Study Protocol and Statistical Analysis Plan

EFFECTIVENESS OF COMBINED AEROBIC AND STRENGTH TRAINING IN ACUTE AND CHRONIC ADAPTATIONS IN PATIENTS WITH HEART FAILURE

Date: 19/10/2017

PROTOCOL

Title

Effectiveness of combined aerobic and strength training in acute and chronic adaptations in patients with heart failure

Participants

Patients with chronic heart failure (CHF) that underwent to a hospital-based cardiac rehabilitation (CR) program in the Lisbon district Hospitals will be recruited. The study will be performed in the Cardiovascular Rehabilitation Center of the University of Lisbon (CRECUL) at the Lisbon University Stadium (EUL). The participants will be randomized into one of the following exercise groups: A) combined exercise training with more aerobic training and less strength training (CAT); B) combined exercise training with more strength training and less aerobic training (CST); Inclusion criteria: CHF patients; receiving optimal medical therapy for CHF (including an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a beta-blocker unless a contraindication is evident) with a stable condition for more than 1 month (no hospitalization for heart failure (HF), no change in medication, and no change in New York Heart Association (NYHA) functional class. Exclusion criteria: if they are younger than 18 years or are unable to sign informed consent; unstable angina pectoris; and orthopedic or neurological limitations to exercise. Patients will be stratified (by age and etiology) and randomized consecutively to CAT or CST in the beginning of the exercise at community. There will be 2 assessment moments (M): M0) before starting the exercise training (ExT) program (baseline) and M1) 3 month after starting the ExT.

Sample size was calculated (G-Power,*Version3.1.3)* assuming a difference in carotid intima-media thickness (IMT) between groups of 5% to be a clinical important difference with a SD of 0.16, α=0.05, 1-β=0.95 and an expected dropout rate of 26%. The calculations yielded a total minimum sample size of 28 participants (14 in each group).

Recruitment

Participants with established CHF after finishing in average a 3-month hospital based CR program at the Hospital will be invited and recruited to start a community based CR program at the EUL. The Clinical Director of the CR program at the Pulido de Valente Hospital and the Clinical Director of the community based CR program at the EUL, will make one of the connections to invite all the patients with the mentioned inclusion criteria to join the community based program. All patients will have access to informed consent (is attached the file of informed consent) where the entire project will be clearly explained.

Other forms to promote the recruitment in other Hospitals in the Lisbon district will be the distribution of a leaflet, with the contacts and brief information about the community based program. It will be presented and asked to each of the Clinical Director of the CR program at the Hospitals in Lisbon district the authorization to give to all the patients who completed the hospital based program the information leaflet.

All the information provided at the flyer will be online at the website of the University of Lisbon, Faculty of Human Kinetics – University of Lisbon (FMH-UL) and Faculty of Medicine – University of Lisbon.

Project

INTRODUCTION

CHF is the major public health problem in the world [**1**], highly prevalent in older individuals and a major cause of disability, hospitalizations, morbidity and mortality [**2**]. Generally, CHF patients have reduced exercise capacity, with main symptoms of effort intolerance, early fatigue and breathlessness [**3**], also exhibiting increased peripheral and central chemosensitivity, and impaired sympathovagal balance with sympathetic activation (SA) predominance [**4**].

Understanding the oxidative metabolism and intracellular energy transfer in both skeletal and cardiac muscle, mechanisms of endothelial dysfunction, and the role of SA and inflammatory cytokines provide possible mechanistic explanations of the pathophysiologic factors involved in the development of exercise intolerance [**5, 6**]. It has been shown in CHF patients that increased arterial stiffness is associated with cardiovascular morbidity and mortality [**7**]. There are evidences that increased arterial stiffness predicts exercise intolerance in CHF patients [**8**].

Increased carotid IMT is associated with subclinical left ventricular (LV) myocardial dysfunction, suggesting a possible role of carotid IMT in HF risk determination [**9**]. CHF is associated too with endothelial dysfunction including impaired endothelium-mediated, flow-dependent dilation (FMD). Since endothelial function is thought to play an important role in coordinating tissue perfusion and modulating arterial compliance, interventions to improve endothelial dysfunction are imperative.

Systemic vasoconstriction and impaired peripheral perfusion are hallmarks in advanced CHF. While a number of factors, including increased sympathetic tone and an activated renin-angiotensin system, have been proposed to be involved in the reduced arterial vasodilatory capacity in HF, the pivotal role of the endothelium in coordinating tissue perfusion has now been recognized.

Several clinical studies have documented endothelial dysfunction of large conduit and small resistance vessels in patients with CHF. Endothelial dysfunction may affect the cardiovascular system in two ways: first, endothelial dysfunction of resistance vessels may impair peripheral perfusion, and, second, endothelial dysfunction of large conduit vessels may limit the increase in blood flow provided by the supplying large vessels and may increase impedance of the failing LV and consequently impair LV ejection fraction (LVEF). An important functional consequence of endothelial dysfunction is the inability to release nitric oxide (NO) in response to physiological stimuli such as increases in flow, reflecting impaired FMD [**10**]. Conversely, chronically increased blood flow enhances the release of NO in experimental models, by upregulation of NO synthase, the enzyme that uses L-arginine to generate NO.

The intermittent increases of blood flow by physical training may increase the capability of the endothelium to release NO and therefore may restore endothelial function in patients with CHF who are usually subjected to a limited degree of physical activity[**5**]. The dysfunctional endothelium contributes to increased vascular stiffness and impaired arterial distensibility, augmenting myocardial damage [**10**].

The direct relationship between exercise and vascular health is certain, but the complex set of metabolic pathways, haemodynamic effects of exercise on cardiovascular cells/tissues, and the regulation of genetic expression activated by exercise is still largely undefined [**11**]. The effects of aerobic and resistance exercise on clinical blood pressure might be different, because they have different mechanical characteristics. Aerobic training (AT) is characterized by the execution of cyclic exercises, carried out with large muscle groups contracting at mild to moderate intensities for a long period of time. On the other hand, strength training (ST) is characterized by the execution of exercises in which muscles from a specific body segment are contracted against a force that opposes the movement[**12**].

Aerobic capacity is directly related to arterial function, including endothelial function, arterial stiffness and wave reflection. In addition, coupling of arterial and cardiac function is a major determinant of aerobic capacity. Thus, poor resting arterial function likely limits aerobic capacity, but it is also possible that changes in arterial function during acute exercise may play a role. Arterial function is not only associated with aerobic capacity, but is also an independent predictor of mortality[**5**].

Controlled clinical trials have shown that in HF patients ExT programs improve peripheral and cardiac adaptations and also the aerobic capacity, delay the onset of anaerobic metabolism, and improve the autonomic balance [**1, 13**]. Apart from adaptation in maximal cardiac output, heart contractility, and stroke volume, aerobic ExT is also able to promote amelioration in the peripheral microvascular background by reducing resistance to flow, increasing the compliance of the arteries and endothelial function [**13**]. Abnormalities in endothelium and FMD are a key phenomenon in the blunted vasodilatory response in CHF patients. ExT enables the improvement of both basal endothelial NO formation and agonist-mediated FMD of the skeletal muscle (SM) vasculature in CHF patients. The correction of endothelial dysfunction is associated with a significant improvement in exercise capacity evidenced by a 26% increase in peak oxygen uptake (VO_2peak) [**14**].

Previous studies in HF have been show that 16.4% of 171 patients had cachexia, and the mortality at 18 months of follow-up was as high as 50% in the subset of patients with cachexia compared with 17% in those without cachexia. Cardiac cachexia is defined as an advanced stage of HF

associated with involuntary loss of at least 5% of non-oedematous body weight. And muscle wasting, also known as sarcopenia, is the loss of muscle mass (MM) and strength, whereas cachexia describes loss of weight. Distinction of the two clinical conditions might also be challenging, because cachexia and muscle wasting can co-exist in the same patient. Indeed, cachexia might lead to muscle wasting and *vice versa*, although muscle wasting can occur earlier in the course of the disease[**15**].

SM strength, in upper and lower limbs, are parameters that independently predict survival [**16, 17, 18**]. This alternative treatment should focus on increasing MM, strength and power in the limbs to improve functionality and performance [**19**]. SM dysfunction includes reduced cardiac contractile performance that contributes to changes in SM physiology, muscle atrophy, weakness and reduced oxidative capacity [**20**]. Muscle function is also enhanced in response to ST in CHF patients, including myofilament function and whole muscle [**21**] as well as SM oxidative capacity [**21**].

It's crucial that the ExT in such patients should be train the peripheral muscles effectively without producing great cardiovascular stress. An alternative treatment approach should focus on the application of specific resistance exercise program to improve body composition [**22**], increase the crosssectional area, muscle fibre [**23**], all of which counteract muscle wasting and may be cornerstone in the prevention of sarcopenia and cardiac cachexia in CHF patients [**24**].

ExT is a major component of rehabilitation/secondary prevention interventions, inducing significant beneficial changes in mechanisms of pathophysiology, exercise tolerance, functional capacity and QoL, while a positive impact on hospitalization and mortality reduction. There has been growing interest in the characteristics and modalities of exercise training able to induce optimal benefits. High intensity and interval mode have been shown to induce greater benefits than moderate intensity and continuous mode regimes. Considering the current body of evidence of high-intensity interval training (HIIT) in CHF, HIIT demonstrated to be more efficient, result in long term adherence, which be an important practical aspect to consider during the ExT and consequently optimized improvements in central and peripheral adaptations [**25**]. More studies are needed to proof their safety and benefits on this type of patients.

Additionally, there has been sound rationale for the inclusion of ST to the HIIT, which has been also shown able to yield benefits in terms of exercise capacity and QoL. It is well known that combined AT and ST is the preferred exercise intervention to reverse or attenuate the loss of MM and improve exercise and functional capacity, muscle strength in this individuals [**19**]. But there are underlying mechanisms from the ST in the CHF patient's peripheral capacity that remains unidentified. And isn't known what is the benefits of combine different proportions of AT and ST.

For that reason, the investigators will test two proportions in combined training, CAT and CST. There haven't been any data on the so called combined regimes, which include both aerobic exercise with HIIT and ST and the investigators will evaluate the effects of acute and chronic response.

PURPOSE

The research project will contribute to a better understanding in several aspects that are unexplained by scientific research. The purpose of this research project are:

1) To determine the effectiveness of a ExT programme with different proportions of CAT and CST in promoting cumulative effects in acute and chronic adaptations in CHF patients;

2) To identify the mechanisms of the potential improvement in effectiveness promoted by ST;

This research project is going to employ state of the art methods focusing peripheral adaptations analysis in both groups namely in echocardiography variables, cardiopulmonary exercise testing, arterial stiffness, functional physical fitness, QoL and body composition in 2 distinguished moments: M1) baseline and M2) 3 month.

Plan and Methods

This project will assess the acute and chronic effects in central and peripheral adaptations of a combined training to patients with CHF would address a number of important breaches in scientific knowledge with potential clinical benefits.

STUDY DESIGN

A longitudinal randomized control trial (RCT) research design using two distinct ExT prescriptions (CAT and CST) will be applied in CHF patients. All the same assessments will be done in two moments: M0 - baseline and M1 - 3 months after starting the ExT. The patients will be randomized into either one of the two ExT group.

Recruitment and screening will last 9 months (September 2017 to May 2018) and the patient assessment will last until August 2018. It is expected to finish the project with peer-review redaction submitted and/or accepted in December 2018 (time line attached).

The following assessments on the 4 moments will be performed at the Pulido Valente Hospital, FMH-UL and Academia de Fitness at EUL: Echocardiogram (Echo) (MyLab Alpha, ESAOTE);

cardiopulmonary exercise test (CPET) (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen); arterial stiffness - Complior Analyse (ALAM Medical); Intima-media thickness - ultrasound (ESAOTE MyLanOne); body composition - dual energy radiographic absorptiometry (DXA, Hologic Explorer-W); functional physical fitness - Fullerton Functional Fitness Test; isometric strength – portable hand dynamometer JAMAR plus digital (Sammons Preston); maximal strength – 1RM and QoL questionnaire.

All assessment moments will be done in 5 days:

Day 1 – Echo will be performed at the Pulido Valente Hospital;

Day 2 and 3 – during one day and time of the ExT session at the EUL, the patient will perform the functional physical fitness tests; maximal strength; isometric strength and QoL questionnaire. In other day the investigators will perform the arterial stiffness and the IMT before the session in rest and after the ExT;

Day 4 – In FMH, the CPET and dual energy radiographic absorptiometry (DXA) exam.

Individual reports will be sent by email or delivered on paper. During the 1-year project the multidisciplinary team will have bimonthly meetings to update the study information and discuss the patient's progress.

TASK DENOMINATION

1. ECHOCARDIOGRAM

A resting transthoracic echocardiogram will be performed with MyLab Alpha, ESAOTE, Italy. The exam will be performed by the echocardiography laboratory cardiologists, who will be blinded to experimental protocol and group randomization, with the usual measurements of systolic and diastolic function, particularly the calculation of LVEF by Simpson`s formula, telediastolic and telessystolic volumes and diameters, doppler analysis of the transmitral flow, tissue doppler and quantification of mitral valve regurgitation.

2. CARDIOPULMONARY EXERCISE TEST

CPET is the best technique to obtain the maximal functional capacity. This test will be performed with the subjects in a non-fasting condition and under the regular medication.

Symptom-limited exercise test

A symptom-limited ramp incremental CPET, will be performed on a cycle ergometer (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany) with breath-by-breath gas exchange measurements. For cardiorespiratory recording will be used a mask that does not interfere with breathing and can cause discomfort. Gas exchange analysis provides a highly reproducible measurement of exercise limitation and insights into the differentiation between cardiac or respiratory cause of dyspnea, assesses ventilator efficiency and carries prognostic information. After 2 minutes rest followed by 3 minutes unloaded pedaling, each patient will be encouraged to exercise to exhaustion, as defined by intolerance, leg fatigue or dyspnea unless clinical criteria for test termination occurred. Patients will continue seated on the cycle ergometer as soon as they stop, while recovery measurements are taken. Blood pressure will be recorded at baseline, during each stage, at peak exercise and during recovery. Peak oxygen capacity will be considered the highest attained VO_2 during the final 30 sec. of exercise and ventilator AT will be estimate by the V-slope method. Heart Rate (HR) recovery as a simple marker of parasympathetic activity will be calculated as the difference between peak HR and HR one minute later. The recovery period will continue until 6 minutes after peak effort. Chronotropic response (ChR) to exercise will be evaluated by the % of HR reserve (HRR) used at peak exercise. ChR= [peak HR – resting HR/(220 – age – resting HR)x100]. A failure to use 80% of the HRR is defined as chronotropic incompetence. All patients should achieve a respiratory exchange ratio of >1.1, an indicator of maximal effort in the CPET. The CPET will provide clinical information to patient screening and exercise intensity prescription.

The investigators will study, the HR max and recovery at 1st and 3rd minutes, the VO_2 peak, respiratory exrespiratory exchange ratios, respiratory quotient, ventilatory anaerobic threshold, the ventilatory equivalent for O_2 and C O_2.

3. ARTERIAL STIFFNESS

Arterial stiffness will be measured by pulse wave velocity (PWV) obtained by applanation tonometry will be measured during a 15 and 30-minute rest. A single operator locates the carotid, femoral, radial and distal posterial tibial arteries on the right side of the body and mark the point for capturing the corresponding pressure curves with two specific pressure sensitive transducers. The distance between the carotid and femoral, radial and distal posterial tibial arteries will be measured directly and entered into the Complior Analyse software (ALAM Medical, Paris, France). Right brachial blood pressure will be measured and entered into the Complior Analyse software, and then

signal acquisition is launched. The operator position the carotid sensor with the help of its specific holder and manually held the femoral sensor on the femoral artery and the distal sensor in the distal posterial tibial artery. When the operator observes 10 carotid pulse waveforms of at least 90% quality showed on the software, simultaneous carotid and femoral, radial and distal posterial tibial pressure curves will be recorded for 10 pulse waveforms. The time delay (aortic transit time) between the two pulse waveforms is then calculated automatically. Values obtained from the carotid to femoral artery, carotid to radial artery and carotid to distal posterial tibial artery are taken as indices of central/aortic, upper and lower limb arterial stiffness, respectively. The investigators will study the pulse pressure (PP), the carotid stiffness index β, augmentation index (Aix), and peak wave velocity (PWV)

4. INTIMA-MEDIA THICKNESS

Carotid intima media thickness (cIMT) will be defined as the distance between the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall of the right carotid artery using an ultrasound scanner equipped (ESAOTE MyLanOne) with a linear 13 MHz probe and implemented with a previously validated radiofrequency-based tracking of arterial wall that allows a real-time determination of common carotid far-wall thickness with high spatial and temporal resolution [**26**]. cIMT is automatically measured, and distension curves are acquired within a segment of the carotid artery about 1 cm before the flow divider, where the operator places the region of interest. The coefficients of variation for repeated measurements in our laboratory for cIMT and diameter are reported elsewhere [**26**].

To evaluate the acute effects of ExT, at the pre-exercise measurement at 15 and 30-minutes rest, blood pressure (BP) was measured twice on the right upper arm using an automatic cuff in a dorsal decubitus position. If the difference in systolic BP (SBP) between the two measurements was larger than 10 mmHg, another BP measurement was performed. The final measured value was used for the analysis. Immediately after measuring BP. Post-exercise measurement was carried out with the same methods.

From this test, the investigators will study the diameter and distensibility of the artery, intima–media thickness in the carotid arteries (cIMT), PWV, brachial blood pressure, and the alpha and beta index.

5. BODY COMPOSITION - DUAL ENERGY RADIOGRAPHIC ABSORPTIOMETRY

All the patients will be tested in the morning with a 12-h fasted no caffeine and alcohol, refrained from the moderate to vigorous exercise at least 24-h. Total and regional body mass (bone mineral content, lean soft- tissue and fat mass) is estimated using dual energy radiographic absorptiometry (DXA) (Hologic Explorer-W, fan-beam densitometer, software QDR for windows version 12.4, Hologic, USA). The attenuation of x-rays pulsed between 70 and 140 KV synchronously with the line frequency for each pixel of the scanned image. This technique uses RX with a low radiation dose (1-3µSv / test), much lower than usual exposure to our natural involvement (5-8µSv / day) or RX to the chest (50-150µSv / test). The same lab technician will perform the scans, and execute the analyses according to the standard analysis protocol. Total body skeletal muscle mass (TBSMM) will be calculated as TBSMM = (1.13 ALST) – (0.02 age) + (0.61 sex) + 0.97, where ALST means appendicular lean soft tissue. Skeletal muscle mass (kg) will be normalized by height (kg/m^2) and termed skeletal muscle index to verify the level of physical disability risk. Height will be measured to the nearest 0.5 cm with a stadiometer (SECA, Hamburg, Germany), body weight (SECA, Hamburg, Germany) and body mass index (BMI) (kg/m^2) will be calculate for height and body weight from the DXA. Body circumferences at the waist will also be measured using an inelastic flexible metallic tape (Lufkin W606PM, Vancouver, Canada), to the nearest 0.1cm. All anthropometric procedures will be led by the same certified technician.

The investigators will study the bone mineral content, lean soft- tissue and fat mass, total and regional body mass.

6. OBJECTIVE MEASURED PHYSICAL ACTIVITY

Each participant will use the ActiGraph GT3X+ and given oral and written instructions on how to wear the accelerometers for the following 7 days. The ActiGraph GT3X+ (AG; ActiGraph, Pensacola, FL) is able to assess acceleration in the vertical, antero-posterior and medio-lateral axes. It is a reliable instrument with high inter-instrument reliability and intra-instrument reliability within frequencies that are common in human activities. This device has been widely used in research, with good validity for measuring physical activity levels. The ActiGraph GT3X+ will be attached to an elastic waist belt and placed in line with the axillary line of the right iliac crest. Participants will be asked to wear the accelerometer from the moment they wake up until they go to bed at night, and requested to remove it only during water-based activities such as showering and swimming and

when they go to bed. ActiGraph GT3X+ will be initialized using a sample rate of 30 Hz and then downloaded using the low filter extension option in Actilife5 Software v5.7.4 (ActiGraph, Pensacola, FL). The cut off points previously used in an older sample of adults to calculate daily times in each activity intensity band will be: sedentary (<1.5 MET) 0–199 counts per minute (cpm); light (1.5– 3 MET) 200–1998 cpm; moderate to vigorous physical activity (>3 MET): ≥1999 cpm. Sensitivity analyses will also be performed using a more conservative cut point of zero cpm to differentiate sedentary time from activity. All physical activity variables will be converted to time (in minutes) per valid day.

7. FUNCTIONAL PHYSICAL FITNESS TESTS

The functional physical fitness tests are a simple, reproducible, readily available tool frequently employed to assess submaximal functional capacity and evaluate the response to intervention. The six minute walking test (6MWT) will be performed indoors, along a long flat, straight, enclosed 20-meter corridor with a hard surface that is seldom. Patients will be instructed to walk at their own pace according to their tolerance to exercise for 6 minutes, with rest stops as needed. The final result will be the distance in meters covered in the 6 minutes. Total distance during the test will be recorded. Because the body weight of patients directly affect the energy and work required to walk, it will be used the body weight-walking distance (body weight × walking distance) to assess the walking capacity of subjects. The aim of the 6MWT is to assess aerobic endurance. The 30-second chair stand, assesses the lower body strength, needed for numerous tasks such as climbing stairs or walking. Patients will be instructed to sit and stand as faster as they can in 30 seconds with arms folded across chest. The 8-foot (2.44 meters) up and go test evaluates the agility/dynamic balance, which is important in tasks that require quick maneuvering. It will be evaluated the time in seconds that the participant needed to get up, walk the distance of 2.44 meters and return to the initial position. For the flexibility, it will be assessed in both upper and lower body. The chair sit-and-reach aim to assess the lower body flexibility from a sitting position at front of a chair with the leg extended and hands reaching toward the toes, the number of cm between extended fingers and tip toes (+ or -) will be measured. To assess the upper body (shoulder) flexibility, it will be used the back scratch test with one hand reaching over the shoulder and one up the middle of the back, it will be taken the number of cm between extended middle fingers (+ or -).

8. ISOMETRIC STRENGTH

Handgrip strength will be assessed by a portable hand dynamometer JAMAR plus digital (Sammons Preston, Bolingbrook, IL). Subjects will be assessed on both hands alternately. Handgrip assessment will be conducted with the patients in a seated comfortable position, with the shoulder adducted and close to, but not supported by, the trunk. The elbow of the assessed limb should be flexed to 90 degrees and the forearm should be in a neutral position (halfway between supine and pronation position). A variation of 0-30 degrees in the wrist extension will be allowed. Each subject will be assessed in three attempts for both hands alternately. In each attempt the subject will exert the maximal grip strength on the hand dynamometer with the assessed limb during 5 seconds. After each attempt, there will be a resting period of 60 seconds that will be used both for recovery and for changing the handgrip dynamometer to the opposite hand. All patients will be instructed not to perform a Valsalva manoeuvre during the tests.

9. MAXIMAL STRENGTH

Maximal strength will be assessed by 1RM test for each of six weight exercises on variable resistance machines (Life Fitness) available at the EUL as follows, leg press, leg extension, leg curl, low row, chest press and lat pull down. The protocol test of 1RM was determined as previously described in our prior studies[**27**]. The protocol will include four pre-test sessions to familiarize each patient with the test procedures. Correct exercise and breathing techniques (avoidance of the Valsalva manoeuvre) will be practiced. Prior to the 1RM determination, each subject warmed-up for 15 min on a treadmill at 50% of HRR and then performed ten stretching exercises. To warm-up before using a machine, each patient will be asked to perform eight repetitions using a relatively light resistance, followed by a 30 second rest. A second set of four repetitions using a moderate resistance will be then used, followed by a 1 minute rest. After that each patient will be asked to perform single repetitions until the 1RM was reached. The rests between attempts will be 1–2 min. The resistance will be increased by approximately 5 kg, or by 2.5 kg when the subject was near his maximum. Strength will be recorded as the maximal number of kilograms lifted in one full range of motion. The order of the tests will be the same for all patients, and these exercises will be the same as those used for the ExT.

10. QUALITY OF LIFE QUESTIONNAIRE

The Short Form-36 Health Survey (SF-36) is a self-assessment health status questionnaire

composed of 36 questions about socio-demographic, health and personal behavior[**28**]. It was designed for use in clinical practice and research, health policy evaluations and general population surveys. The 36 questions in the SF- 36 survey capture the subject's perception of their general health by sorting them into multi-item scales that assess 8 concepts. The 8 subscales are as follows: physical functioning (10 questions); role/physical (4 questions); bodily pain (2 questions); general health (10 questions); vitality/energy (4 questions); social functioning (2 questions); role/emotional (3 questions); mental health/emotional wellbeing (5 questions). The SF-36 also provides 2 important summery measures of health-related QoL: physical component summary and mental component summary scales. The strength of both scales lies in their ability to distinguish a physical from a mental outcome. The items and dimensions in SF-36 were constructed using the likert method of summated ratings. This questionnaire has been used in CR programs[**29**]. A Portuguese validated version of SF-36 is available[**30**].

11. EXERCISE TRAINING PROGRAM

The ExT program will be carried out mostly in groups at the EUL gymnasium, 3 or 2 times a week (depending on the availability of the patient for complete the 90% of prescribed sessions), 60 minutes per session, on non-consecutive days and supervised for both groups. All sessions will include 10 minutes of warm up and cool down standardized for both groups. The warm up will focus on pulse raising, mobility and preparatory stretching for the conditioning component. Cool down will include transition from conditioning component to the stretching phase, which comprises static and dynamic stretching exercises for all major muscle groups. Muscle strength is intentionally performed before the aerobic exercises to maximize training effects. Sessions will be deemed completed when at least 90% of the prescribed exercises have been successfully performed.

All patients will do in the strength part the same 6 machines (3 to the upper limbs and 3 for de lower limbs): leg press, leg extension, leg curl, low row, chest press and lat pull down. The periodization created allows for a slow progressive increase in strength exercise intensity, volume and density(effort/rest).

CAT group: The subjects will perform in ST part, always only 1 set in the 6 machines early mentioned. During the first and second week they will do 12 repetitions at 40% - 50% of 1 RM. In the third and fourth week progress to 10 repetitions at 60%-70% of 1 RM, and in the second and third month, 8 repetitions at 70%-80% of 1 RM. In the AT part the HIIT protocol is based on a ratio 2 min : 1 min. Consisted of 10 interval training periods (2 min of high intensity at 85% - 90% of heart rate

reserve (HRreser) and 9 pauses (1 min in passive pause) between interval training periods. During the first week of training will start with a continuous training, in the second week the investigators will start with 5 intervals of HIIT, and in the second and third months they are doing the 10 stages of HIIT.

CST group: During the first and second week subjects will perform 1 sets with 12 repetitions at 40% - 50% of 1 RM in the 6 machines mentioned before. In the third and fourth week strength exercises progress to 2 sets of 10 repetitions, at 60%-70% of 1 RM, and in the second and third month consists of 3 sets at 8 repetitions, at 70%-80% of 1 RM. . In the AT part the HIIT protocol is based on a ratio 2 min : 1 min. Consisted of of 5 interval training periods (2 min of high intensity: 85% - 90% of HRreser) and 4 pauses (1 min in passive pause) between interval training periods. During the first week of training will start with a continuous training, in the second week we will start with 3 intervals of HIIT, and after the third/fourth week they are doing the 5 stages of HIIT.

The patients will be instructed in correct exercise techniques and to avoid the Valsalva maneuver. All patients will be continuously monitored using telemetry (NORAV) during the execution of the exercise session in order to achieve the HR training. Blood pressure will be assessed before and after completing each session. If necessary, the blood pressure will be measured during the ExT session.

12. DATA BASE MANAGEMENT AND REPORTS

This task includes the treatment of the variables obtained during the data collection period. In order to assure the confidentiality of the participants an ID code will be attributed to each participant in the database and all the equipment's and sheets used. All personal data (identification documents) of the participants will be destroyed after the passage to the unknown database. A single researcher will perform the database management.

Patient's individual reports will be completed within 2 weeks after evaluation, including quantitative and qualitative information on all assessments made at M0 and M1.

13. STATISTICAL ANALYSIS

Data will be analyzed in M0 and M1. It will be tested the data for normality and homogeneity of variance with the Shapiro Wilk and Levene's tests, respectively. Data analysis will be described according to the established purposes for this project (descriptive values: mean, standard deviation, range, % change) and comparisons of means will be used for all purposed

outcomes intra and inter groups. Baseline characteristics between groups will be evaluated with oneway ANOVA. Mixed between within subjects ANOVA will be conducted in a 2 (pre vs post ExT) design to assess efficiency of the program. When a significant interaction is observed, t tests, or Wilcoxon signed-rank tests will be used to determine where the interaction occurred.

M0 versus M1 will be compared to evaluate the changes in patients and trace the necessary timespan for such changes using General Linear Mixed Model Analysis for repeated measures with Tukey's posthoc procedure for the mean comparisons. Pearson product moment correlation coefficient or Spearman's rank correlation coefficient will be used to study the relationship between different variables by group and correlation coefficients will be compared between groups. Statistical significance will be set at an alpha level of 0.05. Other statistical procedures can be done.

Statistical analyses will be conducted using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM SPSS Statistics, Chicago, IL, USA).

Data analysis will allow peer reviews publication, slide presentations and oral communications in national and international conferences, during year of 2018 and beginning of 2019 to present all the results of the project.

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