THE EFFECT OF STROPHANTHIN ON THE CORONARY CIRCULATION AND CARDIAC OXYGEN INTAKE IN EXPERIMENTAL MYOCARDITIS

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Cardiac glycosides are extensively used to treat various diseases of the cardiovascular system often attended by coronary insufficiency. Despite the large number of works concerned with this question, however, the data describing the effect of cardiac glycosides on coronary circulation are rather inconsistent. Several authors, for example, assert that preparations of this group, used in doses the authors considered to approximate the therapeutic, either do not alter or somewhat increase the coronary blood flow [1, 7, 8-12, 18, 19, 25, 31, 37]. The works of other researchers have demonstrated that cardiac glycosides diminish the coronary blood flow [14, 16, 17, 33]. The majority of researchers concur in the fact that preparations of this group diminish the coronary blood flow when administered in toxic doses.

Research on the effect of cardiac glycosides on the oxygen intake of the heart muscle has produced data just as inconsistent as the results of the investigations studying the effect of these agents on the coronary circulation. It has been demonstrated on myocardial sections taken from different animals that cardiac glycosides in therapeutic doses increase the oxygen intake, but that when larger doses of these substances are administered, a considerable decrease in the oxygen intake occurs immediately after its increase [13, 15, 24, 29, 30, 35, 39]; it was further observed that the increase in oxygen intake was more pronounced on sections taken from a heart muscle poisoned with barbiturates [26]. In experiments with a contracting heart, it was demonstrated that strophanthin either does not effect the cardiac oxygen intake or increases it [7, 21, 23, 27, 28, 32, 34, 38], the latter being extremely pronounced if the oxygen intake was considerably reduced initially [35, 36]. The investigations of other authors, however, show the opposite, i.e., that strophanthin reduces the oxygen intake of the heart muscle [22, 33].

In this work, we studied the effect of therapeutic and toxic doses of strophanthin on the coronary circulation and cardiac oxygen intake of healthy animals and animals with experimental myocarditis. There are no data in the literature on the question of how cardiac glycosides affect the coronary circulation and the myocardial oxygen intake under conditions of experimental myocarditis, although this is a question of great importance to the more rational utilization of the given preparations.

METHODS AND RESULTS

Experiments were performed on cats (40 experiments) anesthetized with urethan and chloralose, and a few (eight experiments) were performed on healthy dogs. The change in coronary circulation was estimated according to the volumetric rate of the outflow of blood from the cat's coronary sinus by the method described in detail by N. V. Kaverina [5].

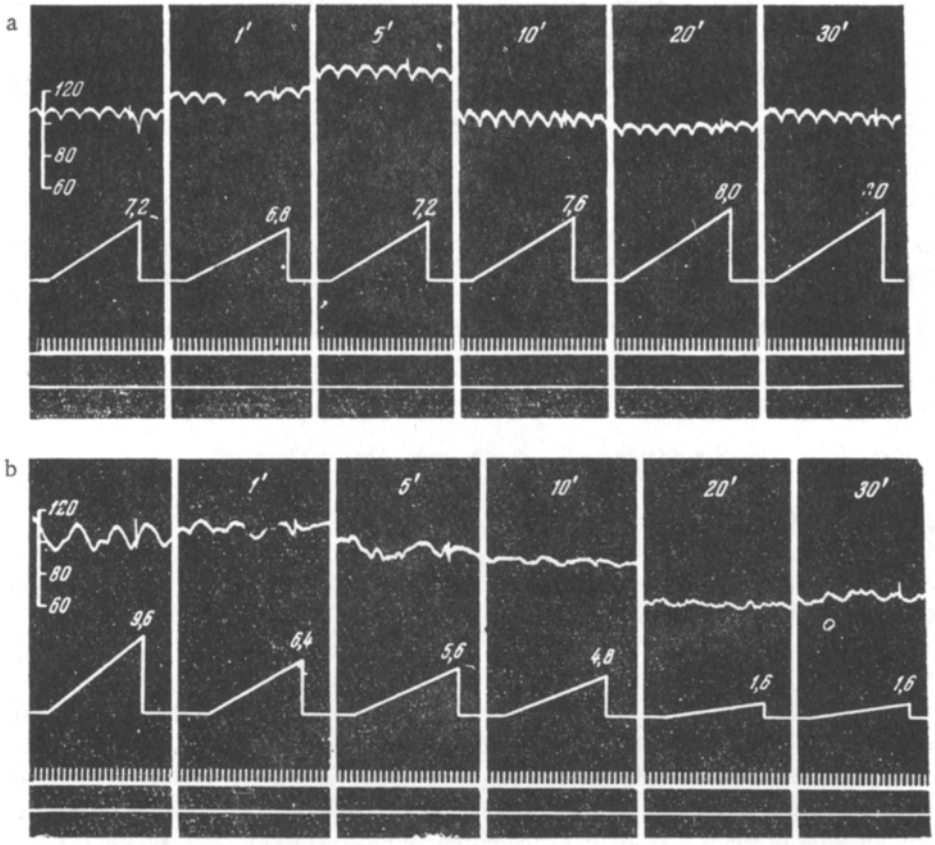

Fig. 1. Change in the volumetric rate of the coronary blood flow effected by strophanthin in doses of 20 μg/kg (a) and 50 μg/kg (b). Curves show (from top to bottom): blood pressure, volumetric rate of coronary blood flow (figures give volumetric rate of blood outflow in 1 min); time in seconds.

Oxyhemoglobin was determined in the blood flowing from the coronary sinus with the aid of an oxyhemometer. The cardiac oxygen intake was derived from the formula:

$$A = \frac{1.34\,(C_1 - C_2)\,V \cdot H}{100},$$

in which A is the amount of oxygen in ml/min, C_1, the oxyhemoglobin content of the arterial blood in %, C_2, the oxyhemoglobin content of the venous blood flowing out of the coronary sinus in %, V is the volumetric rate of outflow of blood from the coronary sinus in ml/min and N is the hemoglobin content in grams of 1 ml of blood.

The blood pressure was recorded in the carotid artery with a mercury manometer. Myocarditis was induced in the cats by the successive administration of theophylline (0.75 mg/kg) and adrenalin (1:1000 – 0.35 ml/kg). The presence of myocarditis was established by histology and electrocardiography.

The experiments showed that the effect of strophanthin on the coronary circulation and cardiac oxygen intake depends on the doses used and on the initial physiologic condition. For example, strophanthin in a dose of 10 μg/kg did not alter the volumetric rate of the coronary blood flow or the cardiac oxygen intake. In a dose of 20 μg/kg, strophanthin caused a slight increase in both the coronary blood flow and the cardiac oxygen intake (5-7%, see Fig. 1). In these doses, strophanthin had little effect on the heart rhythm or blood pressure; accelerated rhythm and slightly increased blood pressure were observed in a few experiments. In a dose of 30 μg/kg, strophanthin almost doubled the volumetric rate of the coronary blood flow. The increase in the coronary blood was attended by an increase in the myocardial oxygen intake, the latter increase being more pronounced (oxyhemoglobin content of the blood issuing from the coronary sinus was somewhat reduced). In a dose of 50 μg/kg, strophanthin caused a considerable decrease in the volumetric rate of the coronary blood flow (65%) and in the

cardiac oxygen intake (71%), a fall of blood pressure and the development of bradycardia. The decrease in the cardiac oxygen intake was usually more pronounced than that in the volumetric rate of the coronary blood flow (oxyhemoglobin content of the blood from the coronary sinus increased somewhat).

The coincidence of the changes effected by strophanthin in the volumetric rate of the coronary blood flow and the cardiac oxygen intake is physiologically wholly normal.

A different qualitative reaction was observed with the administration of strophanthin under conditions of experimental myocarditis (Fig. 2). In a dose of 10 μg/kg, strophanthin caused a considerable increase in the volumetric rate of the coronary blood flow (42%) and cardiac oxygen intake (39%).

In a dose of 20 μg/kg, strophanthin caused a considerable decrease in the volumetric rate of the coronary blood flow (43%) and the cardiac oxygen intake (50%). The decrease in the cardiac oxygen intake was stronger than that in the volumetric rate of the coronary blood flow, causing some increase in the oxygen content of the blood from the coronary sinus. Under conditions of experimental myocarditis, the decrease in the coronary blood flow induced by 20 μg/kg was attended by the development of bradycardia, which was not observed when these doses were administered to the healthy animals (Fig. 3).

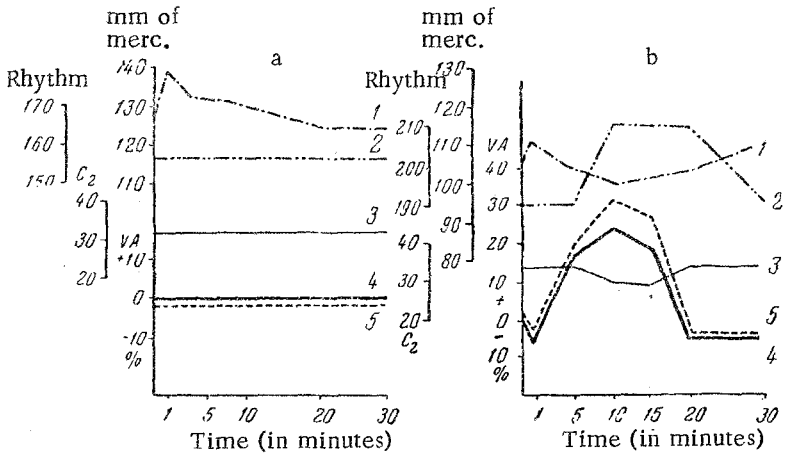

Fig. 2. Change in volumetric rate of coronary blood flow and cardiac oxygen intake effected by strophanthin in a dose of 10 μg/kg in normal animals (a) and in those with experimental myocarditis (b). 1) blood pressure; 2) rhythm; 3) oxyhemoglobin of blood of coronary sinus (C_2); 4) volumetric rate of coronary blood flow (V); 5) cardiac oxygen intake (A).

Under conditions of experimental myocarditis, the decrease effected by 20 μg/kg strophanthin in the volumetric rate of the coronary blood flow often did not fit the changes in the blood pressure and the frequency of the cardiac contractions. During the first minutes of strophanthin's action, for example, the blood pressure rose 10-20 mm of mercury and the heart rhythm either remained the same or became somewhat faster, but the volumetric rate of the coronary blood flow decreased considerably, even though one would expect an increased coronary blood flow under the given conditions.

Transection of the vagus nerves carried out on a background of the decrease in the volumetric rate of the coronary blood flow arrested this decrease, and some increase was even observed. After preliminary bilateral vagotomy, the decrease in the blood flow caused by strophanthin in a dose of 20 μg/kg was not as pronounced. For example, although strophanthin in this dose caused an average decrease of 43% in the blood flow, starting almost immediately after the administration of the preparation, after preliminary transection of the vagus nerves, the decrease in the volumetric rate of the coronary blood flow did not start until the 20th minute of the preparation's action and then constituted an average of only 9%; in some experiments, no decrease at all was observed—in fact, the blood flow increased somewhat during the early minutes of strophanthin's effect. After the preliminary administration of atropine in a dose of 1 mg/kg, no decrease was observed in the blood flow.

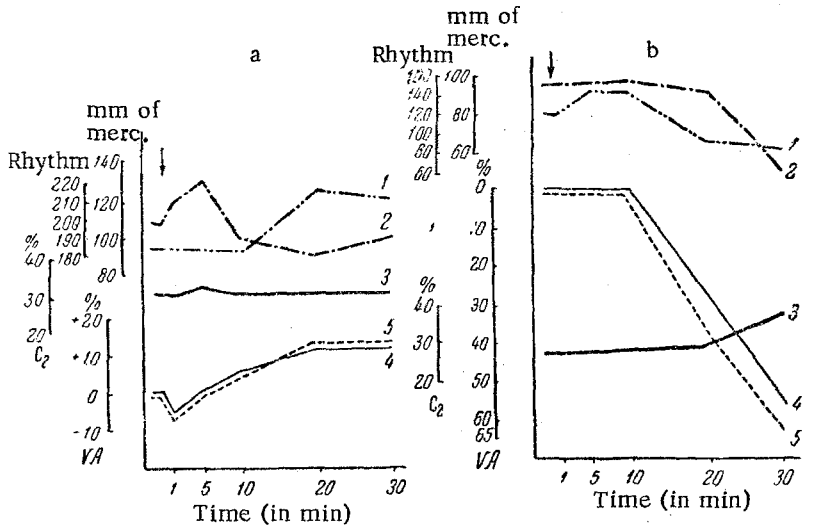

Fig. 3. Change in the volumetric rate of the coronary blood flow and in the cardiac oxygen intake effected by strophanthin in a dose of 20 μg/kg in normal animals (a) and in animals with experimental myocarditis (b). Curves the same as in Fig. 2.

Our study of the volumetric rate of the coronary blood flow and the cardiac oxygen intake of healthy dogs allowed us to establish that strophanthin in a dose of 30 μg/kg almost doubles the coronary blood flow and cardiac oxygen intake and that both these factors increase concurrently. In doses of 50-60 μg/kg, strophanthin decreases the coronary blood flow, cardiac oxygen intake and blood pressure and causes bradycardia.

We also conducted a series of experiments determining the toxicity of strophanthin according to the Wiengaarden method in healthy cats and in those with experimental myocarditis. It was established that strophanthin is considerably more toxic under conditions of experimental myocarditis. The average dose inducing cardiac arrest in healthy cats was 104 mg/kg* (with a variation of 0.095-0.111 mg/kg); under conditions of experimental myocarditis, this dose decreased to 0.76 mg/kg (with a variation of 0.050-0.097 mg/kg).

We also conducted investigations of cats to record the transmission of vagal excitation to the myocardium with continuous passage of a 1:200 000 strophanthin solution until cardiac arrest. We used both healthy animals and animals with experimentally induced myocarditis in the experiments. After transecting the vagal nerve, we stimulated its peripheral end with an electronic stimulator with a frequency of 30 hertz, each stimulus lasting 0.5 msec. The experiments showed that strophanthin considerably facilitates the transmission of stimulation from the vagus nerve to the myocardium under conditions of experimental myocarditis, but hinders the transmission of stimulation in healthy animals.

On the basis of the results obtained, one can conclude that strophanthin, administered in therapeutic doses to healthy animals, does not materially affect the coronary circulation of myocardial oxygen intake; usually, these indices either do not change or somewhat increase. In toxic doses, strophanthin causes the coronary blood flow, cardiac oxygen intake and blood pressure to decrease and bradycardia to develop.

The effect of strophanthin changes considerably under conditions of experimental myocarditis. In a dose of 10 μg/kg, strophanthin increases the volumetric rate of the coronary blood flow and the cardiac oxygen intake in cats with experimentally induced myocarditis. In the case of animals with experimental myocarditis, unlike that of healthy animals, strophanthin in a dose of 20 μg/kg diminishes the coronary blood flow and myocardial oxygen intake. This reaction is the most pronounced at the later periods in the development of myocarditis; on the seventh day of the development of myocarditis, strophanthin administered in these doses even caused death in some cases. There is a greater decrease under these conditions in the myocardial oxygen intake than in the volumetric rate of the coronary blood flow, which is typical of stimulation of the vagus nerves [20].

With experimental myocarditis, strophanthin in a dose of 20 μg/kg not only decreases the coronary blood flow and cardiac oxygen intake, but also induces bradycardia, which does not occur in healthy animals given these doses.

*Value given is as it appears in original Russian article. Value should probably be 1.04 mg/kg.

The different qualitative reaction to strophanthin exhibited by the animals with experimental myocarditis may be partly due to the increased sensitivity of a heart in this condition to cardiac glycosides. The increased toxicity of cardiac glycosides in experimental myocarditis has been mentioned in several works [2, 3, 6]. There is also the fact that strophanthin hinders the transmission of stimulation from the vagus nerves to the myocardium in healthy animals, but considerably facilitates it under conditions of experimental myocarditis [4].

The influence of the vagus nerves on the development of strophanthin's effect is further confirmed by the fact that the decrease in the coronary blood flow effected by these doses of the preparation in experimental myocarditis is only slightly apparent after transection of the vagus nerves, while transection of the vagus nerves carried out on a background of decrease in the coronary blood flow effected by strophanthin causes the blood flow to increase. In similar investigations with preliminary vagotomy, no decrease in the coronary blood flow was observed with the action of cardiac glycosides [17].

However, it is difficult to say whether the decrease in the coronary blood flow is due to the direct influence of the vagus nerves on the coronary vessels or is caused by changes in the heart action or metabolic processes which occur during stimulation of the vagus nerves.

The data indicating the increased toxicity of strophanthin in experimental myocarditis and the decrease in the coronary blood flow effected by doses which do not materially affect the volumetric rate of the coronary blood flow in healthy animals should be taken into account by clinicians.

SUMMARY

Strophanthin given in therapeutic doses to healthy animals has no significant effect upon the coronary circulation and oxygen intake by the cardiac muscle. Toxic doses reduce the coronary circulation, the cardiac oxygen intake and the blood pressure; bradycardia appears. The dose of 20 μg/kg, which causes no changes in the coronary blood flow or the cardiac oxygen intake in the healthy animals, considerably reduces these values in animals with experimentally induced myocarditis. The different qualitative reactions occurring in response to strophanthin administration to animals with experimentally induced myocarditis may be partially explained by the increased cardiac sensitivity to strophanthin in this condition and the intensified excitation of the vagus nerves; the reflex character of the latter effect follows from experiments with vagotomy.

The data on the increase in strophanthin toxicity and the different qualitative reaction of the coronary circulation observed in experimental myocarditis should be taken into consideration by clinicians treating diseases of the cardio vascular system with cardiac glycosides.

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