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Original article

Exercise Training and Inflammatory Markers in Coronary Artery Disease Patients

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SUMMARY

Aim. To evaluate the influence of exercise training on inflammatory markers and exercise tolerance in coronary artery disease (CAD) patients.
Patients and methods. A total of 54 subjects were enrolled in the present study, including 34 CAD patients (CAD group: 59.2 ± 8.2 years) and 20 healthy controls (C group: 54.2 ± 8.0 years). C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC), and placental growth factor (PIGF) were determined, and an exercise test was performed in both groups at baseline and once again in CAD group after the supervised 3 weeks of aerobic exercise training.
Results. At baseline, CRP, ESR and PIGF were significantly higher in the CAD group compared to the C group ($p = 0.038$, $p = 0.019$ and $p = 0.002$), while exercise capacity was significantly higher in the C group ($p < 0.01$). After 3 weeks of exercise training, CRP, ESR, WBC count and PIGF significantly decreased ($p = 0.048$, $p < 0.001$, $p = 0.002$ and $p < 0.001$ respectively), while exercise capacity significantly increased ($p < 0.001$) in the CAD group. In the CAD group, CRP decrease significantly correlated with WBC and PIGF decrease ($r = 0.816$, $p = 0.002$ and $r = 0.988$, $p < 0.001$), as well as with exercise capacity increase ($r = 0.834$, $p < 0.001$). Also, WBC decrease significantly correlated both with PIGF decrease ($r = 0.768$, $p < 0.001$) and exercise capacity increase ($r = 0.548$, $p = 0.012$), while PIGF decrease significantly correlated with exercise capacity increase ($r = 0.548$, $p = 0.013$).
Conclusion. Residential exercise training in CAD patients reduces inflammation, expressed through a significant decrease in CRP, ESR, WBC count and PIGF levels. Those positive changes in inflammatory markers are associated with significant improvement in exercise capacity.

Keywords: **exercise, inflammatory markers, coronary artery disease**

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INTRODUCTION

Inflammation was demonstrated to have a crucial role in the initiation and progression of atherosclerosis and atherosclerotic events, starting from the formation of atherosclerotic plaques in the arterial wall to plaque destabilization, therefore leading to plaque rupture and atherothrombotic events (1 - 3). For that reason, the correction of inflammation has become one of the most important goals of the therapy. The levels of local and systemic inflammation can be reduced by different lifestyle changes and pharmacological interventions including drugs, weight loss, smoking cessation and exercise (2 - 4). Thus, exercise is recommended as an anti-inflammatory therapy for patients with chronic inflammatory diseases, including cardiovascular (CV) disease (5-7). Regular long-term exercise downregulates the resting levels of proinflammatory cytokines indicative of low-grade inflammation, such as interleukine 6, tumor necrosis factor alpha and C-reactive protein (CRP) (8, 9). The concentration of inflammatory markers in serum or plasma can be useful to assess CV risk and monitor disease activity over the years. During the last decades, substantial improvements have been achieved in medical as well as in lifestyle management of coronary artery disease (CAD), all of which may lead to a reduction in inflammatory activity. Despite this, the risk for recurrent cardiac events exists in many patients with CAD, probably due to residual inflammation (10, 11). Elevated inflammatory markers, such as CRP, erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count are well-known risk markers for CAD, as well as the placental growth factor (PIGF), which was demonstrated to contribute to atherogenesis through vascular inflammation and plaque destabilization.

The aim of the present study was to evaluate the influence of exercise training on CRP, ESR, WBC count, PIGF levels and exercise tolerance in CAD patients, admitted to the second stage of cardiac rehabilitation (CR) in Institute of Cardiology "Niška Banja", Niš, Serbia.

PATIENTS AND METHODS

A total of 54 subjects were enrolled in the present study, including 34 CAD patients (CAD group: 59.2 ± 8.2 years, 26 men and 8 women) and 20 healthy controls (C group: 54.2 ± 8.0 years, 13 men and 7 women). CAD group was recruited from outpatient clinics and admitted to CR in the Institute of Cardiology "Niška Banja", Niš, Serbia.

A detailed medical evaluation was performed at baseline, recording underlying risk factors, comorbidities and previous medical history. According to previously diagnosed comorbidities, concomitant treatment may have included regular use of cardioprotective (antiplatelets, β-blockers, angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers) and lipid-lowering drugs (statins).

Inflammation markers, including CRP, ESR, WBC count and PIGF were determined at baseline, as well as an exercise test in order to evaluate exercise capacity. After the initial study, the CAD group underwent the supervised 3 weeks of aerobic exercise training at the residential center and after that period, CRP, ESR, WBC count, PIGF and exercise capacity were determined again. Blood samples for biochemical analyses were taken from the antecubital vein after an overnight fast.

Human PIGF (human placenta growth factor) was measured by using the quantitative sandwich enzyme immunoassay, based on microplate-coated monoclonal antibody for PIGF (RnDSystems, Minneapolis, USA). The assay was performed according to the manufacturer's instructions. Calculation of the concentrations was made by using appropriate standard curve. Minimum detectable concentration was less than 7 pg/mL. Erythrocyte sedimentation rate and WBC were determined from peripheral blood samples by using the automated hematology analyzer. C-reactive protein was determined from anticoagulated venous blood by using the automated biochemistry analyzer.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD); categorical variables were presented as counts and percentages. The distribution of variables was checked by Shapiro-Wilk and Kolmogorov–Smirnov tests. Between-group characteristics were compared by independent-sample t-test, Mann–Whitney rank sum test or Chi-Square test, as appropriate; and for ingroup repeted measures, paired-sample t-test and Wilcoxon signed-rank test were used. Pearson correlation was used to explore the strength of the relationship between two continuous variables. The correlation coefficient (Pearson r) provided an indication of the linear rela-

tionship between variables. The strenght was defined through the Pearson r coefficient ((.90 to 1.00 (−.90 to −1.00). Very high positive (negative) correlation: .70 to .90 (−.70 to −.90);. high (strong) positive (negative) correlation; .50 to .70 (−.50 to −.70); moderate positive (negative) correlation: .30 to .50 (−.30 to −.50); low positive (negative) correlation: .00 to .30 (.00 to −.30) negligible correlation)). P-value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS package version 21.0 (Chicago, L, USA).

RESULTS

The main characteristics of all enrolled participants are shown in Table 1 and 2.

At baseline, exercise capacity was significantly higher in the C group compared to the CAD group ($p < 0.01$) (Table 3). However, it significantly increased in the CAD group ($p < 0.001$) (Table 4) after 3 weeks of exercise training.

Inflammation markers, including CRP, ESR and PIGF were significantly higher in the CAD group at baseline, compared to the C group ($p = 0.038$, $p = 0.019$ and $p = 0.002$, respectively) (Table 3).

After 3 weeks of exercise training, CRP, ESR, WBC count and PIGF significantly decreased ($p = 0.048$, $p < 0.001$, $p < 0.01$ and $p = 0.002$, respectively) in the CAD group (Table 4).

At the end of the study, no significant differences in inflammatory markers were recorded between the groups (Table 5).

In the CAD group, CRP decrease significantly correlated with WBC and PIGF decrease ($r = 0.816$, $p = 0.002$ and $r = 0.988$, $p < 0.001$, respectively), as well as with exercise capacity increase ($r = 0.834$, $p < 0.001$) (Graph 1).

Also, WBC decrease significantly correlated with both PIGF decrease ($r = 0.768$, $p < 0.001$) and exercise capacity increase ($r = 0.548$, $p = 0.012$), while PIGF decrease significantly correlated with exercise capacity increase ($r = 0.548$, $p = 0.013$) (Graph 1).

Table 1. *Baseline characteristics in the CAD and C group*

	CAD group (N = 34)	C group (N = 20)	P value
Demographics			
Male gender, n (%)	26 (76.5%)	13 (65.0%)	0.395
Age (years), mean (± SD)	59.2 ± 8.2	54.2 ± 8.0	0.031
BMI (Kg/m2), mean (± SD)	26.6 ± 3.5	24.5 ± 2.8	**0.025**
Physical examination			
Systolic BP (mmHg), mean (± SD)	119.5 ± 13.7	124.7 ± 11.8	0.159
Diastolic BP (mmHg), mean (± SD)	71.9 ± 8.5	78.6 ± 7.1	**0.004**
Heart rate (bpm), mean (± SD)	77.6 ± 14.9	76.3 ± 10.5	0.700
Laboratory			
Haemoglobin (g/L), mean (± SD)	150.6 ± 10.6	148.6 ± 11.7	0.505
Potasium (mEq/L), mean (± SD)	4.9 ± 0.4	4.5 ± 0.6	**0.007**
Creatinine (μmol/L), mean (± SD)	97.2 ± 16.3	87.47 ± 14.5	**0.030**
Cholesterol (mmol/L), mean (± SD)	4.5 ± 0.9	5.3 ± 0.8	**0.003**
Glucose (mmol/L), mean (± SD)	6.4 ± 1.2	5.4 ± 0.5	**< 0.001**

Legend: CAD group - coronary artery disease group; C group - healthy controls; BMI - body mass index; SD - standard deviation; BP - blood pressure

Table 2. *Baseline characteristics in the CAD group*

	CAD group (N=34)
Medical history, n (%)	
Hypertension	26 (76.5)
Diabetes	8 (23.5)
Coronary artery disease	34 (100)
Dyslipidemia	30 (88.2)
Smoking (current, previous)	21 (61.8)
Therapy, n (%)	
Beta-blocker	29 (85.3)
ACE-i or ARB	31 (91.2)
Ca blocker	5 (14.7)
Aspirin	29 (85.3)
Clopidogrel	21 (61.8)
Statin	27 (79.4)
Nitrates	6 (17.6)
Diuretics	12 (35.3)
Aldosterone antagonist	3 (8.8)

CAD group, coronary artery disease group; ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Ca blocker, calcium blocker

Table 3. *Baseline values of CRP, ESR, WBC count, PIGF and exercise capacity in CAD and control groups*

Variable	CAD group	Control group	P
CRP (μmol/L)	8.34 ± 3.20	6.19 ± 2.24	= 0.038
ESR (mm/1hour)	11.95 ± 8.07	6.76 ± 5.59	= 0.019
WBC count (10^9/L)	8.17 ± 2.01	7.45 ± 1.96	ns
PIGF (pg/mL)	8.81 ± 4.45	4.27 ± 4.05	= 0.002
Exercise capacity (METs)	5.75 ± 2.11	7.85 ± 2.35	< 0.01

Legend. CRP - C reactive protein; ESR - Erythrocyte sedimentation rate; WBC - White blood cell; PIGF - Placental growth factor; METs - Metabolic equivalents of task

Table 4. *Values of CRP, ESR, WBC count, PIGF and exercise capacity in CAD group before and after 3 weeks of exercise training*

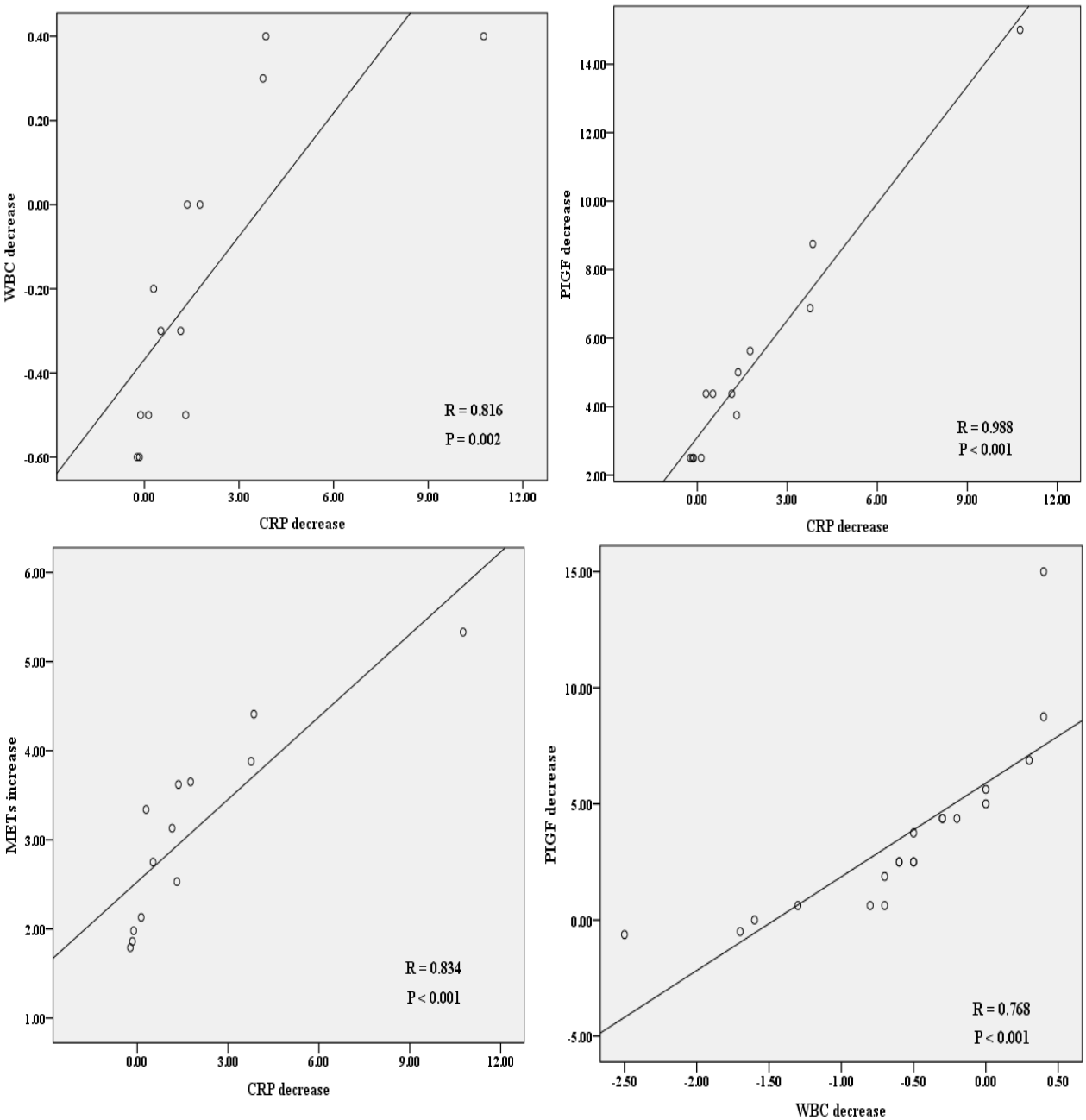
Variable	Before	After 3 weeks	P
CRP(μmol/L)	8.34 ± 3.20	6.62 ± 1.75	= 0.048
ESR (mm/1hour)	11.95 ± 8.07	10.31 ± 7.33	< 0.001
WBC count (10^9/L)	8.17 ± 2.01	7.58 ± 1.80	= 0.002
PIGF (pg/mL)	8.81 ± 4.45	5.28 ± 3.54	< 0.001
Exercise capacity (METs)	5.75 ± 2.11	7.45 ± 2.33	< 0.001

Legend. CRP - C reactive protein; ESR - Erythrocyte sedimentation rate; WBC - White blood cell; PIGF - Placental growth factor; METs - Metabolic equivalents of task

Table 5. *Values of CRP, ESR, WBC count and exercise capacity in CAD and control groups after 3 weeks*

Variable	CAD group	Control group	P
CRP (μmol/L)	6.62 ± 1.75	6.19 ± 2.24	ns
ESR (mm/1hour)	10.31 ± 7.33	6.76 ± 5.59	ns
WBC count (10^9/L)	7.58 ± 1.80	7.45 ± 1.96	ns
PIGF (pg/mL)	5.28 ± 3.54	4.27 ± 4.05	ns
Exercise capacity (METs)	7.45 ± 2.33	7.85 ± 2.35	ns

Legend. CRP - C reactive protein; ESR - Erythrocyte sedimentation rate; WBC - White blood cell; PIGF - Placental growth factor; METs - Metabolic equivalents of task



Graph 1. *Correlation between different inflammatory markers (according to their change during rehabilitation period)*

DISCUSSION

Physical training has been postulated and employed as an important method of rehabilitation in patients suffering from CV diseases (12 - 14). CR aims to delay disease progression and to increase physical recovery with a significant decrease of the risk of recurrent CV events enabling to return to daily activity. Patients who suffered from MI and were rehabilitated by exercise training displayed a lower risk of future infarction, lower cardiac mortality, and reduced mortality due to other causes (15, 16). However, despite the known benefits of regular exercise, many CAD patients are still insufficiently engaged in physical activity and report substantially less physical activity than recommended in current guidelines (17, 18). Accordingly, baseline assessment of the present study showed a significantly higher level of exercise capacity in the C group, compared with the CAD group ($p < 0.01$). However, after 3 weeks of exercise training, exercise capacity significantly increased in the CAD group ($p < 0.001$) and, therefore, no significant inter-group differences were recorded at the end of the study.

High sensitive CRP (HsCRP) appears to be not only a marker but also an active mediator of atherogenesis. Whether CRP contributes causally to the development of CAD or it is just a surrogate marker of underlying chronic inflammation and generalized atherosclerosis still remains controversial. Several large studies have reported that genetic variations in the CRP gene, associated with increased CRP levels, were not associated with an increased risk of CAD (19). These results question the causality between CRP and CAD and indicate that an elevated CRP is a marker for the extent of atherosclerosis, inflammatory activity and vulnerability of atherosclerotic plaques without playing an active role in the process. Studies have demonstrated CRP elevations immediately after an acute MI, indicating that the protein might also react as an acute marker of destabilized atherosclerotic plaques (20, 21). It remains to be uncovered whether it is a dynamic biomarker synthesized and released as a response to minor episodes of reversible myocardial ischemia. The results of the present study showed at baseline significantly higher CRP in the CAD group compared to the C group ($p = 0.038$). However, after 3 weeks of exercise training, CRP significantly decreased ($p = 0.048$) in the CAD group (Table 4), and, for that reason, no significant inter-group changes in CRP were recorded at the end of the study. In the CAD group, CRP decrease significantly correlated with WBC and PIGF decrease ($r = 0.816$, $p = 0.002$ and $r = 0.988$, $p < 0.001$ respectively), as well as with exercise capacity increase ($r = 0.834$, $p < 0.001$).

Among the various inflammatory markers, the WBC count and whole subtypes of WBC count, including neutrophils, monocytes and lymphocytes are associated with the incidence of CV events (22 - 24). Previous studies have demonstrated that lymphocyte count was inversely correlated with inflammation, and therefore lower lymphocyte count represented an increased CV risk and mortality (25). As opposed to this, it seems that there is a positive and potentially causal relationship between lymphocyte count and systolic and diastolic blood pressure (26). On the other hand, neutrophil count in men is consistently associated with fatal and nonfatal CV diseases (27). Also, neutrophil to lymphocyte ratios was demonstrated to be emerging markers of the incidence and severity of CAD (28). Furthermore, lower lymphocyte counts and higher monocyte counts were associated with adverse CV endpoints in CAD patients (29, 30).

Some of these studies clearly reported a positive correlation between the frequency of circulating WBC count or WBC subsets with adverse outcomes in apparently healthy individuals with the perivascular disease, CAD patients and in patients with heart failure (31 - 34). Further, a few studies demonstrated the relationship between WBC count and the presence, severity and progression of the atherosclerotic plaque in patients with either acute coronary syndromes (ACS) or stable CAD (35 - 37). On the other hand, in patients with moderate and high-risk for non-ST-segment elevation ACS, an increased WBC count on admission was an independent predictor of major bleeding at 30 days and one-year mortality. Moreover, it seems that high neutrophil to lymphocyte ratio affects in-hospital and long-term mortality in patients with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) (38). Based on these studies, high WBC count and its subsets counts, even within the normal range, appeared not only to be linked to systemic inflammatory response, but also to increased CV risk and adverse prognosis. Although there was no significant difference for WBC count between the CAD and C groups at baseline, WBC count significantly decreased after 3 weeks of exercise training in the CAD group ($p = 0.002$), following

a significant increase in exercise capacity ($p < 0.001$). No significant inter-group differences in WBC count were recorded at the end of the study. The results of the present study have also demonstrated that WBC decrease significantly correlated not only with exercise capacity increase ($r = 0.548$, $p = 0.012$) but also with PIGF decrease ($r=0.768$, $p < 0.001$).

A high value of ESR has been suggested as an indicator of CAD development at the threatening level. Individuals with an ESR equal to or higher than 15 mm/h were in a group of high risk of CV mortality. Gillum et al. showed the relationship between ESR and CAD in patients with ESR higher than 21 mm/h (39). On the other hand, the literature suggests that healthy men aged between 50 and 60 years should have ESR below 14 mm/h (40). Therefore, ESR can be considered one of the most important markers linked to atherosclerosis, both in healthy subjects and CAD patients. As far as the results of the present study are concerned, ESR was significantly higher in the CAD group compared to the C group ($p = 0.019$) at baseline, following a significantly higher exercise tolerance level in the C group compared with the CAD group ($p < 0.01$) (Table 3). However, at follow-up, after 3 weeks of exercise training, ESR significantly decreased ($p < 0.001$), while exercise capacity significantly increased in the CAD group ($p < 0.001$) (Table 4), and no significant inter-group differences were recorded at the end of the study (Table 5).

PlGF is a platelet-derived protein, a proangiogenic factor, demonstrated to play an important role in the development of coronary atherosclerosis (41). PlGF is a member of the vascular endothelial growth factor (VEGF) cytokine family, which accelerates atherosclerosis by enhancing intramural angiogenesis and stimulating the migration of inflammatory monocytes and macrophages into the arterial wall (42). Although there still remains inconsistency among researchers, an acute elevation of PlGF in the plasma seems to correlate with adverse outcomes in ACS patients (43) and may represent a new therapeutic target for mitigating the disease process behind ACS. Plasma PlGF appears to extend the predictive and prognostic information gained from traditional biomarkers of necrosis, platelet activation and systemic inflammation. It is increased in ACS regardless of the troponin T (TnT) concentration, which implies that it is a biomarker of ischemic events such as plaque instability, plaque disruption and impending thrombosis in the context of ACS. Moreover, it seems that PIGF represents a strong predictor of outcomes in ischemic heart diseases and heart failure (44). The results of the present study clearly demonstrated significantly higher PIGF in the CAD group compared to the C group ($p = 0.002$) at baseline, as well as its significant decrease in the CAD group after 3 weeks of exercise training ($p < 0.001$). For that reason, at the end of the study, no significant inter-group differences in PIGF were recorded. The recorded PIGF decrease significantly correlated with exercise capacity increase ($r = 0.548$, $p = 0.013$).

The development of CV disease is associated with oxidative stress since atherosclerosis and CAD are caused and followed by increased production of reactive oxygen species (ROS) (45, 46). Cardiac patients, particularly after ACS, usually have markedly reduced tolerance to physical activity (47), as demonstrated in the present study at baseline, although non-strenuous, repetitive physical activity and mild oxidative stress can positively affect patients with cardiac diseases. Physical training induces many hematological, hormonal and metabolic changes (48), which are mainly dependent on the current health state, intensity and duration of exercise. Repetitive training induces physical and biochemical modifications such as increased oxygenation, improved blood flow and increased metabolism. Contrary to the acute state, moderate oxidative stress increases the capacity of endogenous antioxidative systems, which may attenuate preexisting disease-dependent oxidative stress (49). Most of the studies on the the influence of physical activity in cardiac patients have been focused on the risk factors associated with physical fitness, fibrinolytic system, or lipid profile, whereas the investigation of the changes induced in the blood remains scarce (50). However, among many positive metabolic and functional changes in the body, exercise induces significant improvement in blood and erythrocyte rheology (51, 52). In our study, exercise training reduced inflammation in patients with coronary artery disease.

CONCLUSION

Residential exercise training in CAD patients reduced inflammation, expressed through a significant decrease in CRP, ESR, WBC count and PIGF levels. These positive changes in inflammatory

markers were associated with a significant improvement in exercise capacity.

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Conflicts of interest

Nothing to declare.

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Uticaj fizičkog treninga na markere inflamacije kod bolesnika sa koronarnom arterijskom bolešću

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SAŽETAK

Cilj. Cilj rada bio je proceniti uticaj fizičkog treninga na markere inflamacije i toleranciju fizičkog napora kod bolesnika sa koronarnom arterijskom bolešću (KAB).
Materijal i metode. Ukupno 54 ispitanika uključeno je u ovu studiju; 34 bolesnika sa KAB (KAB grupa: 59,2 godine ± 8,2 godine) i 20 zdravih osoba (K grupa: 54,2 godine ± 8,0 godina). Markeri inflamacije – C reaktivni protein (CRP), brzina sedimentacije eritrocita (SED), leukociti (Leu), faktor rasta placente (egl. placent growing factor – PIGF) i test fizičkim opterećenjem urađeni su kod ispitanika obe grupe na početku studije. Merenja su ponovo urađena nakon sprovođenja tronedeljne kardiovaskularne rehabilitacije kod bolesnika sa KAB.
Rezultati. Na početku, CRP, SED i PIGF bili su značajno viši kod ispitanika u KAB grupi u poređenju sa ispitanicima K grupe ($p = 0,038$, $p = 0,019$ i $p = 0,002$), dok je tolerancija napora bila značajno veća kod ispitanika u K grupi ($p < 0,01$). Posle tri nedelje vežbanja, vrednosti CRP, SED, Leu i PIGF značajno su redukovane ($p = 0,048$, $p < 0,001$, $p = 0,002$ i $p < 0,001$), dok je tolerancija napora značajno poboljšana ($p < 0,001$) kod ispitanika u KAB grupi. Kod ispitanika u KAB grupi smanjenje CRP značajno je koreliralo sa smanjenjem Leu i PIGF ($r = 0,816$, $p = 0,002$ i $r = 0,988$, $p < 0,001$), kao i sa poboljšanjem tolerancije napora ($r = 0,834$, $p < 0,001$). Takođe, smanjenje Leu značajno je koreliralo sa smanjenjem PIGF ($r = 0,768$, $p < 0,001$) i sa poboljšanjem tolerancije napora ($r = 0,548$, $p = 0,012$), dok je smanjenje PIGF bilo značajno povezano sa poboljšanjem tolerancije napora ($r = 0,548$, $p = 0,013$).
Zaključak. Fizički trening kod bolesnika sa KAB doveo je do redukcije markera inflamacije – CRP, SED, Leu i PIGF nivoa i značajnog poboljšanja tolerancije napora.

Ključne reči: **fizički trening, markeri inflamacije, koronarna arterijska bolest**