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Eicosanoid Biosynthesis in Patients With Stable Angina: Beneficial Effects of Very Low Dose Aspirin

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Objectives. **We assessed the production of eicosanoids and the effects of very low dose aspirin in patients with stable angina under basal conditions and during rapid atrial pacing.**

Background. **Platelet activation occurs in acute ischemic syndromes but is still controversial in stable angina. Very low dose aspirin is known to be platelet selective and can be used to test the hypothesis of the platelet origin of increased thromboxane production in stable angina.**

Methods. **Urinary excretion of eicosanoids was measured in 42 patients, including 24 patients with and 18 patients without coronary artery disease. The effects of 50 mg/day of aspirin were measured at rest and during pacing-induced ischemia in 10 patients with stable angina and were compared with a similar group of patients not treated by aspirin.**

Results. **Excretion of 11-dehydro-thromboxane B_2 was 2.6 times higher in patients with stable angina than in healthy subjects (mean [±SEM] 74.8 ± 13.0 [24 patients] vs. 29.0 ± 5.4 [18 patients] ng/mmol of creatinine, $p < 0.01$). Urinary prostacyclin metabolite levels did not differ between the two groups. Treatment for 8 days with 50 mg/day of aspirin inhibited platelet cyclooxygenase, as reflected by the 97% reduction of in vitro serum thromboxane production. This aspirin regimen normalized the level of urinary thromboxane metabolites in patients with angina (17.3 ± 3.4 ng/mmol of creatinine [10 patients], $p < 0.001$ from baseline level before treatment) and did not change prostacyclin metabolite levels. Atrial pacing in patients with angina not treated with aspirin caused lactate and thromboxane release into the coronary sinus. In patients with very low dose aspirin therapy, pacing did not cause thromboxane release despite inducing myocardial ischemia. However, fractional lactate extraction decreased less sharply in patients with than without aspirin therapy.**

Conclusions. **Thromboxane production is greatly increased in patients with stable angina. Very low dose aspirin administered to these patients reduces thromboxane synthesis to normal levels, preserves prostacyclin biosynthesis and prevents acute thromboxane release into the coronary circulation during pacing-induced ischemia. Our data suggest that platelets (not monocytes/macrophages) are activated in stable angina to produce thromboxane.**

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Thromboxane A_2 derives from arachidonic acid, is a potent agonist of platelet aggregation and has vasoconstrictive properties (1,2). Platelet activation and cardiac release of thromboxane undoubtedly occur during acute ischemic syndromes and coronary thrombolysis (3–7). In contrast, many studies have suggested a lack of platelet activation in stable angina (6,8–11). Paradoxically, we and others have reported that thromboxane was released into the coronary bed during rapid atrial pacing in patients with stable angina pectoris, whereas a similar pacing in control subjects did not cause thromboxane release (12–16). However, we found neither platelet trapping in the myocardium nor signs of platelet alpha-granule release concomitant with thromboxane production in our patients with coronary artery disease undergoing pacing-induced ischemia (16). These results raised the question of an extraplatelet source of thromboxane; leukocytes, monocytes, macrophages or resident vascular cells might synthesize thromboxane during reversible episodes of ischemia (16,17). The use of low dose aspirin, which has been demonstrated to selectively inhibit platelet cyclooxygenase, could help to determine the source of thromboxane in patients with stable angina.

Aspirin irreversibly acetylates the serine residue Ser 529 in the cyclooxygenase enzyme (18). Sustained inhibition of this enzyme prevents both thromboxane and prostacyclin synthesis. A selective action of aspirin on thromboxane A_2 synthesis by platelets has been proposed by reducing the daily dose of aspirin (19). The cumulative intake of low doses of aspirin suppresses platelet thromboxane A_2 synthesis for the lifetime of the cell, whereas prostacyclin is still produced by endothelial cells, which are nucleated and can resynthesize new cyclooxygenase. Prostacyclin has beneficial antiaggregatory and vasodilative effects, and it has been suggested

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that inhibition of prostacyclin production may limit the antithrombotic effects of aspirin (20).

In this study, we evaluated the levels of chronic thromboxane production in patients with stable angina, treated or not treated by very low dose aspirin (50 mg/day). We used low dose aspirin to test the hypothesis of a platelet (or extraplatelet) source of thromboxane in patients with stable coronary heart disease. Low doses of aspirin do not block the cyclooxygenase of nucleated cells (endothelial cells, monocytes/macrophages) and preserve their biosynthesis of prostaglandins, which was assessed by measuring the urinary levels of 2,3-dinor-6-keto-prostaglandin F_{1alpha} originating mainly from endothelial cells. In contrast, inhibition of platelet cyclooxygenase by 50 mg/day of aspirin was assessed using the in vitro serum thromboxane concentration originating from platelets. Subsequently, the cellular source of thromboxane in patients with stable angina was determined by the evolution of in vivo levels of thromboxane metabolites after treatment with low dose aspirin. Furthermore, we determined the effects of this very low dose aspirin therapy on the acute release of thromboxane into the coronary sinus plasma during pacing-induced myocardial ischemia. These results may improve our understanding of the mechanisms of the benefits of very low dose aspirin in patients with stable angina and determine the cellular origin of thromboxane in these patients.

Methods

Patients. We studied 42 patients (mean [±SEM] age 52 ± 13 years) who abstained from drugs inhibiting cyclooxygenase for at least 10 days. All patients provided a urinary sample without previous hydration. Twenty-four of these patients had typical effort angina pectoris, underwent a positive exercise stress test and had angiographically proved coronary artery disease. As described in our previous studies, patients were in stable condition, with significant ischemic ST segment depression after mild exercise (>1 mm at ≥80% of the age-predicted maximal heart rate) (16,21). Seven of the 24 patients with stable angina, free of aspirin therapy for >10 days, underwent rapid atrial pacing. Ten other patients with angina, who enrolled for the 8-day protocol on very low dose aspirin, underwent atrial stimulation on the eighth day of the protocol. Treatment compliance was monitored by tablet count and serum thromboxane measurement. Only 8 of these 10 patients completed the protocol. Patients received information about the study and gave their written consent. The study protocol had been approved previously by the hospital's Ethics Committee.

To compare urinary eicosanoid levels of patients with coronary artery disease, we also studied 18 healthy ambulatory age- and gender-matched subjects free of aspirin and any other cyclooxygenase-inhibiting drugs. They provided urinary samples under the same conditions as the patients with coronary heart disease. The control subjects had no complaints of chest pain, and each performed a stress test, which was negative.

Study protocol. Urinary samples were collected for all patients selected for the study. Patients unable to void or who could not provide a sufficient urinary volume for analysis were excluded from the study. In the 10 patients included in the 8-day protocol, blood samples were collected on the first day to measure total serum thromboxane B_2 production before aspirin therapy was started. Treatment was started with one 50-mg tablet of aspirin per day. The patients received a blister pack of 10 tablets; they were asked to bring it back, and the remaining pills were counted. On the seventh day, they stopped all antianginal medications. On the eighth day, each patient provided a urinary sample, and blood was measured to reevaluate total serum thromboxane B_2 production during aspirin therapy. Patients were then brought to the catheterization laboratory for atrial pacing.

As previously described, atrial stimulation was performed with a 7F pacing and sampling catheter (United States Catheter and Instrument Company [USCI]) positioned in the coronary sinus (16,21,22). A catheter was placed in the ascending aorta for arterial blood sampling. The lines were kept patent by intermittent flushing with saline solution without heparin. A 12-lead electrocardiogram (ECG) was recorded continuously. After a 10-min rest, coronary sinus pacing was begun at the rate of 90 beats/min and increased progressively to 150 beats/min; this rate was maintained for 10 min. If atrioventricular block was induced, atropine (0.5 mg) was administered intravenously. Our criteria for ceasing atrial stimulation were chest pain, significant ST segment depression (>1 mm) or a 10-min period of pacing at the maximal rate (150 beats/min). Considering the dynamics of metabolite release into the coronary sinus (16,21), three sets of blood samples were collected: at rest before pacing, during the last minute of pacing and immediately after pacing was discontinued. At each measurement, blood samples were taken simultaneously from the aorta and the coronary sinus and then placed on ice before centrifugation. To avoid artifacts in the dynamics of thromboxane release, the lines were flushed frequently (test tubes contained indomethacin). A late sample was taken after ceasing atrial pacing to check for the absence of a continuous increase in thromboxane levels, which returned to baseline values. Simultaneous aortic and coronary sinus samples were taken to provide transmyocardial values (16).

Eicosanoid measurements. Plasma thromboxane B_2 concentrations in patients undergoing atrial stimulation were measured by collecting 4 ml of blood in test tubes containing ethylenediaminetetraacetic acid and indomethacin (5 mmol/liter and 10 μmol/liter final concentrations, respectively). Samples were transferred to ice immediately, centrifuged at 3,000 × *g* for 10 min, and the plasma was stored at −70°C until further analysis. Thromboxane B_2 analyses were performed by enzyme immunoassay (23).

To determine serum thromboxane production by platelets, nonanticoagulated blood was allowed to clot at 37°C for

3 h. Serum was collected and aliquots were kept at −70°C until assayed for thromboxane.

Urine was analyzed using solid-phase extraction followed by a thin-layer chromatography purification procedure; quantitation was done by enzyme immunoassay analysis (23) according to previously published procedure that has been validated by gas chromatography/mass spectrophotometry (24).

Lactate determinations. Lactate levels were measured immediately after sampling with the YSI 27 analyzer (Yellow Springs Instrument Co.) using a specific L-lactate oxidase membrane. We calculated the percent lactate extraction by subtracting the coronary sinus concentration from the arterial concentration and dividing by the arterial concentration. Myocardial ischemia was defined as a decrease in fractional lactate extraction >5% (16,21).

Statistics. All data are expressed as mean values ± SEM. Changes of variables within groups were evaluated by the Wilcoxon test for paired data. Comparisons between two groups were made by the Mann-Whitney test. Comparisons between three groups were made using the nonparametric Kruskall-Wallis analysis of variance, followed by the Dunn multiple comparison procedure based on ranked sums (25). A p value < 0.05 was regarded as significant.

Results

In vitro serum thromboxane production. Total serum thromboxane B_2 concentration in patients before aspirin therapy was 141 ± 17 ng/ml and decreased to 4 ± 1 ng/ml ($p < 0.001$) after they received 50 mg of aspirin/day for 8 days. The 97% reduction of thromboxane production in serum confirms that maximal inhibition of thromboxane A_2 platelet synthesis was obtained using very low dose aspirin.

Urinary eicosanoid levels. Mean urinary level of 11-dehydro-thromboxane B_2 was 29 ± 5.4 ng/mmol of creatinine in the control group of 18 patients without coronary heart disease. Excretion of the thromboxane A_2 metabolite was 2.6 times higher in the 24 patients with proved coronary artery disease (74.8 ± 13.0 ng/mmol of creatinine, $p < 0.01$ between both groups) (Fig. 1). Thromboxane production was depressed by 73% in 10 patients with angina who received the very low dose aspirin regimen after 8 days of aspirin therapy (17.3 ± 3.4 ng/mmol of creatinine, $p < 0.001$) (Fig. 1). Thus, the very low dose aspirin regimen decreased the excretion of thromboxane A_2 metabolites in patients with stable angina to levels similar to those measured in control subjects (p = NS between groups) (Fig. 1).

Prostacyclin biosynthesis, as reflected by the urinary excretion of 2,3-dinor-6-keto-prostaglandin F_{1alpha}, was comparable in patients with angina and control subjects (27.6 ± 3.6 vs. 43.3 ± 15.7 ng/mmol of creatinine, respectively, p = NS). The very low dose aspirin regimen did not alter prostacyclin biosynthesis in patients with coronary heart disease (Fig. 1).

Myocardial ischemia induced by rapid atrial pacing. All patients recruited for atrial stimulation had severe stenoses

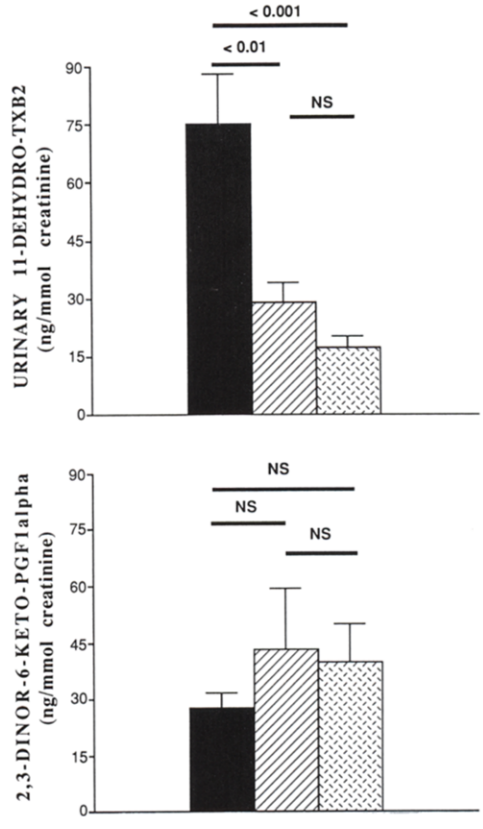

Figure 1. **Top,** Mean urinary levels of 11-dehydro-thromboxane (Tx) B_2 in 24 patients with angina without aspirin therapy (**solid bars**), 18 healthy control subjects (**hatched bars**) and 10 patients with angina with very low dose aspirin (**crosshatched bars**). **Bottom,** Mean urinary levels of 2,3-dinor-6-keto-prostaglandin (PG) F_{1alpha} in the same patients.

of the left coronary territory. Ten patients underwent right heart catheterization on the eighth day of the aspirin protocol. In one patient, the coronary sinus was not catheterized for technical reasons, and pacing was not performed in this patient. In another patient, myocardial ischemia was not induced. Subsequently, these two patients were not considered in the analysis of the dynamics of lactates and thromboxane B_2 during pacing; only eight patients completed the aspirin protocol, with the occurrence of significant ischemia during rapid atrial pacing. Seven more patients with angiographically proved disease of the left coronary territory, not treated by any cyclooxygenase-inhibiting drug, underwent atrial pacing and demonstrated significant myocardial ischemia. Atrial stimulation caused a significant decrease in fractional lactate extraction during pacing in both control patients with angina and aspirin-treated patients with angina ($p < 0.01$, different from baseline measurements in both groups).

The percent of lactate extraction during atrial pacing in patients with angina not treated by aspirin decreased sharply and was lower during the last minute of pacing than in patients following the aspirin regimen (lactate extraction was

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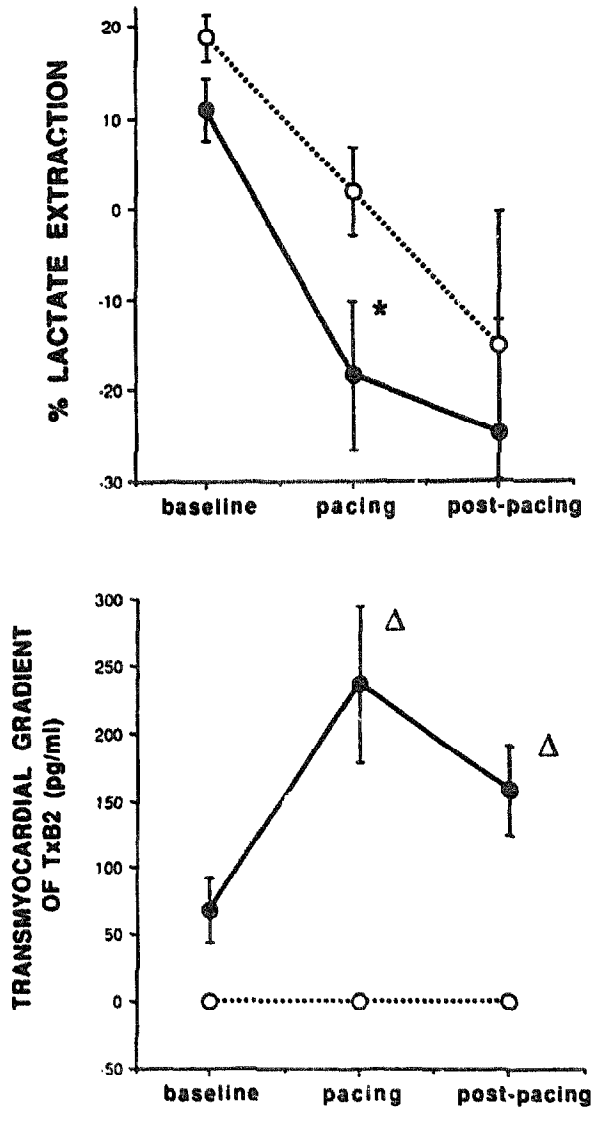

Figure 2. Changes in percent lactate extraction (top) and simultaneous changes in coronary sinus–arterial gradient of thromboxane B_2 (TxB2) (bottom) induced by pacing in eight patients with angina with aspirin therapy (open circles) and seven patients with angina without aspirin therapy (solid circles). Measurements were obtained before pacing (baseline), during the last minute of pacing (pacing) and immediately after the end of pacing (post-pacing). *$p < 0.05$ between both groups of patients. $^{\Delta}p < 0.001$, different from baseline measurements.

−18.4 ± 8.1% in seven patients without aspirin vs. 1.8 ± 4.8% in eight patients with aspirin, $p = 0.02$ between groups) (Fig. 2). However, final ischemia measured immediately after pacing was discontinued did not differ significantly between the two groups (lactate extraction was −24.7 ± 12.5% in patients without aspirin vs. −15.1 ± 14.7% in patients with aspirin, p = NS between both groups) (Fig. 2).

Plasma eicosanoid levels. Baseline coronary sinus plasma levels of thromboxane B_2 measured at rest in patients with stable angina were higher in the control group than in the group with very low dose aspirin regimen (217 ± 35 and 16 ± 3 pg/ml, respectively, $p < 0.001$ between groups). Pacing-induced ischemia was associated with the acute release of thromboxane into the coronary sinus plasma of patients not treated by aspirin (mean plasma levels of thromboxane B_2 increased from 217 ± 35 pg/ml at baseline to 437 ± 74 pg/ml during pacing [seven patients], $p < 0.01$ from baseline), causing a positive coronary sinus–arterial gradient of thromboxane B_2 (Fig. 2). The correlation between changes in thromboxane gradient and concomitant fractional lactate extraction was not significant ($r = 0.64$, $p = 0.11$, seven patients). Coronary sinus plasma thromboxane B_2 levels did not change significantly during pacing in patients receiving aspirin therapy and there was no transcardiac gradient of thromboxane B_2, indicating that myocardial production of thromboxane did not occur in treated patients. Therefore, during pacing-induced ischemia the two groups of patients differed significantly with respect to both coronary sinus plasma levels and transmyocardial gradients of thromboxane B_2 ($p < 0.001$ between groups).

Discussion

This study demonstrates that thromboxane production is greatly increased in patients with stable coronary artery disease because the excretion of thromboxane metabolites is 2.6 times higher in patients with angina than in control subjects. The administration of very low dose aspirin in patients with angina reduces chronic thromboxane production to a normal level (Fig. 1). Another important finding is that rapid atrial pacing, which consistently provokes the acute release of both lactate and thromboxane in the coronary sinus of patients with effort angina, does not induce myocardial production of thromboxane in patients treated with 50 mg of aspirin daily (Fig. 2). Thus, very low dose aspirin totally prevents the acute release of thromboxane into the coronary bed during reversible ischemic episodes and normalizes the urinary excretion of thromboxane metabolites but does not alter the endothelial prostacyclin biosynthesis (Fig. 1). The relative biochemical selectivity of aspirin for thromboxane A_2, when used at very low doses, confirms that either endothelial cells and other nucleated cells (monocytes/macrophages) are spared by this low dose regimen or that they retain the capacity for generating new cyclooxygenase enzyme to synthesize eicosanoids. Our data sustain the hypothesis that plasma thromboxane is released by platelets, not by macrophages, and that platelet activation occurs in patients with stable angina, particularly during episodes of ischemia.

Thromboxane and myocardial ischemia. We and others have demonstrated that pacing-induced ischemia in patients with stable angina is associated consistently with the simultaneous and acute release of thromboxane B_2 in the coronary sinus (12–16,21,22). In the present study, patients who had pacing-induced myocardial ischemia under a very low dose aspirin regimen did not demonstrate increased thromboxane production. It is likely that circulating levels of thromboxane play a minor role in the degree of ischemia because the final levels of lactates were not statistically different between

both groups of paced patients. However, myocardial ischemia occurred more rapidly in patients not treated by aspirin, simultaneous with the peak of thromboxane in the coronary bed. It suggests that plasma thromboxane may accelerate myocardial ischemia in patients with stable angina, but the precise relation between the effects of thromboxane on coronary arteries and the severity of myocardial ischemia remains unknown. Furthermore, aspirin attains very low plasma concentrations because of its hydrolysis by intestinal hepatic and plasma esterases. These low concentrations of the active form of aspirin are sufficient to inhibit thromboxane production by circulating cells but may well be unable to reach tissue cyclooxygenase. We cannot exclude the possibility that the extravascular production of thromboxane plays a role in the ischemic process, whereas the formation of thromboxane by circulating platelets contributes little to the final degree of ischemia, as observed in our patients (Fig. 2).

Platelet activation in stable angina. Major platelet activation and resulting aggregation occur in acute coronary syndromes, but the role of platelets in stable coronary artery disease remains controversial (6,8–11). A variety of methods have been used to evaluate platelet activation in this clinical setting and may account for the conflicting results (26,27). In previous studies, we found that other markers of platelet activation were not present at the time of marked thromboxane release into the coronary bed of patients with stable angina undergoing atrial pacing (16,21). An alternative hypothesis to platelet activation in stable angina was that a different cellular source released thromboxane. Several experimental studies have pointed out the potential role of other cells, such as monocytes/macrophages, in the production of thromboxane (17,28,29). Our present data demonstrate that very low dose aspirin does not inhibit prostacyclin biosynthesis from nucleated cells (as evaluated by the sparing of 2,3-dinor-6-keto-prostaglandin F_{1alpha} from endothelial cells). It confirms that under the very low dose aspirin regimen, the capacity of eicosanoid biosynthesis of other nucleated cells like monocytes/macrophages was preserved and that thromboxane production would have occurred if these cells had been activated in stable angina. Our findings that very low dose aspirin reduces the level of urinary 11-dehydro-thromboxane B_2 by 73% and completely prevents the acute release of thromboxane during pacing-induced ischemia strongly suggest that platelets are the source of thromboxane in patients with angina not treated by aspirin. These results support a recent study using whole-blood impedance aggregometry that demonstrated platelet activation across the coronary circulation during rapid atrial pacing of patients with stable coronary heart disease (27). Tachycardia caused a 64% increase in platelet aggregation in the coronary sinus blood of these patients with significant left coronary artery disease (27). Taken together, these data confirm the hypothesis of platelet activation during rapid atrial pacing in patients with stable angina. The similarities between pacing- and effort-induced ischemia suggest that platelets may be activated during the ischemic episodes of patients with stable angina. The increased urinary excretion of thromboxane metabolites in these patients may reflect repetitive episodes of platelet activation across the coronary bed, which could be clinically silent. The inhibition of platelet thromboxane in the serum (97% reduction of the in vitro production) by very low dose aspirin was parallel to that of the platelet-derived urinary thromboxane metabolite, whereas that of the nucleated vascular cell-derived urinary metabolite was virtually unchanged. This normalization of the 11-dehydro-thromboxane B_2 levels related to the effective inhibition of the ex vivo serum production of thromboxane demonstrates that control of platelet activation was obtained by the low dose aspirin regimen.

Benefits of low doses of aspirin. High doses of aspirin (>300 mg/day) suppress synthesis of both eicosanoids (thromboxane A_2 and prostacyclin). Low doses of aspirin tested in a previous report (80 mg/day) (30) and in this study (50 mg/day) inhibit thromboxane A_2 production in coronary patients, both at rest and after platelet stimulation during coronary angioplasty, in the study of Braden et al. (30), and during rapid atrial pacing, in this work. Furthermore, these low dose aspirin treatments preserve the basal endothelial biosynthesis of prostacyclin. However, this does not imply that the vasculature can increase the prostacyclin production in response to a stimulus (30,31). The very low dose of aspirin that we used did not totally reduce the in vivo thromboxane biosynthesis. Also, we measured a residual urinary concentration of 11-dehydro-thromboxane B_2 (27% with 50 mg/day), which was similar to the residual excretion reported elsewhere with a low dose aspirin regimen (30). Higher doses of aspirin further decreased the residual 11-dehydro-thromboxane B_2 concentration (22% with 320 mg/day) but never suppressed it (9% with 1,280 mg/day) (32). Considering the near-maximal effect of these doses of aspirin on platelet thromboxane production, the residual synthesis might come from cells other than platelets. Finally, very low dose aspirin has good effects on eicosanoid biosynthesis in patients with stable angina and may contribute to avoiding precipitation of acute ischemic events. Recent prevention trials have demonstrated the clinical benefits of low dose aspirin in patients with stable angina (33,34).

Conclusions. Patients with stable coronary artery disease produced much more thromboxane than healthy subjects. Platelets (and not macrophages) appear to be activated and to release thromboxane, particularly during episodes of pacing-induced ischemia. However, prevention of thromboxane release into the coronary bed by low dose aspirin does not avoid the induction of a similar myocardial ischemia. Very low dose aspirin therapy in patients with stable angina can reduce significantly chronic thromboxane synthesis, prevent acute release of thromboxane into plasma during episodes of ischemia and preserve endothelial prostacyclin biosynthesis. These findings may provide the basis for explaining the protective clinical effects of low dose aspirin reported recently in patients with stable angina. The reduc-

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tion of the incidence of dose-related complications is another potential benefit of very low doses of aspirin.

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