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Interrelation between Sympathetic and Parasympathetic Cardiac Nerves within Ontogenesis.

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ABSTRACT

We have studied the formation of interrelation between sympathetic and parasympathetic influences on the heart in dogs and rats in ontogenesis during electrical stimulation of nerves. To achieve the tasks set we have carried out acute experiments on adult dogs and puppies of the first, second and third age groups using artificial respiration, as well as on intact and sympathectomized growing and adult rats with natural respiration. The basic principle of interrelation in adult animals is an intercompensatory principle against the activity of both parts of nervous system. Intercompensatory principle develops gradually as the influence of sympathetic and parasympathetic outflows on the heart grows. With increasing activity of the sympathetic nervous system, the compensatory growing of influence of the parasympathetic outflow protects the heart from overloading. After sympathectomy, we revealed age-related features in the reaction of the heart to electrical stimulation of the vagus nerve. Sympathectomized rats had lesser stroke volume than intact rats, except for age of 14 days, which is compensated by higher heart rates. The obtained data on changes in heart rate and stroke volume in the right- and left-sided vagus nerve stimulation confirm that the intercompensation develops gradually in ontogenesis as one of the basic principles of interrelation between the influences of sympathetic and parasympathetic outflows on the heart in the active state.

Keywords: heart, vagus nerve, sympathetic nerve, intercompensation, ontogenesis, sympathectomy.

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INTRODUCTION

There are several points of view regarding the interrelation between the sympathetic and parasympathetic cardiac nerves such as antagonism, synergism, intercompensation and accentuated antagonism. Single electrical stimulation of these nerves can give the opposite results [1, 2], which can be attributed to a laboratory phenomenon [3, 4].

M.G. Udelnov, a well-known expert on the cardiac physiology, [5] wrote that "the question of under what circumstances and how the regulatory interaction between the parasympathetic and sympathetic influences is organized is one of the most important variables of the problem of the nervous control of the heart."

Academician A.A. Ukhtomskii [6] noted while explaining the origin of the vagus-escape phenomenon that "the impossibility of long-term cardiac arrest starting from vagus lies rather in the compensation of vagus effect with sympathetic one than in “fatigue” of the motor end organ. At the same time, the issue is about compensatory feature of the sympathicus and not “antagonistic." Our experiments on dogs with the long-term stimulation (up to 3 hours) of Pavlov augmenter nerve showed the positive inotropic effect remaining [7]. This is another confirmation of the fact that cause of "escape" lies not just in fatigue of nerve agents, but also in the relations of sympathetic and parasympathetic control mechanisms. We further obtained new data from the experiments on dogs by stimulating a vagus nerve (VN) and sympathetic nerve in various combinations of their intercompensatory relations [8, 9]. We have proved that the increased activity of the sympathetic nerves accelerates the vagus-escape and compensatory influence of VN during prolonged stimulation of the sympathetic nerve levels the sympathetic effect [8], which leads to a high content of acetylcholine in the blood as a humoral factor of sympathetic effect compensation [7].

Another confirmation of VN compensatory influence on the sympathetic effect is that the barbamilum anesthesia has longer adaptation period than the hexenalum anesthesia [7]. It is known that barbiturates inhibit the VN excitability BN stronger and this effect is peripheral in nature [10].

Accentuated antagonism lies in that “the higher the level of sympathetic activity, the stronger the inhibiting effect of this level of parasympathetic activity is expressed" [11], which we could observe in our experiments. A.A. Ukhtomskii [6] gave earlier such interpretation of the relations of these nerves, but the works of our physiologists have not always reached foreign researchers.

The main methods for studying the role of cardiac nerves is the investigation of the effects of irritation and cardiac nerve transection, the use of pharmacological agents [12, 13] having a stimulating or blocking action on different receptors [14, 15, 16].

These findings were obtained from the experiments on adult animals, but the establishment of relations between cholinergic and adrenergic effects on the heart in ontogenesis had not been studied, which became the objective of this paper. We also set a task to identify the influence of sympathectomy on the VN stimulation effect.

RESEARCH TECHNIQUE

To achieve the tasks set we have carried out acute experiments on adult dogs and puppies of the first, second and third age groups using artificial respiration. The dogs were anesthetized with 10% barbamilum and hexenalum solution. Age classification was according to I.A. Arshavskii [17]: up to 16-18 days – puppies of the first group, up to 2-2.5 months – puppies of the second group, and older – puppies of the third age group. Cut-down approach to the sympathetic nerves was carried out through a window in the chest. Nerves were excited by rectangular pulses from the pacemaker ECL-2 (1 ms, 30 Hz) via submersible platinum electrodes. Mechanogram and ECG were recorded in the second standard derivation. The amount of acetylcholine (ACh) in the blood was determined by testing the isolated lung.

Sympathectomy was carried out by daily administration of guanetidina sulfate solution heated to 38ºC based on 10 ml/kg of body weight for 28 days after birth [18] in seven age groups: at the age of 14, 21, 28, 42, 56, 70 and 120 days.

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The rats were anesthetized with 25% urethane solution based on 1.2 g/kg of body weight and fixed on the operating table, where the VN was dissected with the use of binocular microscope MBS-1. The vagus nerves were stimulated by pulses of 0.5-5 V, 1-12 Hz, and 5 msec. To analyze the cardiac activity, we recorded ECG and differentiated rheogram for 15 minutes after each experimental intervention. We processed the results in an integrated electrophysiology laboratory, which is based on the method of ECG processing by R.M. Baevskii, with the option to process the differentiated rheogram for calculating stroke volume (SV) by the Kubicek formula [19].

Statistical processing of findings was performed by Student t-test and a paired test using Microsoft Excel.

RESULTS AND DISCUSSION

Table 1 shows the values of the recovery period of contraction force of the left ventricle during prolonged stimulation of the sympathetic nerve. As it follows from findings, the positive inotropic effect is more pronounced in the adult animals, because the influences of the sympathetic nerves on the myocardial contractility in 2-2.5 month puppies are in the process of maturation. Puppies of this age group have tonic and reflex influence of VN on their heart, i.e., inhibitory action on sympathetic effect is poorly expressed, therefore adaptation period is longer.

Table 1: Heart adaptation rate during prolonged stimulation of the sympathetic nerve

No.	Age of animals	Positive inotropic effect (%)	Time of adaptation
1	Adults (n=10)	254±16	2 min 20 sec in all experiments
2	Puppies of 2nd age group (n=27)	173±4.7 22% of experiments	4 min in 22% of experiments

This can explain the fact that puppies have lower ACh blood content ($4x10^{-13.7}$ g/ml) than the adult dogs ($4x10^{-9.5\pm0.6}$ g/ml). In addition, ACh content in the blood of adult dogs increases during the sympathetic influence ($4x10^{-9.6}$ to $4x10^{-8.1}$ g/ml), which is not observed in puppies ($4x10^{-11.5}$ и $4x10^{-11.1}$ g/ml).

Consequently, the intercompensatory value of VN in ontogenesis manifests during structural and functional maturation of the cholinergic cardiac system [17], ensuring the protection of the heart during sympathetic influences, overloads and hypoxia, and its rapid recovery after exercise, which is also confirmed by the literature data [2, 21, 22].

A theory of systems (Le Chatelier's principle) also confirms the intercompensatory principle and states that if there is a shift in balance of the system, the latter will respond with such processes that counteract the resulting changes or bring them to naught.

We thought that the interaction of extracardiac nerves should be also manifested in the influence of sympathetic nerves on the cardiac response to the cholinergic effects. To test this hypothesis, we conducted the study on the sympathectomized rats of different age groups.

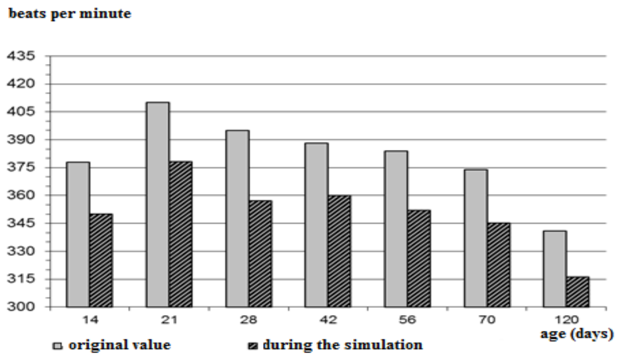

Figure 1: Heart rate change in intact rats of different age during right VN stimulation

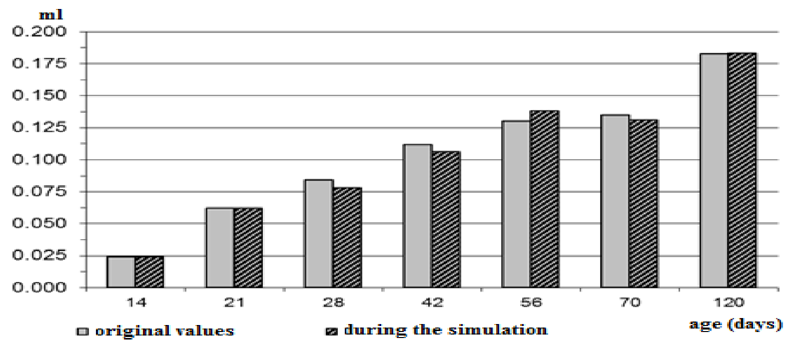

Figure 2: Stroke volume change in intact rats of different age during right VN stimulation

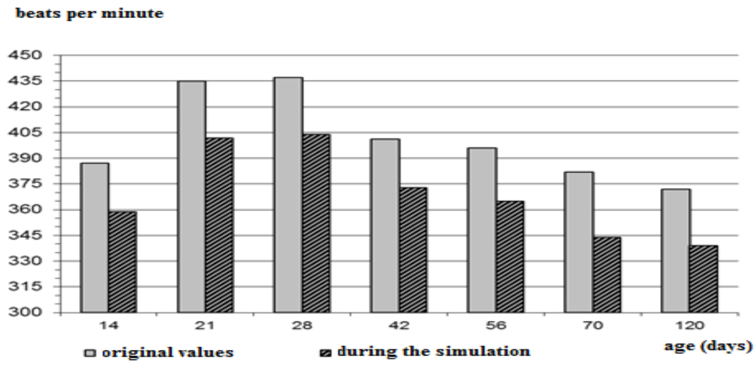

Figure 3: Heart rate change in sympathectomized rats of different age during right VN stimulation

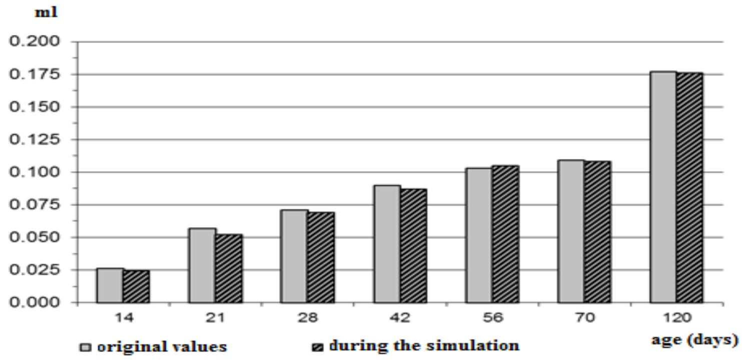

Figure 4: Stroke volume change in sympathectomized rats of different age during right VN stimulation

Right-sided VN stimulation in rats with threshold current causes a significant decrease in heart rate in all age groups we study. But, there is a bidirectional dynamics of the stroke volume. For example, the 14 and 21-day-old intact rats show reduction in heart rate only (Figure 1.2), while sympathectomized animals of similar age show reduction in both heart rate and cardiac ejection volume during stimulation of right VN that can result from the impairment of compensatory response of the heart in sympathectomized animals (Figure 3.4).

28- and 42-day-old animals also show negative inotropic response to the left VN stimulation, and the control animals show an accentuated decrease in their stroke volume (Figure 2). Significant slowing of heart rate in 28-day-old intact rats during stimulation results in the decrease in their stroke volume by 7.1%, in 42-day-old rats - by 4.8%, while sympathectomized rats of the same age have a stroke volume decreased only by 2.5%. 56-day-old intact rats respond to the left VN stimulation with the increase in their stroke volume by 5.9%, while sympathectomized rats have no significant changes in their stroke volume in response to this experimental intervention (Figure 4). 70-day-old and adult animals of both groups have no significant changes in their stroke volume during stimulation that may be due to the formation of asymmetry between the VN impact on the heart rate and force at this age.

Left-sided as well as right-sided VN stimulation causes a significant slowing of the heart rate (Figure 5.7), while this requires higher current. However, the stroke volume changes are of different nature in this case (Figure 6.8).

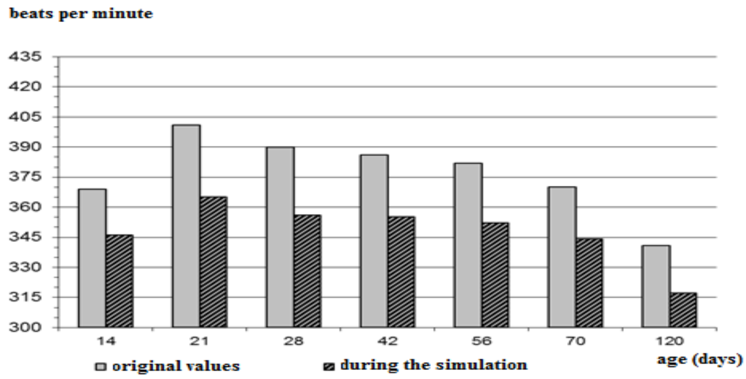

Figure 5: Heart rate change in intact rats of different age during left VN stimulation

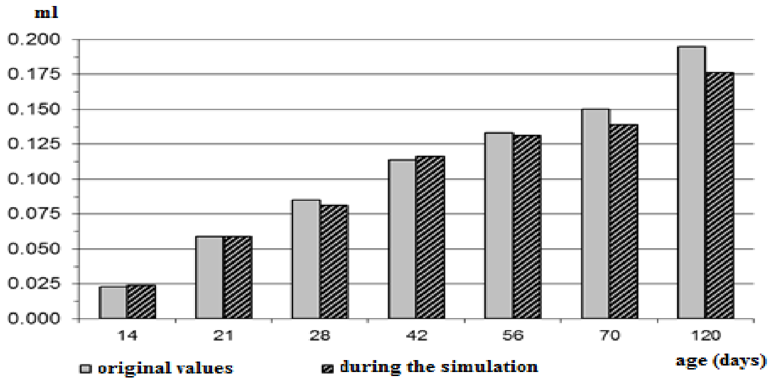

Figure 6: Stroke volume change in intact rats of different age during left VN stimulation

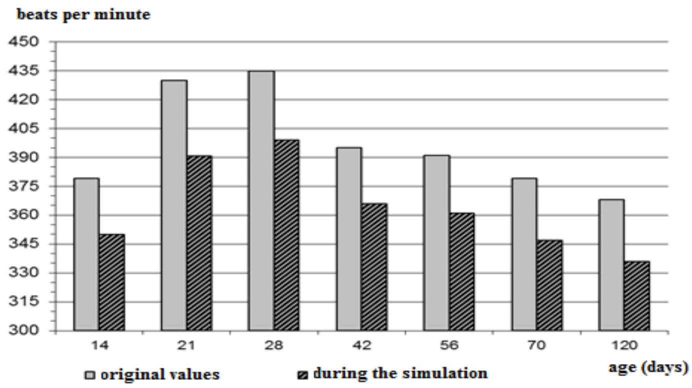

Figure 7: Heart rate change in sympathectomized rats of different age during left VN stimulation

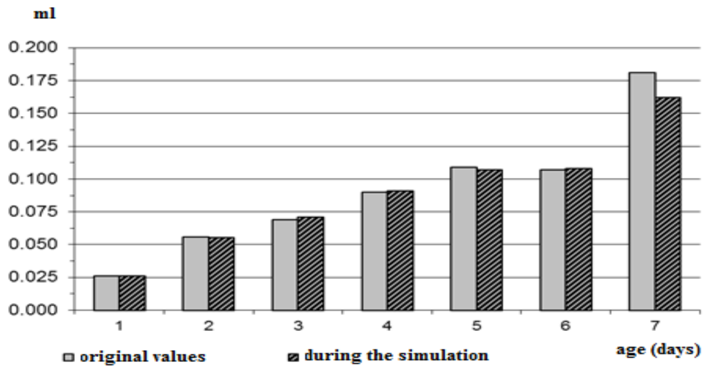

Figure 8: Stroke volume change in sympathectomized rats of different age during left VN stimulation

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During left VN stimulation with threshold current in 14-day-old rats of the control group we can observe some increase in their stroke volume (Figure 6), while left-sided stimulation in sympathectomized animals of the same age results in slowing the heart rate without changing the stroke volume (Figure 8). During left VN stimulation with threshold current in 21-day-old rats of both groups we can observe a significant slowing of their heart rate and no significant changes in the stoke volume. During left VN stimulation with threshold current in 28-day-old rats we can observe a negative response in the stroke volume against the significant slowing of the heart rate, while sympathectomized animals show a positive response, however, these changes are poorly expressed and insignificant. During left VN stimulation with threshold current in 42- and 56-day-old rats of both groups we can observe no significant changes in the stoke volume.

During left VN stimulation with threshold current in 70-day-old and adult rats we can observe a negative response in the stroke volume against the significant slowing of the heart rate, while this slowing is significant in adult animals. 70-day-old sympathectomized animals have no significant changes in their stroke volume during VN stimulation, while adult rats have the same decreased ($p<0.001$), as well as the rats of control group.

As can be seen from these findings, the sympathectomized rats had lesser stroke volume than intact rats, except for age of 14 days, which is compensated by higher heart rates. This is a compensatory response for maintaining a constant cardiac minute output.

During right and left VN stimulation we observed significant changes in heart rate in the animals of all age groups, while the same in stroke volume were insignificant. Only the left VN stimulation in adult rats (120-day-old) caused a significant reduction in stroke volume, which indicates the formation of VN regulatory influences on contractile myocardium.

T.L. Zefirov [2, 23] also pointed to the lack of differences in cardiac response to electrical stimulation of vagus nerve in both sympathectomized and intact rats.

3 week old rats have the highest heart rate. It decreases as the influence of parasympathetic system increases. The mechanism of training bradycardia is based on the interaction of sympathetic and parasympathetic influences, namely the relative prevalence of VN against the decrease in sympathetic activity. There are also age-related features of the training bradycardia. Immature animals show a significant predominance of cholinergic factor [24].

According to our data, formation of heart rate occurs in school-age children (especially of prepubertal and pubertal period) at a constant mutual influence of the sympathetic and parasympathetic regulation parts of the heart [25].

SUMMARY

Based on the above stated we can conclude that the intercompensatory value of VN in ontogenesis manifests during structural and functional maturation of the cholinergic cardiac system [17], ensuring the protection of the heart during sympathetic influences and overloads, and its rapid recovery after exercise.

CONCLUSION

Intercompensation develops gradually in ontogenesis as one of the basic principles of interrelation between the influences of sympathetic and parasympathetic outflows on the heart in the active state.

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