Atherosclerosis 239 (2015) 150–157

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

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

Nórton Luís Oliveira [a, *], Fernando Ribeiro [b], Gustavo Silva [a], Alberto Jorge Alves [a, c], Nuno Silva [d], João Tiago Guimarães [d], Madalena Teixeira [e], José Oliveira [a]

[a] Research Centre in Physical Activity, Health and Leisure, Faculty of Sport, University of Porto, Rua Dr. Plácido Costa, 91, 4200.450 Porto, Portugal
[b] School of Health Sciences, University of Aveiro, Agras do Crasto, Campus Universitário de Santiago, 3810.193 Aveiro, Portugal
[c] Higher Institute of Educational Sciences, Rua Dr. Luís Gonzaga F. Moreira, 4610.177 Felgueiras, Portugal
[d] Department of Clinical Pathology, S. João Hospital, Alameda Prof. Hernâni Monteiro, 4200.319 Porto, Portugal
[e] Cardiology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, Vila Nova de Gaia, 4434.502 Espinho, Portugal

ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form
19 December 2014
Accepted 24 December 2014
Available online 14 January 2015

Keywords:
Pulse wave velocity
Inflammation
Chronic exercise
Secondary prevention
Cardiovascular disease

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.

© 2015 Elsevier Ireland Ltd. All rights reserved.

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].

* Corresponding author.
E-mail addresses: nloedfisica@gmail.com (N.L. Oliveira), fernando.ribeiro@ua.pt (F. Ribeiro), gugonsilva@gmail.com (G. Silva), aljo.alves@gmail.com (A.J. Alves), nunosilva.box@gmail.com (N. Silva), jtguimar@med.up.pt (J.T. Guimarães), mteix@chvng.min-saude.pt (M. Teixeira), joliveira@fade.up.pt (J. Oliveira).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.057
0021-9150/© 2015 Elsevier Ireland Ltd. All rights reserved.

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

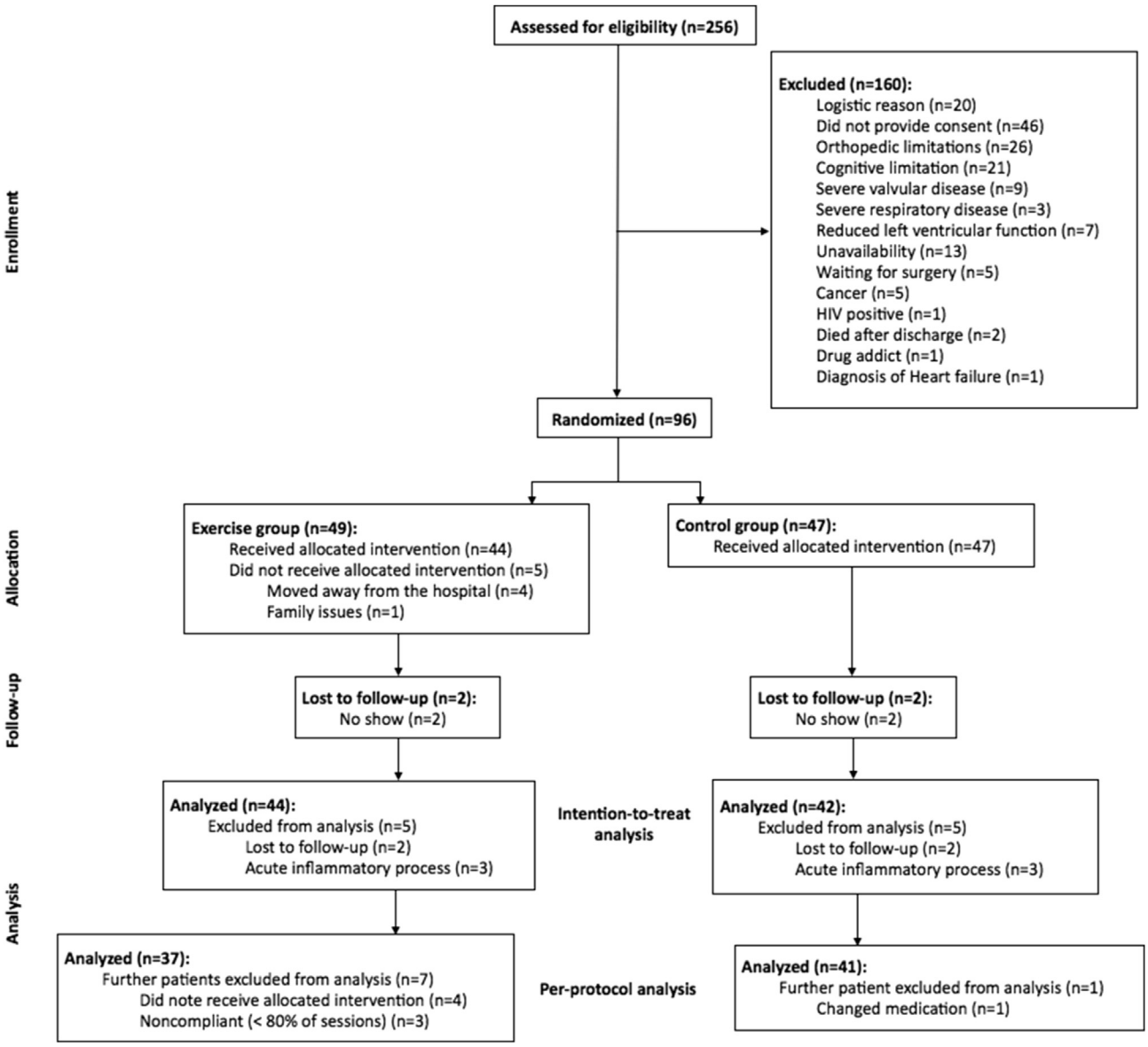

Fig. 1. Flow diagram of patients.

pulse wave velocity by a standard deviation value of <10% of mean velocity. All measurements were performed in duplicate by the same trained researcher and the mean value was calculated.

2.3.5. Daily physical activity

Patients wore an accelerometer (Actigraph GT1M; ActiGraph, LLC, Pensacola, FL, USA) positioned on the right hip during the daytime for seven consecutive days, except while sleeping, bathing, and during aquatic activities. The software PROPERO (developed by University of Southern Denmark) was used to reduce raw activity data from the accelerometers into daily physical activity. The average min per day spent at different physical activity intensities was determined according to cut points relating counts/min to physical activity intensity [21].

2.3.6. Dietary intake

Patients recorded their intakes of food and beverage for 4 days (Sunday and 3 weekdays). Nutritionists performed comprehensive nutrient analysis (i.e., total energy intake, consumption of protein, carbohydrates, total fibber, sodium, total fat, saturated fat, monounsaturated fat, cholesterol, and n-3 and n-6 fatty acids) with Food Processor Plus (version 7.02; ESHA Research, Salem, OR, USA).

2.3.7. Exercise-based cardiac rehabilitation program

This program was essentially composed by exercise training and usual medical care (i.e., regular appointments with a cardiologist and optimized medication). Additionally, patients received general nutritional counseling from a nutritionist in the beginning and in the final of the program period. Three supervised exercise sessions per week were performed for 8 weeks (10 min of warm-up, 30 min of aerobic exercise on a cycloergometer or treadmill at 70–85% of the maximal heart rate achieved during the exercise test, and 10 min of cool-down). Heart rate and levels of exertion (i.e., Borg scale) were continuously monitored during exercise sessions.

2.3.8. Sample size calculation and statistical analysis

Power calculation was computed a priori. Based on a beta error of 10% (power = 0.90), an alpha error of 5%, a total sample size of 68

Table 1
Baseline demographic and clinical characteristics (intention-to-treat analysis).

	Exercise group (n = 44)	Control group (n = 42)	*p*
Age (years)	55.0 (10.7)	58.5 (10.7)	0.127
Sex (male)	38 (86.4%)	34 (81.0%)	0.699
Family history	10 (22.7%)	5 (11.9%)	0.299
Diabetes mellitus	7 (15.9%)	12 (28.6%)	0.248
Hypertension	40 (90.9%)	41 (97.6%)	0.385
Currently smoking	21 (47.7%)	22 (52.4%)	0.829
Hyperlipidemia	44 (100%)	42 (100%)	–
Overweight/obesity	31 (70.5%)	33 (78.6%)	0.538
LVEF (%)	52.8 (9.5)	54.6 (7.6)	0.331
Site of infarction (anterior)	20 (45.5%)	14 (33.3%)	0.353
Number of coronary vessels involved			
One vessel	35 (79.5%)	35 (83.3%)	0.862
Two vessels	9 (20.5%)	7 (16.7%)	
Number of infarctions			
First	40 (90.9%)	35 (83.3%)	0.239
Second	4 (9.1%)	7 (16.7%)	
PTCA	42 (95.5%)	36 (85.7%)	0.237
Days hospitalized	5.3 (3.6)	4.1 (1.6)	0.133
Antiplatelets	44 (100%)	42 (100%)	–
ACE Inhibitors	40 (90.9%)	39 (92.9%)	1.000
Beta-blockers	41 (93.2%)	42 (100%)	0.257
Lipid-lowering drugs	39 (88.6%)	39 (92.9%)	0.762
Nitrates	10 (22.7%)	2 (4.8%)	0.036
ARBs	2 (4.5%)	–	0.495
Diuretics	3 (6.8%)	4 (9.5%)	0.949
Calcium channel blockers	1 (2.3%)	3 (7.1%)	0.576
Fasting glucose (mg/dL)	89.0 (83.0–98.6)	92.0 (82.7–107.2)	0.297
Total cholesterol (mg/dL)	132.0 (109.0–144.0)	136.0 (121.7–155.5)	0.325
HDL cholesterol (mg/dL)	38.0 (33.0–42.0)	39.7 (34.0–43.2)	0.440
LDL cholesterol (mg/dL)	72.0 (54.0–85.0)	71.1 (59.0–87.7)	0.480
Triglycerides (mg/dL)	104.1 (75.0–138.0)	112.7 (91.0–139.0)	0.183

Data are mean (SD), number (%) or median (25th–75th percentile). Criteria for diabetes are based on fasting blood glucose level >125 mg/dL or current treatment with insulin or oral antidiabetic agents; Hypertension are based on seated blood pressure >140/90 mm Hg or antihypertensive treatment; Overweight are based on body mass index ≥25 < 30 kg/m^2; Obesity are based on body mass index ≥30 kg/m^2 and hyperlipidemia are based on fasting total cholesterol >175 mg/dL or use of antilipidemic medication. ACE Inhibitors: angiotensin-converting-enzyme inhibitor; ARBs: angiotensin II receptor blockers; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; PTCA: percutaneous transluminal coronary angioplasty.

subjects was required to detect an effect size of 0.2 in PWV using repeated measures ANOVA (within-between interaction). A target of 75 patients was identified to accommodate an expected maximal dropout rate of 10%.

Before analysis, logarithm or square root transformations of the data were performed to normalize skewed distribution. Nevertheless, the data are presented in the original scale for clarity. At baseline, between-treatment comparisons were performed through Student's independent t-test and Chi-square test, as appropriate. Comparisons of changes in outcomes between treatments over time (treatment × time) were performed through the Repeated measures ANOVA with Bonferroni correction. When a significant treatment × time interaction was observed, a univariate general linear model (treatment as fixed factor) was performed to ascertain the differences at the final assessment between treatments. Primary analysis of the main outcomes as arterial stiffness and circulatory biomarkers were performed using the baseline measurements as covariates. Sensitive analyses were also carried out without covariates or with the differences between treatments at baseline as covariates, this last only when biological plausibility existed.

To analyze the outcomes for all participants only on the basis of their assigned treatments, the intention-to-treat principle was applied. Additionally, to examine the biological effects of the treatment, a per-protocol analysis was also conducted without participants who had not attended at least 80% of the exercise sessions or changed medication. Partial eta-squared (η^2_p) was reported as the effect size measure. Statistical significance was set at $p < 0.05$ for all tests. SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for all analysis.

3. Results

3.1. Intention-to-treat analysis

A total of 96 patients were enrolled and randomly assigned to the EG or CG (Fig. 1). Following baseline assessments, 2 patients of each group dropped out and were excluded from data analysis. Nevertheless, there were no significant differences between baseline values of the patients who dropped out and those who completed the study ($p > 0.05$). Additionally, 3 patients of each group were excluded since their hs-CRP levels were >10 mg/L. For the remaining patients (n = 86), baseline characteristics and values of the EG (n = 44) and CG (n = 42) were similar, except for the proportion of patients using nitrate medication ($\chi^2 = 4.37$, $p = 0.036$) and hs-CRP levels ($p = 0.026$) (Tables 1 and 2).

Patients of the EG attended 19.1 ± 6.9 exercise sessions on average. No significant treatment × time interaction was found in the anthropometrics, resting hemodynamic, endothelial dysfunction and inflammatory biomarkers, central aortic pressures, AIx, AIx@75, or cf-PWV ($p > 0.05$) (Table 2). A significant treatment × time interaction was observed in the VO_{2peak} ($\eta^2_p = 0.102$). This finding was confirmed by a significant mean difference in VO_{2peak} between groups ($p = 0.003$, $\eta^2_p = 0.100$) observed at the final assessment (Table 2). Thus, VO_{2peak} improved significantly in the EG (2.18 ± 4.01 ml kg^{-1} min^{-1}) compared to the CG (−0.11 ± 2.70 ml kg^{-1} min^{-1}).

Data on daily physical activity were available for 67 patients (Supplementary Table 1). Missing data stemmed from nonuse of accelerometers. A significant treatment × time interaction was observed in total physical activity ($\eta^2_p = 0.063$). However, no significant difference was found between groups in this variable at the final assessment ($p > 0.05$) (Supplementary Table 1). Regarding dietary intake, 79 patients provided complete data (Supplementary Table 2). No significant changes on the nutrients intake were observed between groups ($p > 0.05$) and none of the patients reported the use of any kind of supplementation. Results were not substantially altered in the sensitive analysis, as for example in the main parameter of arterial stiffness (cf-PWV) and circulatory biomarkers (hs-CRP). No significant treatment × time interaction was found for cf-PWV ($p = 0.195$) and for hs-CRP ($p = 0.682$), as well as no between-treatments difference at final assessment in cf-PWV (mean difference = −0.78; 95% CI = −1.65 to 0.09; $p = 0.078$) and in hs-CRP (mean difference = −0.31; 95% CI = −0.59 to 0.30; $p = 0.310$) in the unadjusted analysis. Adjusting for imbalanced factors at baseline (hs-CRP and nitrates) there was no significant treatment × time interaction for cf-PWV ($p = 0.242$), neither between-treatments difference at final assessment (mean difference = −0.74; 95% CI = −1.67 to 0.20; $p = 0.120$). hs-CRP was already adjusted for the baseline differences (Table 2).

3.2. Per-protocol analysis

A per-protocol analysis was performed (Fig. 1), since the benefits of exercise training on several outcomes appear to be dose dependent [22]. At baseline, the only difference between groups was in nitrate medication use ($\chi^2 = 4.57$, $p = 0.032$) (Table 3). Regarding the main outcomes, the major difference in the results compared to the intention-to-treat analysis was a significant

Table 2
Changes in anthropometrics, resting hemodynamic, cardiorespiratory fitness, circulatory biomarkers, pulse wave analysis and pulse wave velocity (intention-to-treat analysis).

	Exercise group (n = 44)		Control group (n = 42)		P^{d}	Difference (95% CI) at final assessment	P^{e}
	Baseline	Final	Baseline	Final			
Anthropometrics							
Height (cm)	168.1 (8.9)	–	165.1 (7.5)	–	–	–	
Body mass (kg)[a]	74.6 (71.5–85.2)	73.9 (69.9–84.5)	73.9 (66.0–80.9)	74.3 (67.2–80.3)	0.088	0.004 (−0.06 to 0.06)	0.908
Body mass index (kg/m^2)[a]	26.1 (24.5–29.1)	26.1 (24.1–28.9)	26.9 (25.3–29.0)	26.7 (25.3–29.2)	0.088	−0.03 (−0.09 to 0.02)	0.259
Fat percentage (%)	26.5 (6.4)	26.1 (6.8)	28.4 (6.8)	28.7 (7.2)	0.128	−2.58 (−5.59 to 0.42)	0.091
Waist circumference (cm)	95.7 (8.4)	94.8 (9.3)	96.6 (8.7)	96.6 (8.9)	0.200	−1.82 (−5.73 to 2.10)	0.359
Resting hemodynamic[b]							
Systolic blood pressure (mm Hg)[a]	121.0 (108.5–137.7)	122.5 (111.2–131.0)	129.5 (119.5–143.2)	127.0 (120.5–136.7)	0.211	0.006 (−0.02 to 0.04)	0.725
Diastolic blood pressure (mm Hg)	71.3 (8.6)	70.8 (7.5)	74.0 (8.7)	72.5 (6.9)	0.529	−0.43 (−3.01 to 2.14)	0.739
Mean blood pressure (mm Hg)	89.3 (11.7)	88.9 (10.1)	93.3 (10.2)	91.1 (7.8)	0.354	−0.13 (−3.16 to 2.90)	0.930
Resting heart rate (beats/min)	58.7 (8.4)	58.2 (8.2)	61.6 (10.3)	60.8 (8.1)	0.854	−1.20 (−4.18 to 1.77)	0.424
Cardiorespiratory fitness[b]							
VO_{2peak} (ml kg^{-1} min^{-1})	27.8 (7.3)	30.0 (8.9)	27.1 (5.6)	27.0 (6.1)	0.003	2.24 (0.77 to 3.72)	0.003
Circulatory biomarkers[b]							
hs-CRP (mg/L)[a]	1.3 (0.5–2.4)[c]	1.3 (0.5–2.7)	1.8 (0.8–3.3)	1.8 (0.9–3.8)	0.682	−0.15 (−0.40 to 0.10)	0.239
hs-RANTES (ng/mL)[a]	48.6 (30.6–81.4)	57.3 (25.9–74.7)	49.6 (40.1–86.2)	63.7 (38.5–87.0)	0.348	−0.85 (−1.93 to 0.23)	0.121
hs-IL-6 (pg/mL)[a]	1.5 (0.9–2.0)	1.2 (0.7–1.7)	1.2 (0.8–2.3)	1.3 (0.5–2.8)	0.914	−0.005 (−0.22 to 0.21)	0.964
hs-IL-10 (pg/mL)[a]	7.7 (4.9–14.7)	7.9 (5.0–12.5)	6.3 (4.4–11.7)	9.7 (4.7–14.7)	0.702	−0.09 (−1.32 to 1.12)	0.873
hs-TNF-α (pg/mL)[a]	7.9 (5.9–10.0)	7.4 (5.9–10.1)	7.5 (5.3–10.2)	7.4 (5.7–10.7)	0.725	−0.02 (−0.15 to 0.10)	0.716
hs-sICAM-1 (ng/mL)[a]	270.6 (226.3–349.8)	263.1 (210.0–386.4)	282.7 (229.3–385.3)	300.2 (234.7–406.2)	0.608	−0.02 (−0.11 to 0.06)	0.555
hs-sVCAM-1 (ng/mL)[a]	946.9 (650.1–1261.8)	799.1 (628.1–1122.3)	915.3- (569.2–1376.8)	752.2 (580.1–1255.6)	0.980	0.009 (−0.08 to 0.10)	0.842
PWA and PWV[b]							
CASP (mm Hg)	117.3 (20.2)	116.8 (16.6)	124.2 (16.3)	121.5 (13.2)	0.394	−0.41 (−4.77 to 3.95)	0.852
CADP (mm Hg)	71.9 (8.5)	71.4 (7.4)	74.6 (8.8)	73.5 (6.9)	0.745	−0.90 (−3.47 to 1.67)	0.489
CAPP (mm Hg)[a]	42.5 (36.2–52.7)	42.0 (37.0–49.0)	48.0 (40.7–55.2)	45.0 (39.7–54.0)	0.171	0.01 (−0.04 to 0.07)	0.619
CAMP (mm Hg)	90.0 (11.9)	89.3 (9.9)	94.6 (10.8)	93.1 (8.3)	0.698	−1.46 (−4.54 to 1.61)	0.347
AIx (%)	29.9 (10.2)	31.8 (8.7)	33.4 (7.7)	34.9 (9.1)	0.819	−0.94 (−4.00 to 2.10)	0.539
AIx@75 (%)	22.1 (11.8)	22.5 (9.1)	25.0 (8.3)	27.1 (9.9)	0.334	−2.84 (−5.94 to 0.26)	0.073
cf-PWV (m/s)	8.0 (2.2)	7.7 (1.7)	8.4 (2.1)	8.5 (2.3)	0.195	−0.47 (−1.00 to 0.05)	0.077

Data are mean (SD) or median (25th–75th percentile).
AIx: augmentation index; AIx@75: augmentation index normalized for heart rate of 75 bpm; CADP: central aortic diastolic pressure; CAMP: central aortic mean pressure; CAPP: central aortic pulse pressure; CASP: central aortic systolic pressure; cf-PWV: carotid-femoral pulse wave velocity; CRP: C-reactive protein; hs: high-sensitivity; IL: interleukin; PWA: pulse wave analysis; RANTES: regulated on activation, normal T cell expressed and secreted; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; TNF-α: tumor necrosis factor-α; VO_{2peak}: peak volume of oxygen consumption.
[a] Variables transformed for analysis (not normally distributed).
[b] Univariate general linear model of these variables was adjusted for baseline measurement.
[c] $P < 0.05$ vs. control group at baseline.
[d] For treatment × time interaction with repeated measures ANOVA.
[e] For univariate general linear model. Positive and negative differences are in favor of the exercise group.

treatment × time interaction observed in cf-PWV ($\eta^2_p = 0.054$) (Table 4, Supplementary Tables 3 and 4). Additionally, comparisons between groups of the final assessment showed significant differences for cf-PWV ($p = 0.008$, $\eta^2_p = 0.090$) (Table 4). Contrary to the CG, the cf-PWV decreased in the EG [change (m/s): EG (−0.46 ± 1.30) vs. CG (0.11 ± 1.12)]. Again, results were not substantially altered in the sensitive analysis. Unadjusted analysis and adjusted for imbalanced factor at baseline (nitrates) showed a significant treatment × time interaction for cf-PWV ($p = 0.042$ and $p = 0.031$, respectively) confirmed by a significant difference between-treatments at final assessment (mean difference = −1.05; 95% CI = −1.96 to −0.15; $p = 0.022$ and mean difference = −1.09; 95% CI = −2.03 to −0.15; $p = 0.023$, respectively). Regarding hs-CRP, neither a significant treatment × time interaction ($p = 0.566$), nor a significant difference between-treatments at final assessment were observed (mean difference = −0.29; 95% CI = −0.58 to 0.00; $p = 0.053$) in the unadjusted analysis. No adverse events were registered during the ECR program.

4. Discussion

The main findings of the present study indicate that 8 weeks of an ECR program in general (i.e., intention-to-treat analysis) did not promote changes in AS, endothelial dysfunction and inflammatory biomarkers, despite increasing cardiorespiratory fitness of post-MI patients. On the other hand, when we considered only those EG patients who attended at least 80% of the exercise sessions, it was observed a significant reduction in AS. However, due to the large number of comparisons performed, this single effect on cf-PWV might be considered a false positive result and, therefore we decided to follow the recommendations of the CONSORT statement (Consolidated Standards of Reporting Trials) to focus in the results of the intention-to-treat analysis [23].

This is the first randomized controlled trial to evaluate the effects of an ECR program on AS in post-MI patients while taking into account changes in potential lifestyle contributors (i.e., daily physical activity and dietary intake). The physical activity and dietary intake of our sample did not change significantly during the study and most of their components were already within the recommendations [24,25], suggesting that these two lifestyle contributors did not interfere significantly in the variation of the main variables during the study period.

The failure to promote an effect on cf-PWV by the ECR program disagrees with early studies of stable CAD [26] and post-MI patients

Table 3
Baseline demographic and clinical characteristics (per-protocol analysis).

	Exercise group (n = 37)	Control group (n = 41)	*p*
Age (years)	54.8 (11.1)	58.9 (10.6)	0.099
Sex (male)	32 (86.5%)	33 (80.5%)	0.685
Family history	10 (27%)	5 (12.2%)	0.170
Diabetes mellitus	5 (13.5%)	12 (29.3%)	0.159
Hypertension	34 (91.9%)	40 (97.6%)	0.536
Currently smoking	18 (48.6%)	22 (53.7%)	0.830
Hyperlipidemia	37 (100%)	41 (100%)	–
Overweight/obesity	26 (70.3%)	32 (78%)	0.599
LVEF (%)	52.8 (8.9)	54.7 (7.6)	0.330
Site of infarction (anterior)	15 (40.5%)	14 (34.1%)	0.727
Number of coronary vessels involved			
One vessel	29 (78.4%)	34 (82.9%)	0.825
Two vessels	8 (21.6%)	7 (17.1%)	
Number of infarctions			
First	35 (94.6%)	34 (82.9%)	0.209
Second	2 (5.4%)	7 (17.1%)	
PTCA	35 (94.6%)	35 (85.4%)	0.333
Days hospitalized	5.4 (3.9)	4.1 (1.7)	0.156
Antiplatelets	37 (100%)	41 (100%)	–
ACE inhibitors	34 (91.9%)	38 (92.7%)	1.000
Beta-blockers	35 (94.6%)	41 (100%)	0.429
Lipid-lowering drugs	34 (91.9%)	38 (92.7%)	1.000
Nitrates	9 (24.3%)	2 (4.9%)	0.032
ARBs	2 (5.4%)	–	0.429
Diuretics	1 (2.7%)	4 (9.8%)	0.420
Calcium channel blockers	–	2 (4.9%)	0.520
Fasting glucose (mg/dL)	88.5 (82.2–96.0)	92.0 (82.5–107.5)	0.247
Total cholesterol (mg/dL)	131.3 (109.2–143.9)	137.0 (121.9–156.0)	0.257
HDL cholesterol (mg/dL)	37.5 (33.2–42.0)	39.8 (34.0–43.5)	0.436
LDL cholesterol (mg/dL)	70.7 (54.0–84.5)	71.2 (59.5–88.5)	0.450
Triglycerides (mg/dL)	101.6 (73.0–131.7)	112.5 (91.0–140.0)	0.092

Data are mean (SD), number (%) or median (25th–75th percentile). Criteria for diabetes are based on fasting blood glucose level >125 mg/dL or current treatment with insulin or oral antidiabetic agents; Hypertension are based on seated blood pressure >140/90 mm Hg or antihypertensive treatment; Overweight are based on body mass index $\geq$25 < 30 kg/m^2; Obesity are based on body mass index $\geq$30 kg/m^2 and hyperlipidemia are based on fasting total cholesterol >175 mg/dL or use of antilipidemic medication. ACE Inhibitors: angiotensin-converting-enzyme inhibitor; ARBs: angiotensin II receptor blockers; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; PTCA: percutaneous transluminal coronary angioplasty.

[3]. One plausible explanation could derive from program duration (8 weeks in the present study vs. 20 weeks in Laskey et al. [26]). Agreeing with this supposition, Laskey et al. [26] observed a superior degree of decrease in cf-PWV among patients who had trained longer (20 vs. 12 weeks). Trzos et al. [3] counters this explanation by using an exercise program of only 6 weeks and reporting a higher change in cf-PWV (−4.1 m/s) than Laskey et al. [26] (−0.70 m/s). However, the cf-PWV values at baseline of that study [3] were too high (above 12 m/s) compared to those reported by Laskey et al. [26] (approximately 7 m/s) and those of our study (approximately 8 m/s), thus having a great room for improvement. Actually, a value of 7 m/s is below and 8 m/s is within the "normal" age-related range for the populations studied [27], which could explain the slight change observed. Another explanation to the decrease observed in the already reduced levels of cf-PWV in the Laskey et al. [26] study and not in our study could be the additional exercise time performed by their patients at home between ECR sessions (e.g., walking).

Endothelial dysfunction and inflammation are involved in vascular remodeling and changes in modulation of vascular tone [28], which in turn appear to be associated with the chronic and acute elevation of AS [10,28,29], respectively. Before this study, only one study [12] had simultaneously evaluated the effects of exercise on AS and inflammation in CAD patients. Toyama et al. [12], in an uncontrolled study, reported a significant correlation between decreases in brachial-ankle PWV and basophil count after 20 weeks of an exercise program combined with rosuvastatin. In contrast, our results did not show significant changes in cf-PWW, endothelial dysfunction and inflammatory biomarkers in the EG. The observed lack of improvements in the circulating biomarkers after exercise training partly agrees with the results reported by a recent meta-analysis [30]. Indeed, except for a reduction in CRP, all other biomarkers examined in the meta-analysis (IL-6, TNF-α, s-ICAM-1, and s-VCAM-1) failed to improve after exercise interventions in the controlled studies. The reason for the discrepant results observed in CRP appears to derive from the different baseline levels between studies [30,31]. Swardfager et al. [30] reported that higher baseline CRP concentrations predicted greater reductions in CRP, while Lakka et al. [31] showed that only the group classified as high risk for CAD (i.e., CRP > 3.0 mg/L) improved their CRP levels following a 20-week exercise training program. Since the median baseline value of CRP in EG of the current study was 1.3 (0.5–2.4) mg/L (intention-to-treat analysis) and 1.4 (0.5–2.6) mg/L (per-protocol analysis), this argument is plausible and reinforced by these results.

The increase in VO_{2peak} is a well-known benefit of aerobic exercise training. In this study the mean change in VO_{2peak} in the EG was 2.2 ml kg^{-1} min^{-1} in the intention-to-treat analysis and 2.9 ml kg^{-1} min^{-1} in the per-protocol analysis, despite the already high baseline values presented by our patients compared to those of other studies [32]. This mean change is consistent with that reported (2.6 ± 1.6 ml kg^{-1} min^{-1}) by a recent systematic review and meta-analysis of CAD patients [32].

Some limitations of the present study should be addressed. On average, our sample consisted of patients with low levels of AS and inflammation and with most other measured parameters near or at the recommended levels already at baseline, which limits the generalization of our findings for patients with a more debilitated clinical condition. Furthermore, data on daily physical activity and dietary intake were not available for the whole sample. Nevertheless, a representative number of patients (intention-to-treat: EG = 68%, CG = 88%; per-protocol analysis: EG = 70%, CG = 88%) provided data on physical activity, and a substantial number of patients (intention-to-treat: EG = 84%, CG = 100%; per-protocol analysis: EG = 89%, CG = 100%) on dietary intake.

In conclusion, results of the present study showed that an ECR program performed for 8 weeks is not effective in improving AS, endothelial dysfunction and inflammatory biomarkers in post-MI patients, who were under optimal medication and presented low levels of these parameters already at baseline. However, the reduction of cf-PWV in the EG observed in the per-protocol analysis suggests that further investigation should be done to clarify whether ECR may actually have any effect on this variable, perhaps using an intervention program with greater duration.

Conflict of interest

None declared.

Acknowledgments

This work was supported by European Regional Development Fund through the Operational Competitiveness Programme, and by Foundation for Science and Technology (FCT) of Portugal – within the projects FCOMP-01-0124-FEDER-014706 (Reference. FCT: PTDC/DES/113753/2009) and PEst-OE/SAU/UI0617/2011. The FCT supported the authors Norton Luis Oliveira (grant number SFRH/BD/48875/2008) and Fernando Ribeiro (grant number SFRH/BPD/69965/2010).

Table 4
Changes in anthropometrics, resting hemodynamic, cardiorespiratory fitness, circulatory biomarkers, pulse wave analysis and pulse wave velocity (per-protocol analysis).

	Exercise group (n = 37)		Control group (n = 41)		P^c	Difference (95% CI) at final assessment	P^d
	Baseline	Final	Baseline	Final			
Anthropometrics							
Height (cm)	167.4 (8.8)	–	165.2 (7.5)	–	–	–	–
Body mass (kg)[a]	74.0 (70.6–83.2)	73.2 (68.1–83.4)	74.4 (65.8–81.4)	75.3 (66.8–80.5)	0.032	−0.01 (−0.08 to 0.05)	0.648
Body mass index (kg/m^2)[a]	26.0 (24.6–28.8)	26.1 (24.0–28.6)	26.9 (25.2–29.1)	26.7 (25.3–29.2)	0.032	−0.04 (−0.10 to 0.02)	0.174
Fat percentage (%)	26.1 (6.5)	25.6 (6.9)	28.4 (6.8)	28.8 (7.3)	0.096	−3.14 (−6.33 to 0.06)	0.054
Waist circumference (cm)	94.8 (8.4)	93.5 (9.0)	96.6 (8.8)	96.6 (9.0)	0.091	−3.08 (−7.16 to 0.99)	0.136
Resting hemodynamic[b]							
Systolic blood pressure (mm Hg)[a]	121.0 (109.0–134.0)	121.0 (109.0–130.0)	129.0 (119.0–142.5)	127.0 (120.0–137.5)	0.371	0.001 (−0.03 to 0.03)	0.959
Diastolic blood pressure (mm Hg)	71.2 (8.8)	70.6 (8.1)	73.7 (8.6)	72.4 (6.9)	0.662	−0.49 (−3.26 to 2.28)	0.726
Mean blood pressure (mm Hg)	89.2 (12.1)	88.5 (10.8)	93.0 (10.1)	91.0 (7.9)	0.516	−0.37 (−3.57 to 2.81)	0.814
Resting heart rate (beats/min)	56.2 (7.9)	54.9 (6.8)	57.9 (7.6)	59.2 (8.2)	0.792	−2.65 (−5.60 to 0.29)	0.077
Cardiorespiratory fitness[b]							
VO_{2peak} (ml kg^{-1} min^{-1})	28.4 (7.3)	31.3 (8.7)	26.9 (5.6)	26.7 (5.9)	<0.001	3.15 (1.68 to 4.62)	<0.001
Circulatory biomarkers[b]							
hs-CRP (mg/L)[a]	1.4 (0.5–2.6)	1.2 (0.6–2.6)	1.6 (0.8–3.2)	1.8 (0.9–3.7)	0.566	−0.14 (−0.39 to 0.10)	0.250
hs-RANTES (ng/mL)[a]	52.4 (33.6–89.8)	56.3 (25.9–71.5)	49.2 (40.0–80.4)	64.9 (37.8–87.9)	0.136	−1.05 (−2.19 to 0.08)	0.069
hs-IL-6 (pg/mL)[a]	1.2 (0.8–1.8)	1.1 (0.7–1.5)	1.2 (0.8–2.3)	1.2 (0.5–2.8)	0.241	−0.12 (−0.33 to 0.08)	0.250
hs-IL-10 (pg/mL)[a]	7.8 (4.5–14.4)	7.5 (4.7–12.5)	6.3 (4.3–11.3)	9.1 (4.6–14.9)	0.715	−0.12 (−1.44 to 1.20)	0.857
hs-TNF-α (pg/mL)[a]	7.2 (5.8–10.0)	7.1 (5.5–9.6)	7.4 (5.3–9.9)	7.3 (5.6–10.6)	0.452	−0.05 (−0.17 to 0.07)	0.421
hs-sICAM-1 (ng/mL)[a]	258.3 (215.6–333.7)	256.6 (208.3–367.0)	285.4 (228.6–393.3)	299.6 (232.9–406.2)	0.955	−0.006 (−0.10 to 0.09)	0.907
hs-sVCAM-1 (ng/mL)[a]	982.4 (663.1–1300.2)	812.3 (637.7–1187.6)	940.7 (562.8–1388.9)	756.9 (577.8–1257.2)	0.987	0.01 (−0.08 to 0.11)	0.726
PWA and PWV[b]							
CASP (mm Hg)	117.3 (21.2)	116.4 (17.3)	123.8 (16.3)	121.4 (13.4)	0.596	−0.90 (−5.35 to 3.53)	0.685
CADP (mm Hg)	71.9 (8.6)	71.2 (7.9)	74.3 (8.6)	73.4 (6.9)	0.904	−0.98 (−3.75 to 1.77)	0.479
CAPP (mm Hg)[a]	42.0 (36.0–52.5)	42.0 (37.0–48.5)	48.0 (40.5–55.5)	45.0 (39.5–55.0)	0.277	0.007 (−0.05 to 0.06)	0.814
CAMP (mm Hg)	90.2 (12.4)	89.1 (10.6)	94.3 (10.7)	93.0 (8.4)	0.944	−1.69 (−4.95 to 1.55)	0.301
AIx (%)	30.3 (10.5)	32.2 (8.7)	33.3 (7.8)	34.9 (9.2)	0.856	−0.88 (−4.15 to 2.39)	0.593
AIx@75 (%)	21.4 (9.9)	22.5 (9.5)	25.1 (8.4)	27.3 (9.9)	0.540	−1.92 (−5.12 to 1.26)	0.233
cf-PWV (m/s)	7.9 (2.2)	7.5 (1.6)	8.4 (2.1)	8.5 (2.3)	0.042	−0.68 (−1.19 to −0.18)	0.008

Data are mean (SD) or median (25th–75th percentile).
AIx: augmentation index; AIx@75: augmentation index normalized for heart rate of 75 bpm; CADP: central aortic diastolic pressure; CAMP: central aortic mean pressure; CAPP: central aortic pulse pressure; CASP: central aortic systolic pressure; cf-PWV: carotid-femoral pulse wave velocity; CRP: C-reactive protein; hs: high-sensitivity; IL: interleukin; PWA: pulse wave analysis; RANTES: regulated on activation, normal T cell expressed and secreted; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; TNF-α: tumor necrosis factor-α; VO_{2peak}: peak volume of oxygen consumption.
[a] Variables transformed for analysis (not normally distributed).
[b] Univariate general linear model of these variables was adjusted for baseline measurement.
[c] For treatment × time interaction with repeated measures ANOVA.
[d] For univariate general linear model. Positive and negative differences are in favor of the exercise group.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.057.

References

[1] R. Ross, Atherosclerosis – an inflammatory disease, N. Engl. J. Med. 340 (1999) 115–126.
[2] N.M. van Popele, D.E. Grobbee, M.L. Bots, R. Asmar, J. Topouchian, R.S. Reneman, et al., Association between arterial stiffness and atherosclerosis: the Rotterdam study, Stroke 32 (2001) 454–460.
[3] E. Trzos, M. Kurpesa, T. Rechcinski, K. Wierzbowska-Drabik, M. Krzeminska-Pakula, The influence of physical rehabilitation on arterial compliance in patients after myocardial infarction, Cardiol. J. 14 (2007) 366–371.
[4] S.S. Franklin, Wt Gustin, N.D. Wong, M.G. Larson, M.A. Weber, W.B. Kannel, et al., Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study, Circulation 96 (1997) 308–315.
[5] B.A. Kingwell, Large artery stiffness: implications for exercise capacity and cardiovascular risk, Clin. Exp. Pharmacol. Physiol. 29 (2002) 214–217.
[6] S. Laurent, J. Cockcroft, L. Van Bortel, P. Boutouyrie, C. Giannattasio, D. Hayoz, et al., Expert consensus document on arterial stiffness: methodological issues and clinical applications, Eur. Heart J. 27 (2006) 2588–2605.
[7] C. Vlachopoulos, K. Aznaouridis, C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 55 (2010) 1318–1327.
[8] J.L. Torres, P.M. Ridker, Clinical use of high sensitivity C-reactive protein for the prediction of adverse cardiovascular events, Curr. Opin. Cardiol. 18 (2003) 471–478.
[9] S. Blankenberg, H.J. Rupprecht, C. Bickel, D. Peetz, G. Hafner, L. Tiret, et al., Circulating cell adhesion molecules and death in patients with coronary artery disease, Circulation 104 (2001) 1336–1342.
[10] B.C. van Bussel, F. Schouten, R.M. Henry, C.G. Schalkwijk, M.R. de Boer, I. Ferreira, et al., Endothelial dysfunction and low-grade inflammation are associated with greater arterial stiffness over a 6-year period, Hypertension 58 (2011) 588–595.
[11] N.L. Oliveira, F. Ribeiro, A.J. Alves, L. Campos, J. Oliveira, The effects of exercise training on arterial stiffness in coronary artery disease patients: a state-of-the-art review, Clin. Physiol. Funct. Imaging 34 (2014) 254–262.
[12] K. Toyama, S. Sugiyama, H. Oka, Y. Iwasaki, H. Sumida, T. Tanaka, et al., Combination treatment of rosuvastatin or atorvastatin, with regular exercise improves arterial wall stiffness in patients with coronary artery disease, PLoS One 7 (2012) e41369.
[13] N.M. Edwards, S.R. Daniels, R.P. Claytor, P.R. Khoury, L.M. Dolan, T.R. Kimball, et al., Physical activity is independently associated with multiple measures of arterial stiffness in adolescents and young adults, Metabolism 61 (2012) 869–872.
[14] B.C. Bock, R.E. Carmona-Barros, J.L. Esler, P.L. Tilkemeier, Program participation and physical activity maintenance after cardiac rehabilitation, Behav. Modif. 27 (2003) 37–53.
[15] M.P. Pase, N.A. Grima, J. Sarris, The effects of dietary and nutrient interventions on arterial stiffness: a systematic review, Am. J. Clin. Nutr. 93 (2011) 446–454.
[16] B. Clyne, J.S. Olshaker, The C-reactive protein, J. Emerg. Med. 17 (1999) 1019–1025.
[17] C. Vlachopoulos, I. Dima, K. Aznaouridis, C. Vasiliadou, N. Ioakeimidis, C. Aggeli, et al., Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals, Circulation 112 (2005)

2193–2200.
[18] D. Gallagher, A. Adji, M.F. O'Rourke, Validation of the transfer function technique for generating central from peripheral upper limb pressure waveform, Am. J. Hypertens. 17 (2004) 1059–1067.
[19] C. Vlachopoulos, K. Aznaouridis, M.F. O'Rourke, M.E. Safar, K. Baou, C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis, Eur. Heart J. 31 (2010) 1865–1871.
[20] I.B. Wilkinson, S.A. Fuchs, I.M. Jansen, J.C. Spratt, G.D. Murray, J.R. Cockcroft, et al., Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis, J. Hypertens. 16 (1998) 2079–2084.
[21] R.P. Troiano, D. Berrigan, K.W. Dodd, L.C. Masse, T. Tilert, M. McDowell, Physical activity in the United States measured by accelerometer, Med. Sci. Sports Exerc. 40 (2008) 181–188.
[22] B.G. Hammill, L.H. Curtis, K.A. Schulman, D.J. Whellan, Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly medicare beneficiaries, Circulation 121 (2010) 63–70.
[23] D. Moher, S. Hopewell, K.F. Schulz, V. Montori, P.C. Gotzsche, P.J. Devereaux, et al., CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials, BMJ 340 (2010) c869.
[24] S.C. Smith Jr., E.J. Benjamin, R.O. Bonow, L.T. Braun, M.A. Creager, B.A. Franklin, et al., AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation, Circulation 124 (2011) 2458–2473.
[25] A.H. Lichtenstein, L.J. Appel, M. Brands, M. Carnethon, S. Daniels, H.A. Franch, et al., Summary of American Heart Association diet and lifestyle recommendations revision 2006, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2186–2191.
[26] W. Laskey, S. Siddiqi, C. Wells, R. Lueker, Improvement in arterial stiffness following cardiac rehabilitation, Int. J. Cardiol. 167 (2013) 2734–2738.
[27] The Reference Values for Arterial Stiffness' Collaboration, Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values', Eur. Heart J. 31 (2010) 2338–2350.
[28] S.J. Zieman, V. Melenovsky, D.A. Kass, Mechanisms, pathophysiology, and therapy of arterial stiffness, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 932–943.
[29] K.M. Maki-Petaja, I.B. Wilkinson, Anti-inflammatory drugs and statins for arterial stiffness reduction, Curr. Pharm. Des. 15 (2009) 290–303.
[30] W. Swardfager, N. Herrmann, S. Cornish, G. Mazereeuw, S. Marzolini, L. Sham, et al., Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis, Am. Heart J. 163 (2012), 666-676.e1–e3.
[31] T.A. Lakka, H.M. Lakka, T. Rankinen, A.S. Leon, D.C. Rao, J.S. Skinner, et al., Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study, Eur. Heart J. 26 (2005) 2018–2025.
[32] H. Valkeinen, S. Aaltonen, U.M. Kujala, Effects of exercise training on oxygen uptake in coronary heart disease: a systematic review and meta-analysis, Scand. J. Med. Sci. Sports 20 (2010) 545–555.