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STUDY PROTOCOL

Effects of arm-crank exercise on cardiovascular function, functional capacity, cognition and quality of life in patients with peripheral artery disease: Study protocol for a randomized controlled trial

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Abstract

Background

Arm-crank exercise training (ACT) is an alternative exercise strategy for patients with symptomatic peripheral artery disease (PAD) due to the attenuation of pain symptoms during the exercise, as well as the benefits to functional capacity.

Purpose

The aim of this study is to describe the study protocol to analyze the effects of ACT exercise on cardiovascular function, functional capacity, cognition and quality of life in patients with symptomatic PAD.

Methods

This is a three-armed randomized, prospective, single-blind data collection, single-center, controlled study enrolling 45 patients with symptomatic PAD who will be randomized into 3 intervention groups: walking training (WT), ACT and control group. The WT and ACT will perform 2 sessions/week, 15 to 10 sets of 2 to 5 minutes at values of 13 to 15 on the Borg scale. Before and after 12 weeks of intervention, cardiovascular function (ambulatory blood pressure, office blood pressure, central blood pressure, heart rate variability, arterial stiffness and vascular function), functional capacity (six-minute walk test, 2 minute step test, handgrip test, Walking impairment questionnaire, Walking estimated limitation calculated by history, Baltimore activity scale for intermittent claudication, and short physical performance battery), cognition (executive function and memory), and quality of life (vascular quality of life questionnaire and World Health Organization Quality of Life) will be assessed.

design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Results

This is the first trial to evaluate the effects of ACT on regulatory mechanisms of the cardiovascular system in PAD patients. If the results are as expected, they will provide evidence the ability of ACT to promote cardiovascular benefits in the symptomatic PAD population.

Introduction

Peripheral artery disease (PAD) is the result of a chronic atherosclerotic process, which progressively leads to partial or total obstruction of the arteries that irrigate peripheral regions of the human body [1]. The main symptom of PAD is called intermittent claudication, which is characterized by pain, cramps, or burning that occurs in the lower limbs during physical activity and are relieved with rest [2].

Walking training (WT) is indicated as the initial and preferred form of clinical treatment for patients with symptomatic PAD [3], due to its benefits to functional capacity (e.g. increasing pain-free walking distance and total walking distance) [4], some parameters of cardiovascular health (e.g. lowering office blood pressure [BP], improving cardiac autonomic modulation, blood flow, and endothelial function), and quality of life [4–8]. Despite these benefits, WT usually implies in symptoms of pain in the lower limbs during execution, which could be considered as a barrier for long-term adherence to this modality of exercise program [9, 10]. Thus, identifying exercise modalities that have a positive effect on functional capacity, cardiovascular health, and quality of life and that, at the same time, minimize pain symptoms could be an interesting strategy for these patients.

Arm crank exercise training (ACT) has been applied as a non-painful modality strategy in patients with PAD with positive benefits on functional capacity and quality of life [11–13]. Regarding cardiovascular parameters, two previous studies demonstrated that ACT decreased office systolic BP in patients with symptomatic PAD [12, 13]. However, in these two studies, cardiovascular parameters were considered outcomes secondary and, therefore, they did not have an adequate study design, requiring further studies. In this context, the effects of ACT on other cardiovascular parameters (e.g. office and ambulatory BP, cardiac autonomic modulation, arterial stiffness, and vascular function), as well as on other parameters besides the cardiovascular system, such as cognitive function, which are impaired in these patients and have been related to the severity of the disease, are not known [14–17]. Thus, the aim of this study is to describe the protocol of a study protocol to analyze the effects of ACT on primary outcomes: office and ambulatory BP; and on secondary outcomes: BP determinants (i.e. heart rate variability, arterial stiffness and vascular function), functional capacity, cognition, and quality of life in patients with symptomatic PAD.

Materials and methods

Eligible participants

Patients with symptomatic PAD will be recruited from hospitals in São Paulo, Brazil. The inclusion criteria include: a) age $>$ 40 years old; b) ankle brachial index (ABI) $<$ 0.90 in one or both limbs; c) if the woman is in the post-menopausal period, without hormone replacement therapy; and d) able to perform physical exercise in upper and lower limbs. Exclusion criteria include: a) a change in medication during participation in the study; b) the presence of health problems that preclude performance of physical exercise during the participation in the study.

After agreeing to participate in the study, each patient will undergo a clinical evaluation. To confirm the PAD diagnosis, ABI will be assessed in accordance with previous guidelines [18]. Briefly, ABI will be measured as the highest systolic blood pressure in the posterior tibial or dorsalispedis artery, divided by the highest systolic blood pressure in the brachial artery. Blood pressure measurements will be recorded in both limbs using a doppler vascular monitor (DV160, Medmega, Brazil) and a sphygmomanometer.

To identify possible cardiovascular abnormalities during exercise, patients will be submitted to maximal treadmill test with a specific protocol for the PAD population [19]. The test will start at a constant speed of 3.2 km/h, with 2% incline increments every two minutes until exhaustion. During the test, heart rate will be continuously monitored by an electrocardiogram and BP will be obtained every two minutes using a mercury sphygmomanometer. Only patients with no restrictions to perform physical exercise training will be included.

Study design

This is a randomized clinical trial with single-blind data collection. The Recommendations for Interventional Trials (SPIRIT) flow chart and enrolment schedule, details of interventions, and assessments for the trial are given in Fig 1. The protocol study will be conducted according to the ethical principles governing research involving human subjects stipulated in Resolution 466/2012 of the Brazilian National Board of Health. The study protocol was approved by the Research Ethics Committee of Human Research of the Hospital Israelita Albert Einstein, Brazil (February 2020—CAAE: 81187317.6.0000.0071), Hospital das Clínicas, Faculty of Medicine, University of São Paulo, Brazil (March 2020—CAAE: 81187317.6.3002.0068),and registered and published in the ClinicalTrials.gov (registration number: NCT03837639). All participants will read and sign an informed consent form before enrollment. Participation will be voluntary, and all ethical principles of confidentiality and data protection will be maintained. The Research Ethics Committee of Human Research of the Hospital Israelita Albert Einstein will periodically monitor the study performance.

Patients will perform two visits, with an interval of at least 48 hours. In the first visit, patients will perform the functional tests (i.e., 6-min walk test, 2 minute step test [2 MST], handgrip test, walking impairment questionnaire [WIQ], walking estimated limitation calculated by history [WELCH], Baltimore activity scale for intermittent claudication, and short physical performance battery [SPPB]), cognitive assessments, and answer the quality of life questionnaires (vascular quality of life questionnaire [VASCUQOL-6] and World Health Organization Quality of Life [WHOQOL brief]). On the second visit, patients will undergo cardiovascular assessments (i.e., office BP, ambulatory BP, central BP, heart rate variability, arterial stiffness and vascular function). Patients will then be randomly allocated in blocks to one of the three intervention groups (WT, ACT, and control groups [CG]) and will be re-evaluated after 12 weeks. The random allocation sequence will be generated by Researcher Randomizer (https://www.randomizer.org). These data will be collected by a trained kinesiologist who will be blind to the interventions. The study design is shown in Fig 2.

During the study, patients will be discontinued if they they choose to withdraw from the study or change their medication or present any health impairment that contraindicates the continuation of the practice of physical exercise during the study.

Interventions—Arm crank exercise, treadmill exercise, and control group

Before starting the program, patients randomized to the ACT group will perform an adaptation session for familiarization with the ergometer and also to identify the training load. For this, patients will perform 10 bouts of two minutes of exercising with a minimum load and two

	STUDY PERIOD				
	Enrolment	Pré-evaluation	Allocation	Intervention	Post-evaluation
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation			X		
INTERVENTIONS:					
Arm-crank exercise				X	
Waking training				X	
Control				X	
ASSESSMENTS:					
Functional Capacity		X			X
Cognition		X			X
Cardiovascular Function	X	X			X
Quality of life		X			X

Fig 1. The recommendations for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments.

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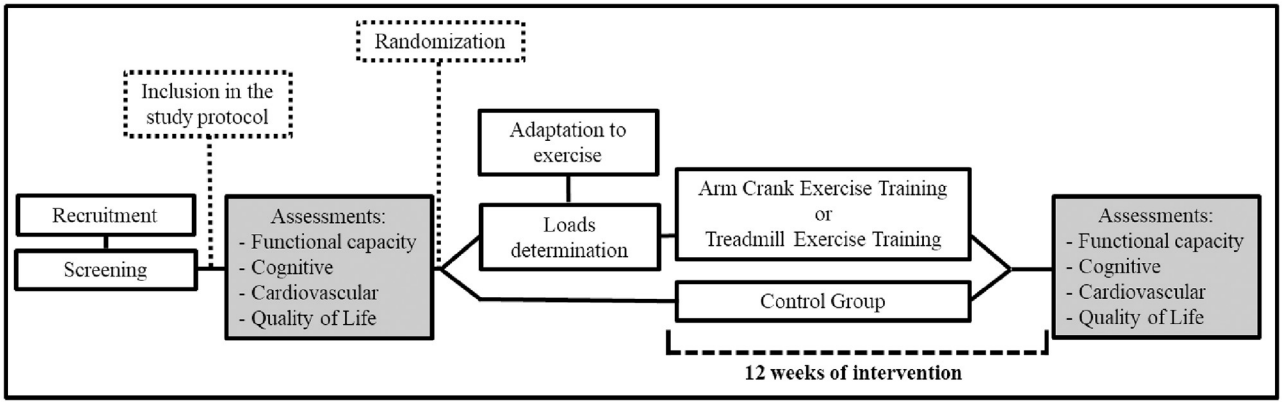

Fig 2. Design study.

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minute passive intervals between bouts. Patients will be instructed to maintain 50 revolutions per minute (RPM) during the exercise. Subsequently, to determine the training load for each session, patients will perform a progressive test where the load will be increased by 10 watts every minute of the test, following the protocol of two minutes of exercise with two minutes of interval until the patient reports values of 13–15 on the subjective effort perception scale (Borg scale—6 to 20) [20].

Similarly, patients randomized to the WT group will perform 10 bouts of two minutes at 3.2 km/h, without incline, on the treadmill. Subsequently, the load will be progressively increased by 0.3 km/h every minute of the test until the patient reports values of 13–15 on the Borg scale. In both adaptations (ACT and WT), heart rate will be continuously monitored via a heart rate monitor (Polar A300, Polar, Finland) and the subjective effort perception scale (Borg scale—6 to 20) will be obtained at the end of each minute during the exercise.

Thus, during the first training sessions (i.e., ACT and WT), the workload corresponding to values of 13–15 on the Borg scale obtained in the progressive test will be employed. The Arm Crank exercise training and WT training will be performed twice a week for 12 weeks. The periodization of the training is shown in Table 1. In the first 3 weeks, each session will consist of 15 bouts of two minutes of exercise with two minutes of passive recovery. After that, the exercise time will be progressively increased by one minute every 3 weeks and the recovery period will be decreased, to a final maximum volume of 10 bouts of 5 minutes of exercise with 1 minute of passive recovery. The intensity of both exercise groups will be determined by the intensity equivalent to the range of 13–15 on the Borg scale (Borg scale—6 to 20 [20]. In addition, the intensity assessment will be performed during (each exercise bout) and at the end of each training session. All sessions will be supervised by a qualified kinesiologist with experience in vascular disease rehabilitation. Safety will be assessed by the proportion of participants who experience intervention-related adverse events during the study period.

Patients randomized to the CG will also attend to meetings with the researcher team twice a week during the 12 weeks in order to minimize the effects of the patient's bi-weekly commitment and displacement to the training site, to minimize the influence of the patient-researcher contact, and also minimize the convivial effect among the patients themselves, which will occur in the other two groups. During the meetings, patients will perform manual tasks with the use of artistic materials, cultural programs, cooking classes and home care, without any exercise component.

All patients included in the study will also receive recommendations to increase their levels of physical activity, which is the standard recommendation for clinical treatment for these patients [21].

Measurements

For all measurements, patients will be instructed to eat a light meal 2 h beforehand, to avoid caffeinated beverages on the experimental days, and not to perform exercise in the previous 48 hours. With the exception of the six-minute walk test that will be performed along a 30-meter-

Table 1. Periodization during the 12 weeks of training.

Weeks	Bouts	Active exercise	Total active time	Interval	Total interval time	Total session time
1–3 Week	15	2'	30'	2'	30'	60'
4–6 Week	14	3'	42'	1'30"	19'30"	62'
7–9 Week	12	4'	48'	1'	11'	59'
10–12 Week	10	5'	50'	1'	9'	59'

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long corridor, the other evaluations will be conducted at a laboratory, in a quiet environment, with monitored temperature, and no interruptions. The time of the day of the preintervention measurements of each patient will be maintained in the post-intervention evaluations.

Outcomes. The primary outcomes of the study are office and ambulatory BP. Secondary outcomes are: (1) cardiovascular function (central BP, heart rate variability, arterial stiffness, and vascular function); (2) functional capacity (six-minute walking test, 2 minute step test, handgrip test, Walking impairment questionnaire, Walking estimated limitation calculated by history, Baltimore activity scale for intermittent claudication, and short physical performance battery); (3) cognition (executive function and memory); and (4) quality of life (vascular quality of life questionnaire and World Health Organization Quality of Life).

Primary outcome

Office blood pressure. Systolic and diastolic office BP will be measured by an automatic monitor (HEM-742, Omron Healthcare, Japan), during ten minutes at rest in a supine position. Three consecutive measurements will be performed with a one-minute interval between them, in both arms, and with the appropriate cuff size. The value used will be the average of the final two measures.

Ambulatory blood pressure. Ambulatory BP will be assessed by an oscillometric device (Dyna-MAPA, Cardios, Brazil) programmed to take measurements every 15 min for 24 hours. The recordings will only be accepted if at least 80% of the readings are successfully performed. Patients will be instructed to complete a diary to record the time of sleep, waking and daytime activities. Ambulatory data will be analysed using the averages of 24 h, awake, and asleep periods [22].

Secondary outcomes

Cardiovascular function. *Central blood pressure*. Central BP will be obtained by the pulse wave analysis recorded in the left radial artery using applanation tonometry (SphygmoCor AtcorMedical, Sydney, Australia) and a validated transfer function algorithm provided by the Sphygmocor® software will be use to estimate the central values of systolic, diastolic, and mean BP [23].

Heart rate variability. Heart rate variability will be assessed from the beat to beat intervals obtained using a heart rate monitor (V800, Polar Electro, Finland) for 10 min, with the patient in the supine position. Continuous stationary data recorded for at least 5 min will be used for analysis. All analyses will be performed using software (Kubios HRV, Biosignal Analysis and Medical Imaging Group, Finland) according to the recommendations of the Task Force for heart rate variability [24]. The time-domain parameters (SDNN—standard deviation of all RR intervals, RMSSD—root mean square of the squared differences between adjacent normal RR intervals, pNN50 –the percentage of adjacent intervals over 50ms) and frequency-domain (low frequency, high frequency, and low frequency/high frequency) parameters will be analyzed as previously described [24].

Arterial stiffness. The arterial stiffness parameters, such as pulse pressure (difference between systolic and diastolic blood pressure) and augmentation index (the proportion of pulse pressure that is attributed to the reflected pulse wave) will be obtained through applanation tonometry (SphygmoCor, AtCor Medical, Australia), in the radial artery. Carotid-femoral pulse wave velocity will be measured by applanation tonometry (Sphygmocor, AtCor Medical, Australia) following the guidelines of the Clinical Application of Arterial Stiffness, Task Force III [23]. The distance from the carotid artery to the suprasternal notch and the femoral artery to the suprasternal notch will be measured using a standard tape. Electrocardiogram will be

simultaneously assessed to obtain heart rate and, according to a "foot-to-foot" method, the time difference between the points will be measured. The distance between the two arteries will then be divided by the time difference.

Vascular function. Vascular function will be estimated by resting blood flow and flow-mediated dilation measurements obtained by an ultrasound technique according to recent recommendations [25]. Images of the brachial arteries will be recorded by a two-dimensional ultrasound with a spectral Doppler and linear transducer (Ultra-0122, Philips, The Netherlands). For this, each patient will remain in the supine position for at least 20 minutes. After location of the arteries, the transducer will be positioned and to attest to the good quality of the arterial pulse obtained, the Doppler sound will be activated.

The contrast resolution, depth, and gain will be adjusted to optimize the longitudinal images of the lumen/arterial wall interface. Insonation angle, corrected at 60˚, blood velocity spectra will be simultaneously recorded via the pulsed-wave mode at linear frequencies of 13 and 6.0 MHz, respectively.

Baseline diameter and blood velocity waveforms will be continuously recorded over 120 s. After that, a cuff, placed distal to the image capture, will be inflated with a pressure above 50 mm Hg of the systolic BP measured before the examination. The image and Doppler recordings will be resumed 30 s before deflation and will be maintained for 180s after deflation.

The diameters and post-occlusion blood flow velocities will be measured after the release. The vasodilatory capacity will be calculated by the flow-mediated dilation, the percentage increase in diameter of the brachial artery post occlusion compared to their baseline values.

Functional capacity. *Six-minute walk test*. The six-minute walk test will be performed along a 30-meter-long corridor, as previously described [26, 27]. Briefly, patients will be encouraged to "walk at their usual pace for six-minutes and cover as much ground as possible" and rest if necessary. The outcomes will be the onset claudication distance (distance walked when the patients related the occurrence of symptoms of intermittent claudication) and six-minute total walking distance (maximum distance achieved by the patient at the end of the test).

Two-minute step test. The two-minutes step test will be performed as previously described [28]. Patients will be required to walk on the spot for 2 minutes, and the maximum number of steps will be counted. The walk will consist of alternate elevation of the knees to the mean height of the thigh (midpoint between the patella and the anterior superior iliac spine). Patients will be instructed to complete as many steps as possible during the test.

Walking impairment questionnaire. The walking impairment questionnaire [29] contains three domains measuring three factors of walking impairment: walking distance, walking speed, and the ability to climb stairs. Patients will be asked how difficult it was to walk in these situations and will be required to answer from among the options "none, slight, some, much, or unable". Each domain is scored on a 0 to 100 scale, where 0 represents extreme limitation and 100 represents no difficulties walking long distances, walking rapidly, or climbing 3 flights of stairs, respectively.

Walking estimated limitation calculated by history. The walking estimated-limitation calculated by history is a four-question questionnaire, in which the first 3 questions are related to how long patients can perform the task easily on level ground and without stopping at different walking speeds and the last question is related to speed comparisons with their relatives, friends, or people of the same age. The score (ranges from 0 to 100) is calculated as the sum of the values for the first three, minus one, multiplied by the coefficient for the final (walking speed) questionnaire item [30].

Handgrip test. The handgrip test will be performed to evaluate the handgrip strength. The test will be performed using a dynamometer with digital display (EH101, Camry, USA),

calibrated with a scale from 0 to 100 kgf, following a previous protocol [31]. Patients will be evaluated seated with a slightly adducted shoulder, elbow flexed at 90˚, forearm and wrist in neutral position. Three attempts at the test will be performed in each of the dominant and non-dominant hands, alternately, and the highest value will be used for analysis.

Baltimore activity scale for intermittent claudication. The Baltimore Activity Scale for Intermittent Claudication will be obtained following a previous protocol [32]. The scale consists of five questions related to the symptoms of intermittent claudication. For each question, the patient selects the answer that best describes their symptoms and level of physical activity. Values range from 0 to 2 points, and the total score is the sum of the points from the 5 questions. The score ranges from 0 to 10, with zero being the lowest level of physical activity and ten being the highest [32].

Short physical performance battery. Functional capacity will also be obtained by the short physical performance battery, as previously described [33]. The short physical performance battery is a group of measures that combines the results of gait speed, chair stand, and balance tests. The total score will be calculated from the performance in the three tests, ranging from 0 to 12, with 0 representing the worst function and 12 the best function.

Cognition. Standardized cognitive tasks to quantify executive function and memory will be evaluated as previously described [34]. These assessments will be carried out on paper and include: a) executive function—Test A and B, coding of digit symbols; b) memory: Hopkins verbal learning test (immediate and delayed recovery), forward and backward digit range; c) verbal fluency: task of generating words ("S" and animals).

Quality of life. *Vascular quality of life questionnaire– 6*. The quality of life will be evaluated by the vascular quality of life questionnaire VascuQoL-6, as previously described [35]. The questionnaire is composed of six items to evaluate the impact of disease on social aspects and the capacity to perform daily activities. Each item is scored from 1–4. The total score is achieved by summarizing the score on each item, resulting in a score between 6 and 24. A higher value indicates better health status.

World Health Organization Quality of Life (WHOQOL) brief. The WHOQOL-brief instrument measures different aspects of physical and mental health, which include the following dimensions: general health status, functional capacity, physical aspects, pain, vitality, mental health, emotional aspects, and social aspects of life. Each answer receives a score, which is added to a constant to determine the different components of quality of life [36].

Intervening variables

In order to minimize the possible influences of intervening variables, and to ensure that the changes generated in the outcomes are caused by ACT or WT interventions, medications, dietary pattern, and physical activity levels will be monitored.

To control medication, each week the researcher will be responsible for filling a container with the medications prescribed for the patient, according to the frequency, time, and recommended dosage. At the end of the week (in the second weekly session), the researcher will check if the patient correctly took the medications. Patients will be followed during the 12 week period of the intervention.

For food monitoring, before and after the intervention period, patients will be asked to complete a food diary for four days of the week, including at least one day of the weekend. Based on this information, it will be possible to analyze changes in the dietary patterns of the patients, as well as to estimate the caloric intake ingested before and after the intervention period.

Finally, patients will use a smartwatch (A300, Polar, Finland) to estimate their physical activity levels. The POLAR A300 is a monitor coupled with a 3D accelerometer that records patient's movements. With the watch, it is possible to analyze the frequency, intensity, and regularity of the movements and, consequently, to determine physical activity levels. Patients will use this monitor for one week before the first evaluation and one week after the final week of training, to allowing identification of possible changes in physical activity level after the ACT, WT, and CG interventions.

Statistical analysis

Power and sample size. The sample size was determined by the a priori specific sample calculation for clinical trials involving parallel groups, in this case two-way ANOVA with repeated measures, suggested by Beck (2013) [37]. Using GPower 3.1.9.2 software it was considered an effect size of 0.25; α of 0.05; power (1—β) of 0.80; correlation coefficient between repeated measures of 0.6; non-spherical correction (ε) of 1 and three groups two measures. Thus, the minimum total size reached 36 subjects (12 per group) with 83% power. Considering the possibility of sample loss, the sample was inflated by 20%, resulting in a sample of 45 patients (15 per group).

Analysis plan. The normality and homogeneity of variance will be performed using the Shapiro-Wilks and Levene test. For pre-intervention comparisons, we will use one-way ANOVA or Qui-square. For the pre and post comparison, we will use ANOVA for repeated measures, establishing as the main factors: intervention (WT, ACT and control) and time (pre- and post-intervention). Newman-Keuls post-hoc test will be used with $P < 0.05$ value as significant. Intention-to-treat will be used for the patients with incomplete follow-period.

Trial status

Enrollment of patients started in December 2019. Collection was suspended between March 2020 and July 2021 because of the COVID-19 pandemic. Thirty percent of the data collection has already been completed. Recruitment is scheduled to be completed on 31.11.2022.

Discussion

Previous studies [13, 38] comparing ACT versus WT have shown similar improvement in the pain-free walking distance and total walking distance during the treadmill exercise test. However, the effects of ACT on the walking capacity in other conditions (e.g., walking fast, climbing stairs, the six-minute walking test, etc), as well as on the other parameters of functional capacity, such as strength and balance, are still unclear. This is relevant, since these patients also present alterations in different parameters of functional capacity [10, 27, 29, 39].

Regarding cardiovascular parameters, two previous studies [12, 13] demonstrated the benefits of ACT on systolic BP compared to the control group. We expect to confirm these results, and expand the analysis to other cardiovascular parameters, including ambulatory BP, arterial stiffness, cardiac autonomic regulation, and vascular function. Due to the systemic effects of exercise training for upper limbs on cardiovascular function [40], we expect similar results with ACT to those observed in WT, which includes improvements in cardiac autonomic modulation [7], vascular function [7], and ambulatory blood pressure variability [5].

Patients with symptomatic PAD usually present impairments in cognitive function [15] however, the effect of exercise training on the cognitive function of these patients is still unclear. In other populations without PAD (e.g. older people, etc.) exercise training has been shown to improve cognitive function [41–45]. Several mechanisms have been proposed to explain the effects of exercise training on cognitive function, including improvements in

vascular function of cerebral arteries [46]. In this context, as patients with PAD commonly present impairments in cerebral vascular functions [46, 47], it is possible that the systemic cardiovascular effects of ACT can improve cognitive functions.

Patients with PAD have limited exercise capacity, reduced functional performance, and poor cardiorespiratory fitness, as well as several comorbidities that can lead to a significant impairment in health-related quality of life [48]. Thus, full understanding of the health benefits resulting from exercise training must include outcomes related to quality of life [49]. Since both modalities employed in this study can significantly improve physical and cardiovascular function, we expect that these aspects may help to alleviate the burden of the disease (improving symptoms and reducing comorbidities related to PAD), which could have a strong bearing on perceived health-related quality of life.

In summary, the present study aims to provide a broader analysis of the effects of ACT in patients with symptomatic PAD. The current study might reinforce and expand the use of ACT as a treatment strategy for patients with PAD and intermittent claudication.

Supporting information

S1 Checklist. SPIRIT 2013 checklist: Recommended items to address in a clinical trial protocol and related documents*.
(DOC)

S1 File. Ethical approval document.
(PDF)

S2 File. Translation ethics.
(DOCX)

S3 File. Ethical approval document.
(PDF)

S4 File. Translation ethics.
(DOCX)

S5 File. Study protocol approved.
(DOCX)

S6 File. Translation of the study protocol approved.
(DOCX)

S7 File. Questionnaire on inclusivity in global research.
(DOCX)

Author Contributions

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