Impact of physical exercise on cardiotoxicity and cardiac health outcomes in women with breast cancer undergoing anthracycline-containing chemotherapy: a study protocol for a randomized controlled trial

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Abstract

**Background:** Anthracyclines are chemotherapeutic agents frequently used in breast cancer (BC) treatment. Although improving disease-free and overall survival, the use of anthracyclines is associated with a cumulative risk of cardiac toxicity. Preventive strategies to optimize and balance cardiac health are needed, being exercise proposed as a potential non-pharmacological approach for counteracting of anthracycline-related cardiotoxicity (ARC). Despite most of the data analysing the role of exercise against cardiac toxicity and dysfunction caused by anthracyclines derived from animal studies, human studies claim for more accurate and valuable clinical biomarkers. Moreover, clinical trials in real-world setting and large samples are of pivotal importance.

**Methods:** This protocol describes a two-arm prospective randomized controlled trial that will explore the cardioprotective effect of a structured exercise program against ARC in women with BC. Eighty-six adult women with early BC and with a therapeutic decision to receive anthracycline-containing chemotherapy (ACT) will be randomly assigned (1:1) to an intervention group or to a control group. Patients allocated to the intervention group will perform a 3-weekly supervised exercise program combining resistance and aerobic training with progressive intensity (light-to-vigorous), during the overall ACT. The control group will receive standard BC care. Primary outcomes related to cardiac (dys)function will be circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, resting left ventricular (LV) longitudinal strain, and resting LV ejection fraction. Secondary outcomes will include the assessment of resting blood pressure, resting heart rate (HR), resting HR variability (HRV) and recovery HR. Exploratory outcomes include physical function outcomes, self-reported physical activity level, health related to quality of life and fatigue. Data will be obtained at baseline (t0), after the end of anthracycline-treatment (t1), and three months after t2 (t2). Additionally, NT-proBNP levels will be measured between 1-24 hours prior to each anthracycline-treatment cycle.

**Discussion:** The implementation of the present study design, using novel clinical biomarkers and “between” outcomes’ associations, will help to understand the effectiveness of structured exercise interventions at mitigating ARC, further contributing to the improvement of supportive cancer care.

**Trial registration:** ISRCTN, ISRCTN32617901. Registered on 24 October 2018. Last updated on 11
Background

Over the last three decades the epidemiology of breast cancer (BC) has been marked by the clear increase in survival rates (1). The accessibility of screening and the discovery of new therapeutic options are among some relevant factors related to the improved management of cancer. However, despite their undeniable clinical importance, anti-cancer treatments are also associated with a frequent induction of side effects. Among those, cardiotoxicity emerges as a major challenge limiting treatment options (2) and contributing to morbidity and mortality in this patient population (3-5).

In the BC setting, cardiotoxicity is typically associated with exposure to traditional cytotoxic therapies, and particularly to the use of anthracyclines (6). Anthracyclines are important and effective chemotherapeutic agents, frequently administered in curative and palliative regimens for BC, although their clinical use is limited by cardiac dysfunction, usually designated as cardiotoxicity (7) it has been proposed that anthracycline-related cardiotoxicity (ARC) is an evolutionary (9) and dose-dependent phenomenon (10) that starts with an acute myocardial damage (11) which can be detected by the elevation of circulating cardiac biomarkers (12) and by the impairment in left ventricular (LV) longitudinal strain (13), in turn preceding the commonly reported LV ejection fraction progressive decline (9). Particularly when underestimated, not or insufficiently prevented and untreated, ARC may ultimately lead to overt heart failure (9).

Unfortunately, and in addition to the manifestations associated with treatment with anthracyclines, BC survivors often exhibit a phenotype characterized by the presence of risk factors for cardiovascular disease (CVD) development including: advanced age, obesity, prior CVD, poor cardiorespiratory fitness, and inappropriate lifestyles (smoking, alcoholism and a sedentary lifestyle) (14, 15). It is therefore not surprising that when compared to healthy individuals of a similar age, this patient population have higher prevalence and risk mortality of CVD (4). Considering the high risk of cardiac dysfunction, the study of holistic preventive strategies in this setting presents an emerging
and unmet need, as they may act in the mitigation of the cardiac damage associated with the use of cardiotoxic agents and could be associated with improvements in overall cardiovascular health as well as in overall physical fitness.

In adults with CVD without cancer, exercise training is recognised as an important approach in cardiac rehabilitation (16). Particularly, data from a meta-analysis has highlighted the favourable effects of exercise in the management of patients with heart failure, such as the attenuation of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (17) and the mitigation of LV remodelling (18). Also, in the oncological setting, it has become clear that exercise is a safe and effective supportive therapy in the management of several treatment-related side effects and in improving overall physical fitness (19, 20). Furthermore, the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology suggests in a recent position paper the possible utility of aerobic exercise as a promising strategy to attenuate ARC (21). However, this position remains to be complementarily analysed as data are so far mainly supported by evidence from studies with animal models (22, 23), and human studies performed with large number of patients and using analytical markers and endpoints of early cardiac (dys)function are lacking (24-26). Further clinical studies conducted in women with BC are thus needed to better understand the effectiveness of exercise in mitigation of ARC.

**Research aims and hypothesis**

The primary aim of this study is to ascertain whether a structured exercise program mitigates ARC, measured by the level change of circulating biomarkers (NT-proBNP) and cardiac (dys)function endpoints (LV global longitudinal strain and LV ejection fraction). The secondary aim is to evaluate the effectiveness of the intervention in the regulation of some cardiac health parameters: resting blood pressure, resting heart rate (HR), resting HR (HRV) and recovery HR. As exploratory objectives, we will assess physical function (cardiorespiratory capacity, upper limb strength and lower limb functionality), self-reported physical activity level, health related to quality of life (HR-QOL) and fatigue. We hypothesize that exercise may limit the degradation of cardiac function and structure and benefit cardiac outcomes. We also believe that patients in the intervention group will improve overall
physical fitness, HR-QOL, decrease their perception of fatigue and increase physical activity levels.

Methods

Study Design

This is a study protocol for a two-arm prospective randomized controlled trial, that will explore the cardioprotective effect of exercise, by comparing the effects of a structured supervised exercise program versus standard BC care, in adult women undergoing anthracycline-containing chemotherapy (AC-CT) for early BC. The study design and protocol adhere to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Additional file 1). The study design is outlined in Figure 1.

Ethical approval

This study will be conducted in compliance with the Declaration of Helsinki Ethical Principles (1975) and it received approval by the Ethics Committee of the Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E; Vila Nova de Gaia, Portugal) (reference number: 145/2018-1). The study is registered in the International Standard Randomised Controlled Trial Number (ISRCTN32617901). Any protocol amendments will be submitted to the CHVNG/E for ethical approval and updated on the ISRCTN.

Participant recruitment

We intend to recruit 86 adult women with early invasive BC, scheduled to receive AC-CT and followed-up in the Medical Oncology Department of the CHVNG/E. Participants will be recruited considering the eligibility criteria presented in Table 1. Recruitment will take place in two distinct phases. In a first instance, potential participants will be identified in the multidisciplinary consultation involving medical oncologists, surgeons and radioncologists. After this preliminary phase, the eligibility of each patient will be confirmed in the medical consultation by the medical oncologist himself. The oncologist will present the study to the patients considered eligible, explaining, offering the inclusion and providing written informed consent. Written informed consent will be obtained from all patients and they will be informed that they are under no obligation to participate and they may withdraw their consent at any time. Where possible the reasons for withdrawal from the study will be recorded. All the participants
will be followed-up from the acceptance period and up to 3 months after the end of the treatment period. If recruitment is not achieving the target sample size, we will extend the recruitment for additional hospitals.

**Randomization**

After confirmation of eligibility, patients will be randomized through an Internet software (www.sealedenvelope.com), with a 1:1 ratio between a supervised exercise group (intervention group) and a usual care group (control group), using a permutated block design with random block sizes (4, 6, 8) with stratification by two dichotomous variables, known as risk factors for ARC: Age (Under/50 years or older). Receive anti-HER2 therapy (Yes/No).

This process will be performed by an external individual who is blinded to the study and who will place the sequence in a numbered, opaque, sealed envelope. The allocation of participants will then be reported to an oncologist (AJ) who will subsequently inform the patients about the assignment group.

**Study arms**

**Intervention group**

Patients allocated to the intervention group will perform a supervised exercise program specifically developed for BC patients, based in the guidelines of the American College of Sports Medicine (27) and in a close cooperation between physical sports researchers (PA, DE, AA) and medical staff (oncologists, surgeons, radiologists, psychiatrist, and physiotherapist) of the CHVNG/E. The exercise program comprises 3 weekly sessions guided in small groups (<5 patients) in an appropriately equipped room of the CHVNG/E, supervised by the main author (PA) and a physiotherapist. Each session will involve an initial warm-up (5 min), followed by resistance and aerobic training (60 min), and ending with a cooldown phase (5 min). The program will be started after 1-2 days of the first AC-CT session and will be conducted over the respective treatment of each patient. It should be noted that the proposed exercise intervention will never be intended to replace or interfere with the current standard BC care.

**Resistance training:** It will include upper body (shoulder press, chest press, lat pulldown, biceps curls,
and triceps extension) and lower body (squat, calf raise, leg press, leg extension, and leg curl) weight-training exercises. All the exercises will be performed at the maximum possible joint range of motion, using resistance machines and free weights. Rating perceived exertion (RPE) will be measured using a 0-10-point OMNI-Resistance Exercise Scale (OMNI-RES, minimal effort = 0; maximum effort = 10) (28). During the first week, participants will perform 2 sets and 10 repetitions of each exercise without additional resistance or with the lowest available [reporting 2-4 (‘easy’ to ‘somewhat easy’) on the OMNI-RES]. After this phase, if no adverse events or symptoms were reported for a specific exercise, resistance will be added so that each participant could be able to perform 3 sets with 12 maximal repetitions (12-RM) of each exercise. When the participants can complete 3 sets and more than 12-RM at the set weight in 3 consecutive sessions, then the resistance will be increased between 5%-10%.

**Aerobic training:** It will be performed in a treadmill, stationary bike, and stepping. This phase will be monitored through HR (each participant will wear a heart rate monitor during exercise training sessions) and RPE measure by a 0-10 point modified Borg Scale (minimal effort = 0; maximum effort = 10) (29). During the first two weeks, the participants will perform 20 minutes of aerobic training in a light intensity [<50% of measured HR reserve (based on maximum HR reached in the cardiorespiratory test), reporting 2-4 (‘easy’ to ‘somewhat easy’) on modified Borg scale]. After this period, 3 minutes will be added every two weeks until a volume of 30 minutes of aerobic training is reached. At this stage, participants will be encouraged to perform moderate-to-high intensity training [65%-80% of measured HR reserve, reporting 5-8 (‘somewhat hard’ to ‘hard’) on modified Borg scale] until the end of the intervention.

Participants will be weekly reminded (through email and phone) of their exercise training schedule and the importance of adherence to achieve the established objectives.

**Usual care group**

Patients allocated to the usual care group will receive the standard BC care, not being given any specific advice regarding physical activity. In compensation for the participation in this study, it will be offered the possibility of performing the same exercise program after the final assessments are
completed.

**Study assessments**

The schedule of the study outcome assessments is outlined in Figure 2. Study assessments will be scheduled upfront and participants will be regularly reminded (through email and phone) to ensure a complete follow-up. Primary, secondary and exploratory outcomes will be measured in all participants at three different moments:

- $t_0$ (baseline assessments): Between 0-14 days prior to the first AC-CT session.
- $t_2$ (post-treatment assessments): Between 1-5 days after the end of AC-CT.
- $t_3$ (follow-up assessments): After 3 months of $t_2$.

In addition, for analysis of circulating NT-proBNP, blood samples will be collected between 1-24 hours before the beginning of each AC-CT cycle ($t_1$: during-treatment assessments). Patients will be instructed and remembered to avoid drinking alcoholic and caffeine-containing beverages, to abstain from smoking for 12 hours prior and to avoid vigorous physical activities 24 hours prior to all examinations.

**Study outcomes**

**Primary outcomes**

- Circulating NT-proBNP levels
- Resting LV global longitudinal strain
- Resting LV ejection fraction

**Secondary outcomes**

- Cardiac health outcomes:
  - Resting blood pressure
  - Resting HR
  - Resting HRV
  - Recovery HR

**Exploratory outcomes**

- Physical function
- Cardiorespiratory fitness
- Upper limb strength
- Lower limb functionality
- Self-reported physical activity level
- Health-related quality of life
- Fatigue

**Assessment of the primary outcomes**
**Resting LV ejection fraction and resting LV longitudinal strain**

Resting LV ejection fraction will be calculated using the biplane method of disks (modified Simpson’s rule) from the apical four- and two-chamber view (30). For resting LV global longitudinal strain assessment, two-dimensional grey-scale images will be acquired in the apical four-, two- and three-chamber views, with a frame rate of 60 to 100 fps. Three cardiac cycles will be digitally stored and Velocity Vector Imaging (VVI) software (Siemens Medical Solutions United States of America Inc) will be used in the analysis. Echocardiographic acquisitions will be performed by a single experienced cardiologist blinded to the patient assignment group.

**Circulating NT-proBNP levels**

Nonfasting venous blood samples will be drawn by a nurse oncologist. The assessment of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels will be conducted in the local clinical analysis laboratories of the CHVNG/E, which are certified by the United Kingdom National External Quality Assessment Service. This professional staff will be blinded to the patient assignment group.

**Assessment of the secondary outcomes**

**Resting blood pressure and resting HR**

Resting blood pressure (systolic and diastolic blood pressure) and resting HR will be measured using a standard automated device Philips SureSignsVM6 (Philips Medical System, Andover, United States of America). Two measurements will be carried out. The first measurement will be preceded by 5 minutes resting period and a second reading will be taken after 3 minutes. If necessary, additional records shall be obtained until two consecutive stable measurements (differences <5 mmHg for blood pressure and <7 bpm for HR) are obtained. The average of the two stable measurements will be considered for the analysis. This procedure will be carried out by a study investigator (ALA) not blinded to the patient assignment group.

**Resting HRV**

HRV is a non-invasive method to analyse cardiac autonomic function through the measurement of successive heart beats variations (RR). Resting HRV will be analysed using a HR monitor Polar V800 (Polar Electro Oy, Kempele, Finland) with a Polar H7 chest strap. During the RR recording, patients will
be seated in a comfortable position. They shall be required to breathe spontaneously, to avoid any movements and to maintain neutral thoughts during the time of data acquisition. The first 5 minutes will be excluded (stabilization period) and the remaining 5 minutes will be used to calculate the time-domain (standard deviation of successive normal RR [SDNN], and root mean square of successive normal RR [RMSSD]) and frequency-domain indices (low-frequency spectral component [LF], and high-frequency spectral component [HF]). In all the cases, the RR recordings will be exported to the Kubios v2 HRV software (Biosignal Analysis and Medical Imaging Group at the Department of Applied Physics, University of Kuopio, Kuopio, Finland). Occasional, artefact noise shall be automatically replaced with the interpolated adjacent RR interval values (filter power <low). This procedure will be carry out by the first author (PA) not blinded to the patient assignment group.

**Recovery HR**

Recovery HR will be determined as the absolute difference between the HR at peak effort during the cardiorespiratory exercise test (CRET) and the HR at 60-seconds, and 120-seconds post-exercise. HR values will be derived from a continuous record obtained via CRET (Mortara X-Scribe, Mortara, United States of America). This procedure will be carried out by study investigators (EV, MT), blinded to the patient assignment group.

**Assessment of the exploratory outcomes**

**Cardiorespiratory fitness**

Cardiorespiratory fitness will be evaluated by means of a symptom-limited CRET on a treadmill (Mortara X-Scribe, Mortara, United States of America), using a modified version of the Bruce protocol (31). Expired gases will be continuously collected throughout exercise and analysed for ventilatory volume (VE) and for oxygen (O2) and carbon dioxide (CO2) content, using dedicated analysers. Standard spirometry [forced expiratory volume in 1 second (FEV1)] and forced vital capacity (FVC) will also be undertaken before the test. Equipment calibration and measurements will be done in accordance to the recommendations of the American Thoracic Society and American College of Chest Physicians (32). The following parameters will be calculated and considered for analysis: peak oxygen consumption (peak V\textsubscript{O2}, measured in millilitre per kilogram per minute), peak respiratory exchange
ratio (RER), defined by the ratio of CO2 production to O2 consumption at peak effort, oxygen consumption at the anaerobic threshold (AT), defined as the point at which CO2 production increases disproportionately in relation to O2 consumption, obtained from a graph plotting O2 consumption against CO2 production, and total exercise duration (measured in seconds). The maximum HR achieved will also be recorded. Patients will not be asked to discontinue current medication before the test. The assessment of results derived from the CRET will be carried out by study investigators (EV, MT) blinded to the patient assignment group.

**Upper limb strength**

Upper limb strength will be evaluated by the maximal voluntary grip strength (measured in kilograms), using a digital handgrip dynamometer (Saehan Corporation, Masan, South Korea - model SH5003). Each subject will perform six trials, three in each arm, with an alternating bilateral sequence. The results will be given by the average of the three trials, respectively for operated and non-operated limb. This procedure will be carried out by the first author (PA), not blinded to the patient assignment group.

**Lower limb functionality**

Lower limb functionality will be evaluated by the sit-to-stand test using a straight-backed chair (40-centimetre high). It will be required that each subject, keeping plantar support flat on the floor and arms crossed at the chest, sit and stand as many times as possible for 30 seconds. The score of the test will be determined by the number of repetitions done respecting the above procedure. This procedure will be carried out by the first author (PA), not blinded to the patient assignment group.

**Self-reported physical activity level**

*International Physical Activity Questionnaire-Short (IPAQ-SF)* will be used to calculate the metabolic equivalent (MET) minutes per week spent in walking, moderate and vigorous activities. Sedentary behaviour will be determined based on time spent sitting per day (minutes). Considering the obtained scoring, participants will be categorised as a low, moderate, or high physical activity level. In this study will be used the Portuguese language of the IPAQ-SF (33). Scoring will be analysed by the first author (PA), not blinded to the patient assignment group.
Health-related to quality of life and fatigue

The European Organization for Research and Treatment in Cancer (EORTC) Quality of Life C-30 (QOL-C30) is a self-administered, validated questionnaire to assess HR-QOL in cancer patients (34). It is composed of nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. Additionally, there are five single items of commonly reported symptoms by cancer patients (dyspnea, sleep disturbance, appetite loss, constipation and diarrhea), and an item that evaluates the perceived financial impact of the disease. In this study, the third version of this questionnaire will be used, in the Portuguese language (35). Analyses will include the five functional scales, fatigue scale and the global health and quality-of-life scale. The scoring of the several scales will be carried out by the first author (PA), not blinded to the patient assignment group.

Demographic, anthropometric and clinical data

Demographic, anthropometric and clinical data will be recorded during the enrolment process (\(-t_0\)). Demographic data includes age, sex, and education. Anthropometric data includes weight, height, and body mass index. Clinical data includes disease, treatment information, past medical history and current medication. These data will be extracted from the patients’ electronic medical files by two study coordinators (ALA, AJ) not blinded to the patient assignment group.

Safety

The safety of the intervention will be assessed by weekly tracking and monitoring the number of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). A meeting between the study investigators will be held every weekly to analyse and debate the possible adverse events. Potential serious adverse events will be immediately reported to all study members, to the oncologist who follows the patient, to the CHVNG/E ethics commission and will be reported in the study results.

Data management

Study data will be managed by two study investigators (PA, AJ) using a predesigned criterion to data
collection form [Microsoft Office Excel version 2016 (Microsoft Corporation, Redmond, WA, United States of America] and Statistical Package for the Social Sciences files version 23.0 (IBM Corporation, Armonk, NY, United States of America)] with double-entry. Regularly data checks will be performed to ensure data quality. To ensure patients’ anonymity, they will be identified by codes and only the authors involved in the trial will have access to the full identification. The total number of patients who meet the study eligibility will be recorded, as will the number of patients who will agree or not agree to participate in the study, the number of patients who assigned to each study arm, the number of patients who participated in all sessions, the attendance of each patient in the intervention sessions, the number of patients who provided follow-up data, the number of patients included in the final analysis and the number of withdrawals.

**Sample size calculation**

Sample size was carried out by a power calculation based on resting LV ejection fraction outcome, using a non-commercial statistical power analysis program (G*Power Version 3.1.9.2). Based on an effect size of 0.6 in resting LV ejection fraction presented in a previous study (26), to ensure a statistical power of 80% and a significance level of 0.05, through a t-test for two independent groups, the recruitment of 72 participants is required. Predicting a 20% dropout rate (19), we estimate that a total of 86 patients will be needed (n= 43 in each arm).

**Statistical analyses**

**Statistical data analysis** will be performed using Statistical Package for the Social Sciences. The statistical significance will be set at a p< 0.05.

Data analysis will start with standard descriptive statistical methods to describe the data (means and standard deviations will be calculated for continuous variables and absolute and relative frequencies for categorical variables). The comparison of the continuous variables between the two study groups will be made using independent samples t test or the Mann-Whitney test (if the assumptions underlying to conducting a t test are violated). Normality will be verified by the Kolmogorov-Smirnov test. The chi-squared test will be used to check the existence of a relationship between categorical variables.
The efficacy of the supervised exercise program, changes in primary, secondary and exploratory outcomes will be analysed using a two-way mixed design ANOVA. Bonferroni’s post-hoc procedure will be performed to locate the pairwise differences. Effect size will be calculated to estimate variance between moments through partial eta-squared. The cut-off values were interpreted as 0.02 for small effect size, 0.13 for moderate and 0.26 for large (36). No interim analyses will be conducted.

**Blinding**

This study will involve the prescription of exercise sessions. To carry out a rigorous exercise prescription and to ensure an adequate follow-up of each patient, participants, physical trainer (PA), medical oncologists (AJ) and nurse oncologists (ALA) will not be blinded to group assignment. Due to the lack of resources, only the evaluators that will make the acquisition of echocardiographic outcomes (resting LV ejection fraction and LV global longitudinal strain), circulating NT-proBNP levels, cardiorespiratory fitness and recovery HR data, will be blinded to the group assignment.

**Limitations**

There are some limitations to this study, which should be noted. Firstly, we will only include patients followed in the CHVNG/E. Secondly, due to the impossibility of blinding patients and some of the involved authors about the study group assignment, we will use an open design which may influence the retention rate of participants in the control group. Thirdly, we will stratify our sample considering the age (under/over 50 years old) and use of trastuzumab (yes/no). However, there are other risk factors associated with ARC, including: total cumulative anthracycline dose, pre-existing cardiac disease and treatment with mediastinal radiation, that should also be considered (19). Although these hinderances should be acknowledged, we believe the findings from the present study will provide important data which will be of relevance to the contemporary literature in this subject.

**Dissemination**

Findings of this study will be involved in a doctoral thesis of the main author and will be submitted to a peer-reviewed journal for publication and presented at relevant conferences and to the whole community concerned.
Discussion
CVD is one of the leading causes of death among women with BC (3-5) and a foremost concern in the clinical practice of oncology (2). According with Gernaat et al (4) BC survivors have an absolute risk of dying from CVD that ranges from 1.6% to 10.4%. The recurrent use of cardiotoxic therapies and the presence of risk-factors for the development and worsening of cardiovascular health are the main factors related to this phenomenon. The implementation of preventive strategies aiming to optimize cardiovascular care in BC survivors is therefore an emerging need. Until now, these include: early identification of potential risk-factors, the management of anthracycline cumulative dose (and possible use of ancillary therapies), or the use of heart failure drugs (beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonists) (21). However, beyond limited, these approaches were mainly established to reduce the toxicity of therapeutic agents, ensuring their efficacy but not providing a general cardiovascular approach. It is thus pivotal to investigate the effects of non-pharmacological approaches prevention strategies of a holistic nature in order to counteract ARC and related complications in BC patients.
Currently, exercise is recognised as a safe and effective supportive intervention to improve physical function and HR-QOL in BC survivors during (19) or after treatment (20). Furthermore, exercise has also been proposed as a potential tool to mitigate ARC in humans (21, 37), although but this thesis remains uncertain since this is manly supported through data from animal studies and/or using less accurate biomarkers (22, 23). In fact, there is limited data on whether the benefits of exercise also include protection from anthracycline-related cardiac damage in women with BC. To the best of our knowledge, Kirkham et al (24) were the first to test this hypothesis by analysing the efficacy of a single aerobic bout performed 24 hours prior to each treatment. The authors observed positive effects on systemic outcomes (cardiac output, resting HR, body weight, and psychological symptoms) but did not observe relevant changes in echocardiographic outcomes (LV mass, LV ejection fraction, strain imaging and the E/A ratio) or circulating cardiac biomarkers (troponin t and NT-proBNP). In a recent non-randomized trial, Howden et al (26) verified that performing a 2-weekly supervised exercise program plus a weekly unsupervised aerobic session have attenuated the reduction in p peak Vo2 and
the increase of troponin levels in women with BC undergoing AC-CT, when compared to a usual care group. However, these authors did not also observe any relevant changes in the measured echocardiographic outcomes. So far, the overall clinical significance of exercise in preventing cardiac dysfunction associated with treatment with anthracyclines remains to be clarified in controlled clinical settings.

The present study will be conducted to explore the cardioprotective role of exercise in the mitigation of ARC and highlight its possible effects in different cardiac health outcomes. A total of 86 adult women with early BC and with therapeutic decision to receive AC-CT from the CHVNG/E will be enrolled. Recruitment will take place between 1 November 2018 and 31 November 2020 (expected data of recruitment completion). Follow-up is expected to be completed by 30 June 2021.

We anticipate that the results achieved by this study will add new knowledge to what the literature currently offers, clarifying the effects of a supervised exercise program in different established markers and more accurate biomarkers of cardiotoxicity in women with a BC undergoing AC-CT. Furthermore, we expect that the findings from this study may help in future policies related to cancer care management and contribute to the ascertainment of the role of exercise programs during antineoplastic in-hospital treatment.

Abbreviations
AC-CT: Anthracycline-Containing Chemotherapy; ARC: Anthracycline-Related Cardiotoxicity; AT: Anaerobic Threshold; BC: Breast Cancer; CRET: Cardiorespiratory Exercise Test; CO2: Carbon Dioxide; EORTC: European Organization for Research and Treatment in Cancer; FVC: Forced Vital Capacity; HF: High-Frequency Spectral Component; HR: Heart Rate; HR-QOL: Health Related to Quality of Life; HRV: Heart Rate Variability; IPAQ-SF: International Physical Activity Questionnaire-Short; LF: Low-Frequency Spectral Component; LV: Left Ventricular; MET: Metabolic Equivalent; NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide; O2: Oxygen; peak Vo2: Peak Oxygen Consumption; QOL-C30: Quality of Life C-30; RER: Respiratory Exchange Ratio; RMSSD: Root Mean Square of Successive Normal RR; RR: Successive Heart Beats Variations; SDNN: Standard Deviation of Successive Normal RR; VE:
Ventilatory Volume; VVI: Velocity Vector Imaging.

Declarations

**Trial Status**

Recruitment started on 1st November 2018 and is expected to be completed by 31st November 2020.

Last edited: 11th January 2019.

**Ethics approval and consent to participate**

Ethics approval of this protocol was conferred by the ethics Committee of the Centro CHVNG/E (reference number: 145/2018-1). The trial will be conducted in compliance with the Declaration of Helsinki Ethical Principles (1975). Informed written consent will be obtained from all participants before enrolment.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data that will support the findings of this study will be available on request from the corresponding author. The request will be analysed by the research team and the ethics committee that ethically approved the study.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

The idea of the above-mentioned trial was conceived and designed by PA and AJ. PA, DE, AA and AJ designed the intervention. CN and PA developed the statistical analysis and sample size calculation. EV and MT designed and will perform the cardiorespiratory assessments. FS designed the
echocardiography acquisition. ALA will collect some secondary outcomes and together with AJ will record demographic, anthropometric and clinical data. PA and AJ will be responsible for the management of study data. PA drafted the manuscript, which underwent revision by all other authors. All authors read and approved the publication of this final manuscript.

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Tables

| Table 1 Eligibility criteria |
|-------------------------------|
| **INCLUSION CRITERIA:**       |
| · Female gender.              |
| · Aged 18 years or older.     |
| · Histological diagnosis of stage IA-IIIC breast carcinoma. |
| · Scheduled to receive AC-CT. |
| · Follow-up at the Medical Oncology clinic at the CHVNG / E. |
| · Consent of the assistant oncologist for the practice of exercise. |
| · Able to provide informed consent. |
| · Acceptance of randomization to intervention group or control group. |
| · Baseline assessments before starting AC-CT. |

| **EXCLUSION CRITERIA:**       |
| · Contraindications to maximal exercise testing. |
| · Decompensated diabetes mellitus. |
| · Severe anaemia (<8g / dL) uncorrectable with transfusion and / or iron and / or vitamin deficiency replacement. |
| · Pregnancy. |
| · Known significant heart disease (myocardial infarction, congestive heart failure, cardiomyopathy). |
| · Usual medication-containing beta-blockers. |

Figures
Figure 1

Study flow. ACH: anthracycline-containing chemotherapy; SCC: standard breast cancer care;
SEP: structured exercise program.

| TIMEPOINT | Enrolment | Allocation | Post-allocation | Follow-up |
|-----------|-----------|------------|-----------------|-----------|
|           | -t₀       | 0          | t₀              | t₁        | t₂        | t₃        |

**ENROLMENT:**
- Eligibility screen ✓
- Informed consent ✓
- Demographic data ✓
- Anthropometric data ✓
- Clinical data ✓
- Allocation ✓

**INTERVENTIONS:**
- Supervised exercise program
- Usual cancer care

**ASSESSMENTS:**
- Primary outcomes
  - NT-proBNP ✓ ✓ ✓ ✓ ✓
  - Resting LV global longitudinal strain ✓ ✓ ✓ ✓
  - Resting LV ejection fraction ✓ ✓ ✓ ✓
- Secondary outcomes
  - Resting blood pressure ✓ ✓ ✓ ✓
  - Resting heart rate ✓ ✓ ✓ ✓
  - Resting heart rate variability ✓ ✓ ✓ ✓
  - Heart rate recovery ✓ ✓ ✓ ✓
- Exploratory outcomes
  - Physical Function:
    - Cardiopulmonary capacity ✓ ✓ ✓ ✓
    - Upper limb strength ✓ ✓ ✓ ✓
    - Lower limb functionality ✓ ✓ ✓ ✓
    - Self-reported physical activity level ✓ ✓ ✓ ✓
    - Health Related to Quality of Life ✓ ✓ ✓ ✓
    - Fatigue ✓ ✓ ✓ ✓

Figure 2

The schedule of enrolment, interventions, and assessments. -t₀ Enrolment process t₀
Baseline, t1 During anthracycline-containing chemotherapy, t2 Post anthracycline-containing chemotherapy (which coincides with the end of the intervention), t3 After 3 months of t2, NT-proBNP N-Terminal pro-Brain Natriuretic Peptide, LV Left ventricular.

Supplementary Files
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