Studies of the Antiadrenergic Effects of Nitroglycerin on the Dog Heart

By Richard W. Eckstein, M.D., William B. Newberry, M.D., James A. McEachen, M.D., and George Smith, F.R.C.S.

Using anesthetized dogs, the possible antiadrenergic effects of nitroglycerin upon the myocardium were studied. Observations were made upon changes in heart rate, myocardial oxygen consumption, systolic vigor, and the electrocardiograms. Data are presented showing the effects of nitroglycerin and adrenergic agents when given separately and in combination. Results indicate that in dogs, nitroglycerin produces no antiadrenergic effects on the myocardium. The suggestion is made that the T wave changes seen after adrenergic stimulation in dogs may not be due to anoxia.

The beneficial effects of nitroglycerin in the anginal syndrome have been considered to be due either to coronary dilation with an improvement in myocardial oxygenation, or to the reduction in peripheral resistance and cardiac work, or to both, resulting in a decrease in myocardial oxygen requirement. However, in view of recent evidence of heart rate and electrocardiographic changes in atropinized cats, Raab1-3 suggests that nitroglycerin acts in a different manner. He postulates that it interferes with the metabolic, anoxia producing effects of the sympathomimetic amines on the myocardium. Although this hypothesis is attractive, Raab admits that its proof depends upon further evidence.

The question then arises as to the criteria required for more conclusive study of this problem. Large increases in myocardial oxygen consumption in dogs occur after cardiac accelerator nerve stimulation with little or no increases in heart rate.4-8 The records of Raab3 show rather small rate increases after stimulation of the stellate ganglion or after the infusion of epinephrine. Therefore, it would seem that changes in heart rate do not critically demonstrate adrenergic anoxating effects. Whether the depression of the T wave in the electrocardiogram which is seen after adrenergic stimulation is due to anoxia or to some other myocardial effect of adrenergic agents is more difficult to establish. (See Discussion.)

There are, however, two changes induced by adrenergic agents which occur together, and which can serve as indicators for testing any deviation in the adrenergic effects upon the myocardium. These are (1) changes in vigor of contraction, as indicated in the aortic pressure pulse, and (2) changes in myocardial oxygen consumption.4-8 The present report deals with our attempts to modify these adrenergically induced myocardial changes in dogs by the use of nitroglycerin.

Methods

Dogs were anesthetized with pentobarbital, and under artificial respiration the left chest was opened between the third and fourth ribs. The blood was made noncoagulable with 100 to 150 mg. of heparin. The left jugular vein was cannulated to administer fluid and to return coronary sinus blood. The coronary sinus was cannulated via the right auricle, and the cannula was made secure in the sinus by the inflation of a small balloon at the cannula tip.

The left common coronary artery was dissected free and was cannulated by means of the special cannula previously described.9 The cannula was connected to the constant pressure apparatus and a Shipley rotameter described elsewhere.9,10 In a few cases adjustment of the position of the cannula was necessary to get adequate sealing without leakage or restriction of coronary inflow. The possibility of leakage was tested in two ways: (1) With perfusion pressure above aortic pressure, a ligature was tightened about the common left artery distal to the cannula. The rotameter was then observed for evidence of flow and therefore of leakage. (2) After clamping the inflow rotameter tube, a side arm on
the outflow side of the rotameter was opened. Leakage was present when a steady flow occurred from the open side arm. When this occurred slight repositioning of the cannula stopped the leakage and produced a to and fro motion of blood at the open side arm. After the proper placing of the cannula, leakage never developed during the course of the experiment.

In a few instances the septal artery was occluded by the cannula. In each such case the origin of this artery was very far central. Its occlusion was always suspected because of rapid decreases in blood pressure with abnormal rhythms or pulsus alternans.

In most of the experiments a portion of the coronary sinus blood was led through the cuvette of a Waters-Conley oximeter to indicate directional sinus oxygen changes and proper timing for blood samples. In some cases electrocardiograms were taken. Usually lead II was used.

In all experiments the following data were obtained: aortic pressure, perfusion pressure, total left coronary flow, arterial and coronary sinus oxygen levels by the method of Van Slyke and Niell,\textsuperscript{11} and oxygen consumption per 100 Gm. of perfused myocardium. After the control studies were made, the observations were repeated following the use of nitroglycerin, Parke-Davis Adrenalin, \textit{l}-epinephrine,\textsuperscript{*} \textit{l}-Arterenol\textsuperscript{*} and stimulation of the cardiac accelerator nerves as described below. The rotameter was calibrated with the animals’ own blood. At the end of each experiment dilute India ink was injected into the coronary cannula and the injected area was cut out and weighed.

**Results**

1. **Effects of Nitroglycerin Alone.** After controls were obtained, nitroglycerin was injected into the coronary cannula with a motor-driven syringe. The results in table 1A show that nitroglycerin produced elevations in coronary flow and coronary sinus oxygen content with no appreciable change in myocardial oxygen consumption or heart rate. The doses of nitroglycerin were purposely small in order to produce coronary dilation without marked changes in blood pressure.

2. **Effects of Nitroglycerin during Cardiac Accelerator Nerve Stimulation.** Control data were obtained. The left cardiac accelerator nerve was stimulated after section from the stellate ganglion. New observations were made and immediately nitroglycerin was injected into the coronary cannula. Further observations were made. The results (table 1B) show that nerve stimulation, as is usual, resulted in increased coronary flow and oxygen consumption with a decreased coronary sinus oxygen content. The injection of nitroglycerin produced further increases in coronary flow with an elevation of sinus oxygen content in all but one experiment (D6). There was no significant change in oxygen consumption or consistent alteration of heart rate except in D1. Our records (not shown) gave no evidence that nitroglycerin altered the form of the aortic pressure pulse. Larger doses of nitroglycerin produced the typical fall in blood pressure but did not influence the vigor of contraction.

3. **Effects of Nitroglycerin on the Action of Commercial Adrenalin.** These experiments were done in two ways. (A) After the controls were obtained Adrenalin was injected into the perfusion chamber or into the coronary cannula. As soon as blood samples were drawn, nitroglycerin was injected. Blood samples were again drawn. (B) In these experiments blood samples and records were obtained in the following order: (1) control, (2) after injection of Adrenalin, (3) control, (4) after injection of Adrenalin plus nitroglycerin. Table 1C shows the results. Again it is striking that nitroglycerin in doses sufficient to dilate the coronary arteries produces no consistent change in oxygen consumption. In experiments D4, D9 and D10 significant cardiac slowing occurred. However, since these dogs were not atropinized and blood pressure tended to rise, reflex slowing is likely.

4. **Effects of Nitroglycerin on the Action of \textit{l}-Epinephrine and \textit{l}-Arterenol.** These experiments were done as in 3 above. \textit{l}-Epinephrine was given in doses of 1 gamma and nitroglycerin in a dose of 0.84 mg. The dose of \textit{l}-Arterenol was 0.5 gamma. The results of these experiments (table 1D) indicate that nitroglycerin did not modify the heart rate or the oxygen consumption. The electrocardiogram revealed the usual T-wave inversion after these adrenergic drugs. Intracoronary injection of even this huge dose of nitroglycerin did not modify this T-wave response. Figure 1 shows a typical record. A and B show the effects

\* The \textit{l}-epinephrine and \textit{l}-Arterenol were supplied by the Sterling Winthrop Research Institute, Rensselaer, New York.
 Table 1

<table>
<thead>
<tr>
<th>Exp</th>
<th>Procedure</th>
<th>M.B.P. mm. Hg</th>
<th>Heart Rate</th>
<th>Coronary Sinus O₂ Volumes %</th>
<th>A-V O₂ Diff.</th>
<th>Left Coronary Flow cc./100 Gm./1 min.</th>
<th>O₂ Consumption cc./100 Gm./1 min.</th>
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A. Effects of Nitroglycerin on Control Heart

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<th>A-V O₂ Diff.</th>
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<td>188</td>
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B. Effects of Nitroglycerin during Sympathetic Nerve Stimulation

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<th>Exp</th>
<th>Procedure</th>
<th>M.B.P. mm. Hg</th>
<th>Heart Rate</th>
<th>Coronary Sinus O₂ Volumes %</th>
<th>A-V O₂ Diff.</th>
<th>Left Coronary Flow cc./100 Gm./1 min.</th>
<th>O₂ Consumption cc./100 Gm./1 min.</th>
<th>Remarks</th>
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<tr>
<td>D4</td>
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<td>190</td>
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<td>5.0</td>
<td>159</td>
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<td>200 γ into Perfusion Chamber</td>
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<td></td>
<td>After Commercial Adrenalin</td>
<td>84</td>
<td>178</td>
<td>4.7</td>
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<td>220</td>
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<td>152</td>
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C. Effects of Nitroglycerin on the Action of Commercial Adrenalin
of l-Arterenol on the aortic pressure pulse, total left coronary flow and continuous oximeter cuvette tracings of changes in coronary sinus oxygen level. The record shows the usual changes induced by adrenergic agents; namely, the shortening of systole, the temporary increase in blood pressure and the increase in coronary flow. Since the oximeter does not receive capillary blood immediately, there is a lag in its response, the length of which depends upon the speed of blood flow. B shows that in spite of the increase in blood flow the oximeter response shows a decreasing coronary sinus oxygen content.

In contrast to records A and B, records C, D and E show the effects of a mixture of l-Arterenol and nitroglycerin. The coronary flow curve shows striking differences in that it increases much earlier and its rate of increase is more rapid. The oximeter curve in D shows at first a rise in sinus oxygen content due to the coronary dilation induced by nitroglycerin. Nevertheless, in E the oximeter curve shows that the effect of the adrenergic agent is to decrease the sinus oxygen content in spite of a marked fall in blood pressure.

5. Effects of the Intravenous Injections of Nitroglycerin and l-Arterenol. For these experi-

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### Table 1—Continued

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<thead>
<tr>
<th>Exp.</th>
<th>Procedure</th>
<th>M.B.P. mm. Hg</th>
<th>Heart Rate</th>
<th>Coro. Sinus O₂ Vol. %</th>
<th>A-V O₂ Diff.</th>
<th>Left Coron. Flow cc./100 Gm./1 min.</th>
<th>O₂ Consump. cc./100 Gm./1 min.</th>
<th>Remarks</th>
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**C. Effects of Nitrogen on the Action of Commercial Adrenalin—Continued**

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**D. Effects of Nitroglycerin on the Action of l-Epinephrine and l-Arterenol (Intracoronary Injections)**

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<th>Exp.</th>
<th>Procedure</th>
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<th>Coro. Sinus O₂ Vol. %</th>
<th>A-V O₂ Diff.</th>
<th>Left Coron. Flow cc./100 Gm./1 min.</th>
<th>O₂ Consump. cc./100 Gm./1 min.</th>
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**E. Effects of Nitroglycerin on the Action of l-Arterenol (Intravenous Injection)**

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<th>M.B.P. mm. Hg</th>
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<th>Coro. Sinus O₂ Vol. %</th>
<th>A-V O₂ Diff.</th>
<th>Left Coron. Flow cc./100 Gm./1 min.</th>
<th>O₂ Consump. cc./100 Gm./1 min.</th>
<th>Remarks</th>
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ments, after control observations were made l-Arterenol (10 gamma) was injected intravenously and data obtained. Again controls were established and were followed by the intravenous injection of a mixture of 10 gamma of l-Arterenol and 1.84 mg. of nitroglycerin. Table 1E shows the results when both the

rate after nitroglycerin. The points above and below C show effects of adrenergic agents on oxygen consumption and heart rate respectively. The points above and below D indicate similarly the changes after both adrenergic agents and nitroglycerin. Line E indicates the average percentage change in oxygen consump-

Fig. 1. Actual record showing effects of intracoronary injection of l-Arterenol in A and B and mixture of 0.5 gamma of l-Arterenol and 0.84 mg. of nitroglycerin in C, D and E. P.P., perfusion pressure; A.P., aortic pressure; C.F., coronary flow; O, oximeter cuvette tracing. Upward deflection indicates rising coronary sinus oxygen content. Arrows indicate point of injection. Time in 1/5 and 1/50 second.

peripheral and cardiac effects of these drugs are in operation. Here again nitroglycerin does not modify the changes either in oxygen consumption or in the electrocardiogram which are induced by l-Arterenol.

Figure 2 is a composite of all the experiments and shows the changes (expressed in per cent of the control values) in heart rate and oxygen consumption. The effects of nitroglycerin alone on oxygen consumption are shown by the points at A. The points at B show the heart

tion. No average line has been drawn for changes in heart rate. This composite indicates (1) that the intracoronary injection of physiologically active amounts of nitroglycerin does not modify oxygen consumption or heart rate, (2) that nitroglycerin does not alter the adrenergically induced elevation in oxygen consumption, and (3) that the increase in myocardial oxygen consumption produced by adrenergic agents may occur without increases in heart rate.
Since our results were at variance with those of Raab it was thought that the use of atropine might have produced the differences. Therefore, atropine, 1 mg. per Kg., was given to support to the view that the peripheral coronary responses are not altered either by damage to the central vessels or even by their actual section. Since other nerves exist, these obser-

![Diagram](https://example.com/diagram.png)

**Fig. 2.** Composite graph of all experiments showing percentile changes from control values of oxygen consumption and heart rate. A, oxygen consumption, and B, heart rates, after nitroglycerin alone. Points above and below C show changes in oxygen consumption and heart rate respectively after adrenergic agents. Points above and below D show data after nitroglycerin and adrenergic agents. E shows average percentile change in oxygen consumption.

dogs. Even in these animals nitroglycerin did not modify the changes in pulse rate or in the T wave induced by adrenergic agents.

**Comment**

The use of the new coronary cannula in these and other experiments has been highly satisfactory. With this instrument, cannulation of the left common coronary has become a simple procedure. The usual patterns of coronary behavior in magnitude, time or direction of response have not been modified. With previous cannulas, the use of a tight ligature certainly damaged the arterial walls and probably blocked the intra-arterial nerves. The constancy of results by all methods lends sup-

vations do not necessarily prove the absence of coronary reflexes.

It is clear from the experiments on dogs that nitroglycerin even in large doses does not modify the changes in myocardial oxygen consumption, in systolic vigor, in heart rate, or in the electrocardiogram which are induced by adrenergic stimulation.

These results do not support the theses of Raab, namely that nitroglycerin metabolically reduces the anoxating properties of adrenergic agents. The evidence presented by Raab, however, is indirect since it is not based on actual measurements of changes in myocardial oxygen consumption, but rather on heart rate and electrocardiographic changes. It is noteworthy,
too, that our results in dogs even fail to support
his electrocardiographic and heart rate findings.
These differences raise the questions (1) as
to whether cats and dogs differ in their response
to nitroglycerin and the adrenergic agents, and
(2) as to whether the observed T-wave inver-
sions are due to anoxia. A comparison of our
records with those of Raab do reveal a rather
striking difference in that in our dogs the T
wave inverted very promptly while in his
records the T-wave inversion occurred much
later. However, the answer to the second ques-
tion is of far more importance. We seriously
doubt that the T-wave pattern produced by
adrenergic agents in our experiments is due to
myocardial anoxia. There are several reasons
for such a view. In our experiments it was
extremely difficult to produce such T-wave
changes even by prolonged clamping of the
common left coronary. They occurred only
after profound myocardial anoxia resulting in
decreases in blood pressure. Adrenergic stimu-
lation even in the presence of myocardial
anoxia always produced the usual deep T-wave
inversion. Therefore, we suggest that adrenergic
agents must in some way alter the direction of
repolarization which may bear no relationship
to their anoxating properties. In our opinion
conclusions as to the degree of myocardial
oxygenation which are based on simple T-wave
inversion in the presence of adrenergic stimu-
lation are open to criticism. Finally, it should
be stated that this work does not alter the views
that nitroglycerin may improve myocardial
oxygenation by coronary dilation and/or that
it may reduce the myocardial oxygen require-
ment by a reduction in peripheral resistance.

SUMMARY

The effects of nitroglycerin upon heart rate,
myocardial oxygen consumption and electro-
cardiograms were studied, both before and
after adrenergic stimulation. The results in-
dicate that in dogs, nitroglycerin, even in large
doses, produces no metabolic effect upon the
myocardium which can be considered as anti-
adrenergic. The suggestion is made that the T-
wave changes seen after adrenergic stimulation
in dogs may not be due to anoxia.

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