Ineffectiveness of Nitroglycerin as an Antiadrenergic Agent on the Cat Heart

By NICHOLAS R. POPOVICH, FRED F. ROBERTS, RODNEY L. CRISLIP AND HERMANN MENGES, JR.

Under the supervision of Richard W. Eckstein, M.D.

The possibility that nitroglycerin modifies the metabolic effects of the sympathomimetic amines was tested in cats. Changes in the heart rate, blood pressure, height of the electrocardiographic T-wave and myocardial oxygen consumption following the injection of epinephrine or 1-arterenol were compared with changes in these indices after nitroglycerin was given with these sympathomimetic amines. The conclusion is reached that nitroglycerin does not significantly influence the effects of epinephrine or 1-arterenol on the heart rate, the height of the electrocardiographic T-wave or myocardial oxygen consumption. There is no evidence in these experiments to support the concept that nitroglycerin metabolically neutralizes the myocardial anoxating properties of the sympathomimetic amines.

The exact cause of the benefit derived from nitroglycerin in the anginal syndrome is far from clear. Usually it is attributed to improved myocardial oxygenation resulting from coronary dilation and/or reduced peripheral resistance with a reduction in myocardial oxygen requirement. Recently, Raab has suggested that the effect of nitroglycerin in the anginal syndrome depends on a metabolic neutralization of the anoxating properties of the sympathomimetic agents on the myocardium. The evidence for this hypothesis is based upon electrocardiographic and heart rate changes in atropinized cats. Raab observed that the T-wave depression and the heart rate acceleration induced by commercial adrenaline and by l-arterenol were prevented when nitroglycerin was given prior to or in combination with these drugs. In the present study the experimental work of Raab was repeated and experiments giving a direct index of myocardial metabolism were performed.

METHODS

Part I. Fifteen cats were anesthetized with pentobarbital and after cannulation of the left jugular vein the blood was rendered noncoagulable with heparin (50 mg.). The right carotid artery was cannulated and connected to a Gregg manometer for optical recording of blood pressure. Electrocardiograms from lead CR4 and blood pressure were simultaneously recorded during and after drug administration.

The cats were atropinized (2 mg./Kg.) and control records were obtained. The separate effects of adrenaline, adrenaline with nitroglycerin, and nitroglycerin alone were measured. The drugs were given slowly with a motor driven syringe or injected rapidly into the left jugular vein and followed by a 5 ml. saline wash. Each injection was made 5 min. subsequent to the disappearance of the observable effects of the previous drug. The effects of 1-arterenol alone and together with nitroglycerin were also studied. Fifty micrograms of adrenaline and l-arterenol and from 1 to 10 mg. of nitroglycerin were used. The aortic pressure and electrocardiograms were recorded continuously for the first 2 min. after drug administration and then at 15 sec. intervals over a 3 min. period. The effects of the injection of the adrenaline and l-arterenol were repeated randomly in a manner to ensure that the effects were not due to the saline wash.

The aortic pressure and electrocardiograms were recorded continuously for the first 2 min. after drug administration and then at 15 sec. intervals over a 3 min. period. The effects of the injection of the
5 ml of saline were measured for control purposes. In 3 animals the adrenal arteries and veins were ligated prior to drug administration. Measurements were made of the changes induced by adrenaline and l-arterenol in heart rate, mean blood pressure, and T-wave height. Measurement of the changes in these indices were also made following the injection of nitroglycerin together with each of these sympathomimetic amines. The changes induced by the amine plus nitroglycerin were subtracted from the respective changes induced by the amine alone. The significance of these differences was tested.

Part II. Ten additional animals were anesthetized with pentobarbital and after cannulation of the left femoral vein, atropine (2 mg./Kg.) and heparin (50 mg.) were administered. The right carotid artery was cannulated and the coronary sinus was dissected free. Polyethylene tubing was introduced through the tip of the right atrium and tied in the coronary sinus. Blood from the sinus was led into the cannulated femoral vein. Appropriate arrangements of stopcocks permitted coronary sinus outflow to be measured in a graduated cylinder for periods of 1 min. while simultaneous samples of arterial and sinus blood were drawn into oiled syringes. The volume of the sinus sample was added to the volume collected in the graduate to give total sinus outflow per minute. The blood samples were analyzed for oxygen content by the method of Roughton and Scholander. Mean arterial pressure was recorded throughout the experiment with a mercury manometer connected to the carotid artery.

After control data were obtained 2 ml of saline containing 50 μg. of l-epinephrine were rapidly injected into the femoral vein of 5 animals. Coronary sinus outflow was again measured while simultaneous samples of arterial and sinus blood were drawn. Two ml of saline containing 50 μg. of l-epinephrine and 1.8 mg. of nitroglycerin were injected into the remaining 5 animals. After coronary sinus outflow had returned to normal the experiment was repeated in the 10 animals. The animals were sacrificed and a dilute solution of India ink was injected into the coronary sinus. The stained myocardium was dissected out and weighed, and myocardial oxygen consumption per 100 cm. of heart was calculated.

**RESULTS**

**Blood Pressure, Heart Rate and T-Wave Changes**

**Effects of Adrenaline and l-Arterenol.** The administration of these drugs resulted in increases in heart rate which ranged from 21 to 90 beats/min. The rise in mean arterial pressure ranged from 59 to 145 mm. Hg. Preliminary temporary increases in the height of the T-wave occurred and were replaced by T-wave depressions or atypical inversions in every instance (fig. 1). However, only in 1 instance were typical T-wave inversions obtained after the administration of l-arterenol (record not shown).

**Effects of Nitroglycerin on the Action of Adrenaline.** The injection of adrenaline plus nitroglycerin resulted in heart rates which ranged from 2 beats/min. below to 21 beats/min. above those due to adrenaline alone. (Mean difference = 0.8 beats/min., p = .8). The addition of nitroglycerin had no influence on the T-wave inversion resulting from adrenaline alone (mean difference = 0 mm., p = 1). However, the mean arterial blood pressure following the injection of adrenaline plus nitroglycerin ranged from 4 to 86 mm. Hg lower than that measured after the use of adrenaline alone (mean difference = —42 mm. Hg, p > .001).

**Effects of Nitroglycerin on the Action of l-Arterenol.** The heart rates resulting from the injection of l-arterenol together with nitroglycerin ranged from 2 beats/min. below to 32 beats/min. above those due to l-arterenol alone (mean difference = 1.7 beats/min., p = .8). The height of the T-wave in 2 animals was not influenced by the addition of nitroglycerin and in 4 animals the T-wave was 1 to 3 mm. less...
Table 1.—Myocardial Oxygen Consumption—cc./min./100 Gm.

<table>
<thead>
<tr>
<th>Cat no.</th>
<th>Control</th>
<th>1-epinephrine</th>
<th>Increase</th>
<th>Cat no.</th>
<th>Control</th>
<th>1-epinephrine and nitroglycerin</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.9</td>
<td>10.9</td>
<td>3.0</td>
<td>6</td>
<td>6.9</td>
<td>8.2</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>6.4</td>
<td>2.2</td>
<td>7</td>
<td>5.6</td>
<td>6.9</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>13.3</td>
<td>6.4</td>
<td>8</td>
<td>5.8</td>
<td>6.7</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>9.4</td>
<td>14.6</td>
<td>5.2</td>
<td>9</td>
<td>5.3</td>
<td>9.9</td>
<td>4.6</td>
</tr>
<tr>
<td>5</td>
<td>6.4</td>
<td>12.5</td>
<td>6.1</td>
<td>10</td>
<td>6.5</td>
<td>10.1</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>6.2</td>
<td>7.4</td>
<td>1.2</td>
<td>11</td>
<td>8.0</td>
<td>9.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>10.4</td>
<td>12.4</td>
<td>2.0</td>
<td>12</td>
<td>3.9</td>
<td>8.3</td>
<td>4.4</td>
</tr>
<tr>
<td>8</td>
<td>5.5</td>
<td>8.8</td>
<td>3.3</td>
<td></td>
<td>4.0</td>
<td>5.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Mean 6.7 10.3 3.6 5.7 8.2 2.5

\[ p < .001 \]

Depressed than with l-arterenol alone (mean difference = —1.4 mm., \( p = .2 \)). The typical T-wave inversion produced in one instance by l-arterenol was not modified by nitroglycerin. The injection of l-arterenol plus nitroglycerin resulted in rises in mean arterial pressure which ranged from 8 mm. Hg above to 60 mm. Hg below those induced by l-arterenol alone (mean difference = —31.4 mm. Hg, \( p = .09 \)).

Effects of Nitroglycerin Alone. Neither rapid nor slow intravenous injection of nitroglycerin resulted in any appreciable change in either the electrocardiogram or heart rate (fig. 1, bottom). However, the mean arterial blood pressure was depressed an average of 15 mm. Hg.

Effects of Saline. After the injection of 5 ml. of saline intravenously for control purposes, the heart rate, T-wave height and arterial pressure remained constant.

Effects of Ligation of Adrenal Arteries and Veins. The 3 cats in which this procedure was performed were handled as described above. In no case was there appreciable difference in the responses of these animals and in those with intact adrenals.

Myocardial Oxygen Consumption

The results shown in table 1 indicate that both l-epinephrine alone and l-epinephrine with nitroglycerin result in significant increases in myocardial oxygen consumption. However, the magnitude of these increases in myocardial oxygen consumption is not significantly different under the 2 conditions. Control coronary sinus outflow ranged from 27 to 204 ml./100 Gm./min. (average 77), while coronary sinus blood oxygen content ranged from 0.9 to 6.7 vol. per cent (average 2.7). After the injection of l-epinephrine the coronary sinus outflow was increased in all cats but 1 and ranged from 48 to 226 ml./100 Gm./min. (average 174). Following the injection of l-epinephrine plus nitroglycerin the coronary sinus outflow ranged from 27 to 336 ml./100 Gm./min. (average 197) and coronary sinus blood oxygen content increased above the control in all cats and ranged from 1.5 to 6.8 vol. per cent (average 4.4).

Discussion

Statistical analyses of the differences in the heart rate and T-wave in cats lead to the conclusion that nitroglycerin does not significantly modify the changes in these indices induced by adrenaline or l-arterenol. The fact that the elevation of blood pressure following these agents was prevented to a significant degree by the addition of nitroglycerin, indicates that adequate pharmacologic doses of nitroglycerin were employed. Our data indicate that even large doses of nitroglycerin fail to prevent elevations in myocardial oxygen consumption induced by l-epinephrine in the cat heart.
The coronary sinus blood flow measurements which serve as the basis for the calculation of myocardial oxygen consumption in these experiments represent an unknown fraction of total coronary flow. Consequently, the calculations of myocardial oxygen consumption probably only approximate the true values. However, since all the experiments were done under the same conditions and with similar techniques the relative changes are comparable.

The conclusion that nitroglycerin is ineffective as a metabolic antiadrenergic agent on the myocardium of cats agrees with that of Eckstein\(^4\) who worked with dogs. It is believed that these results, which are based on actual measurements of myocardial oxygen consumption, render untenable the hypothesis that nitroglycerin neutralizes the metabolic effects of the sympathomimetic amines.

**Summary**

The effects of nitroglycerin on the action of adrenaline and l-arterenol were studied by measurements of changes in myocardial oxygen consumption, arterial pressure, heart rate and the electrocardiographic T-wave in cats. The results indicate that nitroglycerin does not significantly neutralize the effects of these 2 drugs on the T-wave, or heart rate. Increases in myocardial oxygen consumption induced by l-epinephrine in a group of cats were compared with the increases obtained with l-epinephrine and nitroglycerin in a second similar group. The results reveal no significant difference and indicate that in cats nitroglycerin produces no known metabolic effect which may be regarded as antiadrenergic.

**Summary in Interlingua**

Le effecto de nitroglycerina super le action de adrenalina e l-arterenol esseva studiate per mesurar le alterationes del consumption myocardial de oxygeno, le pression arteria, le velocitate del corde, e le unda T del electrocardiogramma in cattos. Le resultatos indica que nitroglycerina non neutraliza significative mente le effecto de ille duo drogas super le unda T o le velocitate del corde. Augmentos del consumption myocardial de oxygeno, inducite in un grupo de cattos per l-epinephrina, esseva comparate con le augmentos del consumption myocardial de oxygeno, inducite in un secunde e simile grupo per l-epinephrina e nitroglycerina. Le resultatos monstra nulle differentias significative. Illos indica que in cattos nitroglycerina non effectua ulle cognoscite influentia metabolic que poterea esser considerate como antiadrenergic.

**References**

Ineffectiveness of Nitroglycerin as an Antiadrenergic Agent on the Cat Heart
NICHOLAS R. POPOVICH, FRED F. ROBERTS, RODNEY L. CRISLIP, HERMANN MENGES, JR. and RICHARD W. ECKSTEIN

_Circ Res._ 1956;4:727-730
doi: 10.1161/01.RES.4.6.727

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/4/6/727

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/