Effects of a single bout of walking exercise on blood coagulation parameters in obese women

Manfred Lamprecht,1,2 Herve Moussalli,1 Gerhard Ledinski,1 Bettina Leschnik,3 Axel Schlagenhauf,3 Martin Koestenberger,3 Guenter Pölt,2 and Gerhard Cvirn1

1Institute of Physiological Chemistry, Medical University of Graz, Graz, Austria; 2Green Beat-Institute of Nutrient Research and Sport Nutrition, Graz, Austria; and 3Department of Pediatrics, Medical University of Graz, Graz, Austria

Submitted 11 February 2013; accepted in final form 19 April 2013

Lamprecht M, Moussalli H, Ledinski G, Leschnik B, Schlagenhauf A, Koestenberger M, Pöl G, Cvirn G. Effects of a single bout of walking exercise on blood coagulation parameters in obese women. J Appl Physiol 115: 57–63, 2013. First published April 25, 2013; doi:10.1152/japplphysiol.00187.2013.—Obesity is associated with increased prevalence of thromboembolic events. We aimed to investigate whether obese women might benefit from vigorous aerobic exercise. Forty-two overweight and obese women performed a 30-min walking exercise test (treadmill ergometer) at an intensity of 70% of individual peak oxygen uptake. Blood samples were collected before and immediately after exercise. Thrombelastometry and platelet function measurements were performed on whole blood. Standard coagulation times, thrombin generation curves, markers of thrombin generation, fibrinolytic parameters, plasma levels of pro- and anticoagulatory factors, and microparticle procoagulant activity were determined in platelet-poor plasma samples. Thrombelastometry revealed a significant prolongation of clot formation time (P = 0.037) and a significant deceleration of fibrin build up (alpha angle, P = 0.034) after exercise. Calibrated automated thrombography revealed a significant exercise-induced decrease in endogenous thrombin potential (P = 0.039). Moreover, thrombin formation stopped earlier postexercise, reflected in shortened StartTail (P = 0.046). Significantly elevated tissue-plasminogen activator levels (P = 0.001) indicate an exercise-induced activation of the fibrinolytic system. White blood cell count increased significantly from pre- to postexercise (P = 0.045), indicating a mild exercise-induced leukocytosis. The results of this study demonstrate that vigorous aerobic exercise might be a suitable tool to protect obese women from thrombotic events. We show that a single bout of vigorous aerobic exercise is clearly associated with an activation of the fibrinolytic system and a decreased readiness of the postexercise thrombin generation curves; markers of thrombin formation; fibrinolytic parameters; levels of the pro- and anticoagulatory factors; and microparticle procoagulant activity.

The majority of the studies suggesting an anticoagulant effect of vigorous exercise were performed in young and healthy men, so are not applicable to obese women. The aim of this study was to quantify coagulation changes in response to a single controlled exercise bout with vigorous intensity at 70% of individual peak oxygen uptake (V̇O₂) in obese pemenopausal Austrian women at risk for thromboembolic complications (34).

Most studies dealing with the effects of exercise on hemostasis were performed in platelet-poor plasma (PPP) samples. However, while PPP contains many of the coagulation factors implicated in the coagulation process, whole blood (WB) includes phospholipid-bearing cells and platelets, which support coagulation. Therefore, in the present study, hemostatic profiling was performed in both WB samples (blood cell counts, course of clot development, platelet function) as well as in PPP samples [coagulation times, i.e., activated partial thromboplastin time (APTT) and prothrombin time (PT)]; thrombin generation curves; markers of thrombin formation; fibrinolytic parameters; levels of the pro- and anticoagulatory factors; and microparticle procoagulant activity.

MATERIALS AND METHODS

Subjects. Forty-two overweight and obese women participated in this trial. Inclusion criteria were as follows: female, age 35–50 yr, pre- or perimenopausal, eligible to participate in exercise, nonsmokers, sedentary work and lifestyle, body mass index between 28 and 40 kg/m², no dietary or nutritional supplement use within 4 wk prior to the walking exercise test. Exclusion criteria were as follow: smokers, women who failed exercise eligibility testing as described by the Austrian and German standards in sports medicine (8), chronic or excessive alcohol consumption, recent surgery or illness, diabetes, dyslipemia, current participation in a weight management program, diagnosis of osteoporosis or osteopenia, and current use of any medication known to significantly influence hemostasis. In addition to these inclusion and exclusion criteria, a standard blood chemistry panel, exercise echocardiography, and peak VO₂ were determined in all women to confirm general health prior to study enrollment (for subject characteristics, see Table 1). All subjects also completed a medical history and a physical activity/well-being questionnaire.

Ethical aspects and recruitment. All subjects provided written informed consent prior to participating in this investigation. This study was conducted according to the guidelines of the Declaration of Helsinki for research on human subjects 1989 and was approved by the Ethical Review Committee of the Medical University of Graz, Austria. The trial was registered under www.clinicaltrials.gov, identifier: NCT01476033.

The study focused on office workers and was announced in local newspapers. A telephone screening conducted by the study staff resulted in 59 volunteers for further eligibility testing. From those, 42

CARDIOVASCULAR DISEASE (CVD) is a major cause of mortality and morbidity in the Western world. Obesity and sedentary lifestyle have been shown to be associated with increased prevalence of CVD and disturbed hemostasis (24, 39). As a consequence, official recommendations suggest that each individual should conduct 20–60 min of cardiorespiratory exercise 3–5 days/wk (8, 15, 20). These official recommendations are based on studies demonstrating that vigorous physical exercise reduces the risk of CVD by tipping the delicate balance between coagulation and fibrinolysis toward an anticoagulant state (44).

Address for reprint requests and other correspondence: G. Cvirn, Institute of Physiological Chemistry, Medical Univ. of Graz, Harrachgasse 21/II, 8010 Graz, Austria (e-mail: gerhard.cvirn@medunigraz.at).

http://www.jappl.org 8750-7587/13 Copyright © 2013 the American Physiological Society 57
women met the inclusion and exclusion criteria and were enrolled in the study program.

Study design and time schedule. This was a controlled clinical intervention study. All eligibility testing was finalized 4 wk prior to the 30-min walking exercise test. On the morning of the exercise test a standardized breakfast (2–3 h prior to exercise) was provided. The women came to the laboratory to perform the 30-min walking exercise test at 3 km/h on the treadmill, which was supervised by a physician. Blood pressure (RR) was measured at the beginning, after 10 and 20 min, and at the end of the test.

Collection of WB and preparation of plasma. Each subject had blood collected in the supine position from a medial cubital vein before exercise (Pre) and immediately after exercise (Post). Blood (2.7 ml) was collected into precitrated S-Monovette premarked tubes (3 from each individual) from Sarstedt (Nümbrecht, Germany), containing 300 μl of 0.106 mol/l sodium citrate. The first tube was discarded. The whole blood from the two remaining tubes was pooled and subsequently used for determination of blood cell counts as well as for thrombelastometry and platelet function measurements. The remaining WB was centrifuged at room temperature for 15 min at 1,200 g to obtain PPP for subsequent determination of standard coagulation times, thrombin generation curves, markers of thrombin generation, fibrinolytic parameters, plasma levels of pro- and anticoagulatory factors, and microparticle procoagulant activity.

Blood cell counts. Blood cell counts were determined on a Sysmex KX-21N Automated Hematometry Analyzer from Sysmex.

WB tissue factor triggered thrombelastometry assay. The thrombelastometry (TEM) coagulation analyser (ROTEM 05) (Matel Medizintechnik, Graz, Austria) was used to measure coagulation time (CT), the time from initiation of the test to the initial fibrin formation; clot formation time (CFT), the time from the beginning of clot formation until the amplitude of thrombelastogram reaches 20 mm; maximum clot firmness (MCF), the maximum strength in millimeters of the final clot; and alpha, the angle between the line in the middle of the TEM tracing and the line tangential to the developing “body” of the TEM tracing. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking. This method has been described in detail recently (37).

WB platelet aggregation assay. Whole blood aggregation assessments were performed using a Chrono-Log Whole Blood Aggregometer (APTT 590 from Protem and Go (Endingen, Germany), which is based on the impedance method (30, 32). Impedance aggregometry results are expressed as amplitude (or maximum aggregation) in ohms at 6 min after reagent addition and as lag time (or aggregation time) in seconds, the time interval until the onset of platelet aggregation. The rate of platelet aggregation is expressed as slope in ohms per minute. Collagen was used as platelet agonist, as previously described (11).

WB platelet adhesion assay. Platelet adhesion was assessed using a Cone and Platelet Analyzer (CPA) (DiaMed, Linz, Austria). The method has been described previously (41). Briefly, 130 μl of citrated WB is placed in polystyrene tubes and allowed to flow (1,300 s−1) for 1 min with a rotating Teflon cone. The wells were washed with phosphate-buffered saline, stained with May–Grünewald solution and analyzed with an image analysis system. The three platelet function values, i.e., surface coverage (SC), average size (AS), and number of adhering objects (objects), were evaluated. SC is expressed as the percentage of total area covered by platelets. Average size is defined as the average size of the surface bound objects (28).

Table 1. Baseline characteristics, performance, and clinical chemistry data of 42 premenopausal, obese, but otherwise healthy women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Rangea</th>
<th>42 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41.1 ± 3.8</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>34.4 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>92.0 ± 12.1</td>
<td></td>
</tr>
<tr>
<td>Peak VO2, ml</td>
<td>2,198 ± 147</td>
<td></td>
</tr>
<tr>
<td>Peak VO2, ml·kg−1·min−1</td>
<td>25.8 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>VT, ml</td>
<td>1,952 ± 145</td>
<td></td>
</tr>
<tr>
<td>VT, % of peak VO2</td>
<td>88.8 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>70% of peak VO2, ml</td>
<td>1,539 ± 128</td>
<td></td>
</tr>
<tr>
<td>70% of peak VO2, % of VT</td>
<td>78.9 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>Pmax, km/h + slope (%)</td>
<td>6 + 7 (±1.77)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means ± SD. BMI, body mass index; VO2, oxygen uptake; VT, ventilatory threshold; HDL, high-density lipoprotein; Pmax, maximum performance; Παkt+3.1% peak VO2, performance at 68% peak VO2 expressed via speed.

aSee Ref. 40.
time), time to peak (tPeak), peak height (Peak), and endogenous thrombin potential (ETP), and the time point at which free thrombin has disappeared (StartTail). Measurements were carried out in the presence of 5 pmol/l of tissue factor (TF) (final concentration).

Markers of thrombin generation. Plasma levels of prothrombin fragment 1+2 (F 1+2) and thrombin-antithrombin complexes (TAT) were determined using ELISA kits from Behring Diagnostics (Marburg, Germany).

Fibrinolytic values. Plasma levels of tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor-I (PAI-I) were determined using the assays IMUBIND tPA ELISA kit and IMUBIND PAI-I Plasma ELISA, respectively, from American Diagnostica (Pfungstadt, Germany).

Procoagulatory factors. Plasma levels of prothrombin (FII), FVII, and FVIII were determined on a BM/Hitachi 917 from Roche (Vienna, Austria). TF was determined by means of the assay ACTICHROME Tissue Factor ELISA from American Diagnostica.

Anticoagulatory factors. Plasma levels of tissue factor pathway inhibitor (TFPI) were determined using the ACTICHROME Total TFPI ELISA assay from American Diagnostica.

Microparticle procoagulant activity. Microparticle procoagulant activity was determined using the functional assay ZYMUPHEN MP-Activity from HYPHEN BioMed (Neuville, France) on a Microplate Scanning Spectrometer (Bio-Tek Instruments, Winooski, VT). Plasma samples, supplemented with calcium, FXa and FIIa inhibitors were introduced to microplate wells coated with streptavidin and biotinylated annexin V. Then FXa-FVa mixtures containing calcium and purified prothrombin were introduced. Microparticles bind to annexin V and expose their phospholipid surface, thus allowing conversion of prothrombin to thrombin. Phospholipid binding potential (ETP), and the time point at which free thrombin has disappeared (StartTail). Measurements were carried out in the presence of 5 pmol/l of tissue factor (TF) (final concentration).

Statistical analyses. All statistical analyses were performed using SPSS for Windows software, version 19.0. Data are presented as means ± SD. All data were adjusted for plasma volume changes as described elsewhere (16). Statistical significance was set at P < 0.05. The Shapiro-Wilk test was used to determine normal distribution and the Levene test for homogeneity of variances. Pre- and postexercise data were compared by paired Student’s t-test.

Table 2. Coagulation values in WB samples prior and after the 30-min aerobic walking exercise test

<table>
<thead>
<tr>
<th>Blood cell counts</th>
<th>Preexercise (Mean ± SD)</th>
<th>Postexercise (Mean ± SD)</th>
<th>Reference Values Mean (95% Range) or Mean ± SD</th>
<th>Significance (Pre vs. Post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, ×10^3 µl⁻¹</td>
<td>6.7 ± 1.8</td>
<td>7.5 ± 1.9</td>
<td>7.0 (4.3–10.0)</td>
<td>0.045</td>
</tr>
<tr>
<td>RBC, ×10^6 ml⁻¹</td>
<td>4.1 ± 0.3</td>
<td>4.2 ± 0.4</td>
<td>4.5 (3.5–5.5)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>12.6 ± 0.8</td>
<td>12.9 ± 0.8</td>
<td>13.5 (12–15)</td>
<td>0.072</td>
</tr>
<tr>
<td>Hct, %</td>
<td>38.3 ± 1.8</td>
<td>39.0 ± 1.8</td>
<td>42 (36–48)</td>
<td>0.077</td>
</tr>
<tr>
<td>Platelets, ×10³ ml⁻¹</td>
<td>239 ± 56</td>
<td>257 ± 64</td>
<td>250 (125–318)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Thrombelastometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT, s</td>
<td>382 ± 86</td>
<td>398 ± 83</td>
<td>322 ± 55</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>CFT, s</td>
<td>142 ± 31</td>
<td>165 ± 47</td>
<td>119 ± 28</td>
<td>0.037</td>
</tr>
<tr>
<td>MCF, mm</td>
<td>60.9 ± 3.6</td>
<td>61.6 ± 4.2</td>
<td>61.3 ± 5</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Alpha, c</td>
<td>63.2 ± 6.2</td>
<td>59.8 ± 7.7</td>
<td></td>
<td>0.034</td>
</tr>
</tbody>
</table>

Platelet aggregation:
- Lag time, s 133.1 ± 95.1 131.6 ± 84.4 58.6 ± 9.7 >0.1
- Slope, ohms/min 9.6 ± 4.8 10.2 ± 4.4 8.4 ± 2.0 >0.1
- Amplitude, ohms 12.1 ± 3.1 12.9 ± 3.2 13.6 ± 1.4 >0.1
- Platelet adhesion Surface coverage, % 12.5 ± 3.9 12.8 ± 4.1 14.9 ± 2.5 >0.1
- Average size, µm² 41.7 ± 16.9 38.1 ± 14.0 39.4 ± 5.2 >0.1
- Objects, counts 1.853 ± 415 2.002 ± 512 1.380 >0.1

WB. whole blood; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Hct, hematocrit; CT, coagulation time; CFT, clot formation time; MCF, maximum clot firmness; Pre, preexercise; Post, postexercise. See text for definition of alpha angle. *See Ref. 21; †see Ref. 11; ‡see Ref. 10; §see Ref. 15; ¶see Ref. 25. Boldface indicates significant difference, Pre vs. Post.

Sample size calculation based on ETP and CFT estimated 37 subjects, depending on parameter, SD, and effect size, to reach a probability of error (alpha/2) of 5% and 80% power. Allowing for a drop-out rate of 10% during recruiting (between maximal VO₂ testing and first walking test), 42 subjects were recruited for the study.

RESULTS

Thirty-minute controlled walking exercise. The postexercise analyses revealed that women performed de facto at 68.2 ± 3.1% of individual peak VO₂ (which was determined 4 wk before). This demonstrates that the women could hold the preset intensity at 70% of peak VO₂ over 30 min accurately. The average walking speed was 6 ± 0.59 km/h at this exercise intensity. Performance and clinical chemistry data are shown in Table 1.

Blood cell counts pre- vs. postexercise. WBC count increased significantly from pre- to postexercise (P = 0.045), indicating a mild exercise-induced leukocytosis (18). IL-6 and TNF-alpha remained unchanged (data not shown). Red blood cell count did not change, although there was a trend to increased hematocrit and hemoglobin (P = 0.077 and 0.072 respectively). Data are shown in Table 2.

Thrombelastometry values pre- vs. postexercise. Thrombelastometry values were compared pre- and postexercise with respect to CT, CFT, MCF, and alpha angle. The 30-min walking exercise caused a significant prolongation of CFT (P = 0.037) compared with preexercise and a significant reduction of alpha angle (P = 0.034). There were no differences concerning CT and MCF. CTs and CFTs in both pre- and postexercise samples were slightly prolonged compared with apparently healthy women (37). Data are shown in Table 2.

WB platelet aggregation pre- vs. postexercise. WB platelet aggregation values were compared pre- and postexercise with respect to amplitude, slope, and lag time. These parameters were not affected by this model of exercise. Platelet aggregation in terms of amplitude and slope was slightly less pronounced in the obese women compared with apparently healthy young women.
healthy adults; lag times were markedly prolonged compared with healthy adults (11). Data are shown in Table 2.

**WB platelet adhesion pre- vs. postexercise.** WB platelet adhesion values were compared pre- and postexercise with respect to SC, AS, and number of objects. No differences were found for these parameters. Platelet adhesion in terms of SC and AS was comparable to that of healthy adults; number of objects was higher in the obese women. Data are shown in Table 2.

**APTT and PT (INR) pre- vs. postexercise.** No statistically significant differences were found between pre- and postexercise.

**Data are shown in Table 3.**

**Thrombin generation values pre- vs. postexercise.** Thrombin generation was compared pre- and postexercise with respect to Lag Time, tPeak, Peak, ETP, and StartTail. In the postexercise PPP samples, ETP was significantly decreased (P = 0.039) and thrombin formation ceased earlier, reflected in shortened StartTail (P = 0.046). Lag Time, tPeak, and Peak remained unaffected by exercise. Data are shown in Table 3.

**Markers of thrombin generation pre- vs. postexercise.** Plasma levels of F1 + 2 as well as of TAT were not affected by the model of exercise. F1 + 2 levels were above normal in both pre- and postexercise PPP samples. Data are shown in Table 3.

**Fibrinolytic values pre- vs. postexercise.** Significantly elevated t-PA levels (P = 0.001) postexercise indicated an exercise-induced activation of the fibrinolytic system. Levels of PAI-1 were not affected by the model of exercise. Data are shown in Table 3.

**Levels of procoagulatory factors pre- vs. postexercise.** Plasma levels of FII and FVII were not affected by exercise. However, both markers were distinctly above normal in both pre- and postexercise samples. FVIII levels exceeded 168% in both pre- and postexercise samples. No exercise-induced increase in plasma levels of TF was observed. Data are shown in Table 3.

**Microparticle procoagulant activity pre- vs. postexercise.** Microparticle procoagulant activity, evaluated by means of enzyme-linked immunosorbent assay, was not affected by the model of exercise. However, the values were distinctly above normal in both pre- and postexercise PPP samples. Data are shown in Table 3.

**Concentration of anticoagulatory factors pre- vs. postexercise.** Exercise did not cause significant changes in plasma levels of TFPI. Levels of TFPI were lower than normal in both pre- and postexercise PPP samples. Data are shown in Table 3.

**DISCUSSION**

Numerous studies, undertaken to examine the effects of physical activity on hemostasis, report on both pre- as well as on anticoagulant effects of exercise. A field synopsis leads to the assumption that the hemostatic response to exercise is mainly influenced by the intensity of exercise (26, 27, 39). Heavy exercise (83% \( \dot{V}O_2_{\text{max}} \)) activates both the coagulation and the fibrinolysis system (43) whereas vigorous exercise (68% \( \dot{V}O_2_{\text{max}} \)) is associated with an enhancement of fibrinolysis without a concomitant increase in markers of blood coagulation (44). Wang et al. (42) have shown that platelet adhesiveness and aggregation are upregulated by strenuous but not by vigorous exercise.

In this study the aim was to investigate whether otherwise healthy obese women, assumed to be at an elevated risk for thrombotic events, might show a hemostatic benefit from a controlled bout of vigorous exercise.

Hemostatic profiling of the preexercise PPP, but not of the WB samples, suggests that, in accordance with the above-

---

**Table 3. Coagulation values in PPP samples prior and after the 30-min aerobic walking exercise test**

<table>
<thead>
<tr>
<th>Test</th>
<th>Preexercise Mean ± SD</th>
<th>Postexercise Mean ± SD</th>
<th>Reference Range</th>
<th>Significance (Pre vs. Post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT, s</td>
<td>35.2 ± 4.0</td>
<td>36.1 ± 4.7</td>
<td>30–40</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>INR</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>ETP, nmol · l⁻¹·min⁻¹</td>
<td>2.07 ± 0.5</td>
<td>2.1 ± 0.3</td>
<td>3.1 ± 1.4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Peak, nmol/l</td>
<td>479 ± 56</td>
<td>463 ± 59</td>
<td>458 ± 60</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Time to peak, min</td>
<td>3.8 ± 0.7</td>
<td>3.7 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start tail, min</td>
<td>19.2 ± 2.0</td>
<td>18.4 ± 2.1</td>
<td></td>
<td>0.046</td>
</tr>
<tr>
<td>FII + 2, pmol/l</td>
<td>247.9 ± 97.0</td>
<td>268.2 ± 107.0</td>
<td>69–229</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>PAI-1 Ag, ng/ml</td>
<td>6.26 ± 10.7</td>
<td>3.1 ± 1.2</td>
<td>1.0–4.1</td>
<td>0.064</td>
</tr>
<tr>
<td>t-PA Ag, ng/ml</td>
<td>6.4 ± 2.2</td>
<td>8.6 ± 3.1</td>
<td>1.4–8.4</td>
<td>0.001</td>
</tr>
<tr>
<td>FV, %</td>
<td>145.1 ± 24.6</td>
<td>148.1 ± 22.0</td>
<td>70–120</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>FVIII, %</td>
<td>143.0 ± 34.9</td>
<td>142.6 ± 35.2</td>
<td>70–120</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>MP procoagulant activity,</td>
<td>120 ± 6</td>
<td>115 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI-1 Ag, ng/ml</td>
<td>16.5 ± 13.9</td>
<td>15.1 ± 11.6</td>
<td>3–40</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

**PPP, platelet-poor plasma; APTT, activated partial thromboplastin time; INR, international normalized ratio; ETP, endogenous thrombin potential; F 1+2, prothrombin fragment 1+2; TAT, thrombin-antithrombin complex; t-PA, tissue-plasminogen activator; PAI-1, plasminogen activator inhibitor I; TF, tissue factor; MP, microparticles; TFPI, tissue factor pathway inhibitor. *See Ref. 17; †according to Dade Behring (unpublished observations); ‡see Ref. 9; §see Ref. 30; ¶see Ref. 3. Boldface indicates significant difference, Pre vs. Post.**
mentioned assumption, these women were in a hypercoagulable state compared with healthy, nonobese subjects. Preexercise plasma levels of F1+2 were markedly higher than those of healthy nonobese subjects, indicating elevated formation of thrombin. Moreover, preexercise plasma levels of FII, FVII, and FVIII were markedly higher than normal. Elevated plasma levels of these three coagulation factors have been shown to be associated with an increased readiness to form thrombin (4, 7, 22). Further evidence of a hypercoagulable state in these obese women was the low level of TFPI. Low levels of TFPI have been shown to have a procoagulant effect by facilitating the initiation of thrombin generation (1, 4). Evidently, these obese women were apparently in a hypercoagulable state prior to exercise due to a markedly elevated procoagulant activity of microparticles compared with healthy young men (38). These results emphasize the importance of an antithrombotic prophylaxis/treatment of obese women.

The data show that regular vigorous exercise might be a suitable tool to shift the hemostatic system of obese women toward an anticoagulant state. 1) The fibrinolytic system was significantly activated; and both the 2) clot-forming capacity as well as the 3) thrombin-forming capacity were significantly decreased in the postexercise samples.

1) Obesity-related atherothrombotic risk has been shown to be associated with an impaired capability of endothelial cells to release t-PA, the pivotal enzyme initiating the endogenous fibrinolytic response (5, 40). The present study showed, in accordance with others, significantly elevated t-PA levels in the postexercise PPP samples (29, 36, 45). We conclude that particularly obese women, known to be at an elevated risk for thromboembolic complications, might benefit from the exercise-induced high plasma levels of t-PA known to enhance the efficacy of endogenous fibrinolysis (23).

2) TEM measurements revealed an impaired clot-formation capacity of the postexercise WB samples. CFTs were significantly prolonged and alpha angles were significantly lower in the postexercise compared with the preexercise WB samples, indicating impaired fibrin build up and cross-linking (37). Presumably, this impaired clot formation is attributable, at least in part, to the exercise-induced increase of t-PA. Several groups have reported impaired clot development in the presence of increasing amounts of t-PA. Nielsen et al. (31) have shown significantly decreased TTP (total thrombus generation) in the presence of increasing amounts of t-PA. Ploppa et al. (33) have shown significantly impaired clot formation in a patient with a massive pulmonary embolism after administration of recombinant t-PA, and D’Amico et al. (14) have shown reduced MCFs and prolonged CTs in the presence of recombinant t-PA (1 μg/ml).

3) CAT measurements revealed an impaired thrombin-forming capacity after vigorous exercise. Free thrombin was generated in significantly lower amounts (reflected by lower ETP values) and disappeared significantly earlier (reflected by shorter StartTails) in the postexercise PPP samples stimulated by addition of TF. The underlying mechanisms leading to this diminished capability of the postexercise PPP samples to generate thrombin remain to be elucidated. The two most reasonable explanations, decreased plasma levels of prothrombin and/or decreased plasma levels of TF, do not apply. It has been shown that thrombin generation dose dependently decreases in the presence of decreasing amounts of prothrombin (2) as well as of TF (2, 22). However, in the present study, both prothrombin and TF levels were virtually the same in the pre- and postexercise samples. Another explanation for the diminished capability of the postexercise PPP samples to generate thrombin might be exercise-induced elevated levels of antithrombin (AT) or alpha 2-macroglobulin (α2-M), the two most efficient inhibitors of thrombin (4). A dose-dependent decrease of ETP in the presence of increasing amounts of AT and α2-M has been shown previously (13). In the present study AT and α2-M plasma levels were not determined. However, it is unlikely that the vigorous exercise applied here resulted in significantly elevated plasma levels of these two inhibitors. Huisveld et al. (23) have shown elevated AT and α2-M levels after exhaustive exercise, but that increase was completely attributable to hemoconcentration, and Cernecah et al. (6) have shown modest, yet significant, increases in AT levels after exhaustive exercise in trained but not in untrained individuals. Despite this, plasma levels of AT as well as of α2-M remain to be monitored in future studies dealing with exercise and coagulation.

In a similar study, Beltan et al. (2a) have shown a decrease of APTT in healthy subjects after a 15 min duration exercise conducted at almost the same intensity as in the present study indicating no such decrease. It has been suggested that the decrease of APTT is, at least partially, attributable to an exercise-induced increase of FVIII coagulant activity. In contrast to the study of Beltan et al. (2a), our subjects were already in a hypercoagulable state prior to testing, reflected by, e.g., increased levels of FVIII. Thus an exercise-induced increase of already elevated FVIII levels apparently does not result in shortened APTT. This assumption is supported by the findings of van Veen et al. (47). They have shown that the procoagulant action of FVIII dose dependently increases (by measuring thrombin generation curves) within a range of 1 to 100% of normal value and reaches a plateau at ~150%.

Presumably, the anticoagulant effect of vigorous exercise might be dampened by leukocytosis. In agreement with various other studies this work showed significantly elevated WBC counts (by ~12%) in the postexercise WB samples (35). Leukocyte procoagulant activity and the capability of leukocyte products to augment the ability of endothelial cells to activate coagulation have been shown previously (17). However, this leukocytosis-induced procoagulant effect is modest in this vigorous exercise experiment, although it might be of importance in studies dealing with intense exercise (19).

At this time it is unknown how long the effect of a single exercise bout on blood coagulation persists. Further research is required to estimate the effects of standardized chronic exercise programs over several weeks or months on hemostasis in obese women.

In conclusion, these findings demonstrate that a single bout of vigorous aerobic exercise is clearly associated with an activation of the fibrinolytic system and with a decreased readiness of the postexercise samples to form a clot and to generate thrombin, the pivotal enzyme of hemostasis.

ACKNOWLEDGMENTS

We thank Guenther Juergens, PhD, for revising the manuscript, and Anita M. Boddie, PhD, for proofreading of the manuscript as a native English speaker.
Exercise and Coagulation in Obese Women • Lamprecht M et al.

REFERENCES


