Effect of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men

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Van den Burg, P. J. M., J. E. H. Hosppers, M. Van Vliet, W. L. Mosterd, B. N. Bouma, and I. A. Huisveld. Effect of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men. J. Appl. Physiol. 82(2): 613–620, 1997.—The effect of 12 wk of submaximal training on hemostatic variables was studied in 20 young sedentary men (Tr) and 19 nontraining matched controls (Con). After training, a more pronounced increase in factor VIII coagulant activity (P < 0.01), reflected in a decrease in activated partial thromboplastin time (P < 0.01) during maximal exercise, was seen. Both basal plasminogen activator inhibitor 1 antigen (PAI-1 Ag) and activity (PAI-1 Act; P < 0.05), as well as basal and exercise-induced tissue-type plasminogen activator antigen (t-PA Ag; P < 0.05), were decreased after training. The overall effect on fibrinolysis was reflected in an increase in the t-PA Act/t-PA Ag ratio in the Tr group. In contrast, during the same period (February–June), the Con group demonstrated an increase in basal PAI-1 Ag and PAI-1 Act (P < 0.05), together with an increase in basal and exercise-induced t-PA Ag (P < 0.05). Both basal and exercise-induced t-PA Ag were unchanged, but t-PA Act/t-PA Ag was decreased (P < 0.05) in the Con group. We conclude that physical training promotes both coagulation and fibrinolytic potential during exercise and may reverse unfavorable seasonal effects on fibrinolysis.

exercise; training; season; hemostasis

Physics INACTIVITY is associated with an enhanced risk for cardiovascular disease (6). Detrimental effects of the sedentary lifestyle have been observed on blood pressure, serum lipoprotein profiles, and carbohydrate metabolism. Adjustment of confounding effects of these traditional risk factors has indicated that physical inactivity is also an independent risk factor for coronary disease (4). To what extent thrombogenic processes are influenced by physical (in)activity is not clear.

Coagulation and fibrinolysis constitute two important physiological opponents in the process of hemostasis and thrombus formation. Activation of the coagulation system induces the formation of fibrin, whereas activation of the fibrinolytic mechanism results in the degradation of fibrin clots. Both systems are regulated by a balance between activators and inhibitors. Several acute stimuli, such as strenuous exercise (27) and mental stress (17), are known to enhance the activity levels of coagulation and fibrinolysis.

The effect of physical conditioning, i.e., regular exercise training, on coagulation potential has received little attention, with conflicting results. A training-related decrease in clotting time has been reported (20); however, in another study (11) this increase in coagulation activity could not be confirmed.

In contrast, the effect of physical conditioning on fibrinolysis, using clot lysis and fibrin plate lysis assays, has been studied extensively. As early as 1967, Menon et al. (23) reported an enhanced exercise-induced increase in overall fibrinolytic activity in trained athletes in comparison with untrained subjects. This finding has been confirmed by the majority of investigators (11, 25, 27, 34), who observed increases in fibrinolytic potential suggestive of an enhanced fibrinolytic reserve in trained subjects. Recently, more sophisticated tests for the determination of individual fibrinolytic factors have become available. Results from cross-sectional studies indicate that fibrinolytic activity (tissue-type plasminogen activator activity (t-PA Act)) (26) at rest and during venous occlusion (euglobulin clot lysis time) (34) is increased as a result of physical training. Stratton et al. (26) suggest that a decrease in the plasminogen activator inhibitor 1 (PAI-1) is responsible for the training-related effects.

Many other factors such as age (1), anthropometry (16, 30), dietary habits and body mass reduction (14), and diurnal (19) and seasonal variations (5) have recently been reported to affect plasma levels of a number of hemostatic factors. These observations stress the importance of an extremely careful experimental design when the effects of acute exercise and physical training on the hemostatic balance are to be studied. We were interested in the effect of moderate physical training on coagulation and fibrinolysis, two important opponent systems that play a role in thrombogenesis and atherosclerosis.

We meticulously standardized our experimental design and included a group of nontraining matched control (Con) subjects in the study. Plasma levels of coagulation and fibrinolytic variables were determined both at rest (basal) and under exercise and recovery conditions. Participants were tested before and after 6 and 12 wk of training, respectively, at a submaximal [60–70% maximal O2 uptake (Vo2max)] exercise intensity.

METHODS
Participants

Sedentary men between 20 and 30 yr of age were recruited by an advertisement in a local newspaper. Respondents were asked to fill in a questionnaire, providing information about their daily activity pattern and other health and lifestyle factors. Subjects were characterized as sedentary when they worked in sedentary jobs and did not participate in any form
of sporting activity during leisure time. Other inclusion
criteria were no sporting activities during the previous five
years, apparent health, no medication, being a nonsmoker,
and only moderate alcohol use. Forty participants were
selected and randomly divided into a trained group (Tr; n = 20)
and a Con group (n = 20). The study was approved by the
Ethical Commission of the Utrecht University Hospital, and
participants joined the study after written informed consent
was obtained.

Training and Test Procedure (Fig. 1)
Training. The Tr group participated for 12 wk (February-
June) in supervised training sessions that were performed in
an exercise room in the laboratory. Participants exercised
twice a week for 1 h at a constant submaximal level. The work
rate was adjusted continuously for each individual during
each training session to maintain a heart rate corresponding
with that at 60–70% VO2 max. At this submaximal level, on the
basis of recommendations for recreational sporting activities,
clear training-induced changes can be expected (2).

Anthropometry and diet analysis. Height, body mass, and
four skinfolds were measured as described before (3), and
body mass index (BMI; kg/m2) and fat percent were calculated.

Participants completed a 3-day food record (two weekdays
and one weekend day) before the start, after 6 wk, and in the
last week of the program. These data were analyzed by an
experienced dietician for the macronutrients proteins, fats,
carbohydrates, and fibers. The results were expressed as
percentage of the total caloric intake.

The experimental design of the study is presented in Fig. 1.

VO2 max test. VO2 max was determined with an increasing
workload test on a cycle ergometer (Lode, Groningen, The
Netherlands). Subjects started with an initial load of 1 W/kg
(60 rounds/min), which was increased every 2 min by 1 W/kg.
When a heart rate (HR) of 150 beats/min was attained, the
load was increased 0.5 W/kg every 2 min until participants
reached their maximal performance. Participants were encour-
gaged to exert themselves maximally. Maximal performance
was indicated by the inability to continue, predicted maximal
HR (HRmax) (2), and by a respiratory exchange ratio > 1.15.
The total work capacity was calculated, at each step during
the VO2 max test, as the product of load (W = J/s) and time (s).
The total amount of work (J) is expressed per kilogram of
body mass. Ventilatory parameters were determined with an
Oxycon-β (Mijnhardt, The Netherlands), which was cali-
bated before and after each test. The electrocardiograph was
monitored continuously by using three leads (CC5, CM5, and
CB5) with a megacart electrocardiograph (Siemens, The
Netherlands). In addition, HRmax and the HR at 60 and 70%
VO2 max, respectively, were recorded. These parameters were
used for the standardization of the exercise test (Ex-test)
procedure (see below) and training intensity.

Fig. 1. Training (Tr) and control (Con) groups were tested before (B; February) and after 6 wk (T6; April) and 12 (T12; June) wk of
training. In 1st wk (filled bars) of each test period, maximal O2 uptake (VO2 max) tests, anthropometric measurements, and diet analy-
sis were performed. In 2nd wk (open bars), exercise test and blood
collection were performed. All 3 VO2 max and exercise tests were
scheduled at same time of day and same day of week for each
individual.

Ex-test. This standardized test (Fig. 2), designed for the
collection of blood samples at rest and during (sub)maximal
exercise and recovery, was scheduled between 8.00 and 10.00
A. M. Participants refrained from drinking alcohol and coffee
for 12 h before the test. On the day of the Ex-test, they had a
light breakfast, consisting of tea and toast.

Ex-tests were performed on a cycle ergometer and com-
passed four consecutive periods: 1) the initial 10 min, during
which the load was gradually increased until the HR was
reached that corresponded with the participant’s HR at 70%
VO2 max; 2) 15-min submaximal exercise, during which the
load was continuously adjusted to maintain a constant HR
corresponding with 70% VO2 max; 3) a period during which the
load was increased in four steps of 1 min to attain the HR
responding with the HR at each participant’s VO2 max; and
4) recovery, which comprised 10 min of active recovery
whereby participants cycled at a load of 1 W/kg, followed by
15-min passive recovery during which the participants re-
maine upright.

During this Ex-test, blood was drawn at 0, 10, 15, 20, and
25 min immediately after maximal performance and at 5, 10,
15, and 25 min of the recovery, respectively.

Blood-collection procedure. Blood was drawn via a cannula
(Vasculor 2, 18 gauge, Viggo, Sweden) that was placed in the
antecubital vein. The first 2 ml of each blood sample were
voided, and the cannula was flushed with 3 ml saline after
each sampling procedure. Blood was collected in tubes contain-
ing chilled 3.8% (0.11 mmol/l) trisodium citrate and in
EDTA-coated tubes. For the determination of t-PA, 1 ml of
citrate blood was immediately mixed with an equal amount
of sodium acetate buffer (0.2 mol/l, pH 3.9). Blood for PAl-1
antigen (PAI-1 Ag) determinations was collected in tubes
containing citric acid, theophillin, adenosine, and dipryd-
damole (Becton-Dickinson). Within 10 min after collection, plasma
was separated by centrifugation at 2,000 g for 20 min at 4°C,
divided into small aliquots of 200 µl, snap-frozen in liquid
nitrogen, and stored at −80°C.

Hematologic parameters. Samples from each individual
obtained before, after 6 wk, and after 12 wk of training were
tested simultaneously in one run to eliminate the intra-assay
variation. Each assay run comprised an equal number of Tr
and Con subjects.

Coagulation activity of factor VII (FVII:c), factor VIII
(FVIII:c), factor IX (FIX:c), factor XII (FXII:c), and fibrinogen
(Fbg) as well as activated partial thromboplastin time (APTT)
and prothrombin time were determined, according to the
manufacturer’s instructions, with a laser-nephelometric cen-
trifugal analyzer (ACL 200, Instrumentation Laboratory,
IJsselstein, The Netherlands). Deficient plasmas were ob-
tained from Organon Teknika Nederland (Boxtel, The Nether-
lands). Cephaline, calcium chloride, and calcium thromboplas-
tin were provided by Instrumentation Laboratory. Blood for the normal plasma pool was donated by 40 healthy men.

$\text{t-PA Ag}$ was measured with a commercially enzyme-linked immunoassay (Imulyse t-PA Biopool, Umeå, Sweden), and $\text{t-PA Act}$ was determined by using a commercially available kit (CoaSet t-PA, Chromogenix, Sweden). Basal $\text{PAI-1 Ag}$ and $\text{PAI-1 Act}$ were determined with CoaSet PAI-1 and CoaSet PAI (Chromogenix), respectively. Urokinase-type plasminogen activator antigen (u-PAAg) was determined as described before (9).

Hemoglobin and hematocrit were determined with a Sysmex NE 8000 analyzer (Toa Medical Electronics, Japan). Changes in plasma volume were calculated according to Dill and Costill (8).

Statistics

Statistical analyses were performed with Superior Performing Software Systems (SPSS), version 4.01. Deviations from normality of distribution were checked for each variable. The distributions of $\text{FVIII:c}$, APTT, t-PA Ag, t-PA Act, and u-PAAg were slightly skewed, and, for these variables, log10 transformations were performed. Repeated-measures multivariate analyses of variance were used for analysis of each variable. Differences between $\text{Tr}$ and Con and differences within and between $\text{Tr}$ and Con in time (training) were calculated. Results are expressed as means ± SE. Two-sided probability values were considered significant at $P < 0.05$.

RESULTS

Participants

Due to an outdoor injury, one participant in the Con group did not complete the program. The remaining 39 subjects completed all the tests before, during, and after intervention. $\text{Tr}$ and Con were comparable with respect to age (25.8 ± 0.7 and 24.5 ± 0.8 yr, respectively), body mass, BMI, and fat percentage, and no changes were observed in either group during the experimental period (Table 1).

Consumption of macronutrients did not differ from the normalized Dutch Food Standards in either group and did not change during the intervention (Table 2).

Training Indexes

Close attendance of the subjects in the $\text{Tr}$ group resulted in an extremely high compliance (98% training sessions).

$\text{VO}_{2\text{max}}$ and total work capacity were increased in April at 6 wk (T6) and in June at 12 wk (T12) of training (11 ± 2 and 24 ± 4%, respectively, $P < 0.05$) and showed additional (although not significant) increments at T12 (14 ± 2 and 36 ± 4%, respectively) in the $\text{Tr}$ group. The Con group did not demonstrate any change in these parameters (Table 1).

Hemostatic Variables in February Before (B) Training Intervention

At B, no significant differences between the $\text{Tr}$ and Con groups were observed in basal (preexercise) and exercise-related plasma levels of any of the hemostatic variables under study (Figs. 3–5, Table 3).

Hemostatic Variables at T6 and T12

Coagulation (Figs. 3 and 4). Basal plasma levels. No change was observed in the basal levels of any of the coagulation parameters under study during the entire intervention period, in either the $\text{Tr}$ or the Con group.

Exercise-related plasma levels. During exercise and recovery, plasma levels of $\text{FVIII:c}$ tended to be higher at T6 and were significantly enhanced ($P < 0.01$) at T12 in the $\text{Tr}$ group. These changes were reflected in a significant ($P < 0.01$) training-related decrease in APTT at T12.

No change in $\text{FVII:c}$ or APTT was seen in the Con group during the same period (Fig. 3). Exercise-related plasma levels of $\text{FVII:c}$, FXI:c, FXII:c, Fbg, and prothrombin time did not change during intervention in either the $\text{Tr}$ or Con group (see Fig. 4).

Fibrinolysis (Table 3, Fig. 5). In contrast to the relative stability of the clotting factors in the Con group, opposite changes in fibrinolytic components were observed during the intervention (February-June) period in the $\text{Tr}$ and the Con group.

Basal plasma levels (Table 3). At T6 no significant changes were observed in basal levels of any of the fibrinolytic components in either the $\text{Tr}$ or Con group.

At T12 a divergent pattern was seen in the $\text{Tr}$ and Con groups. Basal $\text{PAI-1 Ag}$, $\text{PAI-1 Act}$, and $\text{t-PA Ag}$ decreased in the $\text{Tr}$ group and increased in the Con group. Although the effects per se did not reach significance levels within the groups, the differences between $\text{Tr}$ and Con became significant ($P < 0.05$). Fibrinolytic

Table 1. Anthropometric and exercise characteristics of participants

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<tr>
<td>Body mass, kg</td>
<td>76 ± 2</td>
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<td>BMI, kg/m²</td>
<td>22.6 ± 0.3</td>
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<td>Body fat, %</td>
<td>19.9 ± 0.9</td>
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<td>$\text{VO}_{2\text{max}}, l/min$</td>
<td>3.62 ± 0.09</td>
<td>3.74 ± 0.08</td>
<td>3.98 ± 0.07</td>
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<td>$\text{HR}_{\text{max}}, \text{beats/min}$</td>
<td>190 ± 2</td>
<td>192 ± 2</td>
<td>191 ± 2</td>
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<tr>
<td>$\text{TWC}, J/kg$</td>
<td>1.62 ± 0.08</td>
<td>1.73 ± 0.11</td>
<td>2.04 ± 0.10</td>
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<tr>
<td>HB, mmol/l</td>
<td>9.3 ± 0.11</td>
<td>9.4 ± 0.10</td>
<td>9.3 ± 0.11</td>
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<tr>
<td>Hct</td>
<td>0.41 ± 0.01</td>
<td>0.42 ± 0.01</td>
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Values are means ± SE; $n = 39$ subjects. B, before training (February); T6, 6th wk of training (April); T12, 12th wk of training (June); $\text{Tr}$, training group; Con, control group; $\text{VO}_{2\text{max}}$, maximum $\text{O}_{2}$ uptake; BMI, body mass index; HR, heart rate; TWC, total work capacity; HB, hemoglobin; Hct, hematocrit. *Significant increase in $\text{Tr}$ group from B to T6, $P < 0.05$. 
efficiency, represented as the t-PA Act/Ag ratio, tended to increase in the Tr group and decrease in the Con group. Again, the effects per se did not reach significant levels within the groups, but the differences between Tr and Con groups became significant (P < 0.05).

**Exercise-related plasma levels (Fig. 5).** Comparable changes to those observed in basal levels were seen in the exercise-related levels of t-PA Ag and t-PA Act/Ag.

The percent increase in t-PA Ag during maximal performance was not changed in either the Tr (B, T6, and T12: 280 ± 33, 310 ± 34, and 291 ± 26%, respectively) or the Con groups (B, T6, and T12: 268 ± 25, 316 ± 35, and 296 ± 28%, respectively). The results indicate that the changes in basal levels, rather than the magnitude of the exercise-induced changes, are responsible for the significant differences between Tr and Con groups at T12.

**Fig. 3.** Tr and Con groups were tested at B (A), T6 (B), and T12 (C). Values are means ± SE for n = 20 subjects (Tr) and n = 19 subjects (Con). j, Tr group; r, Con group. Acute exercise induces a significant increase in factor VIII coagulation activity (FVIII:c) and a significant decrease in activated partial thromboplastin time (APTT) at B, T6, and T12 (not shown). Max, maximal exercise performance; NP, normal plasma pool. *Significant difference within Tr group and between Tr and Con groups in exercise-induced changes as a result of training (B vs. T12), P < 0.05.

**Discussion**

Physical inactivity is associated with an almost twofold increased risk of developing coronary heart disease (4) and constitutes an important modifiable lifestyle risk factor. More recently, in a joint position statement of the World Health Organization, physical inactivity has been declared an independent risk factor for coronary heart disease (4, 21). A sedentary lifestyle may result in the development of cardiovascular complications through various pathophysiological mechanisms. Regular physical exercise has been shown to produce several beneficial effects. Favorable changes in

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<th>Table 2. Dietary analysis: macronutrients</th>
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<td>Energy, MJ</td>
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<td>Carbohydrate, En%</td>
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<td>Fiber, g/MJ</td>
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Values are means ± SE; n = 39 subjects. En%, percentage of total energy intake. No significant differences between or within Tr and Con groups at B or during training were observed.

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cholesterol metabolism (36) and blood pressure regulation (33) have been reported. We were interested in the effect of moderate physical training in subjects not accustomed to any form of recreational physical exertion.

Because the precise nature of the mechanism by which physical activity exerts its protective effect is not known, we have focused our attention on components of the hemostatic balance. Coagulation plays a role in the process of clot formation, whereas fibrinolysis is responsible for clot resolution.

Beneficial effects of strenuous physical training on fibrinolytic activity in athletes have been reported (26–28, 34) predominantly in cross-sectional designs. Well-designed longitudinal studies are scarce. In contrast to the fibrinolytic system, the coagulation system has so far received little attention (27).

In the present study, the effect of physical conditioning on components of both coagulation and fibrinolysis was investigated. A Tr group of sedentary men participated in a highly standardized test and training program, whereas a group of matched men served as Con.

Acute exhaustive exercise is known to induce an increase in both coagulation and fibrinolytic activity. During the subsequent recovery period, a sharp fall in fibrinolytic activity parallel to a persistent coagulant activity is observed. This phenomenon may constitute an additional risk factor for coronary thrombosis in susceptible persons (32).
The results of the present study indicate that the training-induced increase in physical fitness is associated with a significantly enhanced coagulation activity. During maximal exercise and recovery, the magnitude of the increase in FVIII:c was significantly enhanced. This enhancement was reflected in a more pronounced shortening of the APTT. A high correlation ($r = 0.58$) was observed between the training-induced increase in $V\text{O}_{2\text{max}}$ and the training-induced changes (increase with respect to decrease) in FVIII:c and APTT during exercise. These results underscore those of Korsan-Bengtsson et al. (20) obtained in a cross-sectional study. They investigated 722 men (mean age 54 yr) and reported that individuals with a higher degree of physical activity had shorter clotting times. This training-related enhanced hypercoagulability during maximal exercise

### Table 3. Basal level of fibrinolytic variables

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<td>Tr</td>
<td>Con</td>
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<td>Tr</td>
<td>Con</td>
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<tr>
<td>PAI-1 Ag, ng/ml</td>
<td>40 ± 7</td>
<td>38 ± 6</td>
<td>39 ± 9</td>
<td>39 ± 7</td>
<td>30 ± 3</td>
<td>49 ± 7*</td>
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<tr>
<td>PAI-1 Act, IU/ml</td>
<td>3.7 ± 1.4</td>
<td>2.8 ± 1.6</td>
<td>3.8 ± 1.3</td>
<td>3.7 ± 1.7</td>
<td>3.0 ± 0.8</td>
<td>6.1 ± 1.8*</td>
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<td>t-PA Ag, ng/ml</td>
<td>4.5 ± 0.4</td>
<td>4.9 ± 0.6</td>
<td>4.0 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>5.1 ± 0.6*</td>
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<tr>
<td>t-PA Act, IU/ml</td>
<td>1.3 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
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<tr>
<td>t-PA Act/Ag</td>
<td>0.34 ± 0.05</td>
<td>0.38 ± 0.05</td>
<td>0.38 ± 0.07</td>
<td>0.40 ± 0.06</td>
<td>0.39 ± 0.06</td>
<td>0.31 ± 0.05*</td>
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Values are means ± SE; $n = 39$ subjects. PAI-1, plasminogen activator inhibitor; Ag, antigen; Act, activity; t-PA, tissue-type plasminogen activator; IU, international unit. *Significantly different between Tr and Con groups at T12, $P < 0.05$. 
and recovery could account for cardiovascular events observed after exhaustive exertion (21) in persons with an increased risk profile.

Gris et al. (12) described a decrease in FVII:c after training; however, additional analysis revealed that the reduction in FVII:c was related to the concomitant weight reduction of the participants. In the present study, body composition and dietary habits remained stable during the entire program, and no changes in FVII:c or other coagulation factors (except for FVIII:c) were observed.

Far more attention has been paid to the effect of regular training on overall fibrinolytic activity (11, 27). More recent investigations, dealing with individual components, report higher t-PA Act and lower PAI-1 Ag levels to be responsible for this enhanced fibrinolytic potential (21, 26, 28).

We could not demonstrate a direct effect of training on either t-PA or PAI-1. The (submaximal) training intensity and the (young) age of our subjects may have been important determinants in the outcome of our study. Rankinen et al. (24) trained healthy sedentary men at a comparable submaximal intensity and did not observe training-related changes in basal levels of t-PA or PAI-1. Stratton et al. (26) observed a significant effect of training on t-PA and PAI-1 levels in old male subjects but not in the young participants.

We did, however, observe divergent patterns in PAI-1 and t-PA plasma levels of the Tr and the Con groups that are suggestive of seasonal fluctuations. In the Con group, t-PA Ag as well as PAI-1 Ag and PAI-1 Act showed an unfavorable tendency (29) to increase during the intervention period from February to June, whereas in the Tr group an opposite tendency was observed. This divergent pattern resulted in significant difference among t-PA Ag, t-PA Act/Ag (reflecting fibrinolytic efficacy), and PAI-1 Ag and PAI-1 Act levels of the Tr and Con groups at the end of the intervention period (T12) that could not be attributed to changes in anthropometry (16, 30) or dietary regimen (14).

Comparable seasonal variations in PAI-1 Ag plasma levels of healthy subjects have been observed by Huisveld et al. (16), a finding that has been confirmed by others (7). In patients with rheumatoid arthritis, low PAI-1 levels that cannot be attributed to changes in the carrier protein fibronectin (10) have been observed in early summer (22).

Although higher levels of FVII and Fbg in wintertime that are associated with a higher incidence of cardiovascular diseases have been reported (18, 35), the clinical implications of variations in fibrinolytic components can only be speculated on. The results of the present study suggest that the adverse seasonal effects observed in the Con group are compensated for by the exercise training performed by the Tr group. In addition to body composition (30), dietary habits (15), and physical activity, seasonal variation may influence PAI-1 plasma levels.

The exercise-induced relative (percent) changes in t-PA Ag levels were of a comparable magnitude for both Tr and Con, indicating that not the exercise-induced response but rather the basal plasma levels determine the outcome, as noted before (5). Most likely, PAI-1 is the major fibrinolytic determinant that strongly influences both basal and exercise-induced fibrinolytic activity (13).

Little is known about u-PA in relation to (in)activity. This fibrinolytic activator, like t-PA, demonstrates an increase during exercise, but the regulatory mechanism is vastly different (31).

In both Tr and Con groups, the exercise-induced increase in u-PA was significantly enhanced during intervention. The increase in u-PA Ag was significantly more prominent in the Tr group, suggesting that the training-induced effects were superimposed on the (seasonal) changes that occurred from February to June.

We conclude that regular submaximal physical activity, i.e., training, is associated with an enhanced coagulation (FVIII:c) potential and an enhanced fibrinolytic (u-PA) potential. Variations seen in t-PA and PAI-1 in the Con group during the intervention period suggest (unfavorable) seasonal changes that can be reversed by regular physical activity. The observations also stress the importance of the inclusion of Con groups in longitudinal study designs.

The authors thank Dr. E. Bol for statistical advice, Dr. G. Dooljewaard for providing the u-PA antibodies, J. de Nooyer for the dietary analyses, and J. J. H. de Wit for preparing the illustrations. This study was supported by Netherlands Heart Foundation Grant 90.059.

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REFERENCES


