Cigarette Smoking, Cotinine, and Blood Pressure

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The primary coronary heart disease (CHD) risk factors are often positively correlated in that many persons who have undesirable levels of one also have undesirable levels of others. Nevertheless, we should not lose sight of risk factors that tend to be inversely related, such as cigarette smoking and blood pressure. A lower mean blood pressure among cigarette smokers than nonsmokers has been demonstrated in several studies based on assessment of smoking habits by questionnaire.1,2 In this issue of Circulation, Benowitz and Sharp3 have confirmed this negative association among normotensive bus drivers, using serum cotinine levels as an index of cigarette exposure. Cotinine, a metabolite of nicotine and a relatively stable marker of nicotine exposure, is used increasingly in epidemiologic studies as an objective measure of cigarette smoking.

At first glance, it is tempting to explain away this negative association by the fact that cigarette smokers tend to be thinner than nonsmokers.4 However, the negative association persisted when body mass index was taken into account. One is also tempted to suggest that because cigarette smoking is often associated with alcohol use in our society, the difference between blood pressures of smokers and nonsmokers would be even more were it not for the blood pressure-raising effects of the alcohol that smokers drink. This bias is also counteracted by control for alcohol consumption in the multivariate analyses performed by Benowitz and Sharp.3 Two possible confounding factors that were not considered are diet and caffeine intake. It is conceivable that dietary differences between smokers and nonsmokers (e.g., differences in salt or meat intake) underlie the observed blood pressure differences. Although caffeine can acutely raise blood pressure, habitual coffee and tea drinking have been associated with slightly lower blood pressures.5,6 Coffee consumption is associated with cigarette smoking7 and, ideally, should also be taken into account in studies of smoking or cotinine and blood pressure.

Because an acute effect of nicotine exposure is raised blood pressure,8 it is fair to ask whether chronic smoking actually causes a decrease in blood pressure. Most of the studies that have shown lower blood pressures in smokers have been cross-sectional, raising the question of time sequence, a crucial issue in judging whether statistical associations are causal. At least one large follow-up study found that the incidence of hypertension was actually higher among cigarette smokers than among nonsmokers.9 However, we could neither confirm nor find a preventive effect of cigarette smoking (GD Friedman, JV Selby, and CP Quesenberry Jr., unpublished data) in a recent large longitudinal study of precursors of hypertension.10 Although the dose-response relation found by Benowitz and Sharp supports causality, uncertainty remains, and a controlled randomized experiment on the effects of the chronic smoking habit would not be feasible or ethical. Intensive longitudinal observations on groups of people who stop and resume or start and stop a long-term smoking habit would contribute much to resolving this issue. Studies of changes in blood pressure among persons who quit smoking have been inconclusive but, fortunately, do not suggest that quitting smoking leads to important rises in blood pressure.2

Ordinarily, people do not smoke during medical examinations. Thus, the lower blood pressure found in smokers may not represent their typical or mean levels. It may be speculated that the pressor effect of nicotine leads to compensating blood pressure-lowering adjustments that are more evident between cigarettes than during smoking. If the experience during smoking is included, it may be that smokers' mean blood pressure over the course of a day is closer to that of nonsmokers than the studies to date suggest.

In addition to the possible depressor as well as pressor actions of nicotine and other alkaloids in cigarette smoke, Benowitz and Sharp3 raise the interesting possibility that depressor effects of cotinine itself explain the lower mean blood pressure
among cigarette smokers. If this proves to be true, then their recommendation that cotinine be measured in studies of cigarette smoking and blood pressure is well taken. The interrelations of smoking, cotinine, and blood pressure become even more intriguing in light of the fact that young adult blacks, who are more prone to hypertension than whites, may differ from whites with respect to cotinine metabolism. They appear to have higher cotinine values at equivalent levels of reported cigarette smoking.11

If cotinine does not play a direct role in producing the end point under study, then is it needed as an objective measure of smoking for epidemiologic investigations? In certain settings, such as risk-factor intervention studies, some subjects may be tempted to underreport their smoking habit to please the investigators. In others, where smoking habits are assessed in a nondirective and nonjudgmental environment, there is no reason for subjects to underreport, and questionnaire information may be as good as can be obtained. In one study, where serum thiocyanate and expired-air carbon monoxide levels were evaluated as objective measures of cigarette smoking, the questionnaire was judged to be more accurate, at least in distinguishing smokers from nonsmokers.12 However, Benowitz and Sharp3 found no difference in blood pressure among smokers based on their reported cigarette consumption grouping, but the cotinine-blood pressure relation persisted when attention was similarly confined to the smokers. If it can be confirmed that cotinine level is more strongly correlated with blood pressure than reported number of cigarettes smoked per day, this would certainly support the wider use of a cotinine measurement in studies of smoking and blood pressure.

Finally, as Benowitz and Sharp remind us,3 hypertension and cigarette smoking appear to be synergistic in elevating the risk of atherosclerotic disease. Even if smoking does lower blood pressure slightly, it should be scrupulously avoided by hypertensive patients as well as the rest of the population in view of its well-known adverse effects on health.

References

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