Long-term cardiac rehabilitation program favorably influences fibrinolysis and lipid concentrations in acute myocardial infarction

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Abstract

Background and Objective. The control of well-known atherosclerotic risk factors represents the optimal strategy in the prevention of acute coronary syndromes. It was the aim of this work to analyze the effects of a long-term cardiac rehabilitation program on the changes of fibrinolysis parameters and plasma lipid profile in coronary patients.

Design and Methods. The study was carried out in 30 (M/F:22/8, mean age 47 years) survivors of a first acute myocardial infarction (AMI) and in 30 healthy controls who underwent a cardiac rehabilitation program (9 months duration). Samples were taken before, at 3 and 9 months after the beginning of the program to measure: tissue-type plasminogen activator (t-PA) antigen and plasminogen activator inhibitor (PAI-1) activity and antigen. A lipid profile including cholesterol (both HDL and LDL) and lipoprotein(a) was also assessed. The Wilcoxon and Mann-Whitney tests were used for statistical comparisons.

Results. There was a marked decrease of functional PAI-1 after 3 and 9 months as compared with baseline in AMI patients (p<0.01). Results showed a significant increase of HDL-cholesterol (p<0.01) and decrease of lipoprotein(a) levels after the exercise program (p <0.01).

Interpretation and Conclusions. The cardiac rehabilitation program improved fibrinolysis, by reducing the functional levels of PAI-1, and ameliorated the lipid profile by decreasing lipoprotein(a) and increasing HDL-cholesterol in patients with AMI. A long-term cardiac rehabilitation has positive effects on some risk factors for coronary disease.
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Fibrin formation and subsequent thrombus growth at the site of atherosclerotic plaque disruption is the most common cause of acute coronary syndromes.[1] Multiple interacting factors are involved in the development of the atheroma plaque, including disturbed lipid metabolism, endothelial cell damage and disorders of the fibrin balance with persisting fibrin deposits. Several reports have evaluated the possible relationship between deficient fibrinolysis and cardiovascular processes, particularly coronary heart disease (CHD) and atherosclerosis (reviewed in refs. #2-4). Fibrinolysis is the mechanism involved in fibrin degradation through the proteolytic action of the serine protease plasmin.[5] This enzyme originates from the activation of the proenzyme plasminogen by tissue plasminogen activator (t-PA) released into the circulation from the endothelium and rapidly inactivated by the endothelial type plasminogen activator inhibitor (PAI-1). Impaired fibrinolysis may result from either low t-PA or elevated PAI-1 levels (reviewed in refs. #4 and #6). Taking into account the potential link between impaired fibrinolysis and CHD,[7-10] the modification of the fibrinolytic system appears as an attractive therapeutic approach.

It is generally accepted that physical exercise enhances the plasma fibrinolytic activity and induces changes in some hemostatic parameters. An increase in t-PA activity and decrease in PAI-1 and fibrinogen levels have been described in healthy subjects following long-term exercise training.[11,12] It has been suggested that exercise could favorably influence the clinical course of patients with coronary artery disease (CAD) through a reduction of PAI-1 levels.[13,14] Evidence also accumulates indicating that exercise might favorably modify several of the conventional coronary heart disease risk factors including blood lipids, obesity, blood pressure and insulin levels.[15,16]

The aim of this study was to evaluate the influence of a rehabilitation sport program on the t-PA and PAI-1 levels, as well on the lipid profile, in a group of survivors of a first acute myocardial infarction (AMI).

Patients and Methods

Patients

Thirty consecutive outpatients (male/female: 22/8, mean age 47 years) with confirmed myocardial infarction undergoing an exercise test were studied. Results were compared with those obtained in 30 healthy subjects (male/female: 19/11, mean age 49 years)

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with no history of myocardial infarction, diabetes, hypertension, obesity, smoking or medication use.

The *Ethical Committee of the University Clinic of Navarra* approved the study protocol and oral informed consent was obtained from all patients.

Exercise test

All subjects, patients and controls, followed a nine month training program consisting of three weekly sessions (40 minutes/session) where the maximal oxygen uptake, aerobic and anaerobic thresholds were assessed in maximal ergospirometry test using an electrically braked bicycle ergometer. Subjective (Borg scale) or objective (increase in oxygen consumption less than 150 mL per minute despite of increasing workload) tests were used as stopping criteria for the exercise. The training program started within a month from the diagnosis of AMI.

The maximal oxygen uptake was recorded in all patients.

Biochemical analysis

The study was performed before starting the exercise program and again 3 and 9 months after the beginning of the study. Blood was drawn between 8.00 and 9.30 a.m. in patients and controls after 30 minutes rest. Samples were collected by venipuncture from the antecubital vein into 0.13 M trisodium citrate (9:1) and centrifuged at 2000 g for 20 minutes at 4°C. Plasma was immediately prepared by centrifugation and kept on ice or frozen at –70°C until tested.

Tissue-type plasminogen activator (t-PA) antigen was determined with a commercially available monoclonal antibody based ELISA[17] (TintElize t-PA, Biopool, Sweden). PAI activity was measured by adding a certain amount of t-PA to diluted plasma and assessing residual t-PA activity as previously described,[18] using a commercially available kit (Coatest PAI, Chromogenix, Stockholm, Sweden). Inhibitor activity was expressed in units of t-PA inhibited per mL. Plasminogen activator inhibitor-1 (PAI-1) antigen was measured by a commercial ELISA (TintElize PAI-1, Biopool, Sweden) basically following the method described by Declerck *et al.*[19] Lipoprotein(a) [Lp(a)] concentration was determined by enzymoimmunoanalysis using a commercially available ELISA kit (Coaliza Lp(a), Chromogenix,

Sweden).[20] Whole serum cholesterol and triglycerides were measured by standard enzymatic methods. HDL-cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid and Mg^{++}. LDL-cholesterol was calculate according to the Friedewald's formula.

Statistical analysis

Results are expressed as mean ± SD. Comparisons of the levels before and after exercise test within each group were performed by means of the Wilcoxon test (paired values). Comparisons of the levels of the different parameters between control and IAM groups were performed by means of the Mann-Whitney test. Statistical significance was reached at p < 0.05.

Results

The study was carried out in 30 patients of both sexes with a first AMI less than one month before entering to the study. All patients were subjected to a cardiac rehabilitation program during 9 months. The control group consisted of 30 non-smokers, non-obese and normotensive subjects without previous history of coronary disease, who underwent the same exercise program.

Baseline fibrinolytic activity and lipid profile

As shown in Table 1, a significant increase of t-PA antigen and PAI-1 activity and antigen was observed before exercise in the group of patients as compared with the control group (p<0.01). As regards the lipid profile (Table 2), there was a significant elevation of total cholesterol (p<0.05), triglycerides (p<0.01) and LDL-cholesterol (p<0.05) in the patients group. A 3-fold increase in Lp(a) levels was also demonstrated in this group (138.2±71.8 mg/dL) as compared with controls (43.8±21.8 mg/dL) (p<0.01). Levels of HDL-cholesterol were also significantly reduced in the patients group (p< 0.01).

Effects of physical exercise on fibrinolysis parameters

Whereas no significant differences in the t-PA levels were observed in patients and controls at 3 and 9 months after the exercise program as compared to baseline, we found a significant improvement of fib-

Table 1. Fibrinolysis parameters before and after 3 and 9 months, respectively, the cardiac rehabilitation program. Mean±SD is shown.

Parameter	Control			Acute myocardial infarction		
	Basal	3 months	9 months	Basal	3 months	9 months
t-PA antigen (ng/mL)	5.7±3.2	5.3±2.1	6.2±2.2	8.6±4.1°	7.7±2.3	9.1±3.7
PAI-1 activity (U/mL)	8.3±2.9	9.2±6.5	9.4±3.6	19.6±8.9°	12.8±6.2**	13.1±7.8**
PAI-1 antigen (ng/mL)	26.1±14.2	29.4±16.6	29.6±13.1	43.1±21.1°	37.7±12.7	36.9±12.5*

°p < 0.01 with respect to control; *p < 0.05 and **p < 0.01 with respect to values before exercise in both groups.

Table 2. Influence of physical exercise on lipid profile in patients and controls. Values represent the mean±SD.

Parameter	Control			Acute myocardial infarction		
	Basal	*3 months*	*9 months*	*Basal*	*3 months*	*9 months*
Cholesterol (mg/dL)	198.9±24.5	202.3±33.9	205.6±37.1	227.7±43.1°	212.7±33.3	221.6±36.3
Tryglicerides (mg/dL)	72.8±29.2	69.1±24.9	73.4±55.8	153.2±60.3°°	136.6±87.8	131.1±93.7
HDL-cholesterol (mg/dL)	47.1±10.8	50.1±11.8	58.5±14.7**	30.9±9.1°°	35.5±11.3*	40.2±9.7**
LDL-cholesterol (mg/dL)	136.8±20.6	140.9±31.7	139.6±27.1	156.7±44.1°	151.1±32.8	158.7±33.7
Lipoprotein(a) (mg/dL)	43.8±21.8	35.4±19.5	28.9±13.6	138.2±71.8°°	90.4±75.1**	86.3±80.6**

°$p < 0.05$ and °° $p < 0.01$ with respect to control; *$p < 0.05$ and **$p < 0.01$ with respect to values before exercise in both groups.

rinolysis, via reduction of PAI-1 levels, in AMI patients.

Figure 1 shows the behavior of PAI-1 activity and antigen in patients and controls throughout the cardiac rehabilitation program. There was a marked decrease ($p<0.01$) of functional PAI-1 in AMI patients (12.8±6.2 U/mL after 3 months and 13.1±7.8 U/mL after 9 months as compared with baseline value of 19.6±8.9 U/mL). Despite this reduction PAI-1 activity levels still remained significantly higher at the end of the program as compared to control values ($p < 0.01$). A tendency to a reduction in the antigen levels was also observed at 3 months, being slightly significant ($p<0.05$) 9 months after the beginning of the program, although the levels remained significantly higher ($p<0.05$) in relation to controls (Figure 1). No differences in PAI-1 activity or antigen could be detected throughout the program in the control group.

A marked increase of maximal oxygen uptake was observed in both groups 3 and 9 months after exercise. The mean values in AMI patients ranged from 18 mL/kg/min before exercise to 22 mL/kg/min at 3 months ($p<0.001$) and 23 mL/kg/min at 9 months ($p<0.001$).

Other biochemical changes induced by physical exercise

The evolution of the different lipid measurements in control group and AMI patients throughout the rehabilitation program is shown in Table 2. A significant increase in plasma HDL-cholesterol was observed in the AMI patients after 3 ($p<0.05$) and 9 months ($p<0.01$) of exercise as compared with baseline values. That increase was also present in the control group after 9 months. On the other hand, as shown in Figure 2, physical exercise induced a marked decrease ($p<0.01$) in the Lp(a) concentration in the AMI group, both 3 and 9 months after the cardiac rehabilitation program, whereas a slight decrease was observed in the control group at 9 months without reaching statistical significance. However, the Lp(a) levels still remained significantly enhanced and HDL-cholesterol concentrations more reduced in the

group of patients at the end of the program as compared to control values ($p<0.01$).

Discussion

We have evaluated the effects of an exercise test on the t-PA and PAI-1 levels as well as on the lipid profile in a group of patients with CHD. The major findings of this study are that a long-term cardiac rehabilitation program improves fibrinolysis by reducing the functional levels of PAI-1, and reduces the Lp(a) concentrations while increasing HDL-cholesterol in patients with AMI.

Epidemiological and clinical studies have revealed a positive association of impaired fibrinolysis due to abnormally high levels of PAI-1 not only with the extent of CHD but also with the appearance of reinfarction in AMI survivors.[9,10,21] In aggregate, impaired fibrinolysis resulting from increased plasma or plaque PAI-1 might contribute to the development and/or progression of atherosclerosis by promoting thrombosis or matrix deposition.[2,3] Finally, in situ analysis of the atherosclerotic plaque also revealed increased expression of PAI-1.[22]

We, therefore, tried to analyze whether a long-term cardiac rehabilitation program would be able to modify the impaired fibrinolysis. In this study significant fibrinolysis abnormalities as a consequence of increased t-PA antigen and PAI-1 activity and antigen levels were observed in the AMI patients before entering the cardiac rehabilitation program, in agreement with previous reports (reviewed in refs. #4 and 6). However, we found a significant reduction in PAI-1 activity after regular long-term (9 months duration) physical exercise indicating that this training program had beneficial effect on fibrinolysis. Nevertheless, PAI-1 levels did not reach the values observed in the control group, suggesting that the exercise program was not able to completely improve the impaired fibrinolytic response in AMI patients. Similar results were reported by Speiser et al.[23] in individuals with different sporting activities and Estellés et al.,[14,24] after an ergometric test performed 3 and 6 months after AMI. According to our results it is unlikely that a longer term program could further improve the fibri-

nolytic potential in AMI patients.

Although it is generally accepted that physical exercise improves fibrinolytic activity in healthy people[11,25] and in series of patients with CHD,[14,23] we did not observe significant changes in the t-PA antigen levels. There are conflicting results as regards to the exercise-induced changes on fibrinolysis, reporting the resting fibrinolytic activity increases, decreases or remains unchanged.[26-30] It has also been reported that intensive physical exercise in postinfarction patients may actually lead to increased clotting tendency.[31] The great diversity of results is due to the wide variation in training regimens, the differences in the clinical characteristics of patients included, and the methodology applied.

Whereas the reason for the PAI-1 reduction after exercise is not completely understood, the observed increase in the maximal oxygen uptake at 3 and 9 months after the physical training seems to be relevant to explain such reduction. Physical training,

which increases liver blood flow, induces the release of t-PA and improves insulin sensitivity would favor reduced PAI-1 synthesis.[30] On the other hand, since CHD is associated with endothelial dysfunction and altered vascular endothelium generates abnormally higher PAI-1 levels, it could be speculated that physical exercise would improve endothelial function in patients with CHD.[32] It is unlikely that PAI-1 reduction could be ascribed exclusively to the resolution of the acute-phase phenomenon, since we and others have demonstrated that PAI-1 remains elevated months after the acute episode,[9,33] which rules out the possibility that the observed changes could be exclusively attributed to a time-related phenomenon.

When considering the exercise-induced changes in the lipid profile in the studied population we observed increased levels of HDL-cholesterol and a reduction in the plasma Lp(a) concentration, suggesting an additional beneficial effect in AMI through lipid modification.
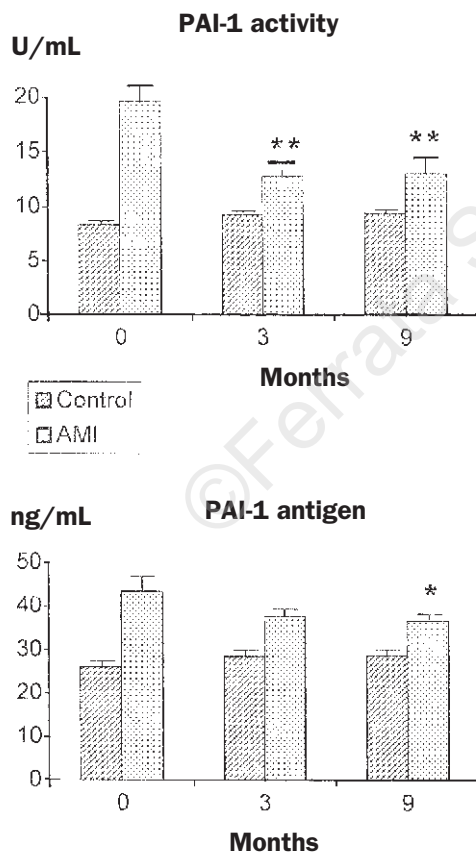

Figure 1. PAI-1 activity (top) and antigen (bottom) in control group and AMI patients before and 3 and 9 months after the cardiac rehabilitation program. Mean ± SEM is shown. *p<0.05 and **p<0.01 with respect to values before exercise.
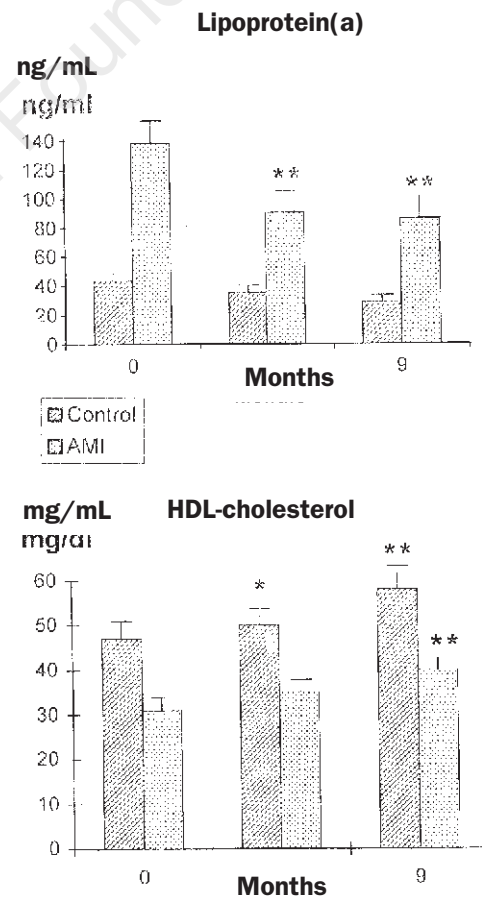

Figure 2. Lipoprotein(a) levels (top) and HDL-cholesterol (bottom) in the control group and AMI patients before and 3 and 9 months after the cardiac rehabilitation program. Mean ± SEM is shown. *p<0.05 and **p<0.01 with respect to values before exercise.

Whereas several reports have shown high Lp(a) levels as a powerful risk factor for coronary disease,[34,35] epidemiological studies suggest that regular physical exercise may reduce cardiovascular risk through a modification of several of the coronary risk factors including blood lipids.[15,16] However, studies analyzing the influence of physical exercise on plasma lipid concentrations in healthy subjects and CHD patients have given contradictory results.[36,37] A recent report exploring the relationship of exercise to Lp(a) levels in patients with insulin-dependent diabetes mellitus showed that physical fitness, measured by V02 max during bicycle ergometer, correlated inversely with Lp(a), suggesting that it may decrease the risk of CHD through modulating lipid levels.[38]

An interesting but unresolved issue is whether the atherothrombotic activity of Lp(a) might be attributed at least in part to an inhibitory role on plasmin formation, by competing with plasminogen for the binding to fibrin.[39] From our results it can be speculated that the significant Lp(a) decrease observed in the AMI group 3 and 9 months after the rehabilitation program would facilitate the binding of plasminogen to fibrin thus accelerating the plasmin generation rate. Whether a reduction in Lp(a) level is associated with a reduction in cardiovascular events, as reported with cholesterol-lowering therapy, has not yet been determined. Finally, our results confirm previous studies showing that exercise is associated with an increase in HDL-cholesterol, thus improving lipid metabolism.[40,41]

Taking all these data together it could be speculated that a controlled cardiac rehabilitation training program ameliorates both PAI-1 and blood lipid composition in coronary patients, possibly through changes in insulin sensitivity and body fat mass.[42,43]

In conclusion, our results strongly indicate that the maintenance of a regular physical exercise program has a beneficial effect in AMI patients by improving both thrombogenic and atherogenic risk factors for coronary disease. Future studies should address the ability of exercise training to modify fibrinolytic variables in other cardiovascular groups and whether other training protocols are capable of improving more significantly the altered fibrinolysis in patients with coronary disease, since despite the exercise-induced improvement, both PAI-1 and Lp(a) still remained above the normal values.

Contributions and Acknowledgements

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