CRITICAL REVIEW

Effect of Cigarette Smoking and of Carbon Monoxide on Coronary Heart Disease*

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Numerous studies have documented that cigarette smoking is a significant risk factor contributing to the pathogenesis of coronary heart disease, especially in young and middle-aged men.1-6 Cigarette smoking is associated with a higher incidence of myocardial infarction, with an increased mortality from coronary heart disease, and with an increased incidence of sudden death from coronary heart disease.1-7 Heavy cigarette smokers have a higher incidence of myocardial infarction and mortality from coronary heart disease than light cigarette smokers.2,6 Cigarette smokers who stop smoking have a lower incidence of myocardial infarction and mortality from coronary heart disease than those who continue to smoke.1,4 In addition, autopsy studies have also demonstrated a significant association between cigarette smoking and the presence of coronary atherosclerosis, even in men without a history of clinical coronary heart disease.8,9

A significant association between cigarette smoking and the incidence of angina pectoris has been demonstrated in some studies6,10 but not in other studies;1,5 however, cigarette smoking causes patients with angina pectoris to have a decrease in exercise performance before the onset of anginal pain.11-14 Smoking cigarettes with a high nicotine content11 aggravates exercise-induced angina more than does smoking cigarettes with a low nicotine content13 or non-nicotine cigarettes.1,15 Smoking low-nicotine cigarettes13 aggravates exercise-induced angina more than does smoking non-nicotine cigarettes.15 Patients with angina pectoris develop an increase in myocardial ischemia after smoking high-nicotine, low-nicotine, or non-nicotine cigarettes.16 This increase in myocardial ischemia is greatest after smoking high-nicotine cigarettes and is least after smoking non-nicotine cigarettes.16 Patients with angina pectoris who stop smoking experience fewer anginal episodes and can perform more exercise before developing an attack of angina pectoris.

Smoking high-nicotine11,12,17-19 or low-nicotine15,17 cigarettes causes an increase in systolic and diastolic blood pressure, an increase in heart rate, and no change in systolic ejection period, consequently increasing the myocardial oxygen demand. This increase in systolic and diastolic blood pressure and in heart rate does not occur after smoking non-nicotine cigarettes14,15,17 and is greater after smoking high-nicotine cigarettes than after smoking low-nicotine cigarettes.17

Nicotine causes the increase in systolic and diastolic arterial pressure and in heart rate by increasing the discharge of catecholamines from the adrenal medulla and from chromaffin tissue in the heart.20,21 Nicotine also acts on chemoreceptors in the carotid and aortic bodies, reflexly causing increases in systolic and diastolic arterial pressure and in heart rate.22 In addition, low concentrations of nicotine can stimulate sympathetic ganglion cells.

Smoking high-nicotine, low-nicotine, or non-nicotine cigarettes causes an increased carboxyhemoglobin level,12,14,17,19 which reduces the amount of oxygen available to the myocardium. As cigarette smoke exposes the pulmonary capillary blood to carbon monoxide levels of at least 400 ppm, smokers who inhale develop high carboxyhemoglobin levels. As the affinity of hemoglobin for carbon monoxide is approximately 245 times greater than its affinity for oxygen, carbon monoxide displaces oxygen from hemoglobin, reducing the amount of oxygen available to the myocardium. Carbon monoxide also in-

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duces a leftward shift of the oxyhemoglobin dissociation curve, causing tighter binding of oxygen to hemoglobin, further decreasing the availability of oxygen to the myocardium.\textsuperscript{23} The rise in left ventricular end-diastolic pressure and the fall in stroke index after cigarette smoking\textsuperscript{18,19} are due to the negative inotropic effect on the myocardium caused by an increase in the carboxyhemoglobin level.\textsuperscript{19} In addition, carboxyhemoglobin causes myocardial oxygen extraction and extraction ratios to be reduced and the myocardial lactate extraction ratio to be changed to lactate production in patients with coronary heart disease.\textsuperscript{24}

Carbon monoxide also combines with myoglobin and can impair the facilitated diffusion of oxygen to the mitochondria.\textsuperscript{25} Furthermore, carbon monoxide combines directly with cytochrome oxidase (a\textsubscript{s}), slowing oxidation of reduced nicotinamide-adenine dinucleotide.\textsuperscript{26}

Therefore, patients with angina pectoris develop anginal pain sooner after exercise following cigarette smoking for at least two reasons: (1) nicotine increases the myocardial oxygen demand, and (2) carboxyhemoglobin reduces oxygen delivery to the myocardium.

The increase in nonfatal and in fatal myocardial infarction and in sudden death from coronary heart disease in cigarette smokers\textsuperscript{15-17} may be related (1) to nicotine increasing the myocardial oxygen demand but not the myocardial oxygen supply during an episode of myocardial ischemia, (2) to nicotine increasing platelet adhesiveness, thereby increasing a thrombotic tendency,\textsuperscript{27} and (3) to nicotine lowering the threshold for ventricular fibrillation during an episode of myocardial ischemia.\textsuperscript{28,29} Smoking cigarettes containing nicotine also increases serum corticoid levels, in addition to serum epinephrine levels.\textsuperscript{30} The possible role of increased serum corticoid levels following inhalation of nicotine, sensitizing the myocardium to the effects of catecholamines, possibly contributing to ventricular arrhythmias and myocardial infarction, needs to be investigated.

The increase in nonfatal and fatal myocardial infarction and in sudden death from coronary heart disease in cigarette smokers may also be related (1) to carboxyhemoglobin interfering with myocardial oxygen delivery and aggravating an episode of myocardial ischemia,\textsuperscript{31} (2) to the negative inotropic effect of carboxyhemoglobin\textsuperscript{19} aggravating an attack of myocardial ischemia, (3) to carboxyhemoglobin reducing the threshold for ventricular fibrillation during an episode of myocardial ischemia,\textsuperscript{32} and (4) to carboxyhemoglobin increasing platelet stickiness,\textsuperscript{33} thereby increasing a thrombotic tendency.

In my opinion, both nicotine and carbon monoxide contribute to the increased incidence of nonfatal and fatal myocardial infarction and sudden death from coronary heart disease in cigarette smokers. Cigarette smoking may also impair pulmonary function, contributing to arterial hypoxia and further reducing the amount of oxygen available to the myocardium.

Increased carboxyhemoglobin levels may also result from passive smoking. Transient peak levels of carbon monoxide up to 90 ppm were measured passing across the face of a person who sat next to an individual smoking a cigarette for ten minutes in an exposure chamber.\textsuperscript{34} Therefore, restrictions on smoking in public places are necessary to protect patients with coronary heart disease.\textsuperscript{35,36}

**Pathogenesis of Coronary Atherosclerosis**

Coronary heart disease is a multifactorial disorder. The presence of other risk factors in addition to smoking (including hypercholesterolemia, hypertension, hypertriglyceridemia, diabetes mellitus, marked obesity, and sedentary living) increases the risk of developing coronary heart disease. The greater the tobacco consumption, the greater the number of coronary risk factors, and the greater the degree of abnormality of these risk factors, the higher the risk of developing coronary heart disease.

Wald and associates\textsuperscript{37} have demonstrated that carboxyhemoglobin levels in tobacco smokers correlate better than the smoking history with the development of angina pectoris, myocardial infarction, and intermittent claudication. These investigators have shown that the relative risk of developing coronary heart disease or intermittent claudication was 21.2 times greater in individuals with carboxyhemoglobin levels of 5 percent or greater than in persons with carboxyhemoglobin levels below 3 percent; however, it should be pointed out that the higher levels of carboxyhemoglobin may also reflect the absorption of other constituents of tobacco smoke in addition to carbon monoxide.

In animal experiments, nicotine does not cause coronary atherosclerosis when administered in amounts much greater than the nicotine uptake by a smoker;\textsuperscript{38} however, experimental data have implicated carbon monoxide in the concentrations found in heavy tobacco smokers in the pathogenesis of coronary atherosclerosis.\textsuperscript{39,40-44} Astrup\textsuperscript{38,40} demonstrated that carbon monoxide or decreased oxygen tension enhances coronary atherosclerosis in cholesterol-fed rabbits. Birmstingl and associates\textsuperscript{41} confirmed that carbon monoxide enhances coronary atherosclerosis in cholesterol-fed rabbits. In addition, Webster and co-workers\textsuperscript{42}
demonstrated that carbon monoxide aggravates coronary atherosclerosis in cholesterol-fed squirrel monkeys.

Tilmanns and associates\textsuperscript{47} measured lipid synthesis and cholesterol uptake in vitro in perfused human coronary arteries obtained at autopsy. They found that nicotine failed to influence cholesterol uptake or lipid synthesis and that carbon monoxide did not influence lipid synthesis in the arterial wall; however, these investigators\textsuperscript{48} showed that carbon monoxide leads to a marked increase in cholesterol uptake in perfused human coronary arteries, regardless of the concentration of carbon monoxide in the perfused fluid.

In addition to nicotine and carbon monoxide, tobacco smoke contains other inhaled components, including oxides of nitrogen and hydrogen cyanide, which may possibly play a role in aggravating coronary heart disease. This needs to be investigated.

**Atmospheric Carbon Monoxide Pollution**

Heavy atmospheric carbon monoxide pollution may also lead to increased carboxyhemoglobin levels. A major source of carbon monoxide in the urban atmosphere is automobile exhaust. The emission of carbon monoxide in motor vehicle exhaust is greatest during idling and deceleration. Peak exposures to atmospheric carbon monoxide have been reported to reach as high as 147 ppm in Los Angeles freeway traffic and 141 ppm in New York expressway traffic,\textsuperscript{45} 135 ppm at traffic intersections in Dayton, Ohio,\textsuperscript{46} and 217 ppm for one hour in a tollbooth at the Queens midtown tunnel in New York.\textsuperscript{47} We found that patients with angina pectoris who were driven for 90 minutes in peak early-morning freeway traffic in Los Angeles County during winter months increased their mean arterial carboxyhemoglobin level from 1.12 percent to 5.08 percent.\textsuperscript{48}

The increased carboxyhemoglobin level after exposure to heavy freeway traffic caused a reduction in the exercise time until the onset of angina pectoris, associated with a decrease in the product of systolic blood pressure times heart rate at the onset of angina, both immediately after and two hours after breathing freeway air.\textsuperscript{48} Since the patients with angina pectoris could not adequately increase their coronary blood flow while exercising, and since their increased carboxyhemoglobin level made less oxygen available for delivery to the myocardium, their myocardial oxygen demand exceeded their myocardial oxygen supply, inducing angina pectoris sooner and after less myocardial work. That this reduction in exercise performance until the onset of anginal pain, associated with a decrease in the product of systolic blood pressure times heart rate at the onset of angina pectoris, was related to carbon monoxide absorption rather than to the stress of freeway travel was supported by the absence of these findings when compressed purified air was supplied to the same patients during an equivalent freeway trip three weeks later.

We also observed that three of the ten patients with angina pectoris developed ischemic ST-segment depression of greater than or equal to 1.0 mm more while breathing freeway air during peak freeway traffic than the ST-segment depression observed in the control continuous electrocardiographic recordings (Holter), whereas ischemic ST-segment depression did not develop in any of the ten patients while they were breathing compressed purified air during peak freeway traffic.\textsuperscript{48} The increased carboxyhemoglobin level, plus exposure to other pollutants and the stress of being driven during heavy freeway traffic, may have precipitated the electrocardiographic abnormalities. No significant difference in the amount of ischemic ST-segment depression at the onset of exercise-induced angina occurred after breathing freeway air in comparison with the control periods or with the period after breathing compressed purified air; however, ischemic ST-segment depression greater than or equal to 1.0 mm at the onset of exercise-induced angina occurred earlier, after less exertion, and at a lower product of systolic blood pressure times heart rate both immediately after and two hours after breathing freeway air when compared with the control periods or after breathing compressed purified air.\textsuperscript{48}

Two double-blind randomized studies have also confirmed that exposure to carbon monoxide in concentrations found during heavy atmospheric carbon monoxide pollution aggravates exercise-induced angina.\textsuperscript{49,50} Anderson and associates\textsuperscript{49} demonstrated in a double-blind randomized study that patients with angina pectoris who breathed carbon monoxide concentrations of 50 ppm for four hours to raise their mean venous carboxyhemoglobin level from 1.3 percent to 2.9 percent had a reduction in exercise time until the onset of angina compared to that found after breathing compressed purified air. These investigators also observed that, in general, ischemic ST-segment depression after exercise-induced angina appeared earlier and was deeper after breathing carbon monoxide compared to that found after breathing compressed purified air.

We\textsuperscript{50} showed in a double-blind randomized study that patients with angina pectoris due to angiographically documented coronary artery disease who breathed carbon monoxide levels of 50 ppm for two hours to raise their mean venous carboxyhemoglobin
globin level from 1.03 percent to 2.68 percent had a reduction in exercise time until the onset of angina and a decrease in the product of systolic blood pressure times heart rate at the onset of angina compared to the control periods or that found after breathing compressed purified air.\textsuperscript{56} Ischemic ST-segment depression was not observed in the continuous electrocardiographic recordings (Holter) while these patients were breathing carbon monoxide or compressed purified air. The amount of ischemic ST-segment depression at the onset of exercise-induced angina was also not significantly different after the patients had breathed carbon monoxide compared to the control periods or that found after breathing compressed purified air; however, ischemic ST-segment depression greater than or equal to 1.0 mm after exercise-induced angina occurred earlier, after less exercise, and at a lower product of systolic blood pressure times heart rate at the onset of angina after the patients had breathed carbon monoxide compared to the control periods or that seen after breathing compressed purified air.

We\textsuperscript{51} also demonstrated in a double-blind randomized study that patients with intermittent claudication of the calf or thigh due to angiographically documented iliofemoral occlusive arterial disease who breathed carbon monoxide levels of 50 ppm for two hours to raise their mean venous carboxyhemoglobin level from 1.08 percent to 2.77 percent had a decrease in exercise time until the onset of intermittent claudication compared to the control periods or after breathing compressed purified air. Since the patients with documented iliofemoral occlusive arterial disease could not adequately increase the blood flow to their calf and thigh muscles while exercising, and since their increased carboxyhemoglobin level made less oxygen available for delivery to their calf and thigh muscles, the oxygen demand exceeded the oxygen supply to these muscles, inducing intermittent claudication sooner, following less exercise.

Finally, Cohen and associates\textsuperscript{52} found an association between atmospheric carbon monoxide pollution in Los Angeles and fatality rates in patients with acute myocardial infarction admitted to 35 Los Angeles hospitals; however, adequate prospective epidemiologic studies need to be performed to determine the effect of atmospheric carbon monoxide pollution on mortality from coronary heart disease.

REFERENCES


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