Biochemical evidence of a chronic abnormality in platelet and vascular function in healthy individuals who smoke cigarettes

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ABSTRACT  Cigarette smoking is associated with increased mortality from cardiovascular disease that declines after cessation. This study extends the evidence regarding the effects of chronic smoking on platelets and the vessel wall in vivo. Excretion of a major urinary thromboxane metabolite, 2,3-dinor-thromboxane B2, is significantly (p < .01) elevated in apparently healthy chronic smokers (20 cigarettes daily) compared with that in nonsmoking control subjects. This difference in excretion of 2,3-dinor-thromboxane B2 was abolished by the administration of 20 mg aspirin twice daily, a dose shown to selectively inhibit platelet cyclooxygenase. After aspirin, the return of the excretion of 2,3-dinor-thromboxane B2 to pretreatment levels paralleled the recovery of platelet cyclooxygenase. These findings indicate that excessive thromboxane A2 generation in chronic smokers predominantly derives from platelets. The urinary excretion of the prostacyclin metabolite 2,3-dinor-6-keto-prostaglandin F1α also is increased during chronic cigarette smoking, as is the case with other diseases associated with accelerated interaction of platelets with the vessel wall. We have found evidence of platelet and vascular dysfunction in vivo in chronic cigarette smokers before the manifestation of overt cardiovascular disease. The results would also be consistent with the hypothesis that in chronic smokers, the platelet defect is largely reflective of smoking-induced vascular injury.


SUBSTANTIAL EVIDENCE implicates tobacco smoking as an important risk factor in the development of cardiovascular disease.1,2 In the United States alone it has been estimated that smoking results in 325,000 premature deaths per year, the majority of them from cardiovascular causes.3 Cessation of smoking results in a decrease in cardiovascular mortality in patients with established disease.4–6 Although it is unknown precisely how long it takes for the excess risk to return to that of a nonsmoker, the estimated relative risk of myocardial infarction has declined to almost unity within 2 years of quitting smoking.7

Platelet activation is thought to be of importance in the genesis of vascular occlusive syndromes in vivo, both due to its role in the initiation of thrombosis8 and because of the potential contribution of platelet-related growth factors to the atherogenic process.9 Postmortem studies have documented a high incidence of platelet thrombi in the coronary vessels of patients who have suffered sudden death,10,11 and sudden death is particularly strongly related to cigarette smoking.12

Previous studies have suggested that platelets may be activated during chronic cigarette smoking. Mustard and Murphy13 demonstrated a reduced survival of DF-32P-labeled platelets by 20%, a uniform effect in all patients studied. Using 51Cr-labeled platelets, Fuster et al.14 also noted a shortened half-life of platelet survival in apparently normal individuals who were chronic smokers. These data were considered consistent with intravascular activation of platelets, but the authors recognized that other mechanisms could have shortened platelet survival.15

To further examine the hypothesis that chronic smoking causes activation of platelets in vivo, we examined the biosynthesis of thromboxane A2, the principle arachidonic acid metabolite formed by platelets,
in apparently healthy individuals who smoked. In an initial investigation, it was determined that chronic cigarette smokers excrete elevated quantities of the urinary thromboxane metabolite of 2,3-dinor-thromboxane B₂. This observation has recently been confirmed by others. We have previously reported that the abnormality in thromboxane biosynthesis declines significantly as early as 1 week after cessation of cigarette smoking. This indicates that altered formation of this eicosanoid is a direct effect of smoking rather than reflective of a coincidental phenomenon, such as subclinical vascular disease unrelated to cigarette smoking, in these individuals. The present study explores the cellular origin of thromboxane A₂ in chronic smokers and addresses the hypothesis that the excessive thromboxane metabolite formation during cigarette smoking might indeed reflect platelet activation. Thromboxane A₂ is the major cyclooxygenase product of arachidonic acid in human platelets and pulmonary macrophages, two cell types that may be activated during cigarette smoking. The origin of the excessive thromboxane metabolite excretion was examined by determination of the proportion of the metabolite that was inhibited by a very low dose of aspirin. We have previously demonstrated that aspirin in doses of 20 to 40 mg daily is a relatively selective inhibitor of platelet cyclooxygenase in healthy individuals, blocking platelet thromboxane generation with little effect on the biosynthesis of prostacyclin. An aspirin dose of 20 mg twice daily was chosen for the present study based on pharmacokinetic modeling indicating that such a dosing frequency might be necessary to obtain maximum inhibition of platelet cyclooxygenase in the presence of accelerated platelet turnover.

In several human syndromes of platelet activation, including severe atherosclerosis with limb ischemia, unstable angina, and Raynaud’s phenomenon with systemic sclerosis, prostacyclin biosynthesis is increased in response to the platelet–vessel wall interaction. On the other hand, nicotine has been shown to depress formation of prostacyclin-like bioactivity in human vascular tissue in vitro. To assess whether prostacyclin biosynthesis is altered during chronic cigarette smoking, we also examined the urinary excretion of the prostacyclin metabolite, 2,3-dinor-6-keto-prostaglandin (PG) F₁₀.

Methods

Study design. Six healthy male habitual smokers from 24 to 46 years old were recruited from the university community. No abnormalities were detected by detailed history and physical examination, electrocardiography, or biochemical screening (full blood count, SMA-12). They were matched for age with six healthy nonsmoking volunteers. All study participants had abstained from aspirin-like drugs for at least 2 weeks before the initiation of the investigation. The protocol was approved by the Vanderbilt University Committee for the Protection of Human Subjects and conducted at the Elliot V. Newman Clinical Research Center (CRC).

The smokers were brought to steady state at the CRC by smoking 20 high-nicotine cigarettes a day (1.3 mg nicotine; Winston king size, filtered; 2 cigarettes/hr over 10 hr) for the 2 days before the initiation of the study. On days 3 and 4 of the study, 12 hr urine collections were performed for analyses of eicosanoid metabolites. Blood samples for measurements of thromboxane B₂ formation in serum, platelet granule constituents, nicotine, and cotinine were obtained after 4 hr fasting, at 4 P.M., on the same days. An additional sample was drawn for measurement of platelet aggregation ex vivo in both groups on the second day of the study. All volunteers were then treated for 10 days with 20 mg aspirin twice a day, administered as capsules (prepared by the Vanderbilt pharmacy).

On the last (tenth) day of this treatment, 12 hr urine collections were obtained and blood samples were collected for six consecutive days and on days 8 and 10 after treatment. Blood samples for platelet aggregation studies were obtained 10 days after treatment with aspirin.

Biochemical analyses

Measurement of thromboxane B₂ in serum. Immediately after sampling the blood was incubated at 37°C for 45 min, and then at 20°C for 2 hr. The samples were then centrifuged at 2000 g for 10 min and the serum was stored at −70°C for further analyses. Immunoassay thromboxane B₂ was measured in 0.1 ml of serum as previously described.

Measurement of plasma β-thromboglobulin and platelet factor 4. Four milliliters of blood was drawn without stasis by a two-syringe technique and mixed immediately with 1 ml of ACD-solution (citric acid: sodium citrate: glucose; 8.0: 22.0: 24.5, weight/vol) containing indomethacin and PGE₁ (final concentrations 10 and 1 μM, respectively). The samples were kept on ice until centrifuged for 20 min at 20,000 g at +4°C within 20 min after collection. The plasma was then stored at −70°C before subsequent analysis by radioimmunoassay. Radioimmunoassays for β-thromboglobulin and platelet factor 4 were performed with the use of commercially available kits from the Amersham Corporation (Arlington Heights, IL) and Abbott Laboratories (Chicago), respectively.

Quantitation of 2,3-dinor-thromboxane B₂ (TX-M) and TXB₂ in urine. TX-M and thromboxane B₂ were analyzed in 5 ml aliquots of urine by a stable isotope dilution assay using gas chromatography–chemical ionization–mass spectrometry (GC-NICI-MS), as previously described. In these studies, the purification procedures were modified to incorporate the use of immunoaffinity columns in which the gels were labeled with an antibody to thromboxane B₂ with a high (55%) cross-reactivity for TX-M. After spiking with 2.5 ng of each of the appropriate tetradeterated internal standards, the urine was extracted with the use of 10.0 × 10.0 mm columns of octadecylsilica silica (Sep-Pak, Waters Associates) primed with 10 ml of methanol followed by 10 ml of water. After application of the samples, the columns were washed with 10 ml of water and 10 ml of hexane and the thromboxane metabolites were eluted with 4 ml of ethyl acetate. The eluate was evaporated and the residue was dissolved in 2 ml of polyvinylpyrrolidine (PVP) buffer (Trizma 0.01 M, NaCl 0.15 M, pH 7.4) containing 1.0 g/1000 ml, weight/vol, of PVP (PVP-40, Sigma Chemicals, St. Louis), 1.6 ml/1000 ml, vol/vol, of 0.1M CaCl₂, and 3.4 ml/1000 ml, vol/vol, of 0.5M MgSO₄. The solution was then applied to the antibody affinity columns. After washing with 5 ml of PVP
buffer and 5 ml of water, elution from the columns was accomplished with 5 ml of a mixture of acetone: sodium acetate buffer (pH 3.0) (80:20, vol/vol). The acetone was then evaporated with a stream of nitrogen and the thromboxane metabolites extracted from the water phase with 4 ml of ethyl acetate that was dried under nitrogen. The residue was subsequently derivatized as the methoxime-pentafluorobenzyl esters and further purified by thin-layer chromatography in a solvent system of ethyl acetate:iso-octane:water (65:10:50, vol/vol, organic phase). The derivatization was completed by formation of trimethylsilyl ether derivatives and the quantitative analyses were accomplished with the use of a Nermag R 10-10 mass spectrometer coupled to a Varian Vista 6000 gas chromatograph and operating in the negative ion mode, monitoring m/z = 586 for endogenous Tx-M, m/z = 590 for the tetradeuterated internal standard of Tx-M, m/z = 614 for endogenous thromboxane B₂, and m/z = 618 for tetradeuterated internal standard of thromboxane B₂.

Quantitation of 2,3-dinor-6-keto-PGF₁α (PGI-M). PGI-M was analyzed by GC-NICI-MS in 5 ml aliquots of urine by use of a previously described procedure. Briefly, after adding 1 ng of a tetradeuterated internal standard, the samples were subjected to extraction and reextraction procedures under alkaline and acidic conditions. This was followed by formation of the methoxime, pentafluorobenzyl ester and further purification by thin-layer chromatography. The derivatization was completed by formation of the trimethylsilyl ether derivative. Quantitative analysis was accomplished with a Hewlett-Packard 5980 instrument operating in the negative ion mode and monitoring m/z = 586 for endogenous PGI-M and m/z = 590 for the tetradeuterated internal standard.

Measurements of nicotine and cotinine in serum and urine. Serum and urine nicotine and cotinine levels were measured by a previously described method. Briefly, nicotine and its metabolite were extracted from acidified samples on silica gel columns (Bond Elut, Analyticalchem International, Harbor City, CA) and their concentrations were determined by high-pressure liquid chromatography with absorbance at 254 nm.

Platelet aggregation studies. Aggregation studies were performed in platelet-rich plasma (PRP) according to the light transmission method of Born and with the use of a dual-channel aggregometer (Payton Associates, Buffalo, NY) in the manner previously described. Briefly, after collection of the blood by the two-syringe method in 0.11M citrate buffer (pH 5.0) to make a final blood/buffer ratio of 9:1, the platelet count in PRP was adjusted to 300,000/ml with the use of autologous platelet-poor plasma. The aggregation baseline (10% light transmission) was set with the use of PRP and the full light transmission (90%) was defined with platelet-poor plasma. Aggregating agents used were ADP (Sigma Chemicals Co., St. Louis) at doses of 0.5, 1.0, 2.5, and 5.0 μM and epinephrine (Park Davis, Inc., Detroit) at doses of 1.0, 2.0, 5.0, and 10.0 μM. Aggregation response attained at 6 min after addition of the aggregating agent was measured and expressed as a percentage of maximal light transmission.

Statistical analysis. The data were subjected to two-way analysis of variance (Friedman’s test) as appropriate. A nonparametric approach was used since we did not wish to make assumptions as to the variables of interest in view of the sample size. Where the test statistic (F) attained a level of significance corresponding p < .05, we proceeded to perform distribution from pairwise comparisons. These were performed with the use of Wilcoxon’s signed-ranks test for paired and unpaired cases as well as Lord’s U-test. Alterations in metabolite excretion were assessed by pairwise comparison of the mean data obtained on the 2 days before aspirin was given and the final 2 days after aspirin withdrawal.

Results

Serum thromboxane B₂. Before the administration of aspirin, serum thromboxane B₂ did not differ significantly between the smokers (480 ± 73 ng/ml) and the nonsmokers (395 ± 63 ng/ml). Dosing with 20 mg aspirin bid for 10 days caused a highly significant (p < .001) and comparable fall in serum thromboxane B₂ in both groups (figure 1). After aspirin withdrawal, the recovery of serum thromboxane B₂ was gradual, attaining pretreatment values 8 to 10 days after aspirin withdrawal. The rate of recovery did not differ detectably between the smokers and nonsmokers.

Excretion of thromboxane metabolites. This investigation confirmed our preliminary observation that the excretion of the thromboxane metabolite Tx-M was significantly higher in smokers than in the nonsmoking volunteers (18.7 ± 2.1 vs 10.1 ± 1.4 ng/hr; p < .005) (figure 2). This difference was also highly significant if the excretion of the metabolite was corrected for creatinine excretion (230 ± 22.6 vs 143 ± 18 pg/mg creatinine; p < .005). No apparent variation in metabolite excretion as a result of smoking history before entry into the study was noted.

The administration of low-dose aspirin significantly depressed Tx-M excretion and abolished the differences between the two groups (figure 2). After aspirin withdrawal, the recovery of Tx-M excretion was gradual, corresponding to the pattern observed with serum thromboxane B₂. No significantly detectable difference in the rate of recovery was observed between the groups. Tx-M excretion returned to pretreatment values 8 to 10 days after aspirin withdrawal, by which time biosynthesis was once again higher in the smoking group (figure 2).

Thromboxane B₂ excretion was also elevated in the chronic smokers (3.7 ± 0.3 vs 2.7 ± 0.3 ng/hr; p < .05). Consistent with this index deriving in part from a nonplatelet source, low-dose aspirin caused a less pronounced depression in excretion of the parent compound than in that of Tx-M. However, the distinction between the groups was abolished by aspirin and was reestablished 8 to 10 days after aspirin withdrawal (table 1).

Excretion of the prostacyclin metabolite. PGI-M excretion was significantly higher in the smokers than in the nonsmokers. This difference was evident both for the 2 days before smoking (figure 3; p < .01) and for the final 2 days after aspirin withdrawal (p < .01). Administration of aspirin tended to depress PGI-M excretion only in the smoking group, but this decline failed to attain statistical significance. No significant difference in PGI-M excretion was noted between the two groups.
FIGURE 1. Inhibition of thromboxane B₂ formation in serum after treatment with aspirin (ASA) for 10 days (5 to 14) and its recovery during the following 10 days. Mean postdosing thromboxane B₂ values are presented as a percentage of the corresponding predose control.

FIGURE 2. The urinary excretion rates of Tx-M before and during a 10 day period following treatment with aspirin (ASA) for 10 days (5 to 14). The differences between smokers and non-smokers are indicated. *p < .05; **p < .01.
during the initial 6 days after administration of aspirin.

**Platelet granule constituents.** Plasma β-thromboglobulin tended to be higher (34 ± 10 vs 23 ± 2 ng/ml; p = .27) in the smoking group. Levels of platelet factor 4 were comparable (6 ± 5 vs 4 ± 1 ng/ml), suggesting that ex vivo platelet activation was not a major source of artifact.37

**Platelet aggregation studies.** Overall, the platelet response to the agonists ADP and epinephrine ex vivo tended to be depressed rather than enhanced in the chronic smokers (figure 4). For example, this difference attained statistical significance (p < .05) after recovery from aspirin treatment when the responses to both epinephrine (5 μM) and ADP (2.5 μM) were lower in the smokers (19 ± 13% vs 56 ± 9% and 24 ± 13% vs 87 ± 2%) than in the nonsmoking volunteers.

| Concentrations of urinary thromboxane B2 (ng/hr) in smokers and nonsmokers before (days 3 and 4) and after (days 14 to 24) a 10 day period of treatment with low-dose aspirin (20 mg bid) |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Day 3 | Day 4 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 22 | Day 24 |
| Smokers | 3.7±0.4 | 3.7±0.5 | 1.1±0.3 | 1.0±0.4 | 2.3±0.5 | 3.7±0.8 | 2.3±0.7 | 2.5±0.5 | 3.0±0.5 | 3.3±0.5 |
| Nonsmokers | 2.5±0.4 | 2.9±0.5 | 1.6±0.3 | 1.3±0.2 | 1.7±0.6 | 2.8±0.7 | 2.5±0.4 | 1.8±0.3 | 2.1±0.2 | 2.4±0.4 |

All values are expressed as mean ± SE and the significant differences between the two subject groups are indicated.

**Nicotine and cotinine measurements.** Before administration of aspirin, serum concentrations of nicotine and cotinine were 26 ± 18 and 165 ± 61 ng/ml, respectively, in the smokers. The excretion of the two compounds in urine averaged 1152 ± 295 and 1307 ± 783 ng/ml, respectively. Neither nicotine nor cotinine was detectable in serum and urine samples obtained from the nonsmoking volunteers.

**Discussion**

These results indicate that thromboxane biosynthesis is increased in apparently healthy individuals who are chronic smokers. Furthermore, our experiments with low-dose aspirin suggest that the platelet is the predominant source of this increment in thromboxane formation. These data provide biochemical evidence of a chronic disturbance in platelet function that may

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** The urinary excretion of PGI-M before and during 10 day period following treatment with aspirin (ASA) for 10 days (5 to 14). The differences between smokers and nonsmokers are indicated. **p < .01.
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days, but not at 2 and 7 days, of feeding in the rat. However, these problems are unlikely to have confounded our approach to monitoring the formation of prostanooids in vivo in the present study. First, the dinor metabolites are formed by a β-oxidation reaction and the β-oxidase is a mitochondrial enzyme, and therefore uninfluenced by tobacco smoke. Importantly, the dinor metabolites are not subject to further metabolism by omega oxidation. Second, in previous studies of the metabolism of prostacyclin and thromboxane B₂ in humans, several of the volunteers infused with prostacyclin (4/10) and thromboxane B₂ (2/5) were chronic smokers and the fractional conversion to these metabolites in the smokers was no different from that in their nonsmoking peers.

To address the origin of thromboxane formation we used low-dose aspirin as a selective inhibitor of platelet cyclooxygenase. We have previously demonstrated that aspirin in doses of 20 to 40 mg is a relatively selective inhibitor of thromboxane biosynthesis in healthy individuals. We chose 20 mg twice a day for the present study because we concluded from pharmacokinetic modeling that such a dosing frequency might be necessary to attain maximal inhibition of platelet cyclooxygenase in the presence of accelerated platelet turnover.

The results of the present study indicate a significant increase in excretion of Tx-M in chronic smokers. This does not reflect a difference in the capacity of platelets to form thromboxane since the concentration of thromboxane B₂ generated in serum was comparable in both groups. The dinor metabolite represents a noninvasive index of extrarenal thromboxane formation in vivo, which, under physiologic conditions, derives largely from the platelet. Depression of dinor thromboxane excretion to similar levels in both smokers and nonsmokers by low-dose aspirin and the recovery pattern of thromboxane biosynthesis after aspirin supports the conclusion that enhanced formation of this eicosanoid in smokers results from increased platelet activation. The recovery pattern of thromboxane B₂ formation or excretion of its dinor metabolite did not differ between the groups. Although this appears surprising in view of findings of earlier studies using radiolabeled platelets, the comparative sensitivity of this approach to the estimation of platelet turnover remains to be determined.

An alternative explanation for our findings would be that the increment in dinor thromboxane excretion derived from a source other than platelets, such as the pulmonary macrophage. However, McDermott* has


FIGURE 4. The aggregation response of platelets ex vivo to different doses of ADP and epinephrine expressed as Tₘax 6 min after addition of the respective agonist. The response curve to epinephrine and ADP for smokers at the end of the study period differed significantly (p < .05) from that for nonsmoking peers, as indicated on the figure. The studies after aspirin were performed on day 24 of the study when serum thromboxane B₂ had returned to preaspirin levels (i.e., the effects of aspirin on platelet cyclooxygenase were no longer evident).

contribute to the development of the vasoocclusive disease associated with cigarette smoking.

We designed the present study to address the hypothesis that thromboxane biosynthesis is altered in chronic smokers and to elucidate the origin of such an increase. Eicosanoid biosynthesis was primarily assessed by monitoring excretion of enzymatic metabolites of the parent compounds. It is well known that cigarette smoking induces microsomal enzyme systems that accelerate drug metabolism and may influence the metabolism of eicosanoids. For example, both oral tobacco and nicotine increase the rate of hepatic microsomal N-demethylation after 28
studied the effects of aspirin on thromboxane formation by isolated pulmonary macrophages. Unlike the platelet, recovery of synthesis by these cells rapidly (within 4 to 6 hr) returns to preexposure values.

Abundant evidence suggests that cigarette smoking causes vascular damage. Ultrastructural abnormalities have been demonstrated in the umbilical arteries of infants born to smoking mothers and in the uterine arteries of female smokers. Subendothelial damage, ultrastructural lesions, and platelet adhesion in low-shear areas have been described in the aortas of rats exposed to cigarette smoke. Finally, chronic oral consumption of nicotine has been shown to result in endothelial damage in rabbits and increased aortic endothelial cell turnover in mice, while endothelial cell counts in venous blood are increased after smoking tobacco but not tobacco-free cigarettes in human volunteers.

To assess the effects of cigarette smoking on vascular function, we measured excretion of a major metabolite of prostacyclin, the predominant product of arachidonic acid metabolism in endothelial cells. Prostacyclin is a potent inhibitor of platelet aggregation in vitro and is thought to limit the local deposition of platelets on healthy endothelium in vivo. In keeping with such a local homeostatic role, we have previously observed increased biosynthesis of this eicosanoid in syndromes putatively associated with increased platelet–vessel wall interactions. In the present study, prostacyclin biosynthesis was increased in chronic smokers, consistent with vascular dysfunction in vivo. It has previously been reported that nicotine inhibits formation of prostacyclin-like activity by human vascular tissue in vitro and that the formation of 6-keto-PGF₁α (the hydration product of prostacyclin) is depressed in endothelial cells exposed to cigarette smoke and in endothelial cells cultured from the umbilical veins of infants whose mothers smoked compared with those who did not. It is possible that the concentrations of nicotine necessary to produce these effects in vitro are not attained after cigarette smoking in vivo. However, even if this effect does apply in vivo, the discrepancy between the capacity of tissues to synthesize eicosanoids and their actual production rates in vivo would still theoretically permit an increase in prostacyclin formation in vivo in response to physical and/or chemical stimuli, despite a reduction in the capacity to generate this eicosanoid. In the present study, selective inhibition of platelet thromboxane formation resulted in a tendency for prostacyclin metabolite excretion to decline in the chronic smokers. However, the difference between the groups was not completely abolished, suggesting that other factors, such as platelet derived mediators, thrombin, and direct smoking–induced vascular injury, were likely to have contributed to the increment in prostacyclin formation in the smokers.

In contrast to the evidence of platelet activation in vivo, the response of platelets to aggregating agonists ex vivo was depressed rather than increased. This is in accord with other studies of chronic smokers. Conflicting data have been obtained after acute smoking and overnight abstinence, suggesting both increased and decreased responsiveness to aggregating agonists ex vivo. The relevance of such studies to platelet function in vivo is questionable. For example, chelation of calcium by citrate alters the response of platelets to aggregating agonists. At physiologic concentrations of calcium, epinephrine often does not cause aggregation, nor does ADP cause secondary aggregation or the release reaction. However, such factors might not be expected to differentially confound the results obtained in smokers and nonsmokers. The difference in the ex vivo aggregation studies between the groups might then be explained if the effects of cigarette smoking on platelet function in vivo resulted primarily from vascular damage rather than a primary effect on platelets themselves. For example, in experimental animals, repeated vascular damage will shorten platelet survival in the absence of thrombosis, whereas intravascular thrombosis that is unassociated with extensive vascular damage does not result in a shortened platelet survival. It has been suggested that such “battered platelets” that have undergone reversible contact interactions in vivo might be so modified as to be more rapidly cleared from the circulation; they might also be less susceptible to aggregating agonists ex vivo.

In summary, we have found abnormalities in the biosynthesis of both thromboxane A₂ and prostacyclin in apparently healthy individuals who are chronic smokers. These findings indicate that cigarette smoking induces both platelet and vascular dysfunction, which precedes the clinical manifestation of smoking-associated cardiovascular disease.

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