Oral contraceptives and fibrinolysis among female cyclists before and after exercise

INGE A. HUISVELD, ANNELIES J. H. HOSPERS, MARJOLIJN J. E. BERNINK, MARIETTE W. A. BIERSTEKER, WIETZE B. M. ERICH, AND BONNO N. BOUMA
Departments of Physiology and Haematology, State University of Utrecht, Utrecht 3521 GG, The Netherlands

HUISVELD, INGE A., ANNELIES J. H. HOSPERS, MARJOLIJN J. E. BERNINK, MARIETTE W. A. BIERSTEKER, WIETZE B. M. ERICH, AND BONNO N. BOUMA. *Oral contraceptives and fibrinolysis among female cyclists before and after exercise.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 53(2): 330–334, 1982.—The effect of oral contraceptives on a number of plasma fibrinolytic variables and antithrombin III was studied in 20 highly trained women before and immediately after exhaustive exercise on a bicycle ergometer. Two groups were studied, 11 women using an oral contraceptive agent (OCA group) and 9 women not using an oral contraceptive (control group). Factor XII, prekallikrein, plasminogen, α_2-antiplasmin, and antithrombin III activities were determined in plasma as well as a number of cardiovascular, respiratory, and metabolic components. Resting values showed a significantly higher level of prekallikrein and plasminogen in the OCA group compared with the control group. Exercise plasma values of components of the fibrinolytic system were significantly higher than resting values in both groups. However, when corrected for plasma volume changes, the exercise levels of prekallikrein and antithrombin III were significantly decreased in the OCA group only, whereas α_2-antiplasmin exercise level was significantly lower in both groups. Our results indicate that use of OCA even with an estrogen dosage as low as 30 μg has an effect on resting and exercise fibrinolytic variables; an effect, however, which does not seem to interfere with maximal performance in trained women.

factor XII; prekallikrein; plasminogen; α_2-antiplasmin; antithrombin III; hemoconcentration

IN SPORTS more and more top trained women are using oral contraceptive agents (OCA). It is therefore important to assess whether the combination of exertion and the use of OCA has any adverse effect on physical performance of trained female athletes. Both exercise (6, 9–11, 28) and OCA (5, 8, 22, 29), as well as the combination of the two (15, 16), are known to induce changes in the hemostatic and fibrinolytic mechanisms. These changes are usually attributed to either an increase or a decrease in the levels of the various components. However, no unanimity as to the extent and direction of changes of the respective mechanisms exists as yet, and conflicting results are still reported (9, 16, 24). We think that this may be due in part to differences in physical conditioning of the subjects under investigation. It is generally accepted that untrained individuals and highly or even moderately trained athletes show different physiological reaction patterns to exercise. This may also be true for the hemostatic and fibrinolytic responses. Another factor that may be responsible for discrepancies in results of various studies is that changes in plasma volume which occur with exercise are not uniformly accounted for. Most authors do not correct for this phenomenon. However, when results are interpreted in terms of an absolute increase or decrease in the level of high-molecular-weight components involved in the process, corrections for changes in plasma volume should be applied.

We studied the effect of oral contraceptives on a number of plasma components of the fibrinolytic system and on antithrombin III in highly conditioned women. Two groups of female athletes were exercised on a bicycle ergometer under identical conditions. The OCA group was composed of women who had been using OCA for more than a year. The control group was composed of women who had never used OCA. Factor XII, prekallikrein, plasminogen, α_2-antiplasmin, and antithrombin III were determined in resting and exercise plasma samples. Changes in plasma volume were calculated for each individual, and exercise fibrinolytic and antithrombin III data were corrected for hemoconcentration.

SUBJECT DESCRIPTION

Twenty top trained female cyclists including participants in the 1979 world championship, after presentation of the study design, gave their consent to participate. They were divided into two groups on the basis of the use of oral contraceptives. The OCA group consisted of 11 women (mean age 23.9 ± 4.4 yr) who had been using OCA for more than 12 mo. Seven athletes used OCA composed of 30 μg ethinylestradiol and 150 μg norgestrel, and the other four used a combination of 50 μg ethinylestradiol and 1 mg lynestrenol. OCA were taken for 21 or 22 consecutive days during one menstrual cycle. The control group was composed of nine women (mean age 19.7 ± 2.3 yr) who had never used OCA. All participants trained intensively for at least 3 h/day. Anthropometric characteristics are given in Table 1.

METHODS

Body composition. Percent body fat was calculated according to the formula of Brozek et al. (7) from body

TABLE 1. *Anthropometric characteristics of the participants*

	OCA Group (n = 11)	Control Group (n = 9)
Age, yr	23.9 ± 4.4	19.7 ± 2.3
Height, m	1.70 ± 0.05	1.70 ± 0.08
Weight, kg	58.9 ± 4.9	64.7 ± 5.2
Body fat, %	20.6 ± 4.1	21.4 ± 5.5
Lean body mass, kg	46.7 ± 3.4	50.8 ± 5.0

Values are means ± SD. OCA, oral contraceptive agents.

density as measured by underwater weighing. The volume of air in the lungs at the moment of underwater weighing was determined with the bag-in-box He-dilution method (27). Lean body mass was then calculated.

Bicycle ergometer test. The subjects were exercised to exhaustion while performing an incremental work-load test on a bicycle ergometer (Lode, Groningen). This was followed by a recovery period of 6 min during which a decreasing load was presented. Details of the test are given in Fig. 1. Intensity of the maximal performance was indicated by a combination of heart rate >180 beats/min, respiratory quotient >1.01, and an inability to continue the test. QRS intervals of the electrocardiogram (ECG) were measured electronically and converted to heart rate. Respiratory rate was determined by means of a thermistor in the inspiratory tube of the mouthpiece. Both heart rate and respiratory rate were recorded continuously. ECG recording (Elema-Schönander cardiograph) and gas sampling were performed during the last minute of each step. The volume of the expired air collected in Douglas bags was measured and corrected to BTPS. The composition of the air was analyzed by Godart paramagnetic O_2 and CO_2 infrared absorption analyzers and expressed as STPD. All tests were performed in the morning hours after a light breakfast. Participants were tested in the first half of each individual's menstrual cycle.

Blood sampling and analysis. Venous blood samples were drawn with the subject in an upright position just before the start of the exercise test and immediately after termination of peak exercise, i.e., in the 1st min of the recovery period. Blood was collected from an antecubital vein by clean venipuncture using a 1.2-mm-bore needle and sampled in the following sequence: *1*) the first 2 ml were discarded; *2*) 9 ml were collected in a plastic tube containing 1 ml of 3.8% sodium citrate; *3*) 5 ml were collected in a disodium ethylenediaminetetraacetic acid-coated tube for hemoglobin, hematocrit, and lactic acid determinations.

Citrated blood was immediately centrifuged (4×10^3 *g*) for 10 min at room temperature. Platelet-poor plasma was then divided into small aliquots, snap frozen in liquid nitrogen, and stored at −70°C until tested for factor XII, prekallikrein, plasminogen, α_2-antiplasmin, and antithrombin III activity. The clotting activity of factor XII was determined using the partial thromboplastin time assay as previously described (13). Chromogenic peptide substrates were used to assess amidolytic activity of the following factors: prekallikrein according to Kluft et al. (19) with Chromozym PK (Boehringer Mannheim); plasminogen and α_2-antiplasmin with S-2251 (Kabi); and antithrombin II with S-2238 (Kabi) according to manufacturer's instructions.

The results of the fibrinolytic components and of antithrombin III were expressed as percent of the amount present in 1 ml of a normal plasma pool from 40 healthy donors. Reference plasma was also stored at −70°C. Hemoglobin (Hb) was measured spectrophotometrically by the cyanmethemoglobin method. Hematocrit (Hct) was determined in quadruplicate by spinning blood-filled capillary tubes for 5 min at 1.5×10^4 *g*. Lactic acid concentrations were measured enzymatically (lactate test, Boehringer Mannheim). Plasma volume changes were calculated from resting and exercise Hct values. According to van Beaumont (2), who postulated a formula by which short-term plasma volume changes (ΔPV) can be calculated from pre- (pr) and post- (po) exercise values of Hct

$$\%\Delta PV = [100/(100 - Hct_{pr})] \times [100(Hct_{pr} - Hct_{po})/Hct_{po}]$$

STATISTICAL ANALYSIS

Means and standard deviations were calculated, and the results were analyzed with the Student's *t* test for paired and independent samples. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The cardiovascular and respiratory data obtained at rest and following exercise (Table 2) indicated that both groups were well matched with respect to physical conditioning and reaction to exercise. The maximum oxygen uptake ($\dot{V}O_2$) of 3.48 ± 0.38 $l \cdot min^{-1}$ for the OCA group and 3.64 ± 0.35 $l \cdot min^{-1}$ for the control group is in good agreement with the values given by Åstrand and Rodahl (1) for endurance-trained women, indicating a high aerobic training level.

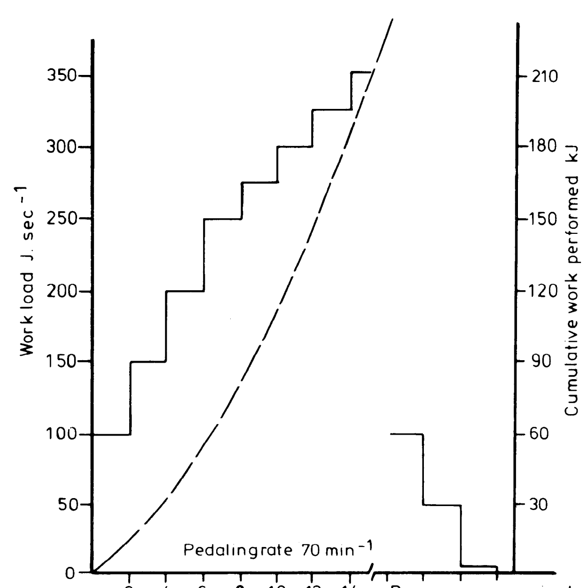

FIG. 1. Time-load schedule followed during increased-work-load test. *Dashed line* indicates cumulative (i.e., total) work performed.

Maximum heart rates of 191 ± 7 and 194 ± 3 beats·min^{-1}, maximum $\dot{V}O_2$ per lean body mass of 75.0 ± 9.7 and 71.8 ± 5.0 ml·min^{-1}·kg^{-1}, and respiratory quotients of 1.08 ± 0.05 and 1.11 ± 0.10 for OCA and control groups, respectively, were indicative of the exhaustive intensity of the exercise. The mean duration of the test was 10.6 ± 1.5 min for the OCA group and 11.6 ± 0.5 min for the control group. This was not significantly different. During exercise the Hct increased from 0.42 ± 0.02 to 0.46 ± 0.02 in the OCA group and from 0.41 ± 0.03 to 0.45 ± 0.03 in the control group. Hb showed an increase from 8.5 ± 0.7 to 9.3 ± 0.7 mmol·l^{-1} and from 8.4 ± 0.6 to 9.2 ± 0.6 mmol·l^{-1} in OCA and control groups, respectively. The same degree of hemoconcentration was seen in both groups (Table 2).

Activity of the fibrinolytic plasma components and of antithrombin III are presented in Table 3.

Preexercise results. Comparison of the resting fibrinolytic and antithrombin III data revealed significantly higher prekallikrein ($P < 0.02$) and plasminogen ($P < 0.001$) activities in the group of women who used OCA.

Exercise results without correction for hemoconcentration. Strenuous exercise resulted in a significant increase in the activity of all fibrinolytic variables and of antithrombin III in both groups. The percentage change that occurred with exercise was not significantly different in the two groups except for plasminogen, which showed a higher increase ($P < 0.01$) in the OCA group (Table 4).

Exercise results after correction for hemoconcentration. To eliminate the effect of an increase in concentration of high-molecular-weight substances due to hemoconcentration, exercise data were corrected for the changes in plasma volume as they occurred in each individual. The results thus obtained showed a significant decrease in prekallikrein ($P < 0.001$), α_2-antiplasmin ($P < 0.001$), and antithrombin III ($P < 0.01$) in the OCA group. The control group demonstrated a significant decrease in α_2-antiplasmin level ($P < 0.05$) only. Prekallikrein decreased significantly more ($P < 0.05$) with exercise in the OCA group than in the control group (Table 4). Although the results obtained from athletes using 30 and 50 μg were comparable with respect to their fibrinolytic response, the size of the groups was too small to justify any conclusions.

TABLE 2. *Cardiovascular, respiratory, and metabolic values at maximum exercise*

	OCA Group (n = 11)	Control Group (n = 9)
Heart rate, beats·min^{-1}	191 ± 7	194 ± 3
$\dot{V}O_2$, l·min^{-1}	3.48 ± 0.38	3.64 ± 0.35
$\dot{V}O_2$/body mass, ml·min^{-1}·kg^{-1}	59.5 ± 8.0	56.4 ± 4.2
$\dot{V}O_2$/lean body mass, ml·min^{-1}·kg^{-1}	75.0 ± 9.7	71.8 ± 5.0
Respiratory quotient	1.08 ± 0.05	1.11 ± 0.10
Lactic acid, mmol·l^{-1}	8.6 ± 1.4	8.6 ± 1.7
ΔHct, %	9.74 ± 3.53	9.75 ± 3.20
ΔHb, %	9.71 ± 3.32	9.79 ± 3.98
ΔPlasma volume Hct corrected, %	−15.02 ± 4.77	−14.89 ± 4.02

Values are means ± SD. OCA, oral contraceptive agents; $\dot{V}O_2$, oxygen uptake; Hct, hematocrit; Hb, hemoglobin.

DISCUSSION

The aim of this study was to evaluate the effect of the use of OCA on the factor XII-dependent fibrinolytic system and on antithrombin III in highly trained women at rest and immediately after strenuous exercise. The effects of exercise and of OCA on blood coagulation and fibrinolysis have been extensively investigated in untrained individuals. Shortening of partial thromboplastin times (9, 11, 18, 28) and changes in the activities of a number of coagulation factors (6, 9, 18) after moderate and strenuous exercise have been reported. Increases in fibrinolytic activity as measured by euglobulin lysis time, fibrin plate lysis, and the activities of various fibrinolytic components during exercise (10, 11, 20) have also been described. In addition the use of OCA has been observed to result in comparable changes in hemostatic and fibrinolytic activities (12, 15–17), which are often associated with an increased risk of thromboembolic complications.

We studied the effects of OCA on the fibrinolytic system and on antithrombin III in two groups of highly conditioned women who were well matched in their physiological response to ergometer testing (see exercise results in Table 2). Of the variables we determined, factor XII and prekallikrein play an important role not only in the intrinsic, i.e., factor XII-dependent coagulation pathway, but also in the intrinsic fibrinolytic system by the direct activation of plasminogen to plasmin (4). α_2-Antiplasmin serves as the major inhibitor of plasmin (26). Antithrombin III inhibits not only activated coagulation factors such as factor XIIa and kallikrein but may also inhibit plasmin when α_2-antiplasmin level decreases (26).

Comparison of the resting plasmas revealed a significantly higher prekallikrein and plasminogen and a

TABLE 3. *Resting and exercise values with respect to fibrinolytic activity*

	OCA Group (n = 11)					Control Group (n = 9)				
	R	EU	EC	P EU/R	P EC/R	R	EU	EC	P EU/R	P EC/R
Factor XII	132 ± 21	154 ± 20	131 ± 22	<0.002	NS	110 ± 31	128 ± 37	110 ± 32	<0.05	NS
Prekallikrein	112 ± 12	119 ± 17	100 ± 13	<0.05	<0.001	94 ± 18	102 ± 20	88 ± 18	<0.01	NS
Plasminogen	117 ± 15	136 ± 16	115 ± 12	<0.001	NS	85 ± 11	95 ± 9	82 ± 8	<0.002	NS
α_2-Antiplasmin	110 ± 7	122 ± 8	103 ± 8	<0.001	<0.001	116 ± 9	128 ± 10	111 ± 7	<0.01	<0.05
Antithrombin III	112 ± 12	123 ± 11	104 ± 9	<0.01	<0.01	114 ± 7	127 ± 9	109 ± 8	<0.002	NS

Values are means ± SD expressed as percent of amount present in 1 ml of a normal plasma pool. OCA, oral contraceptive agents. R, resting data; EU, exercise data not corrected for hemoconcentration; EC, exercise data corrected for hemoconcentration; NS, not significant. $P < 0.05$ was considered significant.

TABLE 4. *Changes in fibrinolytic variables with maximum exercise*

	EU			EC		
	OCA Group	Control Group	*P*	OCA Group	Control Group	*P*
Factor XII	21.4 ±16.1	17.7 ±15.6	NS	−1.18 ±17.1	−0.3 ±16.1	NS
Prekallikrein	6.6 ±5.8	7.8 ±5.8	NS	−12.6 ±5.7	−6.1 ±8.1	0.05
Plasminogen	18.8 ±9.9	9.4 ±5.7	0.01	−1.9 ±10.3	−3.4 ±5.5	NS
α_2-Antiplasmin	11.6 ±6.5	11.9 ±8.5	NS	−7.0 ±5.0	−5.8 ±7.4	NS
Antithrombin III	11.1 ± 9.8	13.1 ±8.2	NS	−7.8 ±8.1	−4.4 ±8.5	NS

Values are means ± SD expressed as percent change from resting level. EU, data not corrected for hemoconcentration; EC, data corrected for hemoconcentration; OCA, oral contraceptive agent; NS, not significant. $P < 0.05$ was considered significant.

slightly higher (not significant) factor XII level in the OCA group. These observations are in agreement with the results of various authors (8, 9, 15, 16). Gordon et al. (12) reported not only an increase in factor XII in women using OCA, but demonstrated in addition a decrease in C1-esterase inhibitor (C1-INH). Our recent results with respect to trained athletes are in agreement (17). C1-INH inhibits not only the activated first component of complement but also activated factor XII and kallikrein. A decrease of C1-INH levels in combination with an increase in factor XII, prekallikrein, and plasminogen, as is the case in the OCA group, may make the fibrinolytic system more susceptible for activation. In contrast to many reports (3, 5, 29) we were unable to demonstrate lower antithrombin III levels in the OCA group. An explanation for this phenomenon could be that the intermittent decrease in antithrombin III as it occurs during exercise, i.e., regular training sessions, may have led to a relatively increased production.

Strenuous exercise resulted in a significant increase in all plasma protein components under study (Table 3). The change in plasminogen with exercise was significantly higher in the OCA group. Physical exertion of short duration is known to be attended with transvascular fluid shifts (13, 23) resulting in a decrease in plasma volume. The percent change in total protein content remains essentially unchanged during this exercise period (13). To correct for hemoconcentration we calculated our exercise fibrinolytic data as suggested by van Beaumont (2). The average Hct increase in our experiment was 9.7% for both groups. This is quite considerable in comparison with results of other investigators who studied changes in hemostatic variables, but not unusual for well-conditioned individuals (13). Poller et al. (21) found an increase of 5.2% after a 400-m run, but from their study no conclusions can be drawn as to tbe relative intensity of the performance. Davis et al. (10) reported changes of 7% following exhaustive exercise on a bicycle ergometer, and Hedlin et al. (16) mentioned a Hct increase of 5–6% following a submaximal performance on a treadmill for approximately 5 min. Few authors (10, 16), however, applied corrections for hemoconcentrations occurring with exercise, if a plasma volume decrease was mentioned at all. Application of the formula of van Beaumont (2) on the individual exercise values showed mean plasma volume changes of −14.89 and −15.02% for the OCA group and the control group, respectively. Table 3 shows how the exercise results are affected when we corrected our data for the hemoconcentration, and this may explain at least in part the discrepancies reported in other studies.

When corrected for hemoconcentration exercise factor XII levels in both groups did not differ significantly from resting levels, which is in agreement with the findings of Collen et al. (9) but at variance with those of Iatridis and Ferguson (18) who noted a considerable increase of 318% following an exhaustive treadmill test. No significant changes in plasminogen levels were demonstrated by us or by other authors (9, 24). The fact that no changes occurred with exercise could indicate that conversion and production of factor XII and of plasminogen were balanced as was demonstrated by Collen et al. (9) for plasminogen. Their turnover studies revealed an increase in the catabolic rate of plasminogen during exercise while the plasma concentration remained constant. Prekallikrein, α_2-antiplasmin, and antithrombin III decreased significantly in the OCA group, while α_2-antiplasmin showed a significant decrease in the control group only. Since no significant change in prekallikrein levels following exercise was observed by us or by Saito et al. (25), the effect of OCA is reflected in the significant decrease in exercise level as seen in the OCA group only. This again is in accordance with the lower C1-INH activity, which may lead to a facilitated kallikrein formation and a subsequent activation of plasminogen. The potentiating effect of OCA on plasminogen activation is also reflected in the more (although not significantly) pronounced decrease of the inhibitors α_2-antiplasmin and antithrombin III in the OCA group.

The results of our study indicate that an enhanced fibrinolytic activity following exercise is reflected in a decreased α_2-antiplasmin level. OCA seems to potentiate this effect as is demonstrated by a more pronounced decrease in prekallikrein, α_2-antiplasmin, and antithrombin III levels. No adverse effects of OCA on physical performance of trained athletes were demonstrated.

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