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Source / Izvornik: **Collegium antropologicum, 2008, 32, 285 - 291**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:168076>

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Download date / Datum preuzimanja: **2024-12-09**



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Anti-Inflammatory Effects of Exercise Training in the Early Period after Myocardial Infarction

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ABSTRACT

The aim of this investigation was to determine the effect of exercise training on the levels of plasma cytokines and acute phase reactants in the early post acute myocardial infarction (AMI) period. Sixty patients were enrolled into this three-week cardiac rehabilitation study. The mean time from AMI was 7.08±1.60 days, and the patient mean age was 60±10 years. Subjects were randomly assigned to one of the two groups: the control group treated with standard measures, and the group with additional regular moderate-intensity exercise training. Physical activity was based on the ergospirometry test results. Apart from clinical follow-up and routine laboratory analysis we determined the levels of plasma cytokines: tumor necrosis factor (TNF- α), soluble TNF- α receptor 1(TNF- α SR1), interleukin (IL)-8, IL-10, and acute phase reactants: high sensitivity C-reactive protein (hsCRP) and fibrinogen. The obtained results confirmed the hypothesis that the early post AMI period is an inflammatory state the intensity of which gradually decreases with standard treatment during the first month after AMI, while including patients into early exercise training improves their inflammatory profile by decreasing the level of acute phase reactant and TNF- α SR1.

Key words: early cardiac rehabilitation, cytokine, acute phase reactants

Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality and one of the greatest health problems in the developing countries. Investigating mechanisms of their origin and the possibilities of improving existing healthcare are therefore of particular importance. In spite of the established significance of the degree of coronary obstruction¹ and great expectations regarding the investigation of endothelial dysfunction², the existing scientific data demonstrate that inflammation is one of the crucial factors of occurrence and clinical course of most CVD. It is actively involved in all levels of atherogenesis, and so today atherosclerosis is recognized as a low grade inflammatory vascular disease¹. In a series of

therapeutic possibilities affecting the inflammatory component of atherosclerotic disease, exercise training is the most outstanding. The success of regular exercise in reducing the risk of coronary disease development and complications was convincingly associated with the reduction of C-reactive protein (CRP) and fibrinogen³ levels, while on a sample of 28 263 healthy postmenopausal women a prospective study of Ridker et al. has demonstrated the predictive values of CRP and interleukin-6 (IL-6) on the development of cardiovascular events⁴. Some results have shown a relation between increased CRP and soluble tumor necrosis factor- α (TNF- α) values with increased risk of coronary disease in both gen-

ders^{5,6}. The inverse correlation of the cardiorespiratory exercise level with CRP values reported in a study of Church et al. is an interesting observation, especially considering the fact that precisely CRP is defined as a significant predictor of the development of myocardial reinfarction^{7,8}. In patients with congestive heart failure (CHF), proinflammatory cytokines TNF α , soluble TNF α receptor 1 (TNF α SR1), IL-6 and CRP are significantly elevated, and their profile improves with regular physical activity^{9,10}. The positive influence of exercise training on the reduction of IL-6 and TNF α SR1 is demonstrated in a group of patients with moderately severe and severe CHF and ischemic heart disease⁹. The IL-8 is also an atherogenic factor, a potent chemoattractant that may be responsible for the recruitment of inflammatory cells into the subendothelial space, adhesion of monocyte, the migration of vascular smooth muscle cells and the promotion of metalloproteinase expression. According to the IL-8 therapeutic responses, there is a paucity of data on the effects of regular physical training. The anti-inflammatory cytokine IL-10 primarily inhibits the release of TNF α . Exercise induces a cascade of cytokine inhibitors, but also the protective role of IL-10¹⁰.

Although the time of early rehabilitation after acute myocardial infarction (AMI) covers a period of critical changes in the postinfarction CHF development, it is generally very poorly investigated¹¹. According to accessible data, the positive effects of exercise training on inflammation have not yet been examined in the early period after AMI during which the most important adaptive changes with long-term effects develop.

The aim of this investigation was to determine the influence of exercise training on the levels of plasma cytokines and acute phase reactants in the early post AMI period.

Materials and Methods

Patients after AMI (n=60) were enrolled into this randomized, multi-center study. All patients had successfully undergone a percutaneous coronary intervention (PCI), approximately 6–9 days before entry into the study. They were included in the second phase of a three-week rehabilitation program. During a three week follow-up there were no significant complications. All enrolled patients successfully completed the program.

Exclusion criteria were: uncontrolled arrhythmias, uncontrolled hypertension (systolic blood pressure >180

mmHg or diastolic >100 mmHg), unstable post-infarction angina, acute heart failure, abnormal hemodynamic response or ischemic changes on electrocardiogram (ECG) during the initial incremental load of 50 W on the ergo-spirometry test, uncontrolled metabolic diseases, significant orthopedic limitations, significant peripheral vascular disease, infectious states or other inflammatory diseases, and over 80 years of age.

Patients were randomized into the exercise training (n=30) and the control group (n=30) by flipping a coin. The control group without active training was provided with standard care, whereas the training group participated in regular physical training. Before starting exercise training patients were ergospirometry tested with a Meta Max 2 Cortex (Leipzig, Germany) device, the VO₂ peak was established by the respiratory spectrometry which is routine measurement for oxygen uptake in compliance with the guidelines of the American Heart Association¹⁰. Exercise training consisted of a 45-minute aerobic activity on a cycle-ergometer with exercise intensity reaching a level of heart rate 50–60 % peak oxygen uptake (VO₂peak) monitored on ergospirometry. Addition to this training was a daily 30-minute organized program of supervised walking on a standardized track.

All subjects had given informed consent to the inclusion in the study and the research was carried out in accordance with the principles of the Declaration of Helsinki.

Inflammatory markers were determined at rest on the second and twentieth day of the rehabilitation program. Blood samples were collected for all investigated patients at the same time, under the same conditions, by venipuncture without homeostasis, after a 20 minute rest and no physical training for 24 hours before. Test values were determined in duplicate. Cytokines measured in the study were: TNF α , TNF α SR1, IL-8 and IL-10, while from the acute phase reactants we analyzed: high sensitivity C-reactive protein (hsCRP) and fibrinogen.

The commercial enzyme-linked immunosorbent assay (ELISA) test (Amersham Biosciences, UK), was used for the analysis of serum values of IL-8, IL-10 and TNF α , as well as for TNF α SR1 (R&S Systems), whereas fibrinogen serum values were determined by an automated coagulation analyzer, and hsCRP by a immunoturbidimetric commercial method (both (Dade-Behring, USA).

Data base created by the MS Excel program was statistically analyzed on a PC using the Statistical Data

TABLE 1
DEMOGRAPHIC AND ANTHROPOMETRIC PARAMETERS

| | All patients (N=60) | Training group (N=30) | Controls (N=30) | p |
|--------------------------|---------------------|-----------------------|-----------------|-------|
| Age (years) | 60±10 | 59±9 | 61±10 | 0.376 |
| Gender (M/F) | 44/16 | 21/9 | 23/7 | 0.559 |
| BMI (kg/m ²) | 28.4±3.8 | 28.8±3.8 | 28.0±3.8 | 0.392 |
| Waist / hip ratio | 1.030±0.059 | 1.026±0.073 | 1.034±0.066 | 0.640 |

Analysis Software System, Version 7.1 StatSoft, Inc. 2005. Results are shown by average values with standard deviations or by medians with quartile ranges; for comparing two sets of results, we used Student's t-test, Wilcoxon paired test or Mann-Whitney test (where p-value <0.05 was considered statistically significant).

Results

Patients' demographic and anthropometric data are listed in Table 1. There was no significant difference in age, sex, body mass index (BMI) and waist/hip ratio at the start of the trial. To the end, BMI significantly decreased in the total sample (28.4 ± 3.8 kg/m² to 28.2 ± 3.6 kg/m², $p = 0.047$), but without significant changes within the analyzed groups (in trained patients BMI changed from 28.8 ± 3.8 kg/m² to 28.6 ± 3.5 kg/m², $p = 0.120$ while in the control group 28.0 ± 3.8 kg/m² to 27.9 ± 3.8 kg/m², $p = 0.226$), and without changes in the waist / hip ratio (for

total sample 1.03 ± 0.06 changed to 1.02 ± 0.08 , $p = 0.626$; for trained patients from 1.026 ± 0.07 to 1.027 ± 0.08 , $p = 0.975$ and for controls from 1.034 ± 0.07 to 1.022 ± 0.07 , $p = 0.299$).

Of the total sample 43.3 % of patients had diabetes or glucose intolerance, without significant difference in the prevalence between the trained (40.0 %) and the control (46.7 %, $p = 0.587$) group. Standard medical therapy did not differ between studied groups, and it was not discontinued during the investigation. Angiotensin converting enzyme inhibitor (ACE-inhibitor) was administered to 98.3 % of patients, β -blockers to 91.67 %, Aspirin to 96.67 %, clopidogrel or ticlopidine to 70 %, statins to 98.33 %, calcium-blocking agents to 23.33 %, diuretics to 20.0 %, nitrates to 20.0 %, peroral antidiabetics to 36.67 % and 10.41 % of patients were on insulin therapy.

The initial ergospirometry test reached VO₂ peak values of 18.9 ± 4.6 mL/kg min for the entire group (training

TABLE 2
CHANGES IN CLINICAL-LABORATORY PARAMETERS OF CARDIOVASCULAR RISK

| | All patients (N=60) | Training group (N=30) | Controls (N=30) | p |
|--|---------------------|-----------------------|-----------------|-------|
| Total cholesterol (mmol/L) | | | | |
| Baseline | 4.50±1.36 | 4.66±1.60 | 4.35±1.08 | 0.388 |
| Week 3 | 3.96±1.06 | 3.95±1.21 | 3.97±0.90 | 0.919 |
| Δ* | -0.10±0.16 | -0.14±0.14 | -0.07±0.18 | 0.093 |
| P | <0.001 | <0.001 | 0.022 | |
| Triglyceride (mmol/L) | | | | |
| Baseline | 1.65±0.80 | 1.81±0.98 | 1.49±0.54 | 0.125 |
| Week 3 | 1.53±0.86 | 1.60±1.02 | 1.47±0.68 | 0.554 |
| Δ* | -0.06±0.30 | -0.11±0.27 | -0.01±0.32 | 0.186 |
| p | 0.088 | 0.030 | 0.815 | |
| HDL-cholesterol (mmol/L) | | | | |
| Baseline | 0.75±0.21 | 0.72±0.17 | 0.77±0.24 | 0.347 |
| Week 3 | 0.82±0.31 | 0.84±0.32 | 0.80±0.30 | 0.640 |
| Δ* | 0.10±0.36 | 0.17±0.41 | 0.04±0.30 | 0.169 |
| p | 0.045 | 0.039 | 0.566 | |
| LDL-cholesterol (mmol/L) | | | | |
| Baseline | 2.98±0.99 | 2.96±1.03 | 2.99±0.96 | 0.920 |
| Week 3 | 2.50±0.79 | 2.27±0.72 | 2.73±0.81 | 0.025 |
| Δ* | -0.14±0.21 | -0.22±0.17 | -0.06±0.22 | 0.003 |
| p) | <0.001 | <0.001 | 0.038 | |
| Total cholesterol / HDL-cholesterol | | | | |
| Baseline | 6.4±2.8 | 6.8±3.0 | 6.1±2.5 | 0.384 |
| Week 3 | 5.5±2.3 | 5.5±2.7 | 5.5±2.0 | 0.952 |
| Δ* | -0.14±0.26 | -0.22±0.25 | -0.06±0.25 | 0.015 |
| p | 0.009 | 0.046 | 0.069 | |
| Hb_{A1C} (%) | | | | |
| Baseline | 6.5±1.3 | 6.7±1.5 | 6.3±1.1 | 0.190 |
| Week 3 | 6.3±1.2 | 6.4±1.2 | 6.2±1.2 | 0.445 |
| p | 0.044 | 0.048 | 0.539 | |

relative change = [(week 3 value – baseline value) / baseline value]

TABLE 3
CHANGES IN CIRCULATING LEVELS OF INFLAMMATORY MARKERS

| | All patients (N=60) | Training group (N=30) | Controls (N=30) | p |
|--|---------------------|-----------------------|------------------|---------------------|
| Fibrinogen (g/L) | | | | |
| Baseline | 5.7±1.6 | 5.4±1.7 | 6.0±1.4 | 0.103 |
| Week 3 | 4.8±1.6 | 4.3±1.2 | 5.3±1.8 | 0.018 |
| P | <0.001 | <0.001 | 0.017 | |
| hsCRP (mg/L) | | | | |
| Baseline | 14.0 (6.5–5) | 13.5 (5–19) | 16.5 (7–25) | 0.225 [†] |
| Week 3 | 9.0 (4–15) | 5.0 (3–9) | 14.0 (9–17) | <0.001 [†] |
| P* | <0.001 | <0.001 | 0.027 | |
| IL-8 (pg/mL) | | | | |
| Baseline | 12.1 (8.3–17.4) | 11.6 (8.1–15.1) | 13.3 (9.0–18.4) | 0.420 [†] |
| Week 3 | 9.3 (6.4–14.2) | 7.7 (5.8–10.5) | 11.4 (8.9–19.9) | 0.004 [†] |
| P* | <0.001 | <0.001 | <0.001 | |
| IL-10 (pg/mL) | | | | |
| Baseline | 3.0 (2.4–4.8) | 2.9 (2.4–4.6) | 3.0 (2.2–5.3) | 0.842 [†] |
| Week 3 | 3.3 (2.3–5.6) | 4.0 (2.8–5.4) | 3.0 (2.0–6.0) | 0.139 [†] |
| P* | 0.080 | 0.018 | 0.710 | |
| TNFα (pg/mL) | | | | |
| Baseline | 45.9 (27.3–60.0) | 50.0 (27.0–60.1) | 44.9 (27.5–56.3) | 0.717 [†] |
| Week 3 | 41.3 (20.5–63.1) | 49.8 (15.1–72.4) | 35.9 (26.5–49.8) | 0.333 [†] |
| P* | 0.491 | 0.845 | 0.044 | |
| TNFαSR1 (pg/mL) | | | | |
| Baseline | 1470 (1277–1882) | 1403 (1287–1751) | 1553 (1267–2174) | 0.420 [†] |
| Week 3 | 1319 (1140–1715) | 1231 (1030–1475) | 1579 (1251–2028) | 0.004 [†] |
| P* | <0.001 | <0.001 | 0.361 | |

*Wilcoxon paired test, [†] Mann-Whitney test

group 20.0±4.4, controls 17.9±4.6 mL/kg min, $p = 0.076$). At the end of the investigation VO_2 peak values increased considerably in the trained patients (23.2±6.0 mL/kg min, $p < 0.001$), while there was no significant change (18.5±5.3 mL/kg min, $p = 0.339$) in the control group. Comparison of VO_2 peak values after three weeks of rehabilitation revealed significantly higher values in trained patients ($p = 0.002$).

Changes in the clinical-laboratory parameters of cardiovascular risk are shown in Table 2. A significant decrease of total-cholesterol, LDL-cholesterol, tryglycerides and glycolised hemoglobin (Hb_{A1C}) values, and a significant rise of HDL-cholesterol were found among trained patients after three weeks of treatment, while in the group with standard treatment only the total and LDL-cholesterol were lower.

Changes in the circulating levels of inflammatory markers are shown in Table 3. During the early post AMI period, the values of fibrinogen, hsCRP and IL-8 decreased in both study groups and they were significantly lower in the group of patients with regular physical training at the end of the study. Anti-inflammatory cytokine IL-10 increased significantly in the trained group, while the change in the control group was insignificant.

The changes of TNF- α serum concentration were of borderline significance in the control group, with no difference with regard to training during the study, but the values of TNF- α SR1 dropped significantly in trained patients reaching statistically significant lower values at the final measurements.

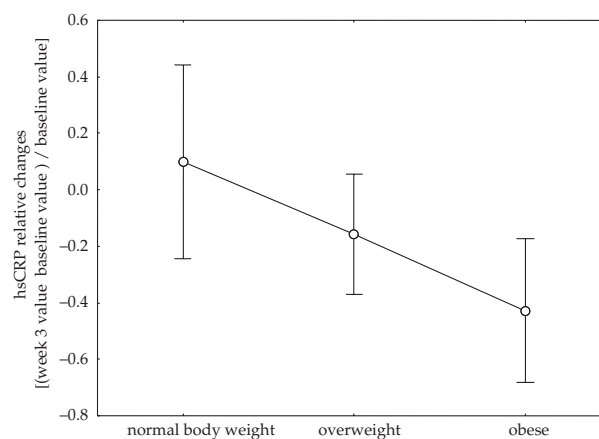


Fig. 1. Relative hsCRP changes in different body mass index (BMI) category.

At the beginning, the decrease of hsCRP values in the study revealed a reverse correlation with the patient BMI. The decrease of hsCRP for the normal (BMI <25 kg/m²), overweight (BMI 24–30 kg/m²) and obese (>30 kg/m²) weight groups is presented graphically (Figure 1). In accordance with the study design, its focus on the first 3 postinfarction weeks and the absence of significant anthropometric value changes in analyzed patients groups, we found no correlation of these parameters with the inflammatory markers, hsCRP included.

Discussion

We demonstrated in our study that the early period of reaching clinical stability after AMI is marked by a generalized inflammatory reaction. Passive recovery and continued medical treatment during the following three weeks led to slow inflammatory regression, while physical training of moderate intensity had an additional anti-inflammatory effect. Considering the study design, we excluded the unstable and high-risk patients and established that the applied training protocol is safe and effective in the early period of uncomplicated AMI. Beside the inflammatory markers, active rehabilitation triggered a significant improvement of the metabolic risk profile.

The VO₂ peak was defined as the best single predictor of cardiac and total mortality in patients with known CVD, and is considered one of the best indicators of survival¹¹. Early rehabilitation after AMI is inadequately researched¹². Most studies investigating the effects of regular physical training on cardiovascular capacity and the inflammatory status of cardiovascular patients are based on modalities of chronic stable coronary disease.

Regular exercise training of 40–90 % VO₂peak intensity is recommended to patients with coronary disease^{13–15}, although such training programs are performed at lower values in that range¹⁶. The starting VO₂peak in our research corresponds to values registered during early cardiac rehabilitation^{17–19}. However, the VO₂peak increase of 16 % recorded during early post-infarction training of moderate intensity corresponds more to the high-intensity (18 %) training results^{16–18} than to a moderate-intensity regime (8 %) in late cardiac rehabilitation¹⁵. These data could suggest significantly higher cardiorespiratory effects of the same training protocol in the early post-infarction phase than if applied later.

Serum hsCRP values increase after AMI as a consequence of tissue lesions. Their levels are slightly increased immediately after myocardial infarction; they double after 8 hours, reach maximal levels on the second to fourth day, and return to normal 3–4 weeks after AMI²⁰. In our study, changes in hsCRP concentration clearly correlate with exercise training and the degree of BMI. Since the anthropometric parameters of the subjects have not changed significantly during the three weeks of investigation, registered changes of hsCRP cannot be attributed to the decreased body weight. The correlation between hsCRP regression and weight loss is the

major limitation of all investigations with exercise training of longer duration, because it leaves an open possibility for their association and relativizes the direct anti-inflammatory effect of physical activity. Considering the great public health and clinical importance of obesity²¹, our study introduces an interesting observation: hsCRP decrease inversely correlates with BMI. Since adipose tissue is the source of IL-6, which is the precursor of CRP, we presume that exercise training could directly affect the fatty cells metabolism and cause suppression of the inflammatory pathway. Although additional research is required, these data suggest that overweight and obese patients, who for their inclination towards the metabolic syndrome represent a high-risk group in secondary cardiovascular prevention, would particularly benefit from early rehabilitation after AMI.

A number of studies investigated the effect of physical activity on specific inflammatory markers. Thus, in patients with CHF a 12-week aerobic training reduces TNF- α concentration²², 6-week bicycle ergometry training reduces the concentration of TNF- α SR2²³, and a 16-week combined aerobic/endurance training reduces the values of both TNF soluble receptors, but not of TNF- α . In our investigation of post infarction TNF- α and TNF- α SR1 dynamics we recorded a decrease of only TNF- α SR1 values in the trained group. The absence of TNF- α change supports the earlier reports on the lower sensitivity of its serum concentration in relation to TNF- α SR1^{22–25} suggesting that a greater sample size is required to reliably evaluate the influence of an intervention on TNF- α concentration than for TNF- α SR1. In the study, we measured only the immunoactivity of the free trimeric TNF- α molecule. It is therefore also possible that a non significant reduction in TNF- α is linked to the significant reduction of its soluble receptor in the trained group, while in the control group the significantly lower value of TNF- α is defined by the absence of its soluble receptor decrease.

Effects of regular training on IL-10 levels are poorly investigated. A study by Smith et al. reported an increase of IL-10 by 36 % in subjects with high risk of developing CVD during a 6-month exercise training²⁶. In our study, a similar increase of IL-10 was associated with exercise training of post-myocardial patients in a significantly shorter period. The initial values of inflammatory markers in our study are higher than those in other studies of secondary cardiovascular prevention^{26,27}, possibly because they include patients with stable coronary disease.

The significant role of IL-8 in stimulating atherosclerosis is well documented²⁸ and considered one of the leading generators of increased cardiovascular risk in diabetic and obese subjects^{29,30}. Our study has shown that IL-8 plasma concentration in the control and training group decreased significantly but the decrease is more obvious in trained patients. Comparing our results with the study of Niessner A. et al., it becomes evident that training decreased circulating IL-8, which may to some extent explain its beneficial effect on coronary risk.³¹

The Framingham study established fibrinogen a cardiovascular risk factor of equal significance as elevated blood pressure, obesity, smoking and diabetes³², stressing the fact that extended physical activity correlates with the decrease of fibrinogen levels and with the increase of fibrinolytic capacity^{33,34}. Our study demonstrated the decrease of fibrinogen with exercise training in the early period after AMI, for which there are no elaborated data.

Data presented in this study pointing out the possible positive effects of early postinfarction physical training are new reference points for further investigation of the cardiovascular diseases associated with low intensity inflammations, first of all atherosclerotic CVD that are of great importance for public health³². The obtained results confirmed the hypothesis that the early post AMI

period is an inflammatory state the intensity of which gradually decreases with standard treatment during the first month after AMI, while including patients into early exercise training improves their inflammatory profile by decreasing the level of acute phase reactant and TNF- α SR1.

According to the results of cardiorespiratory improvement and anti-inflammatory potentials, the modality of early exercise training after AMI that we have tested is a safe and effective procedure that may possibly become a routine modality in current cardiological practice. However, long-term effects, especially those on post-infarction myocardial remodeling, require further verification and assessment.

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PROTUUPALNI UČINCI FIZIČKOG TRENINGA U RANOM RAZDOBLJU NAKON AKUTNOG INFARKTA MIOKARDA

S A Ž E T A K

Cilj ovog rada je bio odrediti utjecaj fizičkog treninga na vrijednosti plazmatskih citokina i rektanata akutne faze upale u ranom razdoblju nakon akutnog infarkta miokarda (AIM). U trojnednu studiju bolničke kardiološke rehabilitacije bilo je uključeno 60 pacijenata. Prosječno vrijeme od AIM je iznosilo 7,08±1,60 dana. Bolesnici dobi 60±10 godina bili su randomizirani u dvije skupine: kontrolnu koja je imala na raspolaganju standardne mjere liječenja i u skupinu s dodatnim redovitim fizičkim treningom srednjeg intenziteta. Fizička aktivnost dozirana je prema nalazu ergospirome-

trijskog testa. Pored kliničkog praćenja i rutinskih laboratorijskih nalaza, određivane su razine plazmatskih citokina: tumor nekrotizirajućeg faktora α (TNF- α), topivog TNF- α receptora 1 (TNF- α SR1), interleukina 8 (IL-8), IL-10 i reaktanata akutne faze: visokoosjetljivog C-reaktivnog proteina (hsCRP) i fibrinogena. Dobiveni rezultati potvrđuju pretpostavku da upalno stanje u ranom razdoblju nakon AIM postupno regredira uz standardne mjere liječenja tijekom prvog mjeseca praćenja, dok uključenje u rani fizički trening dodatno poboljšava upalni status poticanjem značajnijeg pada reaktanata akutne faze upale i TNF- α SR1.