

THE MECHANISM OF NITROGLYCERIN ACTION ON THE CARDIAC VESSELS

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Nitroglycerin is one of the oldest agents used in the treatment of angina pectoris. In the opinion of most clinicians, clinical practice has not yet found any pharmacological substance which acts as quickly and reliably at the time of an angina pectoris attack as nitroglycerin. The efficiency of nitroglycerin is believed to be due to its vasodilative effect on various vascular regions of the organism, particularly the vessels of the heart.

However, examination of the literature on this question shows this seemingly indisputable theory to be based on extremely contradictory data. As early as the beginning of the twentieth century, it was established experimentally that nitroglycerin has a relaxant effect on the smooth musculature of the cardiac vessels [12,14]. This fact was subsequently confirmed at various dates by other researchers experimenting with isolated heart preparations [5, 6, 13].

However, nitroglycerin's vasodilative effect on the cardiac vessels has been shown by experiments to be much less pronounced in the case of an intact organism. A considerable increase in the coronary blood flow (30-100%) under the influence of nitroglycerin has only been noted by authors who used the thermoelectric method of recording the blood flow in their experiments [10, 11]. These observations, however, are not sufficiently conclusive, because it is known that this method cannot be expected to produce quantitatively exact results [8]. Other researchers, who used more exact methods of measuring the coronary output (diaphragm or bubble gauges), found that nitroglycerin and sodium nitrite caused only a slight (7-9%), brief increase in the volumetric rate of the coronary blood flow when injected intravenously in relatively large doses. The effect of these substances was considerably weaker than that of papaverine or Euphyllin [7, 9].

In our laboratory, I. E. Kisin [2] recently investigated nitroglycerin's effect on the volumetric rate of the outflow of blood from a cat's coronary sinus and on the tonus of the coronary vessels under conditions of the autoperfusion of the latter. He established that nitroglycerin, injected intravenously (0.1-0.5 mg/kg) or administered per os (1-2 mg/kg), does not materially

affect the outflow of blood from the coronary vessels or the resistance of the coronary vessels to the blood flow.

It is evident from the literary data cited that the effect of nitroglycerin on the coronary vessels of an intact organism is slight. This leads one to believe that nitroglycerin's efficiency in angina pectoris cannot be explained solely by its vasodilative effect on the coronary vessels.

The fact that nitroglycerin, unlike most pharmacological substances used in the treatment and prophylaxis of coronary insufficiency, is an agent which is effective only to clear up attacks of angina pectoris. Moreover, reflex effects which act on the cardiac vessels and cause them to constrict are known to play an essential part in the development of attacks of angina pectoris.

On the basis of these considerations, we conducted this investigation in order to study the effect of nitroglycerin on reflex changes in the tonus of the coronary vessels.

EXPERIMENTAL METHODS

The experiments were performed on cats anesthetized with urethan (500 mg/kg) and chloralose (40 mg/kg). Because vasomotor reflexes do not affect solely the cardiac vessels, but also cause changes in the arterial pressure, it is difficult to demonstrate these reflexes by measuring the rate of the blood flow in the vessels of the heart. Variations in the blood pressure cause mechanical changes in the blood flow. Artificial stabilization of the blood flow in the coronary vessels, done by perfusing the vessels with the animal's own blood with the aid of a special pump, eliminates the hemodynamic effect of blood pressure changes. Under these conditions, the pressure in the coronary vessels is determined only by the minute volume of the blood supplied by the pump and by the hydraulic resistance of the vessels. Dilatation of the vessels causes the perfusion pressure to fall; their constriction causes it to rise. This method, known as resistography, therefore makes it possible to study the reflex reactions of the coronary vessels in the presence of simultaneous changes in the systemic arterial pressure [3].

The construction of the pump used in the perfusion of the coronary vessels was analogous to that described by V. M. Khayutin, V. M. Danchakov, and V. L. Tsaturov [4]. After opening the thoracic cavity under conditions of artificial respiration, we dissected out the left common coronary artery, placing a special cannula (issuing from the left subclavian artery and connected with the outlet of the perfusion pump) in its mouth. The blood entered the pump from the carotid artery. The perfusion pressure was recorded between the left coronary artery and the outlet valve of the pump. We have already depicted the diagram for experiments with autoperfusion in an earlier work [1]. The blood pressure was recorded in the femoral artery.

Heparin (1000-1500 units per 1 kg) was used to prevent blood coagulation. Nitroglycerin was administered intravenously or per os.

In the experiments, we studied the reflexes on the coronary vessels and the blood pressure induced by stimulation of the carotid sinus receptors (by pressure on the carotid artery) and of the central sections of the femoral and median nerves. The nerves were stimulated with pulses of 2-10 volts from an electronic stimulator 30-50 cps in frequency and 1-2 msec in duration.

EXPERIMENTAL RESULTS

We note first of all that, as in the experiments of other authors, in spite of the considerable fall of blood pressure in our experiments with the administration of nitroglycerin (intravenously in doses of 0.1-0.5 mg/kg or perorally in doses of 1-2 mg/kg), there were no distinctly expressed changes in the tonus of the coronary vessels. In several experiments, moreover, there was even some constriction of the cardiac vessels (Fig. 1).

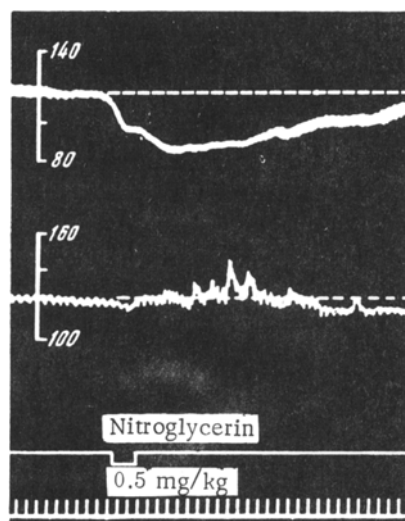


Fig. 1. Effect of nitroglycerin on the resistance of the coronary vessels. Curves (from top to bottom): blood pressure; perfusion pressure (resistogram); administration of substance; time (in 5-second marks). Original levels of blood and perfusion pressures shown by -----.

We also studied the effect of nitroglycerin on the tonus of the coronary vessels under conditions of experimental spasm of the latter, induced by the intravenous injection of Pituitrin (1.5-2 units per 1 kg). In these experiments, nitroglycerin somewhat lowered the resistance of the coronary vessels. Complete elimination of the spasm of the coronary vessels induced by Pituitrin was not observed, even with the administration of nitroglycerin in relatively large doses (0.5-0.7 mg/kg).

Stimulation of the carotid sinus mechanoreceptors and stimulation of the afferent fibers of the tibial and median nerves both produced reflex changes in the tonus of the coronary vessels. In a majority of experiments, pressure on the carotid artery resulted in a reflex constriction of the coronary vessels, although in a few cases, dilatation of the vessels could be observed in response to this stimulation. The same was true of the reflex changes in the tonus of the cardiac vessels produced by stimulating the afferent fibers of the tibial and median nerves.

In doses of 0.1-0.25 mg/kg, nitroglycerin sharply depressed (by 40-80 % of the original level) the reflexes on the coronary vessels in response to stimulation of all the experimental reflexogenic zones. Increasing the nitroglycerin dose to 0.3-0.5 mg/kg completely depressed the reflexes. The effect lasted 15-18 minutes. It is particularly noteworthy that, in most of the experiments conducted, nitroglycerin's effect on the reflex reactions showed a pronounced selectivity with respect to the coronary vessels. When the reflexes on the cardiac vessels were completely suppressed, the reflexes on the blood pressure only decreased an average of 30-50 % of the original level in value (see Fig. 2). In several experiments with the injection of nitroglycerin in doses of 0.1-0.25 mg/kg, the reflexes on the coronary vessels changed in character. Instead of reflex constriction of the vessels, we observed their dilatation (Fig. 3, b). Increasing the nitroglycerin dose to 0.3-0.5 mg/kg led in these cases to complete suppression of the regional reflexes (Fig. 3 d).

In the experiments with the peroral administration of nitroglycerin (1-2 mg/kg), as in those with its intravenous administration, depression of the reflexes on the coronary vessels was observed. The condition of the vessels themselves, however, was not noticeably changed.

Therefore, the investigations conducted allowed us to establish that nitroglycerin does not cause pronounced dilatation of the vessels of the heart, but does depress their reflex reactions. These data make it imperative to revise the earlier notions concerning nitroglycerin's effect on the cardiac vessels. Obviously, the earlier notion that its efficiency in angina pectoris is due solely to a direct vasodilative effect is invalidated. Our observations, which have demonstrated nitroglycerin's ability to cause selective depression of the reflexes on the coronary vessels, allow the hypothesis that these properties play a significant role in the mechanism of its effect on coronary circulation.

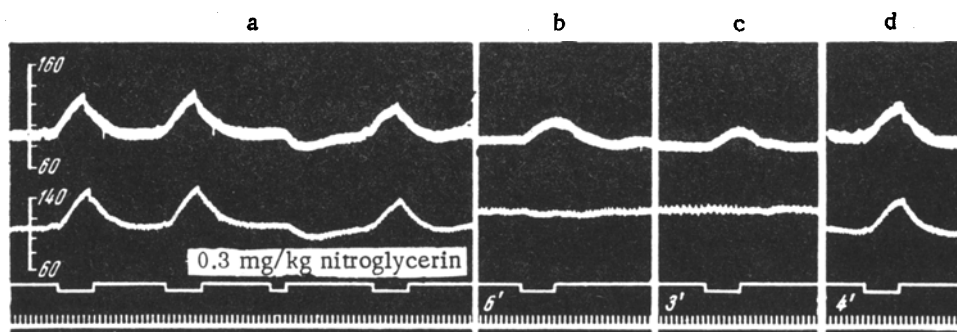


Fig. 2. Effect of nitroglycerin on the reflex changes in the resistance of the cardiac vessels induced by stimulation of the carotid sinus receptors. Symbols the same as in Fig. 1.

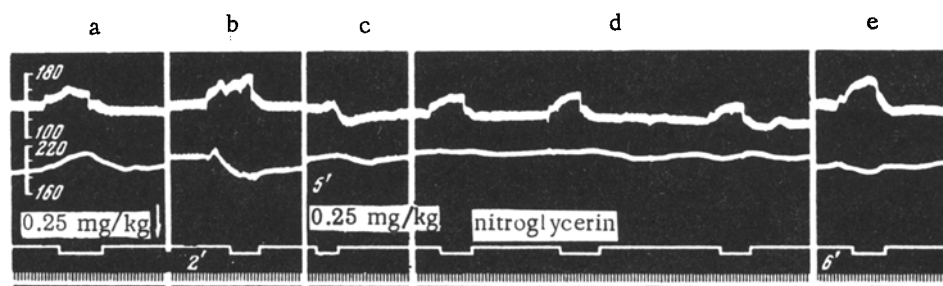


Fig. 3. Effect of nitroglycerin on the reflex changes in the resistance of the cardiac vessels induced by stimulation of the afferent fibers of the tibial nerve. Symbols the same as in Fig. 1.

SUMMARY

The authors studied the effect of nitroglycerine on the reflex resistance changes in the coronary vessels provoked by stimulation of carotid sinus receptors and afferent nerves. While failing to provoke pronounced dilatation of the cardiac vessels, nitroglycerin completely depresses their reflex reactions.

LITERATURE CITED

1. N. V. Kaverina, Byull. Éksp. Biol. i Med. 47, 67 (1959).*
2. I. E. Kisin, The Effect of Certain Pharmacological Substances Used to Treat Angina Pectoris on Coronary Circulation (Dissertation) [in Russian] (1958).
3. V. M. Khayutin, Fiziol. Zhur. 64, 646 (1958).
4. V. M. Khayutin, V. M. Danchakov, and V. L. Tsaturov, Byull. Éksp. Biol. i Med. No. 2, 117 (1958).*
5. Yu. S. Chechulin, Arkh. Patol. No. 4, 40 (1958).
6. R. Bodo, J. Physiol. 64, 365 (1927).
7. N. H. Boyer and H. D. Green, Am. Heart. J. 21, 199 (1941).
8. J. Dorner, Arch. Exp. Path. and Pharm. 221, 312 (1954).
9. J. E. Eckenhoff and J. H. Hafkenschiel, J. Pharm. and Exp. Therap. 91, 362 (1947).
10. H. E. Essex, J. F. Herrick, E. J. Baldes, and F. C. Mann, Am. Journ. Physiol. 117, 271 (1936).
11. H. E. Essex, R. Wegria, J. F. Herrick, and F. C. Mann, Am. Heart J. 19, 554 (1940).
12. C. A. Francois-Franck, Compt. rend. Soc. Biol. 55, 1448 (1903).
13. L. N. Katz, E. Linder, W. Weinstein, D. J. Abramson, and K. Jochim, Arch. int. pharmacodyn. et de therap. 59, 339 (1938).
14. K. Schloss, Deutsches Arch. f. klin. Med. 111, 310 (1913).

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