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Activation of Coagulation and Fibrinolysis during Maximal Physical Exercise

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Introduction

Changes in haemostatic parameters induced by physical exercise have been described in the literature by many authors (1–6). There is general agreement that physical exercise elicits a rise in the factor VIII clotting activity and in the fibrinolytic activity of blood. The latter has been attributed to a release of plasminogen activator into the circulating blood, which accounts for the shortening of the euglobulin clot lysis time, an increase in the lysis zone on fibrin plates (7) and also for an increase in extrinsic plasminogen activator as measured by immunoradiometric assay (8).

Most authors claim that a significant increase in the fibrinolytic activity does occur only after exhaustive physical exercise.

At present, the general view is that despite increased level of plasminogen activator, plasmin formation only occurs in the presence of fibrin (9). The most sensitive parameter of fibrin formation in vivo is the level of fibrinopeptide A (11). Only a few reports in the literature have studied fibrinopeptide A levels.

In this study we investigated several parameters of coagulation and fibrinolysis during graded exercise, in order to elucidate to which degree coagulation and fibrinolysis are activated and to see whether there are mechanisms counteracting this activation state of the haemostatic reaction.

Materials and Methods

Exercise protocol: We investigated six healthy male volunteers. Exercise was performed on a bicycle ergometer, starting with a work load of 100 Watt, every three minutes the load was increased by 50 Watt until exhaustion. Blood was processed to obtain platelet-poor plasma in a way to minimize in vitro changes.

Lactate concentrations were determined in serum by an enzymatic-electrochemical method. Racine 1975 (10).

Fibrinopeptide A levels: The FPA levels were measured by radio-immuno-assay, using a simplified procedure as has been described by Van Hulsteijn et al. (11).

Plasminogen activator levels were measured in a bovine plasminogen-rich fibrin plate and expressed in mm² lysis zone (7).

Antithrombin III and α_2 -macroglobulin were quantified in citrated plasma by immunodiffusion in partigen plates according to prescriptions of the manufacturer (Behring Werke A.G., Marburg/Lahn, West Germany).

Haematocrit, thrombin clotting time, reptilase time, FVIII clotting activity, fibrinogen and fibrinogen degradation products were measured according to standard procedures.

Statistics: a paired two-sides student's T test was applied.

Results and Discussion

The results are summarized in Table 1. The lactate concentration rose significantly in all subjects. The haematocrit level showed a mean increase of 7.5%. Fibrinogen levels increased in parallel with the haematocrit.

The thrombin clotting time did not change during exercise. Fibrinogen degradation products were undetectable in an Ouchterlony immunodiffusion method. However, after exercise we found very high levels of fibrinopeptide A (FPA), suggesting thrombin formation and partial proteolysis of fibrinogen by thrombin. The applied sampling procedure excludes the possibility of an important contribution of thrombin formed after sampling. We speculate therefore that thrombin formation in vivo occurs during exercise.

Table 1

N = 6	Mean values and range			p-value	
	before		after		
fibrinogen	2.6 gr/l	(2.2– 2.9)	2.8 gr/l	(2.3– 3.1)	N.S.
FPA	5.6 ng/ml	(1.6–14.8)	157.4 ng/ml	(9.5–1200)	< 0.01
Thrombin time	18.2 sec.	(17.1–20.3)	18.3 sec.	(16.9–19.6)	N.S.
Reptilase time	17.0 sec.	(15.4–19.8)	17.5 sec.	(16.3–20.4)	< 0.02
FVIII:C	0.84 U/ml	(0.55–1.04)	2.4 U/ml	(1.55–3.00)	< 0.05
FDP	negative		negative		
Pig-act.	163.4 mm ²	(49–272)	306.4 mm ²	(83–573)	< 0.001
AT III	33.4 mg%	(31.2–36.8)	37.1 mg%	(34.5–42.3)	< 0.001
α_2 -M	211.9 mg%	(190–242.3)	261.1 mg%	(218.3–294.6)	< 0.001
Lactate	1.8 mmol/l	(1.27–2.94)	10.6 mmol/l	(8.14–12.58)	< 0.001
Haematocrit	42.8	(38–44)	46.0	(40–51)	< 0.01

FPA: fibrinopeptide A

FDP: fibrin(ogen) degradation products

Pig-act. plasminogen activator

ATIII: antithrombin III

 α_2 -M: α_2 -macroglobulin

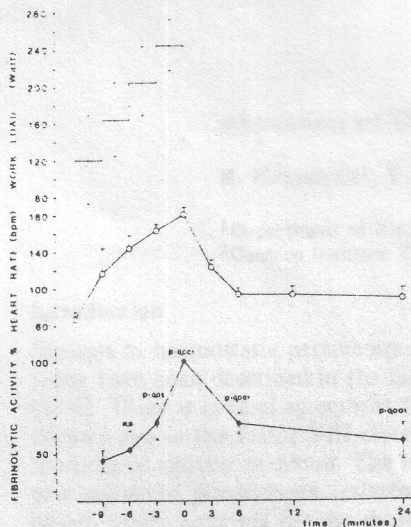


Fig. 1 Changes of heart rate and fibrinolytic activity during and after exhaustive physical exercise. Time in minutes before and after cessation of exercise; fibrinolytic activity in % of maximal fibrinolytic activity, heart rate in beats per minute and work load in Watts. Mean values and S.E.M. are expressed

The antithrombin III concentration increased by 11% in a quantitative determination, concomitant with the rise in haematocrit. Our results are in agreement with the observation of Hyers (4) who found a 20–30 fold increase in FPA after physical exercise, but in disagreement with the findings of Marsh et al. (6). These conflicting results may be explained by different intensities of exercise. Factor VIII clotting activity (FVIII:C) increased from 0.84 U/ml to 2.4 U/ml. An exercise-induced increase of factor VIII:C has been reported by several authors in the literature (1). Brown (1) described a disproportionate rise in factor VIII procoagulant activity and suggested that this can be due to thrombin formation as a consequence of physical exercise. This would be compatible with our findings.

In fig. 1 data on the fibrinolytic activity, heart rate and work load are summarized. As can be seen from this figure, a gradual increase in the fibrinolytic activity occurred during the last nine minutes before exhaustion was reached. Other groups have reported that only very strenuous exercise will raise the fibrinolytic activity. Davis et al. (3) postulated that below 70 to 80% of the maximum heart rate little change can be expected. Previously, Rosing et al. (5) had observed that 30 minutes of treadmill exercise with an intensity corresponding to 40% maximal oxygen uptake, caused only a slight increase in fibrinolytic activity, which remained within normal daily fluctuations. However, recently Wiman et al. (12) demonstrated a gradual increase of plasminogen activator concentration during exercise. After cessation of exercise the fibrinolytic activity dropped fast as has been described by others (4, 5). After exercise both plasmin- α_2 antiplasmin and plasmin- α_2 macroglobulin complexes were demonstrated by crossed immunoelectrophoresis (results not shown). Though this suggested the formation of plasmin, no fibrin(ogen) degradation products could be demonstrated. The formed plasmin is presumably rapidly neutralized. These results suggest that upon maximal physical exercise activation of both the coagulation and the fibrinolytic pathways occur. If these changes are partially due to plasmin formation in vitro, it must be concluded that these changes are enhanced by exercise. Recently we discovered that after exercise free fast acting in-

hibitors of plasminogen activator disappear (13). In the absence of these inhibitors some plasmin may be formed, even when no fibrin is present (14). Regular strenuous physical exercise may deplete endothelial stores of plasminogen activator (15), leaving the possibility of fibrin deposition without securing its removal.

It remains to be established if this short lasting state of activation of the haemostatic reaction is unfavourable, especially in arteriosclerotic patients.

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