Acute Systemic and Coronary Hemodynamic and Serologic Responses to Cigarette Smoking in Long-Term Smokers With Atherosclerotic Coronary Artery Disease

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Previous studies suggested that cigarette smoking 1) inhibits an increase in coronary blood flow that should occur with increased myocardial oxygen demands, and 2) alters thromboxane and prostacyclin production, causing vasoconstriction and platelet aggregation. In 38 smokers (26 men and 12 women, aged 50 ± 8 years [mean $\pm$ standard deviation]) with coronary artery disease, systemic and coronary hemodynamic and serologic variables were measured before and after smoking two cigarettes (in 8 to 10 minutes) (21 patients) or 8 to 10 minutes without smoking (17 patients; control group). No variable changed in the control group. Smoking increased ($p < 0.05$) heart rate-systolic pressure product, cardiac output and maximal first derivative of left ventricular pressure (dP/dt) without significantly changing the coronary sinus concentrations of thromboxane B_2 or 6-keto-prostaglandin $F_{1\alpha}$ (the stable metabolites of thromboxane A_2 and prostacyclin, respectively). Smoking did not increase coronary flow in 6 of 11 patients with greater than 70% stenosis of the proximal left anterior descending or circumflex coronary artery, or both, whereas it caused an increase in coronary flow in all 10 patients without proximal stenoses ($p = 0.006$). To determine if smoking altered the response of coronary flow to increased myocardial oxygen demands, 10 smokers (5 men and 5 women, aged 48 ± 9 years) underwent atrial pacing for 5 minutes followed 15 minutes later by atrial pacing for 5 minutes during smoking. In the five patients without proximal left coronary artery stenoses, coronary flow increased 26 ± 29 ml/min with pacing and 45 ± 21 ml/min with pacing/smoking ($p = 0.018$). In contrast, in the five patients with proximal stenoses, coronary flow increased 39 ± 24 ml/min with pacing, but only 36 ± 16 ml/min with pacing/smoking ($p = NS$). Thus, in smokers with coronary artery disease, smoking increases myocardial oxygen demands. However, in some individuals with severe proximal stenoses of the left coronary artery, it may induce no change or cause a decrease in coronary blood flow. The net effect of smoking on coronary blood flow appears to be influenced by the location and severity of atherosclerotic coronary artery disease.

In healthy experimental animals and human volunteers, cigarette smoking or parenterally administered nicotine increases heart rate, systemic arterial pressure, cardiac output and coronary blood flow (1–12), at least partly because of

augmented concentrations of circulating catecholamines (13). In animals with experimentally induced coronary atherosclerosis and in patients with coronary artery disease, smoking also increases heart rate and systemic arterial pressure (10,14–16), but its effects on coronary blood flow have not been fully characterized. In fact, in individuals with coronary atherosclerosis, some studies (7,14) have suggested that coronary blood flow is not altered by smoking (although myocardial oxygen demands are augmented). More recent investigations (17–19) have even demonstrated that cigarette smoking may cause a decrease in coronary blood flow and a concomitant increase in coronary vascular resistance, especially in individuals with severe proximal stenosis of the left coronary artery (18). In these patients, therefore, smoking may induce an imbalance between myocardial oxygen supply and demand by increasing oxygen utilization

in the setting of limited oxygen delivery. As a result, the patient's anginal threshold is temporarily reduced (17,20).

Platelet aggregation is chronically increased in smokers, and smoking acutely renders platelets more responsive to various proaggregatory stimuli (21). In the experimental animal, nicotine depresses the formation and release of prostacyclin (an endogenous vasodilator and inhibitor of platelet aggregation produced by vascular endothelial cells) without exerting a discernible effect on thromboxane (the powerful vasoconstrictor and promoter of platelet aggregation produced by aggregating platelets) (22–24). In long-term smokers, the coronary sinus concentrations of 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) (the stable metabolite of prostacyclin) are reduced in comparison with levels in nonsmokers (19). As a result of this smoking-induced thromboxane/prostacyclin "imbalance," vasoconstriction and platelet aggregation within the coronary artery system may be enhanced, leading to a diminution in myocardial blood flow.

The present study was performed to: 1) assess the systemic and coronary hemodynamic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease, 2) examine the effects of smoking on the intracoronary concentrations of thromboxane and prostacyclin, and 3) evaluate the interrelations (if any) among the hemodynamic and serologic alterations induced by smoking.

Methods

Patients

From February to October 1983, a total of 48 patients (31 men and 17 women, aged 31 to 65 years) who underwent cardiac catheterization for the evaluation of chest pain at Parkland Memorial Hospital were studied after informed consent had been obtained. All had smoked at least 10 cigarettes a day for longer than 10 years. At the time of selective coronary arteriography, all had greater than 70% luminal diameter narrowing of at least one major epicardial coronary artery (one vessel in 15 patients, two vessels in 14 and three vessels in 19). None of the patients had received glucocorticosteroids or cyclooxygenase inhibitors for at least 10 days before study. Before catheterization, there was no attempt to control or alter antianginal medications, but careful records were maintained of all nitrates, beta-adrenergic blocking agents and calcium antagonists administered within 1 week of study. In all patients, the experimental protocol was performed in the fasting state after premedication with oral diazepam, 10 mg. All hemodynamic measurements and blood sampling were performed before systemic heparinization, left ventriculography and selective coronary arteriography. All subjects had refrained from smoking for at least 4 hours before study.

Hemodynamic and Serologic Responses to Smoking

Experimental protocol. In 38 patients (26 men and 12 women, aged 50 ± 8 years [mean ± standard deviation]), hemodynamic measurements and blood sampling were performed in the baseline state and after random assignment to (a) the smoking of two cigarettes (within 8 to 10 minutes) (n = 21) or (b) an 8 to 10 minute period without smoking (n = 17) (control subjects). In these patients systemic arterial pressure was recorded through a percutaneous femoral artery cannula. Left ventricular pressure was recorded with a high fidelity micromanometer-tipped pigtail catheter (Millar Instruments) advanced to the left ventricle from the femoral artery, and the maximal first derivative of left ventricular pressure (dP/dt) was electronically derived from this pressure tracing. Cardiac output was measured with a flow-directed, balloon-tipped thermodilution catheter (Electronics for Medicine model 62 00 37) advanced to the pulmonary artery from the femoral vein. An average of three thermodilution measurements of cardiac output was used for the final computations. The variability of thermodilution measurements in our laboratory is ± 4%.

In each patient, a 7 or 8 French woven Dacron (Goodale-Lubin) catheter was advanced to the coronary sinus from the right basilic vein. Its position was confirmed oximetrically and by the injection of 3 to 5 ml of contrast material. Samples of coronary sinus blood were obtained, and the catheter's position within the coronary sinus was carefully noted. Subsequently, the Goodale-Lubin catheter was removed and a thermodilution catheter (Wilton Webster Laboratories, model CCS-7U-90B) was advanced to the coronary sinus through the same vein, after which its position within the coronary sinus also was confirmed oximetrically and fluoroscopically. Coronary sinus blood flow was measured with the continuous thermodilution technique (25) in the baseline state and after smoking or an 8 to 10 minute waiting period. During this 8 to 10 minute period, the thermodilution catheter was not moved or manipulated. Subsequent to all measurements of coronary sinus blood flow, the thermodilution catheter was removed and the Goodale-Lubin catheter was reintroduced and advanced to the coronary sinus where a careful attempt was made to position it as closely as possible in its previous location relative to adjacent radiopaque structures (such as the vertebral column and ribs). Once this catheter was satisfactorily placed in the coronary sinus, sampling of blood again was accomplished.

Chemical analyses. The blood specimens for thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ analysis were drawn into heparinized plastic syringes and transferred quickly into iced 10 ml tubes containing indomethacin (10 μg) and heparin 1,000 units). They were immediately centrifuged at 2,000 g for 15 minutes at 4°C. The supernatants were separated and stored at −20°C for subsequent analysis. Thromboxane

B_2 and 6-keto-PGF$_{1\alpha}$ were measured by radioimmunoassay (26).

Analysis of data. All results are reported as mean ± 1 standard deviation. On the basis of the results of selective coronary arteriography, the 21 patients who smoked during the study were divided into those with (n = 11) or without (n = 10) greater than 70% luminal diameter narrowing of the proximal third of the left anterior descending or circumflex coronary artery, or both. Changes occurring from baseline to repeat study (8 to 10 minutes later) within each group (control group, smokers with proximal stenoses and smokers without proximal stenoses) were evaluated using a paired *t* test (27). The three groups were compared using an analysis of variance (27). The patients with and without severe proximal stenoses of the left coronary artery in whom smoking failed to increase coronary sinus blood flow were compared using a chi-square analysis (27). For all analyses, a probability (p) value of less than 0.05 was considered significant.

Effect of Smoking on Pacing-Induced Increases in Coronary Sinus Blood Flow

Experimental protocol. In 10 patients (5 men and 5 women, aged 48 ± 9 years), heart rate, systemic arterial pressure and coronary sinus blood flow were measured before and during rapid atrial pacing, and before and during rapid atrial pacing during smoking. Specifically, a percutaneous femoral artery cannula was inserted for the measurement of arterial pressure, and a thermodilution pacing catheter was positioned in the coronary sinus. Baseline recordings were accomplished, after which rapid atrial pacing was performed for 5 minutes at 120 beats/min. Heart rate, arterial pressure and coronary sinus blood flow were measured during the final 2 minutes of this pacing period. Subsequently, atrial pacing was discontinued.

After a 15 minute delay, baseline recordings were repeated. Next, rapid atrial pacing was performed in an identical manner (5 minutes at 120 beats/min). During this pacing period, the patient smoked a cigarette. Variables were recorded during the final 2 minutes of this pacing/smoking period. In each patient, therefore, coronary sinus blood flow was quantitated before and during atrial pacing alone and before and during atrial pacing and smoking. To exclude the possibility that one pacing period exerted a prolonged effect on the subsequent one, the order in which pacing and pacing/smoking were performed was alternated so that in five patients, pacing alone was performed first and pacing/smoking was performed second; in the remaining five, pacing/smoking was accomplished first and was followed (15 minutes later) by pacing alone.

Analysis of data. On the basis of the results of selective coronary arteriography, these 10 patients were divided into those with (n = 5) or without (n = 5) greater than 70%

narrowing of the proximal third of the left anterior descending or circumflex coronary artery, or both. For each group, the increase in heart rate-systolic pressure product and coronary sinus blood flow during pacing alone was compared with that during pacing/smoking with a paired *t* test. The differences in coronary sinus blood flow between pacing and pacing/smoking in the two groups were compared with Student's *t* test (27). A p value of less than 0.05 was considered significant.

Results

Hemodynamic and Serologic Responses to Smoking

The 17 control patients had smoked an average of 43 ± 18 pack-years of cigarettes. Selective coronary arteriography revealed atherosclerotic one vessel coronary artery disease in five, two vessel disease in six and three vessel disease in six. In these 17 patients, no hemodynamic variable changed from baseline to repeat measurement 8 to 10 minutes later (Table 1, Fig. 1 and 2), and the values for thromboxane B_2 and 6-keto-PGF$_{1\alpha}$ in blood obtained from coronary sinus blood samples were similar at baseline and repeat study (Table 1).

The 21 patients who smoked two cigarettes over an 8 to 10 minute period had smoked an average of 41 ± 25 pack-years of cigarettes. Selective coronary arteriography revealed one vessel coronary artery disease in 6, two vessel disease in 3 and three vessel disease in 12. Of these 21 patients, 11 had greater than 70% stenoses of the proximal left anterior descending or circumflex coronary artery, or both, whereas the other 10 had stenoses of the more distal portions of these arteries. In both groups, smoking induced a significant increase in heart rate, heart rate-systolic pressure product, left ventricular dP/dt and cardiac output (Table 1). In the 10 patients without proximal left coronary artery stenoses, smoking caused an increase (average 20 ± 20 ml/min) in coronary sinus blood flow (p = 0.011) (Fig. 1) and a decrease (average 0.14 ± 0.19 mm Hg/ml per min) (p = 0.045) in coronary vascular resistance (Fig. 2). In contrast, neither coronary blood flow nor resistance was modified significantly by smoking in the 11 patients with proximal stenoses of the left coronary artery (Table 1, Fig. 1 and 2). Coronary sinus blood flow increased only 9 ± 29 ml/min and coronary vascular resistance changed 0.00 ± 0.14 mm Hg/ml per min during smoking (coronary sinus blood flow p = 0.032 and coronary vascular resistance p = 0.078 in comparison with the 10 patients without proximal left coronary artery stenoses). Finally, smoking induced either no change or a decrease in coronary sinus blood flow in 6 of the 11 patients with proximal left coronary artery stenoses, but in none of the 10 with more distal stenoses (chi-square = 7.636, p = 0.006).

Table 1. Hemodynamic and Serologic Responses to Cigarette Smoking

Variable	Control Subjects (n = 17)		Smokers With Proximal LCA Stenoses (n = 11)		Smokers Without Proximal LCA Stenoses (n = 10)	
	Baseline	Repeat	Baseline	Repeat	Baseline	Repeat
Heart rate (beats/min)	78 ± 15	77 ± 14	79 ± 10	84 ± 11*	70 ± 11	76 ± 12*
Systolic blood pressure (mm Hg)	125 ± 24	126 ± 23	129 ± 25	131 ± 24	125 ± 32	131 ± 31
Heart rate-systolic pressure product ($\times$ 10^3)	9.6 ± 2.0	9.6 ± 2.0	10.4 ± 2.7	11.1 ± 2.8*	8.7 ± 2.8	10.0 ± 3.3*
Left ventricular end-diastolic pressure (mm Hg)	19 ± 7	21 ± 6	17 ± 10	17 ± 10	16 ± 5	16 ± 4
Left ventricular dP/dt (mm Hg/s)	1,269 ± 347	1,289 ± 354	1,292 ± 327	1,394 ± 438*	1,222 ± 337	1,444 ± 538*
Cardiac output (liters/min)	4.74 ± 1.07	4.82 ± 1.23	4.76 ± 0.93	5.14 ± 1.19*	5.26 ± 0.73	6.05 ± 1.14*
Coronary sinus blood flow (ml/min)	102 ± 31	104 ± 33	117 ± 39	125 ± 47	99 ± 44	119 ± 52*
Coronary vascular resistance (mm Hg/ml per min)	0.97 ± 0.36	0.88 ± 0.40	0.85 ± 0.17	0.85 ± 0.19	1.10 ± 0.47	0.96 ± 0.44*
Coronary sinus thromboxane B_2 (pg/ml)	123 ± 125	131 ± 103	153 ± 133	174 ± 117	113 ± 90	163 ± 99
Coronary sinus 6 keto-$PGF_{1\alpha}$ (pg/ml)	6 ± 7	9 ± 10	5 ± 7	4 ± 5	2 ± 3	5 ± 7

*$p < 0.05$ in comparison with baseline. All values are mean ± standard deviation. LCA = left coronary artery.

In the 21 patients in whom the hemodynamic and serologic responses to smoking were assessed, there was no relation between the changes in coronary sinus blood flow and the amount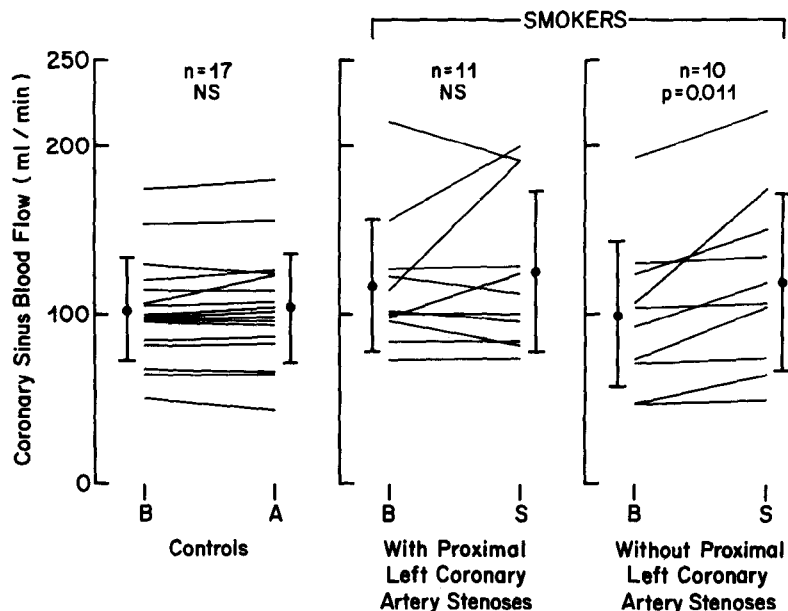 of cigarettes that the patients had smoked (in pack-years) ($r = 0.12$, $p = 0.61$). Similarly, there was no relation between the smoking-induced alterations in coronary blood flow and the changes in the coronary sinus concentrations of thromboxane B_2 and 6-keto-$PGF_{1\alpha}$.

Table 2. Hemodynamic Responses to Pacing and Pacing/Smoking

Variable	Patients With Proximal LCA Stenoses (n = 5)	Patients Without Proximal LCA Stenoses (n = 5)
Pacing alone		
Heart rate-systolic pressure product before pacing ($\times$ 10^3)	9.7 ± 1.2	10.1 ± 0.7
Heart rate-systolic pressure product during pacing ($\times$ 10^3)	14.5 ± 1.5*	16.5 ± 3.6*
Coronary sinus blood flow (ml/min) before pacing	89 ± 18	112 ± 68
Coronary sinus blood flow (ml/min) during pacing	128 ± 39*	139 ± 84*
Average increase in coronary sinus blood flow (ml/min) during pacing	39 ± 24	26 ± 29
Pacing/smoking		
Heart rate-systolic pressure product before pacing/smoking ($\times$ 10^3)	9.1 ± 0.9	10.3 ± 0.8
Heart rate-systolic pressure product during pacing/smoking ($\times$ 10^3)	14.1 ± 1.2*	16.7 ± 4.0*
Coronary sinus blood flow (ml/min) before pacing/smoking	85 ± 33	106 ± 56
Coronary sinus blood flow (ml/min) during pacing/smoking	121 ± 40*	151 ± 65*
Average increase in coronary sinus blood flow (ml/min) during pacing/smoking	36 ± 16	45 ± 21†

*$p < 0.05$ in comparison with values before pacing or pacing/smoking; †$p = 0.018$ in comparison with the average increase during pacing alone. All values are mean ± standard deviation; LCA = left coronary artery.

Figure 1. Coronary sinus blood flow (in ml/min) before (B) and after (A) an 8 to 10 minute period without smoking (**left panel**)(control group) and before (B) and after smoking (S) in patients with (**middle panel**) and without (**right panel**) proximal left coronary artery stenoses. Each line represents the data from one patient, and the mean values ± standard deviations are displayed on either side of each set of lines. In the 17 control patients (**left panel**), coronary sinus blood flow did not change from baseline to the second measurement. In the 11 smokers with severe proximal left coronary artery stenoses (**middle panel**), smoking caused no significant change in coronary sinus blood flow. In contrast, in the 10 smokers without such stenoses (**right panel**), smoking induced a significant increase in coronary sinus blood flow (p = 0.011).

## Influence of Smoking on Pacing-Induced Increases in Coronary Sinus Blood Flow

These 10 patients had smoked 41 ± 24 pack-years of cigarettes. Selective coronary arteriography revealed one vessel disease in four, two vessel disease in five and three vessel disease in one. Stenosis of the proximal left anterior descending or circumflex coronary artery, or both, was present in five and absent in five. The heart rate-systolic pressure product before pacing and pacing/smoking was similar in the two groups of patients, and in both groups the rate-pressure product increased similarly during pacing and pacing/smoking (Table 2). In those without proximal left coronary artery stenoses, coronary sinus blood flow increased

26 ± 29 ml/min during pacing and 45 ± 21 ml/min during pacing/smoking (p = 0.018) (Table 2, Fig. 3). In contrast, in the five patients with proximal left anterior descending or circumflex artery stenoses, or both, coronary sinus blood flow increased 39 ± 24 ml/min during pacing alone, but only 36 ± 16 ml/min during pacing/smoking (p = NS) (Table 2, Fig. 3).

Discussion

Systemic and coronary hemodynamic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease. In patients with and without atherosclerotic coronary artery disease, cigarette

Figure 2. Coronary vascular resistance (in mm Hg/ml per min) before (B) and after (A) an 8 to 10 minute period without smoking (**left panel**) (control group) and before (B) and after smoking (S) in patients with (**middle panel**) and without (**right panel**) proximal left coronary artery stenoses. Each line represents the data from one patient, and the mean values ± standard deviations are displayed on either side of each set of lines. In the 17 control patients (**left panel**), coronary vascular resistance did not change from baseline to the second measurement. In the 11 smokers with severe proximal left coronary artery stenoses (**middle panel**), smoking caused no significant change in vascular resistance. In contrast, in the 10 smokers without severe proximal left coronary artery narrowings (**right panel**), smoking induced a significant decrease in coronary vascular resistance (p = 0.045).
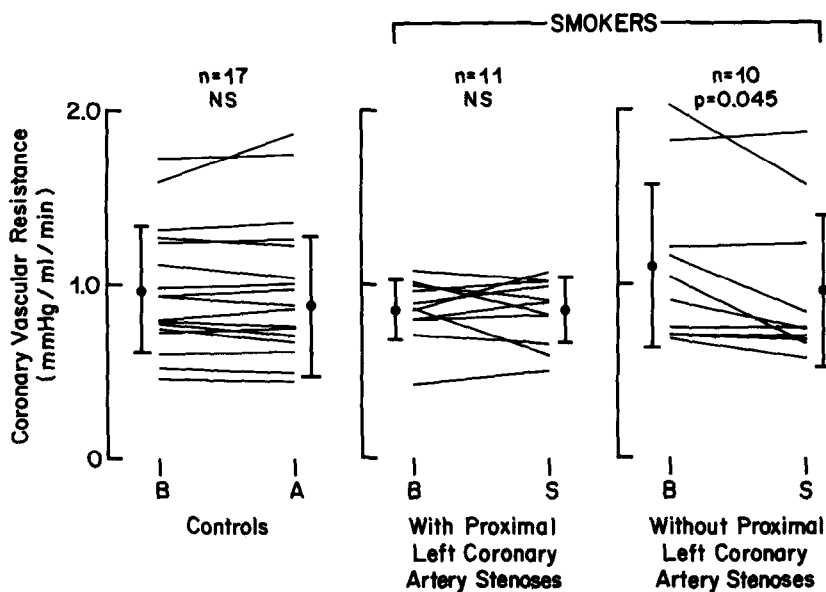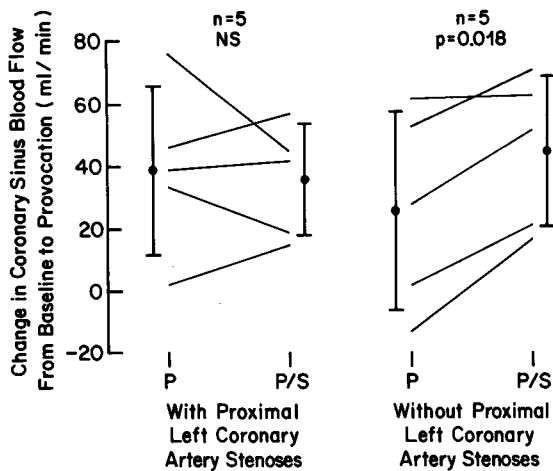
Figure 3. Change in coronary sinus blood flow from baseline to pacing alone (P) and pacing and concomitant smoking (P/S) in the 10 patients in whom these maneuvers were performed 15 minutes apart. Each line represents the data from one patient, and the mean values ± standard deviations are displayed on either side of each set of lines. In the five patients without severe proximal left coronary artery proximal narrowings (**right panel**), the change in coronary sinus blood flow during pacing/smoking was greater (p = 0.018) than during pacing alone. In contrast, in the five patients with proximal stenoses (**left panel**), the change in coronary blood flow during pacing/smoking was similar to that during pacing alone.

smoking increases the heart rate-systolic pressure product, a reflector of myocardial oxygen demands (5,9–16). The response of other hemodynamic variables to smoking appears to be related to the presence or absence of atherosclerotic coronary artery disease. In patients without such disease, smoking augments cardiac output, left ventricular performance and coronary blood flow (5–8, 10–12). In patients with atherosclerotic coronary artery disease, the effect of cigarette smoking on these variables has not been sufficiently clarified. Some studies (8) have demonstrated that smoking increases them, others (7,10,14,16,28) have shown that it exerts no discernible effect and still others (17–19) have suggested that it causes a decrease in coronary blood flow and a commensurate increase in coronary vascular resistance, especially in those with severe proximal stenosis of the left coronary artery (18). Our data demonstate that 1) cigarette smoking augments cardiac output, left ventricular dP/dt and heart rate-systolic pressure product in long-term smokers with coronary artery disease (Table 1), but 2) the response of coronary sinus blood flow and coronary vascular resistance to smoking is heterogeneous and depends on the presence or absence of severe atherosclerotic narrowings of the proximal left anterior descending or circumflex coronary artery, or both.

Role of site and extent of coronary atherosclerosis. Klein et al. (18) previously demonstrated that the presence,

severity and location of coronary artery stenoses may alter the coronary vascular response to smoking; three of their five patients with 75% or greater left main or proximal left anterior descending stenoses exhibited a modest decrease in coronary blood flow during smoking. Our data are in agreement with these observations. Of the 21 patients who smoked during the study, 11 had severe (> 70%) stenoses of the proximal left anterior descending or circumflex coronary artery, or both, 6 (55%) of whom demonstrated no change or a decrease in coronary sinus blood flow during smoking. In contrast, in the 10 patients with more distal coronary artery stenoses, coronary sinus blood flow increased during smoking in all (chi-square = 7.636, p = 0.006). Thus, the influence of cigarette smoking on coronary blood flow and resistance is related to the location and extent of atherosclerotic coronary artery disease.

In an attempt to determine if smoking, in some way, alters the response of coronary blood flow to increased myocardial oxygen demands, we evaluated the response of coronary sinus blood flow to rapid atrial pacing both with and without concomitant smoking in 10 patients with atherosclerotic coronary artery disease, 5 of whom had proximal stenoses of the left coronary artery. In those without proximal stenoses, pacing induced a modest increase in coronary sinus blood flow, whereas pacing/smoking caused an even greater increase (p = 0.018) (Table 2, Fig. 3). In contrast, in the five patients with proximal left coronary artery stenoses, the increase in coronary sinus blood flow induced by pacing/smoking was similar to that which occurred during pacing alone. Thus, in patients with severe atherosclerotic narrowings of the proximal left anterior descending or circumflex coronary artery, or both, smoking causes no augmentation of coronary blood flow when it is performed in conjunction with other provocative maneuvers such as rapid atrial pacing.

Serologic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease. Previous studies (21) suggested that long-term exposure to cigarette smoke augments platelet aggregability and that short-term exposure renders circulating platelets more responsive to various aggregatory stimuli such as adenosine diphosphate. In the experimental animal, nicotine inhibits the formation of prostacyclin by vascular endothelial cells, resulting in platelet hyperaggregability (22–24). In addition, smoking attenuates the hemodynamic alterations induced by the infusion of prostacyclin (29). More recent investigations (19) demonstrated that the coronary sinus concentrations of 6-keto-PGF$_{1\alpha}$ in long-term smokers are lower than those of nonsmokers, but that short-term cigarette smoking does not alter the coronary sinus concentrations of thromboxane B$_2$ or 6-keto-PGF$_{1\alpha}$. Our data are in agreement with this observation (Table 1). The individual alterations in coronary sinus blood flow induced by smoking had no

clear relation to the individual changes in the concentration of thromboxane B_2 or 6-keto-$PGF_{1\alpha}$ in coronary sinus blood.

Limitations of present study. In this study, we measured total coronary sinus blood flow during cigarette smoking, but did not assess its effects on regional myocardial blood flow. Although smoking causes an increase in total flow in some patients, its effects on regional flow are not defined. It is conceivable that cigarette smoking induces a redistribution of myocardial blood flow so that total flow is augmented, but flow to certain regions (those supplied by a severely narrowed coronary artery) is reduced. In support of this possibility, 6 of the 11 patients with severe proximal stenoses of the left coronary artery had no change or a decrease in coronary sinus blood flow during smoking. As a result, some patients may develop myocardial ischemia during smoking or at least may experience a smoking-induced decrease in anginal threshold.

Clinical implications. In long-term smokers with atherosclerotic coronary artery disease, cigarette smoking augments myocardial oxygen demands, but the response of coronary blood flow is heterogeneous. On the one hand, individuals without severe stenoses of the proximal left coronary artery consistently demonstrate an increase in coronary sinus blood flow and a decrease in coronary vascular resistance during smoking. On the other hand, some patients with severe stenoses of the proximal portions of the left coronary artery demonstrate no change or a decrease in coronary sinus blood flow as well as an increase in coronary vascular resistance during smoking. Thus, the effect of cigarette smoking on coronary blood flow appears to be influenced by the location and severity of underlying atherosclerotic coronary artery disease. As suggested previously by Klein et al. (18), smoking may increase coronary artery tone at the site of severe atherosclerotic narrowings. In patients whose stenoses are located proximally, such enhanced tone is likely to cause a decrease in total coronary sinus blood flow and a commensurate increase in calculated coronary vascular resistance.

References

1. West JW, Guzman SV, Bellet S. Cardiac effects of intracoronary arterial injections of nicotine. Circ Res 1953;6:389–95.

2. Kien GA, Sherrod TR. Action of nicotine and smoking on coronary circulation and myocardial oxygen utilization. Ann NY Acad Sci 1960;90:161–73.

3. Ross G, Blesa MI. The effect of nicotine on the coronary circulation of dogs. Am Heart J 1970;79:96–102.

4. Leb G, Derntl F, Robin E, Bing RJ. The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog. J Pharmacol Exp Ther 1970;173:138–44.

5. Thomas CB, Bateman JL, Lindberg EF. Observations on the individual effects of smoking on the blood pressure, heart rate, stroke volume and cardiac output of healthy young adults. Ann Intern Med 1956;44:874–92.

6. Bargeron LM Jr, Ehmke D, Gonlubol F, Castellanos A, Siegel A, Bing RJ. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation 1957;15:251–7.

7. Regan TJ, Frank MJ, McGinty JF, Zobl E, Hellems HK, Bing RJ. Myocardial response to cigarette smoking in normal subjects and patients with coronary disease. Circulation 1961;23:365–9.

8. Irving DW, Yamamoto T. Cigarette smoking and cardiac output. Br Heart J 1963;25:126–32.

9. Aronow WS, Swanson AJ. The effect of low-nicotine cigarettes on angina pectoris. Ann Intern Med 1969;71:599–601.

10. Jain AC, Bowyer AF, Marshall RJ, Asato H. Left ventricular function after cigarette smoking by chronic smokers: comparison of normal subjects and patients with coronary artery disease. Am J Cardiol 1977;39:27–31.

11. Rabinowitz BD, Thorp K, Huber GL, Abelmann WH. Acute hemodynamic effects of cigarette smoking in man assessed by systolic time intervals and echocardiography. Circulation 1979;60:752–60.

12. Klein LW, Pichard AD, Holt J, Smith H, Gorlin R, Teichholz LE. Effects of chronic tobacco smoking on the coronary circulation. J Am Coll Cardiol 1983;1:421–6.

13. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976;295:573–7.

14. Regan TJ, Hellems HK, Bing RF. Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease. Ann NY Acad Sci 1960;90:186–9.

15. Summers DN, Richmond S, Wechsler BM. Cigarette smoke: effects on lactate extraction in the presence of severe coronary atherosclerosis. Am Heart J 1971;82:458–67.

16. Aronow WS, Cassidy J, Vangrow JS, et al. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. Circulation 1974;50:340–7.

17. Reddy CVR, Khan RG, Feit A, Chowdry IH, El Sherif N. Effects of cigarette smoking on coronary hemodynamics in coronary artery disease (abstr). Circulation 1983;68(suppl III):III-165.

18. Klein LW, Ambrose J, Pichard A, Holt J, Gorlin R, Teichholz LE. Acute coronary hemodynamic response to cigarette smoking in patients with coronary artery disease. J Am Coll Cardiol 1984;3:879–86.

19. Martin JL, Wilson JR, Kleaveland JP, et al. Effects of cigarette smoking on systemic and coronary sinus thromboxane and prostacyclin concentrations (abstr). Circulation 1983;68(suppl III):III-165.

20. Aronow WS, Kaplan MA, Jacob D. Tobacco: a precipitating factor in angina patients. Ann Intern Med 1968;69:529–36.

21. Levine PH. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. Circulation 1973;48:619–23.

22. Wennmalm A. Effects of nicotine on cardiac prostaglandin and platelet thromboxane synthesis. Br J Pharmacol 1978;64:559–63.

23. Wennmalm A. Nicotine inhibits hypoxia and arachidonate-induced release of prostacyclin-like activity in rabbit hearts. Br J Pharmacol 1980;69:545–9.

24. Sonnenfeld T, Wennmalm A. Inhibition by nicotine of the formation of prostacyclin-like activity in rabbit and human vascular tissue. Br J Pharmacol 1980;71:609–13.

25. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–95.

26. Hirsh PD, Hillis LD, Campbell WB, Firth BG, Willerson JT. Release

of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease. N Engl J Med 1981;304:685–91.

27. Zar JH. Biostatistical Analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974:152–4.

28. Frankl WS, Winters WL, Soloff LA. The effects of smoking on the

cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 1965;31:42–4.

29. Boura ALA, Hui SCG, Walters WAW. Cigarette smoke inhalation specifically inhibits depressor responses to prostacyclin in the rat. Br J Pharmacol 1981;73:3–5.