Effect of Strenuous, Acute Exercise on $\alpha_2$-Adrenergic Agonist–Potentiated Platelet Activation

Jong-Shyan Wang, Lee-Ju Cheng

Abstract—Vigorous exercise transiently increases the risk of primary cardiac arrest. Strenuous, acute exercise can also increase the release of plasma epinephrine. Previous investigations have indicated that epinephrine can potentiate platelet activation by activating platelet $\alpha_2$-adrenoceptors. This study investigated how strenuous, acute exercise affects $\alpha_2$-adrenergic agonist–potentiated platelet activation by closely examining 15 sedentary men who exercised strenuously on a bicycle ergometer. Before and immediately after exercise, platelet adhesiveness on fibrinogen-coated surfaces, $[\text{Ca}^{2+}]$, in platelets, the number and affinity of $\alpha_2$-adrenergic sites on the platelet surface, and plasma catecholamine levels were determined. The results of this study can be summarized as follows: (1) The affinity of $\alpha_2$-adrenergic receptors on platelets decreases while the maximal binding number significantly increases after strenuous exercise, thereby correlating with the rise in plasma catecholamine levels. (2) Basal, clonidine-treated, ADP-treated, and clonidine plus ADP–treated adhesiveness and $[\text{Ca}^{2+}]$ in platelets increased after strenuous exercise. (3) Strenuous exercise is associated with higher percentages of ADP- and clonidine plus ADP–enhanced platelet adhesiveness and $[\text{Ca}^{2+}]$ than at rest. (4) The synergistic effects of clonidine on ADP-enhanced platelet adhesiveness and $[\text{Ca}^{2+}]$ after strenuous exercise are much greater than those at rest. Therefore, we conclude that strenuous, acute exercise enhances platelet activation, possibly by altering the performance of platelet $\alpha_2$-adrenergic receptors, facilitating the ability of ADP-activated fibrinogen receptors, and enhancing fibrinogen binding to platelet fibrinogen receptors. (Arterioscler Thromb Vasc Biol. 1999;19:1559-1565.)

Key Words: exercise $\square$ platelets $\square$ adhesiveness $\square$ $[\text{Ca}^{2+}]$ $\square$ catecholamines

Platelets play a critical role in the pathogenesis and progression of cardiovascular diseases. Other investigators have postulated that vigorous, short-term exercise may enhance the risk of major vascular thrombotic events and transiently increase the incidence of primary cardiac arrest. According to our previous studies of healthy men and of male patients with stable angina, strenuous, acute exercise can enhance platelet function (ie, platelet adhesiveness on a fibrinogen-coated surface and ADP-induced aggregation). However, the underlying mechanisms of strenuous, acute exercise–induced changes on platelet function remain unclear.

Although strenuous, acute exercise can enhance epinephrine release, the ability of epinephrine to induce human platelets has been the subject of extensive debate. Related investigations have confirmed that epinephrine potentiates human platelet activation; however, epinephrine is not, by itself, an activating agent. Moreover, apyrase blocks epinephrine-induced platelet activation. The aforementioned studies indicated that the platelet-stimulating effect of epinephrine occurs only in the presence of extracellular ADP or another agonist. By acting through $\alpha_2$-adrenergic receptors, epinephrine can enhance the opening of glycoprotein IIb/IIIa binding sites for fibrinogen in the presence of ADP; fibrinogen binding to the active form of the fibrinogen receptor produces platelet aggregation as well. Therefore, we hypothesized that strenuous, acute exercise might alter the performance of platelet $\alpha_2$-adrenergic receptors by increasing the endogenous release of epinephrine, thereby modifying the ability of ADP-activated fibrinogen receptors and fibrinogen to bind to platelet fibrinogen receptors.

In light of the above discussion, this study elucidates how strenuous, acute exercise affects $\alpha_2$-adrenergic agonist–potentiated platelet activation. To specifically assess platelet adhesiveness under various experimental conditions, this study used a tapered, parallel-plate chamber (ie, linear shear stress flow chamber) that provided levels of shear stress covering the entire physiological range in the human circulation. In addition, platelet $[\text{Ca}^{2+}]$, was measured by a dual-wavelength fluorescence spectrophotometer. Moreover, the number and affinity of $\alpha_2$-adrenergic sites on platelet surfaces were assayed by a receptor binding assay, and plasma catecholamine levels were measured by high-performance liquid chromatography.

Methods

Subjects
The protocol had been previously reviewed and approved by an institutional committee for the protection of human subjects. Fifteen

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sedentary men who were young and healthy were studied after they had given their informed consent and understood the experimental procedures. The physical characteristics of these subjects, expressed as mean±SEM, were age, 24.3±1.1 years; height, 169.6±1.7 cm; and body weight, 69.5±3.4 kg. These subjects had not engaged in any regular physical activity for 1 year before the study. To prevent the confounding effect of smoking,22 all subjects were nonsmokers. They abstained from all medications for at least 2 weeks before the study. Before the exercise study, subjects were familiarized with the exercise on a bicycle ergometer (Corval 400) to eliminate the effect of a new experience. They completed a medical history form and a physical activity questionnaire. The subjects then came to the laboratory to receive the exercise protocol. All subjects arrived at 1:30 PM to participate in this study to avoid a possible diurnal influence, as mentioned in a previous study.23

Exercise and Blood Collection Protocols

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 was discarded, and the remainder of the blood sample was used for the baseline assessment of hematological parameters and platelet function. The exercise protocol began at 3 PM and consisted of 2 minutes of unloaded pedaling, followed by pedaling with a continuous increment in workload, 20 to 40 W every 3 minutes, until exhaustion (ie, strenuous exercise up to maximal oxygen consumption; $V\dot{O}_2$ max). Immediately after exercise, another blood sample was collected for the measurement of the same hematological parameters and platelet function.

During exercise, the ECG was continuously monitored by a Gould ECGBiocat, recorded on a 4-channel polygraph (Gould 2400 S portable ink recorder), and a digital display of the heart rate (HR; Gould digital display). Resting blood pressure was monitored by using a sphygmomanometer (Nitinrin). The subject breathed through a large, 2-way valve (Hans Rudolph) into a 5-L mixing chamber. The fractional concentration of $O_2$ and $CO_2$ in the mixed expired gas was continuously sampled and measured with an oxygen analyzer (Ametek S3A/1, Applied Electrochemistry) and a CO$_2$ 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 by a Gould integrator to measure the tidal volume. Therefore, the data for HR, ventilation ($V\dot{I}$), oxygen consumption ($V_{O2}$), and $CO_2$ production ($V_{CO2}$) for each minute were obtained during the resting and exercise periods as described previously.3

Platelet Adhesiveness

A tapered, parallel-plate chamber, which provided shear stress values covering the entire physiological range in the human circulation,24 was used to assess platelet adhesiveness as described in a previous study.7 The linear shear stress flow chamber consisted of 4 components: a stainless steel cover plate, a glass slide plate of the heart gasket, and a plastic distributor. Ten milliliters of blood was transferred to a polypropylene tube containing sodium citrate (3.8 g/dL; 1:9 vol/vol; Sigma) and aspirin (final concentration, 100 $\mu$g/mL; Wako). Platelet-rich plasma was prepared by centrifugation at 120g for 10 minutes at room temperature. Two milliliters of platelet-rich plasma was then mixed with 4 mL of Tyrode’s-HEPES buffer (0.128 mol/L NaCl, 2.7 mol/L KCl, 0.5 $\mu$mol/L MgCl$_2$, 0.36 $\mu$mol/L NaH$_2$PO$_4$, 12 $\mu$mol/L NaHCO$_3$, and 10 $\mu$mol/L HEPES; pH 7.4) in a polypropylene tube with 0.4 mL of albumin (4 g/10 mL) acting as the “cushion” for these platelets. To prevent platelet activation during the experiment, the following inhibitors were added: 0.05 IU/mL apyrase (Sigma) to remove traces of ADP and 0.05 IU/mL hirudin (Sigma) to remove traces of thrombin. The platelet pellets were obtained after centrifugation at 700g for 10 minutes. The platelets were then resuspended in Tyrode’s-HEPES buffer with 2 $\mu$mol/L CaCl$_2$ that was free of apyrase and hirudin, and the platelet count was adjusted to 1.5 to 2.0×10$^9$/mL before measurement of platelet adhesiveness. For certain experiments, various pharmacological reagents, such as 1 $\mu$mol/L ADP (Sigma), 1 $\mu$mol/L clonidine (an $\alpha_2$-adrenergic agonist; Sigma), or 1 $\mu$mol/L Cl, were added to the platelet suspension, which was then warmed to 37°C for 2 minutes. Before the experiment started, a thoroughly cleaned glass plate was coated with 3 mg/dL human fibrinogen (Sigma). After the chamber had been assembled, it was then placed on the stage of an inverted microscope equipped with a CCD video camera (Hamamatsu). The inlet of the chamber was connected to a perfusion system. The platelet suspension was gently infused into the chamber and kept there for 5 minutes to allow the platelets to settle on the fibrinogen-coated surface. The flow chamber was then flushed with Tyrode’s-HEPES buffer for 5 minutes at a flow rate of 0.027 mL/s, which provided the range of shear stress from 55 to 0 dyne/cm$^2$. This flow chamber can generate a linear shear field with a constant shear stress gradient over the entire length of the chamber. Six field locations along the center line were observed at intervals of 1 cm from the downstream end, with $\sim0$ shear stress, and the number of remaining platelets per unit area (0.16 mm$^2$) was counted at each location. A simple linear regression line for adherent platelets, indicated as a percentage of attached platelets at the outlet, at various shear stress fields was obtained. The slope of the attached-platelet percentage versus shear stress was used as an index of platelet adhesiveness (ie, the less negative the slope, the greater the platelet adhesiveness).

Platelet [Ca$^{2+}$]$_i$

Platelets were washed by repeated centrifugation with an albumin cushion and labeled with a calcium-sensitive fluorescent dye, fura-2 AM, as described before.23 [Ca$^{2+}$]$_i$, levels were calculated from ratio values of fluorescence intensities measured at excitation wavelengths of 340 and 380 nm.26

Radioligand Binding Studies

The method used for adrenergic receptor binding assays was adopted from Gleason and Hieble.27 For saturation studies, aliquots of washed platelets ($\sim 140$ mg of protein) were incubated in an assay buffer with various concentrations of [3H]clonidine (ranging from 0.01 to 10 $\mu$mol/L; specific activity, 61.9 Ci/mmol; DuPont-NEN) in a final volume of 500 mL. After incubation for 30 minutes at room temperature, the bound and free forms of [3H]clonidine were separated by vacuum filtration (cell harvester, FH225V, Hoeffer Scientific Instruments) over 0.2% polyethylene imine–pretreated Whatman GF/B glass fiber filters. The filter discs were washed 3 times with an ice-cold, binding-assay buffer (3 mL for each time). Nonspecific binding was determined in a similar manner in the presence of a 100-fold excess of cold clonidine. Specific binding was the difference between the total and nonspecific binding. The amount of radioactivity retained on the filter was determined by liquid scintillation counting (Beckman). Affinity ($K_d$) and receptor number ($B_{max}$) were calculated from a Scatchard plot.

Plasma Levels of Catecholamines

From all subjects, an additional 5-mL blood sample was obtained, placed in a cold centrifuge tube containing EDTA (1.8 mg/mL of blood, Sigma) and glutathione (1.2 mg/mL of blood, Sigma), and immediately centrifuged at 3000g for 10 minutes at 4°C. The plasma was stored at $-80\degree$C until assay. It was analyzed for norepinephrine and epinephrine by high-performance liquid chromatography.28

Statistical Analysis

All data were expressed as mean±SEM. To compare the differences in platelet adhesiveness on fibrinogen-coated surfaces and [Ca$^{2+}$]$_i$, under various experimental conditions, at rest and immediately after exercise, the results were analyzed by the randomized block ANOVA and Tukey’s multiple range test. The $K_d$ and $B_{max}$ of $\alpha_2$-adrenergic receptors on platelets and the plasma levels of catecholamines at rest and immediately after exercise were analyzed by paired t test. Differences were considered significant at $P<0.05$.

Results

Cardiorespiratory variables at rest and maximal exercise performance are shown in Table 1. The plasma levels of both norepinephrine and epinephrine were increased immediately after strenuous, acute exercise (Table 2, $P<0.05$). Figure 1
shows an example of a Scatchard plot of [3H]clonidine binding to platelets obtained at rest and during strenuous exercise. Results demonstrated that strenuous, acute exercise decreased the binding affinity, indicated by a higher dissociation constant ($K_d$), but increased the number of binding sites ($B_{max}$) for platelet $\alpha_2$-adrenergic receptors (Figure 2 and Table 2). Furthermore, the plasma levels of both epinephrine and norepinephrine were positively correlated with $\alpha_2$-adrenergic density on platelets, but only epinephrine was negatively correlated with affinity (Table 3).

The average percentages of attached platelets at the 6 locations under various shear stresses at rest and after severe exercise are shown in Figure 3a and 3b, respectively. Although ADP and clonidine plus ADP could enhance platelet adhesiveness, indicated as the shear versus adhesion area slope, it was not changed significantly by clonidine (Figure 4a). Moreover, ADP plus clonidine—enhanced platelet adhesiveness was much greater than ADP-treated platelet adhesiveness only (Figure 5a). Therefore, although clonidine may potentiate platelet adhesiveness on fibrinogen-coated surfaces, it is not, by itself, an activating agent. Basal, clonidine-treated, ADP-treated, and clonidine plus ADP-treated platelet adhesiveness levels were all increased after strenuous exercise (Figure 4a). However, the synergistic effect of clonidine on ADP-evoked platelet $[Ca^{2+}]$, elevation tended to be more pronounced after strenuous exercise than at rest (Figure 5a, $P<0.05$).

Clonidine apparently did not induce platelet $[Ca^{2+}]$, changes at rest and after strenuous, acute exercise (Figures 4b and 5b). In contrast, platelet $[Ca^{2+}]$, was increased by ADP and by clonidine plus ADP (Figure 4b). Moreover, clonidine could potentiate ADP-evoked platelet $[Ca^{2+}]$, elevations (Figure 5b). Basal, clonidine-treated, ADP-treated, and clonidine plus ADP–treated platelet $[Ca^{2+}]$, levels were increased significantly after strenuous, acute exercise (Figure 4b). An example is demonstrated in Figure 6. However, the synergistic effect of clonidine on ADP-evoked platelet $[Ca^{2+}]$, elevation was more pronounced after strenuous exercise than at rest (Figure 5b, $P<0.05$).

**Discussion**

The results of this study can be summarized as follows: (1) Strenuous, acute exercise increases platelet $\alpha_2$-adrenergic

### TABLE 1. Cardiorespiratory Variables at Rest and After Maximal Exercise Performance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Resting</th>
<th>Maximal Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE, minutes</td>
<td>14.55±1.25</td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>130±8.9</td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>71±2</td>
<td>190±2</td>
</tr>
<tr>
<td>$V_t$, L/min</td>
<td>10.32±0.98</td>
<td>83.31±3.48</td>
</tr>
<tr>
<td>$V_O_2$, mL·min$^{-1}$·kg$^{-1}$</td>
<td>2.98±0.26</td>
<td>31.93±1.99</td>
</tr>
<tr>
<td>$V_CO_2$, mL·min$^{-1}$·kg$^{-1}$</td>
<td>2.11±0.16</td>
<td>38.71±3.28</td>
</tr>
<tr>
<td>$R$</td>
<td>0.73±0.04</td>
<td>1.21±0.04</td>
</tr>
</tbody>
</table>

Values are mean±SEM. TE indicates time to exhaustion; $R$, respiratory exchange ratio.

### TABLE 2. Comparison of Plasma Catecholamine Levels and Receptor Number ($B_{max}$) and Affinity ($K_d$) for [3H]Clonidine Binding Platelets During Rest and After Strenuous, Acute Exercise

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>At Rest</th>
<th>After Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.41±0.09</td>
<td>26.76±0.67*</td>
</tr>
<tr>
<td>Norepinephrine, pmol/mL</td>
<td>0.32±0.01</td>
<td>3.37±0.09*</td>
</tr>
<tr>
<td>Epinephrine, pmol/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$[3H]$Clonidine binding to platelets</td>
<td>B$_{max}$, fmol/mg protein</td>
<td>2.85±0.59</td>
</tr>
<tr>
<td></td>
<td>$K_d$, nmol/L</td>
<td>0.46±0.11</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

* $P<0.05$ rest vs exercise, analyzed by paired t test.
receptor density and is accompanied by a decrease in affinity, thereby correlating with the rise in plasma catecholamine levels. (2) Strenuous exercise increases basal, clonidine-treated, ADP-treated, and clonidine plus ADP–treated platelet adhesiveness and [Ca^{2+}]_i. (3) The percentages of ADP- and clonidine plus ADP–enhanced platelet adhesiveness and [Ca^{2+}]_i, after strenuous, acute exercise are greater than those at rest. (4) Strenuous, acute exercise can enhance clonidine-potentiated platelet adhesiveness on fibrinogen-coated surfaces and [Ca^{2+}]_i elevations.

As is well known, the risk of primary cardiac arrest transiently increases during vigorous exercise.4–6 In addition, strenuous, acute exercise can significantly increase the release of plasma epinephrine.9,10 In vivo and in vitro observations confirm the relevance of epinephrine-mediated platelet activation in thrombosis. In experimental studies, thrombosis has been induced by injecting epinephrine into animals with coronary artery stenosis.29 In vitro studies have demonstrated that epinephrine induces the aggregation of human platelets and potentiates the aggregation induced by low concentrations of various platelet agonists such as ADP,15 platelet-activating factor,20 and thrombin.22 Previous studies have suggested that the intrinsic platelet-activating effect of epinephrine may play a role in activating α_2-adrenoceptors in human platelets to (1) inhibit the adenylate cyclase system through coupling to a G_i protein16 and (2) enhance the opening of glycoprotein IIb/IIIa binding sites for fibrinogen in the presence of ADP or other agonists.18 Our previous study with healthy women as subjects indicated that although the platelet cAMP content remains unchanged after strenuous, acute exercise, severe exercise can enhance prostacyclin production.30 Although epinephrine levels enhanced by severe exercise could inhibit adenylate cyclase activity through activating platelet α_2-adrenoceptors, the effect may be attenuated by exercise-induced prostacyclin production. This study reports, for the first time, that strenuous, acute exercise may alter the performance of platelet α_2-adrenergic receptors by increasing the endogenous release of catecholamines, thereby facilitating the ability of ADP-activated fibrinogen receptors and enhancing fibrinogen binding to platelet fibrinogen receptors. The enhanced platelet activity in severe exercise may accelerate the formation of hemostatic platelet
platelets decreases while the B max significantly increases after exercise, 31 or remains unchanged 32,33 in response to exercise, a result observed in this study; ie, the affinity of 2-adrenergic receptors on exercise-released splenic platelets could be synthesized, or preexisting receptors could be externalized. Alternatively, the apparent increase in receptor density could be ascribed to an increase in the population of splenic platelets with a high density of receptors. However, the splenic platelet population (though having a larger mean platelet volume) appears to have an age and a density distribution similar to those of the population of platelets in the basal circulation.38 Further studies involving platelet 2-adrenergic receptors on exercise-released splenic platelets are necessary to clarify this issue.

In the current study, changes in the density of receptors occurred rapidly, ie, over ~15 minutes. It is unlikely that new receptors could be synthesized during such a short period of time. However, externalization of receptors could have occurred over this period. Previous investigators have observed the rapid externalization of myocardial 2- and 2-adrenergic receptors, accompanied by a local release of endogenous platelet adhesiveness and [Ca2+]i. Moreover, the synergistic effects of clonidine on ADP-enhanced platelet adhesiveness and [Ca2+]i were more pronounced after strenuous exercise than at rest.

Figure 6. Examples of clonidine-potentiated platelet [Ca2+]i elevation at rest (a) and after strenuous, acute exercise (b). Clonidine did not induce changes in platelet [Ca2+]i either at rest or after exercise. In contrast, platelet [Ca2+]i was increased by ADP and ADP plus clonidine. Moreover, clonidine potentiated the ADP-evoked platelet [Ca2+]i elevation. However, the synergistic effect of clonidine on ADP-evoked platelet [Ca2+]i was more pronounced after strenuous exercise than at rest.
catecholamines, after the onset of myocardial ischemia (15 minutes).\textsuperscript{38,39} A previous study also revealed that agonist-promoted internalization and functional uncoupling of the receptors are abolished after acute myocardial ischemia.\textsuperscript{38} In addition, strenuous, acute exercise can increase the release of endogenous catecholamines.\textsuperscript{9,10} Moreover, with the increased extraction of oxygen from the arterial blood during strenuous exercise, the venous blood leaving the muscles has an extremely low oxygen content.\textsuperscript{40} Therefore, venous hypoxia accompanied by the increased epinephrine release due to strenuous, acute exercise may upregulate platelet $\alpha_2$-adrenergic receptors and attenuate the extent of agonist-promoted downregulation, as with myocardial adrenergic receptors after acute ischemia, thus further enhancing $\alpha_2$-adrenergic agonist–potentiated platelet activity.

Previous investigations have demonstrated not only that platelets stimulated by ADP expose fibrinogen receptors (ie, glycoprotein IIb/IIIa) on their surfaces but also that fibrinogen binding to the active form of the fibrinogen receptor produces platelet aggregation.\textsuperscript{41,42} Figures et al\textsuperscript{17} have suggested that the promotion of platelet aggregation and the exposure of fibrinogen receptors by epinephrine depend on ADP. In addition, epinephrine-mediated platelet activation may be attributed to an alteration in the avidity of ADP binding. Moreover, epinephrine that promotes exposure of glycoprotein IIb/IIa sites for fibrinogen binding is also a possible requirement for $\mathrm{Ca}^{2+}$ influx.\textsuperscript{18} Clonidine is an agonist with a high affinity for $\alpha_2$-adrenergic receptors.\textsuperscript{43} Results of this study demonstrate that platelet adhesiveness on fibrinogen-coated surfaces and [Ca$^{2+}$], levels, though enhanced by both ADP and clonidine plus ADP, were not significantly changed by clonidine alone. Moreover, ADP plus clonidine enhanced these platelet functional parameters to a much greater extent than did ADP alone. These results indicate that clonidine may potentiate human platelet activation but is not, by itself, an activating agent.

Regarding the effect of exercise, strenuous exercise increased basal, clonidine-treated, ADP-treated, and clonidine plus ADP–treated platelet adhesiveness on fibrinogen-coated surfaces and [Ca$^{2+}$],. In 1993, Kestin et al\textsuperscript{44} found that strenuous exercise could activate fibrinogen receptors. Their findings correspond to some of our results. Our results further demonstrate that the synergistic effects of an $\alpha_2$-adrenergic agonist on ADP-enhanced platelet adhesiveness and [Ca$^{2+}$], elevation are more pronounced after strenuous exercise than at rest. Therefore, strenuous exercise can enhance $\alpha_2$-adrenergic agonist–potentiated platelet activation.

In conclusion, strenuous, acute exercise can enhance $\alpha_2$-adrenergic agonist–potentiated platelet adhesiveness on fibrinogen-coated surfaces and [Ca$^{2+}$], elevation, possibly attributed to the acute increase in catecholamines in response to exercise, and ultimately enhancing $\alpha_2$-adrenoreceptor performance. The enhanced performance facilitates the activity of fibrinogen receptors and the fibrinogen binding to platelet fibrinogen receptors. Therefore, our findings provide further insight into the notion that strenuous, acute exercise augments the risk of major vascular thrombotic events partially because severe exercise may increase endogenous catecholamines (ie, epinephrine and norepinephrine), which in turn may augment platelet activation.

Acknowledgments

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