

Effect of Cigarette Smoke on the Cardiovascular System in Dogs (35707)

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Small amounts of nicotine (5–20 $\mu\text{g}/\text{kg}$), the active ingredient in tobacco smoke, when injected into the femoral vein or pulmonary artery of cats anesthetized with chloralose caused a fall in blood pressure within a few seconds (1). It is controversial as to whether a similar effect can be produced as the result of inhalation of cigarette smoke.

The present study was undertaken to examine the effect of inhalation of cigarette smoke on the hemodynamics of the dog. Various known pharmacological agents, *e.g.*, tyramine, propranolol, were used to modify the evoked response of tobacco smoke in an attempt to gain insight into the mechanism involved in that effect.

Methods. A total of 15 healthy male mongrel dogs ranging in weight from 19.6 to 25.0 kg were used in this study. The dogs were anesthetized with pentobarbital sodium (25 mg/kg; iv). Breathing in all the experiments was assisted by means of a respirator-smoking apparatus supplying the animal through a tracheal cannula. Renal artery flow was obtained by means of a square-wave electromagnetic flowmeter (North Carolina Medical Electronics); and a corresponding acute probe was placed around the left renal artery, which was exposed by means of a retroperitoneal incision. The central venous pressure and the arterial pressure were obtained by passing polyethylene catheters through the external jugular vein and the common carotid artery, respectively. Intravenous injections were made through the venous catheter. Heparin was used as an anticoagulant in the arterial and venous catheters as required. The pressures were measured by means of Statham transducers, and a Sanborn recorder (7700 Series) was used for the continuous monitoring of central venous pressure, aortic pressure, and renal artery flow. The details of further surgical

procedures are given in the Results and Discussion.

Cigarette smoke was administered in the same metered dose (one puff of 100-cc volume and 2.5 sec duration) throughout this series of experiments. The cigarettes used contained 22 mg of tar and 1.3 mg of nicotine. The dog smoked one cigarette per 10 min. The exact amount of nicotine reaching the blood is uncertain. The respirator-smoking apparatus contained a Harvard Apparatus Company respirator pump drawing puffs of smoke regulated in size, duration, and frequency. The puffs were passed to a reservoir from which a second Harvard pump drew the cigarette smoke and fresh air to respire the dog at its tidal volume. Cardiac output was determined by the dye-dilution method of Hamilton and Stewart. Dilution data from the arterial catheter were obtained by continuous sampling through a cuvette densitometer (Gilson Medical Electronics, Inc.) which was connected to a direct-reading cardiac output computer (Lexington Instruments Corp.). The computer was calibrated and programmed to read out cardiac output directly from the densitometer and reject all curves not arithmetically valid.

The following drugs were used: nicotine (expressed as a base), tyramine hydrochloride, propranolol, and chlorisondamine. Student's *t* test was used for the evaluation of statistical significance (7). Details of dosage of drugs and schedule and route of administration are given in appropriate places under Results and Discussion.

Results and Discussion. Cigarette smoke was administered to five dogs for a period of 90 min. Smoke caused a significant drop in systolic blood pressure ($p < .05$), and lower diastolic pressure, heart rate, and slightly increased renal blood flow; however, these later effects were not statistically significant

($p > .05$). The maximum fall in mean systolic pressure (\pm SE) was 12.8 (\pm 4.7) mm Hg, and occurred after 50 min of smoking time. The mean drop in systolic pressure at 25 min was 11.7 mm Hg and at 75 min was 11.3 mm Hg. Since diastolic pressure did not change significantly, a significant fall in pulse pressure occurred ($p < .01$).

These results differ from those of Armitage (2) who found a rise in blood pressure caused by tobacco smoke in cats anesthetized with chloralose. Differences in sensitivity to nicotine in animals anesthetized with chloralose and pentobarbital may be the reason for this discrepancy.

Effects of tyramine. Tyramine is an indirectly acting amine and acts by a release or norepinephrine from its storage site in post-ganglionic sympathetic nerve endings (3, 4). It was, therefore, thought of interest to determine whether smoking affects the release of norepinephrine by tyramine and thereby alters the response. Doses of tyramine (5, 10, 15, 20, 25, and 30 g/kg) were administered intravenously at intervals of 5–8 min. Smoke administration began 10–15 min after the last dose of tyramine. Thirty minutes after the smoke administration, tyramine administration was repeated.

The alteration in response to tyramine caused by smoking varied from preparation to preparation. Smoking did not alter significantly the effect of tyramine on heart rate or renal artery flow. However, in three dogs, systolic and diastolic blood pressure response after smoking was significantly increased from what which occurred before smoking; while in two dogs, it remained unchanged.

Effects of chlorisondamine. In order to investigate the role of the central nervous system influence on the response of the cardiovascular system to smoking, the central impulse flow was blocked at the ganglionic level by the administration of chlorisondamine (a long-acting ganglionic-blocking agent). Furthermore, vagi were cut. Chlorisondamine (2 mg/kg) caused a significant long-term depression in the systolic and diastolic blood pressures and in the heart rate. The renal artery flow remained unaltered. The data are summarized in Table I.

Chlorisondamine reduced the drop in systolic blood pressure caused by smoke ($p < .10$). The data are summarized in Table II. Smoking did not alter the effect of tyramine on systolic and diastolic blood pressure, renal artery flow, or heart rate in this series.

These results suggest that a central com-

TABLE I. Effects of Chlorisondamine and Propranolol on the Cardiovascular System.^a

Time	Blood pressure (mm Hg)		Heart rate (beats/min)	Renal flow (ml/min)
	Systolic	Diastolic		
Control (with vagus cut)	173.0 \pm 5.0	137.5 \pm 4.1	161.3 \pm 12.4	170.5 \pm 13.0
30 minutes after injection of chlorisondamine	129.8 \pm 4.0	100.0 \pm 3.5	117.0 \pm 2.6	165.6 \pm 9.1
<i>p</i> value				
Paired <i>t</i> test of above data	<0.01	<0.01	<0.01	NS
Control	136.4 \pm 9.9	95.6 \pm 6.0	111.6 \pm 12.8	154.0 \pm 8.6
1–2 minutes after injection of propranolol	115.4 \pm 8.1	72.0 \pm 7.1	102.8 \pm 10.0	129.4 \pm 9.1
30 minutes after injection of propranolol	128.6 \pm 9.8	90.6 \pm 7.4	99.2 \pm 8.0	149.6 \pm 13.0
<i>p</i> value				
paired <i>t</i> test				
Between (control) and (1–2 min after injection)	NS	0.05	NS	0.10
Between (control) and (30 min after injection)	NS	NS	NS	NS

^a Each value is a mean of five experiments. NS = Not significant.

TABLE II. Effect of Chlorisondamine on the Changes in the Cardiovascular System Induced by Smoke (after 25 Minutes of Smoking).

	Without chlorisondamine	With chlorisondamine	p Value ^a
Systolic blood pressure (mm/Hg)	-11.2 ± 5.2	-4.2 ± 0.4	<0.10
Diastolic blood pressure (mm/Hg)	-4.6 ± 3.5	-3.3 ± 1.0	NS
Heart rate (beats/min)	-1.2 ± 4.1	-5.4 ± 0.7	NS
Renal artery flow (ml/min)	-11.4 ± 6.5	+1.5 ± 4.4	NS

^a NS = not significant.

ponent may be involved in the action of tobacco smoke. This is consistent with Solti *et al.* (6) who on the basis of experiments using a cross-circulation technique suggested that hemodynamic changes induced by nicotine had a component of central origin. However, it is difficult to be sure that the decreased response to smoking results from a blockade of central effects since the blood pressure is reduced after chlorisondamine.

Effects of propranolol. Since the drop in systolic pressure caused by smoke was reduced but not abolished by ganglionic block-

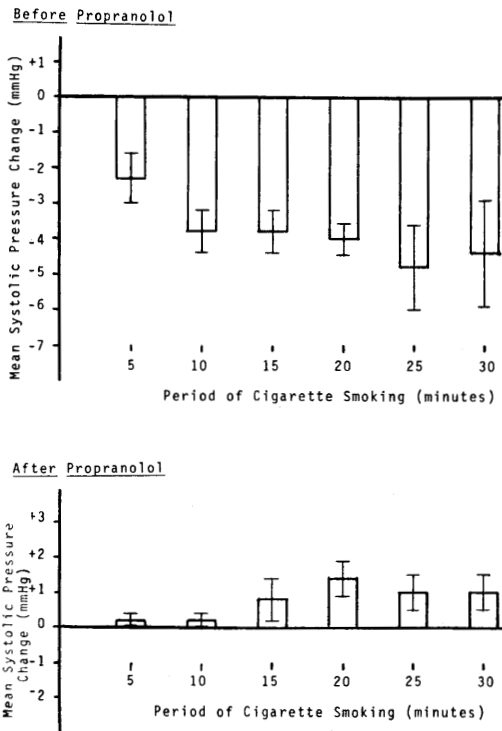


FIG. 1. Effect of propranolol on the response of systolic blood pressure to smoking.

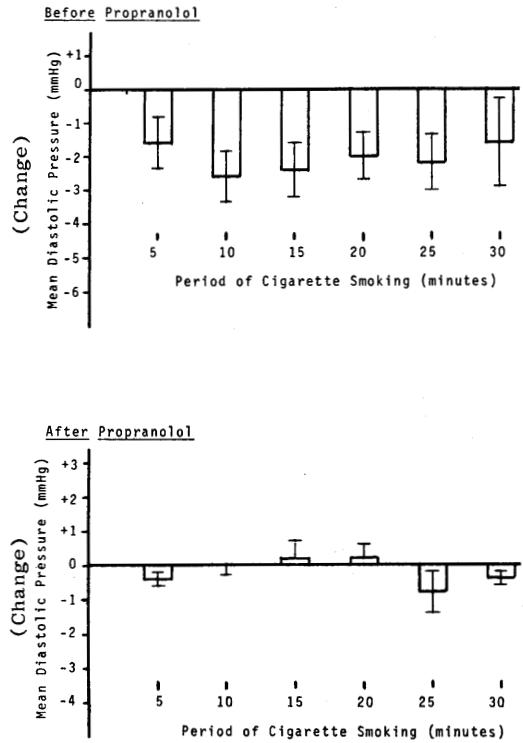


FIG. 2. Effect of propranolol on the response of diastolic blood pressure to smoking.

ing agent, it is possible that nicotine may be causing a release of small amounts of epinephrine from chromaffin tissue which are not affected by ganglionic blockade. This fall in systolic blood pressure may be due to vasodilatation caused by the action of released epinephrine on the peripheral β -receptors. In order to verify this, a third series of experiments was performed in which the β -receptor blocking agent, propranolol, was administered subsequent to the administration of chlorisondamine. The immediate effect (1-2 min) of the propranolol was a significant drop in

systolic and diastolic blood pressures and heart rate. After 30 min the mean blood pressure, heart rate, and renal artery flow were at pre-administration levels. The propranolol either completely abolished, or reversed, the pre-administration response to smoke of systolic pressure (Fig. 1), diastolic pressure (Fig. 2), and heart rate (Fig. 3). These results indicate that the effect of smoke is also due to the action on the vascular system β -receptors of small amounts of epinephrine that are released from their storage sites.

The more important pharmacodynamic actions of nicotine injected or inhaled through

tobacco smoke include stimulation of sympathetic ganglia and the adrenal medulla and the release of catecholamines from sympathetic nerve endings and chromaffin tissue. The response of catecholamine release may be either a fall or a rise in blood pressure depending upon the sensitivity of the vascular receptors and the anesthetic used and on the species of the animal.

Summary and Conclusions. It is concluded that the reduction in aortic blood pressure during smoking in anesthetized animals may be attributed in part to the central effects of nicotine and in part to the vasodilation caused by the action of released catecholamines on the peripheral β -receptors.

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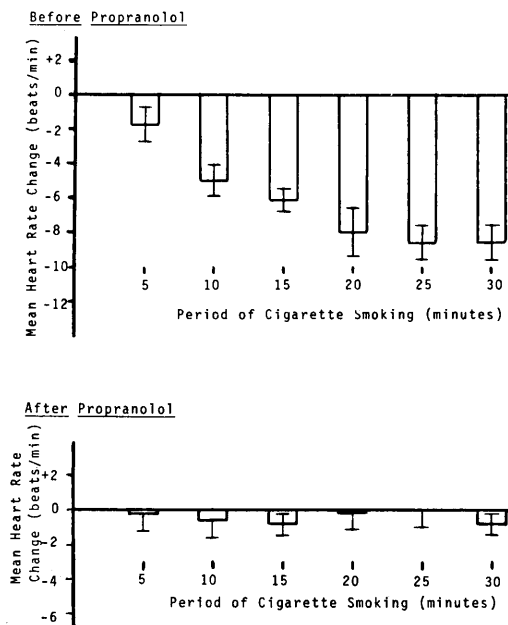


FIG. 3. Effect of propranolol on the response of heart rate to smoking.

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