Anti-Adrenergic Effects of Nitroglycerin on the Heart

By W. Raab, M.D., and E. Lepeschkin, M.D.

The therapeutic effect of nitroglycerin is generally attributed to its coronary dilator effect alone. In contrast, it could be shown that nitroglycerin also counteracts the chronotropic as well as the electrocardiographic T-wave depressing effects of epinephrine, arterenol and cardiac sympathin upon the heart. Accordingly, its therapeutic action in angina pectoris is suspected as being largely due to a chemical protection of the heart muscle against the chemically anoxia-producing effects of sympathomimetic amines.

There is a widespread tendency among cardiologists to interpret the mechanism of functional cardiac changes primarily or exclusively in terms of alterations of the coronary blood flow or of cardiac muscular dynamics, while little or no attention is paid to the fundamental role of myocardial cell metabolism and its neurohormonal regulation. This tendency applies also to the evaluation of the effects of nitroglycerin, the coronary-dilator action of which is generally assumed to explain all of its cardiac manifestations and especially its therapeutic efficiency in angina pectoris.

However, some investigations, dealing with the chemically anoxia-producing effects of sympathomimetic neurohormones and their derivatives, and with the probable pathogenic role of epinephrine and sympathin in the origin of the anginal syndrome, have made the purely mechanistic conception of the action of nitroglycerin on the heart questionable. They have put emphasis on the possibility that nitroglycerin might interfere with the oxygen-consuming, anoxia-producing effects of epinephrine-sympathin on the contractile substance of the heart directly, in a way similar to the direct counteraction exerted by nitroglycerin against the vasopressor effect of epinephrine on the contractile substance of the blood vessels. A specific indication of such an antiadrenergic action of nitroglycerin on the heart was seen in the fact that the cardiovascular effects of epinephrine, of stimulation of the stellate ganglia, and of acetylcholine in the atropinized cat were markedly diminished in the presence of nitroglycerin.

The following experiments were carried out in order to further elucidate the interference of nitroglycerin with adrenergic actions upon the heart.

Methods

Atropinized cats under Nembutal anesthesia, with the adrenal glands tied, and with artificial respiration, were used throughout. Rapid intravenous injections were given in an exposed femoral vein; slow infusions were made with a motor-driven syringe, operating at a constant velocity and connected with a femoral vein. The stellate ganglia were stimulated by means of attached shielded-wire electrodes and a “Variac” transformer at a voltage of 10. The blood pressure was recorded from a common carotid artery. Electrocardiograms were synchronized with corresponding points of the blood pressure curve through a time marker on the kymograph which was connected with the switch of the electrocardiograph. In most instances chest leads CR, and CR, were used, as they were found to be least influenced by the position of the heart. In a few experiments extremity leads and leads from the pericardial surface were registered. The changes of the amplitude of the T waves above and below the zero line were plotted on graph paper together with the blood pressure and heart rate curves. Because of the frequent absence of a distinct T-P segment, caused by a fusion of the T and P wave because of tachycardia, the P-R junction was considered the most reliable representation of the zero line.

Epinephrine and dl-arterenol* (nor-epinephrine, dl-arterenol)

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supposedly identical with sympathin<sup>8</sup>-<sup>10</sup>) and sympathin, extracted from cattle hearts, were injected rapidly (two seconds) in doses of 5 to 40 \( \gamma \) in 4 to 6 cc. of Ringer solution or infused slowly at a speed of 1.0 cc. per minute (each cc. contained 50 \( \gamma \)).

Cardiac sympathin was obtained through extraction from fresh cattle heart by a slight modification<sup>11</sup> of the method of von Euler<sup>3</sup>. The dosage was established through colorimetric assay of the fresh extracts by the method of Shaw<sup>2</sup> as modified by one of us.<sup>12</sup> It was expressed in "\( \gamma \) equivalents," each of which corresponded to the colorimetric and approximately to the vasopressor effect of 1 \( \gamma \) of epinephrine.<sup>11</sup> Immediately before injection the acid extracts were brought to a pH of 7 with sodium bicarbonate.

Nitroglycerin was injected or infused intravenously before or together with the other substances and procedures in doses of 2.0 to 10.0 milligrams.

**Results**

*Epinephrine, Arterenol (Synthetic Sympathomimetic), and Nitroglycerin.* Injections of epinephrine and of arterenol were followed by elevations of the blood pressure (70 to 125 mm. Hg) which were of about the same magnitude with both substances; the injections were also followed by cardiac acceleration (10 to 92 beats per minute) which was practically the same for both substances, and by electrocardiographic manifestations almost identical for both drugs. The electrocardiographic findings consisted essentially of a transient flattening or inversion of the T wave between the 15th and 50th to 150th second and usually a subsequent elevation of the T wave, lasting until about the 200th second (fig. 1). (In most instances there was an early elevation of the T wave, beginning two to six seconds after injection and lasting for only a few seconds. This phenomenon, which was also present on injection of corresponding amounts of plain Ringer solution, is apparently due to cooling of the subendocardial ventricular muscle layers and is not specific for the sympathomimetic amines used.)

Injection of nitroglycerin alone for control purposes was followed by a transient fall of the blood pressure (30 to 60 mm.), usually a slight cardiac acceleration but, in some instances, a very slight retardation, and a minimal to moderate elevation of the T wave, persisting from a few seconds to about two hundred seconds.

When epinephrine or arterenol was injected or infused simultaneously with nitroglycerin, the blood pressure elevation was weakened or transformed into a fall, the cardiac acceleration was diminished or abolished, epinephrine-induced extrasystoles did not recur, and the adrenergic depression of the T wave was weakened (decreased or shortened or both) or entirely abolished (figs. 1 and 2), even if the elevations of the T wave, due to nitroglycerin itself, were taken into consideration (table 1). The succeeding elevation of the T wave, which is probably caused by a transient hyperpotassemia<sup>13</sup>, was not significantly altered. Changing the sequence of nitroglycerin control injections and combined nitroglycerin-epinephrine or arterenol injections did not affect the results.

*Faradic Stimulation of Stellate Ganglia and Nitroglycerin.* Stimulation of the stellate ganglia (both sides simultaneously or the right side alone for ten to thirty seconds) was followed by cardiac acceleration (20 to 80 beats per minute) and by flattening or inversion of the T wave which persisted for one to four minutes (fig. 3). If the stimulation was repeated thirty to forty seconds after intravenous injection of nitroglycerin, at a time when the transient T-wave changes produced by nitroglycerin itself had disappeared, the electrocardiographic effect of the stimulation was diminished or abolished (table 1). No significant diminution of the average cardiac acceleration was observed, in contrast to earlier experiments<sup>14</sup> in which nitroglycerin had been infused simultaneously with the stimulation.

*Injection of Cardiac Sympathin and Nitroglycerin.* Except for a transient initial fall and a somewhat retarded maximal elevation of the blood pressure, the vasopressor, cardioacceleratory, and electrocardiographic effects of sympathin, extracted from the heart muscle of cattle, were in several experiments practically identical with those of colorimetrically equivalent doses (5 to 30 micrograms) of epinephrine or arterenol (fig. 4). Combined injection with nitroglycerin resulted in a weakening of the vasopressor, cardioaccelerator, and electro-
Fig. 1.—The top curve represents the mean blood pressure, the middle curve the amplitude variations of the T wave above and below the zero line, and the lower curve the variations of the heart rate. (Time in seconds.)
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**Fig. 2.**—See legend, figure 1.
TABLE 1.—Average Diminution of Adrenergic Effects on the Heart Through Simultaneous or Preceding Intravenous Administration of Nitroglycerin*

<table>
<thead>
<tr>
<th>Type of Experiments</th>
<th>Cardiac Acceleration</th>
<th>Maximal Depression of T wave (Leads CRi, CRn, II)</th>
<th>Number of Experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine injected</td>
<td>-37%</td>
<td>-33% to -61%</td>
<td>6</td>
</tr>
<tr>
<td>Arterenol injected</td>
<td>-29%</td>
<td>-92% to -100%</td>
<td>4</td>
</tr>
<tr>
<td>Stimulation of stellate ganglia</td>
<td>-6%</td>
<td>-61% to -80%</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac sympathin injected</td>
<td>-14%</td>
<td>-25% to -100%</td>
<td>3</td>
</tr>
</tbody>
</table>

* Expressed in per cent of the original adrenergic effects (with the action of nitroglycerin alone incorporated into the calculation).

Nitroglycerin had been injected before stimulation in these experiments. In earlier experiments (Raab and Humphreys) in which nitroglycerin was infused during stimulation, the cardiac acceleration was markedly diminished.

Cardiographic effects of sympathin, taking the effects of nitroglycerin as such into account (table 1).

COMMENT

Adrenergic cardiac acceleration and T-wave depression in the atropinized cat, whether produced by injection or infusion of epinephrine or of arterenol or of sympathin, extracted from cattle heart, or by stimulation of the cardiac sympathetic nerve, were diminished or entirely abolished by simultaneous or immediately preceding intravenous injection of nitroglycerin.

A similar effect (normalization of epinephrine-induced electrocardiographic changes through intramuscularly injected nitroglycerin) had been shown in one experiment by Douglas, Gelfand, and Shookhoff in 1937, and Melville has observed a protective action of nitroglycerin against epinephrine-chloroform-induced ventricular premature contractions and fibrillation. Russek and associates were able to abolish the depression of S-T and inversion of T in exercise tests on patients with coronary disease by administering 0.75 mg. of nitroglycerin sublingually. All of these authors interpret the phenomena mentioned as being due
exclusively to the coronary dilator effect of nitroglycerin. They give no consideration to the chemically oxygen-consuming and thus anoxia-producing action of epinephrine and its
derivatives upon the heart, as demonstrated by various investigators,\textsuperscript{1, 15, 16, 21, 24, 26} nor to the possibility that nitroglycerin might interfere with this chemical process in the heart muscle cells, apart from its relaxing effect upon the coronary vascular muscle cells.\textsuperscript{3}

It seems unlikely that the T-wave depressions and inversions, elicited by injected or by nitroglycerin is of no significance in accounting for the nitroglycerin-induced diminution of the T wave under depression caused by the sympathomimetic amines, since the T-wave changes have been shown to be entirely independent of the pressor effects of these amines.\textsuperscript{23}

Unless we deliberately disregard the functional significance of myocardial metabolism

neurally discharged\textsuperscript{17} sympathomimetic amines, should be due to a diminution of the coronary flow, since most investigators agree that the coronary flow is increased rather than decreased by these agents\textsuperscript{15, 19, 20} and by stimulation of the cardiac sympathetic fibers.\textsuperscript{20, 21, 24, 26} Likewise, it is improbable that the diminution or abolition of the adrenergic T-wave changes by nitroglycerin should be caused by further dilatation of the coronary arteries, nor can the counteraction of nitroglycerin against the sympathomimetic neurohormonal acceleration of the heart be ascribed simply to coronary dilatation.

The diminution of the pressor effects of epinephrine, arterenol, and cardiac sympathin and its alterations through the adreno-sympathetic neurohormones, we feel compelled to consider the probability that the striking counteraction of nitroglycerin against adrenergic cardiac manifestations is largely, if not entirely, due to a primarily chemical and not merely to a mechanical (coronary dilator) mechanism. Further studies will have to be undertaken before this question can ultimately be settled.

As far as the pathogenesis of angina pectoris is concerned, the therapeutic effect of nitroglycerin cannot be accepted as proof of the existence of a "coronary spasm"; rather does it tend to support the concept of an epineph-
rime-sympathin-induced chemical anoxia of the myocardium as the basis of the anginal syndrome.2

SUMMARY

Nitroglycerin strikingly counteracts the typical cardioaccelerator and T-wave depressing effects of epinephrine, arterenol, and neurally discharged or injected cardiac sympathin.

This phenomenon is interpreted as being due to an interference of nitroglycerin with the metabolic, anoxia-producing effects of the sympathomimetic amines on the heart muscle rather than to the familiar coronary dilator action of nitroglycerin, since coronary dilatation is elicited from the beginning by the sympathomimetic amines themselves.

Implications of this concept in relation to the biochemical adrenosympathogenic mechanism of angina pectoris are briefly discussed.

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