Clinical Studies

Effects of Acute Exercise on Fibrinolysis and Coagulation in Patients With Coronary Artery Disease

Tayfun ACIL,[1] MD, Enver ATALAR,[1] MD, Levent SAHINER,[1] MD, Baris KAYA,[1] MD, Ibrahim C. HAZNEDAROGLU,[2] MD, Lale TOKGOZOGLU,[1] MD, Kenan OVUNC,[1] MD, Kudret AYTEMIR,[1] MD, Necla OZER,[1] MD, Ali OTO,[1] MD, Ferhan OZMEN,[1] MD, Nasih NAZLI,[1] MD, Sirri KES,[1] MD, *and* Serdar AKSOYEK,[1] MD

SUMMARY

Acute physical exertion may trigger an acute coronary syndrome. Furthermore, acute physical exercise may influence hemostatic markers in healthy individuals. However, the effect of acute exercise on blood fibrinolysis and coagulation in patients with coronary artery disease (CAD) is still not well understood.

Nineteen untrained patients with angiographically proven CAD (age, 58 ± 9 years, 12 males), and 25 age- and sex-matched controls without CAD (age, 56 ± 6 years, 16 males) underwent a treadmill exercise test. Global fibrinolytic capacity (GFC) and prothrombin fragment 1 + 2 (F 1 + 2) levels were measured before exercise, at peak exercise, and 2 hours after recovery.

There were no differences between the groups with respect to left ventricular ejection fraction, history of hypertension, body mass index, and serum lipids. Before exercise, GFC was significantly lower in patients with CAD when compared with controls (1.40 ± 0.43 versus 3.28 ± 1.19 μg/mL, respectively; $P < 0.001$). In patients with CAD, F 1 + 2 levels were significantly higher than those of controls (1.15 ± 0.43 versus 0.79 ± 0.10 nmol/L, respectively; $P = 0.002$). In both study groups, GFC levels increased significantly at peak exercise and decreased to baseline values 2 hours after recovery. At peak exercise, F 1 + 2 levels significantly increased in both study groups. However, while F 1 + 2 levels of controls decreased to baseline values 2 hours after recovery (0.79 ± 0.10 versus 0.80 ± 0.10 nmol/L; $P > 0.05$), F 1 + 2 levels of patients with CAD were still significantly elevated (1.15 ± 0.43 versus 1.84 ± 0.06 nmol/L; $P = 0.002$).

Acute exercise increases coagulation and fibrinolysis both in untrained subjects with and without CAD. However, in patients with CAD, the equilibrium between fibrinolysis and coagulation during peak exercise is disturbed in favor of coagulation after recovery.
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Key words: Exercise, Coronary artery disease, Coagulation

From the Departments of [1] Cardiology and [2] Hematology, Hacettepe University School of Medicine, Ankara, Turkey.
Address for correspondence: Tayfun Acil, MD, Başkent Üniversitesi, Adana Araştirma ve Uygulama Merkezi, Dadaloğlu mahallesi, Serin evler, 39. Sokak No: 6, 01250 Yüreğir, Adana, Turkey.
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PREVIOUS studies have found that acute physical exertion may trigger an acute coronary syndrome. One of the possible explanations for this is that acute physical exertion may acutely change the hemostatic milieu in favor of increased coagulation.[1] The preponderance of available data suggests that both the fibrinolytic and coagulative cascades are stimulated by acute exercise in healthy individuals.[2] However, studies evaluating fibrinolytic and/or coagulative changes in response to acute exercise in patients with chronic coronary artery disease (CAD) are sparse.[3-8] Furthermore, differences in exercise protocols, training status of the study subjects, and the analytical methods used for the assessment of the fibrinolytic and/or coagulative system make it difficult to draw a common conclusion from these studies.

Global fibrinolytic capacity (GFC) is a novel assay which reflects the amount of generated D-dimer when the fibrinolysis of a freeze-dried fibrin clot is stopped by introducing aprotinin.[9] *In vitro*, GFC increases in a dose-dependent manner with the addition of tissue-type plasminogen activator (tPA), urinary-type plasminogen activator, prourinary-type plasminogen activator, activated protein C, factor XII, plasminogen, and decreases with the addition of plasminogen activator inhibitor-1 (PAI-1), alpha2-antiplasmin, and histidine-rich-glycoprotein. *In vivo*, GFC is inversely correlated with tPA: Ag and PAI-1. Thus, the GFC assay allows exploration of the fibrinolytic potential of plasma and evaluation of fibrinolytic dysfunctions in a reliable manner. Studies in our laboratory also indicated that GFC is a sensitive method reflecting ongoing subclinical or overt prothrombotic/hypofibrinolytic states, including Behçet's disease and others.[10-13]

The conversion of prothrombin into thrombin is a key event within the coagulation cascade. Through the determination of prothrombin fragment 1 + 2 (F 1 + 2) it is possible to quantify exactly the actual amount of thrombin formed, and hence, the ongoing coagulation process.[14]

The aim of this study was to examine the effect of acute exercise on blood fibrinolysis and coagulation in patients with angiographically proven CAD, by respectively measuring GFC and F 1 + 2 before exercise, at peak exercise, and 2 hours after recovery. The results were compared with 25 age- and sex-matched controls.

METHODS

Study patients: Nineteen patients with angiographically proven CAD (> 50% stenosis of at least one major coronary artery) and 25 age- and sex-matched controls without CAD were included in this study. Controls were selected among volunteers who applied to the outpatient cardiology clinic for routine cardiovascular assessment and were taking aspirin on a daily basis. All control subjects had neg-

ative treadmill exercise tests and echocardiography revealed no segmental myocardial contraction abnormality. Subjects with unstable angina pectoris, atrial fibrillation, peripheral artery disease, diabetes mellitus, obstructive lung disease, malignancy, thyroid disease, hepatic disease, or connective tissue disease were excluded. Regularly exercising subjects, premenopausal women, and subjects taking drugs including warfarin, heparin, corticosteroids, and estrogen hormone were also excluded. All study subjects had to have an echocardiographically determined left ventricular ejection fraction greater than 55%.

Exercise test and blood sampling: All study subjects underwent a treadmill exercise test according to the modified Bruce protocol.[15] All exercise tests were performed in the morning after an overnight fast. All subjects were asked not to smoke at least 24 hours before the exercise test. Blood pressure and a 12-lead ECG were recorded at rest and every minute up to the 10th minute of the recovery period. Venous blood without venostasis was drawn just before exercise, at peak exercise, and 2 hours after the recovery period. A separate venipuncture with a 19-gauge needle was used for each sample. Only direct venipuncture with smooth and rapid withdrawal of blood was considered acceptable, otherwise the needle was removed and a new needle used to perform another venipuncture. Blood samples were discarded if a hematoma developed at the venipuncture site during blood withdrawal. After discarding the first milliliter, the blood was collected into precooled tubes containing Na-citrate. Plasma was obtained by centrifugation at 2300 g for 15 minutes and stored at –80°C until assayed.

Blood assays: Plasma GFC levels were measured by the semiquantitative macrolatex agglutination technique using a commercially available assay (Global Fibrinolytic Capacity STA Liatest D-Di, Diagnostica Stago, Asnieres, France). The main principle of the GFC method is that, in the presence of a constant and limited amount of exogenous tPA, D-dimer generated from a standardized fibrin quantity is measured.[9] For this purpose, a standardized fibrin tablet (containing silica and completely lacking plasminogen) is introduced into a 200 μL plasma sample supplemented with a constant and limited amount of tPA. The mixture is then incubated for 1 hour at 37°C. Fibrinolysis is thereafter stopped by introducing 50 μL of an excess of aprotinin. The amount D-dimer is then measured.

Prothrombin fragment 1 + 2 was measured by an enzyme immunoassay using a commercially available kit (Enzygnost F 1 + 2 micro, Dade Behring, Marburg, Germany).

Statistical analysis: Data analysis was performed using Statistical Package for Social Sciences v 7.5 for Windows (SPSS, Inc., Chicago, IL). Data are given as the mean ± SD for numerical variables and as the number (%) for nominal variables. Student's *t* test and, whenever appropriate, the Mann-Whitney U test was used to analyze differences between CAD patients and controls. The chi-square

test was used for analyses of nominal variables. A one-way analysis of variances (ANOVA) was used to compare intragroup levels of GFC/F 1 + 2 measured just before exercise, at peak exercise, and 2 hours after recovery. When ANOVA indicated the presence of a significant difference, Tukey's post-hoc test was used to ascertain which mean differences were statistically significant. A P value < 0.05 was considered to be statistically significant.

RESULTS

The characteristics and serum lipids of the study subjects are given in Table I. There were no differences between patients with CAD and controls with respect to age, sex, left ventricular ejection fraction, hypertension, body mass

Table I. Characteristics and Serum Lipids of the Study Subjects

	CAD (n = 19)	Control (n = 25)	P
Age (years)	58 ± 9	56 ± 6	NS
Male/female (%)	63/37	65/35	NS
LVEF (%)	61 ± 4	63 ± 4	NS
Hypertension (%)	68	47	NS
Body mass index (kg/m^2)	24.0 ± 1.3	25.3 ± 1.3	NS
Total cholesterol (mg/dL)	203 ± 38	198 ± 45	NS
HDL cholesterol (mg/dL)	45 ± 7	42 ± 8	NS
Triglycerides (mg/dL)	188 ± 65	180 ± 68	NS
Medications (%)			
Nitrate	53	0	0.001
Aspirin	100	100	NS
Beta-blocker	58	27	NS
Calcium-channel antagonist	47	13	NS
Angiotensin-converting enzyme inhibitor/ Angiotensin II receptor antagonist	37	13	NS
Statin	53	27	NS

CAD indicates coronary artery disease and LVEF, left ventricular ejection fraction.

Table II. Global Fibrinolytic Capacity and Prothrombin Fragment 1 + 2 Levels of the Study Subjects

	Baseline		Peak exercise		2 hours after recovery	
	CAD	Control	CAD	Control	CAD	Control
GFC (μg/mL)	1.40 ± 0.43	3.28 ± 1.19*	2.20 ± 0.83**	4.4 ± 1.17**	1.47 ± 0.47	3.24 ± 1.04
F 1+2 (nmol/L)	1.15 ± 0.43	0.79 ± 0.10*	1.94 ± 0.08**	1.95 ± 0.08**	1.84 ± 0.06**	0.80 ± 0.10

GFC indicates global fibrinolytic capacity; F, prothrombin fragment; and CAD, coronary artery disease. *P < 0.05, CAD versus Control. **P < 0.05, intragroup comparisons with values before exercise.

index, total cholesterol, HDL-cholesterol, and triglyceride levels. There were no differences between patients with CAD and controls with respect to medications including aspirin, beta-blockers, calcium-channel antagonists, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, and statins. However, only patients with CAD were taking nitrates. The peak heart rate achieved during exercise was 152 ± 11/min for patients with CAD and 157 ± 10/min for controls ($P > 0.05$). The systolic blood pressure at peak exercise was 175 ± 16 mmHg for patients with CAD and 173 ± 15 mmHg for controls ($P > 0.05$).

GFC and F1 + 2 levels of the study subjects before exercise, at peak exercise, and 2 hours after recovery are summarized in Table II. Figures 1 and 2 demonstrate the changes in GFC and F 1 + 2 levels, respectively, in response to acute exercise. Before exercise, GFC levels of patients with CAD were significantly lower than those of controls. Before exercise, F 1 + 2 levels of patients with CAD were significantly higher than those of controls. In both study groups, GFC levels increased significantly at peak exercise and decreased again to prebaseline values 2 hours after recovery. At peak exercise, F 1 + 2 levels significantly increased in both study groups with respect to F 1 + 2 levels before exercise. However, while F 1 + 2 levels of controls decreased to baseline values 2 hours after recovery, F 1

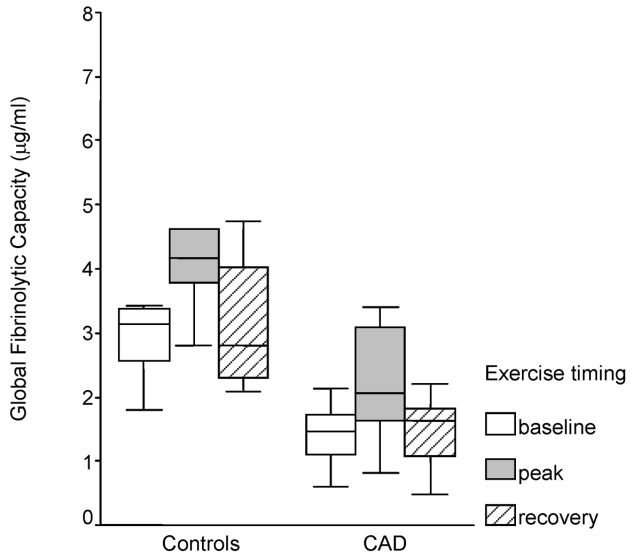

Figure 1. Changes in global fibrinolytic capacity (GFC) levels of the study subjects in response to acute exercise. Note that GFC levels are significantly increased at peak exercise and return to baseline values 2 hours after recovery in both coronary artery disease (CAD) patients and controls.

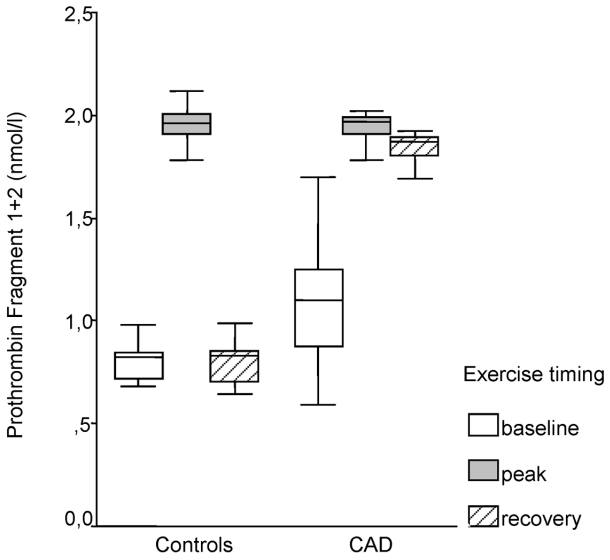

Figure 2. Changes in prothrombin fragment 1 + 2 (F 1 + 2) levels of the study subjects in response to acute exercise. Note that F 1 + 2 levels are significantly increased at peak exercise in both coronary artery disease (CAD) patients and controls. However, while F 1 + 2 levels of controls decreased to baseline values after recovery, F 1 + 2 levels of patients with CAD are still significantly elevated when compared to values before exercise.

+ 2 levels of patients with CAD were still significantly higher when compared to levels before exercise.

DISCUSSION

The present study has several findings. Firstly, patients with angiographically proven CAD had a higher resting coagulation, but a lower resting fibrinolytic activity when compared to controls. Secondly, fibrinolysis increased with acute exercise and then decreased to baseline levels 2 hours after recovery both in patients with CAD and controls. Thirdly, the coagulative activity increased with exercise both in patients with CAD and controls. However, while 2 hours after recovery coagulative activity returned to baseline values in control subjects, it still remained high in patients with CAD. Thus, in patients with CAD acute exercise disturbed the equilibrium between fibrinolysis and coagulation in favor of coagulation.

Various fibrinolytic and coagulative factors have been identified as independent cardiovascular risk factors in prospective studies. Increased levels of fibrinogen, factor VII, PAI-1, or decreased levels of tPA were shown to be associated with increased cardiovascular risk.[16-20] The findings of the present study are in line with these studies, as baseline F 1 + 2 levels are higher and GFC levels are lower in patients with CAD in comparison to subjects without CAD.

Previously, 2 studies investigated the influence of exercise tolerance test on hemostatic variables in patients with CAD, and, similar to the present study, found increases in both fibrinolytic and coagulative parameters at peak exercise.[5,6] Both studies concluded that acute physical exercise is not harmful to patients with CAD in regard to hemostasis. However, in these studies, hemostatic markers were not measured in the recovery period. In the present study, significantly elevated F 1 + 2 levels could be still identified 2 hours after recovery in patients with CAD, although fibrinolytic activity returned to baseline levels at this time.

In the present study, we found that there was an increase both in fibrinolytic and coagulative activity at peak exercise in control subjects. Furthermore, we found that this activation in coagulation and fibrinolysis returned to baseline 2 hours after recovery. Although these findings are in line with the general agreement that acute physical exercise leads to various degrees of activated blood coagulation and enhanced fibrinolysis in healthy subjects, they contrast with the findings of studies which suggested that the exercise-induced activation can persist for some hours after recovery in healthy subjects.[21-24] Differences in exercise protocols, training status of the study subjects, and the hemostatic markers used for the assessment of the coagulative and fibrinolytic system may lead to inconsistent results in studies evaluating the effect of exercise on hemostatic markers.[2]

Study limitations: As only untrained patients with CAD were included in this study, the results should not be extrapolated to patients with a different training status. Coronary artery disease is often accompanied by other comorbid conditions, including systolic heart failure, atrial fibrillation, peripheral artery disease, diabetes mellitus, and obstructive lung disease. Therefore, the results of this study can not be extrapolated to CAD patients with these conditions either.

Conclusion: The results of the present study suggest that acute exercise increases both fibrinolytic and coagulative activity in untrained subjects with and without CAD. Moreover, in patients with CAD, the equilibrium between fibrinolysis and coagulation during peak exercise is disturbed in favor of coagulation 2 hours after recovery.

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