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The Influence of Physical Training on Endothelial Function in Patients with Stable Coronary Artery Disease

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Endothelial damage is the key factor in the pathophysiology of atherosclerosis. Regular physical activity exerts beneficial direct and indirect effects on, among others, cardiovascular system, locomotor system, lipids, carbohydrate and hormonal balance, maintenance of a proper body weight as well as immunological system.
Objectives. The aim of the study included evaluating the effect of a regular, two-month physical training on endothelial function parameters in patients with stable coronary artery disease.
Material and Methods. The study involved 61 patients after coronary angioplasty, 13 women and 48 men aged 62.8 ± 8.7 years. The control group included 21 subjects aged 63.2 ± 9.7 years, 17 of whom had hypertension which was well controlled pharmacologically. Blood for VCAM-1 and ICAM-1 was collected with the subjects remaining for 30 min in supine position, through a venous access inserted in the basilica vein. In the patients' group the blood was collected twice, prior to and after a physical training cycle. In controls the blood was collected once.
Results. The investigated groups differ slightly but not in a statistically significant way with regard to the hemodynamic parameters BP 124.4/75.9 vs. 123.4/76.3 mm Hg, p = ns., HR 66.2 ± 6.8 vs. 68.8 ± 6.3 bpm, p = ns., left ventricular ejection fraction – EF 60.1 ± 7.6 vs. 63.7 ± 5.2 %, $p < 0.05$ and did not differ with regard to the incidence of hypertension or BMI value. The level of soluble ICAM-1 prior to physical training was higher in the investigated group (289.0 ± 97.1 vs. 230.2 ± 47.1 ng/mL, $p < 0.01$) and after the training it decreased but remained higher than in control group (252.4 ± 100.8 ng/mL, $p < 0.05$. vs. control group). The level of soluble VCAM-1 did not differ initially between the groups, nor did it change significantly after the training.
Conclusions. Moderately intense physical training only slightly affects the investigated parameters of the endothelial function in patients with coronary artery disease. A beneficial effect of training on endothelial function was observed as a decrease of the level of soluble ICAM-1. 8-week, moderately intense physical training is sufficient to cause a clinically significant decrease in arterial blood pressure (**Adv Clin Exp Med 2014, 23, 5, 743–748**).

Key words: endothelium function, physical training, ICAM-1, VCAM-1.

Endothelial damage is a key factor in the pathophysiology of atherosclerosis. Numerous factors affecting the development and progression of atherosclerosis exert a negative effect on the condition of endothelial cells, leading to increased permeability of the endothelial barrier to lipoproteins and inflammatory response cells, as well as to weakening of an important antithrombotic function [1, 2]. Endothelium functions are not only a barrier separating the intravascular environment from extracellular elements, but also as an organ with various secretory and metabolic functions.

Endothelium plays a significant role in maintaining homeostasis and regulating vascular functions [3]. Among its various functions, a significant role is attributed to the effect on blood vessels permeability, their wall tone, and the regulation of the properties of vascular surface in homeostasis and in inflammation. Normal functioning of endothelium is conditioned by a balance between endocrine and paracrine factors secreted by the endothelium. The above endothelial functions are controlled by a number of vasoactive molecules. Vasodilating factors produced by the endothelium

include nitric oxide (NO) and prostacyclin (PGI), while endothelium-derived vasoconstricting factors include endothelin-1 (ET-1), thromboxane (TXA 2) and platelet-activating factor (PAF).

Nitric oxide is one of the most significant endothelial molecules whose potent vasodilating and antithrombotic activity is very important for normal functioning of the cardiovascular system. It is a lipophilic molecule with a short half-life of 5–7 s, which easily diffuses across biological membranes [4].

Indicators of an early dysfunction of the vascular endothelium pointing to a decreased thrombogenicity and subclinical activation of inflammation include the level of C-reactive protein as well as the level of adhesion molecules – intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Endothelial cells and leukocytes interactions mediated by adhesion molecules have been demonstrated to play a significant role in the recruitment of leukocytes in the pathogenesis of atherosclerosis [5, 6]. Adhesion molecules ICAM-1 and VCAM-1 mediate in the adhesion of leukocytes to the activated endothelium [7]. An acknowledged evaluation method of the level of both abovementioned molecules consists in the assessment of the level of their soluble fraction not bound with endothelial cells membrane.

Numerous studies have demonstrated that systematic physical activity decreases both mortality due to cardiovascular disease, as well as general mortality. Regular physical activity exerts beneficial direct and indirect effects on, among others, the cardiovascular system, locomotor system, lipids, carbohydrate and hormonal balance, maintenance of an appropriate body weight, as well as immunological system of the organism [8].

Aim of the Study

The aim of the study included evaluating the effect of a regular, 2-month physical training on endothelial function parameters in patients with stable coronary artery disease.

Material and Methods

The study was performed in 61 patients (13 women and 48 men aged 62.8 ± 8.7 years) with stable single vessel coronary artery disease after treatment with coronary artery angioplasty with stent placement (PCI), with preserved left ventricular systolic function, undergoing physical training as a part of cardiac rehabilitation. The coronary artery stenting was performed in LAD in 25 patients, in Cx in 15 patients and in RCA in 26 patients because of symptomatic angina in CCS functional class II and III. The percent of atherosclerotic lesion was assessed as 70 to 90% in 53 patients and as critical 95–99% in 8 patients. Rehabilitation was started from 13 to 127 days after PCI. The patients were administered routine treatment with converting enzyme inhibitor, beta-blocker, acetylsalicylic acid and statins. Some patients were also administered a diuretic and/or a dihydropyridine calcium channel blocker in the management of hypertension, which was diagnosed in 51 patients.

The control group included 21 subjects aged 63.2 ± 9.7 years, with a negative medical history concerning coronary artery disease and a negative ECG stress test result. Seventeen of them had hypertension which was well controlled pharmacologically.

Blood for adhesion molecules estimation was collected with the subjects remaining for 30 min in supine position, through a venous access inserted in the basilic vein. In patients, blood was collected twice, prior to and after physical training cycle. In controls, blood was collected once.

The level of soluble VCAM-1 was evaluated by means of the ELISA method using kits manufactured by R&D Systems, Inc. and it was expressed in ng/mL. The inter-series and intra-series correlation coefficients were 2.6–3.6% and 5.5–7.8%, respectively. The serum level of soluble ICAM-1 was also evaluated by means of the ELISA method using R&D Systems, Inc. kits and expressed in ng/mL. The inter-series and intra-series correlation coefficients were 5.8–10.1% and 5.6–7.6%.

Prior to the rehabilitation cycle, each patient was assessed by a cardiologist and had 12-lead resting ECG and treadmill electrocardiographic test (stress ECG) performed prior to and after the rehabilitation cycle. The stress test taken prior to rehabilitation was used to evaluate possible ischemia of the myocardium as well as to determine the exercise capacity and heart rate training threshold.

All patients undergoing the rehabilitation programme were exercising with a specified intensity of training and training load. For this reason we used a method determining the recommended intensity of training on the basis of the stress test, the so-called heart rate reserve (HRR), and subsequently we calculated the heart rate training threshold. The following parameters were determined:

– Heart rate reserve (HRR) = maximum heart rate (MHR) – resting heart rate (RHR),

– Heart rate training threshold = resting heart rate + 40% to 80% of heart rate reserve.

The training sessions were repeated 3 days a week. The exercises lasted 30–45 min daily. The

cardiac rehabilitation cycle consisted of 24 training sessions performed within 8 weeks. The physical training consisted of 2 stages. The first stage took place in a gym, lasted 30 min and included circuit training preceded by a 2-min warm-up with all-purpose and stretching exercises. The second stage consisted of interval training on a cycloergometer. It included 4 periods of 4 min each with 15-min intervals. Each stage of the training was limited by the heart rate training threshold calculated individually for each participant.

All the investigated patients and control subjects were informed in details about the objective, range and course of the study and gave their consent.

The study protocol was approved by the Bioethical Committee, Wroclaw Medical University.

Statistical Analysis

The investigated parameters were presented as mean values and their standard deviations. The significance of differences in the parameters prior to and after the rehabilitation training was evaluated by means of a non-parametric Wilcoxon rank-sum test. Differences in the studied parameters between groups were evaluated by means of a non-parametric *U* Mann-Whitney test. The significance of correlations between investigated variables was determined by means of the *R* Spearman correlation coefficient. The values of $p < 0.05$ were considered statistically significant.

The STATISTICA 10 statistical software (StatSoft Inc., Tulsa, Oklahoma, USA) was used to perform all statistical analyses.

Results

Table 1 presents demographic and clinical data of the investigated population.

After the physical training cycle the study group revealed a small but statistically significant difference in the heart rate (66.2 ± 6.8 vs. 64.4 ± 5.6 bpm, $p < 0.05$), a statistically significant decrease in the systolic blood pressure (124.4 ± 11.5 vs. 119.1 ± 9.5 mm Hg, $p < 0.01$) and a significant decrease in the diastolic blood pressure (75.9 ± 6.4 vs. 72.0 ± 5.1 mm Hg, $p < 0.05$). Moreover, in the patients' group, a slight, but statistically significant increase in the left ventricular ejection fraction was observed (60.1 ± 7.6 vs. 64.6 ± 5.6%, $p < 0.05$).

Table 2 presents the results of investigated humoral parameters.

Table 1. Demographic and clinical data of the investigated patients and control subjects

	Study group	Control group	p value
Age (years)	62.8 ± 8.7	63.2 ± 9.7	ns.
Gender (female %)	21.3	26.1	ns.
EF (%)	60.1 ± 7.6	63.7 ± 5.2	< 0.05
HR (1/min)	66.2 ± 6.8	68.8 ± 6.3	ns.
RR syst. (mm Hg)	124.4/11.5	123.5 ± 10.4	ns.
RR diast. (mm Hg)	75.9 ± 6.4	76.3 ± 8.3	ns.
Hypertension (%)	83.6	73.9	ns.
Diuretic use (%)	36.1	39.1	ns.
Dihydropyridine CB use (%)	19.7	30.4	ns.
BMI (kg/m^2)	29.6 ± 2.8	29.2 ± 2.6	ns.

Table 2. Investigated humoral factors in the study group and control subjects

	Study group	Control group	p value
ICAM-1 before (ng/mL)	289.0 ± 97.1	230.2 ± 47.1	< 0.01
ICAM-1 after (ng/mL)	252.4 ± 100.8*#	–	–
VCAM-1 before (ng/mL)	1108.6 ± 258.0	1100.1 ± 235.1	ns.
VCAM-1 after (ng/mL)	1170.6 ± 297.5	–	–

* $p < 0.05$ vs. before, # $p < 0.05$ control group vs. study group after.

The study group demonstrated a statistically significant correlation between patients' BMI and the level of VCAM-1 after the training cycle ($R = 0.34$, $p < 0.05$). Moreover, the study group revealed strong statistically significant relationship between ICAM-1 and VCAM-1 levels before and after training: ICAM-1 before and after – $R = 0.67$, $p < 0.05$, VCAM-1 before and after – $R = 0.49$, $p < 0.05$. No other investigated parameters were found to be statistically significantly correlated, neither in the study group, nor in the controls.

Discussion

A moderate, regular physical effort is a recognized beneficial factor in the prevention of cardiovascular diseases. Cardiac rehabilitation decreases mortality due to acute coronary events, delays the progression of coronary artery disease, shortens the duration of treatment in acute cardiac events and exacerbations of angina pectoris, which leads to the accomplishment of the main aims of medical management, such as improvement of the quality and prolongation of life [8].

The benefits of exercise-based cardiac rehabilitation include a modification of risk factors for ischemic heart disease, an increase of physical activity, a decrease of blood pressure values, body mass, a beneficial correction of the lipid profile and carbohydrate metabolism (decreased insulin resistance), inhibition of progress, or even a regression of atherosclerosis and its clinical consequences, an improved function of the circulatory and respiratory systems. Another important factor mentioned among the above benefits concerns improvement of the vascular endothelial function, although the cause-and-effect relationship is not as quite obvious in this case [9].

ICAM-1 and VCAM-1 are the only biochemical markers of inflammation and endothelial dysfunction, elevated levels of which are observed already in the initial stages of atherosclerosis. Observations indicate that the level of these molecules depends on age, gender and BMI, and is higher in elderly people as well as in overweight individuals. The tendency is prominent already at a younger age [10]. Analysis of available literature on the effect of a physical training on the level of adhesion molecules ICAM-1 and VCAM-1 does not give clear results. Some studies on the effect of physical effort on the level of adhesion molecules reported a reduced level of both cytokines after a training cycle, while others observed a decrease of only one of them.

Saetre et al. monitored 29 patients with peripheral artery disease, who participated in supervised physical training. The trial demonstrated that 8-week supervised physical training reduced plasma levels of endothelial ICAM-1 (342.0 vs. 298.0 ng/mL, $p = 0.016$) and resulted in the elongation of the distance of claudication [11]. Both, the levels of ICAM-1, as well as the observed change, were similar to the findings in the present study.

Another study, designed to evaluate the effect of a moderately intense physical training in individuals with stable coronary artery disease, did not demonstrate any beneficial effect of physical activity on the plasma levels of ICAM-1. On the other hand, the study revealed a significant reduction in the levels of VCAM-1 and CRP as well as improvement in BMI. However, it is worthwhile to consider that the physical training in the trial lasted only 6 weeks [12].

A group of 16 patients with type 2 diabetes mellitus, obesity and nicotinism, participating in a moderately intense training repeated twice a week for 6 months revealed, similarly to the present study, a significantly decreased plasma level of ICAM-1, a reduction of body mass, an improvement of glycaemia control and decreased levels of atherogenic lipids. The level of VCAM-1 was not subjected to evaluation in the trial [13].

Brevetti et al. assessed the levels of ICAM-1 and VCAM-1 in patients with atherosclerosis in the arteries of lower limbs and intermittent claudication as well as in healthy individuals from the control group at rest and after physical effort with maximum tolerated intensity. The levels of the abovementioned molecules did not change after the effort in healthy individuals; however, patients with intermittent claudication revealed a significant increase in the levels of ICAM-1 and VCAM-1. The levels were higher in patients with a more advanced disease [14].

Although it was demonstrated that physical effort decreases the progression of atherosclerotic lesions or even causes a regression of atherosclerosis, the evidence is not strong as most of the prospective studies would have to include data on change of lifestyle and treatment strategy. Studies on animals also revealed a beneficial effect of physical effort on a regression of atherosclerosis or slowing of its progression. While findings of studies with the participation of humans as well as with animals prove that physical effort increases endothelium-dependent dilatation of coronary vessels, the evidence that physical effort reverses or inhibits a progression of atherosclerosis in ischemic heart disease is not decisive. This suggests that the beneficial effect of physical effort in coronary artery disease may not be associated with its direct effect on the coronary artery wall [15].

Improvement of the lipid profile is another positive effect of the physical effort. Lipid profile abnormalities are an acknowledged endothelial dysfunction factor which constitutes an initial stage of atherosclerosis. High-cholesterol diet leads to the formation of lipoproteins and recruitment and binding of leukocytes to the vascular wall. The process requires the expression of adhesion molecules, such as vascular adhesion molecule VCAM-1, on the endothelial cells. Aortic endothelial cells in rabbits fed with an atherogenic diet revealed the presence of VCAM-1 molecules, which normally are scarce, and an ICAM-1 focus. ICAM-1 foci appeared soon after the onset of the diet. Lowering of the cholesterol level by means of diet or drugs leads to a decreased expression of VCAM-1. Hypercholesterolemia also hampers dilatation of vessels, among others due to a deterioration of the bioavailability of nitric oxide. Decreasing the level of lipids exerts a beneficial effect on the endothelium, improves the bioavailability of nitric oxide and inhibits inflammatory processes in the coronary arteries [16].

Limitations of the Study

The reports mentioned in the Discussion section presented mostly descriptions of relatively small groups of patients. The physical training protocol used in the present study differed in an obvious way from the majority of training protocols studied by other authors, thus simple conclusions based on other reports are limited.

The investigated control group was relatively small. Moreover, the subjects were not submitted to the training regime; thus the investigated parameters may only be compared in initial conditions.

The effect of cardiac medication administered to patients with coronary artery disease, already mentioned in the Discussion section, on the investigated parameters are inseparable from the effects of training, as both factors are expected to have a positive effect on endothelial function. This is most certainly the key element limiting objective conclusions, both in our study, as well as in numerous reports by other authors.

The authors concluded that eight-week, moderately intense physical training performed as part of cardiac rehabilitation slightly affects the investigated vascular endothelial function parameters in patients with coronary artery disease treated with stent PCI. The training exerted a beneficial effect on the endothelial function in the form of a decreased level of soluble intracellular adhesion molecule-1. Eight-week, moderately intense physical training is sufficient to slightly decrease blood pressure and increase ejection fraction.

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