Carbon Monoxide, Smoking, and Cardiovascular Disease

For many years nicotine has been considered responsible for the association between tobacco smoking and the development of atherosclerotic cardiovascular disease, due to its pronounced pharmacological effects on the cardiovascular system, which have been the subject of several epidemiological studies. In animal experiments, however, nicotine has no atherogenic effect when administered in amounts relatively much higher than the nicotine uptake by a smoker, but may cause necrosis and calcifications of the medial arterial layers, which suggests probable importance in the development of the Mönckeberg type of arteriosclerosis in man.

Intimal-subintimal injuries of arterial walls indistinguishable from atherosclerosis are, however, produced in experimental animals by another compound in tobacco smoke: carbon monoxide. Rabbits exposed to carbon monoxide for 13 weeks, leading to carboxyhemoglobin concentrations of 10-11%, develop focal intimal-subintimal changes in a significantly higher degree than nonexposed control animals. These are characterized first of all by a pronounced subintimal edema with various degenerative and reparative processes, increased formation of mucopolysaccharides and collagen, formation of fibrotic plaques, etc. When feeding carbon monoxide exposed rabbits (16-18% carboxyhemoglobin) cholesterol for 8-10 weeks, the aortic content of cholesterol increases from 2.5 to 5 times. This effect of carbon monoxide has been confirmed by other laboratories. Experiments in primates have shown an increase in the number and size of lipid containing lesions in the intramural coronary arteries with carbon monoxide exposure and cholesterol feeding, but did not show an increase in aortic cholesterol. Exposure to hypoxia (16% oxygen in the breathing air) for 8-10 weeks has a similar effect on the arterial walls as exposure to carbon monoxide, while hyperoxia (26-28% oxygen) has an opposite effect.

The primary effect of carbon monoxide on the cardiovascular system is an increased endothelial permeability, leading to subendothelial edema, which is easily demonstrable by ordinary light microscopy and which looks very dramatic through transmittent or scanning electron microscopy. The edema is thought to be caused by an increased inflow of plasma components through a widening of the gaps between the endothelial cells. It is generally agreed that the occurrence of subendothelial edema indicates early atherosclerotic changes. The edema leads to increased formation of mucopolysaccharides, which may facilitate the precipitation of penetrated lipoproteins and eventually result in accumulation of lipids in fatty streaks or plaques.

Severe ultrastructural changes are also found in the myocardium after 16-18% carboxyhemoglobin is maintained for 2 weeks, the most impressive findings being local areas of partial or total necrosis of the myofibrils and degenerative changes of the mitochondria (unpublished observations). Other observations include extra- and intracellular edema, capillary wall edema, increase in the number of ribosomes, and reparative fibrotic changes. The morphological changes are similar to those found in hypoxia.

Both the arterial and myocardial changes can occur after only 4-5 hours exposure to carbon monoxide (16-18% carboxyhemoglobin).

Since the production of atherosclerosis and myocardial damage by carbon monoxide exposure of experimental animals is achieved by carboxyhemoglobin concentrations comparable to those found in heavy smokers, the experimental results strongly indicate that carbon monoxide in tobacco smoke is a toxic compound of major importance. This was deduced from our earlier findings of high carboxyhemoglobin levels in young smokers with myocardial infarction, Buerger's disease and peripheral arterial insufficiency. An association between carboxyhemoglobin levels in smokers and the occurrence of atherosclerosis has been demonstrated, and it could be calculated that smokers with carboxyhemoglobin levels of 5% or higher had a 21 times higher incidence of atherosclerotic disease than smokers with values of 3% or lower.

Nicotine is probably of minor importance in comparison to carbon monoxide for the association between smoking and atherosclerosis, but it may have a synergistic effect on the carbon monoxide enhanced accumulation of lipids in arterial walls, and it may also be of importance in the occurrence of arrhythmias in smokers with myocardial dam-

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The vasoconstrictory effects of nicotine may further impair oxygen supply to tissues of smokers with high carboxyhemoglobin concentrations, particularly where obliterations occur due to plaques or to carbon monoxide induced subendothelial edema. The edema will also impair diffusion of oxygen and nutrients through the vascular walls, probably having especial significance in the myocardium, and it is very likely that carbon monoxide induced myocardiopathy is related to increased incidence of sudden death in smokers as compared with nonsmokers.

If the hypothesis that carbon monoxide is of major importance for the development of atherosclerotic disease in smokers is correct—and the experimental and clinical data are in favor of that—it might be of interest to evaluate the risk of the individual smoker to develop atherosclerosis and heart disease, and the role of smoking in epidemiological studies, by measuring carboxyhemoglobin concentrations after smoking. The smoking of nicotine weak cigarettes should not influence the smoker's risk of getting cardiovascular disease, as long as the carbon monoxide content in the smoke is not decreased, which probably is impossible. If nicotine is the addictive compound in the tobacco smoke, cigarettes with low content of nicotine may even be more dangerous than usual cigarettes due to their supposed higher degree of inhalation.

Further, the atherogenic effects of carbon monoxide exposure are of interest also for atherosclerosis research. The biochemical mechanisms involved in the effects of carbon monoxide and of hypoxia and hyperoxia on endothelial permeability and on lipid metabolism in arterial walls should be identified, since this might lead to a deeper insight in the mechanism of the atherogenetic process.

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References

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