resting heart rate with chemotherapy treatment. Therefore changes in these other factors could also explain the increase in heart rate in the control group.

**5.4.3 Timing of exercise**

In the current study the effect of exercise 24 hours prior to receipt of treatment was tested to match the timing utilized in the rodent studies that have reported a cardio-protective
This timing proved to be feasible as all exercise sessions were completed and only one-third were 30 minutes or more away from this time frame. However, more flexibility in timing would increase feasibility of this intervention in humans. Future studies should investigate the effect of other times less than 24 hours before, as well as after an anthracycline treatment, as two studies have reported some cardio-protective benefit with exercise performed 24 hours after anthracycline infusion in rodents.\textsuperscript{104,105}

5.4.4 Strengths, limitations, and considerations

Strengths of the current study include translation of a novel preclinical intervention to human breast cancer patients via a RCT design with high fidelity to research protocol regarding timing of exercise and assessments. Implementation of the specific time frames of this study with human participants is exponentially more difficult than with animals, and the potential for confounders is much greater. A strength of this study is recruitment of a fairly homogenous population with respect to demographics, baseline health, and risk factors. Although this homogeneity reduced generalizability of the study findings, it is an important requirement for pilot proof-of-principle studies.

Other limitations of the study include the small sample size, multiple statistical comparisons, and lack of measurement of other potentially explanatory variables including autonomic function and measures of vascular function. Longer-term measurement of blood pressure, such as ambulatory 24-hour blood pressure would strengthen any suggested mechanisms based on the change noted in blood pressure. This was not originally considered during study planning, as there was no previous evidence to indicate that such a large change in blood pressure would occur with AC treatment. The timing of administration of the Rotterdam Symptom Checklist was the day prior to each subsequent treatment in reference to symptoms.
experienced since from the previous treatment (received two to three weeks earlier). This may have reduced the study’s ability to detect a difference in symptoms between groups as reporting of chemotherapy symptoms at a longer time after treatment has been reported to reduce the number and severity of symptoms reported relative to reporting symptoms earlier after treatment. Future studies should consider measuring symptoms a week after each treatment.

5.5 Conclusion

This study investigated whether an acute vigorous intensity exercise bout would confer cardio-protective benefit when performed 24 hours prior to AC treatment for breast cancer. The exercise session did not have an effect on myocardial mechanics, including GLS. The primary finding is that after the first treatment, those that performed the exercise bout had an attenuated increase in NT-proBNP, but otherwise both groups experienced increases in myocardial mechanics parameters, likely secondary to changes in central and peripheral hemodynamics. The overall response at 24 hours after the first treatment, regardless of group, was an increase in end-diastolic volume, stroke volume, and cardiac output with paradoxical decrease in mean arterial pressure. Likely as a result of these loading changes, there was a corresponding increase in GLS, LSR, twist and apical rotation. At 7-14 days after the last anthracycline treatment, there was a similar decrease in mean arterial pressure in the absence of any LV volumetric changes. Here the groups differed, as the control group had an increased cardiac output from baseline attributed to an elevated resting heart rate, while there was no change in the exercise group. LV dimension and wall thickness changes differed between groups, where the exercise group had increased end-systolic posterior wall thickness, and the control group had increased end-systolic dimension. No relevant changes in myocardial mechanics occurred in either group from baseline to post AC. Overall, it appeared that the acute exercise bout 24 hours prior to anthracycline treatment altered
some components of cardiovascular physiology, but the clinical relevance and prognostic significance of these findings remains to be elucidated.
# 5.6 Chapter 5 tables and figures

Table 5.1: Study participant demographics and cancer diagnosis and treatment characteristics

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<td>3 (33%)</td>
<td>6 (60%)</td>
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<tr>
<td>$50,000-79,999</td>
<td>3 (16%)</td>
<td>1 (11%)</td>
<td>2 (20%)</td>
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<td>$30,000-49,999</td>
<td>5 (26%)</td>
<td>4 (44%)</td>
<td>1 (10%)</td>
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<td>&lt;$30,000</td>
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<td>1 (10%)</td>
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<td>1 (11%)</td>
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<td>Comorbid conditions (n %)</td>
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<td>Heart disease/angina</td>
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<tr>
<td>Diabetes</td>
<td>1 (5%)</td>
<td>1 (11%)</td>
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<tr>
<td>Asthma/ lung disease</td>
<td>4 (21%)</td>
<td>2 (22%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4 (21%)</td>
<td>0</td>
<td>4 (40%)</td>
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<tr>
<td>Joint replacement</td>
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<tr>
<td>Osteoporosis/ osteopenia</td>
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<td>0</td>
<td>0</td>
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<td>Hypertension</td>
<td>2 (11%)</td>
<td>1 (11%)</td>
<td>1 (10%)</td>
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<td>Medications (n %)</td>
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<td>1 (11%)</td>
<td>2 (20%)</td>
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<tr>
<td>Statin</td>
<td>3 (16%)</td>
<td>1 (11%)</td>
<td>2 (20%)</td>
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<td>Calcium channel blocker</td>
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<td>1 (10%)</td>
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<td>Beta-blocker</td>
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<td>Metformin</td>
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<tr>
<td>Stage (n %)</td>
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<tr>
<td>I</td>
<td>4 (21%)</td>
<td>3 (33%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>II</td>
<td>11 (58%)</td>
<td>5 (56%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>III</td>
<td>4 (21%)</td>
<td>1 (11%)</td>
<td>3 (30%)</td>
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<tr>
<td>Surgery (n %)</td>
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<tr>
<td>Lumpectomy</td>
<td>9 (47%)</td>
<td>4 (44%)</td>
<td>5 (50%)</td>
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<tr>
<td>Mastectomy</td>
<td>3 (16%)</td>
<td>1 (11%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>None (neoadjuvant therapy)</td>
<td>7 (37%)</td>
<td>4 (21%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Weeks between cycles (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two weeks</td>
<td>14 (74%)</td>
<td>8 (89%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Three weeks</td>
<td>5 (26%)</td>
<td>1 (11%)</td>
<td>4 (40%)</td>
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</tbody>
</table>

Abbreviations: n = sample size; SD = standard deviation
<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Exercise</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>mean±SD</td>
<td>mean±SD</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Baseline</td>
<td>71.7±10.9</td>
<td>67.5±11.4</td>
<td>0.42</td>
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<tr>
<td>Post AC</td>
<td>73.2±9.8</td>
<td>64.9±9.9</td>
<td>0.18</td>
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<tr>
<td>Height (cm)</td>
<td>165±6</td>
<td>166±5</td>
<td>0.51</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26.7±5.0</td>
<td>24.5±5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Post AC</td>
<td>27.2±4.4</td>
<td>23.7±4.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

| 6-month average weekly         |         |          |         |
| MVPA (minutes)                 | 153 (0, 701) | 114 (0, 619) | 0.87    |
| 7-day MVPA (minutes)*          |         |          |         |
| Pre cycle 1                    | 0 (0, 420) | 18 (0, 360) | 0.66    |
| Post cycle 1                   | 0 (0, 225) | 0 (0, 40)  | 0.66    |
| Pre cycle 2                    | 0 (0, 450) | 55 (0, 148) | 0.73    |
| Post cycle 2                   | 0 (0, 180) | 0 (0, 38)  | 0.76    |
| Pre cycle 3                    | 0 (0, 420) | 78 (0, 240) | 0.54    |
| Post cycle 3                   | 0 (0, 300) | 0 (0, 20)  | 1.0     |
| Pre cycle 4                    | 0 (0, 465) | 60 (0, 180) | 0.88    |
| Post cycle 4                   | 0 (0, 600) | 0 (0, 80)  | 0.69    |

Abbreviations: AC = doxorubicin and cyclophosphamide; cm = centimeter; kg = kilogram; m = meter; MVPA = moderate-vigorous physical activity; SD = standard deviation
Table 5.3: Resting heart rate and blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>24-hour</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
<th>Post AC</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seated resting heart rate (bpm)</td>
<td>Control</td>
<td>66±11</td>
<td>69±11</td>
<td>0.03</td>
<td></td>
<td>76±11†</td>
<td>0.09</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>74±9</td>
<td>67±10</td>
<td></td>
<td></td>
<td>79±13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated systolic blood pressure (mmHg)</td>
<td>Control</td>
<td>102±13</td>
<td>101±16</td>
<td>0.33</td>
<td>0.03*</td>
<td>94±11</td>
<td>0.30</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>109±14</td>
<td>104±12</td>
<td></td>
<td></td>
<td>99±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated diastolic blood pressure (mmHg)</td>
<td>Control</td>
<td>70±10</td>
<td>65±12</td>
<td>0.62</td>
<td>&lt;0.01*</td>
<td>60±12</td>
<td>0.22</td>
<td>&lt;0.01*</td>
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<tr>
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<td>68±10</td>
<td>61±10</td>
<td></td>
<td></td>
<td>62±8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated mean arterial blood pressure (mmHg)</td>
<td>Control</td>
<td>80±11</td>
<td>77±13</td>
<td>0.47</td>
<td>&lt;0.01*</td>
<td>71±12</td>
<td>0.56</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>81±11</td>
<td>75±9</td>
<td></td>
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<td>75±8</td>
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</tr>
<tr>
<td>Seated rate pressure product (mmHg·bpm)</td>
<td>Control</td>
<td>6728±1638</td>
<td>7024±2213</td>
<td>0.03</td>
<td></td>
<td>7181±1637</td>
<td>0.02</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>8123±1564</td>
<td>7063±1331†</td>
<td></td>
<td></td>
<td>7851±1795</td>
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</tr>
<tr>
<td>Supine heart rate (bpm)</td>
<td>Control</td>
<td>69±13</td>
<td>67±15</td>
<td>0.21</td>
<td>0.99</td>
<td>75±11†</td>
<td>0.32</td>
<td>0.03*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>71±10</td>
<td>74±13</td>
<td></td>
<td></td>
<td>74±10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine systolic blood pressure (mmHg)</td>
<td>Control</td>
<td>100±12</td>
<td>99±20</td>
<td>0.60</td>
<td>0.76</td>
<td>92±9</td>
<td>0.66</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
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<td>103±14</td>
<td>101±10</td>
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<td>94±13</td>
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<tr>
<td>Supine diastolic blood pressure (mmHg)</td>
<td>Control</td>
<td>65±13</td>
<td>61±13</td>
<td>0.48</td>
<td>0.02*</td>
<td>60±9</td>
<td>0.80</td>
<td>0.02*</td>
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<td>56±9</td>
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<td>57±8</td>
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<tr>
<td>Supine mean arterial blood pressure (mmHg)</td>
<td>Control</td>
<td>77±13</td>
<td>74±15</td>
<td>0.66</td>
<td>0.07</td>
<td>71±9</td>
<td>0.69</td>
<td>&lt;0.01*</td>
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<td></td>
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<td>75±11</td>
<td>71±9</td>
<td></td>
<td></td>
<td>69±9</td>
<td></td>
<td></td>
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<tr>
<td>Supine rate pressure product (mmHg·bpm)</td>
<td>Control</td>
<td>6992±2077</td>
<td>6640±2571</td>
<td>0.40</td>
<td>0.80</td>
<td>6966±1480</td>
<td>0.24</td>
<td>0.43</td>
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<td>Exercise</td>
<td>7358±1560</td>
<td>7539±1894</td>
<td></td>
<td></td>
<td>6955±1224</td>
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<tr>
<td>Systemic vascular resistance (dynes·sec·cm⁻²)</td>
<td>Control</td>
<td>2065±487</td>
<td>1809±555</td>
<td>0.07</td>
<td>&lt;0.01*</td>
<td>1623±209†</td>
<td>0.08</td>
<td>&lt;0.01*</td>
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<td>1903±456</td>
<td>1474±189</td>
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<td>1771±333</td>
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</tbody>
</table>

*Significant main effect for time at p≤0.05
† Significantly different from baseline with pairwise contrast at p≤0.05

Data are mean±SD.

Abbreviations: bpm = beats per minute; cm = centimeter; mmHg = millimeters of mercury; sec = second;
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>24-hour</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
<th>Post AC</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
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<td>LVEF (%)</td>
<td>Control</td>
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<td>59±5</td>
<td>0.68</td>
<td>0.10</td>
<td>58±3</td>
<td>0.58</td>
<td>0.93</td>
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<td>58±4</td>
<td>60±3</td>
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<tr>
<td>End-diastolic volume (mL)</td>
<td>Control</td>
<td>78±10</td>
<td>87±12</td>
<td>0.85</td>
<td>&lt;0.01*</td>
<td>82±15</td>
<td>0.08</td>
<td>0.77</td>
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<td>Exercise</td>
<td>80±15</td>
<td>88±12</td>
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<tr>
<td>End-systolic volume (mL)</td>
<td>Control</td>
<td>33±6</td>
<td>35±7</td>
<td>0.69</td>
<td>0.41</td>
<td>34±7</td>
<td>0.35</td>
<td>0.96</td>
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<td>34±7</td>
<td>35±4</td>
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<tr>
<td>Stroke volume (mL)</td>
<td>Control</td>
<td>45±6</td>
<td>51±8</td>
<td>0.97</td>
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<td>48±8</td>
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<td>0.72</td>
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<td>46±9</td>
<td>53±9</td>
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<tr>
<td>Cardiac output (L/min)</td>
<td>Control</td>
<td>3.0±0.4</td>
<td>3.4±0.8</td>
<td>0.35</td>
<td>&lt;0.01*</td>
<td>3.5±0.5</td>
<td>&lt;0.01*</td>
<td>&lt;0.01</td>
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<td>Exercise</td>
<td>3.3±0.6</td>
<td>3.9±0.6</td>
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<tr>
<td>Mitral E wave (m/s)</td>
<td>Control</td>
<td>0.72±0.18</td>
<td>0.87±0.12</td>
<td>0.53</td>
<td>&lt;0.01*</td>
<td>0.68±0.08</td>
<td>0.26</td>
<td>0.87</td>
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<td>0.65±0.16</td>
<td>0.83±0.12</td>
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<tr>
<td>Mitral A wave (m/s)</td>
<td>Control</td>
<td>0.60±0.16</td>
<td>0.65±0.11</td>
<td>0.75</td>
<td>0.14</td>
<td>0.62±0.12</td>
<td>0.64</td>
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<td>0.61±0.12</td>
<td>0.63±0.12</td>
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<tr>
<td>E/A ratio</td>
<td>Control</td>
<td>1.25±0.35</td>
<td>1.36±0.27</td>
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<td>1.13±0.24</td>
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<td>1.11±0.36</td>
<td>1.36±0.35</td>
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<tr>
<td>IVRT (ms)</td>
<td>Control</td>
<td>82±18</td>
<td>72±19</td>
<td>0.99</td>
<td>0.09</td>
<td>70±12</td>
<td>0.77</td>
<td>0.04*</td>
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<td>87±20</td>
<td>77±15</td>
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<td></td>
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</tr>
<tr>
<td>Mitral E wave DT (ms)</td>
<td>Control</td>
<td>230±43</td>
<td>210±32</td>
<td>0.56</td>
<td>0.10</td>
<td>216±25</td>
<td>0.27</td>
<td>&lt;0.01*</td>
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<td>248±28</td>
<td>238±41</td>
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</tr>
</tbody>
</table>

*Significant main effect for time at p≤0.05
† Significantly different from baseline with pairwise contrast at p≤0.05
Data are mean±SD.
Abbreviations: mL = milliliter; ms = millisecond; m/s = meters per second;
Table 5.5: LV dimensions and wall thicknesses and serum biomarkers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>24-hour</th>
<th>Baseline – 24 hour</th>
<th>Baseline – post AC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interaction p-value</td>
<td>Time p-value</td>
<td>Interaction p-value</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>Control</td>
<td>441±42</td>
<td>442±55</td>
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<td>418±38</td>
<td>442±48</td>
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<tr>
<td>End-systolic diameter (mm)</td>
<td>Control</td>
<td>296±37</td>
<td>283±60</td>
<td>0.71</td>
<td>0.50</td>
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<td>Exercise</td>
<td>295±52</td>
<td>292±51</td>
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<tr>
<td>Fractional shortening (%)</td>
<td>Control</td>
<td>33±8</td>
<td>36±8</td>
<td>0.82</td>
<td>0.12</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>30±8</td>
<td>34±8</td>
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</tr>
<tr>
<td>End-diastolic IVS thickness (mm)</td>
<td>Control</td>
<td>93±18</td>
<td>95±19</td>
<td>0.40</td>
<td>0.65</td>
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<td>Exercise</td>
<td>99±23</td>
<td>95±23</td>
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</tr>
<tr>
<td>End-systolic IVS thickness (mm)</td>
<td>Control</td>
<td>127±22</td>
<td>144±23</td>
<td>0.06</td>
<td>0.05*</td>
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<td>134±29</td>
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<td>End-diastolic posterior wall thickness (mm)</td>
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<td>85±11</td>
<td>87±17</td>
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<td>0.30</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>83±7</td>
<td>89±14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic posterior wall thickness (mm)</td>
<td>Control</td>
<td>130±17</td>
<td>130±19</td>
<td>0.13</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>122±9</td>
<td>130±16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>Control</td>
<td>0.39±0.07</td>
<td>0.40±0.10</td>
<td>0.88</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>0.40±0.04</td>
<td>0.40±0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic wall stress (x10³ dyn·cm⁻²)</td>
<td>Control</td>
<td>55±18</td>
<td>51±13</td>
<td>0.32</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>63±16</td>
<td>55±16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>Control</td>
<td>127±5</td>
<td>132±27</td>
<td>0.17</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>120±20</td>
<td>134±34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>Control</td>
<td>59±36</td>
<td>290±166†</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>40±21</td>
<td>184±56‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin T (pg/mL)</td>
<td>Control</td>
<td>0.8±1.5</td>
<td>1.3±2.4</td>
<td>0.40</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>1.7±2.3</td>
<td>2.9±3.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant main effect for time at p≤0.05
† Significantly different from baseline with pairwise contrast at p≤0.05
‡ Significantly different from control group at same time point at p≤0.05

Data are mean±SD.

Abbreviations: cm = centimeter; dyn = dyne; IVS = interventricular septum; mL = milliliter; mm = millimeter; pg = picogram;
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>24-hour</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
<th>Post AC</th>
<th>Interaction p-value</th>
<th>Time p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>Control</td>
<td>-19.3±2.0</td>
<td>-21.4±1.5</td>
<td>0.79</td>
<td>&lt;0.01*</td>
<td>-20.4±1.7</td>
<td>0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic LSR (sec⁻¹)</td>
<td>Exercise</td>
<td>-19.4±2.2</td>
<td>-21.4±2.1</td>
<td>0.07</td>
<td>&lt;0.01*</td>
<td>-19.3±0.5</td>
<td>0.59</td>
<td>0.02*</td>
</tr>
<tr>
<td>Diastolic LSR (sec⁻¹)</td>
<td>Control</td>
<td>-1.03±0.09</td>
<td>-1.06±0.09</td>
<td>0.99</td>
<td>&lt;0.01*</td>
<td>1.43±0.32</td>
<td>0.95</td>
<td>0.05*</td>
</tr>
<tr>
<td>GRS (%)</td>
<td>Exercise</td>
<td>-1.01±0.16</td>
<td>-1.13±0.20</td>
<td>0.75</td>
<td>0.18</td>
<td>1.32±0.34</td>
<td>0.59</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic RSR (sec⁻¹)</td>
<td>Control</td>
<td>1.27±0.29</td>
<td>1.42±0.30</td>
<td>0.99</td>
<td>&lt;0.01*</td>
<td>1.43±0.32</td>
<td>0.95</td>
<td>0.05*</td>
</tr>
<tr>
<td>Diastolic RSR (sec⁻¹)</td>
<td>Exercise</td>
<td>1.19±0.43</td>
<td>1.37±0.40</td>
<td>0.07</td>
<td>0.02</td>
<td>1.17±0.21</td>
<td>0.59</td>
<td>0.02*</td>
</tr>
<tr>
<td>GRS (%)</td>
<td>Control</td>
<td>40.8±14.4</td>
<td>46.9±13.2</td>
<td>0.75</td>
<td>0.18</td>
<td>44.0±10.5</td>
<td>0.59</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic RSR (sec⁻¹)</td>
<td>Exercise</td>
<td>39.0±11.0</td>
<td>42.4±9.1</td>
<td>0.02</td>
<td>0.02</td>
<td>2.38±0.44</td>
<td>0.40</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic RSR (sec⁻¹)</td>
<td>Control</td>
<td>2.24±0.63</td>
<td>2.35±0.52</td>
<td>0.43</td>
<td>0.05*</td>
<td>2.36±0.51</td>
<td>0.93</td>
<td>0.33</td>
</tr>
<tr>
<td>GCS (%)</td>
<td>Exercise</td>
<td>1.94±0.55</td>
<td>2.95±0.85</td>
<td>0.43</td>
<td>0.05*</td>
<td>2.58±0.88</td>
<td>0.93</td>
<td>0.33</td>
</tr>
<tr>
<td>Systolic CSR (sec⁻¹)</td>
<td>Control</td>
<td>-2.25±0.87</td>
<td>-2.58±0.88</td>
<td>0.19</td>
<td>0.41</td>
<td>2.36±0.51</td>
<td>0.93</td>
<td>0.33</td>
</tr>
<tr>
<td>Diastolic CSR (sec⁻¹)</td>
<td>Exercise</td>
<td>-2.29±0.62</td>
<td>-3.03±0.84</td>
<td>0.95</td>
<td>0.57</td>
<td>-1.03±0.31</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>Apical rotation (°)</td>
<td>Control</td>
<td>15.6±5.9</td>
<td>19.9±3.5</td>
<td>0.41</td>
<td>0.05*</td>
<td>12.0±0.42</td>
<td>0.68</td>
<td>0.62</td>
</tr>
<tr>
<td>Twisting velocity (°·sec⁻¹)</td>
<td>Control</td>
<td>10.6±4.1</td>
<td>12.3±4.4</td>
<td>0.01</td>
<td>0.49</td>
<td>124±27</td>
<td>124±27</td>
<td>0.93</td>
</tr>
<tr>
<td>Untwisting velocity (°·sec⁻¹)</td>
<td>Exercise</td>
<td>8.5±4.6</td>
<td>11.0±3.8</td>
<td>0.01</td>
<td>0.49</td>
<td>124±27</td>
<td>124±27</td>
<td>0.93</td>
</tr>
<tr>
<td>Basal rotation (°)</td>
<td>Control</td>
<td>-6.0±2.4</td>
<td>-8.5±2.1</td>
<td>0.01</td>
<td>0.37</td>
<td>-8.0±2.9</td>
<td>0.03</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>-9.0±5.9</td>
<td>-8.3±3.5</td>
<td>0.01</td>
<td>0.37</td>
<td>-8.0±2.9</td>
<td>0.03</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*Significant main effect for time at p ≤ 0.05
† Significantly different from baseline with pairwise contrast at p ≤ 0.05
Abbreviations: GLS = global longitudinal strain; LSR = global longitudinal strain rate; GRS = global radial strain; RSR = global radial strain rate; GCS, global circumferential strain; CSR = global circumferential strain rate;
Figure 5.1: Participant flow through study

**Ineligible n=28**
- not willing/able to do pre AC baseline n=8
- enrollment in other study n=7
- no AC chemotherapy n=3
- med hx n=3
- current smoker n=3
- BMI> 35kg/m² n=2
- stage IV cancer n=1
- mobility issues n=1

**Declined n=19**
- lives too far away n=5
- too many appointments n=5
- family obligations n=3
- too overwhelmed n=3
- too busy n=2
- no reason given n=1

Referrals
n= 78

Screened
n= 74

Enrolled
n= 20

Randomized to control
n=9

Completed baseline assessment
n=9

Completed 24 hour assessment
n=9

Completed post AC assessment
n=9

Randomized to exercise
n=11

Completed baseline assessment
n=11

Completed 24 hour assessment
n=10

Completed post AC assessment
n=9

No response
n= 4

Ineligible n=28

Declined n=19

Referrals
n= 78

Screened
n= 74

Enrolled
n= 20

Randomized to control
n=9

Completed baseline assessment
n=9

Completed 24 hour assessment
n=9

Completed post AC assessment
n=9

Randomized to exercise
n=11

Completed baseline assessment
n=11

Completed 24 hour assessment
n=10

Completed post AC assessment
n=9

No response
n= 4
Figure 5.2: Mean change from baseline to 24 hours for both groups in end-diastolic volume, cardiac output, stroke volume, heart rate, mean arterial pressure, and NT-proBNP
Figure 5.3: Mean change from baseline to post AC treatment for both groups in end-diastolic volume, cardiac output, stroke volume, heart rate, mean arterial pressure and cardiac troponin T.
Chapter 6 - Conclusion

The theme of this dissertation was to investigate the potential for exercise cardio-protection from anthracycline-containing chemotherapy in human breast cancer patients. Anthracyclines are a class of chemotherapeutic agents commonly used to treat numerous cancer types, including breast cancer. Anthracyclines are among the most effective, but also most toxic treatments ever developed for breast cancer and are associated with dose-limiting cardiotoxicity.\textsuperscript{29} Strategies to reduce this potential side effect, including exercise, are an area of active investigation. Despite overwhelming positive evidence for exercise protection from anthracycline-related myocardial damage at the histological, biochemical and functional levels from preclinical studies, there has been very little investigation into this effect in humans receiving anthracycline treatment. There are requirements for translation of these findings from preclinical to clinical research due to the differences in doing research in animals versus humans. As exercise is now universally recognized as an important aspect of cancer care to improve physical function and quality of life, thanks to numerous high quality RCTs,\textsuperscript{76} this field of research is now challenged with establishing the efficacy of exercise for specific common side effects of treatment and effectiveness of exercise in real-world settings outside the confines of a stringent RCT.\textsuperscript{318}

6.1 Adherence and effectiveness of the recommended exercise prescription during anthracycline chemotherapy for breast cancer (Chapter 3)

The studies in Chapter 3 aimed to investigate the adherence and effectiveness of an exercise program for women receiving adjuvant anthracycline-containing chemotherapy. The exercise program used an exercise prescription following the recommendations for cancer survivors, and the study was a single-arm design in collaboration with a local cancer
centre. There were four adherence outcomes examined with specific hypothesized outcomes, including mean attendance $\geq 70\%$, adherence to intensity and duration prescriptions $\geq 80\%$, and retention of participants $\geq 80\%$. The findings of the study were that the hypothesis regarding adherence to duration was fulfilled, but the others were not. Therefore, the conclusion was that adherence to an exercise program based on current exercise guidelines and the recommended prescription for cancer survivors, was a challenge for women with breast cancer during anthracycline treatment.

This study provides the most comprehensive description of exercise adherence during chemotherapy for breast cancer available. To date, the majority of RCTs examining the efficacy of an exercise intervention during chemotherapy for breast cancer treatment provide limited information on the ability of participants to adhere to the exercise prescription proposed. Another significant contribution of this study is the description of the reasons for non-attendance, non-adherence to the exercise prescription, and withdrawal from the program. A consistent theme was that treatment symptoms were the primary reason for lower adherence and withdrawal after enrolling. Other important issues were distance from home to the gym or having transportation issues to get to the gym, and work interference with gym hours. Clearly these are all inevitable issues to some extent in implementing a supervised exercise program in humans that will affect adherence, and thereby efficacy of exercise on any outcomes. These issues may also be exacerbated during chemotherapy. However the current study’s findings also highlight potential ways to improve exercise adherence during chemotherapy, such as a more realistic or flexible exercise prescription, flexible gym hours or a combined supervised and home-based exercise program. These findings regarding adherence to exercise during chemotherapy treatment highlights a critical
difference between exercise research in animals versus humans. In the preclinical cardio-protection studies (all in rodents), 100% adherence to the often-strenuous exercise prescription is assumed. Whereas, based on the findings of this study, in translating these findings to humans, a certain amount (and wide variance) of adherence must be assumed, and accounted for in the study design and analysis.

In the sub-study in Chapter 3, as hypothesized, higher adherence to the exercise prescription did attenuate the decline in VO$_2$peak observed with adjuvant chemotherapy. Within the subset of women who completed a maximal exercise test before and after their treatment, the mean decline in VO$_2$peak was more than 50% less in those with $\geq$45% adherence to the combination of prescribed frequency, intensity, and duration relative to those who adhered <45% to the combined prescription. Although limited by the small sample size and arbitrary division of adherence based on the median, this finding contributes valuable insights for exercise interventions in breast cancer populations as the few studies that have reported change in maximal exercise capacity with a supervised intervention during chemotherapy for breast cancer have reported only the mean and standard deviation for each study arm, which does not provide any information on the effect of adherence.

The fact that higher adherence to the exercise prescription attenuated the decline in VO$_2$peak reinforces the importance of adherence. But the fact that a beneficial effect of exercise on VO$_2$peak was still achieved despite the issues with adherence to the prescription is a positive and generalizable finding to most breast cancer patients during chemotherapy treatment. While future RCTs comparing effects among different exercise prescriptions are warranted, it may be more relevant to a real world setting to examine naturally occurring levels of adherence to a particular exercise prescription.
The two main findings from this study combined suggest the need for establishment of a minimum effective dose, or the smallest dose of exercise during chemotherapy treatment that will provide a desired outcome, and the need to develop strategies to facilitate adherence to supervised exercise during chemotherapy treatment. In fact, establishment of this dose and communication of this to patients and clinicians may improve adherence to that dose, in research studies, and more importantly, exercise programs in real-world settings.

6.2 Responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy for breast cancer (Chapter 4)

The majority of preclinical studies demonstrating exercise cardio-protection from anthracyclines did so via invasive means and sacrificed the animals. Selection of a noninvasive sensitive measure of cardiac function that is also clinically relevant is a requirement for translation of these findings to humans. Alterations in echocardiography-derived parameters described as myocardial mechanics precede significant reductions in LVEF in individuals receiving cancer therapy, and thus may be novel and sensitive markers of cancer treatment-related cardiotoxicity. A recent systematic review identified GLS measured via 2DSTE as the best myocardial mechanics parameter for this purpose.

The work described in Chapter 4 aimed to investigate the responsiveness of myocardial mechanics to exercise training during anthracycline chemotherapy for breast cancer. Responsiveness to exercise training was assessed by the percent change in myocardial mechanics from before to after anthracycline chemotherapy concurrent with the exercise program examined in Chapter 3. A recent expert consensus indicated that a threshold for a clinically meaningful change in GLS with cancer treatment was 8%, so it was hypothesized that the change would be less than 8% with enrollment in the exercise program.
The mean change in GLS in the 22 women who completed both echocardiograms was less than 3% and was statistically less than the 8% clinically relevant change. Overall GLS was a reliable and responsive outcome measure and appears to be a good choice for assessing the effect of exercise on myocardial mechanics.

The hypothesized dose-response relationship between exercise and GLS was not observed. There was no relationship between percent change in GLS and five different measures of exercise dose, including objective measures of adherence to supervised exercise, and self-reported exercise. However interpretation of the results of this analysis should be cautious given the inherent inter-individual variability in response to exercise and the small sample size. Adherence to the exercise intervention for the sub-group reported in Chapter 4 was similar to that reported for the larger group included in Chapter 3 and was quite variable. Interpreted another way these results could indicate that even a dose of exercise that is lower than current recommended guidelines is beneficial for preventing deterioration in GLS.

To date, only two studies have measured change in cardiac function with exercise training in breast cancer patients, and the assessment of cardiac function was limited to LVEF only. LVEF is the primary parameter of cardiac function used in oncology to monitor treatment-related changes in cardiac function. One study showed no change in LVEF with anthracycline treatment in either arm of the RCT,\textsuperscript{112} while the other single-arm study during trastuzumab treatment showed that exercise training did not prevent deterioration of LVEF.\textsuperscript{116} The latter study reported a similar level of adherence to a similar aerobic exercise prescription relative to the current study, although this study did not measure GLS. These findings combined with those of Chapter 4 suggest that perhaps the role of exercise is different in anthracycline and trastuzumab-related cardiotoxicity. The fact that there was no
change in LVEF in this study is encouraging as some of the observational studies of anthracycline treatment in breast cancer report a statistically significant decrease in LVEF concurrent to a decrease in GLS with similar doses of anthracycline treatment, but other studies report no change.  

The work reported in Chapter 4 is the first study to report the effect of exercise on cardiac function in cancer patients using measures that are sensitive to early changes in cardiac function with anthracycline treatment. This study provided proof-of-principal of exercise training cardio-protection from anthracycline treatment and established a potential reliable and sensitive outcome measure to measure this effect noninvasively in humans. This represents a significant contribution to the field of cancer and exercise in light of the severity of cardiotoxicity and impact of cardiotoxicity on cancer survivor health.  

Ultimately interpretation of the findings in this study is limited by the lack of a control group. A single-arm design was chosen for the study in Chapter 4 based on several key considerations. A RCT design could be less optimal due to risk for poor compliance to random group assignment for two reasons. Firstly, participants recruited to an exercise trial have expressed interest in exercising, so even if assigned to the control group, they may be likely to exercise on their own. Secondly, as experienced in the current study, some individuals who intend to exercise throughout treatment experience severe side effects that ultimately limit their exercise participation. A RCT would require a much larger sample size to account for non-adherence to the intervention. Furthermore, prior to this study it was not known whether GLS would be a responsive outcome measure for exercise training in breast cancer patients. Therefore, it seemed prudent to examine this key aspect of the proposed outcome measures prior to engaging in an RCT. As summarized in Tables 2.3 and 2.4,
numerous studies have reported consistent and statistically significant deterioration in GLS, which allowed for comparison with the current study’s results. However the prevention of anthracycline-related deterioration in GLS with exercise training reported in the work outlined in Chapter 4 will need to be confirmed via a RCT, the gold standard study design for determining efficacy. Based on the findings in this study, other explanatory measurements that would be helpful in future studies to uncover mechanisms for the relationship between exercise training, anthracyclines, and cardiac function include more comprehensive measures of diastolic function, vascular function and structure, and blood volume and red cell mass.

6.3 The effects of a single exercise bout 24 hours prior to anthracycline chemotherapy for breast cancer on myocardial mechanics and cardiac biomarkers (Chapter 5)

The study described in Chapter 5 used GLS as the primary outcome to test the effect of acute exercise timed prior to receipt of adjuvant chemotherapy on markers of cardiotoxicity. Using an RCT design, the hypothesis was that performing a vigorous intensity aerobic exercise bout 24 hours prior to each treatment would reduce markers of cardiotoxicity relative to the control group who did not perform vigorous exercise acutely and chronically. The acute effect was defined as the response at 24 hours after the first treatment, while the chronic effect was defined as the response 7-14 days after the last treatment. In addition to GLS as the primary outcome, secondary outcomes were additional myocardial mechanics parameters and the serum biomarkers of myocardial injury, NT-proBNP and cTnT. Other measures including blood pressure and cardiac function were collected as explanatory variables.

Acutely, exercise attenuated the NT-proBNP response. There were no relevant group differences in myocardial mechanics or cTnT. There was a significant increase in GLS,
systolic and early diastolic LSR, twist, and apical rotation at 24 hours after the first treatment, with no differences between groups. This myocardial mechanics response to chemotherapy was in the opposite direction to all previous studies summarized in Tables 2.4 and 2.5. The disparity likely lies in the timing of the measurement; to the author’s knowledge, no previous studies have measured myocardial mechanics acutely after the first treatment in adults. The changes in loading conditions that occurred concurrently at this time point are in line with the changes in mechanics previously reported in non-cancer populations however. GLS is known to increase with an increase in preload\(^3\)\(^5\)\(^6\) (e.g. such as with the increase in end diastolic volume in the current study). The cause for the increase in end diastolic volume is however unknown, but could be related to blood volume. Peak systolic twist is not affected by preload, but is known to increase with vasodilation\(^3\)\(^6\)\(^8\) (e.g. such as with the decreased mean arterial blood pressure in the current study). The cause of the reduced blood pressure is also unknown but may be related to the blood volume changes as well.

With the chronic response to exercise performed 24 hours prior to every AC treatment, there were no relevant differences between groups in myocardial mechanics or cardiac biomarkers. There was no change in the primary outcome, GLS, from baseline in either group, but systolic and early diastolic LSR had improved. Again these findings do not match those previously reported for similar anthracycline-treated populations, even with similar timing of assessment relative to treatment.\(^4\)\(^6\) As mentioned, myocardial mechanics parameters are load-dependent variables,\(^3\)\(^5\)\(^6\)\(^8\) but the majority of literature around blood pressure and mechanics involves hypertension or an acute vasodilatory intervention, and little is known about the effect of sustained low blood pressure. One striking difference between the current study sample and those in previous observational studies reporting
deterioration in GLS with anthracycline treatment for breast cancer is that the baseline blood pressure was much lower in the current study and also significantly decreased from baseline to post AC. It should be noted that several previous studies fail to report baseline blood pressure and even less report the change in blood pressure over treatment, making the interpretation of these findings in the context of previously reported changes in myocardial mechanics difficult. Future research is needed to more clearly understand the relationship between GLS, low blood pressure, and reductions in blood pressure, especially in the context of anthracycline treatment. Another potential reason for the lack of change in GLS in the control group of this study relative to all previous studies measuring GLS during anthracycline treatment is selection bias of participants enrolled in an exercise study. The participants in the control group were physically active at baseline, and likely continued to perform more exercise during the study period than typical for participants in an observational study during anthracycline treatment. This is in line with the finding in Chapter 4 that a small amount of exercise appears to be beneficial for GLS. Together the findings from the two time points of this study indicate that the acute myocardial response at 24 hours after the first chemotherapy appears to be different than the response at completion of treatment. This result should be considered in planning outcome measure timing in future studies.

A number of hemodynamic changes also occurred acutely, with no differences between groups. End-diastolic volume, stroke volume and cardiac output increased, indicating a potential blood volume increase. Paradoxically, a decrease in diastolic and mean arterial blood pressure also occurred. A reduction in sympathetic nervous control is offered as potential explanation for the lack of increase in mean arterial pressure, but this requires
further investigation. Similar to Chapter 4, these findings indicate the need for assessment of both central and peripheral vascular changes occurring with chemotherapy treatment. These findings provide new knowledge regarding an acute cardiovascular response to the first AC treatment and offer insight into potential mechanisms for future investigation.

For the chronic effect on other cardiovascular measures, while there were no overall changes in LV volumes, cardiac output and heart rate were significantly increased in the control group, and there was no change in the exercise group. This also points to further differences in acute and chronic hemodynamic responses to chemotherapy, as the greater increase in cardiac output that occurred at 24 hours in both groups was attributed to potentially renal-mediated volumetric changes rather than heart rate. Additionally, LV structural differences were apparent between groups. The exercise group had increased end-systolic posterior wall thickness with no change in LV diameter, while the control group had an increase in end-systolic diameter and no change in wall thicknesses. These changes combined with the overall decrease in systolic blood pressure, resulted in no change in estimated end-systolic wall stress for either group.

Overall, whether the difference in the acute NT-proBNP response is clinically relevant is difficult to discern. While it is a known marker of myocardial injury, there was no difference between groups in acute response of other outcomes. One hypothesis was that the exercise bout sensitized the myocardium to stretch such that when the exercise group experienced the chemotherapy-related hemodynamic change, it was not as great an insult. Additionally, there were differences in cardiac output and LV structure at post AC that could potentially be explained by the differential NT-proBNP response if it occurred consistently after each treatment. However, based on the design of this study, the acute response was
only measured after the first AC treatment, so whether this is a plausible mechanism is unknown.

The changes in other explanatory blood pressure and cardiac function variables collected were not expected, but contribute new knowledge regarding the cardiovascular response to AC treatment. The significant changes in blood pressure, cardiac function, and myocardial mechanics that occurred with no differences between groups provide new information on acute and chronic hemodynamic and cardiac responses to AC treatment.

There was also an exploratory hypothesis regarding the beneficial effect of the exercise bout on patient-reported side effects, measured using a valid and reliable tool to measure side effects of chemotherapy. There was no effect of exercise on physical or psychological patient-reported symptoms for any of the treatments. This finding indicates that while the exercise bout did not make symptoms better, it also did not make symptoms worse. In the eighth edition of the ACSM's Guidelines for Exercise Testing and Prescription published in 2010, the gold standard reference for exercise guidelines, there was a recommendation against “exercise within 24 hours” of chemotherapy treatment, without a reference provided for this statement. It is unclear whether this was intended to refer to 24 hours before, 24 hours after, or both, but this statement was not included in the ninth edition published in 2014. The findings reported in Chapter 5 suggest that exercise 24 hours prior to anthracycline treatment does not appear to have a detrimental effect on cardiac function or patient-reported symptoms. Further research that would be useful for continuing to update the exercise guidelines for individuals receiving chemotherapy treatment include investigation of the effect of exercise timing around chemotherapy dose, namely exercise performed at other intervals less than 24 hours before, including immediately before
treatment administration, as well as exercise after an anthracycline treatment. Exploration of additional outcomes that could be key to definitively determining safety such as acute changes in ECG, blood pressure, and inflammatory and immune system markers is also required.

Strengths of this study include translation of a novel preclinical intervention to human breast cancer patients via a RCT design with high fidelity to research protocol. Limitations of this study include the small sample size, lack of more reliable assessment of blood pressure and a measure of sympathetic nervous system activation, and non-generalizability of results to breast cancer patients with comorbid conditions.

In terms of the clinical applicability of exercise timing relative to chemotherapy treatment, a single exercise session format may be an ideal option for individuals who live far from the exercise facility and for individuals whose treatment symptoms reduce their ability to consistently exercise, as the day before the next treatment is likely to be when they would feel their best. Potential participants who were screened for inclusion in the study in Chapter 4 prior to starting their treatment expressed anxiety about committing to a three times per week exercise program during treatment, as they did not know whether they would feel well enough to attend regularly. This was especially the case for those who were not already regularly exercising. If the efficacy of a single exercise session every two to three weeks is demonstrated for key side effects of cancer treatment, such as cardiotoxicity, this type of exercise programming in a clinical setting may be more palatable and may alleviate some of the concerns of these individuals.
6.4 Overall

6.4.1 Strengths and limitations

An overall strength of this dissertation is that the participants in all research chapters were fairly homogenous in disease and treatment characteristics. All participants were scheduled to receive an AC chemotherapy protocol, which is typically administered as four cycles of 60 mg/m$^2$ of doxorubicin and 600 mg/m$^2$ of cyclophosphamide, each three weeks apart, or in a dose dense schedule with a granulocyte colony-stimulating factor, two weeks apart. The majority also received four cycles of 175 mg/m$^2$ of paclitaxel or 12 cycles of 80 mg/m$^2$ of paclitaxel before or after the AC. This treatment protocol is by far the most common at the BCCA for treatment of early stage breast cancer, making the findings of these studies generalizable in that respect. The outcome assessment time points were also homogenous between studies such that the intervention period for all three studies was during AC treatment only.

The study findings are less generalizable with respect to the exclusion criteria applied in the two cardiac function studies, and the low recruitment rate. Physiology is inherently variable between and within individuals, and for this reason, it is prudent for a pilot proof-of-principle study with physiological outcomes to attempt to include a homogeneous sample. The exclusion criteria selected for Chapters 4 and 5 were variables that are known risk factors for cardiotoxicity, or that may potentially be causes for abnormal cardiac function at baseline. Increasing age is a known risk factor for cardiotoxicity, but because a definitive age for risk would be difficult to set, no age cap was used in either study. In Chapter 5, the randomization was stratified by age above or below 50, which is the common mean age for
exercise studies, and would also be an easy method to help equalize groups with respect to menopausal status, another confounding variable for cardiac function.

Recruitment was the biggest difficulty in completion of the studies in Chapter 4 and 5. Recruitment rates were 57% and 26% for Chapters 4 and 5 due to stringent eligibility criteria and lack of willingness to participate. The largest barrier to recruitment was the requirement for the baseline study visit to take place prior to the first AC treatment. This requirement was considered imperative to the study designs because myocardial damage can occur even with the first treatment. A number of individuals were referred to both studies either after completion of their first treatment or a very short time in advance of their first treatment, and were unwilling to attend the baseline study visit, or the study team was unable to coordinate all required parties within the short window prior to their first AC treatment. The latter was not very common, and participants were enrolled in both studies when referred as little as 30 hours in advance of their treatment. Understandably, a number of participants declined participation because they were too overwhelmed and/or too busy with the number of medical appointments they had between receiving their breast cancer diagnosis and starting chemotherapy treatment, and did not want to add study visits. Additionally, many women were working full time at the time of their diagnosis and even if they were planning to take time off during chemotherapy treatment, were working full days until the day of their first treatment. Ultimately, these are all justifiable reasons for a low recruitment rate and may be unavoidable given the population and sensitive timing of this type of study. All together approximately 200 women were referred for participation in the studies included in this dissertation, the vast majority of which were directly referred by their medical oncologist,
which speaks to the recognition of the value of exercise programming and potentially also the specific study objectives for their current and future patients.

The studies in Chapter 4 and 5 that were focused on cardiac function are limited by short follow-up to completion of anthracycline treatment. Traditionally three distinct types of cardiotoxicity have been recognized based on small retrospective studies. Both studies are limited to detection of acute cardiotoxicity, which occurs during or within one week of completion of treatment. \(^{48}\) Whereas early-onset cardiotoxicity occurs within a year of treatment completion, and is the most common and clinically relevant form; late-onset cardiotoxicity can occur years or even decades after the end of treatment. \(^{48}\) Recently, the first prospective study to evaluate the incidence and timing of occurrence of cardiotoxicity in adults treated with anthracyclines reported that 98% of cases occurred within the first year after treatment with a median time to onset of 3.5 months after treatment. \(^{48}\) Therefore in order to determine the clinical relevance of exercise in terms of prevention of cardiotoxicity, future studies should include a one-year follow-up, even if exercise only took place during active treatment. Furthermore, the studies in Chapter 4 and 5 are limited in that they only measure surrogate markers of cardiotoxicity, which may not translate into improved clinical outcomes. \(^{174}\)

6.4.2 Significance

Cardio-oncology or onco-cardiology is a relatively new clinical discipline that focuses on the intersection of oncologic and cardiac disease, the two leading causes of death in North America. \(^{197}\) The need to understand the interrelationship between cancer and cardiac disease is not new, rather this need is newly recognized, owing to the increasing survival rates associated with cancer therapy in recent decades. \(^{197,318}\) Exercise is an
accessible, non-pharmacologic treatment with potential to alter development of cardiotoxicity via a number of molecular mechanisms that act in opposition to known cardiotoxic mechanisms.  Although the role of exercise in cancer care is not new, the potential role of exercise to alter the clinical course of cardiotoxicity is an emerging area of interest. The timeliness of this area of research is indicated by the fact that the majority of publications cited in this dissertation on both exercise cardio-protection and myocardial mechanics have been published in the last five years. Finally, nearly all of the current publications on myocardial mechanics in cancer patients are observational studies. The use of myocardial mechanics to assess the effect of a cardio-protection intervention is a novel application of these outcomes, and Chapters 4 and 5 in this dissertation are the first to report on their use to measure the effect of exercise in a cancer population.

6.4.3 Conclusion

This dissertation investigated the potential of exercise cardio-protection from anthracycline-containing chemotherapy in human breast cancer patients. The primary findings are as follows: 1) attendance for a three times per week supervised exercise training program following the guidelines for cancer survivors during anthracycline treatment varies widely, and is on average lower than previously reported values for RCTs implemented in more optimal settings; 2) more comprehensive measures of adherence to each element of the exercise prescription revealed that participants were better able to meet exercise duration targets than exercise intensity targets, which may help to inform modification of future exercise prescriptions used in research studies and clinical exercise programs; 3) the primary reason for withdrawal, missed supervised sessions and non-adherence to prescribed exercise intensity and/or duration during chemotherapy was treatment symptoms; 3) despite low and
variable adherence, exercise training appears to prevent anthracycline-related deterioration in GLS and systolic LSR, which are consistent and strong predictors of cardiotoxicity; 4) GLS has excellent intra-observer reliability and is consistently measurable in breast cancer patients, and is stronger in these qualities than other parameters of myocardial mechanics, making it an excellent choice for an outcome measure; 5) performance of an acute vigorous intensity aerobic exercise bout 24 hours prior to anthracycline treatment attenuates the NT-proBNP myocardial injury marker response to the first treatment, and alters chronic hemodynamic regulation and cardiac structure after completion of treatment, but has no effect on myocardial mechanics or patient-reported treatment symptoms; 6) regardless of exercise exposure, the first AC treatment resulted in an increase in end-diastolic volume and a paradoxical decrease in mean arterial pressure, which are the likely causes of an increase in GLS and twist at 24 hours post treatment; 7) regardless of exercise exposure, 7-14 days after the last AC treatment, LV volumes are not different than before AC treatment, but mean arterial pressure is decreased. Overall this dissertation provides proof-of-principal for exercise cardio-protection, and contributes valuable information to the literature regarding exercise prescription and outcome measure assessment for future exercise cardio-protection studies during anthracycline treatment for breast cancer.
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