Inverse Relation Between Serum Cotinine Concentration and Blood Pressure in Cigarette Smokers

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Blood pressure is, on average, lower in cigarette smokers than in nonsmokers. In a cross-sectional study of 288 normotensive bus drivers, we found a significant inverse correlation between serum cotinine (the major metabolite of nicotine) and systolic and diastolic blood pressure that could not be accounted for by age, body weight, or alcohol consumption. Over the observed range of cotinine values, the average decrease in blood pressure was 10.7 and 7.0 mm Hg for systolic and diastolic blood pressures, respectively. We suggest that cotinine be measured to assess the influence of cigarette smoking in epidemiologic studies of blood pressure. (Circulation 1989;80:1309–1312)

Many epidemiologic studies have reported that cigarette smokers have lower blood pressure than nonsmokers or former smokers.\(^1\) A dose-response relation of lower blood pressure with a greater level of cigarette consumption, based on number of cigarettes smoked per day, has been observed by some investigators\(^2\)–\(^4\) but not others.\(^1\)\(^5\)

The mechanism of the negative relation between smoking and blood pressure is unknown. Nicotine, either by direct injection or when smoking cigarettes, acutely increases blood pressure,\(^6\) but it may have different effects with long-term exposure. Because people smoke cigarettes differently, there is only a rough correlation between the number of cigarettes smoked per day and the level of nicotine or its major metabolite, cotinine, in the blood.\(^7\) To further explore a possible mechanistic relation between nicotine exposure and blood pressure, we studied the relations between concentrations of nicotine and cotinine in serum and blood pressure in a cross-sectional survey of healthy bus drivers.

Methods

We studied 288 San Francisco Municipal Railway bus drivers who were healthy and not taking antihypertensive medications. During the biennial medical examination in a municipal workers’ occupational health clinic, each driver completed a questionnaire, participated in an interview, had his or her blood pressure measured three times over 20 minutes, and had a venipuncture. Blood pressure was measured by mercury sphygmomanometry (diastolic phase II) with subjects in a sitting position, using the standardized procedure of the Second National Health and Nutrition Surveys (NHANES II).\(^8\) The average of three readings was used for subsequent analysis. The blood was sampled within 2 hours of the blood pressure measurement. The timing between blood pressure measurement and blood sampling was not standardized; however, the schedule of the examination was such that there was at least 15–20 minutes between the opportunity to smoke the last cigarette and the blood pressure measurement. Subjects were free to smoke cigarettes, and blood sampling was performed independent of when the last cigarette was smoked.

Survey information included demographic information and questions on usual tobacco and alcohol use. Smokers were defined as those who had smoked cigarettes within the past year. Cigarette consumption was reported as less than one-half pack, one-half to one pack, one to one and one-half pack, or one and one-half or more packs per day. Those who had smoked previously but not in the past year were
defined as former smokers. Because blood pressure was similar in former smokers and those who had never smoked, these groups were combined for subsequent analyses. Alcohol intake was reported in categories of “daily/almost daily,” “weekly,” “monthly or less,” or “never.”

Serum samples were assayed for concentrations of nicotine and cotinine by gas liquid chromatography with nitrogen-phosphorus detection as described by Jacob et al,9 modified for use of a capillary column and using 5-methylnicotine and 5-methylcotinine as internal standards. Cotinine, a metabolite of nicotine, has a much longer half-life and fluctuates much less throughout the day than does nicotine and is widely used as a marker of daily nicotine intake.10,11 Results from one blood sample were lost for technical reasons.

Data were analyzed by multiple regression with blood pressure as the dependent variable and the serum concentration of cotinine or nicotine as the primary independent variable. Age, gender, body mass index (kg/m²), and alcohol consumption were included as covariates. Age and body mass index were used as continuous variables, while gender and alcohol consumption were discontinuous variables.

Results

The sample population included 261 men and 27 women (mean age (SD) 42.4±7.1 years). Fifty percent used tobacco. The subjects either reported current tobacco use or had a serum cotinine of more than 12.5 ng/ml (71 nmol/l). The latter cutoff was selected to optimize sensitivity and specificity in distinguishing cigarette smokers from nonsmokers.12 Figure 1 shows a frequency distribution histogram for blood cotinine in all subjects. The geometric distribution was trimodal, consistent with populations of nonsmokers with minimal exposure to environmental tobacco smoke, nonsmokers with exposure to environmental tobacco smoke combined with infrequent tobacco users, and current tobacco users. Based on the histogram, a cutoff of 47 ng/ml (267 nmol/l) cotinine was used to (conservatively) define unequivocal tobacco use (“confirmed tobacco users”). Of the 144 self-reported tobacco users, 36 had cotinine values of less than 47 ng/ml. Average cotinine for the remaining 108 confirmed tobacco users was 280±145 ng/ml (SD) (1,589±823 nmol/l).

Systolic and diastolic blood pressure were significantly lower in confirmed tobacco users than in nonusers (systolic blood pressure, 123.0±11.1 versus 126.9±15.7 mm Hg, p<0.05; diastolic blood pressure, 79.7±8.6 versus 82.0±9.3 mm Hg, p<0.05). Within the group of confirmed tobacco users, there was a significant inverse linear regression between serum cotinine and systolic and diastolic blood pressures (Figure 2). The simple regression coefficients were −0.023 mm Hg/ng/ml (95% CI: −0.037, −0.009) for systolic and −0.015 mm Hg/ng/ml (95% CI: −0.026, −0.004) for diastolic blood pressure (both p<0.01). Similar results were obtained when data from all subjects who reported smoking or all subjects with cotinine concentrations of more than 12.5 ng/ml (usual cutoff for cigarette smoking) were analyzed. The regression coefficients and their standard errors were virtually unchanged after adding age, age squared, body mass index (kg/m²), and frequency of alcohol use to the model. There was no difference in blood pressure among smokers based on level of cigarette consumption grouping.

A similar analysis was performed for serum nicotine, using a cutoff of 3 ng/ml (18.5 nmol/l) to confirm tobacco use.12 In the 97 subjects with confirmed tobacco use, the average nicotine level was 18.6±9.5 ng/ml (115±59 nmol/l). Serum nicotine was inversely correlated to systolic and diastolic blood pressure (regression coefficients, −0.086 [95% CI: −0.317,
Discussion

Our findings confirm other epidemiologic studies that report that smokers have on average lower blood pressure than nonsmokers.\textsuperscript{1} In addition, we present the first data examining the relation between tobacco use and blood pressure using quantitative biochemical measures of nicotine exposure. Our data indicate that in smokers the magnitude of blood pressure is inversely related to serum cotinine concentration. Cotinine is a metabolite of nicotine that is eliminated from the body much more slowly than its parent and reflects the daily dose or intake of nicotine.\textsuperscript{10,13} Over a range of serum cotinine of 47 ng/ml (our conservative cutoff for unequivocal tobacco use) and 512 ng/ml (2,903 nmol/l) (90th percentile), the average decreases in systolic and diastolic blood pressures are 10.7 and 7.0 mm Hg, respectively. As reported by others,\textsuperscript{1,2,4,5} the relation between smoking and blood pressure could not be explained by the confounding influences of age, body weight, or alcohol consumption.

The mechanism of smoking-related blood pressure reduction is not known. Our data are consistent with a pharmacologic role of nicotine, although nicotine intake is highly correlated with intake of tar and, to some extent, carbon monoxide and other gaseous components of tobacco smoke.\textsuperscript{14,15} That nicotine or its metabolites might be involved is suggested by findings that blood pressure is lower in pipe smokers than in people who do not use tobacco.\textsuperscript{16} Pipe smokers have levels of nicotine and cotinine as high as cigarette smokers; however, they inhale much less tar or carbon monoxide.\textsuperscript{17} The nicotine is absorbed through the buccal mucosa. Thus, a blood pressure-lowering effect in pipe smokers argues that nicotine rather than tar or gaseous components of tobacco smoke is responsible. The relation between serum nicotine and blood pressure was negative in our study, although it was not statistically significant. Possibly, the lack of significance is due to imprecision introduced by no fixed interval between time of smoking, blood sampling, and measurement of blood pressure. Nicotine levels change quickly after smoking and between cigarettes, so the strength of the relation between nicotine level and blood pressure would be diminished by a variable interval between measurements.\textsuperscript{11}

That blood pressure is lower in smokers is in contrast to the acute blood pressure-elevating effects of smoking a single cigarette or injection of nicotine.\textsuperscript{6} Blood pressure elevation results from stimulation of the sympathoadrenal system, with local and systemic release of catecholamines and, possibly, release of vasopressin. Prolonged administration of nicotine in animals is associated with transient elevation of blood pressure, but blood pressure then returns to baseline levels and tolerance develops to the acute pressor effects of nicotine challenges.\textsuperscript{18–20} Recent evidence indicates that nicotine may have depressor actions. Suggested mediators of this depressor effect include enkephalins, atrial natriuretic factor, or both.\textsuperscript{18,19,21}

Cotinine per se might explain the blood pressure-lowering effect of cigarette smoking. Cotinine relaxes vascular smooth muscle and dilates blood vessels in vitro,\textsuperscript{22} and it decreases blood pressure in anesthetized rats and dogs.\textsuperscript{23,24} In anesthetized rats, cotinine showed dose-dependent depressor responses, with blood pressure lowering observed at the lowest test dose, 6 \( \mu \)mol/kg.\textsuperscript{24} With the volume of distribution of 1.1 l/kg,\textsuperscript{10} a serum cotinine level of 300 ng/ml (an average value for smokers) corresponds to a total body dose of cotinine of 1.9 \( \mu \)M/kg. This level is close enough to the active dose in rats to suggest that cotinine might be potent enough to decrease blood pressure in tobacco users.

Although nicotine is the most abundant alkaloid in tobacco, minor alkaloids such as nornicotine, anatabine, anabasine, and others are also present in amounts of up to 12% of the total alkaloid content of cigarette tobacco.\textsuperscript{25} Nornicotine and anabasine have cardiovascular activity qualitatively similar to that of nicotine\textsuperscript{22,24} and could contribute to the effects of smoking on blood pressure. Components of the gaseous phase of tobacco smoke may also have cardiovascular effects. For example, acetaldehyde is a major constituent of tobacco smoke. Acetaldehyde, by releasing norepinephrine, may acutely increase blood pressure. However, in guanethidine-pretreated hypertensive rats, acetaldehyde decreases blood pressure.\textsuperscript{26} The possibility that chronic exposure to minor tobacco alkaloids, acetaldehyde, or both, such as is relevant to cigarette smokers, plays a role in the depressor action of smoking should be considered.

Other explanations proposed for the blood pressure-lowering effect of smoking include a "training effect" related to the heart rate acceleration seen with regular cigarette smoking and myocardial dysfunction with impaired contractility.\textsuperscript{1}

While smoking may lower blood pressure, it also accelerates the progression and mortality of cardiovascular disease in patients with hypertension and, to a lesser extent, in people without hypertension.\textsuperscript{27,28} Synergistic interactions between cigarette smoking and hypertension in coronary heart disease risk have been reported.\textsuperscript{29} The complex relation between smoking and hypertension and its complications needs to be considered in future epidemiologic studies. Our studies suggest that measurement of cotinine concentrations in the serum (or saliva)\textsuperscript{30} provides a useful quantitative indicator of the tobacco effect on blood pressure and should be considered for inclusion in studies of the epidemiology of hypertension.

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References

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