Different Effects of Strenuous Exercise and Moderate Exercise on Platelet Function in Men

Jong-shyan Wang, MS; Chauying J. Jen, PhD; Hsiue-ching Kung, BS; Li-Jen Lin, MD; Tzuen-Ren Hsiue, MD; Hsiu-ing Chen, PhD

Background Platelets play an important role in the pathogenesis of cardiovascular diseases. It is also noticed that on one hand, regular exercise can reduce the risk of cardiovascular diseases, and on the other hand, vigorous exercise provokes sudden cardiac death. We therefore hypothesize that various intensities of exercise may affect platelet function differently.

Methods and Results Strenuous and moderate exercise (about 50% to 55% of peak oxygen consumption, VO2peak) on a bicycle ergometer in 10 sedentary and 10 physically active healthy young men was executed on two separate occasions. Blood samples were collected before and immediately after exercise. A newly designed tapered parallel plate chamber was used to assess platelet adhesiveness. Platelet aggregation induced by ADP was evaluated by the percentage of reduction in single platelet count. β-Thromboglobulin (β-TG) and platelet factor 4 (PF4) were measured by ELISA. In addition, a similar study on 5 patients with stable angina were also conducted. Our results showed that (1) in the sedentary healthy group, platelet adhesiveness and aggregation were increased by strenuous exercise and depressed by moderate exercise; (2) in the active healthy group, platelet adhesiveness and aggregation were enhanced by severe exercise, whereas only aggregation was decreased by moderate exercise; (3) in the patients with stable angina, platelet adhesiveness and aggregation were enhanced by strenuous exercise and adhesiveness was suppressed by moderate exercise; (4) the degree of hemoconcentration induced by acute exercise tended to be related to the severity of exercise in all subjects; and (5) although severe exercise elevated β-TG and PF4, there were no significant changes in β-TG, PF4, and the ratio of β-TG to PF4 in healthy subjects after exercise.

Conclusions It is concluded that platelet adhesiveness and aggregability may be sensitized by strenuous exercise in both healthy subjects and patients with stable angina. In contrast, platelet function can be suppressed significantly by moderate exercise in the healthy and tends to be depressed in patients with stable angina. The former may increase the risk of cardiac arrest and the latter may protect us from cardiovascular diseases. In addition, the effects of acute exercise tend to be more pronounced in the sedentary than in the active.

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Key Words • platelets • exercise

Pathological and clinical studies have suggested that platelets play an important role in the pathogenesis and progression of cardiovascular diseases. It has also been postulated that regular exercise may reduce the risk of major vascular thrombotic events and protect us against cardiovascular disease. However, Siscovick and coworkers reported that the risk of primary cardiac arrest was transiently increased during exercise. Therefore, physical exercise seems to be able to protect us against cardiovascular disease on the one hand and to provoke sudden cardiac death on the other hand. Accordingly, we hypothesize that different intensities of exercise may affect platelet function differently. Moreover, subjects who are physically active and those who are sedentary may respond differently to the same exercise protocol.

Various studies, including our previous study, found an increase in platelet counts ranging from 18% to 80% immediately after treadmill or bicycle exercise. Despite the increase in platelet number, most studies regarding the effects of exercise on platelet functional behavior, mainly aggregation and secretion, have been either controversial or incomplete (for a review, see References 13 and 14).

References

Fig 1. Microscopic images show that the platelets remained on the fibrinogen-coated surface after being exposed to variable shear stresses for 5 minutes at a flow rate of 0.027 mL/s. These adherent platelets on the fibrinogen-coated surface were nonoverlapping and randomly distributed. The greatest number of adhered platelets was found at the downstream end where the shear stress was low. a, Location, 5.6 cm from inlet; shear stress, 0.99 dyne/cm²; platelet density, 4375 cells/mm². b, Location, 4.1 cm from inlet; shear stress, 15.9 dyne/cm²; platelet density, 3631 cells/mm². c, Location, 2.6 cm from inlet; shear stress, 30.7 dyne/cm²; platelet density, 2488 cells/mm². d, Location, 1.1 cm from inlet; shear stress, 46.6 dyne/cm²; platelet density, 1513 cells/mm².

Methods

Subjects

The protocol had previously been reviewed and approved by an institutional committee for the protection of human subjects. Ten sedentary men and 10 physically active men who were young and healthy were studied after they had given their informed consent and understood the experimental procedures. The sedentary subjects did not engage in any regular physical activity for more than 1 year before the study. The physically active subjects, who were badminton athletes, had engaged in regular physical activity at least three times per week. In addition, 5 male patients with stable angina pectoris, as diagnosed by a typical history and positive exercise test or coronary angiography, were studied under a physician’s supervision. To prevent the confounding effect of smoking, all of the subjects were nonsmokers. The healthy subjects abstained from any medication at least for 2 weeks before the study. None of the patients had taken aspirin or other antiplatelet drugs for 2 weeks before the study. For ethical reasons, however, they were allowed to take regular calcium channel blockers and nitrvasodilators until 2 days and 24 hours, respectively, before the study. Before the actual study, subjects were familiarized with exercise on a bicycle ergometer (Corival 400) to eliminate the novelty effect of a new experience. They completed the medical history form and a physical activity questionnaire. The subjects then came to the laboratory twice on separate days to receive two different exercise protocols. All subjects arrived at 1:30 PM to participate in this study so as to avoid a possible diurnal influence, as mentioned in a previous study.

Exercise and Blood Collection Protocol

After the subject had arrived at the laboratory and rested for 30 minutes, blood samples were drawn from a forearm vein. The first 2 mL of blood was discarded, then the remaining blood sample was used for the measurements of resting hematological parameters and platelet function. Exercise began at 3 PM. The first exercise protocol in healthy subjects consisted of 2 minutes of unloaded pedaling, followed by a continuous increment of workload of 20 to 40 W every 3 minutes until exhaustion (ie, strenuous exercise up to peak oxygen consumption, \( V_{\text{O2peak}} \)). In patients, workload was increased by 10 to 20 W every 3 minutes. After 3 days, the second exercise protocol was performed at about 50% to 55% of predetermined \( V_{\text{O2peak}} \) for 30 minutes (ie, moderate exercise). Immediately after each exercise session, another blood sample was collected for the measurements of postexercise hematological parameters and platelet function. Therefore, four blood samples in total were collected from each person.

During exercise, the ECGs of healthy subjects were simultaneously and continuously monitored by a Gould ECG/Biotach, recorded on a four-channel polygraph (Gould 2400S portable ink recorder), and converted to a digital display of the heart rate (Gould digital display). Blood pressure was intermittently monitored by an automatic blood pressure system (Paramed Technology Inc, model 9300). The subject breathed

![Graph showing example of the relation between the number of remaining platelets on the fibrinogen-coated glass surface and the shear stress. The percentage of attached platelets was calculated as (number of platelets at a given distance divided by number of platelets at the distance of 5.6 cm) times 100%. A simple linear regression line for adhered platelets at various shear-stress fields from 55 to 0 dyne/cm² was obtained. This example showed that the percentage of attached platelets was proportional to the magnitude of the local shear stress (slope, \(-1.51\% \cdot cm^2/dyne; R^2=0.988\)).](http://circ.ahajournals.org/)

**Fig 2.**

TABLE 1. Comparison of Maximal Exercise Performance Between Two Healthy Groups

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>( W_{\text{peak}} ), W</td>
<td>182±6</td>
<td>235±10*</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>16.5±0.6</td>
<td>24.7±1.5*</td>
</tr>
<tr>
<td>( HR_{\text{peak}} ), bpm</td>
<td>194±2</td>
<td>188±2</td>
</tr>
<tr>
<td>( V_{\text{peak}} ), L min⁻¹</td>
<td>79.34±5.39</td>
<td>109.7±6.66*</td>
</tr>
<tr>
<td>( V_{\text{O2peak}} ), mL min⁻¹ \cdot kg⁻¹</td>
<td>33.5±1.1</td>
<td>41.5±1.1*</td>
</tr>
<tr>
<td>( V_{\text{CO2peak}} ), mL min⁻¹ \cdot kg⁻¹</td>
<td>42.3±1.9</td>
<td>59.3±2.8*</td>
</tr>
</tbody>
</table>

\( W_{\text{peak}} \) indicates peak workload; \( HR_{\text{peak}} \), peak heart rate; bpm, beats per minute; \( V_{\text{peak}} \), peak minute ventilation; \( V_{\text{O2peak}} \), peak oxygen consumption; and \( V_{\text{CO2peak}} \), peak \( CO_2 \) production. Values are mean±SEM.

*P<.05, unpaired Student's t test.
TABLE 2. Moderate Exercise Performance in Two Healthy Groups

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>% VO₂peak, %</td>
<td>54.3±2.9</td>
<td>55.3±2.1</td>
</tr>
<tr>
<td>W, W</td>
<td>84±4</td>
<td>114±4*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>136±1</td>
<td>127±2*</td>
</tr>
<tr>
<td>V̇e, L·min⁻¹</td>
<td>31.14±2.05</td>
<td>37.35±1.40*</td>
</tr>
<tr>
<td>VO₂, mL·min⁻¹·kg⁻¹</td>
<td>18.1±0.8</td>
<td>22.8±0.6*</td>
</tr>
<tr>
<td>VCO₂, mL·min⁻¹·kg⁻¹</td>
<td>18.1±1.2</td>
<td>22.7±1.7*</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are mean±SEM. *P<.05, unpaired Student’s t test.

through a large two-way valve (Hans Rudolph) into a 5-L mixing chamber. The fractional concentrations of O₂ and CO₂ in the mixed expired gas were continuously sampled and measured via an oxygen analyzer (Ametek S3A1, Applied Electrochemistry) and a CO₂ analyzer (SensorMedics LB-2). In addition, the inspiratory airflow was monitored by a pneumotachometer (Hans Rudolph), and the signal was passed to a carrier amplifier (Gould). Then, the airflow signal was electronically integrated to measure tidal volume by an integrator (Gould). Therefore, the data of heart rate, blood pressure, minute ventilation (V̇e), oxygen consumption (VO₂), and CO₂ production (VCO₂) for every minute were obtained during the resting and exercise periods as described previously.15 The exercise performance and ECG of patients with angina were monitored by an energy measurement system (model 2900, SensorMedics) and an ECG monitoring system (Q4000, Quinton Instrument Co) while these patients rode on a bicycle ergometer (Corival 400). The exercise test was terminated if the patient reported chest pain or if the ECG showed ST segment depression.

Basic Hematological Parameters

Erythrocyte count (RBC), leukocyte count (WBC), platelet count (Plt), hematocrit (Hct), and hemoglobin concentration (Hb) from the venous blood were determined by electronic counters (Cell Dyn 100 and 400, Meterotech) as described in a previous study.11

Platelet Aggregability

Platelet aggregation induced by ADP was evaluated by the percentage of reduction in single platelet count. Twenty milliliters of blood sample was transferred into a polypropylene tube containing sodium citrate (3.8 g/dL; 1 vol for 9 vol of blood). PRP was prepared by centrifugation at 800 rpm for 10 minutes at room temperature. Platelet-poor plasma (PPP) was obtained after centrifugation at 3000 rpm for 10 minutes. Platelet aggregation kinetics in PRP was measured with a platelet aggregometer (Hema-Tracer 2, NKK) after addition of various concentrations of ADP (Sigma Chemical Co) (ie, 0.25, 0.5, 1, and 2 μmol/L in final concentration). After the optical density had reached a steady value for at least 1 minute, the test tube was then removed from the aggregometer and kept at rest for 90 minutes, allowing the sedimentation of platelet aggregates. Forty microliters of plasma was removed from the upper suspension of the PRP for single platelet count. Results were expressed as the percentage of aggregated platelets to total platelets; ie, (single Plt before ADP—single Plt after ADP)/single Plt before ADP×100%. Preliminary experiments indicated that little sedimentation occurred in ADP-free specimens under this 90-minute waiting period; ie, 0% aggregation for unstimulated samples.

Platelet Adhesiveness

To differentiate platelet adhesiveness from platelet aggregability, a tapered parallel-plate chamber that provided a range of shear stress covering the entire physiological range in human circulation was used to assess platelet adhesiveness as described previously.17 After platelets settled on a fibrinogen-coated glass surface, they were subjected to various fluid shear stresses according to their location. The slope of attached platelets along with various shear stresses was used as an index of platelet adhesiveness. The linear-shear-stress flow chamber consisted of four components: a stainless steel cover plate, a glass slide plate, a Teflon gasket, and a plastic distributor. The glass slide plate and the gasket were fastened between the distributor and the cover plate to create a chamber cavity 5.8 cm long and 0.23 cm in entrance width. The glass slide was coated with 200 nmol/L human fibrinogen that was free of plasminogen, fibronectin, and factor XIII (IMCO). After the chamber had been assembled, it was placed on the stage of an inverted microscope equipped with a CCD video camera (Hamamazu). The inlet of the chamber was connected to a perfusion system. PRP was gently infused into the chamber and kept there for 12 minutes. The flow chamber was then flushed with Tyrode’s-HEPES buffer (0.128 mol/L HCl, 2.7 mmol/L KCl, 0.5 mmol/L MgCl₂, 2 mmol/L CaCl₂, 0.36 mmol/L NaH₂PO₄, 12 mmol/L NaHCO₃, 10 mmol/L HEPES; pH 7.4) for 5 minutes at a flow rate of 0.027 mL/s, which provided the range of shear stress from 55 to 0 dyne/cm². The pressure drop along the flow chamber was measured with a differential pressure transducer (Validyne) for calibrating the fluid shear stress of the flow chamber. Ten field locations along the center line were observed at intervals of 0.5 cm from the downstream end with approximately zero shear stress, and the numbers of remaining platelets per unit area (0.16 mm²) were counted at each location. The greatest number of adhered platelets was found at the downstream end where the shear stress was the lowest (Fig 1). A simple linear regression line for adhered platelets at various shear-stress fields was obtained. It clearly demonstrated that the percentage of adhered platelets was proportional to the magnitude of the local shear stress (Fig 2). When n=40, R²=0.95±0.023 (mean±SD). Therefore, the slope of attached platelets along with various shear stresses was used as an index of platelet adhesiveness (ie, the higher the slope, the greater the platelet adhesiveness). In a pilot study using PRP diluted with various amounts of autologous

TABLE 3. Basic Characteristics of Patients With Stable Angina

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>61</td>
<td>62</td>
<td>162</td>
<td>CAD (left anterior descending)</td>
</tr>
<tr>
<td>b</td>
<td>72</td>
<td>70</td>
<td>171</td>
<td>TIA</td>
</tr>
<tr>
<td>c</td>
<td>42</td>
<td>54</td>
<td>152</td>
<td>CAD (left anterior descending)</td>
</tr>
<tr>
<td>d</td>
<td>59</td>
<td>57</td>
<td>165</td>
<td>CAD (left anterior descending, left circumflex, right coronary)</td>
</tr>
<tr>
<td>e</td>
<td>62</td>
<td>77</td>
<td>172</td>
<td>Angina pectoris, hypertension</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; TIA, transient ischemic attack.
PPP as the testing samples, we found that platelet counts did not alter the slope of the platelet adhesion.

**Secretion of Platelet Proteins**

Both the methods of blood collection and the anticoagulant-antiplatelet agents used largely determined the reliability in measuring PF4 and β-TG levels in plasma samples. Each blood sample (4.5 mL) was collected into a precooled Diatube H (Diagnostica Stago) that contained a mixture of sodium citrate, theophylline, adenosine, and dipyridamole to inhibit the in vitro platelet release reaction. The PPP was obtained after centrifugation at 3000g for 30 minutes at 4°C and subsequently stored at -80°C. Both PF4 and β-TG were measured by ELISA (Diagnostica Stago). Since the ratios of β-TG/PF4 in healthy subjects did not change after acute exercise, this part of the experiments was not carried out in patients with angina.

**Statistics**

The SAS statistical software package was used for analysis of our data. To compare the differences of anthropometric data and exercise performances between the two healthy groups, the results were analyzed by Student’s t test for unpaired samples. The effects of two different intensities of acute exercise on changes of hematological parameters in patients were compared by paired Student’s t test, since they served as their own controls. The comparisons of platelet function and blood cell counts before and after two different intensities of acute exercise in healthy subjects were analyzed by ANOVA followed by Duncan’s or Fisher’s multiple range test. Differences were considered significant at P<.05. The results were expressed as mean±SEM.

**Results**

Anthropometric data of sedentary and active healthy groups are as follows: age, 22.8±0.5 years versus 21.9±0.6 years; height, 171.2±1.9 versus 172.0±2.3 cm; and weight, 66.0±2.7 versus 65.4±1.2 kg, respectively. The above data were not significantly different between the two groups studied. However, the resting heart rate in the active group was lower than in the sedentary, ie, 59±2 versus 77±2 beats per minute, respectively (P<.05). The active group had significantly higher peak workload (Wpeak), peak minute ventilation (Vlpeak), VO2peak, peak CO2 production rate (VCO2peak), and exercise time until exhaustion than the sedentary group in strenuous exercise (Table 1). During moderate exercise tests, the active group had significantly higher exercise workload, Vl, VO2, and VCO2 compared with the sedentary (Table 2). These results indicated that the active group had better exercise performance than the sedentary. The basic characteristics and exercise performance in patients with stable angina in our study are shown in Tables 3 and 4. These patients were much older than the healthy subjects in this study. In addition, their exercise capacities were much lower than those of healthy subjects.

Immediately after acute exercise (ie, strenuous exercise or moderate exercise), both healthy subjects and patients with angina showed increased levels of the hematological parameters, ie, RBC, Hct, Hb, WBC, and

### TABLE 4. Exercise Performance in Patients With Stable Angina

<table>
<thead>
<tr>
<th>Subject</th>
<th>VO2max (mL·min⁻¹·kg⁻¹)</th>
<th>VO2peak (mL·min⁻¹·kg⁻¹)</th>
<th>VCO2max (mL·min⁻¹·kg⁻¹)</th>
<th>VCO2peak (mL·min⁻¹·kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>10.0 (52.4)</td>
<td>7.7</td>
<td>19.1</td>
<td>17.1</td>
</tr>
<tr>
<td>b</td>
<td>11.6 (47.5)</td>
<td>8.4</td>
<td>24.4</td>
<td>20.8</td>
</tr>
<tr>
<td>c</td>
<td>20.3 (51.0)</td>
<td>16.6</td>
<td>39.8</td>
<td>31.8</td>
</tr>
<tr>
<td>d</td>
<td>12.3 (50.0)</td>
<td>8.9</td>
<td>24.6</td>
<td>21.8</td>
</tr>
<tr>
<td>e</td>
<td>9.4 (46.1)</td>
<td>9.0</td>
<td>20.4</td>
<td>19.1</td>
</tr>
<tr>
<td>Mean</td>
<td>12.7 (49.4)</td>
<td>10.1</td>
<td>25.7</td>
<td>22.1</td>
</tr>
<tr>
<td>SEM</td>
<td>±2.0 (±1.2)</td>
<td>±1.6</td>
<td>±3.7</td>
<td>±2.5</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

### TABLE 5. Percent Changes in Blood Cell Counts After Two Different Intensities of Acute Exercise in Healthy Men

<table>
<thead>
<tr>
<th></th>
<th>Percent Change</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sedentary</td>
<td>Active</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>RBC</td>
<td>6.1±1.0</td>
<td>17.1±2.2*</td>
<td>5.8±0.7</td>
</tr>
<tr>
<td>Hct</td>
<td>7.8±1.6</td>
<td>18.0±2.3*</td>
<td>6.6±1.1</td>
</tr>
<tr>
<td>Hb</td>
<td>5.9±1.6</td>
<td>11.4±1.3*</td>
<td>6.9±1.7</td>
</tr>
<tr>
<td>WBC</td>
<td>19.4±6.3</td>
<td>72.0±9.9*</td>
<td>41.2±8.8</td>
</tr>
<tr>
<td>Platelets</td>
<td>13.0±4.5</td>
<td>18.6±4.8</td>
<td>18.2±4.5</td>
</tr>
</tbody>
</table>

Percent change indicates (After–Before)/Before×100%; RBC, erythrocyte count; Hct, hematocrit; Hb, hemoglobin concentration; and WBC, leukocyte count. Values are mean±SEM.

*P<.05, moderate vs severe; ANOVA followed by Duncan’s multiple range test.
†P<.05, sedentary vs active; ANOVA followed by Duncan’s multiple range test.
Platelet adhesiveness increased after strenuous exercise in both healthy groups (Tables 7 and 8; P<.05). In contrast, the reduction of platelet adhesiveness by moderate exercise was seen only in the sedentary healthy group (P<.05; see Table 7). Moderate exercise-induced changes in platelet adhesiveness between sedentary and active healthy groups, ie, 10.8% and 1.5%, respectively, were significantly different (P<.05). In patients with stable angina, the slope of platelet adhesiveness was also significantly increased from −1.49±0.04 of the resting level to −1.20±0.07 by severe exercise (Fig 3, left; P<.05). In contrast, moderate exercise tended to reduce platelet adhesiveness of anginal patients from −1.47±0.05 to −1.72±0.14 (Fig 3, right; P<.05).

Platelet aggregability induced by 0.5 or 0.25 μmol/L of ADP was enhanced after strenuous exercise and was decreased after moderate exercise in both healthy groups (Tables 7 and 8; P<.05). The results of ADP-induced platelet aggregability in patients with stable angina are shown in Fig 4. It was noticed that platelet aggregability at low doses of ADP was increased by severe exercise in all patients and tended to be decreased by moderate exercise in some patients. Although plasma levels of β-TG and PF4 were increased by severe exercise in healthy subjects, no significant change in the ratio of β-TG to PF4 caused by acute exercise in either group was found (Tables 9 and 10).

Discussion

In this study, we have observed that (1) the active group had higher V\textsubscript{\text{peak}}, V\textsubscript{\text{O2peak}}, V\textsubscript{\text{CO2peak}}, W\textsubscript{\text{peak}}, and exercise time to exhaustion than the sedentary; (2) platelet adhesiveness was increased after strenuous exercise in both healthy groups, but it was depressed by moderate exercise only in the sedentary group; (3) platelet aggregation responsive to low doses of ADP was enhanced by strenuous exercise and was decreased after moderate exercise in healthy subjects; (4) in patients with stable angina, platelet adhesiveness and aggregability were remarkably enhanced by severe exercise, whereas only adhesiveness was significantly suppressed by moderate exercise; (5) blood cell counts increased after acute exercise, and the degree of hemoconcentration tended to be related to the severity of acute exercise in the sedentary healthy group and patients with angina, but less so in the active healthy group; and (6) in healthy young subjects, strenuous exercise significantly increased β-TG and PF4 secretion, but no significant change in the ratio of β-TG to PF4 was observed after either strenuous or moderate exercise.

Previous studies have suggested that the risk of primary cardiac arrest is transiently increased during vigorous exercise, whereas habitual physical exercise is associated with an overall decreased risk of primary cardiac arrest.\textsuperscript{4,5,7,8} Our study is the first report to clearly demonstrate that (1) the intensity of acute exercise is an important factor affecting blood platelet function; ie, moderate exercise tends to desensitize platelets, whereas strenuous exercise can potentiate platelets either in healthy subjects or in patients with stable angina, and (2) the exercise effect is more pronounced in the sedentary than in the active. In 1993, Kestin et al\textsuperscript{22} found that strenuous exercise could activate platelets, as assayed by the presence of activation-associated surface antigen on platelets. Their findings were consistent with part of our results. However, they did not study the effect of moderate exercise on platelet function. In 1989, Eidt et al\textsuperscript{23} demonstrated that low-level exercise, ie, treadmill exercise at a speed of 1 mph for 30 minutes, depressed platelet adhesiveness. Our study suggests that moderate exercise also decreases platelet adhesiveness.
minutes, would promote platelet aggregation in experimentally narrowed and endothelium-injured coronary arteries of the dog. Their observation was contradictory to ours. The possible reason is that we used normal men as our study subjects, whereas they used coronary-occluded dogs as an animal model. In their model, the blood circulation through narrowed coronary arteries even under mild exercise might have extremely high shear stress, which in turn could promote platelet aggregation.24 In our study, patients with stable angina had changes in platelet function similar to those in healthy subjects immediately after severe exercise (Figs 3 and 4). Although platelet aggregation of patients with stable angina tended to be suppressed by moderate exercise, this alteration was not statistically significant, possibly because of a small sample size and/or large individual differences in this group (Fig 4).

On one hand, the enhanced platelet activity in severe exercise may accelerate the formation of hemostatic platelet plugging and lead to shortened bleeding time, as described in our previous study.11 This may cause thrombosis in the coronary microcirculation and thus augment the risk of primary cardiac arrest. On the other hand, moderate exercise may reduce the risk of thrombotic events because it decreases platelet adhesiveness and aggregability. These exercise effects are more pronounced in sedentary than in active men. Although the resting platelets in active men seem to be less adhesive than those in sedentary men (see the adhesion slopes before exercise in Tables 7 and 8), there was no statistically significant difference. To investigate the exercise training effect on platelet function, a further longitudinal study is ongoing.

Adhesion, aggregation, and secretion are the major cellular reactions that platelets undergo during hemostasis and thrombosis. In previous studies, platelet adhesion was measured by exposing blood to a glass bead or a rotating glass bulb. Their results showed that platelet adhesiveness was either reduced or unchanged by exercise.9,15,16 These studies were carried out about 20 years ago, and their assays could not distinguish platelet adhesion from aggregation. Moreover, these studies did not control the exercise intensity adequately. In our study, we were able to observe and quantify platelet adhesiveness to a fibrinogen-coated surface exposed to a wide range of shear stress without the complication of aggregation (Figs 1 and 2, Tables 7 and 8). In humans, wall shear stress in blood circulation ranges from >1.5 to <56 dyne/cm²;25 this range is completely covered by our linear-shear-stress flow chamber. Our results showed that platelet adhesiveness increased after strenuous exercise in all subjects. Although it tended to be reduced by moderate exercise, statistically significant differences were seen only in the sedentary men and in patients with stable angina. We recently showed that adhered platelets undergo post-contact morphological changes, including the formation of pseudopods and cytoplasmic spreading.26 Our preliminary results indicated that platelets collected after strenuous exercise formed more pseudopods and spread more severely than platelets collected at rest. These enhanced morphological changes should strengthen the ability of adhered platelets to withstand flow shear stress.

Previous studies of the effect of physical exercise on platelet aggregation provided contradictory results.9,13,14,27 Those who measured platelet aggregation with turbidometry and did not correct for the postexer-
Exercise intensities and platelet function: increase in platelet counts demonstrated an increase in the extent of platelet aggregation after strenuous exercise, whereas those who used specimens with a standardized platelet count showed no change in platelet aggregation after exercise. A possible explanation for the discrepancy is that the turbidity changes in PRP reflect primarily the formation of large platelet aggregates, which is more favored under high platelet density. In recent studies, the platelet aggregability, measured by the disappearance of single platelets, was enhanced by low concentrations of ADP after maximal bicycle exercise. Our results showed that platelet aggregability evoked by low doses of ADP was increased after strenuous exercise in all subjects. This finding was consistent with the previous studies. In addition, we observed that platelet aggregability was decreased after moderate exercise in healthy groups and possibly in patients with stable angina. Previous reports indicated that mild to moderate exercise might stimulate a greater...

**TABLE 9. Platelet Secretion After Two Different Intensities of Acute Exercise in Sedentary Healthy Men**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rest</th>
<th>Moderate Exercise</th>
<th>Severe Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-TG, IU/mL</td>
<td>76.5±17.9</td>
<td>76.2±31.9</td>
<td>195±47.0*</td>
</tr>
<tr>
<td>PF4, IU/mL</td>
<td>36.4±9.8</td>
<td>32.4±15.4</td>
<td>80.9±21.2*</td>
</tr>
<tr>
<td>β-TG/PF4</td>
<td>2.5±0.4</td>
<td>3.2±0.6</td>
<td>2.5±0.2</td>
</tr>
</tbody>
</table>

β-TG indicates β-thrombogloblulin; PF4, platelet factor 4. Values are mean±SEM.
*P<.05, rest vs severe; ANOVA followed by Duncan’s multiple range test.
†P<.05, severe vs moderate; ANOVA followed by Duncan’s multiple range test.

**TABLE 10. Platelet Secretion After Two Different Intensities of Acute Exercise in Active Healthy Men**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Moderate Exercise</th>
<th>Severe Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-TG, IU/mL</td>
<td>77.9±18.7</td>
<td>67.9±16.9</td>
<td>144.6±36.4*</td>
</tr>
<tr>
<td>PF4, IU/mL</td>
<td>29.3±6.8</td>
<td>29.1±6.8</td>
<td>54.2±11.0*</td>
</tr>
<tr>
<td>β-TG/PF4</td>
<td>2.6±0.4</td>
<td>2.4±0.1</td>
<td>2.9±0.4</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 9. Values are mean±SEM.
*P<.05, rest vs severe; ANOVA followed by Duncan’s multiple range test.
†P<.05, severe vs moderate; ANOVA followed by Duncan’s multiple range test.
increase in 6-keto-PGF<sub>1α</sub> concentration than severe exercise did and that severe exercise increased thromboxane levels. It was also noticed that the ratio of 6-keto-PGF<sub>1α</sub> to thromboxane B<sub>2</sub> was elevated after moderate exercise, whereas this ratio was decreased by severe exercise. Moncada and Vane suggested that the ratio between prostacyclin and thromboxane A<sub>2</sub> has an important role in determining the extent of platelet aggregation, and the lower the ratio, the greater one’s predisposition toward platelet aggregation. Hirsh et al also suggested that local thromboxane release might be associated with recent episodes of angina in patients with unstable coronary heart disease. Therefore, the changes of platelet aggregability by two different intensities of acute exercise seen in this study might be explained by the alteration of eicosanoids.

It has been shown that platelets stimulated by ADP would expose fibrinogen receptors (ie, glycoprotein IIb/IIIa) on their surfaces and that fibrinogen binding to the active form of the fibrinogen receptor would produce platelet aggregation. Some previous studies showed that platelet adhesion to a fibrinogen-coated surface also involves the glycoprotein IIb/IIIa and that this adhesion requires some kind of activation-associated conformational change of this receptor complex. In the present study, we found that both ADP-induced platelet aggregability and platelet adhesiveness on a fibrinogen-coated surface may be enhanced by strenuous exercise and tend to be depressed by moderate exercise in men. Therefore, it seems that acute exercise may also somehow alter the performance of platelet fibrinogen receptors.

Both PF4 and β-TG are released from platelet α granules during platelet activation. Although they are present in platelets in similar amounts and released in similar quantities, the plasma levels of β-TG exceed those of PF4 because of rapid removal of PF4 in the circulation. Some investigators found that β-TG or PF4 was increased after acute exercise, while others did not find significant changes after exercise. However, it is known that artifacts resulting from blood sampling and handling can induce elevated β-TG and PF4 levels as measured in plasma. Therefore, it seems plausible to measure the ratio of β-TG to PF4 as the index of secretion for assessing the exercise effects on platelet activation in vivo. Our results showed that although strenuous exercise increased both β-TG and PF4 secretion, it did not cause any significant change in the ratio of β-TG to PF4. This suggested that platelet secretion in vivo may not be activated by acute exercise.

In conclusion, ADP-induced platelet aggregation and platelet adhesiveness on a fibrinogen-coated surface in vitro, but not release, are affected by acute exercise in an intensity-dependent manner; ie, they are augmented by strenuous exercise and suppressed by moderate exercise. Moreover, these exercise effects seem to be more pronounced in sedentary men than in active men.

Acknowledgments

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