



Effects of physical exercise on inflammatory parameters and risk for repeated acute coronary syndrome in patients with ischemic heart disease

Efekat fizičkog vežbanja na parametre inflamacije i rizik od relapsa akutnog koronarnog sindroma kod bolesnika sa ishemijskim oboljenjem srca

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Abstract

Background/Aim. 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 for coronary heart disease (CHD) by mitigating inflammation. The aim of this study was to investigate the effects of aerobic physical exercise on systemic inflammatory response in patients with stable coronary disease participating in a cardiovascular rehabilitation exercise program. **Methods.** Male ($n = 29$) and female ($n = 23$) patients with stable coronary heart disease were enrolled in this study. All the patients were divided into two groups: the group with regular aerobic physical training during cardiovascular rehabilitation program phase II for 3 weeks in our rehabilitation center and 3 weeks after that in their home setting, and sedentary lifestyle group. There were no significant differences in gender distribution among the analysed groups. Student's t -test showed no significant differences in average age, waist circumference (OS) and waist/hip ratio (WHR). **Results.** The degree of obesity was measured by BMI and there was a significant improvement in BMI in the patients who undertook 6-week physical training compared to the controls ($p < 0.05$). Physical training during 6-week appeared not to have any effects on leukocyte count and ICAM-1 levels compared to controls. Exercise induced reduction in plasma CRP levels by 23.72% ($p < 0.001$) and reduction in plasma VCAM-1 levels by 10.23%, ($p < 0.05$). **Conclusion.** Moderate aerobic exercise resulted in a significant reduction of inflammatory state by decreasing CRP and VCAM-1 levels with significant obesity reduction but without visceral obesity reduction. The obtained results indicate that regular physical activity is clinically desirable in primary and secondary prevention of coronary heart diseases.

Key words:

coronary disease; inflammation mediators; exercise therapy; treatment outcome; risk factors.

Apstrakt

Uvod/Cilj. Inflamacija predstavlja važan patogenetski faktor u pojavi i progresiji ateroskleroze. Fizička aktivnost smanjuje rizik od pojave koronarne bolesti srca. Smatra se da je jedan od osnovnih mehanizama pozitivnog delovanja redukcija sistemskog inflamacijskog odgovora. Cilj rada bio je da se ispita efekat aerobnog fizičkog treninga umerenog intenziteta na inflamacijske pokazatelje kod bolesnika sa preležanim infarktom miokarda. **Metode.** U istraživanje je bio uključeno 52 bolesnika (29 muškaraca i 23 žene) sa stabilnom koronarnom bolešću koji su bili podeljeni na grupu sa redovnim fizičkim treningom u trajanju od šest nedelja i sedentarnu grupu. Bolesnici u ispitivanim grupama bili su slične starosti i bez značajnijih razlika u vrednostima obima struka i odnosa struk/kuk. Svi bolesnici uključeni u istraživanje imali su pozitivnu istoriju za postojanje preležanog infarkta miokarda, koronarne revascularizacije ili angiografske potvrde 50% stenozе jednog ili više koronarnih sudova. **Rezultati.** Step en gojavnosti mеren kroz BMI ukazuje na nešto manju gojavnost bolesnika koji su bili podvrgnuti fizičkom treningu. Nije nađena značajnija razlika u vrsti terapijskog rešavanja akutnog koronarnog sindroma. Broj leukocita i koncentracija ICAM-1 molekula nisu se razlikovali između ispitivanih grupa. Efekat fizičkog treninga ogleda se u značajnom smanjenju vrednosti hsCRP za 23,72% ($p < 0,01$) i redukciji koncentracije VCAM-1 molekula za 10,23% ($p < 0,05$). **Zaključak.** Aerobni fizički trening sa submaksimalnim opterećenjem dovodi do značajnog pada inflamacijskih markera CRP i VCAM, čak i bez značajnije redukcije telesne težine ili smanjenja visceralne gojavnosti. Svi ovi efekti fizičkog treninga imaju korisne efekte u redukciji kardiovaskularnog rizika od pojave nakanadnih koronarnih događaja i ukazuju da fizička aktivnost ima značajno mesto u primarnoj i sekundarnoj prevenciji koronarne bolesti.

Ključne reči:

koronarna bolest; zapaljenje, medijatori; lečenje vežbanjem; lečenje, ishod; faktori rizika

Introduction

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^{1,2}. The acute phase reactant, C-reactive protein (CRP) is a sensitive marker of inflammation³. Researches have showed that elevated concentration of CRP is an independent prognostic factor for increased cardiovascular mortality and morbidity, as well as the occurrence of certain clinical manifestations of acute coronary syndrome in both genders⁴.

Physical activity may lower the risk of coronary heart disease. It is thought that one of the basic mechanisms of its favorable impact is the reduction of systemic inflammatory response⁵. Regular physical training can lower the values of CRP⁶. Smith et al.⁷ have reported that there was a CRP reduction trend after 6 months of physical training in persons at high risk of ischemic heart disease. This type of training produces similar tendency of reduction of inflammatory markers in healthy individuals as well⁶. Moreover, physical exercise is most important in the group of individuals at highest risk of coronary disease, since it has been demonstrated that physically active elderly men and women have lower CRP values compared to their less physically active peers⁸. Similar results have been obtained comparing active sportsmen to controls with similar body mass index and sedentary lifestyle⁹.

In addition to these inflammatory indices, significant effects of physical training have been described regarding the reduction of Intracellular Adhesion Molecule-1 (ICAM-1) molecule values and leukocyte count in diabetic individuals¹⁰. Alterations of Vascular Cell Adhesion Molecule-1 (VCAM-1) molecule values after physical exercise in patients with peripheral vascular disease have not been demonstrated; however, it should be mentioned that in animal models long-term training has significantly reduced the expression of P-selectin, VCAM-1, Monocyte Chemoattractant Protein-1 (MCP-1) and Inducible Nitric Oxide Synthase (iNOS) in both healthy and hypercholesterolemic animals^{11,12}.

In spite of the well known effects of aerobic physical training, the published data on its effect on the spectrum of inflammatory markers in individuals with coronary disease are scarce. The aim of this study was, therefore, to investigate the effect of aerobic physical training of moderate intensity on inflammatory indices in patients with stable coronary disease.

Methods

This study enrolled 52 patients with coronary disease treated at the Institute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases in Niška Banja. All the patients were divided into two groups.

In the group I there were 22 patients with stable coronary disease and regular aerobic physical exercise within the program of cardiovascular rehabilitation during 3 weeks, continuing their training for further 3 weeks at home.

In the group II there were 30 patients with stable coronary disease who in the last 6 months did not have physical training recommended after their program of cardiovascular rehabilitation, except for usual household activities.

All the enrolled subjects had positive history of myocardial infarction, coronary revascularization or angiographic confirmation of 50% stenosis of one or more coronary vessels. Unsuitable for our study were those with arrhythmia, hypertension with systolic tension above 180 mmHg or diastolic below 100 mmHg, unstable angina pectoris, poorly controlled cardiac insufficiency, poor hemodynamic response or ischemic changes on ECG during phase I of ergotest (Bruce protocol), or some of the metabolic disorders (diabetes mellitus, hyperthyrosis).

During the study, the enrolled patients took regularly their usual medication, and the same refers to diets recommended during the program of cardiovascular rehabilitation. All the subjects used beta-blockers, ACE inhibitors and statins included in their therapy.

Physical training

The patients undertook regular aerobic physical training for 6 weeks, which consisted of continual aerobic exercise for 45 minutes on a treadmill, room bicycle or walking. The intensity of physical exercise was limited to the submaximal physical capacity at the level of 70-80% of maximal heart frequency at the stress test taken before cardiovascular rehabilitation.

Physical exercise was applied 3 times a week for 6 weeks.

Biochemical tests were done at the start and after 6 weeks' training and compared to the control group values. Blood samples in the group with physical training were taken 24 hours after the last physical training.

Blood pressure was measured by auscultation (sphygmomanometer, Becton Dickinson, USA) three times accordingly to American Heart Association procedure and the average values were adopted.

The methods to assess inflammatory risk factors involved leukocyte count determination with autoanalyzer for blood count Haematolog H1-Technicon. Highly sensitive C reactive protein (hsCRP) determination was done with commercial Dade Behring test on Dimension Expand analyzer. The values were expressed in mg/l. ELISA method and commercial Beckman Coulter Company test (Dual Monoclonal Antibody Sandwich Enzyme Immunoassay) on Bio Systems-elisa reader were employed to determine adhesive molecules ICAM-1 and VCAM-1. The results were expressed in ng/ml.

Anthropometric measurements

Body mass index (BMI) was determined on the occasion of blood sampling; waist circumference (WC) and waist/hip (W/H) ratio were the dimensions of interest. Obesity assessment was done complying with the recommendations of the American Association for Diabetes.

The data was processed using the standard descriptive statistic methods (mean value, standard deviation, percentage). The results were analyzed using the Student's *t*-test for

paired and unpaired samples, χ^2 test and Fisher test of exact probability, depending on the group size, type of variables and type of distribution.

Statistical processing was done in Excel 7.0 and SPSS 11.0 in Windows 98 settings, with results presented in tables and graphs.

Results

Our study enrolled 29 men and 23 women. Their basic characteristics are presented in Table 1.

hsCRP and concentration of VCAM-1 molecule ($p < 0.05$), which became significantly lower in this group compared to control ($p < 0.01$ and $p < 0.05$ prospective) (Table 3).

All examined inflammatory markers were reduced after 6 weeks' training, but only concentration of hsCRP VCAM-1 showed significant reduction ($p < 0.05$).

Discussion

The investigation initiated to examine the effect of aerobic physical training on the degree of inflammation and indices of endothelial function in patients with ischemic

Table 1

| Patients characteristics | | | |
|-----------------------------|-------------------------|----------------|----------|
| | Exercise training group | Control group | <i>p</i> |
| Men/women (n) | 12/10 | 17/13 | NS |
| Age (yrs), $\bar{x} \pm SD$ | 62.7 \pm 7.1 | 58.4 \pm 7.6 | NS |
| MI [n (%)] | 15 (68) | 21 (70) | NS |
| CAB [n (%)] | 3 (14) | 4 (13) | NS |
| PTCA [n (%)] | 4 (18) | 5 (17) | NS |

The results are shown as averages \pm standard deviation; MI-myocardial infarct; CABG-coronary artery by pass grafting; PTCA-percutaneous transluminal coronary angioplasty; CAB – coronary artery bypass

Analysis demonstrated balanced gender distribution and similar average age in the studied groups of coronary patients. The chi-squared test indicated that there were no significant differences in therapeutic approaches to acute coronary syndrome.

Estimation of obesity and the characteristics of some cardiovascular markers before and after finishing of cardiovascular rehabilitation programme are summarized in Table 2.

Student's *t*-test demonstrated that investigated patients were without significant differences in WC, W/H ratio and dTA at start and at the end of observed period. Obesity, measured by way of BMI, was similar at the beginning of observed period, but after 6 weeks it was significantly lower in subjects who undertook physical training ($p < 0.05$) (Table 2).

heart disease on the program of cardiovascular rehabilitation confirmed the hypothesis that physical activity has favorable impact on the reduction of inflammatory indices and improvement of endothelial dysfunction. The studies comparing a wide spectrum of antiinflammatory indices and indices of endothelial function in patients in the physical training programs compared to physically inactive coronary disease patients are very rare in the relevant literature.

In this study there were no differences in gender distribution, age, type of obesity and therapeutic approaches to coronary disease between the groups of patients on physical training and sedentary controls (Table 1).

The effect of 6 weeks' physical exercise is evident in a significant reduction of obesity measured as BMI, but without

Table 2

Influence of exercise training on obesity and arterial blood pressure

| | Exercise training group | | Control group | |
|--------------------------|-------------------------|------------------|-----------------|-------------------|
| | before | after | before | after |
| BMI (kg/m ²) | 29.3 \pm 3.2 | 26.9 \pm 3.6*† | 29.1 \pm 2.7 | 28.5 \pm 2.76 |
| WC (cm) | 102.8 \pm 4.7 | 101 \pm 5.42 | 101.9 \pm 5.2 | 103.16 \pm 6.04 |
| W/H ratio | 0.98 \pm 0.06 | 0.97 \pm 0.07 | 0.97 \pm 0.06 | 0.99 \pm 0.06 |
| sTA (mmHg) | 144.7 \pm 5.8 | 136.1 \pm 4.3† | 139.1 \pm 4.9 | 135 \pm 6.4 |
| dTA (mmHg) | 90.1 \pm 6.7 | 86.8 \pm 5.2 | 87.7 \pm 6.5 | 85.2 \pm 8.3 |

The results are shown as averages \pm standard deviation; BMI-body mass index; WC-waist circumference; W/H – waist/hip; sTA-sistolic blood pressure; dTA diastolic blood pressure; * $p < 0.05$ vs. control; † $p < 0.05$ vs. starting values

The characteristics of inflammatory response before and after physical exercise were examined by way of leukocyte counts, concentration of hsCRP and serum concentration of adhesion molecules (VCAM-1 i ICAM-1). The results are summarized in Table 3.

Leukocyte counts and concentrations of ICAM-1 molecule did not differ between the studied groups. The effects of physical exercise were reflected in a significant reduction of

any important impact on visceral obesity (Table 2). This is important effect because obesity and visceral obesity correlated with many inflammatory markers¹³ and are frequently associated with lipid disorders, hypertension, insulin resistance and coronary artery disease.¹⁴

In the patients with clinically evident atherosclerosis and confirmed coronary heart disease, CRP values before and after the observed period are significantly higher than

those in healthy population (the average value in men in general population is 0.93 mg/l¹⁵). This study demonstrated that physical training and improvement of aerobic capacity in coronary disease patients was followed by the proportional reduction of plasmatic concentration of hsCRP and VCAM-1 molecule, while ICAM-1 and leukocyte count remained unchanged (Table 3).

scribed¹⁰, this effect was not observed in the group of non-diabetic patients in our study (Table 3). Some authors have not observed changes in VCAM-1 molecules after physical training in patients with peripheral vascular disease¹¹; in animal models long-term training has significantly reduced the expression of P-selectin, VCAM-1, MCP-1 and iNOS both in healthy and in hypocholesterolemic animals¹².

Influence of exercise training of inflammatory markers

Table 3

| Inflammatory markers | Exercise training group | | | Control group | | |
|---------------------------------------|-------------------------|----------------|-------|---------------|--------------|-------|
| | before | after | Δ (%) | before | after | Δ (%) |
| Leukocyte count (×10 ⁹ /l) | 6.9 ± 1.7 | 6.23 ± 1.87 | -9.7 | 6.5 ± 1.9 | 6.32 ± 1.33 | -2.8 |
| hsCRP (mg/l) | 5.2 ± 3.1 | 3.89 ± 2.85**† | -25.2 | 4.9 ± 2.9 | 5.1 ± 3.2 | +4.1 |
| VCAM-1 (ng/ml) | 11.1 ± 2.2 | 9.3 ± 1.21*† | -16.2 | 10.8 ± 3.5 | 10.36 ± 3.67 | -4.1 |
| ICAM-1 (ng/ml) | 7.8 ± 1.56 | 7.48 ± 1.35 | -4.1 | 7.2 ± 4.3 | 7.5 ± 6.03 | +4.2 |

The results are shown as averages ± standard deviation; hsCRP – Highly sensitive C reactive protein; VCAM-1 – Vascular Cell Adhesion Molecule-1; ICAM-1 – Intracellular Adhesion Molecule-1; **p* < 0.05, ***p* < 0.01 vs. control; †*p* < 0.05 vs. starting values in the same group

Physical activity exerts its cardioprotective effects most commonly via a large number of mechanisms, including obesity reduction, blood pressure reduction, reduction of the risk and incidence of diabetes mellitus type 2, correction of dyslipidemia and improvement of insulin sensitivity and glycoregulation, improvement of fibrinolysis and endothelial function⁵. Association of physical exercise with lowered level of inflammation and hsCRP can be an additional protective mechanism.

It is well known that high CRP levels are associated with an increased risk for subsequent cardiovascular events, and the results which reflect its reduction after long-term aerobic physical training stress the importance of this treatment modality in coronary disease patients with associated risk factors such as diabetes mellitus⁴.

The exact pathway by which increased physical activity induces CRP reduction has not been elucidated yet, but numerous cross-sectional studies and interventional studies have demonstrated the trend^{6,16}. Potential mechanisms responsible for this effect of physical training could involve the reduced values of interleukins after repeated trainings, responsible for CRP reduction¹⁷. One of the main interleukins responsible in this regard is IL-6, a proinflammatory cytokine secreted by fat tissue which stimulates hepatic CRP synthesis. However, numerous studies demonstrate that after obesity correction, the association of training with low CRP persists, suggesting that some other unknown mechanisms are involved in CRP reduction either via IL-6, or they directly induce reduced CRP production in the liver^{6,8,9}.

Although some significant effects of physical training on the reduction of ICAM-1 molecules in diabetics have been de-

In our study VCAM-1 molecule was markedly reduced after a moderate 6-weeks aerobic physical training. The significance of this finding lies in the fact that although ICAM-1 and VCAM-1 share some structural and functional similarities, in patients with well developed atherosclerotic disease ICAM-1 concentration in the plasma is principally a generalized inflammation marker, while VCAM-1 molecule concentration is an indicator of atheromatous plaque activity or a sign of endothelial dysfunction¹⁸. In that regard, the effect of training on VCAM-1 levels is of enormous importance in view of the reduction of risk for subsequent coronary events caused by destabilization or rupture of the plaque fibrous cap, especially if we are aware of its effect on the degree of oxidative stress¹⁹. It should be noted that our results support the findings that reduced inflammation and oxidative stress represent the best way to reduce the risk of acute coronary syndrome²⁰.

Conclusion

Aerobic physical training with submaximal workload during 6 weeks induces significant reduction of inflammatory markers CRP and VCAM, with significant reduction of general obesity and without changes in visceral obesity.

All these effects of physical training are beneficial regarding the reduction of cardiovascular risk for subsequent coronary events.

The results of this study suggest that physical exercise could have an important place in primary and secondary prevention of coronary disease.

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