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STUDY PROTOCOL

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Modulation of the autonomic system, pulmonary function and sleep disorders in hypertensive patients submitted to aerobic training. A study protocol

Ronivaldo Lameira Dias[1,2], Luis Vicente Franco de Oliveira[3], José Robertto Zaffalon Junior[1,2], Glauber Sá Brandão[4,5], Anderson Soares Silva[6], Francisco kaio Rodrigues Campos[6], Jose Paulo da Silva Júnior[6], Vera Lúcia dos Santos Alves[7], Iransé Oliveira-Silva[3], Paulo de Tarso Camillo de Carvalho[1]

ABSTRACT

Background: Systemic arterial hypertension (SAH) is a common cardiovascular disease that reflects an important incidence and prevalence for public health, with obstructive sleep apnea (OSA) being considered the second cause of SAH. Aerobic exercise is one of the actions to control blood pressure changes. **Objectives:** To verify the anthropometric profile, the physical fitness, the pulmonary function, the presence of respiratory sleep disorders and the behavior of the autonomic activity in hypertensive patients submitted to aerobic training. **Methods/Design:** This is a randomized, controlled, blinded trial. The design, conduct and report of this study followed the guidelines of the CONSORT (CONsolidated Standards of Reporting Trials statement). The study will be conducted between July 2015 and December 2017, and will include controlled hypertensive patients of both gender, aged between 30 and 70 years, with clinical diagnosis of primary hypertension (stage 1, systolic and diastolic blood pressures with variations from 140/79 to 90/109 mmHg), controlled by specific drugs, which do not contain beta-blockers. The patients who do not present clinical release to participate in the training program, with presence of another cardiovascular disease or disease in target organs and who present the risk factors of smoke and alcohol will be in the exclusion criteria. The sample will be of convenience, forwarded from the Health Office of the Bairro Aeroporto Velho and the Reference Unit Specialized - URE of Santarem (PA). Initially, it will be a clinical evaluation performed by a cardiologist and the subjects will undergo several routine tests such as echocardiogram, chest X-ray and laboratory tests (complete blood count, glucose, fasting glucose, total cholesterol and fractions, triglycerides, C-reactive protein, potassium, etc). After the initial medical evaluation, some questionnaires will be applied and other specific tests such as Quality of Life Questionnaire (SF-36), Physical Activity Readiness Questionnaire, Berlin Questionnaire, Epworth Sleepiness Scale, Stanford Sleepiness Scale, Cardiorespiratory Sleep Monitoring, Physical Fitness Questionnaire, heart rate variability monitoring, pulmonary function tests, and Six-minute Walk Test. All patients will perform the tests before and after the 12-week rehabilitation exercise protocol. The aerobic exercise training protocol will last 30 to 60 minutes, with intensity varying between 70% and 85% of the maximum HR reached in the functional assessment effort test and will be performed for three months, three times a week. TRIAL REGISTRATION: This protocol study has been approved by the Research Ethics Committee of the Nove de Julho University (UNINOVE), Brazil, process nº 370474/2010, and will be registered on ensaiosclinicos.gov.br

INTRODUCTION

Systemic arterial hypertension (SAH) is an important risk factor for diseases such as heart failure, coronary heart disease, cerebrovascular disease and chronic renal failure, involving approximately one billion people worldwide and becoming the most important cause of morbidity and mortality(1). Approximately 30% of adults are unaware of their hypertension. More than 40% of the hypertensive subjects are not undergoing treatment and two-thirds of the patients with hypertension do not have controlled blood pressure levels (BP<140/90mmHg). In addition, rates of cardiovascular disease and stroke associated with death rates have slowed in the last decade, however, prevalence and patient hospitalization rates have continued to increase and there is a trend towards increased end-stage renal disease by primary diagnosis. Therefore, undiagnosed, untreated and uncontrolled hypertension requires the attention of health professionals[2].

Key words: Autonomic system; pulmonary function; sleep disorders; hypertension; aerobic training, physical fitness.
Corresponding Author: Luis Vicente Franco Oliveira. Rua Victor Meireles Qd 07, Lt 28, Anápolis (GO), Brazil. CEP 75075-756 e-mail: oliveira.lvf@gmail.com. Phone: 0055 62 999052309 Fax 0055 62 33106600

[3]University Center of Anápolis (UniEVANGÉLICA), Anápolis (GO), Brazil.

All authors contributed equally to this work

Full list of author information is available at the end of the article.

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Proper management of SAH effectively reduces the risk of other diseases. Therefore, its primary and secondary prevention needs to involve community-level actions, including reduction of obesity, reduction of alcohol and salt intake, and increased practice of physical activity. The control of SAH requires the awareness of health professionals and the population in general, an evaluation of the overall risk for cardiovascular diseases and an increase in the efficacy of non-pharmacological and pharmacological interventions[3-5].

Aerobic exercise is one of the non-pharmacological actions necessary to prevent cardiovascular events and control SAH levels. Dimeo et al[6] (2012), showed that regular exercise, as a lifestyle change in hypertensive patients, was able to reduce blood pressure levels. Another study demonstrated that aerobic physical exercise significantly improves the membrane fluidity of erythrocytes in hypertensive subjects, suggesting that exercise may have a beneficial effect on erythrocyte membrane rigidity and restore microcirculation dysfunction in this population[7].

Sleep-disordered breathing is associated with major morbidity and mortality presenting a high prevalence in the general population, being considered now a days as an important global public health problem and affecting about 45% of the world population[8]. Among these, we highlight obstructive sleep apnea (OSA), which has been shown to be a risk factor for serious health problems, such as hypertension, coronary artery disease, stroke, metabolic disorders and excessive daytime sleepiness[9]. OSA is characterized by episodes of partial or complete upper airway obstruction during sleep[10], which was recently recognized as a secondary cause of SAH according to the Seventh Joint National Committee[11]. Studies show that OSA is common among patients with SAH, with a prevalence ranging from 37% to 56%[12,13]. OSA triggers increased sympathetic activity, systemic inflammation and metabolic dysregulation, contributing to change in blood pressure control. In addition, treatment of OSA by continuous positive airway pressure during sleep may reduce blood pressure in these patients[14].

The autonomic nervous system (ANS) plays an important role regulating the physiological processes of the human organism both in normal and pathological conditions. Among the techniques used for its evaluation, the analysis of heart rate variability (HRV) through R-R intervals has emerged as a simple and noninvasive technique of autonomic impulses, representing one of the most promising quantitative markers of autonomic equilibrium[15]. The HRV analysis describes the oscillations in the interval between consecutive heart beats (R-R intervals) as well as oscillations between consecutive instant heart rates. It is a tool that can be used in the evaluation of SNA modulation under physiological conditions, such as in wakefulness and sleep situations, different body positions, physical training, and also in pathological conditions[16]. Changes in HRV patterns provide a sensitive and anticipated indicator of impairments in a subject's homeostasis[17]. A high variability in heart rate (HR) is a sign of good adaptation, characterizing a healthy subject with efficient autonomic mechanisms, whereas low variability is often an indicator of abnormal and insufficient adaptation of the ANS, implying the presence of altered physiological functioning[18].

Question

Through the analysis of the HRV is possible to verify the behavior of the ANS that act in the cardiovascular system releasing the hormones and neurotransmitters, controlling the heart rate. On the other hand, the HR suffers periodic oscillations, being able to be observed in the electrocardiogram (ECG) through the R-R intervals. Analysis of HR modulation is an important indicator for heart and systemic diseases. The findings of high HRV values indicate a good functioning of the modulation and control mechanisms by the ANS, on the other hand the low values denote an indicator of serious risk of heart disease[15,17,18]. Therefore, the verification of the behavior of the autonomic activity in hypertensive patients submitted to a cardiovascular rehabilitation program can bring considerable contributions in order to reduce comorbidities related to hypertension, corroborating to the reduction of morbimortality and improving the quality of life of these patients.

Justification

SAH is one of the most common diseases of the cardiovascular system. This pathology reflects an important incidence and prevalence for public health. It is a disease shaped within complex multifactorial entities, which when untreated can affect target organs such as the heart, developing other pathologies such as SAH, hypertensive encephalopathy, atherosclerotic vascular disease and coronary diseases, hypertensive nephropathy and retinopathy[12,13]. The diagnosis of SAH becomes more common with advancing age, being 45 years for men and 55 years for women and reaching about 8% of subjects between 18 and 24 years of age. Considering BP values ≥ 140/90 mmHg, a prevalence of 50% was observed between 60 to 69 years old and 75% between subjects over 70 years old[3]. It was identified in these studies that, among genders, the prevalence of SAH was 35.8% in men and 30% in women, similar to other countries[1-4]. In the world, there is a prevalence of 37.8% in men and 32.1% in women. Aerobic exercise for its simplicity of execution and low contraindication in the control and treatment of SAH was elected to serve as a physical exercise for rehabilitation worldwide[6].

STUDY OBJECTIVES

Primary Objective

To verify the sympathetic and parasympathetic ANS behavior through the analysis of the HRV in hypertensive subjects submitted to aerobic training.

Secondary Objective

To verify the pulmonary function through spirometry, to study sleep through nocturnal cardiorespiratory home monitoring, and to evaluate the anthropometric and physical conditioning profile of hypertensive patients submitted to aerobic training.

METHODS AND DESIGN

STUDY DESIGN AND SETTING

This is a randomized, controlled, blinded trial. The design, conduct and report of this study followed the guidelines of the CONSORT[19] (CONsolidated Standards of Reporting Trials) statement, according to figure 1.

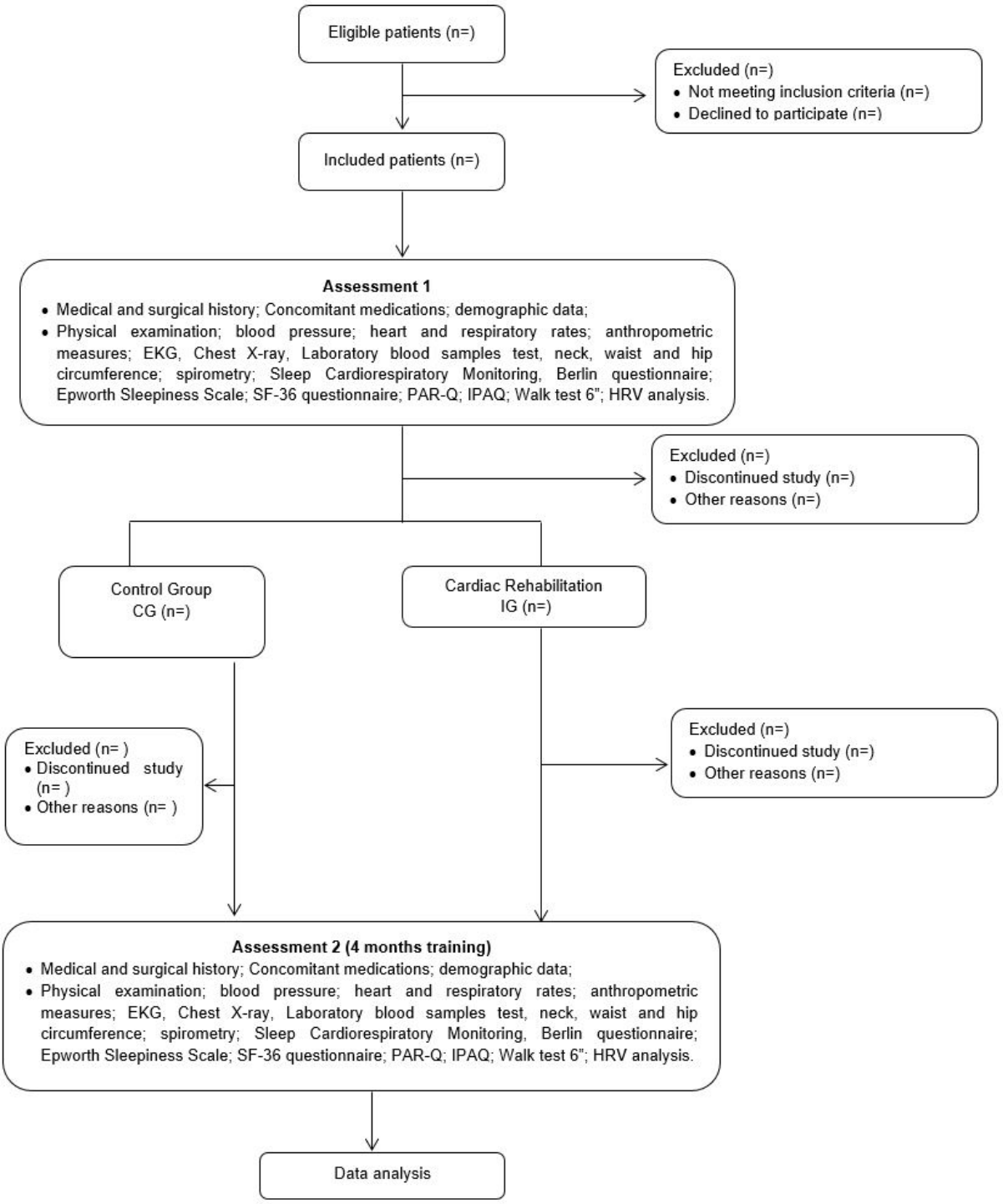

Figure 1. Flow diagram of the study.

ETHICAL AND LEGAL ASPECTS

This study was approved by the Research Ethics Committee of the Nove de Julho University (UNINOVE) with protocol nº 370474/2010. All participants must agree and sign the informed consent form to be part of the study.

RECRUITMENT PROCEDURE

The sample will be of convenience, composed of controlled hypertensive patients forwarded from the Health Office of the Bairro Aeroporto Velho and the Reference Unit Specialized - URE of Santarem (PA).

Eligibility criteria

The study will be conducted between July 2015 and December 2018, and will include controlled hypertensive patients of both gender, aged between 30 and 70 years, with clinical diagnosis of primary hypertension (stage 1, systolic and diastolic blood pressures with variations from 140/79 to 90/109 mmHg), controlled by specific drugs, which do not contain beta-blockers. The patients who do not present clinical release to participate in the training program, with presence of another cardiovascular disease or disease in target organs and who present the risk factors of smoke and alcohol will be in the exclusion criteria. Hypertensive patients will also be part of the control group, who during a period of three months will not perform controlled physical activities. After this period, this group will be reinserted into the cardiovascular rehabilitation group, and the data will be collected

Randomization

It will be used the closed-type randomization, with allocation concealment, generating two groups, a control group (CG) and an intervention group (IG). Research subjects will receive a number in consecutive order of entry into the study, in sequence randomly allocated according to a random sequence generated by Research Randomizer (www.randomizer.org).

CLINICAL EVALUATION

Initially, it will be a clinical evaluation performed by a cardiologist and the subjects will undergo several routine tests such as echocardiogram (ECG), chest X-ray and laboratory tests (complete blood count, glucose, fasting glucose, total cholesterol and fractions, triglycerides, C-reactive protein, potassium, etc). After the initial medical evaluation, some questionnaires will be applied and other specific tests such as Quality of Life Questionnaire (SF-36), Physical Activity Readiness Questionnaire (PAR-Q), Berlin Questionnaire, Epworth Sleepiness Scale (ESS), Stanford Sleepiness Scale, STOP-bang questionnaire, Cardiorespiratory Sleep Monitoring, Physical Fitness Questionnaire (IPAQ), HRV Monitoring, pulmonary function tests, and Six-minute Walk Test. Weight will be measured while wearing light clothing and without shoes, after emptying of the bladder, using a digital scale to the nearest 100 g. Height will be measured without shoes, with a stadiometer to the nearest 0.5 cm (model 200/5; Welmy Industria e Comercio Ltda, Sao Paulo, Brazil). BMI will be calculated by dividing weight (kg) by the square of height (m)[20].

Medical Outcomes Study 36 (SF-36)

The SF-36 (Medical Outcomes Study 36) is a generic instrument for assessing the quality of life, which is easy to administer and understand. This is a multidimensional questionnaire consisting of 36 items, encompassed in 8 scales or domains, which are: functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects and mental health. The instrument has a final score from 0 (zero) to 100 (obtained by means of Raw Scale calculation), in which zero corresponds to the worst general health condition and 100 corresponds to the best health status. It is a well-designed questionnaire, with very good reproducibility, validity and susceptibility to changes, and well demonstrated in several studies. The translation into Portuguese of the SF-36 and its adequacy to the socioeconomic and cultural conditions of our population, as well as the demonstration of their reproducibility and validity, make this instrument an additional useful parameter that can be used in the evaluation of several pathologies[21].

Epworth Sleepiness Scale

The Epworth sleepiness scale (ESS) is a self-administered scale that verifies the occurrence and intensity of excessive daytime sleepiness in eight situations of daily living. Participants are instructed to rate the odds of napping or falling asleep in each of the eight specific situations in a score from 0 to 3, with higher scores indicating a greater chance of napping[22].

Berlin questionnaire

The Berlin questionnaire is a self-administered test to identify patients at high risk of respiratory sleep disorders in a variety of populations with recognized efficacy in distinguishing subjects at high risk of OSA. This test is composed by 10 items organized into 3 categories as follows: snoring and apnea (five items), daytime sleepiness (four items), and systemic arterial hypertension and obesity (one item). All marked responses are considered positive. Scores for each category can be positive or negative. Patients with positive scores in two or more categories are considered with high risk for OSA[23].

Physical Activity Readiness Questionnaire, PAR-Q

The Physical Activity Readiness Questionnaire (PAR-Q) is an internationally known pre-participation screening tool developed on the basis of expert opinion. The PAR-Q has been widely used internationally for many years. This simple

screening tool is intended for completion by anyone who plans to undergo a fitness assessment or to become much more physically active. When a positive response is made to this instrument, the subject is directed to consult with his or her physician to seek clearance to engage in either unrestricted or restricted physical activity[24-26].

International Physical Activity Questionnaire (IPAQ)

IPAQ was developed during a conference in Geneva in 1998 to measure health-related physical activity in general population, that includes time spent in vigorous intensity activity, moderate intensity activity, and walking, which lasted at least 10 min or more per session. It is suitable for use in regional, national, and international monitoring and survey systems and for research projects and public health planning and evaluation. IPAQ has been extensively tested for its reliability and validity around the world and translated into many languages including Portuguese. It was designed and tested for populations aged between 15-69 years. Specific activities within each major heading with its intensity is defined as the ratio of a work metabolic rate to a standard resting metabolic rate (MET). Energy expenditure in MET-minutes, MET-hours, kcal, or kcal per kilogram body weight can be estimated for specific activities by type or MET intensity. MET is an easy way to count the energy cost of different types of physical activities as a multiple of the resting metabolic rate[27, 28].

Cardiorespiratory sleep monitoring

Cardiorespiratory sleep monitoring will be performed at the patient's residence using a portable Apnea Link Air monitoring system (ResMed Corporation, San Diego, CA, USA). ApneaLink™ is a low-cost, Type III diagnostic home sleep exam that gives to the patients the option to undergo sleep testing with the conveniences and comfort of their own home. The equipment records up to five channels of information: respiratory effort, pulse, oxygen saturation, nasal flow, and snoring. All respiratory events will be evaluated manually by the same specialist physician in Sleep Medicine, according to the criteria of the American Academy of Sleep Medicine. AHI will be calculated as the number of apneas and hypopneas per hour of recording and the diagnosis of OSA will be AHI ≥ 5 / hour[29].

Pulmonary Function Tests

Spirometry tests will be performed at the Reference Unit Specialized - URE of Santarem (PA), using the Koko PFT System Version 4.11 Spirometer (nSpire Health, Inc., Louisville, CO, USA). The national guidelines for pulmonary function tests of the Brazilian Society of Pulmonology and Tisiology[30] and the European Respiratory Society will be followed[31]. All pulmonary function tests will be performed by a pulmonologist with the team participating in the research project.

Physical Fitness

The verification of the physical fitness levels will be done through the Rockport Fitness Test[32]. This submaximal predictive test requires subjects to walk as fast as possible on a 200-meter track for eight rounds during which they can decelerate or rest if necessary. Words of encouragement are given during the walk. The HR will be checked with an HR monitor at the end of every 400 m. The calculation of the predicted maximum oxygen consumption (VO2max) is performed by means of a regression equation, using runway walking time, fourth quarter HR, body weight, age and sex. The test-retest reliability was 0.97 and the predicted VO2max showed a high correlation (r = 0.93) with the current VO2max in the elderly[32]. The test implementation follows the guidelines of the ACSM and BP, HR, and the contradictory symptoms will be evaluated before the walking test.

Heart rate variability

The evaluation of HRV will be performed by analyzing the behavior of the R-R intervals through the orthostatic test. All tests will be performed on a stretcher in a controlled and quiet environment in the morning. The orthostatic test will be performed with the subject lying on a stretcher in a relaxed manner, with eyes closed, without talking to the researcher, for a period of 15 minutes. After this period of time, the subject will receive an orientation to get up from the stretcher and stand with eyes open, aiming at the horizon, for a period of 15 minutes. For the purpose of the analysis, the R-R intervals referring to the last five minutes of the period in which the patient was lying down and the first five minutes with the patient standing shall be collected. The R-R records will be obtained at a sampling rate of 1000Hz using an HR monitor (RS800CX, Polar Electro Oy, Finland) widely used in the evaluation of HRV[33]. The records will be transported to the computer and filtered using the software (Polar ProTrainer® version 5.0, POLAR Electro Oy, Kuopio, Finland) followed by export to a dedicated program for HRV analyzes (Kubios HRV v2.0, University of Kuopio, Finland). The HRV variables were be examined according previously studies[15,34]. The variables in the time domain (SDNN and RMSSD), frequency domain (LF and HF in absolute and normalized units) and non-linear measurements (SD1, SD2, Sample Entropy and α1) will be used [15, 16].

INTERVENTION

All patients involved in this study will perform the tests before and after the 12-week rehabilitation exercise protocol to be performed at the Special Reference Unit (URES), Santarém - PA. The aerobic exercise training protocol will last 30 to 60 minutes, with intensity varying between 70% and 85% of the maximum HR reached in the functional assessment effort test, and will be performed for three months, three times a week. Peripheral arterial pressure and heart rate will be measured before exercise

(resting for 5 min), during exercise (after 3 minutes of onset, and at 30, 45 and 60 minutes of physical activity) and after the end of physical activity (10 minutes). Three (3) HR and PAS measurements will be performed, recording the quotient of the average of the three verifications. As for hypertensive and sedentary patients, a period of aerobic and musculoskeletal adaptations will be performed for the quality of aerobic endurance and localized muscular resistance, predicting the improvement of VO_2 max[35].

Period of cardiorespiratory and neuromuscular adaptation.

- (1) during the first five days, continuous aerobic training will be performed within a very light target zone (40-50% of maximum HR), lasting 30 to 45 minutes, ending with relaxation and stretching exercises;
- (2) In the subsequent 3 weeks, 3 days per week, aerobic (walking) exercises will be performed with intervals:
  - (2.1) The first week (65% of maximal HR), 10 walking sessions lasting 30 seconds, intervals with 10 active recovery sessions of 90 seconds (50% of maximum HR), ending with 7 minutes of continuous aerobic exercises -60% of maximum HR for lactate removal);
  - (2.2) In the second week (65% of maximal HR), 10 walking sessions lasting 15 seconds with 10 sessions of active recovery of 45 seconds (50% of maximum HR), ending with 10 minutes of continuous aerobic (50 -60% of maximum HR for lactate removal);
  - (2.3) Third week (65-70% of maximal HR), 10 walking sessions with a duration of 45 seconds intervals with 10 active recovery sessions of 90 seconds (50% of maximum HR), ending with 10 minutes of continuous aerobic removal of lactate).

Period of Cardiovascular Rehabilitation

Part 1 - Warm up, treadmill with speed between 2-3 Km/h, 50-60% of maximum HR (5 minutes);

Part 2 - Main treadmill training 4-7 Km/h, approximately 70-80% of maximum HR (30 minutes);

Part 3 - Cooldown, speed gradually decreased for 5 minutes until reaching the speed of 1.5 (treadmill), approximately 40-50% exercise HR (target zone) or close to resting HR;

Part 4 - Stretching and flexibility (approximately 10 minutes).

STATISTICAL ANALYSIS

The data will be tested on their adherence to the Gaussian curve by the Shapiro-Wilk test. If they present parametric distribution will be expressed in mean and standard deviation or for non-parametric distribution will be expressed in median and interquartile range. For the comparison between the groups (hypertensive and normotensive) will be used the Student t test not paired, however if the distribution is non-parametric the Wilcoxon test will be used. Further comparisons may be made between these groups by the Anova of a factor or Kruskall-Wallis if the data present a parametric or non-parametric distribution, respectively. If there is a difference detected in this analysis, the post-hoc Bonferroni test will be used. Correlations between HRV parameters and apnea time, apnea / hypopnea index will be analyzed by the Pearson or Spearman correlation coefficient, if the variables present a parametric or non-parametric distribution, respectively. A $p < 0.05$ will be considered as significant. The anthropometric variables (height, BMI, PCCQ and CI) will be represented by mean (x) and standard deviation (sd). All statistical procedures will be enhanced through the Statistical Package of Social Sciences SPSS 21.0 (IBM® SPSS version 21, IBM, Armonk, NY, USA).

Sample size

The calculation of sample size was based on a previous study by Duru F. et al.[36] that identified a significant improvement in mean HRV before and after cardiac rehabilitation. Using a two-tailed alpha of 0.05 and 80% power to detect a moderate effect size of difference of 15ms, a sample size of 38 subjects will be necessary to comprise our sample. Eight patients will be added (20%) to each group to allow for possible sample loss.

Outcome measures

Primary outcome

The first expected outcome is the change in sympathetic and parasympathetic nervous system behavior in hypertensive patients submitted to aerobic training verified through HRV analysis.

Secondary outcome

The secondary outcome will be the alteration of the pulmonary function analyzed through spirometry, the quality of the sleep verified through the nocturnal cardiorespiratory home monitoring, the anthropometric profile and the level of physical conditioning of hypertensive patients submitted to aerobic training.

Assessor blinding:

Researchers involved in the interpretation of clinical tests and statistician responsible for data analysis will be blind to the composition of the study groups.

Data monitoring and quality control:

Systematized training of research assistants will be carried out exclusively for the evaluation and follow-up of physical activities.

Description of risks

There will be no risks for included patients.

AUTHOR'S CONTRIBUTION

RLD, LVFO and PTCC defined the concept of the study, created the hypothesis, and wrote the original proposal. IOS, GSB, LVFO, JRZJ, ASS, and PTCC contributed significantly to writing this proposal. VLSA, LVFO and PTCC were involved in the critical review of the manuscript. FKRC, JPSJ, LVFO and ASS wrote this protocol role, with the contribution of all co-authors. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS:

The authors declare that they have no conflict of interests.

AUTHOR DETAILS

[1]Rehabilitation Science PhD Pos Graduation Program, Nove de julho University (UNINOVE), São Paulo (SP), Brazil. [2]University of Estado do Para (UEPA), Santarém (PA), Brazil. [4]Bahiana School of Medicine and Public Health, Salvador (BA), Brazil. [5]University of the Estado da Bahia - UNEB, DEDC-VII, Senhor do Bonfim (BA) Brazil. [6]Postgraduate Program, Master degree in Health Sciences, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil. [7]Physical Therapy Clinic, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil.

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