# The Effect of Nicotine on Regional Blood Flow in the Canine Heart[1] (35897)

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(Introduced by R. J. Bing)
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Nicotine administration elicits a number of complex cardiovascular responses the precise mechanisms of which are not clearly understood. The hemodynamic effects, which have been attributed chiefly to the release of catecholamines, consist mainly of an increase in arterial pressure, heart rate, and stroke work and a resultant increase in coronary blood flow (1–3). The susceptibility of regional myocardial blood flow to changes in ventricular pressure and coronary perfusion has been demonstrated in this laboratory (4), as well as by other investigators (5–7). The present investigations were aimed at studying the effect of nicotine on the regional distribution of capillary flow in the canine heart. The perfusion of the subendocardial portion of the left ventricle was examined because this area has been shown to be especially vulnerable to changes in coronary perfusion and arterial pressure (4, 6, 7). Coronary blood flow was measured by an electromagnetic flowmeter, and the regional distribution of blood flow was estimated by uptake of $^{86}Rb$ after a bolus injection as reported previously (4).

*Methods.* Adult mongrel dogs weighing between 17 and 28 kg were anesthetized with sodium pentobarbital (25 mg/kg wt) and artificially ventilated. Catheters were placed into the superior and inferior vena cava and the descending aorta for the administration of drugs and recording of aortic pressure, respectively. Thoracotomy was performed through the left fifth intercostal space and the pericardium was opened anterior to the left phrenic nerve. Flow through the left descending and circumflex coronary arteries was measured with an electromagnetic flowmeter as described previously (4). The response of coronary blood flow to intravenously administered nicotine was determined by these means.

A total of 26 animals were divided into four groups:

Group I: ($N = 8$) control, flow through the coronary arteries was unobstructed.

Group II: ($N = 6$) myocardial ischemia. In these animals the left circumflex and descending coronary arteries were partially occluded by tying and gradually twisting a 3-0 silk string around the arteries close to the bifurcation of the common left coronary artery. Both branches were gradually occluded until ECG changes of ischemia, *i.e.*, T wave inversion or ST segment depression of at least 2 mm were observed. As a result of the pericardial incision, T waves were frequently inverted; under these circumstances, the ST segment changes were used as guidance. Aortic pressure was continuously recorded.

Group III: ($N = 6$) nicotine (20 $\mu$g/kg/min) was infused until aortic pressure and coronary flow were steady.

Group IV: ($N = 6$) ischemia and nicotine, combination of Group II and III. After myocardial ischemia as documented by EKG changes had been produced, nicotine was (20 $\mu$g/kg/min) infused intravenously until aortic pressure and coronary flow were stable.

When a steady state was reached, 3–5 $\mu$Ci of rubidium 86 were injected into the inferior vena cava as a bolus injection; 45 sec later the heart was rapidly excised at the level of the atrioventricular ring. The left ventricle

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TABLE I. Capillary Flow in Subendocardial Tissue.

| Group | $\frac{E.^{86}Rb\ S.endo}{E.^{86}Rb\ S.epi} \times 100$ (±SE) | *p* value | $\frac{E.^{86}Rb\ S.endo}{E.^{86}Rb\ Septum} \times 100$ (±SE) | *p* value | Av aortic pressure |
|---|---|---|---|---|---|
| I. Control, $N = 8$ | 109.4 ± 2.12 | | | | 119/86 |
| II. Ischemia, $N = 6$ | 108.5 ± 2.24 | I/II >.6 | 87.8 ± 3.42 | | 79/50 |
| III. Nicotine infusion, $N = 6$ | 103.7 ± 2.06 | I/III >.2 | 102.1 ± 2.26 | II/III <.05 | 154/108 |
| IV. Ischemia and nicotine infusion, $N = 6$ | 90.6 ± 3.28 | I/IV <.001 | 76.1 ± 3.30 | III/IV <.001 | 142/98 |

was immediately removed and quickly frozen in liquid nitrogen.

Samples were taken from inner and outer third of the left ventricular wall and processed and counted as reported previously (4, 8).

In experiments in which the left ventricle was rendered ischemic by partial occlusion of left descending and circumflex coronary artery, additional samples were obtained from the interventricular septum. The septal artery has its origin proximal to the bifurcation of the left common coronary artery; hence, the normally perfused septum could serve as an additional control for the ischemia in the left ventricle, because both areas have an equal Rb uptake under normal circumstances (8).

$^{86}Rb$ activity in each specimen was compared with the activity of an aliquot of the injected $^{86}Rb$ solution and calculated on the basis of counts per min per 100 g of tissue. This, in turn, was expressed as percentage of the total injected $^{86}Rb$. Absolute values thus obtained represent the fraction of cardiac output which this area receives. This was taken as an index for capillary flow in subendocardial and subepicardial layers of the heart muscle. For reasons of comparison, values for the epicardium were set as reference of 100%. The relationship of extraction of $^{86}Rb$ in subendocardial and subepicardial layers (extraction subendocardium/extraction subepicardium) × 100 will be referred to as relative subendocardial perfusion.

*Results.* The results are summarized in Tables I and II.

Group I: In normal animals with unobstructed coronary flow the $^{86}Rb$ uptake in subendocardial tissue is 9.5% higher (SE, ±2.1%) than in subepicardial muscle layers, indicating a higher capillary flow in this area.

Group II: In myocardial ischemia following partial ligation of the left circumflex and descending coronary arteries, coronary artery flow diminished in confirmation of the electrocardiographic changes (Table II). The $^{86}Rb$ uptake for the average left ventricle was 22.8% less (SE, ±3.42) than the $^{86}Rb$ uptake of the normally perfused septum, indicating a decreased capillary flow in ventri-

TABLE II. Blood Flow Through Coronary Arteries.

| Group | Anterior descending coronary artery flow (ml/min) | | | Circumflex coronary artery flow (ml/min) | | |
|---|---|---|---|---|---|---|
| | Partial coronary artery occlusion | | After nicotine infusion | Partial coronary artery occlusion | | After nicotine infusion |
| | Before | After | | Before | After | |
| II $N = 6$ Ischemia | 30.0 ± 2.5 | 16.0 ± 4.0 | | 34.5 ± 6.5 | 20.5 ± 5.0 | |
| Change (%) | | −48% | | | −40% | |
| III $N = 6$ nicotine infusion | 29.0 ± 5.5 | | 43.0 ± 6.0 | 37.0 ± 5.0 | | 55.0 ± 6.5 |
| Change (%) | | | +48% | | | +46% |
| IV $N = 6$ Ischemia and nicotine infusion | 31.0 ± 6.5 | 17.0 ± 4.5 | 23.0 ± 5.0 | 39.0 ± 5.0 | 23.5 ± 4.0 | 29.5 ± 5.5 |
| Change (%) | | −45% | +35% | | −40% | +27% |

cular myocardium.

Subendocardial $^{86}$Rb uptake, however, remained 8.56% higher (SE, ±2.2) than subepicardial uptake. The difference from the control of 9.5% was small and not significant.

Group III: Animals receiving an infusion of nicotine (20 μg/kg/min) demonstrated a rise in systolic and diastolic blood pressure to an average of 154/108 (control 119/86), as well as an increase in coronary blood flow, which averaged 47% above the control recording (Table II). However, relative subendocardial perfusion remained higher (3.7 ± 2.1%), suggesting maintenance of a normal subendocardial capillary flow in the presence of increased aortic and consequently left ventricular pressure.

Group IV: In those animals in which the left ventricular myocardium was rendered ischemic before the infusion of nicotine was started, coronary perfusion diminished (Table II). The response to nicotine infusion in both aortic pressure and coronary flow was not as marked as in normal hearts (Table II). The uptake ratio between the subendo- and subepicardial muscle layers was reversed; $^{86}$Rb uptake of subendocardial layers was 9.36% less (SE, ±3.28) than the uptake of subepicardial layers (Table I). Furthermore, a significant reduction in subendocardial flow in comparison to the normally perfused septum could be noted (Table I). This is indicative of a decreased capillary flow in subendocardial in comparison to subepicardial layers. The difference from control was significant ($p < .001$). Ischemia of left ventricular muscle was documented by a 28.5% (SE, ±4.1) higher $^{86}$Rb uptake of the normally perfused septum as compared to the average left ventricle as well as marked ST-T wave changes in the ECG, exceeding those observed following partial coronary artery occlusion alone.

*Discussion.* The administration of nicotine in the dosage employed in the current study (20 μg/kg/min) resulted in an increase in heart rate, aortic pressure, and coronary blood flow. In the presence of normal coronary arteries, no appreciable change in the distribution of capillary flow as measured by uptake of $^{86}$Rb was noted. Partial coronary artery occlusion alone did not result in a significant change in the ratio between subendocardial and subepicardial perfusion. It should be noted, however, that myocardial ischemia, as obtained in the present study, caused a decrease in aortic and consequently intraventricular pressure, which resulted in a reduction in intramyocardial tissue pressure. This may have prevented a greater reduction

in subendocardial perfusion, as compared to subepicardial capillary flow.

When partial occlusion of coronary arteries was followed by nicotine administration (Group IV), the blood pressure increased again. Under these circumstances $^{86}Rb$ uptake in subendocardial tissue was less than in subepicardial layers, and was markedly reduced in comparison to the normally perfused septum. This is indicative of a reduction in capillary flow to the inner portion of the myocardium as compared to septal and subepicardial flow. These changes are significant in comparison to the control and are accompanied by marked ECG changes. It appeared thus that the administration of nicotine in the presence of partial coronary artery stenosis resulted in a decrease in relative subendocardial perfusion, despite an increase in the total coronary flow. These effects may be related to the release of catecholamines (1), and similar observations have been made after the administration of norepinephrine under these circumstances (4).

*Summary.* The effect of nicotine administration on regional myocardial blood flow was examined in normal hearts and after partial coronary artery occlusion. Under normal circumstances as well as after infusion of nicotine in normal hearts the subendocardial portion of the myocardium had a higher capillary flow than the subepicardial fraction. Partial coronary artery constriction alone did not alter this relationship; however, when it was followed by infusion of nicotine, a significant reduction in capillary flow in the inner portion of the myocardium compared to the outer part was observed.

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