PHYSICAL ACTIVITY, EXERCISE AND CANCER

ORIGINAL ARTICLE

A lactate threshold-based incremental treadmill training and assessment protocol (LACTOC) for managing treatment-induced cardiotoxicity in oncology patients

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ABSTRACT

Cardiotoxicity represents a clinically significant complication in oncology patients, manifesting as cardiac dysfunction that impairs functional capacity and quality of life. Physical exercise has emerged as a promising intervention to mitigate treatment-related adverse effects; however, optimal exercise prescription for patients with cardiotoxicity remains poorly defined, as most existing protocols rely on heart rate percentages or peak oxygen consumption—methods imprecise in cardiovascularly compromised populations. This protocol describes the LACTOC program, a 4-week supervised treadmill exercise intervention comprising 12 sessions (three per week, 48-hour recovery intervals) in oncology patients with treatment-induced cardiotoxicity. Each session includes a warm-up (5 min at 3 km/h), a progressive incremental test with 3-minute stages and 1 km/h increments from 4 km/h until reaching 4 mmol/L blood lactate or 85% of theoretical maximal heart rate, and active recovery (5 min at 3 km/h). Comprehensive cardiovascular, metabolic, perceptual, and heart rate variability monitoring is integrated throughout. The protocol is expected to enable individualized exercise prescription based on objective metabolic thresholds, with session-by-session load adjustment guided by daily HRV assessment representing a methodological advance over conventional fixed-prescription approaches. This proposal is positioned as a promising framework for cardio-oncological rehabilitation, providing objective tools to guide safe and effective exercise prescription in patients with treatment-induced cardiotoxicity.
Keywords: Physical activity, Cardiotoxicity, Exercise, Lactate threshold, Autonomic nervous system, Cancer, Heart rate variability.

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INTRODUCTION

Cardiotoxicity is one of the most clinically significant complications observed in oncology patients undergoing systemic cancer treatment. It manifests as a spectrum of cardiac disorders—including left ventricular dysfunction, arrhythmias, myocardial fibrosis, and pericarditis—that collectively compromise functional capacity, quality of life, and long-term cardiovascular prognosis (Scott et al., 2018; Wernhart & Rassaf, 2025). The prevalence of treatment-induced cardiotoxicity varies considerably depending on the therapeutic agent and regimen: rates of up to 65% have been reported with anthracycline-based protocols, up to 34% with trastuzumab, and clinically meaningful cardiovascular impairment has been documented with checkpoint inhibitors, tyrosine kinase inhibitors, and hormonal therapies including androgen deprivation therapy (Scott et al., 2018; Wernhart & Rassaf, 2025; D'Ascenzi et al., 2021). As oncological survival rates continue to improve globally, the long-term cardiovascular sequelae of cancer treatment have become an increasingly prominent concern in clinical oncology management.

The intersection of cardiovascular disease and cancer—the discipline of cardio-oncology—has rapidly evolved in recent years as a distinct clinical and research domain (Wernhart & Rassaf, 2025; D'Ascenzi et al., 2021). Multiple interacting mechanisms underlie treatment-induced cardiotoxicity: direct myocardial cytotoxicity, endothelial dysfunction, oxidative stress, neurohormonal activation, and dysregulation of the autonomic nervous system have all been implicated in its pathogenesis (Scott et al., 2018; Borsati et al., 2025). Among these, autonomic nervous system dysregulation holds particular relevance, as it modulates cardiac function, vascular tone, and inflammatory responses, and its impairment has been associated with increased cardiovascular morbidity in cancer survivors (Scott et al., 2018; Borsati et al., 2025). Heart rate variability (HRV), a non-invasive index of cardiac autonomic modulation derived from the analysis of successive RR intervals, has been proposed as a sensitive biomarker of autonomic dysfunction in this context and has demonstrated clinical utility in monitoring the cardiovascular effects of oncological treatments (Scott et al., 2018; Task Force, 1996).

Physical exercise has emerged as a cornerstone intervention in the supportive care of cancer patients, with robust evidence demonstrating its capacity to mitigate a broad spectrum of treatment-related adverse effects (Amin et al., 2024; Schneider et al., 2023). In the specific context of cardiotoxicity, supervised exercise training has been shown to preserve left ventricular ejection fraction (LVEF), improve cardiorespiratory fitness (VO_2peak), reduce cancer-related fatigue, and attenuate markers of systemic inflammation during and after chemotherapy (Heck & Wackerhage, 2024; Taggart et al., 2013). Meta-analyses of randomized controlled trials have confirmed the safety of supervised exercise in populations at cardiovascular risk during oncological treatment, supporting the clinical viability of exercise-based interventions in this setting (Piepoli et al., 2016; Hurria et al., 2011). Nevertheless, despite growing consensus on the benefits of exercise, the optimal prescription parameters—including exercise modality, intensity, duration, frequency, and progression—for patients with established cardiotoxicity remain insufficiently characterized in the scientific literature (Wernhart & Rassaf, 2025; D'Ascenzi et al., 2021).

A critical limitation of current exercise prescription frameworks for cardiotoxicity management is the reliance on intensity methods that may be systematically imprecise in cardiovascularly compromised populations. The majority of existing protocols base exercise intensity on percentages of maximal heart rate or peak oxygen consumption (VO_2peak) (Borsati et al., 2025; Mendes et al., 2023). However, oncological treatments—particularly anthracyclines and targeted therapies—frequently induce chronotropic incompetence, reduced cardiac reserve, and autonomic dysregulation, which distort the physiological relationship between heart rate responses and metabolic demand, rendering percentage-based prescriptions inherently unreliable in this context (Borsati et al., 2025; Whellan et al., 2014). This imprecision may result in systematic overtraining or undertraining, with potential consequences for both safety and therapeutic efficacy.

Metabolic threshold-based exercise prescription—specifically anchored to the lactate threshold (LT) and the maximal lactate steady state (MLSS)—has been proposed as a more accurate and individualized alternative in cancer survivors (Borsati et al., 2025; Lally & Gardner, 2013). The lactate threshold demarcates the transition from predominantly oxidative to glycolytic metabolism and is considered a robust predictor of endurance performance and cardiovascular adaptability (Janssen, 2001; Beneke et al., 2011). Unlike VO_2peak-percentage methods, LT-based prescription accounts for individual metabolic variability and is not confounded by chemotherapy-induced chronotropic alterations, making it particularly suitable for populations with cardiovascular compromise (Borsati et al., 2025; Jones & Doust, 1996). Despite these theoretical advantages, the systematic integration of lactate threshold-based protocols into supervised cardio-oncology exercise programs remains notably scarce in the literature.

Complementary to metabolic threshold monitoring, heart rate variability offers an additional layer of precision in exercise prescription and recovery guidance. HRV parameters are sensitive to the autonomic imbalance induced by oncological treatments and have been shown to change in response to supervised exercise training in cancer populations (Borsati et al., 2025; Task Force, 1996; Huberty et al., 2019). Their systematic incorporation into daily readiness assessment could facilitate adaptive, data-driven load management throughout an exercise protocol, reducing the risk of overreaching in a population with limited cardiovascular reserve. To date, however, the integration of daily HRV monitoring as a guiding biomarker for session-by-session load adjustment within a cardio-oncology exercise protocol has not been systematically described or validated.

Therefore, the primary objective of this protocol is to design and describe a structured, individualized, lactate threshold-based incremental treadmill exercise program—designated the LACTOC protocol—incorporating comprehensive cardiovascular and autonomic monitoring for oncology patients with treatment-induced cardiotoxicity. The secondary objectives include: (a) describing the systematic progression of exercise intensity based on objective metabolic responses; (b) characterizing the cardiovascular and autonomic parameters to be continuously monitored throughout the intervention; and (c) establishing a replicable methodological framework applicable in cardio-oncology clinical and research settings.

MATERIALS AND METHODS

Study design

The LACTOC protocol is designed as a prospective, single-arm, supervised exercise intervention study employing a longitudinal repeated-measures design. The protocol will be implemented over a 4-week period, comprising 12 supervised exercise sessions at a frequency of three sessions per week, with a mandatory minimum 48-hour recovery interval between consecutive sessions. This frequency aligns with current recommendations in cardio-oncology regarding exercise dose and recovery intervals for patients with cardiovascular compromise (D'Ascenzi et al., 2021; Riebe et al., 2015).

A defining methodological feature of this design is the dual-purpose nature of each session: the incremental treadmill test simultaneously constitutes the therapeutic exercise stimulus and the repeated assessment tool, enabling continuous monitoring of individual metabolic and cardiovascular adaptations across the intervention period. This longitudinal evaluation framework, with session-by-session load adjustment based on objective metabolic and autonomic data, distinguishes the LACTOC protocol from conventional fixed-prescription exercise programs that do not incorporate adaptive individualization. A comprehensive flowchart of the study is presented in Figure 1.

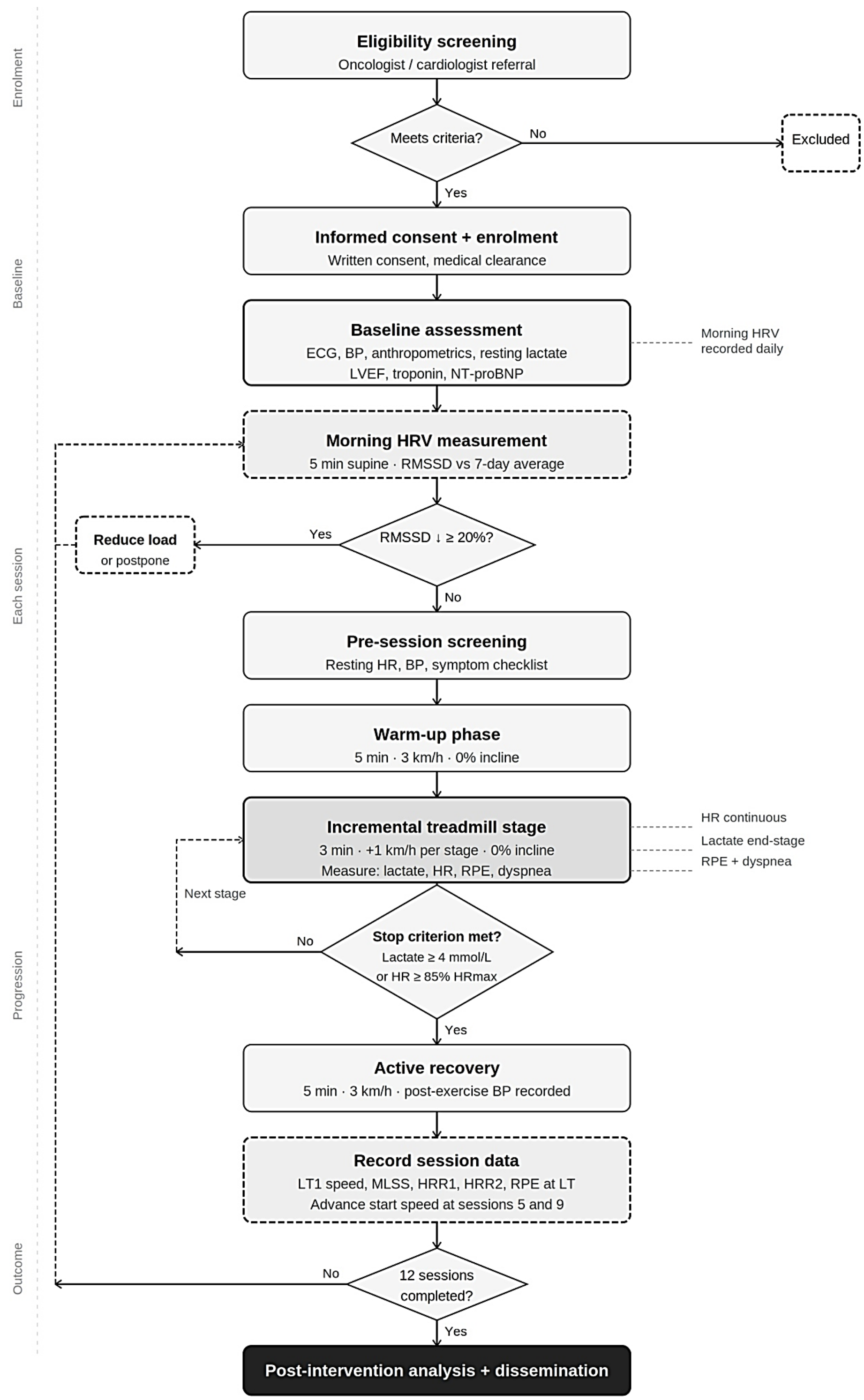

Figure 1. Flowchart of the LACTOC protocol, illustrating session structure, progressive load adjustment, monitoring timeline, and decision criteria for HRV-guided load modification.

Participants

Adult oncology patients with confirmed treatment-induced cardiotoxicity will be recruited from the Urology Unit of the Hospital Clínico Universitario "*Virgen de la Arrixaca*" (Murcia, Spain) and through the OncoSport Never Surrender Foundation. Participants will be referred by treating oncologists and cardiologists following diagnosis of cardiotoxicity according to established criteria, defined as a reduction in LVEF of ≥10 percentage points to a value below 53%, or the development of new signs and symptoms of heart failure attributable to oncological treatment (Scott et al., 2018; Sengupta et al., 2020).

Eligibility criteria for inclusion are: (a) confirmed cancer diagnosis with active or recently completed oncological treatment (chemotherapy, immunotherapy, hormonal therapy, or radiotherapy) within the preceding 12 months; (b) echocardiographically or biomarker-confirmed treatment-induced cardiotoxicity; (c) clinical stability confirmed by the treating cardiologist and/or oncologist, with written authorization to engage in supervised exercise; (d) age between 18 and 80 years; and (e) ambulatory capacity sufficient for treadmill walking without orthopedic restriction.

Exclusion criteria include: (a) absolute contraindications to exercise testing per current clinical guidelines (Gibbons et al., 2002), including unstable angina, uncontrolled arrhythmias, recent acute myocardial infarction (<30 days), severe symptomatic aortic stenosis, acute myocarditis or pericarditis, decompensated heart failure, or acute pulmonary embolism; (b) musculoskeletal conditions preventing treadmill ambulation; (c) cognitive impairment limiting the ability to provide informed consent or follow exercise instructions; and (d) participation in a structured supervised exercise program within the preceding 8 weeks. The sample size and statistical power calculation will be conducted a priori using G*Power software (Faul et al., 2007) based on anticipated effect sizes derived from comparable cardio-oncology exercise trials (Heck & Wackerhage, 2024; Taggart et al., 2013).

All participants will provide written informed consent prior to enrolment. The protocol will be conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and Good Clinical Practice guidelines. The study has received approval from the relevant Institutional Ethics Committee.

Procedures

A comprehensive baseline assessment session will be conducted prior to protocol commencement. This session includes a structured medical and exercise history, resting 12-lead electrocardiogram (ECG), resting blood pressure, anthropometric measurements (body mass, height, BMI, waist circumference), and a resting capillary blood lactate measurement to characterize individual resting lactate baseline values. Echocardiographic data (LVEF, global longitudinal strain) and cardiac biomarkers (high-sensitivity troponin, NT-proBNP) obtained as part of routine clinical follow-up within the preceding 4 weeks will be recorded from clinical records (Scott et al., 2018; Lopez-Fernandez et al., 2023).

Sessions will be conducted on a motorized treadmill in a temperature-controlled environment (18–22°C; 45–65% relative humidity). Participants will be instructed to refrain from strenuous physical activity for 24 hours prior to each session, abstain from caffeine and alcohol for 12 hours prior, and attend each session in a rested, post-absorptive state (minimum 2-hour fast). Standardized pre-session HRV measurement will be performed each morning of the exercise day under controlled conditions, prior to any physical activity.

Blood lactate concentration will be measured using a validated portable analyzer (e.g., Lactate Plus, Nova Biomedical, Waltham, MA, USA) from earlobe or fingertip capillary blood samples (5 µL) collected at the end of each incremental stage. This device has demonstrated acceptable analytical accuracy and reproducibility for field-based lactate assessment (Poole et al., 2021). Heart rate will be continuously recorded using a validated chest-strap monitor with RR interval logging (e.g., Polar H10, Polar Electro, Kempele, Finland) (Norton et al., 2010). Blood pressure will be measured using a validated automated sphygmomanometer immediately before warm-up and within 3 minutes of active recovery completion.

Measurements

Cardiovascular parameters

Heart rate will be continuously recorded throughout all phases of each session. Derived indices will include: resting heart rate (measured supine, 5 minutes pre-session); mean heart rate during the incremental test; maximal heart rate achieved; and heart rate recovery at 1 and 2 minutes post-test (HRR1 and HRR2). Heart rate recovery is calculated as the difference between maximal exercise heart rate and the values recorded at 1 and 2 minutes post-test cessation. Impaired HRR is a recognized marker of autonomic dysregulation and has been independently associated with increased cardiovascular risk in oncology populations (Borsati et al., 2025; Colin-Ramirez et al., 2012; Lauer et al., 1999).

Blood pressure (systolic and diastolic, mmHg) will be recorded at rest and within 3 minutes of active recovery. An exaggerated hypertensive response (systolic BP > 210 mmHg in men; > 190 mmHg in women) or a hypotensive response (systolic BP drop > 10 mmHg from resting value during the incremental test) will be documented as clinical events and will trigger session termination and clinical review in accordance with established exercise testing safety guidelines (Gibbons et al., 2002; Balady et al., 2010).

Metabolic parameters

Blood lactate concentration (mmol/L) will be measured at the end of each 3-minute incremental stage. The first lactate threshold (LT1), defined as the first systematic rise in blood lactate above resting levels, and the MLSS approximation—taken as the stage immediately preceding attainment of 4 mmol/L—will be identified individually for each participant at each session. This individualized approach to intensity determination based on objective metabolic criteria is recognized as superior to population-derived percentage methods in populations with cardiovascular compromise, as it accounts for individual metabolic variability irrespective of heart rate responses (Borsati et al., 2025; Lally & Gardner, 2013; Janssen, 2001). The evolution of LT1 and MLSS-approximated speed across sessions will serve as the primary marker of cardiovascular adaptation to training.

Perceptual parameters

Perceived exertion will be assessed using the Borg Rating of Perceived Exertion (RPE) scale (6–20) at the end of each incremental stage (Borg, 1982). Perceived dyspnea will be concurrently evaluated using a 0–10 numeric scale. Both instruments have been validated for use in cardiology and oncology exercise settings and provide clinically meaningful perceptual data to complement objective physiological measurements (D'Ascenzi et al., 2021; McNair & Depledge, 2001). The RPE value corresponding to the metabolically determined lactate threshold stage will be tracked across sessions as an indicator of psychophysical adaptation to training.

Heart Rate Variability (HRV)

Daily morning HRV will be recorded by each participant for 5 minutes in a supine position, immediately upon waking and prior to any physical activity or food intake, using a validated heart rate monitor with RR interval recording capability (Norton et al., 2010). This standardized morning protocol has been established as the reference methodology for HRV-guided training load management in exercise science (Plews et al., 2013). The following time-domain and frequency-domain parameters will be analyzed using validated software:

RMSSD (root mean square of successive RR interval differences, ms), a primary index of vagal modulation; SDNN (standard deviation of all normal RR intervals, ms), a global variability measure; LF power (0.04–0.15 Hz, ms²); HF power (0.15–0.40 Hz, ms²), reflecting parasympathetic activity; and LF/HF ratio, reflecting sympathovagal balance (Borsati et al., 2025; Task Force, 1996; Malmivuo & Plonsey, 1995).

HRV data will serve a dual role within this protocol: (1) as a longitudinal biomarker of autonomic recovery and cardiovascular adaptation to exercise training; and (2) as a daily readiness indicator for session load adjustment. A morning RMSSD value ≥20% below the rolling 7-day individual average will be considered a signal of insufficient autonomic recovery (Plews et al., 2013; Buchheit, 2014), and the corresponding session will be reduced in intensity or postponed following consultation with the supervising clinician. This individualized, HRV-guided approach to load management is grounded in the established methodology of HRV-based training prescription developed in elite and clinical exercise populations (Plews et al., 2013; Hautala et al., 2006).

Feasibility of the protocol

The following variables will be systematically recorded to evaluate protocol feasibility: recruitment rate (participants enrolled relative to those fulfilling inclusion criteria) (Arfken & Balon, 2011); attrition rate (dropouts and withdrawal reasons); session completion rate (sessions attended relative to the 12 prescribed); adherence (proportion of participants achieving ≥80% session completion) (Graham et al., 2016); and safety and tolerability (adverse events including symptomatic hypotension, angina, arrhythmia, syncope, or musculoskeletal injury documented in standardized report forms). Participants may experience transient muscle soreness or fatigue during the initial sessions, effects that typically diminish with continued training participation (Oviedo et al., 2020). A comprehensive overview of all monitored parameters and their measurement timing is presented in Table 1.

Table 1. Comprehensive monitoring framework of the LACTOC protocol.

Domain	Parameters	Measurement timing
Cardiovascular	Resting, mean, maximal, and recovery HR (1–2 min); pre- and post-exercise blood pressure	Pre-session, each stage, post-session
Metabolic	Blood lactate concentration (mmol/L)	End of each incremental stage
Perceptual	Perceived exertion (Borg 6–20); dyspnoea scale (0–10)	End of each incremental stage
Autonomic (HRV)	RMSSD, SDNN, LF, HF, and LF/HF ratio	Daily morning (5 min supine)

INTERVENTION

Prior to protocol commencement, all supervising educators will receive standardized training covering treadmill operation, capillary blood lactate sampling technique and quality control, HRV recording procedures, emergency protocols, and the progressive load adjustment algorithm. This training will be delivered in a structured workshop format to ensure methodological consistency across participants and potential multi-center application.

Session structure

Each of the 12 exercise sessions follows a three-phase structure: warm-up, incremental exercise test, and active recovery. The warm-up consists of 5 minutes of treadmill walking at a fixed speed of 3 km/h at 0% inclination, designed to achieve gradual cardiovascular activation and standardize the pre-test physiological state across sessions. The active recovery phase mirrors the warm-up (5 minutes at 3 km/h, 0% inclination), facilitating progressive cardiovascular deactivation and metabolic lactate clearance (Beneke et al., 2011). The complete session structure is detailed in Table 2.

Table 2. Structure of each LACTOC exercise session.

Phase	Duration	Speed	Inclination	Stop criterion
Warm-up	5 min	3 km/h	0%	—
Incremental Test	3 min/ stage	From 4 km/h (+1 km/h/stage)	0%	Lactate ≥ 4 mmol/L or HR ≥ 85% HRmax
Active recovery	5 min	3 km/h	0%	—

The core of each session is a progressive incremental treadmill test beginning at an initial speed of 4 km/h (0% inclination), with the speed increased by 1 km/h at the end of each 3-minute stage. This stage duration was selected to allow sufficient time for blood lactate to reach a near-steady-state concentration at each workload, consistent with established incremental test methodology for lactate threshold determination (Janssen, 2001; Poole et al., 2021). The test continues until one of the following pre-established termination criteria is met: (1) attainment of blood lactate ≥ 4 mmol/L, reflecting approach to or surpassing of the MLSS (Beneke et al., 2011); (2) attainment of ≥85% of the participant's theoretical maximal heart rate; or (3) voluntary cessation by the participant or termination by supervising personnel based on clinical safety indicators.

Progressive load adjustment

A key methodological feature of the LACTOC protocol is its systematic progressive overload mechanism. The initial treadmill speed will be increased by 0.5 km/h every four sessions (i.e., at sessions 5 and 9), such that participants commencing at 4 km/h will begin at 4.5 km/h from session 5 and at 5 km/h from session 9. This progression is grounded in the physiological principle of progressive overload and in current understanding of the timeframe required for MLSS adaptations (Janssen, 2001; Beneke et al., 2011). The structured progression schedule is summarized in Table 3.

Table 3. Progressive load adjustment schedule across the 12-session protocol.

Sessions	Initial Speed (km/h)	Progressive goal	HRV-based adjustment
1–4	4.0	Establish LT baseline; familiarization	Monitor; no progression if RMSSD ↓ ≥20%
5–8	4.5	Increase aerobic threshold speed	Suspend progression if recovery insufficient
9–12	5.0	Consolidate cardiovascular adaptation	Individualize final load per HRV trajectory

Load adjustment will additionally be informed by daily morning HRV data. When HRV-based recovery indicators suggest insufficient autonomic recovery (RMSSD ≥ 20% below the rolling 7-day individual average), the planned speed progression will be temporarily suspended or the session load reduced, at the discretion of the supervising educator in consultation with the clinical team (Plews et al., 2013; Buchheit, 2014; Hautala et al., 2006). This individualized, data-driven load management approach represents a clinically meaningful advance over fixed-prescription exercise programs in populations with cardiovascular vulnerability.

Supervision and safety

All sessions will be directly supervised by a certified physical activity and sport sciences educator with clinical exercise experience. Emergency equipment—including an automated external defibrillator (AED), oxygen supply, and access to emergency pharmacological protocols—will be always available at the exercise venue (Riebe et al., 2015; Gibbons et al., 2002). Clear session termination criteria, standardized adverse event reporting forms, and a pre-established emergency action plan will be implemented prior to protocol commencement.

A conservative clinical approach to exercise safety will be maintained throughout. Participants will be instructed to report any symptoms—chest pain or pressure, palpitations, unusual dyspnea, dizziness, or pre-syncope—immediately and without hesitation. The supervising educator will conduct a brief pre-session wellness screening at the start of each session, including resting HR, blood pressure, and a standardized symptom checklist, to detect acute clinical deterioration prior to exercise commencement. This systematic pre-session screening protocol is consistent with current exercise safety standards in cardio-oncology (D'Ascenzi et al., 2021; Riebe et al., 2015; Gibbons et al., 2002).

Statistical analysis

Descriptive statistics will be reported as means ± standard deviations for normally distributed continuous variables, or as medians and interquartile ranges for non-normally distributed variables. Distribution normality will be assessed using the Shapiro-Wilk test. Categorical variables will be reported as frequencies and percentages.

Changes in cardiovascular, metabolic, perceptual, and HRV outcomes across the 12 sessions will be analyzed using repeated measures analysis of variance (ANOVA) or the Friedman test, as appropriate. Post-hoc comparisons will be adjusted using the Bonferroni correction. Pre-to-post intervention changes in primary outcomes (LT speed, maximal HR, HRR1, RMSSD, RPE at LT stage) will be assessed using paired t-tests or Wilcoxon signed-rank tests. Effect sizes will be reported as Cohen's d for parametric comparisons and rank-biserial correlation (r) for non-parametric analyses (Cohen, 1988).

Associations between daily HRV parameters and cardiovascular/metabolic responses during the incremental test will be explored using Pearson or Spearman correlation coefficients, as appropriate. Multivariate regression models will be constructed to identify independent predictors of cardiovascular adaptation, adjusting for potential confounders including age, sex, BMI, cancer type, treatment regimen, and baseline LVEF. Multicollinearity will be assessed using the Variance Inflation Factor (VIF), with VIF > 5 indicating high collinearity (Akinwande et al., 2015). Statistical significance will be set at a two-tailed $p < .05$. All analyses will be conducted using SPSS v26.0 (IBM Corp., Armonk, NY, USA) and R v4.3 (R Core Team, Vienna, Austria).

DISCUSSION

The LACTOC protocol was developed in response to the recognized limitations of conventional exercise prescription approaches in oncology patients with cardiotoxicity. The primary rationale for a lactate threshold-based protocol stems from the well-documented imprecision of heart rate percentage and VO_2peak-derived intensity prescriptions in populations with cardiovascular compromise (Borsati et al., 2025; Whellan et al., 2014). As demonstrated by Schneider et al. (2020), ventilatory and lactate thresholds provide superior individualization relative to VO_2peak-based methods in cancer survivors, and should be considered the preferred reference framework when precise, safe exercise intensity prescription is clinically required. The LACTOC protocol operationalizes this recommendation within a structured, 12-session supervised program.

A distinctive methodological contribution of the LACTOC protocol is its adaptive, data-driven approach to load management, informed by both objective lactate-based session termination criteria and daily HRV monitoring. The rationale for HRV-guided load adjustment is grounded in the established relationship between parasympathetic modulation indices—particularly RMSSD—and acute cardiovascular recovery status (Plews et al., 2013; Buchheit, 2014; Hautala et al., 2006). In healthy athletes, HRV-guided training prescription has been shown to produce superior cardiovascular adaptations compared to fixed-prescription approaches (Hautala et al., 2006); extending this methodology to oncology patients with autonomic dysregulation may offer comparable benefits in terms of both safety and training efficacy (Borsati et al., 2025; Task Force, 1996). The daily monitoring burden imposed on participants is minimal, requiring only a 5-minute supine recording upon waking, and is feasible using widely available consumer-grade heart rate monitors with validated accuracy (Norton et al., 2010; Plews et al., 2017).

The choice of the treadmill as the exercise modality is supported by its clinical ubiquity, the precision of speed control for lactate threshold determination, and the documented tolerability of walking-based exercise in oncology populations (Amin et al., 2024; Schneider et al., 2023). Treadmill-based incremental protocols with blood lactate sampling have an established methodological track record in both sports science and clinical exercise physiology (Janssen, 2001; Beneke et al., 2011; Poole et al., 2021), and their application in oncology settings has been described in the context of cardiorespiratory fitness assessment (Borsati et al., 2025; Whellan et al., 2014). The walking format at moderate speeds is particularly well-tolerated in patients with reduced functional capacity, and the progressive nature of the protocol accommodates a wide range of baseline fitness levels.

The frequency of three sessions per week across four weeks aligns with current cardio-oncology exercise recommendations (D'Ascenzi et al., 2021; Riebe et al., 2015) and has been employed in comparable supervised exercise trials demonstrating cardioprotective effects during chemotherapy (Heck & Wackerhage, 2024; Taggart et al., 2013). While the 4-week duration is shorter than many conventional exercise intervention trials in oncology, it was intentionally designed as a clinically feasible initial intervention window with measurable cardiovascular and autonomic outcomes, minimizing participant burden in a population frequently experiencing treatment-related fatigue and logistical constraints. The protocol architecture is designed to be extended or embedded within longer rehabilitation programs following validation of its safety and feasibility profile.

This protocol is, to the best of our knowledge, the first to propose a combined lactate threshold-based incremental treadmill program with integrated daily HRV monitoring specifically designed for oncology patients with treatment-induced cardiotoxicity. Its methodological contribution lies not only in the lactate-anchored intensity prescription but also in the explicit operationalization of HRV-based readiness criteria for session-by-session load adjustment in a clinically vulnerable population—an aspect that has remained largely unexplored in the cardio-oncology exercise literature (Borsati et al., 2025; Task Force, 1996).

Several potential limitations of this protocol should be acknowledged. First, the absence of a randomized control group in this initial implementation limits the capacity to definitively attribute observed outcomes to the LACTOC intervention, as opposed to natural clinical course or regression to the mean. Future randomized controlled trials incorporating a comparator arm—such as a conventional percentage-based prescription protocol or a usual care control—are warranted to establish superiority. Second, the reliance on self-administered morning HRV recordings introduces variability dependent on participant adherence to standardized measurement conditions. Structured participant education and written protocols will be provided to minimize this source of error, and validity checks of recording quality will be applied during data processing

(Plews et al., 2017). Third, the clinical heterogeneity of the target population—with respect to cancer type, treatment regimen, degree of cardiotoxicity, and baseline fitness—may limit the generalizability of protocol-level findings. Pre-specified subgroup analyses by cancer type, treatment category, and baseline LVEF are planned to partially address this limitation. Lastly, physical activity levels outside supervised sessions will be monitored through self-reported weekly logs, a method subject to recall bias (Lynch et al., 2024); future iterations of this protocol may incorporate accelerometry-based objective activity monitoring.

Future research should investigate the long-term cardiovascular and autonomic adaptations to lactate threshold-based exercise protocols over extended intervention periods of 12–24 weeks, as well as the potential for remote or home-based delivery facilitated by wearable HRV monitoring technologies. Comparative studies evaluating the LACTOC approach against ventilatory threshold-based prescription and high-intensity interval training protocols in cardiotoxicity populations would further strengthen the evidence base for precision exercise medicine in cardio-oncology.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. A.S-L.: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing, Project Administration. E.C-A.: Conceptualization, Supervision, Clinical Oversight. L.H-V.: Supervision, Clinical Oversight. D.G-D.: Methodology, Writing – Review & Editing. D.L-P.: Methodology, Software. R.T-P.: Writing – Original Draft Preparation. A.G-C.: Writing – Review & Editing, Supervision. C.D.G-C.: Conceptualization, Methodology, Software, Writing – Review & Editing, Visualization. All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

ETHICAL APPROVAL

The research protocol was reviewed and approved by the Clinical Research Ethics Committee of the University Clinical Hospital "*Virgen de la Arrixaca*" (Murcia, Spain) and was conducted in accordance with the Declaration of Helsinki.

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