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THE INFLUENCE OF REHABILITATION TRAINING ON SERUM CONCENTRATIONS OF LIPOPROTEIN(A) IN PATIENTS WITH ISCHEMIC HEART DISEASE

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ABSTRACT

This study examined the effect of physical training at an intensity below ventilatory threshold on serum concentrations of lipoprotein(a) [Lp(a)] in patients with ischemic heart disease. Thirty four patients, after myocardial infarction, and 20 patients, after coronary artery bypass grafting, were admitted to a 3-week cardiac rehabilitation program. The program consisted of 15 sessions of continuous exercise, each in duration 40 min. Fifteen subjects with a history of myocardial infarction or coronary artery bypass grafting who did not participate in a rehabilitation program constituted the control group. Serum Lp(a) levels were measured by immunoenzymatic method (Cormay, Poland). Upon admission, 56% of patients after myocardial infarction and 55% of patients after coronary artery bypass grafting had elevated serum lipoprotein(a) levels. The applied physical training of low intensity and prolonged duration resulted in significant decrease in serum Lp(a) levels in both study groups. The reduction of Lp(a) concentrations was observed both in patients with considerable hyperlipoproteinemia(a) and in subjects with Lp(a) levels within the normal range. In the control group Lp(a) levels remained unchanged. The study findings indicate that continuous training based on aerobic exercise favorably alters atherogenic lipoprotein(a) levels and confirm the important role of physical activity in the prevention of ischemic heart disease.

Key words: lipoprotein(a), ischemic heart disease, physical exercise

Lipoprotein(a) [Lp(a)] is regarded as a congenital, major and independent risk factor for atherosclerosis. The risk of ischemic heart disease increases twice when serum Lp(a) level exceeds 30 mg/dl and even more when elevation of lipoprotein(a) is accompanied by concomitant raise in LDL-cholesterol (11). A considerable body of evidence derived from experimental and clinical studies supports the view that increased serum concentrations of Lp(a) favors development of atherosclerotic lesions in coronary and brain arteries (11, 13, 23). Moreover, high levels of lipoprotein(a) have been found to correlate with the development of vein graft stenoses after coronary artery bypass surgery (5, 27). Several attempts have been made to investigate the possible influence of physical exercise on serum lipoprotein(a) levels (4, 8, 9). Ho-

wever, the results of these studies are conflicting and inconclusive. Therefore we addressed the issue of whether cardiac rehabilitation training of intensity below ventilatory threshold affects serum lipoprotein(a) concentrations in patients with ischemic heart disease.

Material and methods

Patients with ischemic heart disease, who had been referred for cardiac rehabilitation to the Cardiac Rehabilitation Hospital in Poznań, were enrolled in the study. The study population consisted of 34 patients who had survived Q-wave myocardial infarction (MI) 2-6 months prior to entering the program [MI group] and 20 patients who had undergone coronary artery bypass grafting (CABG) 2-6 months earlier [CABG group]. The control group consisted of 15 subjects that had survived myocardial infarction or coronary artery bypass grafting, who did not participate in rehabilitation program at the time of the study; all of them entered rehabilitation within 3 weeks after the study was finished. All patients included in the study had good exercise capacity (≥100 Watts in MI group and ≥75 Watts in CABG group) and preserved left ventricle ejection fraction (≥40% in MI group and ≥34% in CABG group).

Exercise tolerance was determined on the basis of symptom-limited bicycle ergometry (SECA Cardiotest 100 ergometer equipped with computer analysis of electrocardiogram [MC 6000, Cambridge]). Exercise tests were performed 2 hours after a light breakfast (one roll with margarine, light tea or decaffeinated coffee). The initial load of 25 Watts was increased by 25 Watts every 2 minutes, while the number of revolutions per minute was constant (58-62 rev./min). Blood pressure was measured by sphigmomanometry and 12-lead electrocardiogram was recorded prior to the beginning of the exercise test, at the end of each stage, and within one, three and five minutes after the test was finished. The indications for termination of the test were as follows: angina, excessive increase in blood pressure (systolic > 230 mm Hg, diastolic > 115 mm Hg), decrease in blood pressure (> 10 mm Hg despite increased load and accompanied by the symptoms of ischemia), arrhythmia or disturbances of conduction, horizontal or down-sloping ST segment depression of > 0.2 mV, elevation of ST segment > 0.1 mV without Q wave, or signs of peripheral hypoperfusion (paleness, cyanosis, cold sweat, pain in legs).

Left ventricle ejection fraction was estimated by two-dimensional echocardiography (Sonos 100 CF, Hewlett Packard, equipped with a mechanical transducer 2.5 MHz); the complete echocardiography included M-mode, two-dimensional, color Doppler and spectral Doppler analysis.

The 3-week rehabilitation training (continuous mode) was performed on a bicycle ergometer five times a week (15 sessions). Each session lasted 40 min and consisted of a 5-min warm-up, 30 min of workload and 5 min of recovery (without workload). The exercise load was 10% lower than that at which ventilatory threshold was reached during the initial exercise test.

The ventilatory threshold was determined on the basis of computer analysis of nonlinear increase in minute ventilation and expiration of carbon dioxide along with linear increase in minute oxygen uptake, the value of the respiratory quotient [VCO_2/VO_2], and a constant increase in respiratory equivalent for oxygen [VE/VO_2] with concomitant lack of increase in respiratory equivalent for carbon dioxide [VE/VCO_2] according to the method described by Beaver et al. (3). The threshold was determined via a bicycle ergometry performed on a Ergo Metrics 900 ergometer

(Germany) equipped with the CardiO2 computer system (ECG Exercise System, Medical Graphics, USA). The initial workload was 25 Watts and was increased by 25 Watts every 3 minutes until the ventilatory threshold was reached.

The mean training load was 66 Watts in patients with a myocardial infarction history and 55 Watts in subjects having had coronary artery bypass grafting. The mean heart rate was 97.2 ± 2.7 beats per minute in MI group and 98.2 ± 2.1 beats per minute in CABG group.

Additionally, patients walked a distance of at least 2 km (30-60 min) each afternoon and took part in recreational activities and team games 30 min daily.

The medication in patients after myocardial infarction, coronary artery bypass grafting and in the control group is shown in Table 1. No changes in medication were introduced during the study period.

Directly before and after completing the 3-week training program, peripheral blood samples were taken after an overnight fast from each subject. Serum lipoprotein(a) levels were determined by an immunoenzymatic assay (ELISA) (Cormay, MP, Poland) at the wavelength of 450 nm. The method is exact to 1 mg/dl.

The study was undertaken after approval by the local Ethics Committee for Research in Humans and informed consent of all patients.

Table 1. *Pharmacological treatment*

Medication	Patients after MI	Patients after CABG	Control Group
Acetylsalicylic acid	100%	90%	100%
Beta-adrenolytic agent	80%	85%	67%
Angiotensin-converting enzyme inhibitor (ACE-inhibitor)	20%	40%	20%
Nitrates	20%		33%
Calcium-channel antagonist		15%	20%
Amiodarone		15%	
Ticlopidine		10%	10%

Table 2. *Baseline anthropometric characteristics of the study groups (x ±SD)*

Study group	N	Age [years]	Time after MI or CABG [days]	Body mass [kg]		BMI [kg/m^2]		HR [beat/min]		Blood pressure [mm Hg]	
				before training	after training	before training	after training	before training	after training	before training	after training
Patients after MI	34	47.9 ± 6.93	81.0 ± 28.49	82.7 ± 9.57	82.8 ± 8.93	26.8 ± 3.03	26.9 ±2.81	78.8 ± 12.72	73.4 ± 13.63	(S) 126.6 ± 17.56 (D) 85.5 ± 8.85	(S)116.1 ±15.12 (D) 80.6 ± 8.41
Patients after CABG	20	58.5 ± 6.23	86.9 ± 59.41	77.0 ± 10.31	77.4 ± 10.41	25.8 ± 3.74	25.9 ± 3.76	72.9 ± 10.01	72.4 ± 11.82	(S) 134.5 ± 17.00 (D) 89.0 ± 7.53	(S) 137.0 ± 25.66 (D) 85.5 ±11.10
Control group	15	50.2 ± 5.94	113.7 ± 68.26	80.9 ±8.08	81.0 ± 7.56	26.1 ± 2.92	26.0 ± 2.74	74.4 ± 14.92	74.0 ±14.41	(S) 122.3 ± 12.65 (D) 87.6 ± 6.77	(S) 122.6 ± 12.79 (D) 84.6 ± 11.87

MI - myocardial infarction; CABG - coronary artery bypass grafting

Results

Anthropometric parameters, resting heart rate and blood pressure values are shown in Table 2. All patients were overweight (BMI 26.9 ± 2.81 in MI group, 25.8 ± 3.74 in CABG group). In patients after myocardial infarction the resting heart rate and blood pressure (systolic and diastolic) significantly decreased after the 3-week training ($p < 0.05$ and $p < 0.01$, respectively). In patients with a history of coronary artery bypass grafting a non-significant increase in systolic blood pressure from 134,5 ± 17.00 to 137.0 ± 25.66 mm Hg with concomitant decrease in diastolic blood pressure from 89.0 ± 7.53 to 8.5 ± 11.10 mm Hg was observed. The resting heart rate remained unchanged.

Table 3. *Changes in lipoprotein(a) concentrations in patients rehabilitated after myocardial infarction (MI) or coronary artery bypass grafting (CABG) (x ± SD)*

Study group	Lp(a) [mg/dl]	N	I term x ± SD	II term x ± SD	Difference I – II [mg/dl]	Wilcoxon Test
Patients after MI	1 - 30	11	18.3 ± 6.69	16.4 ± 6.39	-1.9 ± 5.22	p<0.01
	>30	19	70.6 ± 18.04	61.2 ± 16.65	-9.4 ± 11.87	p<0.01
Patients after CABG	1 - 30	9	16.6 ± 5.40	12.8 ± 7.32	-3.7 ± 5.11	p<0.01
	>30	11	80.1 ± 12.60	70.6 ± 7.60	-9.5 ± 12.25	p<0.01
Control group	1 - 30	9	16.7 ± 6.22	14.3 ± 7.48	-2.4 ± 7.07	NS
	>30	4	81.2 ± 5.73	75.7 ± 5.90	-5.5 ± 6.95	NS

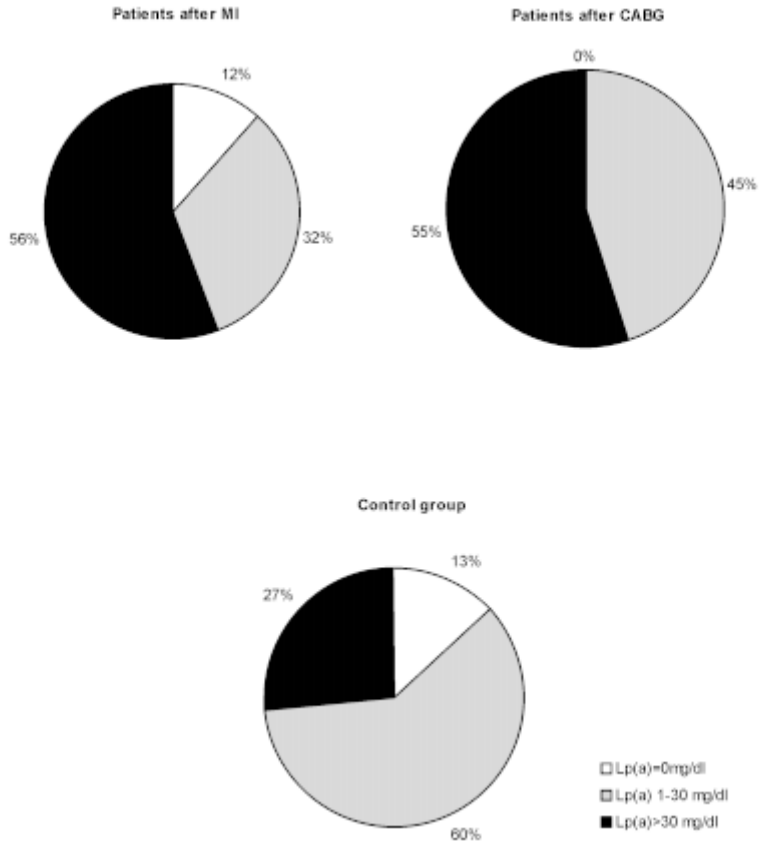

Fig. 1. *Baseline serum lipoprotein(a) levels in patients rehabilitated after myocardial infarction (MI) or coronary artery bypass grafting and in the control group (CABG)*

On admission to the cardiac rehabilitation program, 56% of patients with a history of myocardial infarction and 55% of patients with a history of coronary artery bypass grafting had serum lipoprotein(a) levels exceeding 30 mg/dl (Fig. 1). Overall, 49% of all patients had hyperlipoproteinemia(a).

In both study groups serum Lp(a) concentrations were significantly lower after the rehabilitation training than at the beginning (Tab. 3). The decreases in lipoprotein(a) concentrations were observed both in patients with important hyperlipoproteinemia(a) and in subjects with initial Lp(a) concentrations within normal range ($p < 0.01$). In the control group, the serum Lp(a) levels remained unchanged.

Changes in serum lipoprotein(a) concentrations in individual patients are shown

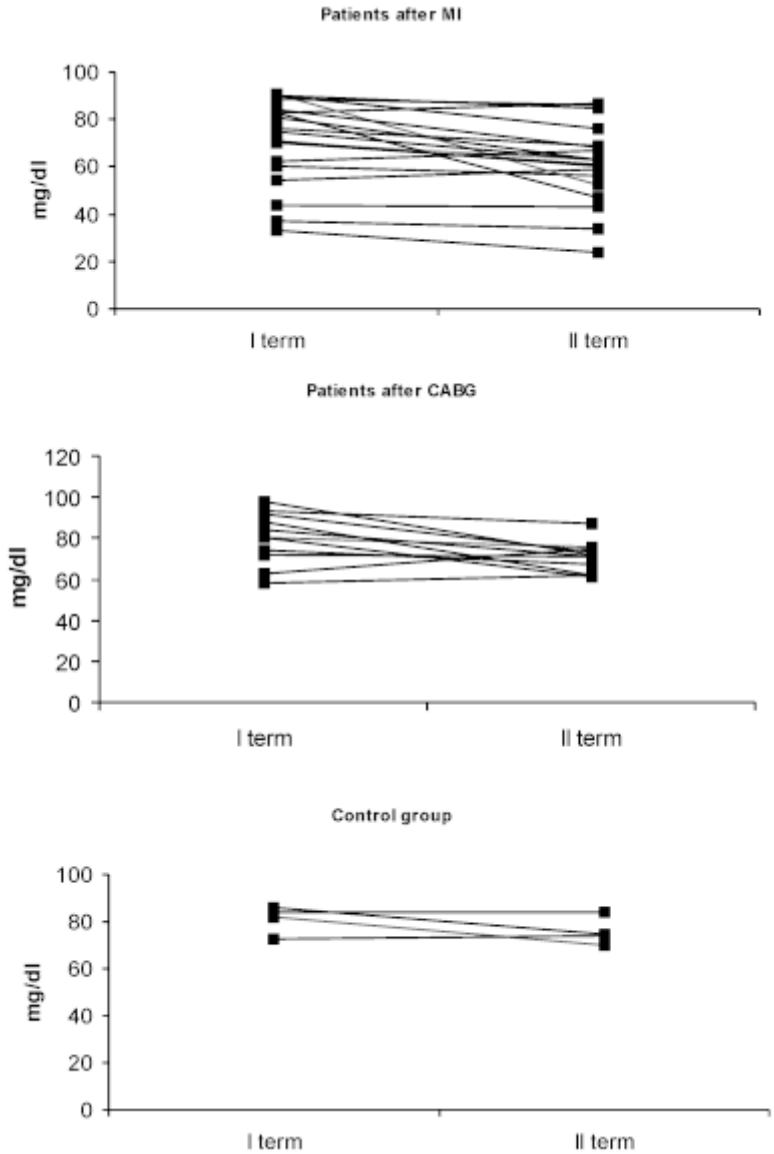

Fig. 2. *Changes in serum lipoprotein(a) concentrations during rehabilitation training in individual patients with hyperlipoproteinemia(a) above 30 mg/dl on admission. MI - myocardial infarction; CABG - coronary artery bypass grafting*

in Fig. 2. Serum lipoprotein(a) levels exceeding 30 mg/dl were found in 19 patients in the MI group, 11 subjects in the CABG group and 4 patients in the control group.

Discussion

There is growing body of evidence that suggests hyperlipoproteinemia(a) exceeding 30 mg/dl correlates with increased risk of atherosclerosis and related diseases (2, 7, 12). Raised Lp(a) levels have been considered one of the most important risk factors for myocardial infarction (following elevated LDL-cholesterol, family history of ischemic heart disease, elevated fibrinogen concentration and low HDL-cholesterol) (6). High incidence of hyperlipoproteinemia(a) in subjects with ischemic heart disease was further confirmed by the results of our study. In both study groups more then 50% of patients had serum Lp(a) levels higher than 30 mg/dl (56% in MI group, 55% in CABG group).

Although examined in several studies, the influence of physical training on serum lipoprotein(a) levels remains unclear. Physical exercise has been shown to decrease Lp(a) concentrations in some studies (14, 15, 21, 24), while other authors have reported unchanged or even raised lipoprotein(a) levels after training (4, 10, 17, 18). Transient increases in Lp(a) concentrations directly following intensive exercise have been explained by the involvement of Lp(a) in repairing muscle cells damaged by reactive oxygen species generated during the exercise (4, 19). In the above mentioned studies elevations of serum Lp(a) paralleled increases in markers of cellular membranes damage, such as creatine kinase and its izoenzyme -2 activities or lactate dehydrogenase (LDH_2) activities. In contrast, Hubinger et al. (17) found that 6-weeks of physical training at an intensity of 60-85% of maximum heart rate does not affect lipoproteinemia(a). The lack of influence of physical training on serum lipoprotein(a) levels has been attributed to the fact that its production is genetically determined (25) and thus hardly modifiable by environmental factors such as physical activity.

In our study, we observed a slight, nonsignificant decrease in lipoprotein(a) levels in the control group. The possible explanation of this finding is that patients followed physicians' instructions concerning diet and lifestyle (recommendations of the European Atherosclerosis Society 1992 (22)) given during the first meeting. Nevertheless, data concerning the influence of diet on the serum lipoprotein(a) levels are sparse, with the exception of the diet rich in omega-3 acids and the reduction diet (15, 25).

We have observed significant decrease in lipoprotein(a) levels in patients with a history of myocardial infarction or coronary artery bypass grafting after a 3-week rehabilitation training. The reduction of Lp(a) observed during the training can probably be attributed to the character of applied exercise. The training workload was 10% lower than that at which ventilatory threshold had been reached; therefore, the performed exercise was entirely aerobic. Such exercise not only does not enhance the generation of reactive oxygen species, but also augments the activity of lipoprotein lipase, an enzyme that facilitates binding of Lp(a) to heparan sulfate on cell membranes and accelerates its catabolism (26). According to some authors, 25% of Lp(a) is degraded by LDL-receptor, despite the fact that in vitro studies have demonstrated a low affinity of Lp(a) to LDL-receptors on macrophages and fibroblasts (1, 20).

The results of our study demonstrate that cardiac rehabilitation training based on continuous aerobic exercise results in a significant reduction in serum lipoprotein(a)

levels both in subjects with considerable hyperlipoproteinemia(a) and in patients with serum Lp(a) levels within normal range (Tab. 3). This favorable influence of training on lipoprotein(a) concentrations was probably associated with low intensity of the applied exercise. In this context, non-significant, favorable changes in serum concentrations of Lp(a) in patients not participating in the rehabilitation program (control group) are difficult to explain. They might result from modifications in the diet (increased intake of soluble cellulose and fish fat) and lifestyle.

As hyperlipoproteinemia(a) is involved in the processes of atherosclerotic plaque formation as well as restenosis after coronary angioplasty (16), the observed decrease in Lp(a) levels during physical training may be of importance in retarding atherogenic process. The study findings support the view of the important role for physical activity in the secondary prevention of ischemic heart disease.

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