REFLEX CHANGES IN THE ACTIVITY OF THE CARDIOVASCULAR SYSTEM UNDER THE INFLUENCE OF CHEMICAL STIMULATION OF PERICARDIAL RECEPTORS

COMMUNICATION I. THE DEPENDENCE OF THE CHARACTER OF REFLEX REACTIONS OF THE CARDIOVASCULAR SYSTEM ON THE INTENSITY OF CHEMICAL STIMULATION OF PERICARDIAL RECEPTORS

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V. N. Chernigovskii [14, 15] has established that stimulation of pericardial receptors in the rabbit with nicotine produces reflex fall of blood pressure and bradycardia, whereas under the influence of novocain a rise of blood pressure and acceleration of the heart rate take place. In recent years it became clear [17, 18] that stimulation of the reflexogenic zones of the thoracic cavity (heart, lungs) with veratrine leads to a sharp fall of blood pressure and bradycardia (the Bezold-Jarisch phenomenon). The work of V. N. Chernigovskii and his collaborators has shown that chemical stimulation of interoceptors in the abdominal viscera leads to reflex rise of blood pressure and acceleration of the heart, while exclusion of these interoceptors results in lowering of blood pressure and slowing of the heart [15, 16].

Faced with the question concerning the reasons for the differences between the influence of thoracic and abdominal reflexogenic zones on the cardiovascular system, we noted that the heart and the areas directly adjacent to it are particularly rich in sensory endings. In the heart itself, particularly in the ventricles, the largest number of receptors are concentrated in the epicardium and the endocardium [2, 6, 8, 9], while in the myocardium their number is relatively small; in the lungs the greatest number of receptors are in the mediastinal pleura which is directly adjacent to the pericardial sac [12, 2, 23]. The epicardial and the endocardial receptors are connected with afferent fibers of the vagus and depressor nerves; the few myocardial receptors arise from the spinal fibers which approach the heart by way of the stellate ganglion [6, 8, 9]. H. Shaefer [26] states that under ordinary conditions the number of afferent impulses travelling in the cardiac nerves is 20 times the number of efferent impulses. The reflexes from the cardiac interoceptors to the cardiovascular system, and especially in the case of the receptors concentrated in the visceral pericardium, have not been sufficiently carefully investigated. In the majority of the investigations concerned with this question [1, 10] attention is directed mainly toward the pericardial mechanoreceptors; however, the undoubted barrier function of the pericardial sac [11] and the close proximity of the epicardial receptors with a powerful lymphatic network [7] which collects lymph from the whole of the myocardium, poor in receptors, suggest that it is the epicardial chemoreceptors which must be of great importance.

The problem dealt with in the present investigation included the most careful possible study of the character of reflexes associated with different intensities of chemical stimulation of pericardial interoceptors and involving the cardiovascular system, to discover whether these characteristics could be related to the high concentration of sensory endings found in the epicardium. Taking into account that V. N. Chernigovskii studied the effect of chemical stimulation of pericardial receptors on unanesthetized rabbits (whereas the usual experimental animal for chemoreceptor studies in other areas are anesthetized cats) we performed experiments on unanesthetized rabbits, anesthetized rabbits (urethan, hexenal) and anesthetized cats (urethan).

EXPERIMENTAL METHOD

The preliminary operation making it possible to apply stimuli to the pericardial receptors was carried out on rabbits by the V. N. Chernigovskii method [14, 15] and on cats by the C. Drinker method [21]. The aim of both operations was to secure the edges of an opening made in the parietal pericardium to the superficial tissues of the thorax in such a way as to preserve the possibility of natural respiration. Solutions of nicotine in Ringer-Locke solution ($1 \cdot 10^{-9}$ to $1 \cdot 10^{-3}$) served as stimuli; they were applied, with a syringe, directly to the surface of the epicardium in amounts of 0.4-1 ml. The stimulating agent was washed off with pure Ringer-Locke solution. The intervals between stimulations were 10-30 min. Blood pressure was recorded in the carotid artery simultaneously by a mercury and a membrane manometer; respiration was recorded by means of a Marey's tambour connected to a tracheotomy cannula. A total of 30 experiments was performed on rabbits and 100 experiments on cats.

EXPERIMENTAL RESULTS

Repeating the experiments of V. N. Chernigovskii, we obtained similar results: the threshold concentration of nicotine solution which produced a reaction of one sort or another from the cardiovascular system of rabbits when applied to the pericardium was $1 \cdot 10^{-6}$. When the concentration of nicotine is raised to $1 \cdot 10^{-3}$ the reflex is enhanced but unaltered in character, manifesting itself always by a drop of blood pressure and bradycardia.

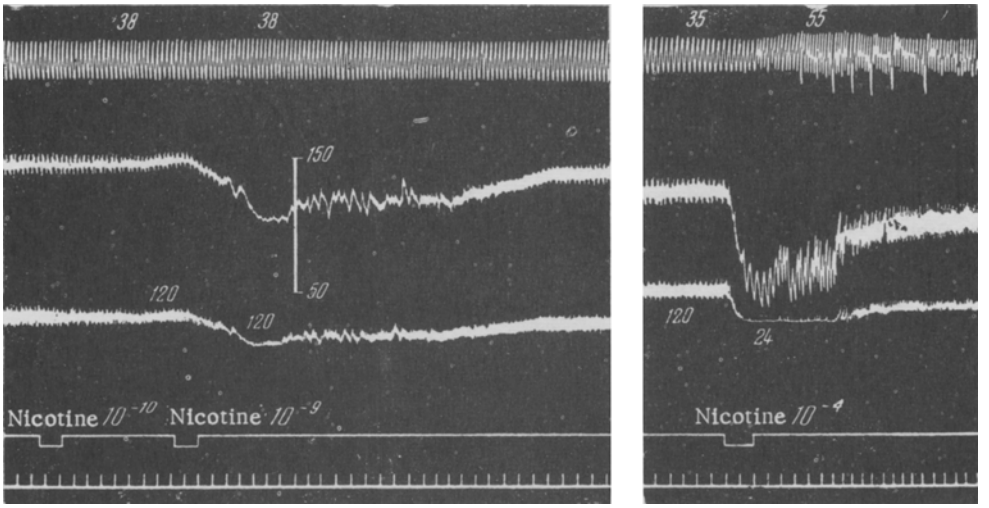

Fig. 1. Circulatory and respiratory reaction of cat to stimulation of pericardial receptors with nicotine in various concentrations. The cat reacted to all concentrations of the stimulating agent only by depressor reactions. Records from above down: respiration, arterial blood pressure (mercury manometer), arterial blood pressure (membrane manometer), stimulus marker, time marker (2 sec). Figures along the tracings recording respiration and blood pressure (membrane manometer) denote respiratory or pulse rate at the given moment calculated per 1 min.

Stimulation of the pericardium with nicotine in cats, unlike unanesthetized rabbits, caused a threshold reflex reaction at considerably lower concentrations of the stimulating agent: $0.4 \cdot 10^{-9}$ to $1 \cdot 10^{-8}$. Moreover, the character of the threshold reaction could be different in different experiments, i. e., pressor or depressor. As the stimulation was increased the sign of the reaction could be either maintained or undergo inversion. Three typical forms of the reaction were demonstrated in different groups of animals. Thus, in one group of animals (15% of the cats), as in rabbits, application of any dose of nicotine (beginning with the threshold) to the pericardium produced a fall of blood pressure and slowing of the heart rate [the cardiac reaction had a somewhat higher threshold (Fig. 1)]; as the stimulation was increased the reaction became greater. In 25% of the animals, application of any concentration of the stimulating agent caused a rise of blood pressure and acceleration of the heart rate (Fig. 2),

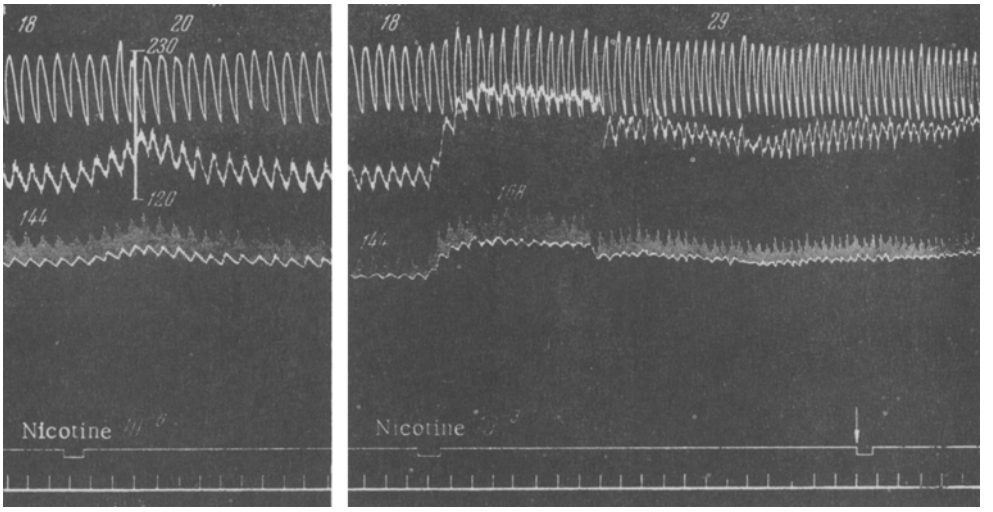

Fig. 2. Circulatory and respiratory reaction in cat to stimulation of pericardial receptors with nicotine in various concentrations. The cat reacted to all concentrations of the stimulating agent only by pressor reactions. Records the same as in Fig. 1. ↓ – washing away of nicotine begun (introduction of 10 ml Ringer-Locke solution into the pericardial cavity).

and increasing the stimulation led to enhancement of both reactions. Finally, most frequently (60% of the cats), increasing the stimulation caused a change not only of the intensity but also of the character of the cardiovascular reaction (Fig. 3): pressor reactions changed to depressor ones. The transition of pressor reactions (elicited in response to weak stimulation) to depressor reactions in response to stronger stimulation was accompanied by replacement of tachycardia by bradycardia; in different experiments this transition occurred when different concentrations of nicotine were used and was sometimes accompanied by the appearance of intermediate diphasic reactions (Fig. 2).

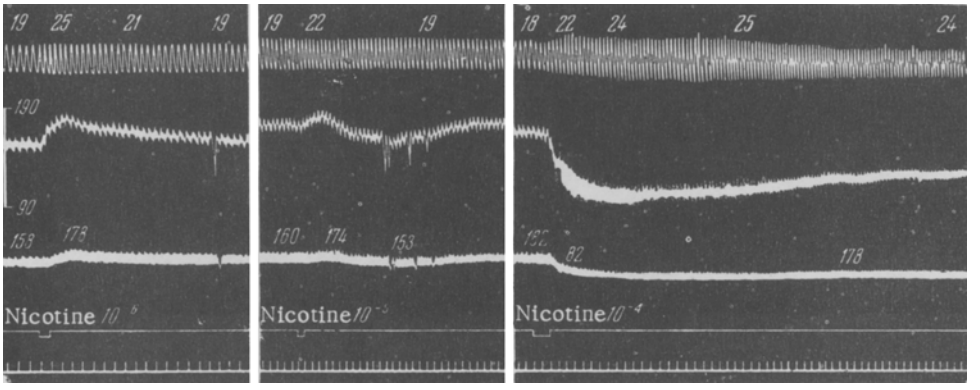

Fig. 3. Transition of the cardiovascular reaction to chemical stimulation of pericardial receptors from pressor to depressor on increasing the concentration of nicotine. Experiment on cat under urethan anesthesia. Records the same as in Fig. 1.

In some experiments, pressor reactions appeared only in response to the weakest stimulation (nicotine $0.4 \cdot 10^{-9}$), larger doses of the stimulating agent causing a fall of blood pressure; in other experiments only the strongest stimulation (nicotine $1 \cdot 10^{-3}$) led to depression, whereas weaker stimuli produced pressor reactions. The boundary between the stimulus strengths eliciting pressor and depressor reactions could lie on any part of the scale of stimulus intensity, but was usually not displaced within the limits of a given experiment.

Respiration always underwent the same change in all the animals irrespective of the direction taken by the cardiovascular reaction: the respiratory movements increased in rate and depth. The threshold of the respiratory reaction was usually higher than the thresholds of the cardiovascular reaction.

Since experiments on unanesthetized rabbits gave results different from those obtained in experiments on cats, we conducted a supplementary series of experiments on rabbits anesthetized with urethan or hexenal. In most of the experiments only depressor reactions were noted, with the exception of 4 out of the 20 experiments.

All the described reactions to chemical stimulation of pericardial receptors are reflex since they disappear after transection of the vagi and depressor nerves in the neck or on introduction of novocain into the pericardial cavity. Data obtained by a number of authors [3, 7, 22, 24, 25] also support the reflex nature of these reactions.

The results obtained in most of the experiments on cats and some on rabbits may be interpreted in two ways: either there are two types of receptors in the pericardium (the excitation of one sort giving rise to tachycardia and rise of blood pressure and excitation of the other to depression and bradycardia) or different degrees of excitation in one or more receptors leads to different results.

W. Douglas and collaborators [19, 20] stimulated the aortic nerve and the vagus in cat, which contain the afferent pathways of the reflexes described by us, and observed 3 different effects: weak stimulation led to a small fall of blood pressure, stronger stimulation resulted in a rise of blood pressure and still stronger stimulation again resulted in a fall of blood pressure, which was more profound than in the former case. The authors explain this result by the presence in the nerves concerned of 3 different types of nerve fibers. However, careful physiologic and morphologic examination carried out by the same authors allows only partial agreement with this: the effect produced by the weakest stimulation of the nerves occurs as the result of stimulation of large fibers associated with the aortic baroreceptors. The authors did not succeed in dividing the fine fibers whose stimulation would cause a rise or profound fall of blood pressure depending on the strength of stimulation. These fibers are evidently associated with the cardiac receptors which were stimulated in our experiments. Consequently, it may be considered that both pressor and depressor reactions elicited by application of nicotine to the pericardium are effected by stimulation of receptors associated with small fibers and that the character of the resultant reaction depends rather on the intensity of stimulation of homogeneous afferent elements than on a hypothetical pressor or depressor specificity of receptors or nerve fibers [4]. Otherwise it would be necessary to suppose that in some animals only "depressor" receptors are present, in others only "pressor" ones, and in the third group of animals both types of receptors, but sometimes one type ceases to manifest itself in the course of an experiment.

M. G. Udel'nov [13] has shown on extensive material that involvement in activity of a small number of efferent elements of the vagus leads to acceleration of the heart rate, whereas increasing the number of simultaneously stimulated homogeneous elements of the vagus produces slowing of the heart rate. This was confirmed by us in experiments on fish [5]. It is possible that the same phenomenon takes place in the experiments described in this work. In our view the transition of pressor reactions to depressor ones on stimulation of the pericardial receptors may be explained by the fact that very large numbers of receptors are present in the epicardium; as the result of this, application of considerable concentrations of the stimulating agent may cause a sufficient flow of impulses to create inhibition in the vasomotor center upon stimulation of this reflexogenic zone.

SUMMARY

Experiments were performed on cats under urethan anesthesia and on cats with normal respiration.

Pericardial receptors stimulated by nicotine ($0.4 \cdot 10^{-9}$ to $1 \cdot 10^{-3}$) cause pronounced reflex changes in the level of the blood pressure, heart rate and respiration. In 60% of experiments, stimulation of pericardial receptors by weak concentrations of nicotine caused increase of the blood pressure and tachycardia, while stimulation by strong concentrations of nicotine resulted in reflex decrease of the blood pressure and bradycardia. In 25% of the experiments, the animals reacted by pressor reactions and tachycardia when pericardial receptors were stimulated [by any concentration of nicotine. In 15% of the experiments, any stimulation of these receptors by nicotine caused depression of the cardiovascular system. In all experiments, any chemical stimulation of pericardial receptors both by weak and strong solutions caused increase of the rate and depth of respiratory movements.

It is suggested that the change of the pressor reaction into depressor is caused not by the stimulation of different types of receptors, but depends on the more intense stimulation of a large number of similar receptors.

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