Heart Muscle Diseases — The Cardiomyopathies Part IV: The State of the Left Ventricular Myocardium Following Cigarette Smoking. Influence of Nicotine Administration and Carbon Monoxide Exposure

By

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Cigarette smokers have been shown to have twice the overall death rate of non-smokers in most western societies (1-3). Similarly sudden death is reported to be strongly related to cigarette smoking (2). On the basis of these and other epidemiologic studies cigarette smoking is considered to be one of the risk factors in the development of cardiac disease and myocardial infarction (3,4). The relative rarity of angina pectoris in smokers with heart disease (3,5) raises the question as to whether myocardial alterations may contribute to the clinical abnormalities of these patients independently of coronary vascular disease.

There is general agreement that atherosclerosis is more severe in smokers than non-smokers (6,7). In addition, an increase in the surface area of atherosclerosis of coronary arteries has been reported for smokers in some studies (8-10) but not confirmed in others (6,7). Even in the former studies, the degree of coronary obstructive disease in smokers and non-smokers either did not differ (10) or was not measured (8,9). Thus neither the myocardial response to cigarette smoking separated from other risk factors nor its effects on left ventricular hemodynamics appear established.

Cardiovascular Effects of Long Term Cigarette Smoking and Nicotine Administration in Beagles.

The role of potential myocardial factor in long term smokers was examined in young beagle dogs (11). This species is characterized by relative lack of coronary atherosclerosis which would complicate the study of myocardial function, morphologic features and composition. Since the acute cardiovascular effects of cigarette smoking and nicotine administration are similar (increased heart rate, increased blood pressure), it has been assumed that this alkaloid may participate in the adverse effects of chronic cigarette smoking. Consequently in this study litter mate beagles were prepared with a permanent tracheostomy and placed into three groups: (1) seven control dogs; (2) nine dogs that smoked

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seven cigarettes per day and (3) eight dogs that received an equivalent amount of nicotine. The details of this study were published earlier (11). The method of smoking ensured the delivery of the smoke into the trachea, to approximate most of the features of smoking in man and the cigarettes were a standard brand manufactured by the University of Kentucky, were without filters and contained 1.25 mg of nicotine per cigarette. Smoking was done in two sessions each day. In the nicotine group 210 micrograms per kilogram were injected intramuscularly twice a day. This dose was considered approximately equivalent to that estimated after smoking seven cigarettes.

After a period of 22 months, the animals were catheterized under anesthesia for assessment of left ventricular function. Heart rate, stroke volume, left ventricular end-diastolic pressure and volume and intraventricular conduction times did not differ significantly in the three groups. Left ventricular ejection fraction was 44±3% (mean ± standard error of the mean) in the control group; 35±3% in dogs that smoked cigarettes ($P < 0.05$) and 27±3% in those given nicotine ($P < 0.01$) despite similar values for end-diastolic variables in the three groups. The first derivative of left ventricular pressure (dp/dt) normalized for pre and afterload was 2.4±0.2 cm/sec/sec in the control group, 1.4±0.12 in the cigarette smoking group ($P < 0.005$) and 1.3±0.08 in the nicotine group ($P < 0.01$). Although mean aortic pressure was significantly elevated in both smoking (127±5 mmHg) & nicotine (127±10 mmHg) groups there was no significant correlation with the contractility indices. Reduction of afterload to normal levels did not affect the abnormal ventricular performance.

Neither chronic group exhibited changes in plasma levels of free fatty acid, triglyceride, cholesterol or phospholipid. The morphological studies revealed no gross disease of the heart in these experimental animals. A longitudinal dissection of the coronary arteries disclosed no detectable encroachment on the arterial lumen or visual lesions of the endocardial surface in either group. There was no hypertrophy or inflammation and the myocardial composition of lipid class and major CAT-ion was normal. No abnormalities of myofibrils or other cell organs were noted on electron microscopy to explain the observed functional alteration in the experimental groups. The sole consistent morphological abnormality on light microscopy consisted of collagen accumulation. This was most evident in the middle laters of the myocardium of both experimental groups, was interstitial in location and was virtually absent from the control specimen. The presence of this collagen was confirmed by chemical analysis in the left ventricular wall. The hydroxyproline was significantly increased in the left ventricular myocardium in the nicotine and smokers compared to the normals.

Since the cardiovascular responses to chronic nicotine administration in the beagle closely paralleled the observations in the smoking animals it would appear likely that the observed chronic effects of smoking are predominantly dependent on the nicotine content of cigarettes.

The mechanism of chronic hypertensive response in these animals consuming a large amount of cigarettes is not known. The vasoconstrictor effect on vascular bed is apparent in view of the elevation of peripheral resistance. Nicotine may be presumed to have a role since the group receiving the alkaloid daily also

exhibited hypertension. Because nicotine is known to stimulate the autonomic nervous system (12), a long term effect on the peripheral vessels, perhaps indirectly through the renin-angiotensin system (13) may be operative. It is also possible that a pathological response in the beagle is due to a species idiosyncrasy, but a similar response may occur in some smokers as an expression of intraspecies variability. Recent studies from Israel (14) have claimed that smoking in man results in hypertension, this however, has not been confirmed by others (15).

The reduction in the indices of left ventricular myocardial contractility were observed without hypertrophy and were apparently independent of hypertension. Thei schemia did not seem to contribute to these abnormalities, since the coronary arteries were normal, as were the myocardial morphology and myocardial CAT-ion content. The only obvious reason appears to be the collagen deposition in the interstitium. The long term exposure to sufficient quantity of cigarette smoke or nicotine may well have increased the synthetic activity of the fibroblast in the interstitium of some muscular tissues without evident loss of myofibers at least in the early stages. It is noteworthy that the smooth muscle layers of the arterial system in human smokers had been observed to have enhanced collagen content (16,17). While the interstitial pathology has no clear link to the observed cardiac malfunction, a change in sarcolemma collagen content might effect the ventricular performance related to a restrain on the velocity of contraction produced by the altered elastic elements (18). Alternatively changes in intracellular calcium flux observed by Naylor (19) during acute nicotine experiments may sustain and contribute to a chronic process or alterations of contractile protein in either structure or enzymatic function. may be at fault.

Role of Carbon Monoxide

Many epidemiologic studies have suggested a high incidence of clinical disease in age and sex-matched smokers with carboxy hemoglobin levels greater than 5%, compared to those with lower levels (20). In addition, atmospheric carbon monoxide appears to be the major source in smokers with substantial elevation of carboxy hemoglobin, on the order of 15% (21). Carboxy hemoglobin levels similar to those found in heavy smokers have also been reported to cause atherosclerotic changes and myocardial damage in animals (22). Carbon monoxide and not nicotine, was therefore considered the toxic component of major importance for the increased risk for smokers to develop atherosclerosis and heart disease (23). Accepting this latter assumption, we repeated the study in the same species to determine whether nicotine or carbon monoxide was a major determinant of heart muscle disease (24).

Since smoking three cigarettes either low nicotine such as Sano (R) or high nicotine content as a regular cigarette over 30 minutes results in similar amounts of carboxy hemoglobin in animals both in the immediate and the late period, six animals smoked seven cigarettes of low nicotine content daily while the eight animals of group 3 received equivalent doses of nicotine parenterally. A group of ten animals served as controls. These studies were conducted in the similar fashion and produced results similar those reported above.

As in the earlier study (11) the major hemodynamic abnormalities were noted only in the animals receiving nicotine injections. These

included development of hypertension, decrease in systolic pump performance characteristics and substantial reduction in myocardial contractility. In contrast the control and the animals smoking cigarettes of low nicotine content were normotensive, had intact systolic function characteristics and preserved myocardial contractility (24). The reduction in left ventricular myocardial contractility was again independent of the increased afterload, and was in no way related to the delay in the spread of excitation of conduction through the myocardium. The ischemia also did not appear to be contributory, since the coronary arteries were normal as were the plasma levels of free fatty acids, triglycerides, cholesterol, phospholipids and major CAT-ions. As noted earlier the sole consistent morphologic abnormality on light microscopy consisted of collagen accumulation seen on trichrome stain in the middle layers of myocardium of animals receiving nicotine only. The presence of this collagen was confirmed by chemical analysis in the left ventricular wall as reported earlier. The hydroxyproline levels were increased significantly in the left ventricular myocardium in animals receiving nicotine only.

Since the above changes were not noted in animals smoking low nicotine cigarettes—myocardial effects appeared predominantly dependent upon nicotine rather than carbon monoxide.

Conclusions

Although cigarette smoking is now a well established risk factor for coronary artery disease and cardiac-disease related sudden deaths, myocardial abnormalities appear to play a significant and independent role. Certain precautions in the direct transfer of these data however are necessary. The quantity of cigarettes smoked was relatively large amounting to more than two packs/day in man on the basis of body weight. A dose response relationship needs to be established and the influence of weight and sex assessed. In addition a pathological response in the beagle may be due to a species idiosyncrasy, but a similar response may occur in some smokers as an expression of intraspecies variability. Since clinically evident disease was not observed in these animals, the conclusion of an epidemiologic study by Dick and Stone (25) that the cardiac risk of long term smoking was evident only when associated with other risk factors may be well founded.

As for the toxic components of cigarettes, while carbon monoxide may be playing some role in the development of coronary atherosclerosis, nicotine appears to be the major toxic components of cigarette smoke. The latter may be the main contributing factor in the observed though transient increase in the adhesiveness of platelets (26,27), acceleration of the heart rate, and thus the myocardial vulnerability to ventricular fibrillation (2) which may be the mechanism of sudden deaths in smokers. The interstitial accumulation of collagen, making the ventricle more stiff with resultant decrease in the systolic performance characteristic will definitely add to the cardiovascular morbidity.

Acknowledgement

We gratefully acknowledge the technical services rendered by many of our colleagues, and technicians in the animal support laboratories. We appreciate the secretarial services of Mrs. Charlotte Blocker in typing this manuscript.

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