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Editorial Comment

Smoking-Induced Coronary Vasoconstriction: Implications for Therapeutic Use of Nicotine*

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Cigarette smoking remains the most important preventable cause of morbidity and mortality from cardiovascular disease. Smoking increases the risk of acute myocardial infarction, unstable angina and sudden death (1). It also impairs the efficacy of antianginal drugs and is a major risk factor for recurrent episodes of vasospastic angina and for restenosis of coronary arteries after thrombolysis or angioplasty (2–5).

Despite the known hazards, many patients with cardiovascular disease continue to smoke. Patients with coronary heart disease who are able to quit benefit tremendously by doing so. After an acute myocardial infarction a smoker who can quit has a better long-term prognosis than does a nonsmoker, because he or she has a powerful risk factor that can be modified. Patients are more likely to quit smoking after acute events such as myocardial infarction than after routine counseling, yet 30% to 50% continue to smoke after myocardial infarction (6). Most of these people are highly addicted to nicotine.

Because of the pharmacologic nature of the addiction process, pharmacotherapy with nicotine replacement therapy makes sense (7). Such therapy has been shown to enhance the likelihood of successful smoking cessation, on average by twofold. Nicotine is also undergoing clinical trials for treatment of ulcerative colitis and Alzheimer's disease. A concern in prescribing nicotine to patients with active coronary heart disease is the possibility that nicotine itself is hazardous.

Effects of nicotine versus effects of smoking in patients with coronary heart disease. To assess the risks versus benefits of nicotine therapy in the presence of coronary heart disease, the potential role of nicotine in the pathogenesis of acute tobacco-related cardiac events needs to be examined. Smoking promotes acute coronary events by increasing myocardial work and oxygen demand and by reducing coronary blood flow and oxygen delivery (8). It increases myocardial work through its hemodynamic effects—increasing heart rate, blood pressure and cardiac output. It reduces coronary blood flow by coronary vasoconstriction and enhancing thrombosis. Carbon monoxide from smoke also contributes to reduced oxygen supply to the heart. Smoking is associated with greater blood viscosity due to polycythemia and increased fibrinogen levels, which may also reduce coronary perfusion. In addition, smoking may promote arrhythmogenesis, thereby making ischemic events more lethal.

The mechanisms by which smoking produces its adverse effects are not fully elucidated. Nicotine appears to be responsible for the hemodynamic effects and for coronary vasoconstriction, each believed to be mediated by local or systemic catecholamine release, or both (9). The role of nicotine in promoting thrombosis is still unclear. After rapid injection nicotine has been shown to activate platelets in animals through an adrenergic mechanism (10); however, nicotine does not activate platelets in vitro and does not do so in animals with longer-term nicotine exposure (9).

The study by Quillen et al. (11) in this issue of the Journal enhances our understanding of smoking effects on coronary vasoconstriction. Using computerized quantitative angiography and intracoronary Doppler measurements, they show that cigarette smoking constricts both epicardial coronary arteries and myocardial resistance vessels. Previous studies indicated that the effects of cigarette smoking on total coronary blood flow are mediated by catecholamines as the effects are blocked by alpha-adrenoceptor blockade (12). Constriction of large vessels could contribute to myocardial ischemia in the presence of coronary atherosclerosis as well as to recurrent vasospastic angina even in the absence of atherosclerosis. Constriction of small vessels could contribute to smoking-related cardiomyopathy. Cardiomyopathy, independent of the extent of epicardial coronary disease, has been reported to be more prevalent in cigarette smokers (13) and could be a consequence of persistent small vessel constriction and ischemia.

Although nicotine itself is potentially harmful to patients with coronary heart disease, cigarette smoking is likely to be much more hazardous. Cigarette smoking delivers not only nicotine, but also carbon monoxide and many other toxic chemicals. Nicotine delivered from cigarette smoking is also likely to be more toxic than nicotine delivered by currently available pharmaceutical preparations.

Nicotine from cigarette smoke is absorbed rapidly through the lungs and into the circulation, and it results in transiently high arterial blood concentrations that are delivered to the brain and heart. After smoking, arterial nicotine concentrations can be ≥80 to 100 ng/ml, whereas venous concentrations are typically ≈20 ng/ml (14, 15). The effects of nicotine are greater when a dose is administered rapidly than when the same dose is given more slowly (16). The rapid high dose delivery of nicotine to the brain is thought to be responsible for much of the psychologic stimulation and reward associated with cigarette smoking; similarly, the high

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levels of nicotine presented to the coronary arteries may be responsible for coronary vasoconstriction. In contrast, nicotine from polacrilex chewing gum or transdermal nicotine patches is absorbed more slowly and does not produce the same degree of cardiovascular stimulation as does cigarette smoking.

The circadian hemodynamic effects of transdermal nicotine are generally similar to but of lesser magnitude than those produced by cigarette smoking. However, although cigarette smoking increases 24-h urinary catecholamine excretion, this increase is not observed after several days of transdermal nicotine treatment (17). Platelet aggregation, assessed by measuring plasma concentrations of platelet alpha-granule constituents and urinary excretion of thromboxane A_2, are also increased during cigarette smoking but not with transdermal nicotine. Thus, if nicotine contributes to cardiovascular disease through catecholamine release (which is likely) or platelet aggregation (which is not clear), it is probable that the transient high levels of nicotine produced by cigarette smoking are more likely to produce such effects than are the lower levels produced by other methods of nicotine delivery.

Risks versus benefits of nicotine replacement therapy. The impact of nicotine replacement therapy on the coronary vessels is unknown. This is of concern, particularly with 24-h nicotine replacement therapy, in which the heart is exposed to higher concentrations of nicotine overnight than occur with cigarette smoking. If coronary vasoconstriction is mediated by the presence of nicotine itself, prolonged exposure to nicotine could be harmful. Conversely, if coronary vasoconstriction is determined by the magnitude of catecholamine release, which depends on the rapidity of dosing and the maximal arterial blood nicotine concentrations, coronary blood flow may be unaffected by sustained low level exposure. The effect of therapeutic administration of nicotine on coronary blood vessels needs to be examined in future research.

Smoking cessation is probably the single most important treatment for patients with cardiovascular disease who are smokers (18). In the absence of definitive data, the available information suggests that the benefit of nicotine replacement therapy to aid in smoking cessation in patients with coronary heart disease who cannot stop smoking without such therapy outweighs the risks of continued smoking or of nicotine replacement therapy itself. If the physician explains the risks and benefits of nicotine therapy to the patient, nicotine replacement therapy is rational and ethical for such patients.

References

1. United States Office of the Surgeon General. Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. Rockville, Maryland: US Department of Health and Human Services, 1989; Public Health Service, publication No. (CDC) 89-8411.
2. Deanfield J, Wright C, Krikler S, Ribeiro P, Fox K. Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. N Engl J Med 1984;310:951–4.
3. Sugiishi M, Takatsu F. Cigarette smoking is a major risk factor for coronary spasm. Circulation 1993;87:76–9.
4. Galan KM, Ubeydullah D, Kern MJ, Chaitman BR, Vandormael MG. Increased frequency of restenosis in patients continuing to smoke cigarettes after percutaneous transluminal coronary angioplasty. Am J Cardiol 1988;61:260–3.
5. Rivers JT, White HD, Cross DB, Williams BF, Norris RM. Reinfarction after thrombolytic therapy for acute myocardial infarction followed by conservative management: incidence and effect of smoking. J Am Coll Cardiol 1990;16:340–8.
6. Taylor CB, Houston-Miller N, Killen JD, DeBusk RF. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. Ann Intern Med 1990;113:118–23.
7. Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. N Engl J Med 1988;319:1318–30.
8. The health consequences of smoking: cardiovascular disease. A report of the Surgeon General. Washington, D.C., US Department of Health and Human Services, 1983; Public Health Service, Office on Smoking and Health, DHHS publication no. (PHS) 84-50204.
9. Benowitz NL. Nicotine and coronary heart disease. Trends Cardiovasc Med 1991;1:315–21.
10. Folts JD, Bonebrake FC. The effects of cigarette smoke and nicotine on platelet thrombus formation in stenosed dog coronary arteries: inhibition with phentolamine. Circulation 1982;65:465–9.
11. Quillen JE, Rossen JD, Oskarsson HJ, Minor RL Jr, Lopez JAG, Winniford MD. Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. J Am Coll Cardiol 1993;22:642–7.
12. Winniford MD, Wheelan KR, Kremers MS, et al. Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: evidence for adrenergically mediated alterations in coronary artery tone. Circulation 1986;73:662–7.
13. Hartz AJ, Anderson AJ, Brooks HJ, Manley JC, Parent GT, Barboriak JJ. The association of smoking with cardiomyopathy. N Engl J Med 1984; 311:1201–6.
14. Henningfield JE, London ED, Benowitz NL. Arterial-venous differences in plasma concentrations of nicotine after cigarette smoking (letter). JAMA 1990;263:2049–50.
15. Moreyra AE, Lacy CR, Wilson AC, Kumar A, Kostis JB. Arterial blood nicotine concentration and coronary vasoconstrictive effect of low-nicotine cigarette smoking. Am Heart J 1992;124:392–7.
16. Porchet HC, Benowitz NL, Sheiner LB, Copeland JR. Apparent tolerance to the acute effect of nicotine results in part from distribution kinetics. J Clin Invest 1987;80:1466–71.
17. Benowitz NL, FitzGerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking (abstr). Clin Pharmacol Ther 1993;53:168.
18. Jonas MA, Oates JA, Ockene JK, Hennekens CH (AHA Writing Group). Statement on smoking and cardiovascular disease for health care professionals. Circulation 1992;86:1664–9.