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Effect of exercise-based cardiac rehabilitation on arterial stiffness and inflammatory and endothelial dysfunction biomarkers: A randomized controlled trial of myocardial infarction patients

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ABSTRACT

Background: Arterial stiffness have shown an independent predictive value for cardiovascular and all-cause mortality.
Objective: This study sought to evaluate the effects of an 8-week exercise-based cardiac rehabilitation program (ECR) on arterial stiffness, and on inflammatory and endothelial dysfunction biomarkers. Additionally, it was assessed two potential confounding variables, daily physical activity and dietary intake.
Methods: In this parallel-group trial, 96 patients (56 ± 10 years) were randomized to either the exercise group (EG) or control group (CG) 4 weeks after suffering acute myocardial infarction (MI). ECR consisted of 8 weeks of aerobic exercise at 70–85% of maximal heart rate during 3 sessions weekly, plus usual care. CG participants received only usual care. Baseline and final assessments included arterial stiffness through carotid-femoral pulse wave velocity (cf-PWV), inflammatory and endothelial dysfunction biomarkers, daily physical activity, and dietary intake. (ClinicalTrials.gov: NCT01432639).
Results: After 8 weeks, no significant changes were found between groups in cf-PWV, inflammatory and endothelial dysfunction biomarkers, daily physical activity, or dietary intake. Excluding those patients (n = 7) who did not attend, at least 80% of the exercise sessions provided similar results, excepting a significant reduction in cf-PWV in the EG compared to the CG.
Conclusions: A short-term ECR does not seem to reduce arterial stiffness and inflammatory and endothelial dysfunction biomarkers of post-MI patients under optimized medication. Nevertheless, the decrease of cf-PWV observed in the EG, when considering only those patients who attended at least 80% of exercise sessions, warrants further investigation.

1. Introduction

Atherosclerosis, defined as a process of endothelial dysfunction and chronic inflammation [1], has been associated with increased arterial stiffness (AS) [2], which has been observed in coronary artery disease (CAD) and post-myocardial infarction (MI) patients [3]. The harmful effects of AS derive from hemodynamic changes, as increases in systolic and pulse pressures [4], which are related to cardiac overload and a reduction in coronary perfusion that can lead to myocardial ischemia [5]. Carotid-femoral pulse wave velocity (cf-PWV), an indicator of aortic wall stiffness, have shown an independent predictive value for cardiovascular and all-cause mortality [6,7]. Additionally, inflammatory and endothelial dysfunction biomarkers, cardiovascular risk predictors in CAD patients [8,9], have been associated with AS [10].

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Therefore, interventions to reduce AS and related factors could be of great significance. However, the effects of aerobic exercise training on AS have been understudied in CAD patients [11]. Likewise, only a small-uncontrolled study was conducted investigating whether an exercise training effect on AS is related to possible changes in inflammatory biomarkers [12]. Nevertheless, this study did not assess the main measure of AS, cf-PWV.

In addition, it has been reported that daily physical activity is independently and inversely associated with several AS indexes [13], and that cardiac rehabilitation programs could increase physical activity levels of patients [14]. Otherwise, a recent systematic review has stated that nutritional intervention could alleviate AS [15]. Despite the associations of daily physical activity and diet with AS [13,15] these two important lifestyle components were not assessed in any study, hindering the evaluation of an independent effect of exercise. Thus, the purpose of the present randomized controlled trial was to examine the effects of an 8-week exercise-based cardiac rehabilitation program (ECR) on AS, endothelial dysfunction, and chronic low-grade inflammation biomarkers in post-MI patients, assessing the potential contributory influences of daily physical activity and dietary intake.

2. Methods

2.1. Study design, randomization and implementation

This randomized controlled trial was performed from May 2011 to November 2012 at the Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal. Patients, 4 weeks after acute MI, were randomly assigned to an ECR program (i.e., the EG) or to the control group (CG), both receiving usual medical care (i.e., regular appointments with a cardiologist and optimized medication). Randomization and allocation sequence was based on a block size fixed to 8 and generated through a computerized random number generator by an investigator not involved in the trial. Patients who agreed to participate provided written informed consent. A cardiologist aware of the study design conducted enrollment and assignment. The outcome evaluators were blinded to group assignment.

The Hospital Ethics Committee granted ethical approval (reference 627/2010), all procedures were conducted according to the Declaration of Helsinki, and the trial has been registered at ClinicalTrials.gov (NCT01432639).

2.2. Participants

Patients aged 18 or over referred to the Hospital Cardiology Department after an acute MI were eligible. Exclusion criteria included the presence of uncontrolled cardiac arrhythmias, unstable angina pectoris, uncontrolled hypertension, significant valvular disease, diagnosis of heart failure, uncontrolled metabolic disease, presence of pulmonary and renal co-morbidities, conditions limiting participation in exercise training, and abnormal hemodynamic responses, myocardial ischemia, and/or severe ventricular arrhythmias during baseline exercise testing.

2.3. Measurements

2.3.1. Anthropometrics

Height, body mass and percentage of fat mass were evaluated with a stadiometer and a Tanita Inner Scan BC-522 (Tanita, Tokyo, Japan), respectively. Body mass index (kg/m^2) was calculated. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest.

2.3.2. Cardiorespiratory fitness

An ergospirometry device (Cardiovit CS-200 Ergo Spiro; Schiller, Baar, Switzerland) was used to measure the peak oxygen uptake (VO_{2peak}) during a maximal or symptom-limited treadmill exercise test (modified Bruce protocol).

2.3.3. Blood collection and analysis

Twelve-hour fasting blood samples were collected by venipuncture of the antecubital vein into serum separator and EDTA-coated tubes, which were centrifuged for approximately 15 min between 1000 and 2000× *g*. Serum and plasma samples were then aliquoted and stored at −80 °C until analysis. Inflammatory biomarkers were measured as follows: high-sensitivity (hs) C-reactive protein (CRP) (plasma) by a highly sensitive immunoturbidimetric assay (Prestige 24i CRP Ultra, P.Z.; Cormay, Lublin, Poland), serum levels of regulated on activation, normal T cell expressed and secreted (RANTES), interleukin (IL)-6, IL-10, and tumor necrosis factor alpha (TNF-α) by a high sensitive Milliplex map kit (Human 4-plex Cytokine panel; Millipore, St. Charles, MO, USA) with the Luminex 200™ analyzer (Luminex Corporation, Austin, TX, USA). Endothelial dysfunction biomarkers were assessed as follows: serum concentrations of soluble intercellular adhesion molecule 1 (sICAM-1) and soluble vascular cell adhesion molecule 1 (sVCAM-1) by enzyme-linked immunosorbent assay kits (IBL International GMBH, Hamburg, Germany) and a microplate reader (450 nm − primary wave length). All determinations were performed in duplicate. Patients were screened and excluded if an indicator of infection and/or any acute inflammatory process (hs-CRP > 10 mg/L) was detected [16] in one of the evaluation periods, since such condition influences AS [17].

2.3.4. Resting hemodynamic and arterial stiffness-related indexes

Participants were asked to avoid strenuous exercise, caffeinated products, and alcohol consumption for at least 24 h and to not smoke or eat for at least 3 h before evaluation. At least 3 blood pressure measurements were made in the right arm, at intervals of 1 min, using Colin model BP 8800 monitor (Critikron, Inc., Tampa, FL, USA) after 20 min of supine resting with the arm supported and relaxed at heart level. The averages of these multiple measurements were used. Pulse wave analysis was performed by applanation tonometry (Sphygmocor System, AtCor Medical, Sydney, Australia) of the radial artery in the right wrist with a high-fidelity strain gauge transducer (Millar Instruments, Houston, TX, USA). In brief, sequential radial pressure waveforms were registered for at least 12 s through this noninvasive method, and a central (aortic) pressure waveform was generated by a validated algorithm [18]. The parameters generated by this analysis were central pressures, augmentation index (AIx), and augmentation index corrected for heart rate of 75 bpm (AIx@75). AIx denotes the contribution of the wave reflection to the central arterial pressure waveform and is expressed as a percentage of central pulse pressure [19]. Assessment of the cf-PWV (i.e., aortic PWV) was conducted using the same valid, reproducible, and reliable system [20]. Sequential and consecutive right carotid and femoral pressure waves were registered with parallel electrocardiogram recording. The electrocardiogram serves as a reference to calculate the wave transit time between the two recording sites (i.e., foot-to-foot method). The distance traveled by the pressure wave results from the difference between the surface distances of the recording point at the femoral artery to the sternal notch and the sternal notch to the recording point at the radial artery. PWV is therefore calculated as the distance traveled in meters by the pressure wave divided by the transit time in seconds. The quality of the waveforms registered was guaranteed during pulse wave analysis by achieving a value >90% in the quality control tool of the Sphygmocor software, as well as in