Excretion of Thromboxane A2 and Prostacyclin Metabolites Before and After Exercise Testing in Patients With and Without Signs of Ischemic Heart Disease

Åke Wennmalm, MD, PhD, Jacek Nowak, MD, PhD, and Thorvald Bjurö, MD, PhD

We addressed the hypothesis that platelets are not activated in association with effort-induced myocardial ischemia in stable coronary disease. Seventy-two patients undergoing a diagnostic bicycle exercise test were stratified according to the development of chest pain (yes/no, 33/39) and of exercise-induced ST-segment depression of at least 200 μV in the electrocardiogram (yes/no, 12/60). Noninvasive indexes of platelet activation and of platelet/vessel wall interaction (urinary excretion of the 2,3-dinor-metabolites of thromboxane A2 [Tx-M] and prostacyclin [PGI-M], respectively) were analyzed in samples collected in the basal state and after the test. Basal Tx-M and PGI-M did not differ in patients with (236±35 and 131±22 pg/mg creatinine, respectively) and without (185±16 and 101±13 pg/mg creatinine, respectively) chest pain, or in those with (178±45 and 162±41 pg/mg, respectively) and without (216±22 and 104±11 pg/mg, respectively) ST-segment depression during the test. Patients without chest pain or without ST-segment depression moderately increased (p<0.05) their urinary Tx-M (by 21% and 13%, respectively) and PGI-M (by 28% and 23%, respectively) after exercise. No significant increases were observed in those developing chest pain or ST depression during exercise. These data indicate that effort-induced myocardial ischemia is not associated with an increase in platelet activation or platelet/vessel wall interaction in patients with stable coronary disease. (Circulation 1990;82:1737–1743)

Thromboxane A2 (Tx-A2) and prostacyclin (PGI2) are the main eicosanoids formed in the cardiovascular system. Tx-A2 is a potent vasoconstrictor and platelet aggregator,1 and PGI2 is a vasodilator and platelet antiaggregatory compound.2,3 On the basis of their pronounced biological actions, these eicosanoids have been implicated in various clinical settings of ischemic heart disease.

To assess the endogenous formation of Tx-A2 and PGI2, in vivo noninvasive procedures are preferable because vascular puncture leads to a rapid and pronounced increase in the biosynthesis of either compound that elevates the true plasma concentration severalfold.4–5 Analysis of the urinary excretion of the 2,3-dinor-metabolites of Tx-A2 (Tx-M)6 and PGI2 (PGI-M)7 offers a noninvasive possibility to circumvent such artifactual formation of these compounds.

With this approach, increased formation rates of both Tx-A2 and PGI2 have been demonstrated in patients with acute myocardial infarction8,9 and unstable angina.10 Several types of evidence supporting an etiological significance of Tx-A2 in ischemic heart disease have also been presented. Lewis et al10 reported that aspirin, an inhibitor of the Tx-A2-forming and PGI2-forming enzyme cyclooxygenase, diminished the incidence of death or acute myocardial infarction by more than 50% in patients with unstable angina. More recently, large epidemiological studies have demonstrated that aspirin may be efficient in the prevention of both primary11 and secondary12 acute myocardial infarction.

The object of platelet activation in patients with stable coronary disease is significant because such patients are often encouraged to perform moderate physical exercise. We hypothesized that effort-induced angina in stable coronary disease is not associated with platelet activation. To test this, we stratified patients undergoing a routine diagnostic exercise test according to the occurrence of signs of
effort-induced myocardial ischemia (EMI), and followed their urinary Tx-M and PGI-M before and after exercise as indexes of platelet activation and platelet–vessel wall interaction.

Methods

Subjects

Patients admitted to the Department of Clinical Physiology at Sahlgrenska Hospital (Gothenburg, Sweden) for a diagnostic bicycle exercise test were studied. The inclusion criteria were an admittance history of suspected angina pectoris, and lack of medication with digitalis or any kind of nonsteroidal anti-inflammatory drug during the week preceding the study. Furthermore, no signs of myocardial infarction or bundle branch block in the electrocardiogram (ECG) were allowed. All patients were informed about the purpose and nature of the study before giving their consent to participate. The exercise test was performed entirely on clinical grounds, and the only procedure performed in addition to routine was the collection of the urinary samples. Ten patients were excluded because they were unable to deliver a basal urinary sample. Another five patients were unable to void after the exercise test, and were likewise excluded. A total of 72 patients were finally included.

In another series performed to control the accuracy of the urine collection intervals, authentic TxB₂ was infused in five healthy volunteers.

Protocol

Before the test, all patients delivered a basal urinary sample. They were then given 250 mL water orally to ensure adequate diuresis. Subsequently, a resting 12-lead ECG was recorded. During exercise, the six chest leads V₁–V₆ were continuously recorded on a modified Mingograph 61 (Siemens-Elema, Stockholm, Sweden). Additionally, an eight-lead bipolar ECG was continuously recorded for subsequent computerized analysis. In this analysis, each ECG signal was sampled at 500 Hz by a PDP 11/40 computer (Digital Equipment, Maynard, Calif.). Averaging was performed in consecutive 10-second periods, after sorting out of aberrant beats. Heart rate was given as the median value over 10-second periods by the computer. The ST amplitude was measured 60 msec after the end of the QRS and referenced to the amplitude 15 msec before the beginning of the QRS.

The bicycle exercise was performed on an electrically braked bicycle ergometer (Siemens-Elema, Stockholm, Sweden) as a continuous ramp, with an increase in work load of 10 W/minute. Besides the continuous ECG, sphygmomanometric blood pressure was recorded every minute, and respiratory frequency every second minute. The patients were asked by the technician running the test or by the supervising physician about experienced fatigue or appearance of chest pain every minute. Fatigue was quantitated by using a 0–20 grade score. Chest pain was evaluated by using a 1–4 grade score, in which the angina was characterized by the patient as light (score 1), moderate (score 2), rather strong (score 3), or severe (score 4).

Patients experiencing no chest pain and no ECG changes were encouraged to continue the exercise as long as possible. If chest pain or other symptoms materialized during the exercise, the supervising physician decided when to interrupt the test, unless the patient did so himself. If chest pain was the only positive finding, the exercise was usually not interrupted until a pain score of 2–3 had been reached. If ECG changes appeared during the exercise, the test might be interrupted by the supervising physician even if no chest pain had appeared. The exercise test was run and supervised by the ordinary staff, and performed in complete accordance with the routine at the department. After the end of the test, that is, 20–30 minutes after the bicycle exercise, the patient was asked to deliver another urinary sample.

In the series of healthy volunteers given TxB₂, a basal urinary sample was collected before the infusion. They were then given 250 mL water orally to ensure adequate diuresis. With onset 10 minutes later, 3.5 μg TxB₂ were infused during 10 minutes. The safety of intravenous infusion of TxB₂ has previously been reported by Roberts et al at 65 ng/kg/min. For infusion, the sodium salt of TxB₂ (Cayman Chemical, Ann Arbor, Mich.) was prepared by dissolving the TxB₂ in an equimolar amount of 50 mM Na₂CO₃. It was then diluted to a final volume of 60 mL with saline. Twenty minutes after the end of the infusion, another urinary sample was collected.

Analyses

Tx-M was analyzed by a stable isotope dilution assay by using gas chromatography/negative ion-chemical ionization mass spectrometry as previously described. Briefly, 2 ng of a deuterated internal standard were added to 5-mL aliquots of urine. The samples were then treated with methoxamine hydrochloride, and the resulting dinor-TxB₂ methoxime was absorbed onto a phenyl boronic acid column. After elution, the dinor-TxB₂ methoxime was further purified on a reversed-phase Sep-Pac (Waters, Milford, Mass.) and eluted into ethyl acetate. The dried residue was applied to a straight-phase thin-layer chromatographic (TLC) plate and developed in the organic layer of ethyl acetate:acetic acid:hexane, shaken with water (54:12:25:100; vol/vol). The area corresponding to 2,3-dinor-TxB₂ methoxime was scraped and eluted in ethyl acetate. The organic layer was transferred to another tube, dried, and converted to its pentafluorobenzyl ester. This material was further purified by another straight-phase TLC/organic layer of iso-octane:ethyl acetate, shaken with water (65:85:100; vol/vol), followed by scraping and elution of the appropriate area on the TLC plate. The derivatization was completed by formation of the trimethylsilyl ether.
Table 1. Patient Characteristics and Basal Cardiovascular Data

<table>
<thead>
<tr>
<th>Characteristics and data</th>
<th>All (n=72)</th>
<th>Pain stratification</th>
<th>ECG stratification (ST-segment depression)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No pain (n=39)</td>
<td>Pain (n=33)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>46/26</td>
<td>24/15</td>
<td>22/11</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57±1</td>
<td>57±2</td>
<td>58±2</td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>173±1</td>
<td>172±2</td>
<td>174±1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76±1</td>
<td>75±2</td>
<td>78±2</td>
</tr>
<tr>
<td>Heart rate at rest (beats/min)</td>
<td>77±2</td>
<td>76±2</td>
<td>78±3</td>
</tr>
<tr>
<td>BP at rest (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143±3</td>
<td>142±4</td>
<td>144±4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>89±1</td>
<td>88±2</td>
<td>91±2</td>
</tr>
<tr>
<td>ST amplitude at rest (µV)</td>
<td>20±6</td>
<td>14±7</td>
<td>26±11</td>
</tr>
<tr>
<td>β-Blocker medication (yes/no)</td>
<td>19/53</td>
<td>8/31</td>
<td>11/22</td>
</tr>
</tbody>
</table>

None of the variables differed between the “no pain” and “pain” groups, or between the “<200 µV” and “≥200 µV” groups. ECG, electrocardiographic; BP, blood pressure.

Quantitative analysis was accomplished by using a Finnigan MAT 4500 mass spectrometer (Finnigan, San Jose, Calif.) coupled to a Varian Vista 6000 gas chromatograph (Varian, Walnut Creek, Calif.), or a Finnigan Incos 50 mass spectrometer coupled to a Varian 3400 gas chromatograph. Either instrument was operated in the negative ion–chemical ionization mode by using methane as the reactant gas and monitoring m/z 586 for endogenous Tx-M and m/z 590 for the tetradeuterated internal standard. Before gas chromatography/mass spectrometry, the trimethylsilyl derivatization mixture was dried under a stream of dry nitrogen and the sample dissolved in 10 µl hexane, of which 2–5 µl were injected into a splitless injector, operated at 250°C. The column oven was kept at 280°C.

PGI-M was also analyzed by a stable isotope dilution assay. In summary, 1 ng of a deuterated internal standard was added to a 5-ml aliquot of urine. The sample was subsequently subjected to extraction and reextraction procedures performed under alkaline and acidic conditions.15 After formation of the methoxime pentafluorobenzyl ester and further purification by TLC, the derivatization was completed by formation of the trimethylsilyl ether. Quantitative analysis was accomplished by using the same instrument, mode, and mass numbers as for analysis of Tx-M.16

Urinary creatinine was determined by a standard liquid chromatography method.

Calculations

All patients were stratified according to experienced chest pain during exercise. Patients not developing chest pain constituted one subgroup (“no chest pain”), and those developing light, moderate, or rather strong chest pain constituted another subgroup (“chest pain”).

The patients were also stratified according to developed ST-segment depression during exercise. The maximal ST-segment depression in any precordial lead at peak exercise was identified visually from the ECG recordings, and the accuracy of this identification was confirmed from the computer sheets, in which the ST-segment amplitude was calculated and presented in µV. An ST-segment depression of at least 200 µV was considered indicative of EMI, and will subsequently be referred to as “ST depression.” An ST-segment depression of less than 200 µV was not considered indicative of EMI, and will be referred to as “no ST depression.”

Urinary excretion of Tx-M and PGI-M is presented in relation to the urinary level of creatinine. All data are presented as mean±SE. Statistical analysis was performed by using Student’s t test (two-tailed) for paired or unpaired means, or by Fisher’s exact test.

Results

The basic data of the study population as well as of the different subgroups are presented in Table 1.

Stratification of the patients on the basis of pain occurrence during exercise resulted in a group of 33 patients who developed light, moderate, or rather strong chest pain, and a group of 39 patients who did not develop chest pain. The basic patient characteristics and hemodynamic data did not differ between these groups (Table 1).

Stratification of the patients on the basis of ST-segment depression during exercise yielded a group of 60 patients without and 12 patients with such depression. There were no differences in sex distribution, body dimensions, or basic hemodynamic data between the groups (Table 1).

The clinical and ECG findings in response to bicycle exercise in the study population and in the subgroups are presented in Table 2. As expected, patients with signs of EMI performed a less heavy exercise than those without EMI, irrespective of the stratification basis. ST-segment depression during exercise was more pronounced in patients with chest pain than in those without.
The urinary excretion of Tx-M and of PGI-M in the entire study group of patients and in the four subgroups is presented in Table 3.

In the subgroup of patients without chest pain during exercise, the excretion of Tx-M was 185±16 pg/mg at rest and 223±24 pg/mg after exercise. The increase is significant (p<0.05). Also, the excretion of PGI-M increased slightly in response to exercise in this group, from 101±13 to 129±13 pg/mg (p<0.05). In the subgroup with chest pain during exercise, Tx-M and PGI-M at rest (236±35 and 131±22 pg/mg, respectively) did not differ from the corresponding figures in the subgroup without chest pain. Patients with chest pain did not increase their Tx-M or PGI-M after exercise (247±38 and 152±33 pg/mg, respectively).

In the subgroup of patients without ST depression during exercise, the excretion of Tx-M was 216±22 pg/mg at rest and 245±23 pg/mg after exercise. The increase is significant (p<0.05). Also, the excretion of PGI-M increased somewhat after exercise in this group of patients, from 104±11 to 128±10 pg/mg (p<0.05). In the subgroup with ST depression during exercise, Tx-M and PGI-M at rest (178±45 and 162±41 pg/mg, respectively) did not differ from the corresponding excretion figures in the subgroup without ST depression. Patients with ST depression did not increase their Tx-M or PGI-M after exercise (182±49 and 190±74 pg/mg, respectively).

In the patients given an intravenous infusion of TxB2, the mean excretion of Tx-M before infusion was 123±18 pg/mg (Table 4). After infusion of TxB2, it rose to an average of 2,460±498 pg/mg. In one patient, the infusion time was for technical reasons prolonged to 20 minutes, whereas postinfusion urine was collected according to the protocol. In this patient, urinary Tx-M was elevated about 7.5 times in comparison to basal. In the others, the Tx-M excretion after infusion was elevated 24.4±1.5 times.

**Discussion**

In the current investigation, patients with stable coronary disease did not excrete more thromboxane metabolite after EMI than before exercise. Furthermore, the urinary Tx-M in these patients did not

### Table 2. Clinical Observations and Electrocardiographic Variables During Maximal Bicycle Exercise

<table>
<thead>
<tr>
<th>Observations and variable</th>
<th>All (n=72)</th>
<th>No pain (n=39)</th>
<th>Pain (n=33)</th>
<th>p</th>
<th>ECG stratification (ST-segment depression)</th>
<th>&lt;200 μV (n=60)</th>
<th>≥200 μV (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum exercise load (W)</td>
<td>143±6</td>
<td>158±9</td>
<td>124±6</td>
<td>&lt;0.01</td>
<td>148±7</td>
<td>118±10</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Maximum exercise HR (beats/min)</td>
<td>145±3</td>
<td>151±4</td>
<td>137±5</td>
<td>&lt;0.05</td>
<td>146±3</td>
<td>140±8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Maximum exercise systolic BP (mm Hg)</td>
<td>210±3</td>
<td>209±5</td>
<td>210±4</td>
<td>NS</td>
<td>210±4</td>
<td>208±6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RPP during exercise (beats·mm Hg·min⁻¹·10⁻³)</td>
<td>305±9</td>
<td>318±12</td>
<td>289±12</td>
<td>NS</td>
<td>307±10</td>
<td>294±21</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Chest pain during exercise Occurrence (yes/no)</td>
<td>33/39</td>
<td>0/39</td>
<td>33/0</td>
<td>&lt;0.001</td>
<td>21/39</td>
<td>7/5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Exercise load at onset (W)*</td>
<td>99±6</td>
<td>...</td>
<td>99±6</td>
<td>...</td>
<td>97±6</td>
<td>104±15</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Intensity (1–4)</td>
<td>0.9±0.1</td>
<td>...</td>
<td>2.0±0.2</td>
<td>...</td>
<td>0.8±0.1</td>
<td>1.3±0.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>No-pain level (W)†</td>
<td>131±7</td>
<td>158±9</td>
<td>99±7</td>
<td>&lt;0.001</td>
<td>137±8</td>
<td>103±11</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ST amplitude (μV)</td>
<td>−112±11</td>
<td>−87±16</td>
<td>−140±15</td>
<td>&lt;0.05</td>
<td>−84±10</td>
<td>−243±12</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

ECG, electrocardiographic; HR, heart rate; BP, blood pressure; RPP, rate pressure product.

*Refers to those developing angina-like chest pain during exercise.

†Refers to all subjects in each group.

### Table 3. Urinary Excretion of Thromboxane A2 and Prostacyclin Metabolites at Rest and During Exercise Test

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>All (n=72)</th>
<th>No pain (n=39)</th>
<th>Pain (n=33)</th>
<th>p</th>
<th>ECG stratification (ST-segment depression)</th>
<th>&lt;200 μV (n=60)</th>
<th>≥200 μV (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx-M (pg/mg creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>209±19</td>
<td>185±16</td>
<td>236±35</td>
<td>NS</td>
<td>216±22</td>
<td>178±45</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>After exercise</td>
<td>234±21</td>
<td>223±24</td>
<td>247±38</td>
<td>NS</td>
<td>245±23</td>
<td>182±49</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PGI-M (pg/mg creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>115±12</td>
<td>101±13</td>
<td>131±22</td>
<td>NS</td>
<td>104±11</td>
<td>162±41</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>After exercise</td>
<td>139±16</td>
<td>129±13</td>
<td>152±33</td>
<td>NS</td>
<td>128±10</td>
<td>190±74</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
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</tbody>
</table>

ECG, electrocardiographic; Tx-M, thromboxane metabolite; PGI-M, prostacyclin metabolite.
differ from the corresponding excretion in patients without signs of stable coronary disease.

All patients in the present study were admitted to exercise testing on the basis of a suspected history of angina pectoris. We used the occurrence of chest pain or ST-segment depression in the exercise ECG to judge whether significant myocardial ischemia was prevailing during the test. Both stratification variables revealed a pronounced difference between the resulting subgroups of patients in working capacity, that is, patients with chest pain or ST depression during exercise had considerably lower working capacity than those who did not develop chest pain or ST depression, respectively, during exercise. Furthermore, the group of patients with chest pain had, as expected, more ST-segment depression than the group of patients without chest pain.

The basal excretion of Tx-M in the present study population was higher than found in a randomized population of healthy young men studied in our laboratory, in which the median excretion was about 130 pg/mg creatinine. Reilly and FitzGerald reported that the excretion of Tx-M in apparently healthy patients aged 50–88 years averaged 223±22 pg/mg creatinine. Such an excretion of Tx-M is similar to that currently observed. Our data consequently support the concept that the formation of TA2 is increased with advancing age.

The possible effect of exercise on platelet activity and on platelet/vessel wall interaction was evaluated by analysis of Tx-M and PGI-M in urine collected after exercise in the present study. The exercise test had an average duration of 5–20 minutes. It was followed by postexercise ECG recording and other routine procedures, implying that postexercise urine was collected 20–30 minutes after the end of the exercise period. To verify that this interval was sufficient for detection of thromboxane formation and release during the preceding exercise, we infused TxB2 in healthy volunteers and collected urine 20 minutes after the end of the infusion. The results clearly demonstrated that 20 minutes is a sufficient collection period for urinary TxA-M to reflect an increased plasma level of TxB2. We did not make a corresponding infusion of 6-keto-PGF1α to verify that PGI-M is also increased within 20 minutes after an increased appearance of PGF1α in the systemic circulation. Both TxA-M and PGI-M are 2,3-dinor derivatives of their respective parent compounds, that is, TxA2 and PGI2; on the basis of this analogy, it may be assumed that their respective degradation and excretion rates are similar and, hence, that the collection period was sufficient to also detect any changes in PGI2 formation. It has earlier been shown that infusion of TxB2 at a rate of 2 ng kg−1 min−1 is followed by a urinary excretion of TxA-M amounting to 300 ng hr−1, whereas infusion of PGF1α at the same rate elevates urinary PGI-M by about 500 ng hr−1. These data indicate that metabolic degradation of prostacyclin to its dinor derivative is at least as efficient as the corresponding metabolism of TxB2, and thereby support the assumption asserted previously.

The facilitating, although only moderately so, effect of leg exercise on the excretion of TxA-M in the subgroups of patients without chest pain or ST-segment depression is in some contrast to previous observations in healthy patients, in whom sustained heavy bicycle exercise does not affect the urinary excretion of TxA-M. The observation may indicate that advancing age is followed not only by an increase in TxA-M excretion at rest (compare with previous discussion), but also that the excretion is further augmented in response to exercise. In contrast, TxA-M was not increased in the present subgroups of patients with positive signs of EMI, whether stratified on the basis of chest pain or with respect to development of ST depression. It may seem surprising that TxA-M was increased in patients without signs of EMI but not in those patients with such signs. In this connection, it should be kept in mind that patients without signs of EMI were subjected to a maximal working load that was approximately 25% higher than the work load in the subgroups of patients with EMI signs. Because the current data do not allow any conclusions concerning a connection between work load and TxA-M excretion in elderly patients, the possibility that such a mechanism might help to explain the present findings is only hypothetical. Nevertheless, the present data provide strong evidence that the excretion of TxA-M is not increased after exercise in patients with EMI.

Earlier studies have provided conflicting results regarding the relation between stable coronary disease and platelet activity. Some of them reported on the basis of arterial and coronary sinus levels of primary prostaglandins and of TxB2 in the 100–500 pg/ml range, cardiac release of eicosanoids during atrial pacing in patients with coronary disease. Later investigations suggested that such plasma levels of eicosanoids may have been due to artificial formation during blood sampling, and provided data indicating that the true circulating levels of eicosanoids are below 4 pg/ml. As an alternative
index of platelet activation, platelet factor 4 has been used in studies on myocardial ischemia. Green and coworkers\textsuperscript{25} observed increased levels of platelet factor 4 in 11 of 20 patients with EMI, and concluded that a subset of patients with coronary disease and EMI may have platelet activation and secretion. In a carefully controlled study, Mathis and coworkers\textsuperscript{26} were unable to confirm those results, and argued that differences in handling of the blood samples may have been partly responsible for the conflicting data obtained. The present study design allowed noninvasive assessment of indexes of platelet activity and platelet/vessel wall interaction, and thereby eliminated the risk of artificial platelet activation. Based on the methodological advantage connected to such noninvasive analysis of eicosanoid formation, we are inclined to conclude that platelet activation is not a characteristic feature in EMI.

The lack of effect of exercise on platelet activity is of clinical significance. It is customary to encourage patients with stable coronary disease to be physically active at a moderate level. In fact, rehabilitation programs including regular training of physical fitness are offered coronary patients at most cardiological centers. Such a mode of rehabilitation requires that physical activity does not increase the risk for coronary events in these patients. The current data indicate that, with respect to platelet function, this is not the case.

The excretion of PGI-M at rest was in accordance with that previously observed in healthy young patients\textsuperscript{17} in the present study population, and failed to display any variation between the subgroups. After exercise, the excretion was increased in the subgroups of patients without signs of EMI. This is in harmony with previous observations in well-trained healthy young patients performing a heavy and sustained bicycle exercise, in which the excretion of PGI-M increased more than threefold.\textsuperscript{21} The increase in prostacyclin formation developing during leg exercise in healthy patients is probably related to the increase in blood flow because shear stress is a powerful stimulus for vascular formation of PGI\textsubscript{2}.\textsuperscript{27,28} In the light of such a relation between flow rate and prostacyclin formation in the vessel wall, the moderate increase in exercise excretion of PGI-M in the present patients without EMI in comparison with that observed in healthy controls\textsuperscript{21} appears logical. Such a flow-linked control of vessel wall formation of prostacyclin may also explain why the patients with EMI displayed no increase in the excretion of PGI-M after exercise; the maximal work load in the patients with EMI was, as previously discussed, considerably lower than in the patients without EMI.

In summary, our study demonstrates that platelet activity noninvasively assessed is not augmented in the basal state of after EMI in patients with stable coronary disease. These observations may be important when admitting patients with stable coronary disease to physical rehabilitation programs.

Acknowledgment

Dr. J. Pike, Upjohn Company, kindly provided the tetradeuterated internal standard for the eicosanoid analyses.

References


**KEY WORDS** • prostacyclin • thromboxane • myocardial ischemia
Excretion of thromboxane A2 and prostacyclin metabolites before and after exercise testing in patients with and without signs of ischemic heart disease.

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