STUDY PROTOCOL AND STATISTICAL ANALYSIS

The Effect Of An Expanded Long Term Periodization Exercise Training In Patients With Cardiovascular Disease: Central And Peripheral Adaptations

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BACKGROUND

Cardiovascular Disease (CVD) remains the main cause of death in most European countries accounting for over four million deaths (47% of all deaths) each year[1,2]. In Portugal CVD is among the main causes of morbidity, mortality and disability[3].

Cardiac Rehabilitation (CR) of patients with CVD has been practiced in Europe to varying degrees since the early 1970s[1]. Coronary heart disease (CHD), if left untreated, is a progressive disease and individuals with CHD are at high risk for recurrent events[4]. CR is a comprehensive, long-term program involving medical evaluation, prescribed exercise training (ET), cardiac risk factor modification, education and counselling. These programs are designed to limit the physiologic and psychological effects of cardiac illness, reduce the risk for sudden death or re-infarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients[5]. Furthermore, it is a safe, useful and an effective treatment for patients with coronary artery disease (CAD)[6,7], particularly after myocardial infarction (MI), but also for patients with cardiac interventions and chronic stable heart failure[8,9]. Being a Class I recommendation from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology, with exercise therapy consistently identified as a central element, guidelines recommend that patients with acute coronary syndromes should be offered comprehensive CR services in order to reduce risk factors that may have an impact on future cardiovascular complications[10].

Exercise adherence after a hospital-based CR program is reported to be poor with only 30% to 60% of those who complete a phase II CR program are still exercising 6 months later and after 12 months, up to 50 to 80% of participants failing to adhere to exercise[11-14]. Despite the benefits associated with regular ET, adherence with supervised exercise-based CR remains low[15]. More studies are needed to assess interventions that may help patients adhere to regular and effective ET after ending a hospital-based CR exercise program.

A brief review of meta-analysis studies that assess the impact of different types of exercise in short term outcomes for participants of CR will now be presented. The findings of a meta-analysis in 2015 indicated that high intensity interval training (HIIT) is more effective than moderate continuous training (MCT) for the improvement of both VO2 peak and the anaerobic threshold (AT) in patients with stable CAD [16]. The greater improvement in VO2 peak following HIIT compared to MCT (4.6 ± 3.1 versus 2.8 ± 2.4 ml/kg/min) is important in the context of a 10-25% survival advantage with every 3.5 ml/kg/min improvement in VO2 peak[17].

Another meta-analysis in 2016, compared HIIT and MCT in their ability to improve patients aerobic exercise capacity and various cardiovascular risk factors. Ten studies with 472 patients were included for analyses (218 HIIT, 254 MCT) and the main conclusions were that HIIT improves the mean VO2 peak in patients with CAD more than MCT, although MCT was associated with a more pronounced numerical decline in patients resting heart rate (HR) and body weight[18].

Current CR guidelines recommend the inclusion of a standardized resistance training (RT) program[10,19]. A recent meta-analysis of ET programs in patients with CAD revealed that the addition of RT training to MCT led to superior improvements in body composition, muscle strength, peak work capacity, and a trend for greater

increases in VO2 peak[20]. Similar to HIIT, RT has not been shown to compromise patient safety or program adherence[20].

Less is known about central and peripheral adaptations during long term effects on HIIT, MCT or even aerobic combined training with RT. In 2016, a systematic review and meta-analysis with a total of 63 studies with 14,486 participants with CHD median follow-up of 12 months were included[21]. It was concluded that exercise-based CR reduces cardiovascular mortality and provides important data showing reductions in hospital admissions and improvements in quality of life[21]. Madssen et al[22], showed that a 12-month maintenance exercise program consisting of infrequent supervised exercise sessions did not result in improved adherence to exercise or increased VO2 peak in CAD patients compared to usual care. One monthly session during a year of HIIT was not enough to improve or maintain exercise capacity. In the literature there is a lack of evidence on the effects in exercise capacity, muscle strength and body composition in long term weekly supervised exercise sessions on a maintenance exercise program in CVD patients.

Current exercise guidelines for CR focus on moderate intensity steady state exercises, with walking and cycling being the most recommended types of ET[10]. The repetitive nature of this type of activity can become monotonous for the patient, affecting exercise adherence, compliance and training outcomes. Multiple training variables can be manipulated during exercise prescription, including repetitions, interval length, rest period length and intensity of resistance. In this regard, much insight could be gained from approaches used in sport conditioning, where exercise prescription is designed to be physiologically and psychologically sustainable using periodization.

Periodization was developed in the 1960's by the Russian physiologist Leo Matveyev[23] and is defined as an organized cyclic program that uses planned variations in intensity, volume, and specificity to minimize fatigue and maximize performance outcomes[24]. Periodized programs are composed of macrocycles, mesocycles and microcycles. The largest cycle or macrocycle is 1 year in length, each macrocycle is then broken into mesocycles, traditionally 1 to 3 months in length. Finally, each mesocycle is broken into individual microcycles[23]. In healthy or trained populations, periodization aims to optimize ET adaptations as compared with non periodized training, to prevent overtraining and to avoid plateauing of training adaptations[25,26]. The classical approach to periodization is linear periodized training, consisting in promoting wave-like progression, typically moving from general training (high volume/low intensity) towards specific training (low volume/high intensity)[27]. Periodized methods are considered to be superior to nonperiodized methods in trained populations[25] and appears to be superior in inactive adults[28]. Interestingly, a recent study investigated the effect of 22 weeks of 2 different types of periodization and 1 non periodization RT protocols on a comprehensive range of physical function and health outcomes in apparently healthy untrained older adults[29]. Contrary of what was hypothesised, all three training models were equally effective for promoting significant improvements in various physical function and physiological health outcomes through RT in this population[29].

In most of the CR programs there are no periodization or exercise progression during medium to long term interventions. Further randomized controlled trials (RCT) are necessary to evaluate long-term periodization outcomes and assess the length of change observed in supervised CR programs.

PURPOSE

To overcome the lack of knowledge regarding the physiological effects after hospital-based CR program, a 12 month RCT study will be performed. This study will hopefully contribute to generate evidence-based exercise prescription approaches to prolong the ET after the end of hospital-based CR programs.

The purpose of this research project is twofold:

1) To conduct a 12-month randomized control trial to evaluate the effects of periodized ET regime versus a non periodized ET regime on VO2 peak, maximal strength, body composition, functionality and quality of life in CVD patients.

2) to differentiate the effects of a 12-month periodized ET regime versus a non periodized ET regime on the different components of the oxygen kinetics response and oxidative adaptations in CVD patients.

The primary end points for aim 1 are: cardiopulmonary exercise testing (CPET) variables such as VO2 peak, AT, peak work rate, ventilatory equivalent of carbon dioxide (VE/VCO2), ventilatory equivalent of oxygen (VE/VO2), minute ventilation (VE), one repetition maximum (1RM), total body bone mineral content, lean and fat tissue mass and percentage of body fat mass, quality of life and functional physical fitness tests. The primary end points for aim 2 are oxygen kinetics and muscle deoxygenation dynamics of the vastus lateralis muscle at the submaximal test.

The hypothesis for this study are: 1) considering that this type of periodization exerts higher stress on the cardiovascular and neuromuscular systems, so that there could be greater adaptations, leading to higher increases in VO2max, muscle strength, body composition and functionality compared to non periodized ET regime; 2) there will be a better improvement microvascular O2 delivery in the exercise transient in response to periodized ET regime that would be associated with a faster adjustment of pulmonary VO2 kinetics than in non periodized group. Improvements in microvascular O2 delivery would be indicated by a better matching between the rate of adjustment of muscle deoxygenation relative to phase II pulmonary VO2, which represents a decreased reliance on O2 extraction for a given pulmonary VO2.

METHODS

PARTICIPANTS

Patients with CVD that underwent to a hospital-based 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: 1) periodized group; 2) non periodized group following the American College of Sports and Medicine (ACSM) guidelines[30]. Patient's eligibility will be assessed according to the risk stratification criteria for patients with CVD for low and/or moderate risk stratification from the American Association of Cardiovascular and Pulmonary Rehabilitation [31]. Male and female participants, ≥ 18 years of age, who had an established history of the following conditions or procedures will be included: MI, or coronary revascularization (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or coronary artery stent), angina pectoris or coronary artery disease defined by angiography. Exclusion criteria

will be participants who had heart failure, heart transplants with either cardiac resynchronization therapy or implantable defibrillators; inability to comply with guidelines for participation in exercise testing and training[30]; and significant limiting and/or unstable comorbidities that would prevent full participation.

Sample size was calculated (G-Power, *Version 3.1.3)* assuming a difference in peak oxygen uptake (VO2 peak) between groups of 3 ml/kg/min to be a clinical important difference with a SD of 3.5 ml/kg/min, α=0.05, 1-β=0.80 and an expected dropout rate of 37%. The calculations yielded a total minimum sample size of 50 participants (25 in each group).

STUDY DESIGN

A longitudinal RCT research design using two distinct ET prescriptions (periodization vs non periodization) will be applied in CVD patients. Briefly, following the informed consent process, patients will be randomized and stratified (by gender and age) to periodization or non periodization groups. The randomization code will be developed with a computer random-number generator to select random permuted blocks. Participants will exercise for a period of 12 months. All the same assessments, except the echocardiogram that will be done in M0 and M3 (for risk stratification), are going to be taken in 4 different time points during a year: M0 - baseline, M1 - 3 months after starting the ET, M2 - 6 months after starting the ET and M3 - 12 months after starting the ET. The patients will be randomized into either one of the two ET group. Recruitment and screening will last 12 months (September 2017 to September 2018) and the patient assessment will last until September 2019. It is expected to finish the project with peer-review redaction submitted and/or accepted in December 2019.

The following assessments on the 4 time points 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); skeletal muscle deoxygenation dynamics (NIMO, Nirox srl); body composition - dual energy radiographic absorptiometry (DXA, Hologic Explorer-W); objective measured physical activity - accelerometer (ActiGraph GT3X+); functional physical fitness - Fullerton Functional Fitness Test; isometric strength – portable hand dynamometer JAMAR plus digital (Sammons Preston); maximal strength – 1RM and Quality of Life questionnaire.

All assessment moments will be done in 1 to 2 weeks:

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

Day 2 and 3 – during the day and time of the ET session at the EUL, the patient will perform: functional physical fitness tests; maximal strength; isometric strength and Quality of Life questionnaire;

Day 4 – In FMH, the dual energy radiographic absorptiometry (DXA) exam and the activation of the accelerometer to measure the objective measured physical activity will be done.

Day 5 – Submaximal CPET with the skeletal muscle deoxygenation dynamics at the Pulido Valente Hospital.

Individual reports will be sent by email or delivered on paper. During the 3-year project the multidisciplinary team will have bimonthly meetings to update the study information and discuss the patient's progress.

MEASUREMENT PROCEDURES

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 left ventricular ejection fraction by Simpson`s formula, telediastolic and telessystolic volumes and diameters, doppler analysis of the transmitral flow, tissue doppler and quantification of mitral valve regurgitation.

EXPECTED RESULTS

The variables measured in this task will provide clinical information to patient screening. Most of the human and animal studies demonstrated that post-MI physical exercise training results in positive effect on myocardial remodeling[32]. These beneficial effects include improved cardiac function, mitigated interstitial myocardial fibrosis, and enhanced physical capacity. It is expected a positive effect on myocardial remodeling in both exercise training groups. It is important to note that the existing studies have only investigated the effects of endurance exercise on post-MI remodeling; therefore, the effects of post-MI resistance training or combined endurance and resistance training have yet to be systematically examined to identify a better exercise mode.

2. CARDIOPULMONARY EXERCISE TEST

CPET is the best technique to obtain the maximal and submaximal functional capacity. Those tests 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, in accordance with the Clinician's Guide to Cardiopulmonary Exercise Testing in Adults[33], will be performed on a cycle ergometer (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany) with breath-by-breath gas exchange measurements. 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 2 minutes unloaded pedaling and 2 more minutes at rest, each patient will be encouraged to exercise to exhaustion (20 Watt+20 Watt/min or 15 Watt+15Watt/min or 10 Watt+10 Watt/min), 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. Twelve-lead ECG will be recorded continuously and blood pressure will be recorded at baseline, every two minutes, at peak exercise and during recovery. Peak oxygen capacity will be considered the highest attained VO_2 during the final 30s of exercise and ventilator AT will be estimate by the V-slope method. 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 (CR) to exercise will be evaluated by the % of HR reserve (HRR) used at peak exercise. CR= [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.

Submaximal exercise test

On a separate day to the maximal test, patients will be recruited for a constant load exercise test. The test load is set at 80% of the value of the work rate corresponding to the AT detected in the maximum test, which was performed first, or 50% of VO2 peak, if the AT could not be adequately determined. Cardiopulmonary data will be recorded for 5 minutes at rest followed by 1 minute unloaded pedaling. After unloaded pedaling, patients will perform the constant load test for 6 min at the work rate described above, followed by unloaded pedaling for 5min. To improve the confidence of the kinetic parameter determination, this test will be performed three times and the averaged profile will be used for the kinetic analysis.

Curve fitting will be performed with Graphics software Origin version 7.0 (Microcal Software Inc., Northampton, Massachusetts, USA) using iterative techniques. The kinetics of the oxygen uptake response to the constant workload exercise will be analyzed by the sequent separate phases.

Before each maximal and submaximal test, the gas analyzer will be calibrated using ambient air and standard calibration gases of known concentration (16.7% O2 and 5.7% CO2). The calibration of the turbine flowmeter will be performed using a 3l syringe (Quinton Instruments, Seattle, Wash.) Twelve-lead ECGs, blood pressure, and ratings of perceived exertion will be recorded during each exercise stage.

EXPECTED RESULTS

The CPET will provide fundamental information to exercise intensity prescription and is a primary endpoint for purpose 1 and 2. We expect increases in VO2max in both training regimes from 5%–15% after 12 months of physical conditioning, with the greatest improvements in the periodized training group.

It is expected that there would be an improved microvascular O2 delivery in the exercise transient in response to both training groups that would be associated with a faster adjustment of VO2 kinetics, with the greatest improvements in the periodized training group.

3. SKELETAL MUSCLE DEOXYGENATION DYNAMICS

The muscle deoxygenation dynamics of the Vastus Lateralis muscle will be evaluated throughout the submaximal CPET. Deoxyhaemoglobin [HHb], oxyhaemoglobin [HbO2], and total haemoglobin [HbT] concentrations will be quantified with a continuous-wave tissue oximeter (NIMO, Nirox srl, Brescia, Italy), based on the Near-infrared Spectroscopy (NIRS) system, which provides continuous, non-invasive monitoring of the relative concentration changes in these variables during rest and exercise. Briefly, this system is based on the oxygen dependency of absorption changes for near infra-red light in haemoglobin and myoglobin and it consists on an emission probe which emits three wave lengths (685, 850 and 905 nm) and a photon detector. The intensity of incident and transmitted light will be record continuously at 40 Hz and used to estimate the concentrations changes relative to baseline for oxygenated, deoxygenated and total haemoglobin. To account for the possible influence of the local fat layer on NIRS a real-time correction using an algorithm included in the software program v2.0 supplied with the spectrometer (Nimo Data Analysis Peak) will be used. Since the HHb signal is less dependent of changes in blood flow it can be used as an indicator of fractional O2 extraction within the microvascular level. This task will be performed at rest, during and immediately following the

submaximal CPET. The off- oxygen consumption and HHb kinetics will be determined using a monoexponential model which incorporates an amplitude, time constant and time delay.

EXPECTED RESULTS

The off- oxygen consumption and HHb kinetics will be determined using a mono-exponential model which incorporates an amplitude, time constant and time delay. As the recovery of muscle and total body oxygenation from both maximal and submaximal exercise is delayed in sedentary participants, it is expected that the exercise training, in particular the periodized training group, induces a decrease of the time constant of the exponential decrease of these parameters.

4. BODY COMPOSITION - DUAL ENERGY RADIOGRAPHIC ABSORPTIOMETRY (DXA)

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. 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/m2) 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/m2) 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.

EXPECTED RESULTS

DXA provides descriptive data on the body composition of all patients from the studied groups and will be important to monitor the changes in body composition over time and to quantify the intervention effects particularly regarding fat free mass and muscle wasting. It will also allow adjustments to the expected differences between groups at the end of the study. It is not probable to find exercise-related changes in body weight but small reductions in percent total body and regional fat are desirable, as well as increases in lean soft tissue of the lower limbs in the exercise groups. The variables obtained in this task are primary endpoints of purpose 1 and secondary endpoints of purpose 2. We expect small reductions in regional fat layer thickness in the exercise groups, especially in periodized training group.

5. 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.

EXPECTED RESULTS

This assessment will be used as a control of the physical activity or inactivity of the participants. The ones who reported at least moderate-intensity cardiorespiratory exercise training for ≥ 30 minutes per day on ≥ 5 days a week for a total of ≥ 150 minutes per week, vigorous-intensity cardiorespiratory exercise training for ≥20 minutes per day on ≥ 3 days a week (≥75 minutes per week), or a combination of moderate and vigorous intensity exercise to achieve a total energy expenditure of ≥ 500-1000 MET minutes per week, consistent with the recommendations of the American College of Sports Medicine[34], will be classified as active. Those not meeting this criterion will be considered inactive. We expect increases in time spent in moderate-to-vigorous physical activity from M0 to M3 in both exercise groups.

6. 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 -).

EXPECTED RESULTS

The variables measured in this task are primary end-points of purpose 1. We expect gradual improvements of the functional fitness test scores from M0 to M3 in both exercise groups, in particular the periodized training group.

7. 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.

EXPECTED RESULTS

The variables measured in this task are secondary aims of the project. It remains to be determined whether a training protocol that specifically focuses on increasing hand grip strength would have a greater impact on overall functional status. Maximal isometric strength is not expected to decrease in both exercise groups.

8. 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[35]. 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 ET.

EXPECTED RESULTS

The variables measured in this task are primary endpoints of aim 1. Significant improvements in maximal strength are possible as high from 50 and 69% of 1-RM among middle-aged CAD participants and over 80% of 1- RM in elderly CAD participants[36].

9. 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[37]. 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 quality of life: 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[38]. A Portuguese validated version of SF-36 is available[39].

EXPECTED RESULTS

The variables measured in this task are primary endpoints of aim 1 of the project, it is expected improvements in the quality of life for both exercise training groups and a bi-directional relationship with increased physical activity and vocational status[40].

10. EXERCISE TRAINING PROGRAM

The ET program will be carried out mostly in groups at the EUL gymnasium, 3 times a week (60 minutes per session) on non-consecutive days for 48 weeks and supervised for both groups. To ensure that total training loads (i.e., volume x intensity) were similar in both groups despite differences in intensity, it will be used the training impulses (TRIMP) method from Edwards[41] for the aerobic component and the volume load method for the RT component[42,43]. 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. In every 10 exercise sessions, it will be prescribed multifunctional exercise with the aim to develop other fitness components such as agility, flexibility and balance. In total, approximately 14 multifunctional exercise sessions will be prescribed during 48 weeks. Sessions will be deemed completed when at least 90% of the prescribed exercises have been successfully performed.

Periodized group: the exercise prescription will be gradually progressed through various combinations of duration, frequency and/or intensity of training. Over the first 15 exercise sessions, it will be prescribed continuous ET: 20 minutes on an ergometer with the intensity of the first AT (AT1) measured on the CPET or 50-60% of the HRR, if the AT could not be adequately determined[44], Borg Rating of Perceived Exertion (RPE) equivalent 9-11; and anatomical RT adaptation (2 sets of 15-20 repetitions 50% 1RM); from the 16th session until the 30th session, it will be prescribed combined ET with HIIT[45]: 4 interval training periods of 2 minutes (AT2 intensity or 80-90% HRR, if AT2 could not be determined[44], RPE 15-17) and 4 active pauses of 2 minutes (below AT1 or 40-50% HRR, RPE 6-9) between interval training periods; and hypertrophy (2 sets 8-12 repetitions at 60% 1RM). From the 31st until the 45th exercise session, after the adjustments of the respectively time point assessments, it will be done 20 minutes of MCT with the intensity between AT1 and

AT2 or of 60-70% HRR, RPE 12-13 and maximal strength (2 sets of 6-8 repetitions at 80% 1RM). From the 46th until the 60th exercise sessions, it will appear again the HIIT with the same pause intensities but different work intensities (above AT2 intensity or > 90% HRR, RPE 17-19 and active pauses at AT1 or 50-60% HRR, RPE 9-11) with hypertrophy (2 sets 8-12 repetitions 60% 1RM). At the end of the 60th session, the same exercise prescription will start over again, MCT with maximal strength, HIIT with hypertrophy, MCT with maximal strength and HIIT with hypertrophy until the 134th session. The 2 types of RT prescribed will focus on the major trunk, upper and lower body muscle groups in circuit weight training [46] and/or machines (Life Fitness, Rosemont, IL, USA). The patients will be instructed about the correct exercise techniques and to avoid the Valsalva maneuver.

Non periodized group: in accordance with the ACSM Guidelines 2014 [30] for CVD, participants will do a combined ET regime (aerobic and RT). Aerobic component: combine moderate (40% HRR) to vigorous (75% HRR) exercises 3 $d.wk^{-1}$ on nonconsecutive days, for 20 min per session, involving major muscle groups using the available ergometers (treadmill, indoor row and cycle ergometer) to perform continuous and rhythmic activities in nature. Resistance component: RT should be performed after the aerobic component of the exercise session to allow for adequate warm-up. Initial load should be trained initially with one set of 10–15 repetitions that can be lifted without straining (~30%–40% 1RM for the upper body; ~50%–60% 1 RM for the lower body). Low-risk patients may progress to 2–4 sets with 8–12 repetitions with a resistance of ~60%–80% 1RM with a rest interval of 2–3 min between sets. Each major muscle group (*i.e.*, chest, shoulders, arms, abdomen, back, hips, and legs) should be trained initially with one set; multiple set regimens may be introduced later as tolerated. Perform 8–10 exercises of the major muscle groups.

By design, the non periodized group involves an identical total training volume and time commitment but differed regarding metabolic stress induced by the periodized group. All patients will be monitored with a HR monitor (H7 Polar, Electro, Kempele, Finland) 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 ET session.

11. TRIMP CALCULATIONS

The quantification of the training load in the aerobic component by the Edwards method[41] will be performed from the division of intensity zones related to maximal HR (HRmax) - Zone 1: 50 at 60% of HRmax; Zone 2: 60 at 70% of HRmax; Zone 3: 70 at 80% of HRmax; Zone 4: 80 at 90% of HRmax; Zone 5: 90 at 100% of HRmax. Since the HR prescription that are being used is in % HRR, it will be converted % HRmax to % HRR as it is possible to observe in *Table 1*. For estimation of the Edwards method, the time accumulated in each zone was multiplied by its value and the results obtained will be summed (*Table 2*).

Table 1: Methods of Estimating Intensity of Cardiorespiratory Exercise (Adapted from Garber et all[34])

Intensity	%HRR or %VO_2R	%HR max	Edwards method Zone
Very light	< 30	< 57	1
Light	30 - < 40	57 - < 64	2
Moderate	40 - < 60	64 - < 76	3
Vigorous	60 - < 90	76 - < 96	4
Near maximal to maximal	≥ 90	≥ 96	5

HRmax, maximal heart rate; HRR, heart rate reserve; VO_2R, oxygen uptake reserve.

Table 2: Intensity and duration, as quantified by daily trimp per every 15 exercise sessions during the training period for the periodized group and the non-periodized group.

		Aerobic Component												
		Linear Periodized Group									Non Periodized Group			
Number of sessions	total time	work sets	work (min)	rest sets	rest (min)	work (zone)	rest (zone)	extra (min)	extra (zone)	TRIMP daily	work sets	work (min)	work (zone)	TRIMP daily
1 to 15	20	1	20	0	0	2	0	0	0	40	1	20	2	40
16 to 30	20	4	2	4	2	4	2	4	1	60	1	20	3	60
31 to 45	20	1	20	0	0	3	0	0	0	60	1	20	3	60
46 to 60	20	4	2	4	2	5	3	4	1	60	1	20	3	60
61 to 75	20	1	20	0	0	3	0	0	0	60	1	20	3	60
76 to 90	20	4	2	4	2	4	2	4	1	60	1	20	3	60
91 to 105	20	1	20	0	0	3	0	0	0	60	1	20	3	60
106 to 120	20	4	2	4	2	5	3	4	1	60	1	20	3	60
121 to 135	20	1	20	0	0	3	0	0	0	60	1	20	3	60
										520				520

The equation for calculating the volume load for the RT is accomplished by multiplying the number of repetitions by the percentage of 1-RM[43]. This equation is represented as the following: *Volume load (kg) = number of sets x number of repetitions x %1RM.* In both groups, TRIMP is similar (Periodized: 12820 vs Non Periodized: 12790).

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. A single researcher will perform the database management.

EXPECTED RESULTS

We expect to add the data collected at M0, M1, M2 and M3 to the database within 2 weeks of the end of the respective evaluation moment, and store it at the FMH-UL web server allowing detailed progress reports and back-ups when needed. Individual reports will be delivered within 2 weeks of the end of the respective evaluation moment.

13. STATISTICAL ANALYSIS

Data will be analyzed in M0, M1, M2 and M3. 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 ET) 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, M0 versus M2, M0 versus M3, M1 versus M2, M2 versus M3 and M1 versus M3 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 redaction, slide presentations and oral communications in national and international conferences at the end of 2017 beginning of 2018.

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