Platelet Hyperaggregability Across the Coronary Bed in Response to Rapid Atrial Pacing in Patients With Stable Coronary Artery Disease

Jean G. Diodati, MD; Richard O. Cannon III, MD; Stephen E. Epstein, MD; and Arshed A. Quyyumi, MD, MRCP

Background. Platelet aggregation is believed to contribute to the precipitation of acute ischemic syndromes. Because physical activity has been proposed as one possible trigger in converting a patient with chronic coronary artery disease to one with an acute ischemic syndrome, we examined the hypothesis that platelets become activated when coronary blood flow velocities (and thereby shear stress) increase across an atherosclerotic bed.

Methods and Results. During catheterization, 82 patients (36 with left coronary artery disease, 12 with only right coronary artery disease, and 34 with normal coronary arteries) had measurement of whole blood platelet aggregation performed on blood samples obtained simultaneously from the coronary sinus and aorta at rest, 2 minutes after onset of rapid atrial pacing, and 10 minutes after pacing was terminated. There was no arteriovenous difference in platelet aggregation under resting conditions in patients with versus those without coronary artery disease. Atrial pacing in patients with left coronary artery disease (≥50% stenosis in a major epicardial vessel) caused an increase in platelet aggregation in the coronary sinus blood (+64±9%, p<0.01) but not in arterial blood (2±8% decrease, p=NS). This increase was transient and returned nearly to baseline 10 minutes after termination of pacing. Patients with nonsignificant left coronary artery disease, those with normal coronary arteries, and patients with significant disease only in the right coronary artery (venous drainage not into the coronary sinus) did not show any changes in either the coronary sinus or arterial blood with atrial pacing.

Conclusions. There is no evidence of platelet activation across a normal or an atherosclerotic coronary bed at rest. When coronary blood flow increases in the presence of significant (≥50%) narrowing of epicardial coronary arteries, however, platelets are activated and aggregate more easily. This mechanism may play a role in the precipitation of acute ischemic syndromes in patients with coronary artery disease.

Key Words • platelets • coronary artery disease • coronary circulation • whole blood impedance aggregometry

Platelet activation and resulting aggregation undoubtedly play an important role in the precipitation of acute ischemic syndromes.1–11 Because the onset of acute ischemic syndromes can at times relate to physical activity12,13 and to emotional stresses,14–16 it has been suggested that platelets become activated when blood flow velocity (and thereby shear stress) increases across an atherosclerotic bed. The results of several investigations directed to this issue in patients with stable coronary artery disease have been conflicting.17–27 Many of these studies, however, have used techniques for measuring platelet aggregation with methodological limitations—either they depended on platelets already having released their products or having aggregated, or they involved extensive preparation of plasma before assessment of aggregability.

Because of these limitations, we have been using ex vivo whole blood impedance platelet aggregometry to assess the effects of various conditions on platelet activation.28 This method makes it possible to study platelet function in whole blood within a few minutes of withdrawal of the sample from the patient. It also avoids the complex processing of blood samples that is required, for example, in preparation of platelet-rich plasma and thus is more likely to represent the in vivo status of platelets at the time the blood sample was obtained. Hence, the purpose of this investigation was to use immediate whole blood impedance aggregometry to define whether platelets are activated in the coronary circulation in patients with coronary artery disease under conditions of either resting or increased coronary blood flow.

Methods

Patient Selection

Eighty-two consecutive patients 31–75 years old (average age, 58 years) undergoing cardiac catheterization with coronary angiography for assessment of their chest pain were included in this study (Table 1). Thirty-six
patients had angiographically documented left coronary artery disease with ≥50% diameter narrowing involving at least one major branch of the left coronary artery. These patients had the majority of the coronary venous drainage of the left system into the coronary sinus. Twelve patients had ≥50% diameter narrowing involving only the right coronary artery, a region generally not drained by the coronary sinus; all of these patients had plaques (<50% stenosis) involving at least one major branch of the left coronary artery. Finally, 34 patients had angiographically normal epicardial coronary arteries; 12 had plaques (<50% diameter narrowing) involving at least one major coronary artery, and the remaining 22 had entirely smooth coronary arteries by angiography.

Patients with unstable angina or a myocardial infarction within 2 months of the study were excluded. All cardiac medications were withdrawn for at least 48 hours before the study, and patients refrained from smoking29 and intake of caffeine for at least 12 hours before the study. Aspirin and other agents known to alter platelet function were discontinued at least 10 days before the study. Factors suspected of affecting platelet aggregation, such as the hematocrit,30,31 platelet count, and total cholesterol,32 were not significantly different in all three diagnostic groups (Table 1). Because of the known circadian variation in platelet aggregation,12 we ensured that the time at which the study was performed was not significantly different among the groups and that all patients remained supine for at least 1 hour before blood sampling for assessment of platelet aggregation was performed.13 Informed consent was obtained from all patients, and the study was approved by the Investigational Review Board of the National Heart, Lung, and Blood Institute.

**Cardiac Catheterization**

Catheter sheaths (10 cm, 8F) were inserted into the femoral artery and vein and the internal jugular vein. Under fluoroscopic control, a 110-cm-long catheter equipped with a pacing electrode (Cordis Lumelec Multipurpose A-2) was advanced via the internal jugular vein into a mid–coronary sinus position. In 22 patients, a 110-cm catheter was also placed into the right atrium via the femoral vein. Heparin was not administered during the study.

Blood samples were obtained simultaneously from the femoral artery, femoral vein, right atrium, and coronary sinus in the first 22 patients and from the femoral artery and coronary sinus in the remaining 60 patients. After uninterrupted blood flow was ensured, 2.25 ml of blood was obtained for testing from each site after the first 3 ml was discarded. Samples were obtained at rest, at the end of a 2-minute period of rapid atrial pacing, and 10 minutes after termination of pacing. The pacing rates varied between 110 and 150 beats per minute (mean, 138 beats per minute) and are summarized in Table 1. Standard three-lead ECG monitoring was used to evaluate ST segment changes before, during, and immediately after rapid atrial pacing. Occurrence of chest pain was also monitored.

**Platelet aggregation studies.** Platelet aggregation was measured with a mobile, four-channel impedance aggregometer (Chronolog Corporation, Havertown, Pa.,),33 which allowed measurement of aggregation beginning 1 minute after collection of the sample from the patient.28 Blood (2.25 ml) was collected in preheated plastic syringes containing 0.25 ml sodium citrate (3.8%) at a pH of 7.4. All materials in contact with blood were kept strictly at 37°C. Platelet aggregation was tested at 37°C in whole blood diluted 1:1 in sterile physiological saline. Samples were never in contact with glass. Aggregation was initiated by adding 2–10 μl of aggregating agents: 1) collagen 2–5 μl (to a final concentration of 2–5 μg/ml) and 2) adenosine diphosphate (ADP) 2.5–10 μl (to a final concentration of 5–20 μM). Aggregation was quantified as 1) the surface area under the curve relating electric impedance to time (ohm · seconds), 2) maximum amplitude (ohms), and 3) maximum rate of rise (ohms per second) 5 minutes after addition of the aggregating agent. Results were similar using either method; therefore, only surface area measurements are reported. In our previous study,28 we had demonstrated, using whole blood technique, that on repeated measurements, platelet aggregation values were within 10% of the previous measurement using ADP and thrombin as platelet-aggregating agents.

A standard screen on the initial blood sample was performed in each patient with both agents at two

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Left coronary artery disease (n=36)</th>
<th>Normal coronary arteries (n=34)</th>
<th>Right coronary artery disease (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>31/5</td>
<td>9/25</td>
<td>6/6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>59±8</td>
<td>55±12</td>
<td>64±6</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit (%), mean±SD</td>
<td>44±4</td>
<td>41±3</td>
<td>42±3</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count (10^9/mm^3), mean±SD</td>
<td>251±54</td>
<td>293±82</td>
<td>267±72</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl, mean±SD)</td>
<td>229±36</td>
<td>231±55</td>
<td>241±38</td>
<td>NS</td>
</tr>
<tr>
<td>Time of study (mean)</td>
<td>11:15 AM</td>
<td>10:00 AM</td>
<td>11:00 AM</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease (≥50%)</td>
<td>One-vessel 7</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two-vessel 10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three-vessel 19</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pacing rate [bpm, range (mean)]</td>
<td>110–150 (133)</td>
<td>130–150 (142)</td>
<td>110–140 (127)</td>
<td>NS</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.
concentrations (collagen, 2 and 5 µg/ml; ADP, 5 and 20 µM) in order to obtain a dose for each agent that would give an intermediate response. Any change in aggregation with further intervention could thus be easily measured.

Lactate, oxygen, and catecholamine measurements. Blood specimens were collected from the artery and the coronary sinus for measurement of oxygen, lactate, and catecholamine content with each intervention. For lactate measurement, blood was collected in tubes containing sodium fluoride and potassium oxytate for inhibition of glycolysis and was immediately centrifuged at 4°C at 5,000 rpm for 5 minutes. The decanted serum was then processed for lactate content on a DuPont automatic clinical analyzer by a modification of the technique of Marbach and Weil. Oxygen content was measured using a Lex-O₂-Con oxygen analyzer (Lexington Instruments). For catecholamine levels, blood was collected in plastic syringes and immediately transferred to chilled, evacuated, heparinized glass tubes and put on ice. The plasma was separated by refrigerated centrifugation and stored at −70°C until assayed. Concentrations of noradrenaline and epinephrine were measured by batch alumina extraction followed by high performance liquid chromatography with electrochemical detection.2

Statistical Analysis
Results are expressed as mean±SEM. Mean values from each site of collection at rest, during pacing, and after recovery in each of the three diagnostic groups were compared by ANOVA for repeated measures. A value of p<0.05 (two-sided test) was considered significant for within-group and between-group differences. Correlation studies were performed with linear regression techniques. Discrete variables were analyzed by Fisher’s exact test. Again, a value of p<0.05 (two-sided test) was considered significant.

Results
Platelet Aggregation at Rest
No differences in platelet aggregation were observed at rest between all four sites of collection in patients with or those without coronary artery disease. Platelet aggregation values pooled from the first 22 patients (eight patients with coronary artery disease and 14 normal patients) who had measurements at baseline from the coronary sinus, the right atrium, the femoral vein, and the aorta were 312±35, 249±36, 283±37, and 308±39 Ω · sec, respectively (p=NS). Thus, there was no difference in platelet aggregation when venous blood sampling was performed with a long catheter (110 cm, right atrium) compared with a short catheter (10 cm, femoral vein). There was also no difference in platelet aggregation between arterial and peripheral venous blood under resting conditions in patients with or those without coronary artery disease. Finally, there was no activation of platelets across the coronary circulation under resting conditions in patients with or those without coronary artery disease; mean platelet aggregation in the 36 patients with left coronary artery disease was 183±18 Ω · sec in the coronary sinus compared with 254±26 Ω · sec in the aorta (p=NS). Similarly, mean platelet aggregation in the 34 patients without significant coronary artery disease was 383±27 Ω · sec in the coronary sinus compared with 420±27 Ω · sec in the aorta (p=NS). However, resting platelet aggregation values were lower in both coronary sinus and arterial samples in the patients with significant coronary artery disease compared with the normal subjects (p<0.05).

Platelet Aggregation With Atrial Pacing
With atrial pacing, platelet aggregation did not increase in coronary sinus blood of patients either with normal coronary arteries or with significant disease only in the right coronary artery, but it did increase (+64±9%) in coronary sinus blood of patients with left coronary artery disease (venous drainage into the coronary sinus) (Figure 1). A representative example of a patient with left coronary artery disease is shown in Figure 2, where an increase in platelet aggregation initiated with collagen is seen only in the coronary sinus blood during rapid atrial pacing. Aggregation initiated with ADP produced results similar to those with collagen. Almost 90% of patients with left coronary artery disease had a ≥10% increase in platelet aggregation after atrial pacing compared with resting value, and about 70% had a ≥50% increase. In contrast, ≥10%
increase in platelet aggregation occurred in only 10% of patients with normal coronary arteries and ≥50% in only 6% of patients (p<0.001) (Figure 3).

Of the 36 patients with ≥50% diameter narrowing in the left coronary artery, there was no correlation between the severity of the coronary stenosis and the extent of platelet activation. Thus, patients with >70% stenosis had activation across the coronary circulation similar to that observed in those with narrowing ranging between 50% and 70% (Table 2).

There were no differences in the paced heart rates among the different diagnostic groups (Table 1) or in patients with compared with those without chest pain. There was also no correlation between the occurrence of chest pain and the severity of stenosis in the patients with ≥50% stenosis.

The increase in platelet aggregation with pacing in patients with left coronary artery disease was reversible and returned to within 10% of baseline (NS) after 10 minutes (Figures 1 and 2).

The magnitude of platelet activation across the coronary circulation in patients with left coronary artery disease was not related to the presence or absence of myocardial ischemia induced by rapid atrial pacing assessed either by the development of chest pain or by ischemic-appearing ST segment changes (Table 2).

In addition, of nine patients in whom lactate content was measured in the coronary arterial and venous circulation, seven demonstrated narrowing of the arteriovenous lactate difference, and two patients demonstrated venous lactate production. There was no correlation between the magnitude of increase in platelet aggregation and the change in lactate content in the coronary sinus. Finally, there was also no correlation between the magnitude of platelet activation and the widening of the arteriovenous oxygen difference across the coronary circulation in the 10 patients in whom it was measured.

Catecholamines were measured in the coronary sinus, femoral artery, and peripheral vein at rest and after pacing in nine patients with left coronary artery disease and in 11 normal patients. The change in catecholamine levels did not correlate with the change in platelet aggregation. Furthermore, there was no difference in the magnitude of catecholamine response between the patients with coronary artery disease and normal subjects.

**Discussion**

In this study, we used immediate whole blood impedance aggregometry to measure platelet aggregation, a method that assesses the extent to which platelets are activated in whole blood immediately after blood is obtained from the patient. With this method, we demonstrated that when coronary flow increases in response to rapid atrial pacing, platelet activation increases across the coronary bed (as reflected by a decreased threshold for aggregation) but only in the coronary circulation of patients with ≥50% narrowing in one or more branches of the left coronary artery. The observed increase is transient, lasting approximately 10 minutes. In contrast, platelets are not activated across the coronary circulation under resting conditions either
in subjects with or in those without significant left coronary artery disease.

Several potential causes might contribute to the tachycardia-induced activation of platelets we observed in patients with significant coronary artery disease. Platelets can be activated by physical interaction with the vessel wall, by circulating substances, or by locally released factors such as thromboxane A$_2$. For example, thromboxane A$_2$ production is stimulated in aggregating platelets by activation of the arachidonic cascade, and subthreshold doses of arachidonic acid result in platelet hyperaggregability during in vitro testing. Other factors produced by aggregating platelets, such as thrombin, ADP, serotonin, and platelet activating factor, can also stimulate further platelet aggregation. Likewise, increasing shear has been demonstrated to cause platelet hyperaggregability in vitro.

The vessel wall can exert proaggregatory effects if it contains atheromatous plaques and the thrombogenic material within a plaque becomes exposed to the circulating blood. If endothelin is released by endothelial cells; it can exert antiaggregatory effects if prostacyclin (PGI$_2$) or endothelin-derived relaxing factors are released by endothelial cells.

Under normal circumstances, the net effect of the proaggregatory and antiaggregatory influences of the vessel wall is such that platelets are not activated, do not adhere to the vessel wall, and do not aggregate. Certain pathophysiological stimuli, however, tilt the balance in favor of platelet activation and aggregation. Thus, with atherosclerosis, endothelial cells covering plaques are probably dysfunctional, such that their capacity to release potent antiaggregatory products is compromised. Hence, during rapid atrial pacing in patients with coronary stenoses, the proaggregatory factors appear to override the antiaggregatory stimuli. This results in priming of platelets in the coronary circulation, which can be detected during ex vivo testing as increased aggregation in response to collagen or ADP. Another example, which is the most common cause of acute ischemic syndromes, is the development of a fissure in an atherosclerotic plaque; this exposes circulating platelets to the potent thrombogenic material contained within the plaque.

The results of our study suggest that atherosclerotic lesions per se do not activate platelets during tachycardia unless there is a hemodynamically significant narrowing of the coronary artery lumen. Thus, several of our patients had only minimal disease of the left coronary artery, and all of our patients with significant disease involving only the right coronary artery also had atherosclerosis (≤50% narrowing) involving the left coronary artery. Platelet activation in response to the pacing-induced increase in coronary blood flow did not occur in the 12 patients with ≥50% stenosis involving the right coronary artery as it did in patients with significant narrowing in the left coronary circulation. By placing the catheter in the mid to high coronary sinus position in these patients, we selectively sampled blood draining the left coronary artery, because the venous drainage from the right coronary artery is either close to the origin of the coronary sinus or directly into the right heart chambers. The lack of increase in platelet activation across the left coronary circulation of these patients provides further evidence that the increased thrombogenicity of hemodynamically insignificant atherosclerotic plaques, if it exists at all, is not sufficient to measurably activate platelets with this methodology, even when coronary blood flow is increased. The increase in activation in patients with hemodynamically significant left coronary artery disease is thus more likely to be the result of stenosis-induced increase in shear stress on the platelet membrane. This concept of a significant stenosis causing increased shear stress, with resultant increase in platelet adhesion and aggregation, is supported by previous in vitro and animal studies.

Influences other than increased shear stress precipitated by the tachycardia-induced increase in flow could have contributed to activation of platelets across the coronary bed. For example, it has been suggested that myocardial ischemia increases platelet activation. If so, it is possible that the pacing stimulus we used caused ischemia, which caused or contributed to platelet activation. We did not find any correlation, however, between

### Table 2. Platelet Aggregation in the Coronary Sinus With Atrial Pacing in Subsets of Patients With Left Coronary Artery Disease

<table>
<thead>
<tr>
<th>Stenosis Category</th>
<th>n</th>
<th>Baseline</th>
<th>Pacing</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease (≥50%)</td>
<td>36</td>
<td>183±18</td>
<td>329±28</td>
<td>NS</td>
</tr>
<tr>
<td>Severity of stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>50–70%</td>
<td>10</td>
<td>160±20</td>
<td>307±19</td>
<td></td>
</tr>
<tr>
<td>&gt;70%</td>
<td>26</td>
<td>192±7</td>
<td>337±31</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>14</td>
<td>182±38</td>
<td>361±36</td>
<td>NS</td>
</tr>
<tr>
<td>Absent</td>
<td>22</td>
<td>183±36</td>
<td>309±27</td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
<td>156±28</td>
<td>291±31</td>
<td>NS</td>
</tr>
<tr>
<td>Absent</td>
<td>19</td>
<td>207±29</td>
<td>363±32</td>
<td></td>
</tr>
<tr>
<td>Chest pain + ST depression</td>
<td>10</td>
<td>151±26</td>
<td>366±46</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>192±22</td>
<td>367±28</td>
<td></td>
</tr>
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</table>

Values are expressed as mean±SEM of extent of platelet aggregation (ohm·seconds).
the magnitude of increase in pacing-induced platelet aggregation and the presence or absence of chest pain, ST segment depression, or changes in lactate or oxygen content in the coronary sinus. Alternatively, catecholamine release may have contributed to platelet activation.65-68 However, the magnitude of change in plasma epinephrine and norepinephrine was similar in patients whose platelets were activated and those whose platelets were not. This finding suggests that catecholamines did not play a role in activating platelets under the conditions of pacing-induced tachycardia and increased coronary flow that we used. Whether other factors, such as fibrinolytic or thrombotic activities, are altered in the coronary circulation during pacing and contribute to platelet activation is at this time unknown and is a limitation of the present study.

A variety of methods have been used in the study of platelet activation, which may account for the diversity of results reported in the literature. Indexes of platelet activation have included measurement of platelet factor IV,69-71 β-thromboglobulin,17,70 thromboxane B2,18-21 and serotonin9,11,72 and actual counting of platelets17,22-25 and platelet aggregate ratios.17,26,27 Not only are controversies involved in these measurements, however, but also an abnormality in any of these parameters depends on either platelet aggregate formation, degranulation, or both occurring in vivo. These indexes may therefore be insensitive tests of increased platelet activation—i.e., the situation in which the threshold for platelet aggregation is lowered but actual platelet release or aggregation has not yet occurred.

Light-transmission aggregometry, a commonly used method of measuring the degree of activation of platelets,17,22-25,73 requires the use of platelet-rich plasma. The extensive preparatory steps and the time involved in the preparation of platelet-rich plasma could modify platelet behavior, lead to the loss of important subpopulations of platelets, and also result in a loss of short-half-life mediators that modify platelet behavior, such as prostacyclin PG12 and thromboxane A2. Furthermore, red blood cells and other components of whole blood, which are known to affect platelet behavior, are excluded from the artificial milieu of platelet-rich plasma. By studying platelet aggregation in whole blood, and doing so within 1 minute of blood collection, we believe we are closer to examining the state of platelet activation in vivo. The advantage of using impedance aggregometry is illustrated in a previous study carried out by one of the authors (J.G.D.).28

We chose ADP and collagen as aggregating agents. There is no evidence to suggest, however, that the demonstration of increased platelet aggregation with a given aggregating agent in vitro (be it ADP, collagen, platelet activating factor, epinephrine, arachidonic acid, thrombin, or ristocetin) implies that there is a causal pathophysiologic link between the agent and platelet aggregation in vivo, because once platelets are activated, they react more to any aggregating agent used in vitro, i.e., the response is nonspecific. Thus, using a more physiological aggregating agent does not help establish the pathophysiologic link between the agent used and the phenomenon described, and such a link could be made only if specific inhibitors were used in vivo.

Resting platelet aggregation was lower in patients with significant coronary artery disease than in normal subjects (Figure 1). Because of frequent repeated episodes of platelet activation in these patients, it is possible that downregulation of certain critical platelet receptors occurs, rendering the platelets relatively refractory to baseline low-intensity stimuli. Receptor downregulation as a result of chronic stimulation has been frequently described in biological systems.74 Another explanation for these lower resting values in patients with coronary artery disease could be related to sex differences. Previous studies have demonstrated higher platelet aggregability in female subjects than in male.75-78 In this study, there were significantly more male patients in the left coronary artery disease group (31 of 36) than in the normal coronary artery group (nine of 34; p<0.05) (Table 1), which may have accounted for the baseline differences in platelet aggregation observed between these two groups. When analyzed separately, however, both male and female patients had similar responses within the three groups. Still, even considering that one or both of these explanations were true and the patients with coronary artery disease had a high threshold for aggregation, the trigger for platelet activation during pacing was strong enough to overcome it.

Conclusions and Implications

The present investigation demonstrates that platelets are activated across the coronary bed when coronary blood flow increases in patients with significant atherosclerotic narrowing of epicardial coronary arteries. By decreasing the threshold necessary to precipitate platelet aggregation, platelet activation may contribute to the precipitation of acute occlusive syndromes (acute myocardial infarction or sudden cardiac death) associated with tachycardia-induced increases in coronary blood flow as occur with exercise and with emotional stresses. Tachycardia-induced platelet activation, with subsequent release of platelet products that have vasoconstrictor activities, may also exacerbate exercise-induced angina. Finally, it is now generally accepted that the migration of smooth muscle cells from the media to the intima and their proliferation in the atherosclerotic plaque contribute importantly to the development and progression of atheroma.79 Therefore, it is possible that repeated tachycardia-induced activation of platelets across the coronary bed over months or years, if accompanied by release of constituents of platelets that have mitogenic properties,80-82 may also contribute to the progression of atherosclerosis.

It must be emphasized that the long-term benefits of exercise may override the theoretical harm of platelet activation in the coronary circulation demonstrated in this study.

Acknowledgments

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