# THE MECHANISM OF BRADYCARDIA CAUSED BY CARDIAC GLUCOSIDES

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Bradycardia is one of the characteristic signs of the action of the cardiac glucosides. The mechanism of its production, despite the abundant work on the subject, remains, however, unexplained and debatable. This is revealed by the contradictory results described in the literature. Several authors explain the bradycardia by the influence of the cardiac glucosides on the vagus nerve centers [8, 9, 18]. Others point out the sensitization of the myocardium to the influence of the vagus and to the action of acetylcholine [4, 16] or the sensitization of the intramural ganglia to acetylcholine [15]. The majority of research workers regard bradycardia as a cardio-cardial reflex [5, 6, 13 and others], although these authors present no direct proof of the reflex mechanism of this action*.

With the possibility of using a new method of transplantation of the heart, suggested by V. P. Demikhov, we carried out the present research for the purpose of studying the mechanism of bradycardia caused by the cardiac glucosides.

## EXPERIMENTAL METHOD AND RESULTS

Experiments were conducted on 12 dogs in which the heart was transplanted by V. P. Demikhov's method. As a result of the transplantation, the animal, after operation, had two hearts: one — its own (with its innervation intact), the other — the grafted heart, "denervated" in the sense of exclusion of central influences. In dogs such as these we studied the action of strophanthin-g and of a standard extract of digitalis in therapeutic and toxic doses. The activity of the heart was recorded by means of a Hürtle's manometer from the brachial arteries of the animal, and in some experiments electrocardiographically. The experiments were performed on dogs under morphine-sodium amytal anesthesia on the day of operation, and on controls on the second day. The results of the investigation enabled the direct influence of the cardiac glucosides on the intramural ganglia of the heart, the M-cholinoceptors** and the myocardium to be elucidated.

It was shown by the experiments on dogs with two hearts that the dog's own heart and the denervated heart reacted differently to injection of the cardiac glucosides. Strophanthin-g, for instance, when injected intravenously in a dose of 50 $\mu$g/kg, caused bradycardia of the dog's own heart. In the course of time the bradycardia increased, and the rate then gradually returned to the original value. Under these circumstances the rate of the denervated heart was quite unchanged.

* A detailed survey of the literature was given in the article by V. V. Zakusov in the journal "Farmakologiya i Toksikologiya", No. 1 (1957).

** Receptors of the parasympathetic system.

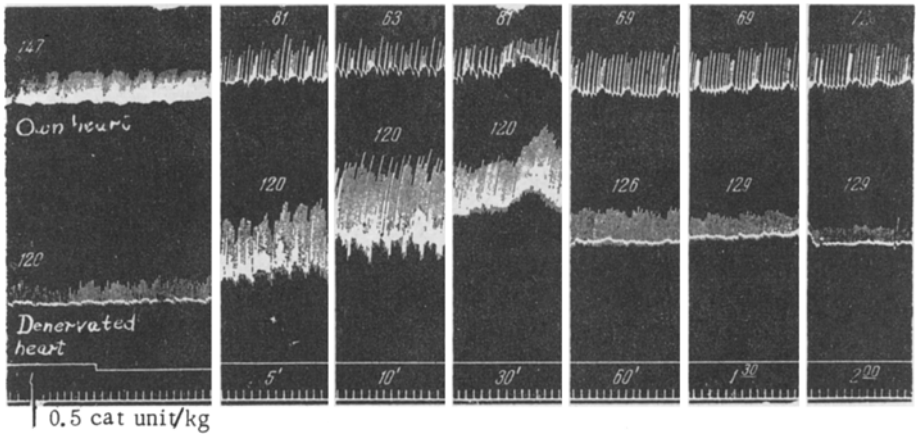


Fig. 1. The effect of a standard extract of digitalis in a dose of 0.5 cat unit/ kg on the rhythm of cardiac contractions. Significance of the curves (from above down): record of the contractions of the dog's own heart· of the denervated heart; injection marker; time marker (2 seconds).

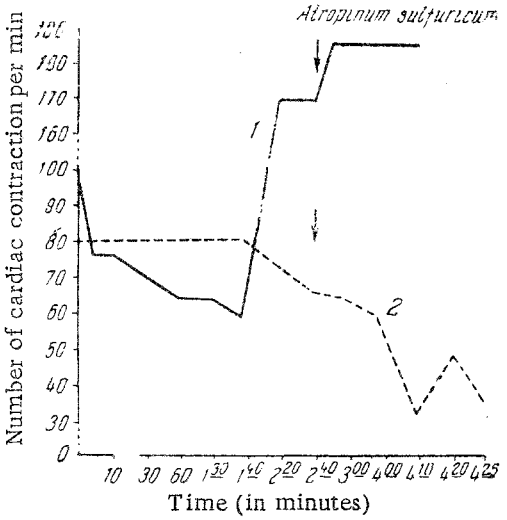


Fig. 2. Change in the rhythm of the heart in response to the action of strophanthin-g (0.15 mg/ kg). 1) Dog's heart; 2) denervated heart.

A similar picture was observed in response to injection of a standard extract of digitalis in a dose of 0.3-0.5 cat units/ kg (Fig. 1).

It may be seen from the kymogram (see Fig. 1) that , under the influence of this preparation, a marked bradycardia of the dog's own heart developed sharply, in individual experiments falling to 40% of the original rate, whereas the rhythm of the denervated heart remained unchanged. It must be mentioned that the rate of the denervated heart subsequently became slightly quickened and extrasystoles appeared, evidently on account of the muscular action. The amplitude of both the dog's own heart and the denervated heart rose considerably during the action of the cardiac glucosides.

In toxic and lethal doses, strophanthin-g caused in the dog's own heart the typical picture of the action of the cardiac glucosides (Fig.2).

For instance, after injection of strophanthin in a dose of 0.15 mg/ kg , in the first period of action of the drug a considerable bradycardia of the dog's own heart developed , to be replaced later by an increase in the rate and then by cardiac arrest. The rhythm of the denervated heart was, as a rule, unchanged in response to the injection of lethal doses of the glucoside during the first hour, and a well-marked slowing of the rhythm then appeared. In some experiments the bradycardia was temporary in character and rapidly changed into tachycardia and arrhythmia.

In order to ascertain the character of the bradycardia developing in response to lethal doses of cardiac glucosides, the dog was given an intravenous injection of atropine sulfate in a dose of 0.5 mg/ kg, and of hexamethonium in a dose of 5 mg/ kg. In these cases atropine caused a quickening of the rate of the dog's own heart and had no effect on that of the denervated heart. Hexamethonium, like atropine, did not abolish the bradycardia of the denervated heart. The standard extract of digitalis in a dose of 1 cat unit/ kg caused similar changes in the rhythm.

Histological examinations of the heart of dogs dying from lethal doses of strophanthin-g, carried out by M. F. Bystrova, showed that after injection of this drug, well-marked vascular changes were observed in the

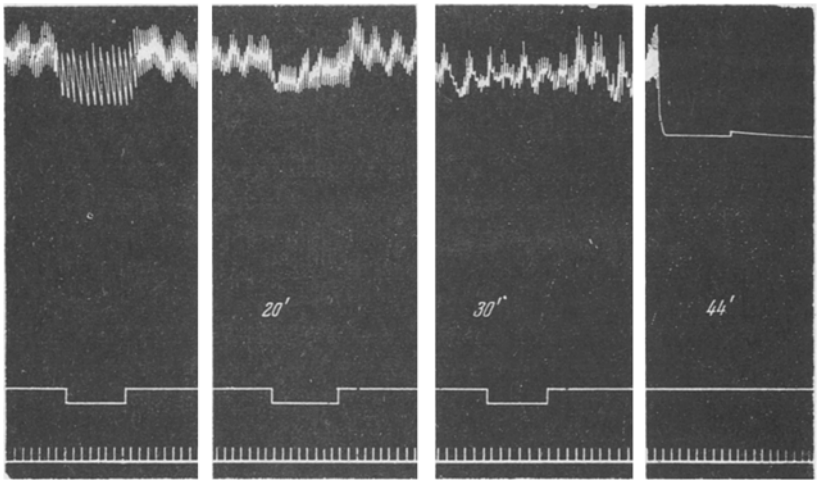


Fig. 3. The influence of strophanthin-g on the transmision of excitation from the vagus nerve to the heart muscle of the cat, during continuous intravenuous infusion of the drug in a concentration of 1: 200,000. Significance of the curves (from above down): recording of the cardiac contractions of the cat; stimulation marker; time marker (1 second). The figures above the stimulation marker correspond to the time from the start of infusion of the strophanthin solution.

myocardium — venous congestion, perivascular edema and hemorrhages, swelling and desquamation of the endothelium, plasmorrhoea and, in individual cases even necrosis of the walls of the arteries, moderate cellular proliferation of the stroma around the vessels, loosening of the endocardium, focal proliferation of the endothelium; scattered subendocardial hemorrhages, in individual experiments the muscle fibers of the myocardium were stained unevenly and granular dystrophy of the protoplasm was observed.

In addition to the investigations on dogs with two hearts, we carried out experiments on cats, in which the transmission of excitation from the vagus nerves to the heart muscle was recorded during continuous infusion of strophanthin in a concentration of 1: 200,000 until arrest of the heart. During the performance of this series of experiments the peripheral end of the vagus nerve was stimulated by means of an electronic stimulator with a frequency of 30 cps, the duration of a single stimulus being 0.5 millisec. The experiments showed that under the influence of strophanthin, the transmission of impulses was impeded; with an increase in the dose the block became more marked, and at doses of 0.5-0.7 cat unit/kg the transmission of impulses ceased altogether (Fig. 3).

To explain the action of the cardiac glucosides on the vagus nerve center, experiments were conducted on dogs with crossed circulation (5 experiments). Both carotid arteries and jugular veins of the donor dog were sutured to the two carotid arteries and jugular veins of the recipient dog. The spinal cord of the recipient dog was as a rule divided or both vertebral arteries were ligated. Blood from the donor dog entered the head of the recipient dog, which was connected to the trunk only by means of the two vagus nerves; the humoral effects of the cardiac glucosides were excluded from the heart of the recipient dog. The activity of the hearts was recorded manometrically, and strophanthin was injected into a vein of the donor dog. Injection of strophanthin in therapeutic and even lethal doses, causing bradycardia and cardiac arrest in the donor dog, had no effect on the rhythm of the heart of the recipient dog, which showed that the cardiac glucosides had no central action.

From an analysis of the experimental findings it may be concluded that the reaction of the dog's own heart and of the denervated heart to injection of cardiac glucosides differed. A standard extract of digitalis and strophanthin-g in therapeutic doses caused a well-marked bradycardia of the dog's own heart, but did not affect the rhythm of the denervated heart. The absence of bradycardia of the transplanted heart gives grounds for the belief that bradycardia during administration of cardiac glucosides is not the result of their stimulating action on the intramural ganglia of the heart and the M-cholinoceptors. The absence of a stimulating action of the cardiac glucosides on the M-cholinoceptors was confirmed by experiments on cats in which the

transmission of excitation from the vagus nerves to the heart muscle was recorded; it was shown in these experiments that strophanthin blocked the transmission of impulses.

Our experimental results are in agreement with the findings of V. V. Zakusov that the transmission of impulses from the vagus nerve to the heart muscle is impeded by the action of the cardiac glucosides. This view is confirmed by the work of a number of investigators [10, 12, 17, 19 and others], who found no enhanced effect from stimulation of the vagus nerves after injection of digitalis and strophanthin.

The experiments thus showed that the cardiac glucosides possess no stimulating action on the intramural ganglia of the heart nor on the M-cholinoceptors. We are left, therefore, with the suggestion that the bradycardia in response to the action of the cardiac glucosides may be due to their influence on the vagus center, or it may be produced reflexly, as a cardiocardial reflex. Experiments on dogs with crossed circulations reveal that the cardiac glucosides have no central stimulating action. Similar conclusions were reached by J. F. Heymans and C. Heymans[ 11] on the basis of their experiments on dogs. The experiments of Green and Peeler [9] on excitation of the vagus center cannot be regarded as affording relevant evidence, for they were carried out only on tortoises, and the authors used large doses of digitalis. The work of D. A. Kharkevich and L. A. Kitaev showed that strophanthin-k stimulates the vagus nerve center in cats only when large, unphysiological doses are used.

It follows from these experiments that the cardiac glucosides have no stimulating action on the ganglia of the heart, the M-cholinoceptors and the vagus nerve center. This gives ground for the belief that, in the development of bradycardia caused by cardiac glucosides, reflex mechanisms of action are of decisive importance. The bradycardia develops as a cardiocardial reflex, like that established by Bezold in relation to veratrin [7]. When lethal doses of cardiac glucosides are given, the bradycardia of the denervated heart is evidently due to the action of the drugs on the myocardium, since it is not abolished by atropine or hexamethonium. This is also confirmed by histological investigations, which reveal considerable myocardial damage at these doses. In this connection the work of Loubatières and Sassine [14] is of interest, showing that in the isolated auricle of the rabbit's atrium, after exclusion of synaptic structures with hexamethonium, strophanthin causes a slowing of the rhythm; this is proof of its direct action on the cardiac muscle of the auricle.

## SUMMARY

V. P. Demikhov's new method of heart transplantation, used for the first time in pharmacological analysis, was employed to study the mechanism of the action of cardiac glucosides. Experiments were conducted on dogs with two hearts: one of them — their own, and another — transplanted, "denervated" i.e., with exclusion of influences from centers). Investigations demonstrated that cardiac glucosides have no exciting effect on the heart ganglia and M-cholinoceptors. This is confirmed by experiments on cats, which showed that under the effect of strophanthin-g the impulse transmission from the vagus nerve to the heart muscle is inhibited. Experiments with cross circulation on dogs demonstrated the absence of any exciting effect of the cardiac glucosides on the vagus center. Hence, under the action of cardiac glucosides, bradycardia assumes a reflex character and develops as a cardiocardial reflex.

## LITERATURE CITED

[1] V. P. Demikhov, Byull. Éksptl. Biol. i Med. No. 4, 246-247 (1950).

[2] V. V. Zakusov, E. A. Spalva, O. V. Ul'yanova, Farmakol. i Toksikol. No. 1, 13-17 (1957).*

[3] D. A. Kharkevich, L. A. Kitaev, Procceedings of the Seventh All-Union Conference of Pharmacologists on Problems of the Pharmacological Regulation of Processes, pp. 158-159. Khar'kov, 1958 [In Russian].

[4] N. O. Abdon, N. A. Nielsen, Skand. Arch. Physiol. Bd. 78, S. 1-7 (1938).

[5] W. Busse, L. Landle, Arch. exper. Path. u. Pharmakol. Bd. 218, S. 159-176 (1953).

[6] W. Busse, S. Loennechen, J. Arch. exper. Path. u. Pharmakol. Bd. 220, S. 232-244 (1953).

[7] A. Bezold, L. Hirt, Untersuchungen der physiol. Lab. in Wurzburg, No. 1, S. 181 (1867).

[8] R. Cushny, J. exp. Therap. N. 7, p. 233 (1915).

[9] C. W. Greene, J. O. Peeler, J. Pharmacol a. exper. Therap. v. 7, p. 591-599 (1915-1916).

* Original Russian pagination. See C.B. Translation.

[10] F. Hohensee, L. Lendle , Arch. exper. Path. u. Pharmakol. Bd. 207, S. 388-407 (1949).

[11] J. F. Heymans, C. J. Heymans, Pharmacol . a. exper. Therap. v. 29, p. 203-221 (1926).

[12] L. Lendle, H. Mercker, H. Rohr, Arch. exper. Path. u. Pharm. Bd. 219, S. 352-361 (1953).

[13] L. Lendle, H. Wienke ,Arch. exper. path. u. Pharm. Bd. 213, S. 373-386 (1951).

[14] A. Loubatieres, A. Sassine, J. physiol. (Paris), v. 46, p. 444-447 (1954).

[15] W. L. M. Perry, H. Reinert, Arch. exper. Path. u. Pharmakol . Bd. 222, S. 201-203 (1954).

[16] W. Straub , A. Heffter., Handbuch der experimentellen Pharmakologie, Berlin-Göttingen, Bd. 2, 2, S. 1422 (1924).

[17] L. Szekeres , Kiserl. orvostud v. 7, N. 3, p. 305 (1955).

[18] L. Traube, cited by F. Hohensee and L. Lendle.

[19] E. Westermann, Arch. exper. Path. u. Pharmakol. Bd. 222, S. 398-407 (1954).