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Editorial Comment

Cigarette Smoking, Atherosclerosis and the Coronary Hemodynamic Response: A Unifying Hypothesis*

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The epidemiologic association between cigarette smoking and atherosclerosis is firmly established. The degree of predisposition to coronary artery disease is clearly related to the number of cigarettes smoked. Numerous studies (1) have demonstrated that chronic smokers are at increased risk of myocardial infarction and sudden death. Furthermore, those who discontinue smoking are at less risk for cardiac events than those who continue to smoke.

The precise mechanism by which smoking contributes to the development and clinical manifestations of coronary disease is unknown. In this issue of the Journal, Nicod et al. (2) report their observations of the acute effects of smoking on coronary hemodynamics and myocardial metabolism. Their findings and those of other recent investigations suggest that cigarette smoking increases coronary tone in patients with coronary disease, either at the site of a significant coronary stenosis or in the distal arteriolar bed. Smoking also has detectable vasoconstrictor properties in the normal coronary vasculature. It is tempting to speculate that a link exists between these pathophysiologic effects and the known clinical sequelae of cigarette smoking.

An attractive hypothesis to consider is that chronic smoking predisposes to accelerated coronary atherosclerosis, at least in part, as a consequence of a cumulation of its acute effects on coronary vasomotor tone. Frequent episodes of acute vascular stress may lead to recurrent coronary vasoconstriction and intimal damage, a potentially important factor in the development of atherosclerosis. Since smoking also promotes platelet aggregability, the interaction between platelets and the vascular endothelium is substantially altered. Thus, in the presence of established coronary disease, smoking results both in increased thrombogenicity and increased coronary tone, which could lead to myocardial infarction and sudden death. Importantly, the incidence of these events is decreased with the cessation of smoking, suggesting that this vasoconstricted and thrombogenic milieu is potentially reversible.

Effects of Chronic Smoking

Coronary reactivity. Chronic cigarette smoking has a demonstrable vasoconstrictor effect on the coronary vasculature. Chronic smokers have reduced coronary vascular reserve despite angiographically normal coronary arteries (3). The degree of reduction in the reactive hyperemic response is related to the amount of prior smoking. This observation implies a diminished capacity of the arteriolar bed to vasodilate and compensate for the potential induction of myocardial ischemia, both in patients with coronary disease and in normal persons. Its possible relation to the occurrence of ischemia in patients with normal coronary angiograms has been noted (4). It may also be partially responsible for the decreased exercise tolerance seen in chronic smokers (5).

The mechanism causing decreased coronary reactivity may be related to nicotine-induced reductions in vascular endothelial prostacyclin (Prostaglandin I_2 [PGI_2]) levels (6–8). Wennmalm and Alster (6,7) found that both cigarette smoking and indomethacin inhibit the reactive hyperemic response in the limb, but that smoking has no additional effect after indomethacin administration. This suggests that both interventions work by the same mechanism, presumably prostaglandin inhibition. Nicotine has been shown to decrease PGI_2 synthesis in vascular endothelium, but to have no effect on thromboxane A_2 production (7). Interestingly, chronic smokers have recently been shown to have reduced PGI_2 levels in the systemic circulation (8,9) and in the coronary sinus (2,8) as compared with nonsmokers.

Coronary atherosclerosis. Chronic smoking alters endothelial structure, denudes the surface of the vessel and promotes platelet adhesion to subendothelial layers (10). These structural changes are believed to be important factors in the development of atherosclerosis (11). Kannel (12) has suggested that the carbon monoxide in cigarette smoke produces endothelial hypoxia, allowing intimal lipid infiltration; in addition, enhanced platelet adhesion to the subendothelial layers may stimulate intimal smooth muscle proliferation, perhaps through prostaglandin-mediated mechanisms.

Furthermore, this alteration in vascular integrity might explain the decreased PGI_2 levels in chronic smokers (13). Alternatively, the endothelial changes could be the result

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of persistently increased coronary tone mediated by decreased PGI_2 synthesis. Increased coronary resistance could result in increased turbulence and shear forces, causing endothelial damage as has been shown in hydraulic models. In addition, the decreased PGI_2 levels take on further significance in view of the theory that a disequilibrium between prostacyclin and thromboxane may be an important factor in the pathogenesis of atherosclerosis. Thus, increased vasomotor tone may represent the connection between chronic smoking and atherosclerotic cardiovascular disease.

Acute Hemodynamic Effects of Smoking

An individual who smokes one pack of cigarettes per day acutely stresses his or her cardiovascular system 20 times in 24 hours. It is possible that these chronic coronary vascular changes are the result of frequent and repeated episodes of acute systemic and coronary arterial hemodynamic stress sustained over the course of years.

Systemic hemodynamics. Cigarette smoking causes increases in heart rate, systolic blood pressure and cardiac output in normal individuals. The neural and hormonal mechanisms that mediate this response have recently been reviewed (14). Direct sympathetic ganglionic stimulation and activation of several neural reflexes produce peripheral vasoconstriction. Systemic blood pressure increases as a consequence of the increased peripheral resistance. Heart rate increases because of direct chronotropic effects and adrenal catecholamine secretion. Although myocardial contractility increases because of the catecholamine effect, changes in stroke volume vary considerably. Cardiac output increases chiefly through the increase in heart rate.

Coronary hemodynamics. These systemic effects augment the workload of the heart. The observed increases in heart rate, afterload and contractility serve to increase myocardial oxygen demand. Elevated carboxyhemoglobin levels reduce the capacity for oxygen exchange in the capillary beds, which has a deleterious effect on myocardial cellular aerobic metabolism. Therefore, the net result of cigarette smoking is to increase myocardial oxygen demand and limit myocardial oxygen supply. Smoking increases arterial-coronary sinus oxygen differences in normal individuals, providing evidence of the increase in myocardial oxygen consumption (15). In response, coronary blood flow increases to prevent an imbalance between oxygen supply and demand (15). Atrial pacing data in patients with nonobstructive coronary disease before and after smoking demonstrate that the coronary flow response is blunted after smoking (16). Thus, although the normal coronary response to smoking is a decrease in coronary resistance and an increase in flow, there is evidence that acute smoking diminishes the coronary reserve.

In patients with coronary artery disease, however, this response is markedly altered despite a similar and often higher myocardial oxygen consumption (15). The coronary flow response is heterogeneous and depends on the site and severity of coronary lesions. Klein et al. (15) and Nicod et al. (2) observed that in many patients with proximal coronary obstructions, coronary resistance increases and coronary blood flow decreases with smoking. Vasoconstrictor responses are less prominent in patients with distal lesions. A preliminary study by Booth et al. (17) in which both great cardiac vein and coronary sinus flows were measured during smoking, as well as our own data, are consistent with the hypothesis that resistance increases in regions subtended by a significant coronary stenosis and decreases in normal regions. These observations suggest that there is an active response to cigarette smoking that results in diminished oxygen supply to myocardium distal to a coronary stenosis.

Measurements of coronary blood flow performed during atrial pacing before and after smoking (16,18) also suggest that cigarette smoke has vasoconstrictor effects in patients with obstructive coronary disease. Coronary flow does not increase as much for the same rate-pressure product (16) as compared with the flows achieved before smoking. The threshold to angina also decreases (18), further implying that acute smoking decreases the coronary reserve. The results of Nicod et al. (2) in this issue confirm these findings.

There are several potential explanations for these observations. Smoking may increase tone at the site of the coronary stenosis, causing decreased blood flow to the distal myocardial bed (15). Although the concept of a coronary atherosclerotic lesion having dynamic features is accepted, the mechanism involved in changes in luminal dimension is not known (19). Stimulation of coronary alpha-adrenergic receptors by nicotine or the catecholamines released with smoking could result in arterial smooth muscle contraction around the stenosis, decreasing the lumen diameter (12). Conceivably, inhibition of a local metabolite with potent vasodilator properties, such as PGI_2, would be another possible stimulus for such smooth muscle contraction. Nadler et al. (20,21) recently observed acute inhibition of urinary PGI_2 excretion with smoking. Mehta and Mehta (9) found a much smaller increase in plasma PGI_2 than in thromboxane A_2; however, Nicod et al. (2) and Martin et al. (8) reported no significant changes in aortic or coronary sinus PGI_2 levels with smoking. The differences in the findings of these studies might be explained on the basis of methodologic problems. The plasma assay for 6 keto-immunoactivity may cross-react with other prostaglandins, and might not accurately reflect PGI_2 levels. Also, because prostaglandins are active only at the site of their release, measurements of metabolites in a distant, central area may not be representative of acute changes in regional levels. Thus, the possibility remains that smoking increases coronary tone at the site of a stenosis by causing small decreases in local PGI_2 levels without compensatory changes in thromboxane A_2 levels, which has counterbalancing vascular effects (22,23).

As suggested by Nicod et al. (2), the decreased PGI_2 levels and increased circulating catecholamines could also

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act by increasing platelet activation, resulting in intermittent platelet aggregation and "plugging" in the stenosis lumen. Experimental data in dog models have shown that obstruction from platelet aggregation in a mechanically constricted lumen can cause blood flow reductions (24), an effect exacerbated by nicotine and cigarette smoke (25). However, no changes in platelet aggregability or platelet factor IV levels in the coronary sinus have been reported after smoking (26, and Martin JL, personal communication). Importantly, either of these PGI_2-mediated effects could also occur in the microvasculature distal to the coronary stenosis, as could catecholamine-mediated adrenergic stimulation. Either local vasoconstrictor effects or intermittent platelet plugging in the small resistive arterioles would explain the observed flow responses. It should be noted that we have not observed angiographic evidence of changes in coronary stenosis caliber with smoking. However, small changes in lumen diameter beyond the limitations of angiographic visual interpretation may have important effects on the flow through a critical lesion (19).

Conclusion

There is increasing evidence to support the hypothesis that smoking-induced changes in coronary vasomotor tone, platelet activation and endothelial integrity are a major component of the development of atherosclerosis and the occurrence of subsequent cardiac events. The acute coronary hemodynamic response to cigarette smoking appears to be a reflection of induced alterations in the hormonal and local metabolic constitution of the coronary vasculature. Chronic smoking results in a vasoconstricted coronary bed, probably through the sum of its acute effects on both the prostacyclin: thromboxane ratio and catecholamine secretion. Smoking may accelerate the progression of atherosclerosis by injuring the vascular intima, possibly as the result of persistently increased coronary artery tone and frequent episodes of hemodynamic stress, and by raising the serum cholesterol (27). Finally, in the presence of a severe coronary lesion, vasoconstriction or enhanced platelet aggregation, or both, at the site of the lesion may explain the increased likelihood of acute cardiac events in chronic smokers and the improved prognosis in those who quit. Further investigation in each of these areas will be necessary before the veracity of this hypothesis can be determined.

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