

THE MECHANISM OF THE ACTION OF DIGITALIS UPON THE HEARTS OF DOGS OF VARYING AGES

V. D. Rozanova

From the Laboratory of the Physiology and Pathology of Growth (Director: Prof. I. A. Arshavsky),
Institute of General and Experimental Pathology (Director: Academician A. D. Speransky) Acad.
Med. Sci. USSR, Moscow.

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The question of the mode of vagotropic action by the cardiac glycosides is not sufficiently clear. Some authors consider that it must be always upon the vagus center [22, 29, 33], others [20, 26, 31, 32, 33] believe that the glycosides act upon the vagus endings in the heart. The reflex mechanisms of glycoside activity have been investigated by a few authors [9, 11, 34].

Of special interest for solving the problem of the mechanism of the vagotropic actions of the glycosides is the study of the reflex influences upon animals of varying ages, especially as the nervous regulation of the heart is followed in the various stages of its ontogeny.

Investigations in the laboratory for the physiology and pathology of growth have established that in puppies until the age of 2-2½ months there is a sympathetic predominance in the regulation of cardiac activity [3, 6, 7, 8, 12, 13, 17]. Also confirmed were the findings [23] that puppies until the age of 12 days have a complete absence of tone in the center for vagal control and that vagus regulation develops only in later growth periods.

In this work we set ourselves the problem of investigating cardiac response to perfusions of digitalis through an isolated sino-carotid zone in puppies of various ages and in adult dogs.

EXPERIMENTAL METHODS

The sino-carotid zone was isolated by the method of Moiseev — Heymans — Anichkov. Bottles with Ringer-Locke solutions and "digital" extract solutions suitably mixed together were elevated to give a pressure corresponding to that of the experimental animal, e.g., from 60 cm in young puppies up to 120 cm in adult dogs. The extract from the leaves of "digitalis" 10:100 we prepared as per the directions of Paragraph 311 of the Pharmacopeia USSR (ed. VII), and so diluted it with the Ringer-Locke solution that 1 liter of the perfusing fluid had in it 50 cat units (CU). The solution is saturated with oxygen, heated to 38° by passing it over a spiral lying in a water bath, and then led to the sino-carotid zone by a cannula inserted into the peripheral stump of the carotid artery. A second cannula was inserted into either the lingual or occipital artery. It served for drainage of the perfusing fluid. Other vessel branches were tied and severed. The carotid sinus nerve was preserved intact. The experiments were conducted under ether narcosis in puppies and under morphine-ether narcosis in adult dogs. Respirations were recorded with the help of a pneumograph and Marey's capsule, and the blood pressure — with a mercury manometer. In the beginning the carotid zone was perfused with Ringer-Locke solution alone. After stabilization of respirations and blood pressure digitalis solution was added to the perfusion for 3-4 minutes. The perfusing fluids were frequently changed.

EXPERIMENTAL RESULTS

Perfusion of the isolated sino-carotid zone with "digitalis" solution in 13 adult dogs in all cases showed not only a negative chronotropism but also revealed a positive inotropic effect. The cardiac rhythm slowed by 40-50 beats per minute, at the same time that damage began to be manifested by the appearance of irregularities in the rhythm. The positive inotropic effect could be seen in the greater amplitude of the systolic contractions of the blood pressure. The maximum blood pressure in some experiments rose somewhat; in others it decreased a trifle. When perfused with "digitalis" and then changed back to Ringer-Locke solution the effect rose and waned not instantly but over 1-1½ minutes.

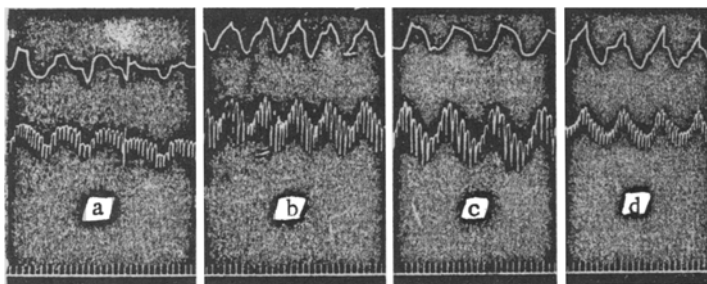


Fig. 1. Changes in breathing and blood pressure under the influence of "digitalis" in an adult dog.

- A) Original cardiac rhythm with perfusion with Ringer-Locke solution.
- B) 2d perfusion with "digitalis" (cat units per liter),
- C) 3d perfusion with "digitalis".
- D) perfusion with Ringer-Locke solution.

Significance of curves (from above down): breathing, blood pressure, time interval (1 sec.), it serving also as base line.

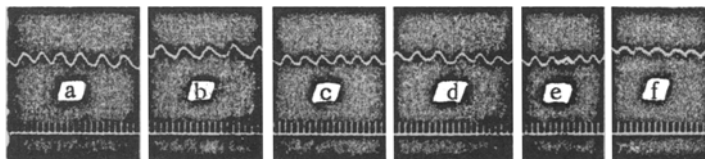


Fig. 2. Changes in blood pressures under influence of "Digitalis" in puppies (14 days).

Significance of curves from above down: blood pressures, time interval, this serving also as base line.

- A, C, E) perfusion with Ringer-Locke solution.
- B, D, E) perfusion with "digitalis" solution. (50 cats units per liter).

Repeated perfusion with "digitalis" led to more pronounced slowing of the heart, thus a summation effect was observed.

Figure 1 demonstrates the chronotropic and inotropic effect of the second and third perfusions of "digitalis" (strips B, C) upon the isolated sino-carotid zone in an adult dog. The first perfusion caused almost no changes as compared with the initial rhythm.

Severing the vagi during the course of the bradycardia which had appeared during the "digitalis" perfusion caused a marked increase in the heart rate and a decrease in the amplitude of the cardiac contractions. Perfusion of "digitalis" through the isolated sino-carotid pocket with the severed sino-carotid nerve did not cause the appearance of bradycardia or an increase in the strength of the cardiac contractions.

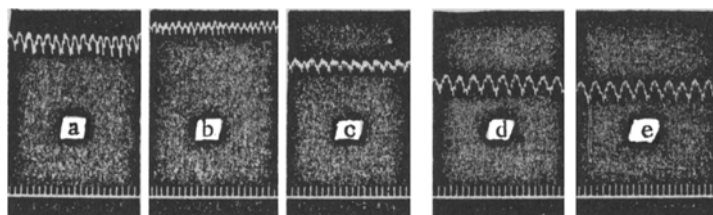


Fig. 3. Changes in blood pressure under the influence of atropine and "digitalis" in puppy (age $1\frac{1}{2}$ months). Significance of markings as in Pict. 1.

I) before atropine

II) after atropine

A, C, D) perfusion with Ringer-Locke solution

B, E) "digitalis" perfusion.

In 9 experiments on puppies of the first age group from 1 to 18 days old perfusion of "digitalis" caused no changes whatever in the cardiac rhythm or in the amplitude of cardiac contractions (Fig. 2, strips B, D, E). The blood pressure with this was elevated but slightly.

In 11 experiments upon puppies of the second age group (from 18 days to $2\frac{1}{2}$ months) "digitalis" perfusion led not to a slowing of the heart, as in adult dogs, but to an acceleration. This acceleration manifested itself only after several repeated perfusions. The amplitude of the heart contractions remained unchanged (Fig. 3).

In strip B. of Fig. 3 is demonstrated an increased cardiac rate and a rise in the blood pressure with the fifth perfusion of "digitalis."

In this fashion, in 20 experiments on puppies of the first and second age groups we saw no slowing of the heart in spite of the fact that in puppies after the eighteenth day of life there appears a constant tone in the vagal center [3, 6, 7, 9, 12, 13]. The difference in the response in puppies of the second age group appears in an acceleration of the heart with perfusion by "digitalis."

Taking into consideration the feebleness of the tone of the vagal innervation of the heart in puppies from the ages 18 days to $2\frac{1}{2}$ months and the predominating sympathetic innervation tone, it might be supposed that the acceleration of the heart with "digitalis" perfusion is connected with a reinforcement of the tone of the sympathetic innervation. If this were true, then this acceleration of the cardiac rate should appear less marked in puppies from 1 to 18 days, as it is in this age that the sympathetic tone is at its highest. But this we did not observe in our experiments.

With the aim of clarifying the mechanism of this phenomenon, puppies of the second age group, after the appearance of the increase in the heart rate, were given atropine in doses 0.05-0.1 mg/kg (Fig. 3, strip D). These experiments show that "digitalis" perfusion after atropine does not cause an acceleration of the heart rate (Fig. 3, strip E).

All this taken together shows that the acceleration in the cardiac rate in puppies in the ages 18 days to $2\frac{1}{2}$ months who received "digitalis" perfusions is associated not with the tone of the sympathetic innervation of the heart, but with the change in the vagal central innervations which as yet does not have a definite inhibiting effect.

In the experiments on adult dogs we observed acceleration of the cardiac rhythm with perfusions of "digitalis" in greater concentrations (200 CU per 1 liter). In this case the change to a perfusion of much lesser strength of "digitalis" (10-20 cat units per 1 liter) caused a relative slowing of the cardiac frequency.

The first slowing of the heart rhythm by the use of "digitalis" solutions through the sino-carotid zone we

observed in experiments on puppies ages $2\frac{1}{2}$ - 3 months (9 experiments). This slowing was not as pronounced as in adult dogs: the majority of experiments gave a slowing of only 12-36 beats per 1 minute. As distinguished from adult dogs, puppies of this age with the negative chronotropic effect do not have an accompanying inotropic effect, with the exception of several experiments in which it appeared but feebly (Fig. 4, strips B and D).

The slowing of the cardiac rhythm in dogs of the third age group is not constant and after 2-3 perfusions is followed by an acceleration (Fig. 4, strip F). The inconstant reaction of slowing of the heart can be explained by its dependence on the feeble resistance of the vagal nerve center of the heart [16] in this age group and testifies of the feebly expressed capacity of this center to respond to summation stimuli.

The marked expression of the time and inotropic effect such as seen in adult dogs, appears in puppies perfused with "digitalis" only in the ages 4-5 months, when the vagus regulation of cardiac activity approaches the degree seen in adult dogs.

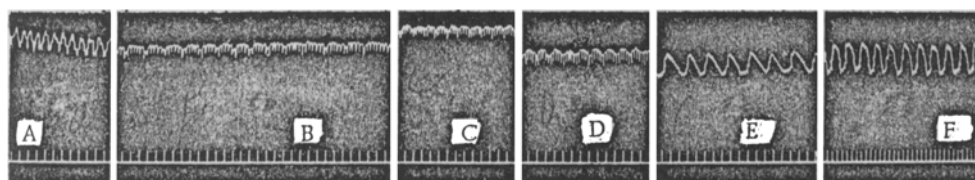


Fig. 4. Changes in blood pressure under the influence of "digitalis" in puppy aged $2\frac{1}{2}$ months.

The explanations are as in Figures 1 and 2.

A, C, E) perfusion with Ringer-Locke solution.

B, D, F) perfusion with "digitalis" solution. (50 CU per liter).

DISCUSSION OF RESULTS

The results obtained permit us to draw the conclusion that "digitalis" acts not only directly upon the heart muscle [1], but in a reflex way— as a result of its influence on the receptor zones of the vascular system. Besides this, as our experiments seem to show the therapeutic vagotropic action of "digitalis", is bound up not only with its actions upon the centers of vagal innervation but with its reflex action upon the receptors.

It is usually thought that the action of "digitalis" mediated through the system of the vagus nerve determines only the chronotropic effect and that the inotropic effect is associated directly with its influence upon the muscle of the heart. Our experiments present experimental evidence that the increased strength of cardiac contractions can be mediated reflexly through the vagus innervation. Severing the vagi during sharply expressed chronotropic and inotropic effects caused by "digitalis" leads to a disappearance not only of the chronotropic effect but also of the inotropic effect.

Contrary to the concept that the vagus nerve depresses all functions of the heart, there is at the present time an ever increasing number of facts pointing to a shortened chronaxie and refractory phase appearing during a state of positive tone of rest or of electro-positiveness during stimulation of the vagus nerve [10, 21, 27, 28].

The mechanism of the positive inotropic action of "digitalis" upon the reflex systems through the effect upon the receptors of the sino-carotid zone can be explained by an examination of the nature of the vagal inhibition of the heart, this showing that the sino-auricular node at this time is in a state of paralytic inhibition, while in the myocardium are observed the contractile changes of the parameter of stimulation [4, 5].

The materials showing the absence of bradycardia in puppies of early age groups during "digitalis" perfusions confirm the findings in the literature that it acts by raising the tone of the vagal center innervating the heart. Only in ages $2\frac{1}{2}$ -4 months when the tone of the center of parasympathetic innervation becomes adequately high can the effects typical for the action of "digitalis" appear. As is well known in rabbits the vagus innervation of the heart is feeble and bradycardia cannot be produced with "digitalis."

The absence in changes of heart rhythm when "digitalis" is perfused in the isolated sinocarotid zone of puppies ages 1 to 18 days can be shown to be a function of the immaturity of the afferent part of the reflex arc [2, 3, 7, 18, 19, 25].

Investigation of the mechanisms of action by the cardiac glycosides in animals of varying ages is of considerable interest in pediatric practice. It is well known that in children of early age bradycardia does not appear when "digitalis" is used.

The first signs of vagus regulation of cardiac activity appears in children only by the age of 3 years [15]. These findings, as well as our materials enable to conclude that the desire to slow the heart in children under the age of 3 by the use of "digitalis" can be considered as a fruitless effort because of the absence in such young organisms of nerve mechanisms by means of which this could be mediated. At the same time the desire of some pediatricians to increase the dosage of "digitalis" in babies [30] is not without dangers, as it has been shown that the concept of a decreased sensitivity to "digitalis" in children and animals of a very young age is not true. [24].

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