Clin. Cardiol. 12, 255-258 (1989)

Does Ergometric Stress Test Induce a Procoagulative Condition in Patients with Previous Myocardial Infarction?

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Summary: A regularly scheduled physical training program seems to have antithrombotic effects. Moreover, the hemostatic changes occurring in patients with coronary artery disease during acute exercise have not been clearly elucidated. Since stress testing is routinely performed in clinical cardiology, it would be helpful to assess whether patients with coronary artery disease are exposed to acute coronary thrombosis during or soon after sustained physical exercise. This study was designed to evaluate the effect of acute physical exercise (stress test by bicycle ergometer) on blood coagulation in a group of patients with previous myocardial infarction, and to determine whether the antithrombotic therapy commonly administered favorably influences hemostatic equilibrium. Our results suggest that exercise testing is not harmful to patients with previous myocardial infarction in regard to hemostasis and fibrinolysis and that antithrombotic therapy reduces postexercise increase in platelets.

Key words: myocardial infarction, antithrombotic therapy, hemostasis, stress test

Introduction

It has been reported that regularly scheduled physical training appears to have antithrombotic effects. In fact, physical conditioning activates fibrinolysis and decreases platelet aggregability.[1-4] In spite of these data, studies on the effect of stress test on blood coagulation and fibrinolysis yielded conflicting results.[5-12] Particularly, the hemostatic changes in patients with coronary artery disease during acute exercise are not clearly elucidated. Some investigators suggested that the majority of patients with myocardial ischemia show increased platelet activity and decreased fibrinolysis at rest,[13] whereas others were unable to demonstrate such changes.[8,14]

Since sustained physical exercise is routinely performed for clinical evaluation in cardiology, it would be helpful to assess whether or not patients with coronary artery disease are exposed to acute coronary thrombosis during or soon after stress testing.

This study was designed to evaluate the effect of acute physical exercise on blood coagulation and fibrinolysis in a group of patients with previous myocardial infarction and to determine whether the antithrombotic therapy commonly administered to postinfarction patients favorably influences the hemostatic equilibrium.

Materials and Methods

We studied 28 asymptomatic postinfarction male patients who gave full informed consent to undergo this study. Thirteen patients (Group A) aged 48–75 (mean age 61 ± 9) had not taken any antithrombotic drug for 20 days. Fifteen patients (Group B) aged 33–78 (mean age 55 ± 13) were under treatment with oral ticlopidine 250 mg/day and subcutaneous calcium heparin 12,500 IU once a day. No significant difference was demonstrated in age by *t*-test between the two groups. Each subject underwent exercise testing on a Siemens-Elema bicycle ergometer beginning exercise at 25 W. The workload was increased by 25 W every 3 min until either the theoretical maximal heart rate was reached or until the onset of symptoms or electrocardiographic changes indicative of effort-induced myocardial ischemia, or until fatigue. Lead V_5 of the electrocardiogram (ECG) was monitored continuously during

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Received: November 30, 1988
Accepted: February 23, 1989

the exercise and during the first 10 min of recovery. Blood pressure and a 12-lead ECG were recorded at rest and every 2 min up to the 10th minute of the recovery period. Blood was collected at rest, just before exercise, and at peak exercise. 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 and then immediately placed in crushed melting ice.

Hemostasis and coagulation have been assessed by the evaluation of the following parameters: platelet count, beta-thromboglobulin (βTG), plasminogen, prothrombin time (PT), activated partial thromboplastin time (APTT), Factor VIII coagulant ($VIII_C$), Factor VIII-related antigen ($VIIIR_{Ag}$), fibrinogen, Factor V, Factor VII, C protein, antithrombin III (ATIII), and fibrinopeptide A (FPA). $VIII_C$ activity was assessed by the one-stage method.[15] $VIIIR_{Ag}$ dosage was carried out with a quantitative electroimmunoassay method.[16] Factor V and Factor VII were assayed by one-stage assay. Fibrinogen was measured according to Clauss.[17] FPA dosage was performed with a radioimmunoassay kit supplied by Mallinckrodt (St. Louis, MO).[18] ATIII was assayed using a synthetic chromogenic peptide substrate (S-2238, Kabi Diagnostica).[19] Plasminogen dosage was carried out with chromogenic peptide substrate method (88-2251, Kabi Diagnostica).[20] Plasma βTG was assayed on platelet-poor plasma collected with the anticoagulant mixture supplied by Radiochemical Center Amersham in accordance with the method of Bolton *et al.*[21] Results were analyzed by multivariate analysis of variance (MANOVA).

Results

Stress Test

Only two Group A patients experienced exercise-induced ischemia showing a flat or downsloping ST-segment depression (>2mm) 0.08 s or larger after the J point on the ECG. The remaining 26 terminated the test because of leg pain or fatigue. The duration of exercise was similar in the two groups. The peak heart rate achieved during exercise was 137±25 for Group A and 129±26 for Group B (difference not significant). The rate-pressure product at peak exercise was 23,811±5,830 for Group A and 23,602±5,372 for Group B (difference not significant).

Hemostasis and Fibrinolysis

The data for each parameter are shown in Table I, whereas statistically significant changes in blood coagulation and fibrinolysis demonstrated by MANOVA are summarized in Table II.

Baseline values. As expected, patients receiving antithrombotic therapy showed significantly longer APTT, higher plasminogen and ATIII levels, and significantly lower FPA values. It is interesting that even though treated with antithrombotic therapy they did not show lower levels of βTG.

Peak exercise values. At peak exercise, PT and APTT were significantly shorter whereas fibrinogen, ATIII, plasminogen, and platelet number were significantly higher than before exercise for all the subjects studied.

Interaction between therapy and exercised. Patients receiving antithrombotic therapy showed a lesser increase in platelet number after stress testing than patients without therapy. This was the only significant effect of therapy

TABLE I Summary of the parameters evaluated before and after exercise

	Group A		Group B	
Parameter	Before	After	Before	After
PT (s)	14±2	13±2	14±2	14±2
APTT (s)	38±6	36±4	43±9	40±6
Fibrinogen (mg/dl)	315±72	338±67	316±79	331±99
Plasminogen (%)	92±13	101±19	106±24	119±27
VIII C (%)	136±45	153±54	163±71	188±58
VII (%)	94±19	97±15	93±17	92±25
V (%)	81±14	82±11	73±19	74±13
βTG (ng/ml)	89±92	75±62	89±47	79±48
FPA (ng/ml)	21±38	20±20	6±7	6±5
PC (%)	101±22	108±22	116±25	114±23
AT III (%)	98±18	105±21	113±22	120±19
PLT ($x10^3/mm^3$)	270.6±68.3	300.5±62.6	287.7±67.3	301.4±66

Group A: Subjects without therapy; Group B: Subjects with therapy. All values expressed as mean±SD.

TABLE II Summary of the statistical analysis by MANOVA

Parameter	Main effect (therapy)	Main effect (exercise)	Interaction
PT	NS	$p<0.05\downarrow$	NS
APTT	$p<0.05\uparrow$	$p<0.05\downarrow$	NS
Fibrinogen	NS	$p<0.05\uparrow$	NS
Plasminogen	$p<0.05\uparrow$	$p<0.001\uparrow$	NS
FPA	$p<0.05\downarrow$	NS	NS
AT III	$p<0.05\uparrow$	$p<0.05\uparrow$	NS
PLT	NS	$p<0.001\uparrow$	$p<0.05^a$

[a]Significantly lesser increase after exercise in patients receiving antithrombotic therapy.
Only parameters with at least one significant difference have been included in the table. ↑=Increased value; ↓=decreased value.

on the parameters evaluated at peak exercise demonstrated by MANOVA.

The hemostatic and coagulative response of the two patients experiencing ischemic changes of the ECG during the stress test parallelled that of the remaining patients.

Discussion

Myocardial ischemia, severe arrhythmias, and even sudden death induced by acute exercise, are well documented.[22-26] Experimental and clinical data suggest that platelets may contribute to these adverse clinical events.[28,29] In fact, autopsy examinations showed platelet aggregates in the coronary circulation.[30] On the other hand, to our knowledge, there is no agreement among authors about the effect of acute strenuous exercise on blood coagulation and fibrinolysis both in patients with coronary artery disease and in healthy subjects. Increased release of the tissue plasminogen activators without significant changes of the inhibiting factors could account for enhanced fibrinolysis after strenuous exercise. It has been demonstrated that short-term vigorous exercise is capable of increasing platelet concentration in peripheral venous blood.[31-33] Furthermore, a postexercise rise in ADP-induced aggregation, βTG, and fibrinogen levels and a decrease in PT and APTT have been documented in normal subjects.[3] It has been demonstrated that following exercise, the dynamic equilibrium between hemostasis and fibrinolysis changes in the direction of an increased clotting tendency and that physical fitness seems to enhance the rate of fibrinolysis.[7] The results of our study indicate that stress testing activates both clotting tendency and fibrinolysis. No significant difference in the parameters evaluated was found between those two subjects who showed ischemic response to stress testing and the remaining patients with coronary artery disease. Our findings suggest that exercise testing for the assessment of patients with coronary artery disease does not seem to affect hemostasis and coagulation negatively. In fact, we observed both enhanced (see the behavior of APTT, PT, fibrinogen, and platelet count in Table II) and decreased blood clotting tendency (see the behavior of ATIII, plasminogen in Table II). On the other hand, the enhanced blood clotting tendency was not linked to increased FPA levels, a commonly considered index of fibrin formation. Likely, the increased ATIII activity induced by exercise is responsible for the nonincrease in fibrin formation. In fact, ATIII is the primary plasma inhibitor of blood coagulation enzymes and is a member of a large superfamily of related proteins that includes several serine proteinase inhibitors.[34] One more evidence that stress testing does not induce fibrin formation is the fact that we did not detect increased levels of activated C protein (a thrombin-activated glycoprotein). Perhaps the rare occurrence of adverse events as ventricular fibrillation and sudden death during or soon after stress test might be due to the lack of fibrin formation as documented by low levels of FPA. These adverse events could not be related to changes of the hemostatic balance or, if related, could be due to a severe pre-exercise impairment of the hemostasis.

In basal conditions, therapy with ticlopidine and heparin does not influence βTG values and platelet count, but enhances plasminogen and decreases FPA levels, showing a protective antithrombotic activity in patients with coronary artery disease. The fact that ticlopidine does not affect plasma levels of βTG is not new. In fact, in a previous article we demonstrated that ticlopidine is effective in inhibiting platelet aggregation, but not in inhibiting platelet-release reaction as demonstrated by unchanged levels of βTG even after 30 days of treatment at the daily dose of 250 mg.[35] FPA is a product of proteolysis of fibrinogen by thrombin; its significantly lower levels found after antithrombotic therapy reduce blood clotting tendency. We confirmed the already well-documented increase in circulating platelets after maximal exercise.[31-33] Several authors claim and other deny that exercise activates platelets.[36-41] The findings of this study are consistent with data suggesting that exercise does not affect platelet activity, as demonstrated by the nonincrease in βTG levels. It is hard to explain why therapy with heparin and ticlopidine reduces the increase of platelet count after physical exercise. Further studies are needed to confirm this observa-

tion suggesting new evidence for the use of these drugs in the secondary prevention of ischemic disease.

All in all, our findings suggest that stress testing does not seem to be harmful to patients with regard to hemostasis and fibrinolysis and that antithrombotic therapy improves hemostatic function in basal conditions and positively affects the hemostatic balance in postinfarction patients who undergo stress test.

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