

## THE EFFECT OF PHYSICAL ACTIVITY ON INFLAMMATORY MARKERS. THE RISK OF NEW CORONARY EVENT IN CORONARY HEART DISEASE PATIENTS

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Inflammation is an important factor in the pathogenesis of atherosclerosis, and several markers of inflammation have been associated with an increased risk of cardiovascular events. Physical activity may lower the risk of coronary heart disease (CHD) by mitigating inflammation. The aim of the study was to investigate the effects of aerobic exercise training on systemic inflammatory response in patients with stable coronary artery disease participating in a cardiovascular rehabilitation exercise program. Male (n=29) and female (n=23) patients with stable coronary heart disease were recruited for this study. All patients were divided into two groups: group with regular aerobic physical training during cardiovascular rehabilitation program phase II along 3 weeks in rehabilitation center and 3 weeks after that in home of patients and sedentary lifestyle group. There were no significant differences in gender distribution among analyzed groups. Student's t test showed no significant difference in mean age, waist circumference (OS) and waist/hip ratio (WHR). Degree of obesity was measured by BMI, and there was a significant improvement in BMI in patients who underwent the six-week physical training compared to control group ( $p<0.05$ ). Physical training during 6 weeks did not show any effects on leukocyte count and ICAM-1 levels compared to control group. The exercise training induced reduction in plasma CRP levels by 23.72%,  $p<0.001$ , and reduction in plasma VCAM-1 levels by 10.23%,  $p<0.05$ .

Moderate aerobic exercise training resulted in a significant reduction of inflammatory state by decreasing CRP and VCAM-1 levels without significant body mass and visceral obesity reduction. The obtained results indicate that regular physical activity is clinically attractive in primary and secondary prevention of coronary heart diseases. *Acta Medica Medianae 2007;46(4):10-14.*

**Key words:** physical activity, inflammation, coronary heart disease

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### Introduction

Inflammation is an important factor in the pathogenesis of atherosclerosis (1), and several markers of inflammation have been associated with an increased risk of cardiovascular events (2). The acute phase reactant C-reactive protein (CRP) is a sensitive marker of inflammation (3). Studies had demonstrated that elevated levels of CRP are independently associated with an increased risk of cardiovascular disease mortality and morbidity as well as acute coronary events in both men and women (4). Physical activity may lower the risk for coronary heart disease (CHD) by mitigating inflammation (5). Regular exercise may decrease CRP values (6). Smith et al. (7) reported a trend for CRP reduction after 6 months of exercise training in individuals at high risk for ischemic heart disease. This type of

training appears to lower inflammatory markers in healthy populations, too (6).

Moreover, physically active elderly men and women have lower CRP levels than their less active counterparts (8). It has been reported that ultramarathon runners have lower CRP levels compared with sedentary controls of similar body mass index (BMI) (9).

Notably, the training-related beneficial changes in plasma ICAM-1 levels are observed in diabetic patients even in the absence of significant variations in body weight and waist circumference (10). Although some authors did not register changing in VCAM-1 molecules serum concentration after physical exercise (11), in animal models long-term exercise training significantly reduced expression of P-selectin, VCAM-1, MCP-1 and iNOS in healthy as well as hypercholesterolemic animals (12).

### Aims

The aim of this study was to investigate the effects of aerobic exercise training on systemic inflammatory response in patients with stable coronary artery disease participating in a cardiovascular rehabilitation exercise program.

## Patients and methods

Fifty-two patients with stable coronary heart disease who had been accepted into the out-patient phase II cardiovascular rehabilitation program at Institute for Treatment and Rehabilitation »Niska Banja«, Nis, Serbia, were recruited for this study. All patients were divided into two groups:

I group - 22 patients with stable coronary heart disease who had regular aerobic physical training during cardiovascular rehabilitation program phase II along 3 weeks in rehabilitation center and 3 weeks after that at home of patients.

II control group - 30 patients with stable coronary heart disease who practiced only regular usual housework without recommended aerobic physical training during last 6 weeks before examination.

Patients were eligible to participate if they had a history of any of the following: myocardial infarction (MI), coronary revascularization, angiographic evidence of more than 50% stenosis in one or more coronary vessels. Subjects were excluded from participation in the study if they had uncontrolled arrhythmias, hypertension (systolic blood pressure >180 mmHg or diastolic BP >100 mmHg), unstable angina pectoris, poorly controlled congestive heart failure, abnormal hemodynamic response or ischemic electrocardiogram changes during stage 1 of the exercise tolerance test (Bruce protocol), or uncontrolled metabolic disease (e.g. uncontrolled diabetes or thyroid disease).

All cardiac-related medication doses were kept constant throughout the study (all patients were on therapy by beta blockers, ACE inhibitors and statins), and patients were required to refrain from any change in their habitual diet.

## Exercise training protocol

Patients underwent 6 weeks of aerobic exercise training consisting of 45 min sessions of continuous aerobic exercise on a treadmill, stationary bicycle or walking. The intensity was maintained at 70–80% of the individual maximum heart rate obtained in the pre-study graded exercise test. All patients trained 3 times/week for 6 weeks.

## Lab tests

Inflammatory risk factors comprise determination of leukocyte count by autoanalyzer for blood samples Haematolog H1-Technicon. Determination of highly sensitive C-reactive protein were done by commercial tests Dade Behring on Dimension Expand analyzer. Serum values of hsCRP are presented in mg/l. Measurement of serum adhesive molecules ICAM-1 and VCAM-1 concentration was done by ELISA. We used commercial test Beckman Coulter Company and Bio Systems-Elisa reader. Values are presented in ng/ml.

## Anthropometry

Fasting body weight, body height, waist and hip circumference were measured. Body mass index (BMI) was calculated as kg/m<sup>2</sup>. We also calculated waist/hip ratio (WHR).

The data were analyzed by standard descriptive methods (mean, standard deviation and percent frequency). Results were obtained by using the Student's t-test, Hi<sup>2</sup> test and Fisher test depending on specimens and type of data.

Statistical analysis were done by software package SPSS 11.0.

## Results

Male (n=29) and female (n=23) patients with stable coronary heart disease were analyzed in this study. Baseline descriptive data for the subjects are shown in Table 1.

Table 1. Baseline descriptive and body composition data of the study participants

	Physical training	Control	p
Male/female (N)	12/10	17/13	NS
Age (years)	62.7±7.1	58.4±7.6	NS
BMI (kg/m <sup>2</sup> )	26.9±3.6	28.5±2.76	0.05
OS (cm)	101±5.42	103.16±6.04	NS
WHR	0.97±0.07	0.99±0.06	NS
MI (N and %)	15 (68)	21 (70)	NS
CABG (N and %)	3 (14)	4 (13)	NS
PTCA (N and %)	4 (18)	5 (17)	NS

Data are presented as the mean±S.D.

BMI-body mass index; OS-waist circumference, WHR-waist/hip ratio, MI-myocardial infarct, CABG- coronary artery bypass graft surgery, PTCA- percutaneous transluminal coronary angioplasty

There were no significant differences in gender distribution among analyzed groups. Hi<sup>2</sup> test showed similar therapeutic approach in resolving acute coronary syndrome. Student's t-test showed no significant differences in average age, waist circumference (OS) and waist/hip ratio (WHR). Degree of obesity was measured by BMI and there was a significant improvement in BMI in patients having underwent the six-week physical training compared to control group (p<0.05) (Table 1).

Leukocyte count, plasma CRP, ICAM-1 and VCAM-1 levels, as a systemic inflammatory markers, were analyzed in response to exercise training (Table 2). Physical training during 6 weeks did not show any effects on leukocyte count and ICAM-1 levels compared to control ones. The exercise training induced reduction in plasma CRP levels by 23.72%, p<0.001, (means±S.D., paired samples t-test), and reduction in plasma VCAM-1 levels by 10.23%, p<0.05 (Table 2).

Table 2. Inflammatory markers

	Control	Physical trainig	$\Delta$ (%)	p
Leukocyte count (G/l)	6.32 $\pm$ 1.33	6.23 $\pm$ 1.87	-1.42	NS
hsCRP (mg/l)	5.1 $\pm$ 3.2	3.89 $\pm$ 2.85	-23.72	0.01
VCAM-1 (ng/ml)	10.36 $\pm$ 3.67	9.3 $\pm$ 1.21	-10.23	0.05
ICAM-1 (ng/ml)	7.5 $\pm$ 6.03	7.48 $\pm$ 1.35	-0.26	NS

Data are presented as the mean $\pm$ S.D. and percent of reduction related to control

## Discussion

In this study, we investigated the effects of aerobic exercise training on systemic inflammatory response and endothelial dysfunction in patients with stable coronary artery disease participating in a cardiovascular rehabilitation exercise program. Specifically, we proved the hypothesis that improvement in aerobic capacity would induce reduction in inflammatory markers and improve endothelial function. To our knowledge, no prior exercise training study has been done comparing effects of exercise training in subjects with documented CHD, in Phase II cardiac rehabilitation with sedentary lifestyle matched patient.

There were not significant gender disproportions as well as significant difference in average age of patients, type of obesity and therapeutic approach between two examined groups of patients. The effects of physical training is expressed only in decreased obesity measured through BMI (Table 1).

As expected for population with known coronary heart disease baseline CRP levels (7,5F4.2 mg/l) were higher than previously reported in healthy populations (median value in men=0,93 mg/l) (13).

We found that exercise training and improvement in aerobic capacity in coronary patients were associated with proportional reductions in plasma levels of CRP and VCAM-1 molecules, while ICAM-1 concentrations and leukocyte count were unchanged (Table 2).

Physical activity most likely confers cardioprotective effect through multiple mechanisms including reducing adiposity, blood pressure, diabetes incidence, dyslipidemia and enhancing insulin sensitivity, glycemic control, fibrinolysis, and endothelial function (5). The association of physical activity with lower levels of inflammation and CRP may provide another cardioprotective mechanism.

Since high levels of CRP had been found to be associated with increased risk of cardiovascular events (4), our data underline the importance of physical activity in CHD patients, and may have enormous clinical importance, especially in population with concomitant presence of other CHD risk factors such as diabetes mellitus.

While no causation can be inferred from cross sectional studies demonstrating that increasing levels of physical activity are associated with lower levels of CRP (14), there are preliminary intervention data that support those cross sectional findings (6).

Potential mechanisms related to exercise and circulating CRP levels could be explained by finding that repeated exercise training may lower basal plasma interleukin concentration (15). One of the most important leukines responsible for the decrease in CRP levels in the individuals following exercise training is IL-6, a pro-inflammatory cytokine, and has been shown to stimulate CRP synthesis in the liver and is secreted from adipocytes in direct proportion to fat mass. However, several studies have observed decrease in CRP concentrations after adjusting for indices of general obesity (6,8,9), suggesting the potential for lower contribution of body fatness to CRP concentrations. Alternatively, exercise may stimulate synthesis of other, as yet unidentified factors that act either to attenuate the IL-6 stimulation of hepatic CRP synthesis or alter its synthesis independently of IL-6.

Notably, the training-related beneficial changes in plasma ICAM-1 levels are observed in diabetic patients even in the absence of significant variations in body weight and waist circumference (10). This effect was not registered in nondiabetic patients examined in this study (Table 2). Although some authors did not registered changing in VCAM-1 molecules serum concentration after physical exercise (11), in animal models long-term exercise training significantly reduced expression of P-selectin, VCAM-1, MCP-1 and iNOS in healthy as well as hypercholesterolemic animals (12).

Our study showed significant decrease in VCAM-1 molecules after moderate 6-week aerobic physical training. The importance of this finding is best visible through function of ICAM-1 and VCAM-1 in patients with CAD. Although ICAM-1 and VCAM-1 are structurally and functionally similar, in patients with advanced atherosclerosis, plasma levels of ICAM-1 may be considered as a more generalized marker of inflammation, whereas those of VCAM-1 seem to be an indicator of plaque burden or activity, or endothelial dysfunction (16). In that way, the effect of physical training is of great importance on subsequent coronary events caused by destabilisation or rupture of atherosclerotic plaque fibromatous cap, especially having in the mind their effect on oxydative stress level (17). It is important that reduction of inflammation and oxidative stress are the best ways to reduce the risk for acute coronary syndrome (18).

## Conclusion

Moderate aerobic exercise training resulted in significant reduction of inflammatory state by decreasing CRP and VCAM-1 levels without significant body mass and visceral obesity reduction.

All of these exercise-related beneficial changes can contribute to a reduction of the cardiovascular risk in these patients.

The obtained results indicate that physical activity plays a significant role in primary and secondary prevention of coronary heart disease.

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## EFEKAT FIZIČKE AKTIVNOSTI NA INFLAMATORNE POKAZATELJE. RIZIK ZA NASTANAK NAKNADNOG KORONARNOG DOGAĐAJA KOD BOLESNIKA SA ISHEMIJSKOM BOLEŠĆU SRCA

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Inflamacija predstavlja važan patogenetski faktor u pojavi i progresiji ateroskleroze. Fizička aktivnost smanjuje rizik za pojavu koronarne bolesti srca. Smatra se da je jedan od osnovnih mehanizama pozitivnog delovanja redukcija sistemskog inflamatornog odgovora. Cilj rada bio je da se ispita efekat aerobnog fizičkog treninga umerenog intenziteta na inflamatorne pokazatelje kod bolesnika sa preležanim infarktomiokarda. U istraživanju je uključeno 52 bolesnika sa stabilnom koronarnom bolešću koji su podeljeni na grupu sa redovnim fizičkim treningom u trajanju od 6 nedelja i sedentarnu grupu. Bolesnici u

ispitivanim grupama su slične starosti i bez značajnijih razlika u vrednostima obima struka i odnosa struk/kuk. Step en gojaznosti meren kroz BMI ukazuje na nešto manju gojaznost bolesnika koji su bili podvrgnuti fizičkom treningu. Broj leukocita i koncentracija ICAM-1 molekula se nisu razlikovale između ispitivanih grupa. Efekat fizičkog treninga se ogleda u značajnom smanjenju vrednosti hsCRP za 23,72% ( $p < 0.01$ ) i redukciji koncentracije VCAM-1 molekula za 10.23% ( $p < 0.05$ ). Aerobni fizički trening sa submaksimalnim opterećenjem dovodi do značajnog pada inflamatornih markera CRP i VCAM čak i bez značajnije redukcije telesne težine ili smanjenja visceralne gojaznosti. Dobijeni rezultati ukazuju da fizička aktivnost ima značajno mesto u primarnoj i sekundarnoj prevenciji koronarne bolesti. *Acta Medica Medianae 2007;46(4):10-14.*

**Ključne reči:** fizički trening, inflamacija, ishemijska bolest srca