Effect of Nicotine on the Coronary Blood Flow and Related Circulatory Parameters

CORRELATIVE STUDY IN NORMAL DOGS AND DOGS WITH CORONARY INSUFFICIENCY

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It has been shown that nicotine and tobacco smoke in the normal dog and human subject increase the coronary blood flow. This is associated with an increase in myocardial oxygen consumption and an increase in cardiac work, whereas coronary resistance declines. A higher oxygen demand caused by the increase in cardiac work can readily be compensated by increase in coronary blood flow in the normal heart with normal coronary arteries. There are few experimental data available relative to the response of the coronary blood flow to nicotine in the presence of coronary artery narrowing and/or occlusion.

Regan et al. studied the effects of cigarette smoking in the human subject with coronary artery disease. Although there was an increase of approximately 30 per cent in left ventricular work in six out of seven patients, they observed no significant change in coronary blood flow and coronary arteriovenous oxygen difference.

Data obtained in rabbits in which coronary atherosclerosis was experimentally produced showed a marked decrease in coronary blood flow, in contrast to rabbits with normal coronary arteries that responded with a flow increase. These authors found that the effect of nicotine differs quantitatively in such animals in that 10 times as much nicotine was required in the "atherosclerotic" rabbit to induce a secondary flow increase comparable to that in the normal rabbit.

Previous studies in our laboratory revealed that normal unanesthetized dogs were able to tolerate fairly high doses of nicotine (0.2 to 0.8 mg./Kg., intramuscularly) without significant electrocardiographic changes. Following myocardial damage produced by coronary artery ligation, marked electrocardiographic changes were obtained with a dose one-fourth of that required to produce only slight changes in the normal animal. These alterations in the electrocardiogram are apparently due to a disparity between the increased cardiac oxygen demand made by the action of nicotine and the inability of the coronary blood flow to increase sufficiently in the presence of coronary artery disease. The present study was undertaken in order to delineate further the action of nicotine on the coronary blood flow in dogs with chronic coronary insufficiency as compared to its action in the normal animal.

Methods

The effect of nicotine on the coronary blood flow was determined in a normal control group (10 dogs) and compared with that of dogs (a) at various periods following coronary artery ligation, which corresponded with the acute, subacute, and healed stages of myocardial infarction (9 dogs), and (b) in the presence of varying degrees of coronary artery narrowing produced by placing casein rings around the circumflex and/or the anterior descending branch of the left coronary artery.
Effect of the injection of nicotine (20 \(\mu\)g./Kg./min., intravenously) on coronary blood flow in the normal dog. (This is a representative graph in one dog.) Note the sudden increase in the coronary blood flow between the first and the fifth minute from 70 to 600 cc. Following a dip down to the normal control, the coronary blood flow levels off to a value higher than the control, ranging between 40 and 70 ml./min. above the control in the following 20 minutes. Note the increase in the heart rate and blood pressure which parallels the increase in the coronary blood flow. (Control period = 10 minutes.) Coronary blood flow (C.B.F.); mean arterial blood pressure (M.A.B.P.); heart rate (H.R.).

METHOD OF CORONARY BLOOD FLOW MEASUREMENTS

One-half hour prior to the experiment, the animals were given morphine sulfate (3 mg./Kg.) intramuscularly, and at the beginning of the experiment they were anesthetized by intravenous injection of equal parts of sodium pentobarbital (60 mg./ml.) and Dial urethane solution (100 and 400 mg./ml., respectively), the dosage being 0.25 ml. of the mixture per kilogram. Anti-coagulation was achieved by intravenous injection of Manuronate (10 mg./Kg.).

Catheterization of the coronary sinus was accomplished in the intact animal with a special coronary sinus catheter (modified Morawitz cannula) inserted via the external jugular vein under fluoroscopic guidance, as previously applied.\(^{14,15}\) The catheter is provided with multiple openings at the tip and an inflatable balloon for securing it in the coronary sinus. The outflow from the coronary sinus is measured at intervals of 30 seconds to one minute by timing a measured volume of blood in a graduated cylinder. The values obtained by this method of measurement are comparable to the nitrous oxide method (Kety-Schmidt) with which average values over a 10-minute period are obtained. In addition, a Shipley-Wilson rotameter was included in the system and used for measurements which were recorded on a Sanborn polyviso electrocardiograph. Indwelling catheters were placed in both femoral arteries: one was used for direct continuous recording of arterial blood pressures via a Statham strain-gauge transducer connected to a direct-writing Sanborn polyviso electrocardiograph; the other served for intermittent blood sampling. Nicotine was infused into one femoral vein; the other femoral vein was utilized for returning the blood from the coronary sinus cannula to the circulation, which was accomplished by a Dale-Schuster or Sigmamotor pump. Control measurements were obtained until the coronary blood flow was stabilized. When coronary flow had reached a steady state (usually within approximately 10 minutes), nicotine was infused intravenously at the rate of 20 \(\mu\)g./Kg./min., for a period of 15 to 20 minutes, during which time the coronary blood flow was obtained continuously at intervals of one minute.

The main pulmonary artery was catheterized to obtain mixed venous blood for the estimation of cardiac output by the direct Fick method. Coronary sinus venous blood samples were collected by means of a small polyethylene catheter inserted in the main coronary sinus catheter. The trachea was intubated for collection of the expired air by a Tissot spirometer. Expired air samples were collected from the Tissot spirometer into a tonometer for analysis of oxygen and carbon dioxide by the technique of Scholander. Oxygen uptake was calculated for periods of five minutes by multiplying the pulmonary ventilation (from the spirometer reading reduced to standard conditions) by the difference between the oxygen contents of inspired and expired air. Analyses of the blood samples for oxygen and carbon dioxide were made by the manometric method of Van Slyke and Neill.\(^{16}\)

The following control data were obtained: coronary blood flow, cardiac output, cardiac work, \(O_2\) consumption, heart rate, and blood pressure. These studies were repeated during, and at various intervals after, nicotine infusion for a period of 30 minutes. At the end of the experiment, the animal was sacrificed and carefully examined to determine the degree of coronary artery narrowing and the state of the heart muscle. In
NICOTINE ON CORONARY CIRCULATION

most instances, the coronary arteries were injected with Cardiographin and x-rays were taken of the injected specimen.

CALCULATIONS
The following parameters were calculated from the data obtained: coronary blood flow in ml./min.; cardiac output in ml./min.; coronary vascular resistance (mean arterial blood pressure + coronary blood flow); coronary oxygen utilization in per cent (coronary arteriovenous oxygen difference + arterial oxygen content in volumes per cent); cardiac work (Kg.-M./min.) from mean arterial blood pressure and cardiac output; cardiac oxygen consumption (coronary flow X coronary arteriovenous oxygen difference); total peripheral resistance (absolute units) according to Pois-

The entire heart was weighed, and the left ventricle was then excised and weighed separately.

Results
NORMAL DOGS: CORONARY BLOOD FLOW
The coronary blood flow was determined by the direct method, as described above, in 10 dogs weighing from 23.1 to 36 Kg., with a mean weight of 24.6 Kg.

The control coronary blood flows ranged between 70 and 120 ml./min., with a mean value of 88 ml./min. During the intravenous infusion of nicotine, there was a rapid increase of flow between the first and fifth minute, with a resultant high early peak which at times attained a height of as much as nine times the control value (fig. 1). Most of the curves showed similar patterns; after the peak, the flow decreased rapidly and leveled off to a value higher than the control for about 15 to 20 minutes (fig. 1).

At the beginning of the cardiac output determinations (usually between the fifth and seventh minute of nicotine infusion when the coronary flow had stabilized), the average value of flow in the 10 dogs was 198 ml./min., an increase of 125 per cent over the mean control value (table 1A).

Additional hemodynamic parameters in normal dogs as studied during the relatively steady state control period, and again five to seven minutes after the start of the nicotine infusion, are listed in table 1A. Our findings correspond closely to those of other investigators.

DOGS WITH CORONARY ARTERY LIGATION
This group consisted of nine dogs (20 to 30 Kg., with a mean weight of 24.7 Kg.), in which ligation of the anterior descending branch of the left coronary artery was performed at various levels. The effect of nicotine on coronary blood flow was studied in these animals between the second and one-hundred and eighteenth day after ligation. Three dogs had acute infarctions (2 to 6 days after ligation), four dogs had subacute infarctions (13 to 19 days) and two dogs had chronic infarctions (98 and 118 days, respectively, after ligation). Most of these dogs showed low control values for the coronary blood flow, ranging from 50 to 93 ml./min., with a mean value of 64.6 ml./min. During nicotine infusion, there was only a moderate and rather slow increase of flow between the

FIGURE 2
Representative graph of the effect of nicotine infusion (20 µg./Kg./min., intravenously) on the coronary blood flow, mean arterial blood pressure and heart rate in a dog with coronary artery ligation and subacute myocardial infarction. The initial low coronary blood flow (C.B.F. = 50 ml./min.) increases in a gradual manner following nicotine infusion, describing a plateau from the fourth to the eighth minute. Then the flow gradually decreases but maintains a higher level than the control for about 15 to 20 minutes. Note that the increase in mean arterial blood pressure is parallel to the coronary blood flow.
### Table 1

#### Mean Values of Hemodynamic Data Before and During Nicotine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>After nicotine</th>
<th>% Increase</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of dogs</strong></td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td><strong>Coronary blood flow</strong></td>
<td>88</td>
<td>198</td>
<td>27.9</td>
<td>334.3</td>
</tr>
<tr>
<td>(ml/min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>264</td>
<td>334.3</td>
<td>27.9</td>
<td>334.3</td>
</tr>
<tr>
<td>(ml/min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac rate</strong></td>
<td>131</td>
<td>192</td>
<td>31.3</td>
<td>143</td>
</tr>
<tr>
<td>(beats/min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>M.A.B.P.</em> (mm. Hg.)</em>*</td>
<td>143</td>
<td>143</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Coronary resistance</strong></td>
<td>1.65</td>
<td>0.65</td>
<td>16.04</td>
<td>2.22</td>
</tr>
<tr>
<td>(P=flow) units</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coronary Ao-Vo</strong> t Volume %</td>
<td>12.03</td>
<td>8.39</td>
<td>28.41</td>
<td>3.45</td>
</tr>
<tr>
<td><strong>Coronary O₂ utilization (V) %</strong></td>
<td>84.1</td>
<td>53</td>
<td>36.8</td>
<td>79</td>
</tr>
<tr>
<td><strong>Cardiac work</strong> (Kg.=M./min.)</td>
<td>5.1</td>
<td>8.43</td>
<td>65.3</td>
<td>3.45</td>
</tr>
<tr>
<td><strong>Myocardial O₂ consumption</strong> (Gm. heart/min.)</td>
<td>10.25</td>
<td>16.04</td>
<td>54.9</td>
<td>28.5</td>
</tr>
<tr>
<td><strong>Cardiac efficiency (%)</strong></td>
<td>79.5</td>
<td>52.6</td>
<td>28.5</td>
<td>28.5</td>
</tr>
<tr>
<td><strong>Total peripheral resistance</strong> (T.P.R.)</td>
<td>4.35</td>
<td>3.22</td>
<td>7.22</td>
<td>2.22</td>
</tr>
</tbody>
</table>

*Mean arterial blood pressure.

**Coronary arteriovenous oxygen difference.

Cardiac output (ml/min.)

Cardiac rate (beats/min.)

M.A.B.P. (mm. Hg.)

Coronary resistance (P=flow) units

Coronary Ao-Vo (Volume %)

Coronary O₂ utilization (%)

Cardiac work (Kg.=M./min.)

Myocardial O₂ consumption (Gm. heart/min.)

Cardiac efficiency (%)

Total peripheral resistance (T.P.R.)
third and sixth minute. At the end of the infusion (fifteenth minute) the coronary blood flow returned to the low control level and remained there until the termination of the experiment (for at least an estimated 15 minutes).

The graphic expression of the blood flow showed a curve without a peak, but with a long "plateau." The response of the coronary blood flow appeared to be related to the acuteness and extent of the myocardial infarction; the more acute and extensive the myocardial infarction, the lower and broader was the plateau of coronary blood flow increase (fig. 2).

The remaining hemodynamic parameters are summarized in table IB. The mean control blood flow was appreciably lower than in normal dogs (average 64.6) and rose on an average of 82.5 per cent, compared to 125 per cent in normal dogs during nicotine infusion. The cardiac output increased by 23.3 per cent, compared to 27.9 per cent in normal controls. These animals were more sensitive to the nicotine infusion and frequently developed in addition to sino-auricular block, ectopic rhythms, e.g., numerous extrasystoles, A-V dissociation, and, in occasional instances, supraventricular and ventricular tachycardia. Despite the development of these arrhythmias, the average heart rates calculated during the periods of nicotine infusion were shown to deviate only slightly from the control values. There was just a minimal decrease of 3.4 per cent, compared to the group of normal animals in which the heart rate decreased 31.3 per cent during nicotine infusion. Since there was no appreciable alteration in the cardiac rate, the increase in cardiac output was mainly due to an increase in stroke volume. However, the increase in the stroke output per beat would have to be considerably less than in the normal group in whom a marked decrease in heart rate was observed during the nicotine infusion. The mean arterial blood pressure showed lower control values but following infusion increased as in normal dogs (35.2 per cent). The control coronary vascular resistance was higher than in the normal group, and showed only a 17 per cent decrease during the nicotine infusion, as opposed to 41.8 per cent in the normal group. This, in turn, led only to a slight decrease of 8.4 per cent in coronary arteriovenous oxygen difference (30.2 per cent in normals) and of 13.9 per cent in coronary oxygen utilization (36.3 per cent in normals). Since the increase in mean arterial blood pressure and cardiac output was similar to that of the normal dogs, so was the resultant increase in cardiac work (65.9 per cent). The control cardiac oxygen consumption was lower than in normal dogs but rose to about the same degree (52.6 per cent) during nicotine infusion. The increase in cardiac efficiency appeared slightly more marked (18.2 per cent) than in normal dogs (10.2 per cent); this figure, however, cannot be regarded as representative since it could only be calculated in three dogs.

**DOGS WITH CORONARY INSUFFICIENCY PRODUCED BY CASEIN RINGS**

In these animals (seven dogs weighing 24 to 29 Kg., with a mean weight of 26.5 Kg.), the control values of coronary blood flow tended to be even lower than those in the dogs with coronary artery ligation (54 ml./
min.), because in five dogs of this group both main branches of the left coronary artery were appreciably narrowed near their point of origin. Furthermore, the control flow values of some of the dogs with ligations in the chronic stage of myocardial infarction approached normal values, whereas in the dogs with two rings the control coronary blood flow was low in all instances. The mean control coronary flow values (54 ml./min.) increased during nicotine infusion by 83.3 per cent, as compared to 82.5 per cent in dogs with ligation of one arterial branch and to 125 per cent in normal dogs.

The graphic expression of the coronary flow was that of an early low peak with a broad base. The early peaking resembled that of the normal dogs but was much less marked. In addition, there was a tendency to form a plateau, as was observed in the dogs with coronary artery ligation (fig. 3).*

The control cardiac output was lower than in both other groups (1,927 ml./min.) and increased 21.4 per cent. This increase was achieved mainly by an increase in stroke volume as in normal dogs. The latter, however, showed a much greater decrease in rate and, therefore, a much more marked increase in stroke volume. The cardiac rate decreased 10.9 per cent, as compared to 31.3 per cent in normal dogs, but the control value averaged 33 beats faster than in normal dogs and 19 beats/min. faster than in dogs with coronary ligation. The reason for these higher rates is the increased irritability of the myocardium resulting in a disturbance of the rhythm during the experimental procedure. The mean arterial blood pressure increased 30.7 per cent from lower mean values (117 mm. Hg.) than in normal dogs (143 mm. Hg.) but from similar levels in dogs with ligation (115.2 mm. Hg.). The coronary resistance, which during the control period was understandably highest in this group (2.20), decreased 26.3 per cent. This, in turn, brought about a 14.5 per cent decrease in coronary arteriovenous oxygen difference and 14.3 per cent in coronary oxygen utilization. Control levels of cardiac work were lowest in this group (3.05 Kg.-M./min.) and increased less than in both other groups (5.6 per cent). Cardiac oxygen consumption increased 51.4 per cent. The increase in cardiac efficiency was calculated as 15.7 per cent.

**PATHOLOGY FINDINGS**

Dogs with ligation of the anterior descending branch of the left coronary artery showed anterolateral wall infarction in an acute, subacute, or chronic state, depending on the period of survival after the coronary artery ligation. The extent of the infarction varied from heart to heart, depending mainly on the level at which ligation was performed.

The hearts in which coronary insufficiency was produced by the casein rings inserted around both the circumflex and anterior descending branches of the left coronary artery showed the arterial lumen to be narrowed to a circumference of 0.7 to 1.2 mm. Occasionally, the lumen was almost completely obliterated by fibrous reactions. The pathological examination of the myocardium revealed the following: (a) no gross areas of infarction; (b) areas of subendocardial necrosis with hemorrhages, confined especially to the left lateral wall; or (c) areas of marked subendocardial fibrosis.

**Discussion**

The experiments in our series of dogs with either coronary artery ligation or narrowing demonstrate a definitely impaired response of the coronary blood flow to nicotine as compared to that of normal controls. This evidence is based upon: (1) the diminution in the control blood flow and considerably less augmentation of the coronary blood flow following nicotine infusion in dogs with occlusion of the anterior descending branch of the left coronary artery; and (2) an even lesser augmentation in the coronary blood flow response to nicotine in animals with constriction of both main branches of the left coronary artery produced by casein rings.

A comparison between these three groups

*Similar results were obtained with seven dogs in which coronary blood flow was obtained with the nitrous oxide method.*
of normal dogs, dogs with ligation of the anterior descending branch and dogs with narrowing of two main branches of the left coronary artery follows:

Nicotine administered intravenously increases cardiac work by increasing the mean arterial blood pressure and the cardiac output. This is associated with an increase in myocardial oxygen consumption. For the normal animal, the marked increase in coronary flow meets the greater myocardial oxygen demand during the administration of nicotine. However, in the dogs with impaired response of the coronary flow this increased demand is not met sufficiently. The more the coronary flow is impaired the more severe is that state of "relative coronary insufficiency." Three dogs with severe narrowing and myocardial infarction showed a fall in both coronary blood flow and blood pressure, in contrast to the rise in all other dogs, and died during nicotine infusion with ventricular fibrillation, presumably due to severe myocardial anoxia. These were not included in this series.

These findings are similar to those obtained by Foltz et al., who studied the response of coronary blood flow and cardiac oxygen metabolism to anoxemia obtained in intact anesthetized dogs where gradual coronary artery narrowing was achieved by surrounding the vessels with cuffs of cellophane and tantalum mesh. In this series, as in our dogs with moderate coronary narrowing, considerably less augmentation of coronary flow under anoxemia was observed. Cardiac oxygen consumption failed to increase as greatly as in normal dogs but the increase in cardiac work was comparable to that of normal animals.

The above findings appear to indicate the increase in cardiac work resulting from nicotine administration is accompanied by an inadequate increase in coronary blood flow in the presence of coronary insufficiency. It is felt that these findings have a bearing on the clinical problem relative to nicotine effects in the presence of coronary artery disease and in patients subject to episodes of coronary insufficiency.

Summary

The effect of intravenously administered nicotine (20 μg./Kg./min.) on the coronary blood flow and related hemodynamic parameters was studied in the normal intact dog and in the dog with chronic coronary insufficiency as produced either by coronary artery ligation or gradual coronary artery narrowing. Nicotine increases cardiac work markedly by an increase in the mean arterial blood pressure and cardiac output. The degree of this increase is similar in normal dogs and dogs with chronic coronary insufficiency. The mean control coronary blood flow was moderately decreased in dogs with coronary artery ligation and markedly decreased in dogs with narrowing of the two main branches of the left coronary artery. Nicotine produced an increase in coronary blood flow which in normal dogs was observed to be as high as 125 per cent on an average over the control value. The average increase was considerably less in dogs with ligation of one coronary artery branch (82.5 per cent) and in dogs with narrowing of two main branches (83.3 per cent). The degree of coronary narrowing and/or occlusion was directly related to the response of the coronary flow; the greater the coronary impairment, the smaller was the increment in coronary blood flow under nicotine administration. The response of the coronary blood flow to nicotine resembled that of anoxemia in the presence of coronary insufficiency. These findings would appear to have a bearing on the clinical problem relative to the effect of nicotine in the human subject with coronary artery disease.

References


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