

## Acute Effect of Cigarette Smoking on Cardiac Prostaglandin Synthesis and Platelet Behavior in Patients with Coronary Heart Disease

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Although cigarette smoking is associated with the development of atherosclerosis (5), the mechanism of action has not yet been clarified. Levine (10) showed that cigarette smoking increased platelet aggregation in peripheral venous blood in healthy volunteers. Several studies showed that adding nicotine to the perfusion medium depressed prostacyclin ( $\text{PGI}_2$ ) production in isolated vascular tissue of a number of species including humans (4,9,18,19,22). In recent years, the role of platelets and arachidonic acid metabolites in the process of arterial thrombosis and atherosclerosis has received considerable attention (7,12,13). The hypothesis, which stresses the importance of an imbalance between platelet aggregability and endothelial  $\text{PGI}_2$  production, is attractive, especially since Mustard and Packham (14) showed that platelets are required to develop atherosclerosis in rats and rabbits. That a decrease in  $\text{PGI}_2$  production renders a subject more vulnerable to atherogenesis has not been described, but a greater tendency to arterial thrombosis has been established in patients who lacked normal  $\text{PGI}_2$  production (3).

In an earlier study we showed that nicotine suppressed  $\text{PGI}_2$  production in isolated human umbilical arteries (18). This suppression was most pronounced in arteries of babies from mothers smoking more than 10 cigarettes daily during their pregnancy. In the same population arteries from women who smoked showed extensive endothelial damage as observed by scanning electron microscopy (23).

In order to understand better the possible role of smoking on platelet aggregation and  $\text{PGI}_2$  production in the development of coronary artery disease, we



investigated the acute effects of cigarette smoking on platelet behavior and coronary prostacyclin synthesis in male smokers with proven coronary heart disease.

### PATIENTS AND METHODS

Ten male smokers, age 37 to 66 years (median 50), were asked to participate in this study. They all suffered from ischemic heart disease, as determined by history and exercise test, and diagnostic cardiac catheterization was indicated. One week before the study all medication was stopped except the use of sublingual nitroglycerine when necessary.

For this study, catheters were placed in the ascending aorta (Millar 7F) and the coronary sinus (Gorlin 7F). The patient was then asked to smoke 2 cigarettes with a high nicotine content (1.95 mg nicotine per cigarette). Blood samples were obtained before and immediately after smoking. The increase in carboxy-hemoglobin from 1.99 to 3.14% ( $p < 0.005$ ) confirmed the appropriate technique of smoking. The samples were analyzed for: (a) CO-hemoglobin (CO-oxymeter 282, Instrumental Laboratories); (b) platelet aggregation in platelet-rich plasma (PRP), adjusted to a platelet count of  $300 \times 10^9/\text{ml}$ , induced by collagen (5  $\mu\text{g}/\text{ml}$ ), and measured by light transmission (Payton minigator); (c) blood samples for epinephrine and norepinephrine (NE) were determined as described by Endert (6); (d)  $\beta$ -thromboglobulin (BTG) in plasma was measured by radioimmunoassay (RIA) (Radiochemical Center, Amersham, Buckinghamshire, England); and (e) blood samples for thromboxane (TX)  $B_2$  and 6-keto-prostaglandin (PG)  $F_{1\alpha}$ -determinations were obtained in test tubes containing sodium citrate and indomethacin (10 mmol/liter) and were placed on ice immediately. Plasma levels were determined by RIA.

### RESULTS

Smoking did not affect platelet aggregation and the release of BTG in the aorta. Catecholamines tended to rise, but the increase was not statistically significant (Fig. 1).

Blood sampled from the coronary sinus showed a significant increase in epinephrine as well as NE. No change in platelet aggregability or BTG release could be detected (Fig. 2). Also the coronary sinus/aorta ratio in platelet aggregation did not change. The difference between BTG in coronary sinus and aorta was reduced after smoking (mean  $\pm$  SEM being  $53.6 \pm 16.0$  and  $-3.7 \pm 12.2$  ng/ml, respectively,  $p < 0.01$ ).

Percentage changes from baseline in  $\text{TXB}_2$  and 6-keto-PGF $_{1\alpha}$  in the aorta are shown in Fig. 3, and those in the coronary sinus are depicted in Fig. 4. Although there was a  $52 \pm 19\%$  (mean  $\pm$  SEM) increase in arterial  $\text{TXB}_2$  concentration ( $p < 0.05$ ), no such phenomenon was observed in the coronary sinus. No consistent smoking-induced changes were seen in arterial 6-keto-PGF $_{1\alpha}$ . Coronary sinus concentrations of the same substance were increased



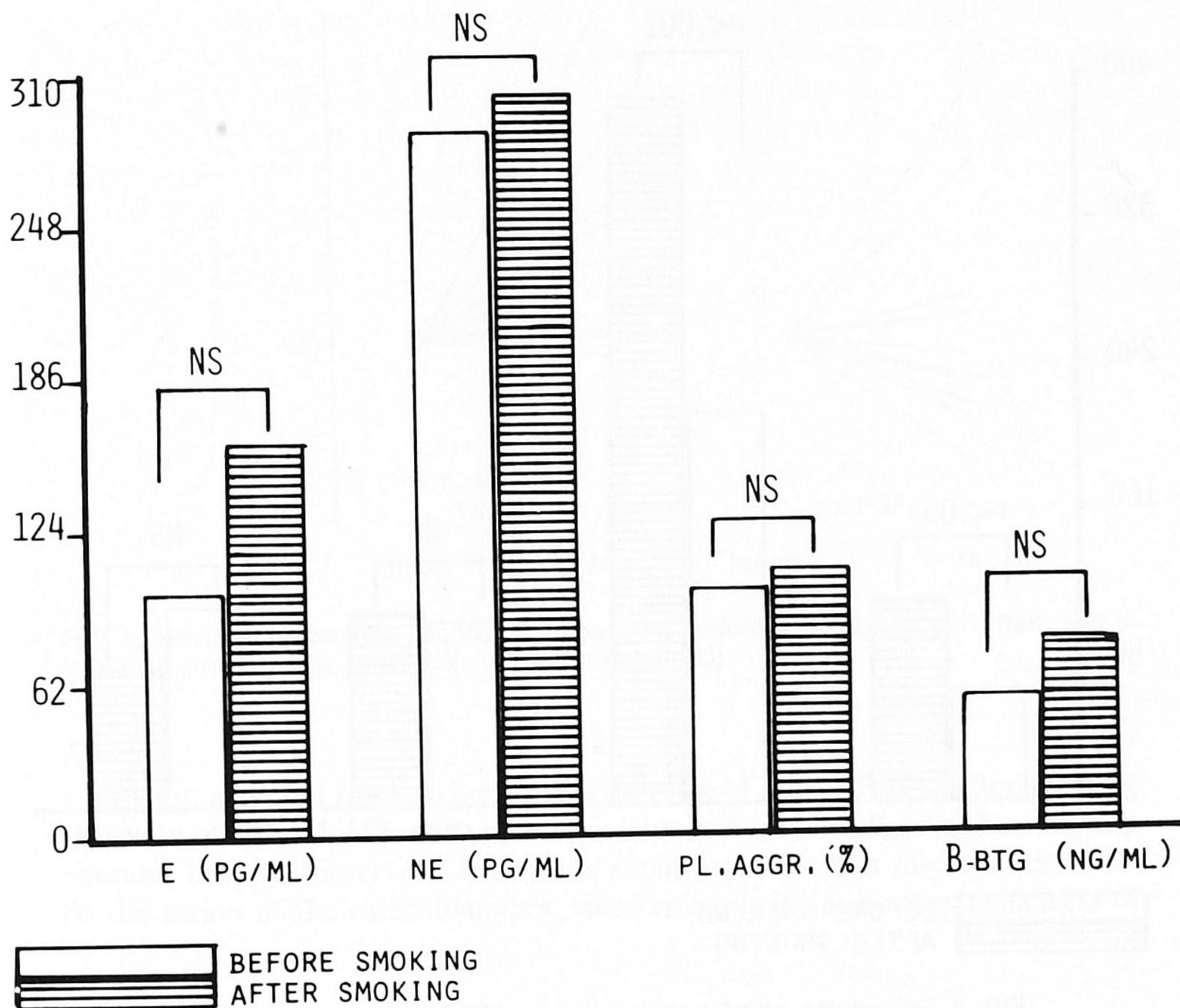


FIG. 1. Epinephrine, platelet aggregation, and BTG in the aorta.

in 7 out of 10 patients after smoking but decreased in the 3 other subjects ( $36 \pm 18\%$  for the whole group).

## DISCUSSION

In isolated perfused hearts, nicotine alone elicits a rise in catecholamines, heart rate, and left ventricular contractility (2). Cigarette smoking results in the same effects in humans. In our study, smoking induced a significant rise in the catecholamine concentration in the coronary sinus, but not in arterial blood. Other investigators reported either increases in arterial and coronary sinus concentrations (8) or no change (17). The reason for those differences is unclear. However, in neither of these studies was myocardial blood flow measured. Pentecost and Shillingford (15) reported that cigarette smoking increases



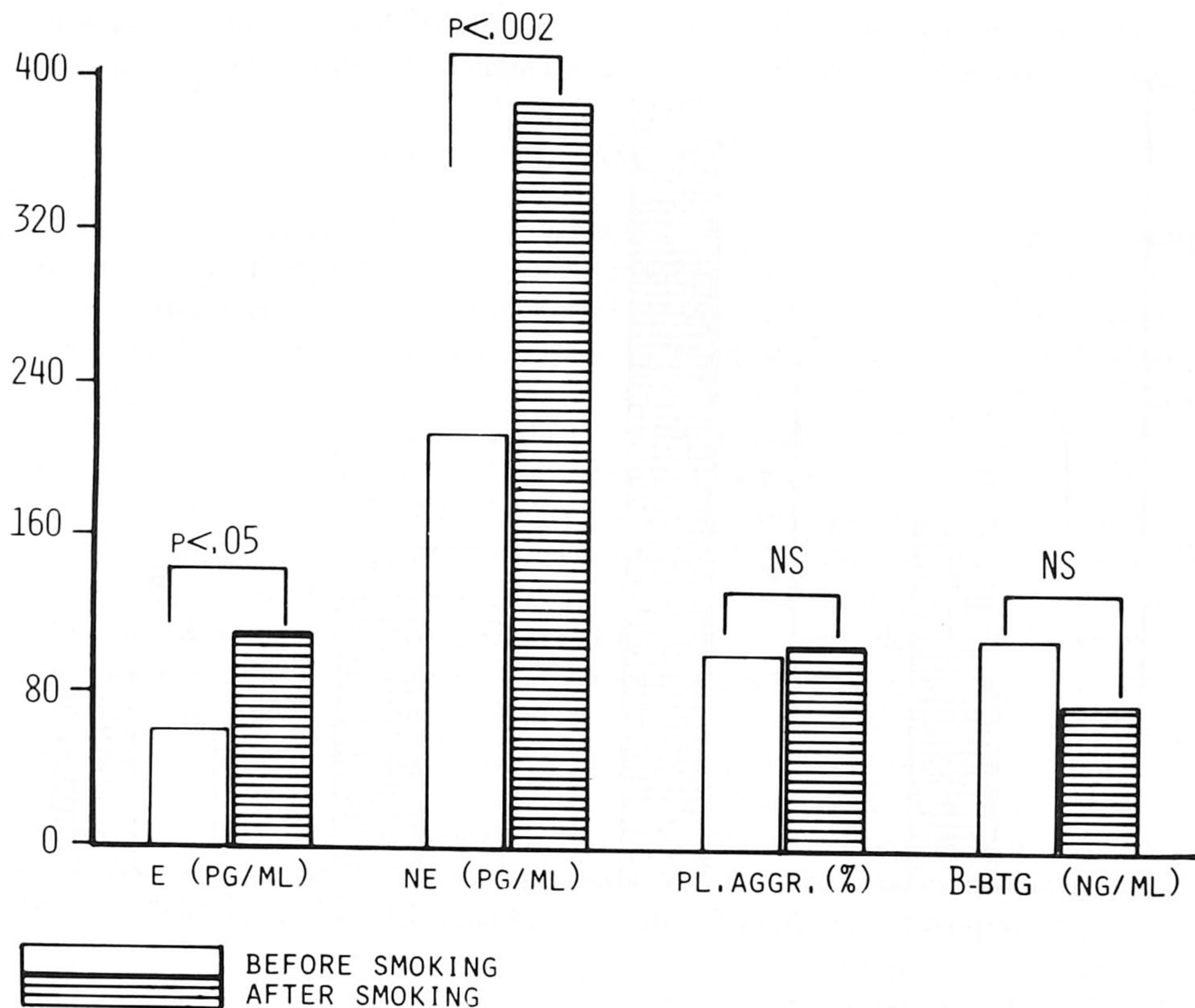
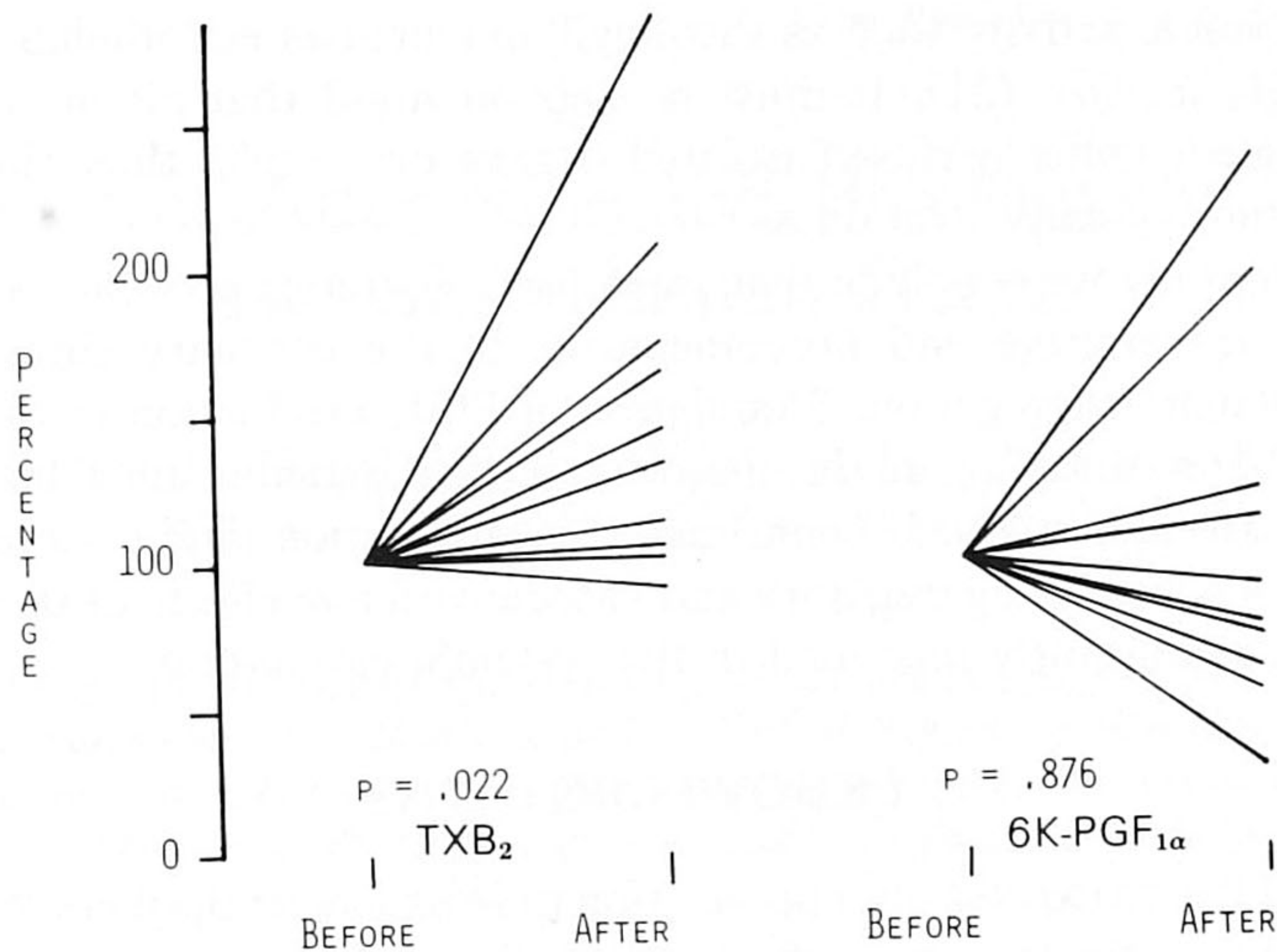


FIG. 2. Epinephrine, platelet aggregation, and BTG in the coronary sinus.

cardiac output, and thus coronary flow, in healthy volunteers, whereas no change could be observed in patients with coronary heart disease (16).

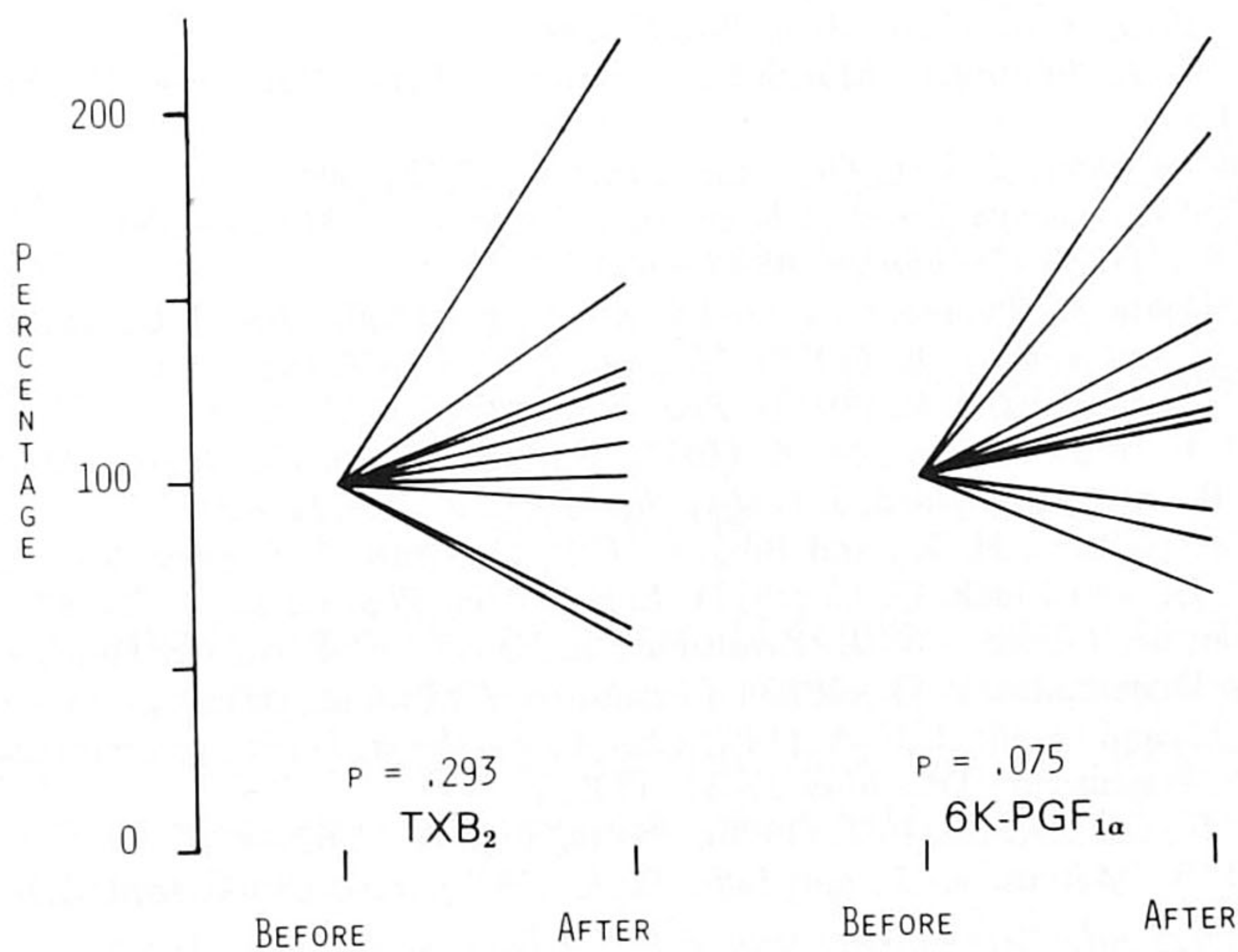
Catecholamines are known to enhance platelet aggregation. Furthermore, several *ex vivo* studies indicate that nicotine inhibits cardiac and vessel wall  $\text{PGI}_2$  formation, probably by an inhibition of cyclooxygenase activity (1). On the other hand, platelet cyclooxygenase activity remains unaffected, thus favoring platelet deposition and aggregation along the vascular lining. However, these results are not unequivocal (20). No change was observed in platelet aggregability, in either the systemic, or in the coronary circulation. Results from BTG and  $\text{TXB}_2$  determinations point toward the same direction. Mehta et al. (11) suggested that in atherosclerotic arteries, hyperactive platelets aggregate and are trapped. That being the case, lower coronary sinus platelet counts would be expected, which did not occur in our study. Levine (10) showed that cigarette smoking increased platelet aggregation in venous blood. Our finding of an increase in  $\text{TXB}_2$  in the aorta might be an exponent of that phenomenon.





**FIG. 3.** Individual percentage changes from baseline (before smoking) for TXB<sub>2</sub> (**left**) and 6-keto-PGF<sub>1α</sub> (**right**) after smoking (after) in the aorta (AO).

We also expected from earlier work a decrease of 6-keto-PGF<sub>1α</sub> after smoking (18). Actually, in 7 out of 10 patients a rise in 6-keto-PGF<sub>1α</sub> in the coronary vascular bed was observed. A possible explanation for this discrepancy could be the action of the catecholamines, since epinephrine and other enhancers of



**FIG. 4.** Individual percentage changes from baseline (before smoking) for TXB<sub>2</sub> (**left**) and 6-keto-PGF<sub>1α</sub> (**right**) after smoking (after) in the coronary sinus.



adenylate cyclase activity such as theophylline increases endothelial cell formation of PGI<sub>2</sub> *in vitro* (21). It must be kept in mind that all *in vitro* studies use denervated, buffer-perfused isolated organs or vessels, thus eliminating a possible action by catecholamines.

From our study we conclude that smoking 2 cigarettes provokes a significant increase in epinephrine and norepinephrine in the coronary sinus, but does not affect platelet aggregation. Stimulation of PGI<sub>2</sub> production in the coronary circulation after smoking in the majority of our patients must be confirmed by a more extensive study. If confirmed, this stimulation might act as a defense mechanism against the aggregatory and vasoconstrictive effects of thromboxane, which were significantly increased in the systemic circulation.

### ACKNOWLEDGMENTS

We would like to express our appreciation to Miss Anette Spijkers for technical assistance and to the nursing staff of the cardiac catheterization laboratory for making this study possible.

This study was supported by Grant No. 79-099 from The Dutch Heart Foundation.

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