Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT

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Abstract

Background: Preclinical studies have reported that a single treadmill session performed 24 h prior to doxorubicin provides cardio-protection. We aimed to characterize the acute change in cardiac function following an initial doxorubicin treatment in humans and determine whether an exercise session performed 24 h prior to treatment changes this response. Methods: Breast cancer patients were randomized to either 30 minutes of vigorous-intensity exercise 24 h prior to the first doxorubicin treatment (n=13), or no vigorous exercise for 72 h prior to treatment (control, n=11). Echocardiographically-derived left ventricular volumes, longitudinal strain, twist, E/A ratio, and circulating NT-proBNP, a marker of later cardiotoxicity, were measured before and 24-48 h after the treatment. Results: Following treatment in the control group, NT-proBNP, end-diastolic and stroke volumes, cardiac output, E/A ratio, strain, diastolic strain rate, twist, and untwist velocity significantly increased (all $p \leq 0.01$). Whereas systemic vascular resistance ($p<0.01$) decreased, and ejection fraction ($p=0.02$) and systolic strain rate ($p<0.01$) increased in the exercise group only. Relative to control, the exercise group had a significantly lower NT-proBNP ($p<0.01$) and a 46% risk reduction of exceeding the cut-point used to exclude acute heart failure. Conclusion: The first doxorubicin treatment is associated with acutely increased NT-proBNP, echocardiographic parameters of myocardial relaxation, left ventricular volume overload, and changes in longitudinal strain and twist opposite in direction to documented longer-term changes. An exercise session performed 24 h prior to treatment attenuated NT-proBNP release and increased systolic function. Future investigations should verify these findings in a larger cohort and across multiple courses of doxorubicin.

1 Introduction

The anthracycline chemotherapy agents doxorubicin and epirubicin are a cornerstone for treatment of early and advanced breast cancer, but are unfortunately associated with a dose-dependent cardiotoxicity [1]. Anthracycline-related cardiotoxicity is theorized to begin with an acute subclinical cardiac injury [1], as evidenced by changes in endomyocardial biopsy morphologic grade, elevation of circulating cardiac troponins or natriuretic peptides, and impairments in left ventricular (LV) longitudinal strain occurring early in treatment [2-4]. When this acute injury occurs repeatedly, as with multiple treatments, or in the presence of other risk factors (e.g. advanced age, diabetes), it may result in adverse LV remodeling [1]. Despite this evidence for cardiac injury early in the course of treatment, acute changes in cardiac function following the first anthracycline treatment have not been evaluated.

Cardio-protective strategies that mitigate myocardial damage early during treatment may aid in preventing long-term cardiotoxicity. Oxidative stress and the related apoptosis of cardiomyocyte mitochondria are primary mechanisms of anthracycline-induced cardiotoxicity [5]. Due to its role in improving myocardial tolerance to oxidative stress, exercise is a potentially attractive non-pharmacological strategy for the prevention of anthracycline-related myocardial injury [5]. Previously, a 60-minute moderate-to-vigorous intensity bout of aerobic exercise has been shown to protect the myocardium in preclinical models of acute myocardial insult, and has recently been shown to either completely prevent or significantly attenuate anthracycline-related systolic and diastolic dysfunction, cardiomyocyte mitochondrial dysfunction and apoptosis in rodents [5,6]. Whether these results can be translated into humans receiving anthracycline treatment is not known.

The aims of this study are to characterize the acute changes in cardiac function following the first doxorubicin treatment; and to determine whether a single exercise session performed 24 h prior to the treatment modifies cardiac function in women with early stage breast cancer. It was hypothesized that the exercise session would attenuate acute changes in circulating and echocardiographic markers of cardiotoxicity.

2 Methods

2.1 Design and ethical approval

This study was a two-arm proof-of-concept randomized controlled trial, where breast cancer patients were randomly allocated to perform either a single supervised exercise session or no exercise prior to the first chemotherapy treatment. A permutated block design, with random block sizes of four and six, and stratification by age ≥50/<50 years was used with a 1:1 allocation ratio generated by a spreadsheet random function by someone not involved in the study, and implemented with sequentially numbered envelops. The first author performed study enrollment and participant assignment. This study complies with the Declaration of Helsinki and was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants provided written informed consent.

2.2 Participants

Participants were recruited through oncologist referral and posters. Women aged 18+ years with stage I - III breast cancer that were scheduled to receive neoadjuvant or adjuvant doxorubicin-containing chemotherapy were eligible. Participants had to agree to accept random allocation to either group, be able to complete the baseline assessment prior to their first doxorubicin treatment, and speak English, Cantonese, or Mandarin. Exclusion criteria included concurrent enrollment in an exercise training or pharmacological cardio-protection trial, current smoker, orthopedic limitations to exercise, a body mass index (BMI) >35 kg/m^2, pre-existing

cardiovascular disease, or previous receipt of anthracyclines, trastuzumab, or thoracic radiotherapy. Participants reporting a history of hypertension, diabetes, or lung disease were included if they reported that the condition was well controlled by medication over the previous year. The Physical Activity Readiness Questionnaire (Canadian Society of Exercise Physiology) was also administered for screening.

2.3 Intervention

The exercise group (EX) performed a single bout of supervised treadmill exercise ending approximately 24 h prior to the participant's treatment time. The session consisted of a 10-minute warm-up, 30 minutes at 70% of age-predicted heart rate (HR) reserve ([(206–0.88 * age)–resting HR] * 0.7 + resting HR), which corresponds to a vigorous intensity, and a 5-minute cool-down. Resting HR used in the calculation was measured immediately prior to the exercise session following five minutes of quiet, seated rest.

Participants in both EX and the control group (CON) were asked to abstain from vigorous intensity exercise (described as "rapid heart beating, sweating a fair amount, and breathing hard.") for 72 h prior to, and 48 h after the treatment. All participants were free to perform light or moderate intensity exercise at any time in agreement with current guidelines for cancer survivors.[7] Prior to exercise sessions and assessments, participants were asked to refrain from caffeine, alcohol and non-vital drugs for 3 h, and food for at least 1 h.

2.4 Outcome measures

All measures were performed within a research setting 0-14 days before the first doxorubicin treatment (baseline) and 24-48 h after the scheduled start time of each participant's first doxorubicin treatment (acute follow-up).

2.4.1 Cardiac biomarkers

The amino terminal of B-type natriuretic peptide (NT-proBNP) was chosen as the primary outcome as it is consistently reported to have a response at 24 h after the first anthracycline treatment [8,9]. NT-proBNP and cardiac Troponin T (cTnT) levels were measured by the proBNP II and Troponin T high sensitive short turnaround time and electrochemiluminescence sandwich immunoassays (Roche Diagnostics, Laval, Quebec). All biomarker levels were compared to normal reference ranges. For NT-proBNP, the commonly used cut-point to *exclude* acute heart failure of 300 pg/mL was used, along with age-related cut-points used to *identify* acute heart failure of 450 pg/mL for <50 years or 900 pg/mL for 50-75 years [10]. For high sensitive cTnT, the 99th percentile of normal for females (8 pg/mL) was used as the cut-point [11].

2.4.2 Cardiac function

Two-dimensional transthoracic echocardiograms (Vivid i Ultrasound, 3S-RS cardiac probe, GE Healthcare, Mississauga, ON) were performed in the left lateral decubitus position according to current guidelines [12] by a certified cardiac sonographer who was blinded to group. A frame rate of 80 fps was used for all images and ultrasound settings were standardized within each participant. LV volumes and ejection fraction (LVEF) were assessed using the modified Simpson's Biplane method. Speckle-tracking was used to assess longitudinal strain and strain rate (SR) from the apical 4-chamber image. LV twist was determined as the peak difference between basal rotation and apical rotation measured in the short axis at the level of the mitral leaflets, and the level proximal to luminal obliteration, respectively.

HR was measured from the ultrasound's electrocardiogram concurrent to the apical 4-chamber image acquisition. Resting blood pressure was measured following the echocardiogram (after ~20 minutes of rest) using manual auscultation as the average of two measurements

performed 60 s apart. Systemic vascular resistance (SVR) was calculated as: 80 * (mean arterial pressure / cardiac output).

A single trained investigator performed all echocardiography analyses blinded on Echopac Version 112 (GE Healthcare, Mississauga, ON). All values were averaged over three cardiac cycles. For the strain analysis, segments without adequate tracking (as assessed by visual inspection) were excluded; at least four segments were required. Custom-made software (2D Strain Analysis Tool, Stuttgart, Germany) was used to adjust for intra and inter-individual variability of HR by normalizing to the percentage of systolic and diastolic duration via cubic spline interpolation [13]. Our test-retest (1-5 days) difference and coefficient of variation for this population for key measurements are: 2.1±1.2 and 2.6±1.4% for LVEF, 1.3±0.6 and 5.0±2.6% for longitudinal strain.

2.4.3 Descriptive variables

A brief questionnaire was used to collect self-reported demographic, diagnosis, treatment, medication and medical history data. Clinical blood assessments were extracted from patient records. The Godin Leisure Time Exercise Questionnaire [14] quantified moderate-to-vigorous intensity aerobic physical activity (MVPA) for the seven days before and after the first treatment.

2.5 Statistical analyses

Baseline characteristics and physical activity were compared using two-tailed independent t-tests or Mann-Whitney U tests as appropriate. The other physical variables were analyzed with a generalized estimating equation in SPSS Version 24.0 (IBM Corporation, NY). The Quasi Likelihood under Independence Model Criterion, and the corrected version of this criterion were respectively used to choose the best fitting model type (i.e. distribution and link function) and working correlation matrix for each variable. Hypothesized differences were

investigated for significant group by time interactions using contrasts (i.e. baseline versus follow-up for each group, and follow-up between groups). However, it is recommended that a non-significant interaction should not preclude pairwise comparisons when there is biological relevance of a potential difference between treatment and control groups [15]. As a compromise to minimize multiple comparisons but not miss potential real effects in this proof-of-principle study, contrasts were performed on non-significant interactions for variables that potentially explain significant findings. The relative risk of the biomarkers exceeding the reference ranges at follow-up was calculated for each group. The $p \leq 0.05$ level was considered significant and adjustments were not made for multiple comparisons.

In the preclinical versions of this study, the effects of exercise on invasive measures of cardiac function were estimated using available data as having a medium effect size (cohen's $d \approx 0.50$). Twenty-four participants total provided 80% power with our repeated measures within-between interaction design to detect a medium (cohen's $f=0.30$) effect size (G*Power 3.0.10; Düsseldorf, Germany).

3 Results

3.1 Recruitment and participants

Twenty-seven participants enrolled in the study between June 2013 and March 2016; one from each group withdrew, and another in CON became ineligible after her treatment protocol was changed to no longer include anthracyclines; leaving n=13 in EX and n=11 in CON who completed the study (Fig 1). The baseline data of the withdrawal was not carried forward to follow-up on the basis that chemotherapy is expected to change the outcome measures. One participant in CON was not willing to have the follow-up echocardiogram, but completed all other measures; all completed data were included. The acute follow-up was performed 25.5±5.4

and 30.1±8.1 h after treatment for EX and CON respectively (p=0.14). All participants received 60 mg/m^2 of doxorubicin and 600 mg/m^2 of cyclophosphamide. Five participants (2 CON, 3 EX) received four cycles of paclitaxel prior to this treatment. Trastuzumab treatment was not started until after study completion. The participant characteristics are described in Table 1. At baseline there were no differences between groups in body mass index (p=0.19), hemoglobin (CON, 12.7±1.1; EX, 13.0±1.0 g/dL, p=0.53), creatinine (CON, 68±13; EX, 66±5 μmol/L, p=0.33), or estimated glomerular filtration rate (CON, 86±20; EX, 89±13 mL/min/1.73m^2, p=0.62).

The exercise sessions were performed an average of 23.7±1.6 h prior to treatment, for the prescribed duration at 71±3% of HR reserve with no adverse events. All participants reported abstaining from vigorous exercise for 72 h prior and 48 h after treatment as requested, and there were no differences in MVPA for the week before (p=0.27) or the week after (p=0.19) the first treatment.

2.2 Cardiac outcomes

There was a significant interaction for NT-proBNP, where both groups increased (p<0.01), but EX's response was significantly attenuated relative to CON (p<0.01) (Fig 2). No participants exceeded the biomarker cut-points at baseline. At follow-up, 1 of 13 (8%) participants in EX exceeded the NT-proBNP cut-point to exclude acute heart failure (300 pg/mL), relative to 6 of 11 (54%) in CON; a relative risk of 0.14 (95% confidence interval 0.02–1.00) and absolute risk reduction of 46%. No participants exceeded the NT-proBNP cut-points for identifying acute heart failure. The interaction or change over time was not significant for cTnT (Table 2), and no participants exceeded the clinical cut-point.

Based on the role that LV load plays in the secretion of NT-proBNP,[3] blood pressure and LV volumes were compared within each group over time and between groups at the follow-

up despite non-significant interactions. There was no change or difference in systolic blood pressure, yet there was a significant decrease in SVR ($p<0.01$), diastolic ($p<0.01$), mean arterial ($p=0.03$), and pulse ($p=0.05$) pressures in EX only (Table 2). Pulse pressure was significantly higher in EX relative to CON at follow-up ($p=0.02$). There was a significant increase in end-diastolic volume in CON ($p<0.01$) only. While CON appeared to have a small increase, and EX a small decrease in end-systolic volume, these changes were not statistically significant. Stroke volume ($p<0.01$) increased significantly in both groups with no differences (Table 2). LVEF was increased in EX only ($p=0.02$).

There was no significant interaction for HR, cardiac output or E/A ratio, yet there was a significant increase with time for cardiac output and E/A ratio ($p\leq0.01$).

While there was no significant interaction for strain or twist, the contrasts were explored given the differential change in end-diastolic volume, and the known preload effect on these variables [16,17]. The increase in strain was significant for both groups ($p<0.01$), with no difference between groups, while the increase in twist was significant for CON only ($p=0.02$). There was a significant interaction for systolic SR, where it increased in EX only ($p<0.01$). There were no significant interactions for early diastolic SR, twist or untwist velocity, but early diastolic SR and untwist increased with time ($p\leq0.01$).

4 Discussion

This is the first study to characterize the acute change in cardiac function following the first doxorubicin treatment for breast cancer, and to show that a single session of exercise performed 24 h prior to treatment can attenuate the acute release of NT-proBNP and reduce the absolute risk of exceeding the cut-point excluding acute heart failure after the first doxorubicin treatment by 46%.

4.1 The acute change in cardiac function following the first doxorubicin treatment

Natriuretic peptides, including NT-proBNP, play a key role in the homeostasis of cardiac pressure and volume [18]. Elevated NT-proBNP in the context of cardiotoxic cancer therapy may reflect pathologic volume overload [3], as higher B-type natriuretic peptide levels during treatment with anthracycline treatment are predictive of development of heart failure, death, and cardiac events [18]. Relevant to the current study, among breast cancer patients being treated with anthracyclines, an NT-proBNP elevation after one treatment, as well as persistent elevations after multiple treatments, are associated with a significant reduction in LVEF over time [8,9]. Although no participant's NT-proBNP levels exceeded the age-related cut-points for identifying acute heart failure, it is likely clinically relevant that acute heart failure could not be excluded for 54% of CON participants following their first of four doxorubicin treatments. This is especially concerning given these participants' prior healthy cardiovascular status.

NT-proBNP is synthesized and secreted by the myocardium in response to increased hemodynamic stress including increased LV end-diastolic volume and pressure [18]. Indeed, in the current study, end-diastolic volume increased with no change in blood pressure in CON, which may be the cause of the increased NT-proBNP secretion. NT-proBNP elevations can enhance myocardial relaxation [19], which is demonstrated in both groups by the increased diastolic SR, untwist velocity, and E/A ratio. While these changes may be in line with expected physiological mechanisms and consequences of NT-proBNP synthesis and secretion, given that greater NT-proBNP release after anthracycline treatment has been associated with later LVEF deterioration [8,9], these changes could be potential targets for cardio-protection.

Similar to previous studies [9], cTnT did not increase significantly following the first doxorubicin treatment perhaps due to variable timing in release kinetics between individuals [3],

or that the cardiac stress detected by NT-proBNP occurs earlier than the cardiomyocyte necrosis that may be detected by cTnT [20].

The significant increase in longitudinal strain and twist from pre-chemotherapy to 24 - 48 h after the first treatment was unexpected. In children and rodents, strain and SR have been reported to deteriorate from pre-treatment by 2 and 24 h after the first anthracycline treatment [21,22]. No studies of adults being treated with anthracyclines have measured strain earlier than the mid-point (typically three cycles) of treatment where deterioration is consistently reported [4]. In terms of the potential mechanisms responsible for the acute increase in strain and twist observed in the present study, an increase in preload has been shown to increase longitudinal strain in patients referred for routine coronary angiography [16], and twist in an isolated perfused canine heart [17]. The cause for the increase in end-diastolic volume in the current study could be related to increased blood volume, but the effect of chemotherapy on blood volume is unknown. Dysfunction of the subendocardium leading to reduced contraction of this layer relative to the subepicardium may also cause an increase in twist [23]. Anthracycline-related morphological cardiomyocyte damage occurs intramurally, but with the highest concentration in the subendocardium [24]. Given that other studies have reported a decrease in twist later during anthracycline treatment [25], it appears that the acute increase in twist is an early compensatory mechanism. Future studies could longitudinally compare acute to chronic changes in twist.

4.2 Attenuation of the acute changes in cardiac function following the first doxorubicin by a single exercise session

Similar to the pre-clinical versions of this study, a single vigorous-intensity aerobic exercise session performed 24 h prior to a doxorubicin treatment attenuated some changes noted in CON, specifically, the increase in NT-proBNP, end-diastolic volume and twist. Several

mechanisms may explain the attenuation of NT-proBNP release following the exercise session: 1) the acute exercise could have changed the physiological conditions at the time of receipt of doxorubicin, such as increased nitric oxide and vasodilation [26], such that less NT-proBNP secretion was required to maintain cardiac pressure and volume homeostasis; 2) short-term adaptations may have occurred in the 24 h between the exercise and chemotherapy such as increased antioxidants or improved cellular calcium handling [27], such that the cardiomyocytes were better able to tolerate the biochemical stress associated with doxorubicin; or 3) the exercise session increased doxorubicin pharmacokinetics and/or metabolism such that the NT-proBNP was either released earlier, cleared earlier, or both. Future studies should include another measurement immediately prior to the doxorubicin treatment in EX to examine changes in blood volume, vagal tone, and nitric oxide bioavailability occurring as a result of acute exercise in this population.

In the current study, systolic SR was increased in EX but did not change in CON. Systolic SR is a better correlate of the peak positive first derivative of LV pressure (dP/dt_{max}), a surrogate of myocardial contractility, than strain [28]. Our systolic SR results were similar to the effect on dP/dt_{max} observed in the preclinical version of the current study, where the exercise session significantly attenuated the decrease in contractility that occurred in the CON [6]. There was also a small but statistically significant increase in LVEF in EX in the current study. Together these two findings potentially indicate an exercise-induced increase in systolic function, perhaps partially due to a reduced afterload, but future studies with larger sample sizes are required to definitively determine differences between groups.

Interestingly, a reduction in longitudinal systolic SR with anthracycline treatment has been associated with increased circulating ROS, as well as a decrease in the antioxidant

glutathione peroxidase [29]. The primary mechanism responsible for aerobic exercise cardio-protection is thought to be the upregulation of antioxidants and subsequent reduction in oxidative stress [30]. Therefore, this study may provide indirect support for this mechanism in humans.

The exercise session also appeared have an effect on peripheral hemodynamics in the current study. In EX, there was a significant decrease in SVR that was proportionally larger than the significant reduction in mean arterial pressure, indicating that cardiac output may have been increased to partially counteract the vasodilation. Increased vasodilation has been reported to occur 12-24 h after acute exercise [26].

4.3 Strengths and limitations

The original features of this study are the measurement of cardiac function and markers of subclinical cardiotoxicity in the characterization of the acute change in cardiac function following doxorubicin treatment, and translation of an innovative cardio-protective intervention from animal models to human breast cancer patients via a randomized controlled design. We strategically recruited a homogenous population with respect to baseline health and risk factors to aid in signal detection in this proof-of-principal study, but this limits generalization to a wider breast cancer population. Another important limitation is that patients enrolled in the study with the expectation that they may be required to exercise. The selection bias inherent to exercise studies also limits the generalizability of these results to a cohort with higher baseline health. We attempted to control for this by stressing to both referring oncologists and potential participants that neither good baseline fitness nor exercise experience were required. Other limitations include the small sample size, multiple statistical comparisons, use of self-reported medical history, and lack of measurement of potentially explanatory variables including autonomic function, vascular function, and blood volume.

In summary, there is a significant acute increase in NT-proBNP in response to the first doxorubicin treatment for breast cancer. Concurrent cardiac function changes included LV volume overload, echocardiographic markers of myocardial relaxation, and increased longitudinal strain and twist. The exercise session attenuated NT-proBNP, reducing the absolute risk of exceeding the cut-point for excluding acute heart failure by 46%, as well as other changes indicating vasodilation and increased systolic function. This study provides preliminary evidence of an accessible and feasible intervention that exerts seemingly positive effects on the cardiac response to doxorubicin in humans. As human patients will receive multiple treatments with doxorubicin, further investigations should examine the utility of this intervention when performed prior to each treatment to enhance the clinical relevance of this finding. A single aerobic exercise session performed prior to each chemotherapy cycle is a widely accessible and scalable intervention that would be feasible for most individuals with cancer.

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Abbreviations list:

BMI = body mass index

CON = control group

cTnT = cardiac troponin T

EX = exercise group

HR = heart rate

LV = left ventricular

MVPA = moderate-to-vigorous physical activity

NT-proBNP = amino terminal of B-type natriuretic peptide

SR = strain rate

SVR = systemic vascular resistance

References

[1] R.M. Witteles, M.B. Fowler, M.L. Telli, Chemotherapy-associated cardiotoxicity: How often does it really occur and how can it be prevented? Heart Fail Clin. 7 (2011) 333–344. doi:10.1016/j.hfc.2011.03.005.

[2] M.R. Bristow, M.B. Lopez, J.W. Mason, M.E. Billingham, M.A. Winchester, Efficacy and cost of cardiac monitoring in patients receiving doxorubicin, Cancer. 50 (1982) 32–41.

[3] A. Dolci, R. Dominici, D. Cardinale, M.T. Sandri, M. Panteghini, Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: systematic review of the literature and recommendations for use, Am J Clin Pathol. 130 (2008) 688–695. doi:10.1309/AJCPB66LRIIVMQDR.

[4] P. Thavendiranathan, F. Poulin, K.-D. Lim, J.C. Plana, A. Woo, T.H. Marwick, Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review, J Am Coll Cardiol. 63 (2014) 2751–2768. doi:10.1016/j.jacc.2014.01.073.

[5] A. Ascensão, J. Lumini Oliveira, N.G. Machado, R.M. Ferreira, I.O. Gonçalves, A.C. Moreira, et al., Acute exercise protects against calcium-induced cardiac mitochondrial permeability transition pore opening in doxorubicin-treated rats, Clin Sci. 120 (2011) 37–49. doi:10.1038/35037710.

[6] K.Y. Wonders, D.S. Hydock, C.M. Schneider, R. Hayward, Acute exercise protects against doxorubicin cardiotoxicity, Integr Cancer Ther. 7 (2008) 147–154. doi:10.1177/1534735408322848.

[7] K.H. Schmitz, K. Courneya, C. Matthews, W. Demark-Wahnefried, D.A. Galvão, B.M.

Pinto, et al., American College of Sports Medicine roundtable on exercise guidelines for cancer survivors, Med Sci Sports Exerc. 42 (2010) 1409–1426. doi:10.1249/MSS.0b013e3181e0c112.

[8] A. Kittiwarawut, Y. Vorasettakarnkij, S. Tanasanvimon, S. Manasnayakorn, V. Sriuranpong, Serum NT-proBNP in the early detection of doxorubicin-induced cardiac dysfunction, Asia-Pac J Clin Oncol. 9 (2012) 155–161. doi:10.1111/j.1743-7563.2012.01588.x.

[9] S. Romano, S. Fratini, E. Ricevuto, V. Procaccini, G. Stifano, M. Mancini, et al., Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients, Br J Cancer. 105 (2011) 1663–1668. doi:10.1038/bjc.2011.439.

[10] J.L. Januzzi, R. van Kimmenade, J. Lainchbury, A. Bayes-Genis, J. Ordonez-Llanos, M. Santalo-Bel, et al., NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study, Eur Heart J. 27 (2006) 330–337. doi:10.1093/eurheartj/ehi631.

[11] A. Mingels, L. Jacobs, E. Michielsen, J. Swaanenburg, W. Wodzig, M. van Dieijen-Visser, Reference Population and Marathon Runner Sera Assessed by Highly Sensitive Cardiac Troponin T and Commercial Cardiac Troponin T and I Assays, Clin Chem. 55 (2008) 101–108. doi:10.1373/clinchem.2008.106427.

[12] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association

of Cardiovascular Imaging, J Am Soc Echocardiogr. 28 (2015) 1–39.e14. doi:10.1016/j.echo.2014.10.003.

[13] E.J. Stöhr, J. González-Alonso, J. Pearson, D.A. Low, L. Ali, H. Barker, et al., Effects of graded heat stress on global left ventricular function and twist mechanics at rest and during exercise in healthy humans, Exp Physiol. 96 (2010) 114–124. doi:10.1113/expphysiol.2010.055137.

[14] G. Godin, R.J. Shephard, Godin leisure-time exercise questionnaire, Med Sci Sports Exerc. 29 (1997) S36.

[15] S.T. Bate, R.A. Clark, The Design and Statistical Analysis of Animal Experiments, Cambridge University Press, New York, NY, 2014.

[16] A.T. Burns, A. La Gerche, J. D'hooge, A.I. MacIsaac, D.L. Prior, Left ventricular strain and strain rate: Characterization of the effect of load in human subjects, Eur J Echocardiogr. 11 (2010) 283–289. doi:10.1093/ejechocard/jep214.

[17] S.J. Dong, P.S. Hees, W.M. Huang, S.A. Buffer, J.L. Weiss, E.P. Shapiro, Independent effects of preload, afterload, and contractility on left ventricular torsion, Am J Physiol. 277 (1999) H1053–60.

[18] D. Skovgaard, P. Hasbak, A. Kjaer, BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography, PLoS ONE. 9 (2014) e96736. doi:10.1371/journal.pone.0096736.t005.

[19] A. Palazzuoli, M. Gallotta, I. Quatrini, R. Nuti, Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure, Vasc Health Risk Manag. 6 (2010) 411–418. https://doi.org/10.2147/VHRM.S5789

[20] R.-Y. Xu, X.-F. Zhu, Y. Yang, P. Ye, High-sensitive cardiac troponin T, J Geriatr

Cardiol. 10 (2013) 102–109. doi:10.3969/j.issn.1671-5411.2013.01.015.

[21] J. Ganame, P. Claus, B. Eyskens, A. Uyttebroeck, M. Renard, J. D'hooge, et al., Acute cardiac functional and morphological changes after anthracycline infusions in children, Am J Cardiol. 99 (2007) 974–977. doi:10.1016/j.amjcard.2006.10.063.

[22] D.S. Jassal, S.-Y. Han, C. Hans, A. Sharma, T. Fang, R. Ahmadie, et al., Utility of tissue Doppler and strain rate imaging in the early detection of trastuzumab and anthracycline mediated cardiomyopathy, J Am Soc Echocardiogr. 22 (2009) 418–424. doi:10.1016/j.echo.2009.01.016.

[23] S. Nakatani, Left ventricular rotation and twist: why should we learn? J Cardiovasc Ultrasound. 19 (2011) 1–6. doi:10.4250/jcu.2011.19.1.1.

[24] S.F. Llesuy, J. Milei, B.S. Gonzalez Flecha, A. Boveris, Myocardial damage induced by doxorubicins: Hydroperoxide-initiated chemiluminescence and morphology, Free Radic Biol Med. 8 (1990) 259–264.

[25] M. Florescu, L.S. Magda, O.A. Enescu, D. Jinga, D. Vinereanu, Early detection of epirubicin-induced cardiotoxicity in patients with breast cancer, J Am Soc Echocardiogr. 27 (2014) 83–92. doi:10.1016/j.echo.2013.10.008.

[26] P.M. Haram, V. Adams, O.J. Kemi, A.O. Brubakk, R. Hambrecht, O. Ellingsen, et al., Time-course of endothelial adaptation following acute and regular exercise, Eur J Cardiovasc Prev Rehabil. 13 (2006) 585–591. doi:10.1097/01.hjr.0000198920.57685.76.

[27] S.M. Somani, S. Frank, L.P. Rybak, Responses of antioxidant system to acute and trained exercise in rat heart subcellular fractions, Pharmacol Biochem Behav. 51 (1995) 627–634.

[28] G.O. Dahle, L. Stangeland, C.A. Moen, P.-R. Salminen, R. Haaverstad, K. Matre, et al.,

The influence of acute unloading on left ventricular strain and strain rate by speckle tracking echocardiography in a porcine model, Am J Physiol Heart Circ Physiol. 310 (2016) H1330–H1339. doi:10.1152/ajpheart.00947.2015.

[29] G. Mercuro, C. Cadeddu, A. Piras, M. Dessi, C. Madeddu, M. Deidda, et al., Early epirubicin-induced myocardial dysfunction revealed by serial tissue doppler echocardiography: Correlation with inflammatory and oxidative stress markers, Oncologist. 12 (2007) 1124–1133. doi:10.1634/theoncologist.12-9-1124.

[30] A.A. Kirkham, M.K. Davis, Exercise prevention of cardiovascular disease in breast cancer survivors, J Oncol. Article ID 917606 (2015).

Table 1: Baseline participant characteristics

	Total n = 24	**Control** n = 11	**Exercise** n = 13
Age (years) (mean±SD)	50±9	50±10	51±9
Body mass index (kg/m^2)		26.7±5.1	25.0±4.8
Menopausal status (n (%))			
Pre-menopausal	8 (33%)	4 (36%)	4 (31%)
Post-menopausal	10 (42%)	6 (55%)	4 (31%)
Peri-menopausal	6 (25%)	1 (9%)	5 (38%)
Ethnicity (n (%))			
Caucasian	18 (75%)	7 (64%)	11 (85%)
Asian	5 (21%)	3 (27%)	2 (15%)
Other	1 (4%)	1 (9%)	0
Marital status (n (%))			
Married/common-law	16 (67%)	8 (73%)	8 (62%)
Divorced/separated/widowed	3 (13%)	2 (18%)	1 (8%)
Single	5 (21%)	1 (9%)	4 (31%)
Education (n (%))			
Bachelor's degree or above	15 (63%)	5 (45%)	10 (77%)
Below Bachelor's degree	9 (37%)	6 (55%)	3 (23%)
Comorbid conditions (n (%))			
Angina	1 (4%)	0	1 (8%)
Diabetes	1 (4%)	1 (9%)	0
Asthma	4 (17%)	2 (18%)	2 (15%)
Arthritis	4 (17%)	0	4 (31%)
Hypertension	2 (8%)	1 (9%)	1 (8%)
Dyslipidemia	0	0	0
Medications (n (%))			
Thyroid replacement	4 (17%)	1 (9%)	3 (23%)
Statin	3 (13%)	1 (9%)	2 (15%)
Calcium channel blocker	1 (4%)	0	1 (8%)
Beta-blocker	1 (4%)	1 (9%)	0
Metformin	1 (4%)	1 (9%)	0
ACE-inhibitor	0	0	0
Angiotensin receptor blocker	0	0	0
Stage (n (%))			
I	4 (17%)	3 (27%)	1 (8%)
II	12 (50%)	5 (45%)	7 (54%)
III	8 (33%)	3 (27%)	5 (38%)
Surgery (n (%))			
Lumpectomy	10 (42%)	4 (36%)	6 (46%)
Mastectomy	6 (25%)	3 (27%)	3 (23%)
None (neoadjuvant therapy)	8 (33%)	4 (36%)	4 (31%)

Abbreviations: ACE = angiotensin-converting enzyme; n = sample size; SD = standard deviation

Table 2: Hemodynamic, left ventricular function, and biomarker data

Parameter	Group	Baseline mean±SD	Acute follow-up mean±SD	Interaction p-value	Time p-value
Circulating cardiac biomarker					
NT-proBNP (pg/mL)	Control	59±35	323±151†	0.01	
	Exercise	52±30	214±77†‡		
Cardiac troponin T (pg/mL)	Control	1.5±2.3	1.9±2.6	0.97	0.23
	Exercise	1.3±2.1	2.6±3.2		
Hemodynamics					
Heart rate (bpm)	Control	69±12	67±13	0.08	0.79
	Exercise	69±11	72±14		
Systolic blood pressure (mmHg)	Control	102±12	98±17	0.82	0.23
	Exercise	102±12	100±10		
Diastolic blood pressure (mmHg)	Control	63±12	61±11	0.19	0.01*
	Exercise	62±10	55±8†		
Pulse pressure (mmHg)	Control	38±8	37±7	0.10	0.27
	Exercise	39±8	44±4†‡		
Mean arterial blood pressure (mmHg)	Control	76±11	74±13	0.43	0.03*
	Exercise	75±10	70±8†		
Systemic vascular resistance (dynes·sec·cm^{-5})	Control	2074±514	1805±503	0.43	<0.01*
	Exercise	1933±445	1556±473†		
LV function					
End-diastolic volume (mL)	Control	77±10	87±13†	0.28	<0.01*
	Exercise	83±17	87±13		
End-systolic volume (mL)	Control	33±6	36±7	0.21	0.73
	Exercise	36±9	34±5		
Stroke volume (mL)	Control	44±6	51±8	0.47	<0.01*
	Exercise	47±9	53±9		
Cardiac output (L/min)	Control	3.0±0.5	3.4±0.7	0.55	<0.01*
	Exercise	3.2±0.6	3.8±0.8		
LVEF (%)	Control	58±3	59±4	0.40	0.03*
	Exercise	57±4	60±3†		
E/A ratio	Control	1.27±0.32	1.35±0.25	0.25	0.01*
	Exercise	1.20±0.37	1.42±0.33		
Longitudinal strain (%)	Control	-19.6±1.9	-21.5±1.6	0.61	<0.01*
	Exercise	-19.2±1.9	-21.4±1.8		
Systolic longitudinal strain rate (sec^{-1})	Control	-1.03±0.08	-1.06±0.09	<0.01	
	Exercise	-0.98±0.15	-1.15±0.20†		
Diastolic longitudinal strain rate (sec^{-1})	Control	1.29±0.26	1.47±0.30	0.49	<0.01*
	Exercise	1.22±0.35	1.49±0.45		
Twist (°)	Control	16.4±5.9	22.4±7.8†	0.50	<0.01*
	Exercise	16.4±7.6	20.3±8.5		
Twist velocity (°·sec^{-1})	Control	109±27	125±47	0.35	0.27
	Exercise	121±32	124±32		
Untwist velocity (°·sec^{-1})	Control	-95±32	-133±39	0.67	0.01*
	Exercise	-95±39	-121±54		

Abbreviations: bpm = beats per minute; cm = centimeter; mL = milliliter; mmHg = millimeters of mercury; ms = millisecond; m/s = meters per second; sec = second;
*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

Fig 1. CONSORT flow diagram

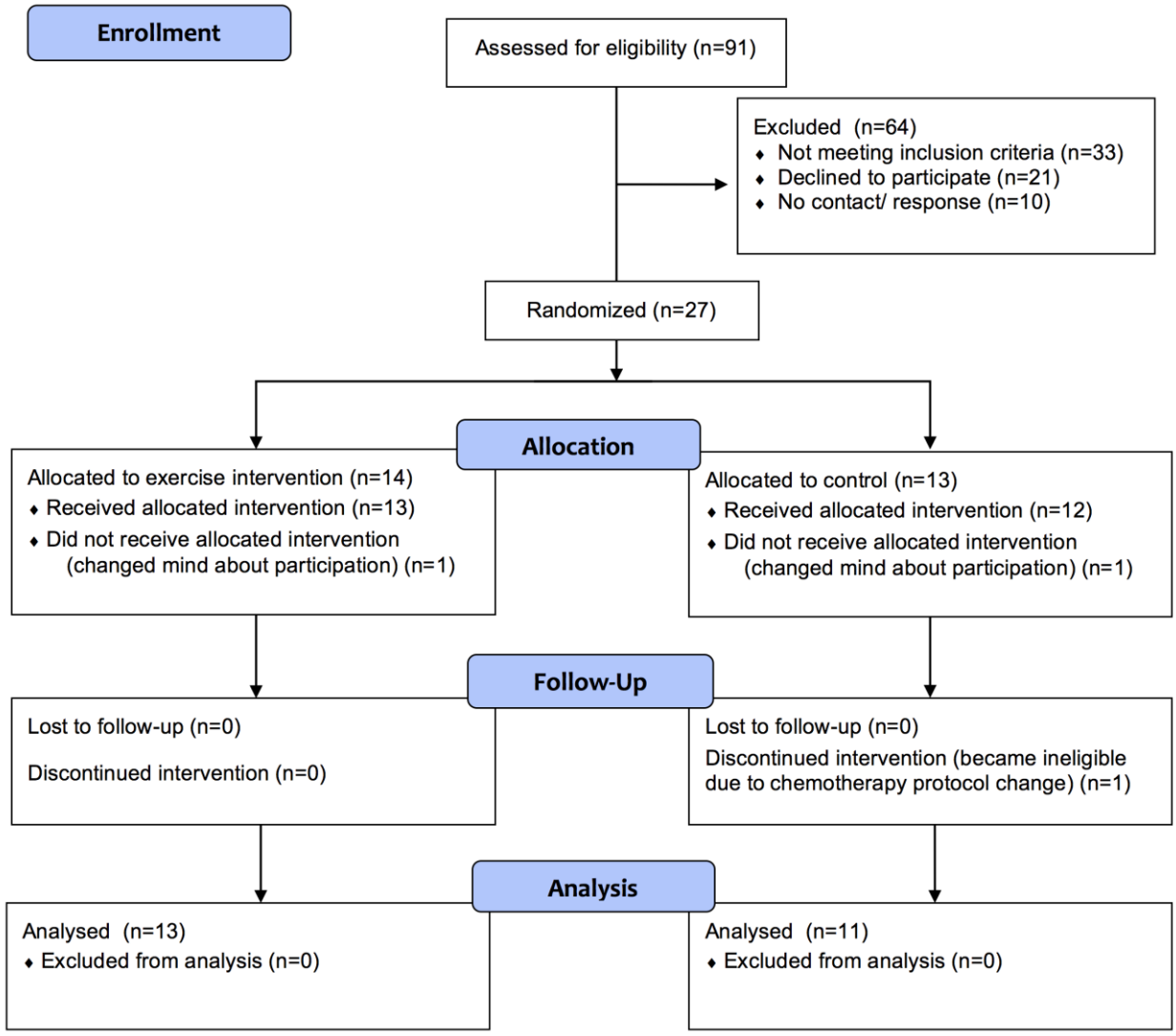

Fig 2. Responses of variables that differed between the exercise and control groups. * indicates statistically significant change or difference at $p \leq 0.05$. Data are estimated marginal mean ± standard error.