provided by Nature Preceding

Title: Integrative Approach - New Level Knowledge of Functions: Opportunities and Prospects

Authors: V. Pokrovskii

Affiliations:

Kuban State Medical University, Department of Normal Physiology, Sedin Street, 4, 350063, Krasnodar, Russia, pokrovskyvm@gmail.com, http://www.pokrovskii.kuban.ru.

Abstract: In this article the example of the mechanisms of heart rhythmogenesis in the intact organism to demonstrate the new capabilities provided by an integrative approach. It is shown, that the rhythm is formed in the brain, is transmitted to the heart in the form of signals along the vagus nerves and reproduces the heart. Evidence: the heart rhythm reproduces the natural efferent signals in the vagus nerves in the cardio-respiratory synchronism and in the intact organism sino-atrial node performs the functions of the latent pacemaker. Integration of the two hierarchical levels of rhythmogenesis (brain and intracardiac) provides the reliability and functional perfection of cardiac rhythm generation in the body. It is expedient to extend the

presented methodology for scientific analysis to other organism systems.

Main Text: The logic and practice of biomedical research in recent decades have led to dramatic breakthroughs in genetics, cell biology, biotechnology and many other areas. Thus, further improvement in scientific research and technology implementation became possible. Such a tendency was the most clearly manifested in medicine, leading to the development of advanced methods of treatment and diagnostics. However, there is an obvious gap in studies of the integrative nature, according to which, the body is assessed as a system with multi-level hierarchical organization. One of the reasons for such situation was an imbalance in scientific research in recent decades at the cellular and molecular level on the one hand and the organism level on the other hand. The absence of impressive successes in the study of integral (intact) organism determined the reserved attitude of the scientific community to the integrative approach in research and practice. At the same time, the development of scientific knowledge will inevitably lead humanity to the need to the assessment of the organism as an integrated system, opening the way to a new stage. In such a way, huge success will open up new horizons in accumulating knowledge of nature. Thus, it will lead to the creation of technologies, unknown today. The need for a holistic understanding was manifested by the increasing interest of scientists around the world in Neuroscience as in an important stage in the understanding of the organism. Perspectives of improving knowledge through research on the integral organism depend on the efficiency of such a methodological approach. In this article the example of heart rhythmogenesis in humans and animals are the facts that enabled the organization to see a qualitatively different functions in contrast to the prevailing notions about her. Finding a previously unknown organization rhythmogenesis was possible only when the integrative approach to the study.

Nowadays, an idea of the heart rhythmogenesis according to which the rhythm is born in the heart is formed. In those rhythmogenical structures (sino-atrial node), and the nervous system performs a corrective function. The signals coming from the parasympathetic nerves, slow down the heart beat, and speed it up by sympathetic ones. These representations are based on two groups of facts: 1 - the ability of the heart to self-excitation (automaticity); 2 - inhibitory effect of parasympathetic nerves and stimulating effect sympathetic ones. However, the work of the heart, as well as the influence of centrifugal nerves on it, are commonly studied on isolated tissues or during numerous experiments on animals in anesthesia. In all these works function was studied in vivo, without any manifestation of vital activity.

We have established new ideas about the hierarchical organization of the heart rhythmogenesis of human and animals. In accordance with these ideas, rhythmogenesis is carried by hierarchical system structures and mechanisms of the brain and heart. Formation of heart rate is primarily carried out in the brain. In rhythmogenesis, multi-tiered system of brain structures is involved. The final form of rhythm is carried out in the medulla oblongata. From the medulla oblongata signals in the form of "bursts" of impulses enter the heart along the vagus nerves. In the heart, all these signals interact with intracardiac rithmogenical structures. As a result of this interaction, the heart rhythm is formed, which reproduces the frequency of the pulses received from the brain to the heart via the vagus nerves (1-4).

The facts underlying the concepts of a hierarchical system of formation of cardiac rhythm in the body, are combined in that article into four main groups.

1. Reproduction in heart rhythm, "salvo" vagus nerve stimulation (vagal-cardiac synchronization).

The vagus nerves stimulated with pulses, combined into groups ("bursts"). This stimulation brings the character of the efferent signals in the nerves to natural ones. Heart rhythm at the same time reproduces the signals along the nerves - Vagal-cardiac synchronization is formed. When vagal-cardiac synchronization in response to each stimulation of the vagus nerve, "salvo" pulse corresponds to a heart contraction. Priority use of "salvo" irritation of the vagus nerves and detection with qualitatively new reactions belong to A.A. Zubkov (5). A.A. Zubkov does not interpret the facts obtained and state the reasons which prompted to undertake such studies. The facts described by A.A. Zubkov, were reproduced in three laboratories (6-8). Unfortunately, the authors of all these messages have the facts beyond any concept and limited statement of the extraordinary phenomenon. In our laboratory on anesthetized cats,

peripheral end of the right vagus nerve was irritated, "bursts" of impulses from the stimulator ESU-1 (pulse amplitude 1,2 \pm 0,04 V, pulse duration - 2 ms, pulse frequency in the volley - 40 Hz) (1). "Bursts" pulses were followed by a gradually increasing frequency. Stimulation resulted in a slowing heart rate. When the frequency of "bursts" of equal slows the heart rate, occurred both synchronization of rhythms - each "bursts" pulses correspond heart contraction, occurs within a certain period of time after application of stimulation to the nerve. Synchronization of the frequency of stimulation and heart rate remained within the range of frequencies from 0.05 to 0.5 Hz. A characteristic feature of the phenomenon of synchronization is the stability of its display, allowing both slows and heart rate become more frequent change of frequency of "bursts". Related sync ranges overlap, forming a total range of adjustable frequency control heart from 129.5 ± 3.6 to 64.1 ± 4.2 min. The blockade of excitation of vagus nerve, during cooling of the distal stimulating electrodes, resulted in desynchronization of rhythms and restore the original heart rate. The parasympathetic nature of the phenomenon is confirmed by its elimination of atropine. Upon stimulation of the right or the left vagus nerve of the range synchronization did not differ significantly. Chronotropical effect in the simultaneous stimulation of two vagus nerves differs little from the effect of stimulation of each of the vagus nerves in particular. The physiological significance of this fact lies in the fact that the right and left vagus nerves may overlap (9).

Vagal-cardiac synchronization seen in newborn animals and improves with age. Synchronization of vagal and cardiac rhythms is a general biological phenomenon. It was found in 10 species of animals: monkeys, dogs, cats, rabbits, rats, guinea pigs, nutria, ducks, pigeons, frogs. The presence of such a reliable general biological phenomenon, which is the synchronization of vagal and cardiac rhythms in volley stimulation of vagus nerves, the reason

for finding the role of this mechanism for rhythmogenesis in the integral organism (I). The first priority was to create a natural signal to the vagus nerves that trigger heart rhythm.

2. Formation in the brain and transmitted via the vagus nerves, forming natural signals.

The way for the creation of natural signals of the vagus nerves that trigger heart rhythm, has opened a commonality of mechanisms of heart and respiratory rhythmogenesis (10). The close functional relationship between the heart and respiratory rhythmogenesis was demonstrated by us. It is shown that the same interneuron in the nuclei of vagal complex of the medulla oblongata showing impulse activity in the respiratory rhythm, the rhythm of systole. During inhalation of its activity is synchronized with the contractions of the diaphragm, and during exhalation is synchronized with the contractions of the heart (Fig.1) (11).

Conjugation of cardiac and respiratory rhythmogenesis in the brain was the basis for finding ways to create a "model" of the brain signals that form the heart rhythm. Breathing is the only autonomic function, amenable to arbitrary control - a person can consciously change the frequency and depth of breathing. It offers a unique possibility to control the heart rhythmogenesis by creating a common respiratory and cardiac rhythms. Such a single rate can be obtained through the involvement of cardiac efferent neurons in the dominant rapid breathing rhythm. The signals generated in the heart efferent neurons enter the heart by the vagus nerves and interact with its rhythmogenical structures, form the heart rate, synchronous with respiration. It is possible to propose a general method of synchronous rhythm of breathing and the heart in man by a man enable a given respiratory rate, heart rate greater than the original - the phenomenon of cardio-respiratory synchronization (12-14).

For identification and analysis of cardio-respiratory synchronization as a method to control the rhythm of the heart in man was created a computer system (15). The system provides synchronous recording, pneumograms and electrocardiogram, detecting cardiac-respiratory synchronism and examines its options. The subject forms the respiratory rhythm to the beat signals on a computer screen. The purpose of each test: establishing the fact of the cardio-respiratory synchronization (Fig. 2). The purpose of the research, which consists of a series of samples: identify the range of synchronization of cardiac and respiratory rhythms.

In the first trial the system sets the respiratory rate at 5% below the initial cardiac rhythm. People with this synchronization occurs rarely. Samples were run with an increase in respiratory rate at each subsequent sample of 5%. Each subsequent test begins after the restoration of the initial cardiac rhythm. The system captures the minimum respiratory rate at which the first was detected cardio-respiratory synchronization and the maximum respiration rate, at which cardio-respiratory synchronization was detected. Thus, a person is determined by the synchronization range of respiratory and cardiac rhythms.

The sequence of the processes developing in the central nervous system of man in the implementation of cardio-respiratory synchronization, may be represented by the following stages: the perception of light or sound signal, which specifies the frequency of breathing, processing and evaluation of the signal, the formation rate of the control problem breathing reproduction rate of respiration in strict accordance with the frequency of the driving signal, the interaction of respiratory and cardiac centers in the brain, synchronizing rhythms, respiratory and cardiac centers, transmission of efferent signals to the heart via the vagus nerves, the interaction of signals arriving at the vagus nerves with rythmogenical structures of the heart, reproduce a heart rate of these signals - the development of cardio-respiratory synchronization. Therefore, in

the formation of cardio-respiratory synchronization is involved multi-tiered system of structures and mechanisms of the nervous system and heart.

In dogs cardio-respiratory synchronization obtained by termotachypnea. Animals were placed in the chamber. The gas composition of air in the chamber corresponded to the atmospheric pressure. The chamber created a temperature 38-38,5°. When the exposure to these conditions for 1-1.5 hours in the animals which developed against the background of tachypnea emerged cardio-respiratory synchronization. Frequency synchronization of cardiac and respiratory rhythms was $50.0 \pm 0.9 (170.0 \pm 10.2 \text{ min})$ and $220 \pm 15.6 \text{ maximum}$ limit of the range) of synchronous cardio-respiratory cycles per minute. To determine the role of the signals along the vagus nerves to the heart, the nerves were cut. For this preliminary finding of vagus nerves under the skin of the neck. The termination of the excitation of the vagus nerves led to the disappearance of cardio-respiratory synchronization. At the same time heart rate and respiration remained high, but were not synchronized. A similar effect was observed with the introduction of animal atropine. These experiments indicate that the signals with simultaneous breathing and heartbeat at cardio-respiratory synchronization, came to the heart via the vagus nerves.

Thus, the view of the possibility of heart contractions in the rhythm of the signals, coming in vivo via the vagus nerves, was confirmed.

3. Electrophysiological processes in the sino-atrial node of the heart while enabling the central (brain) rhythm.

In acute experiments on cats mapping of the sino-atrial node is satisfied with stimulation of the peripheral end of the transected vagus nerve "bursts" of impulses. With the development of vagal-cardiac synchronization focus initiation of excitation increased. With nerve stimulation, "bursts" of the four pulses of the source area for isochronous maps was $35,78 \pm 0,45$ mm², with

eight pulses per volley - $90,28 \pm 0,81$ mm² and sixteen pulses - $172,00 \pm 1,48$ mm². After cutting the vagus nerve distal site of stimulation focus of initiation of excitation, increased by vagal-cardiac synchronization, re-projected at only one point. In the absence of vagal-cardiac synchronization during the "bursts" stimulation of the nerve center of the initiation of excitation has not been increased. In all cases, when the frequency of the "bursts" nerve stimulation exceeded the maximum limit or below the lower boundary has been synchronized (vagal-cardiac synchronism was absent), to map the isochronous center of the initiation of excitation manifested by only one point instead of an area (a group of adjacent pixels) (16).

In chronic experiments on dogs was observed dynamics bioelectrical activity in the sinoatrial region for 4 days. Immediately after the implantation of the electrodes of the matrix in the anesthetized animal activity sino-atrial region was recorded at one point. At the end of the first day after surgery at the exit of the animal from anesthesia area chamber of initiation of excitation was 8.6 ± 0.3 mm² on the second day - 17.7 ± 1.0 mm², on the third day of 22.7 ± 1.4 mm², on the fourth - 28.7 ± 1.4 mm². The introduction of atropine sulfate (2.5 mg / kg) on the fourth day after the operation against the background of a broad focus of the initiation of excitation leads to the localization of the source at only one point.

Mapping of the sino-atrial node to diagnose driving rhythm of becoming a man holds a catheter with six electrodes. A catheter was placed in the epicardium surface of the site and recorded the "cross section" of the source area of the initiation of excitation. Figure 3 shows the mapping of the sino-atrial node in humans who had undergone cardiac surgery. Directly during the operation area early depolarization is limited to a single focus (fragment A). A day early depolarization region covered an area between two electrodes (fragment B), and two days later in the morning - 3 electrodes (fragment B) during the day - 5 electrodes (fragment C) and in the

evening - 6 electrodes (fragment D). These facts demonstrate the inclusion of brain (central) level rhythmogenesis hierarchical system in the rehabilitation of patients in the postoperative period. The analysis of these facts led to the conclusion that the area of the initiation of excitation in the sino-atrial region of the heart is a marker of heart reproduction the signals along the vagus nerves, as in artificial stimulation and in vivo. The latter allows to evaluate the nature of rhythm in the mapping of sino-atrial region. Increasing the initiation area of the excitation points enable in heart rhythm coming from the vagus nerves, the lack of increase in initiation of excitation is evidence that the driving rhythm of the moment by sino-atrial node of the heart.

The fact that the fundamental difference of the size of the initiation of excitation mapping in the intact organism and in the body, located in anesthesia ascertained earlier (17,18). However, he did not interpreted. In our studies, this phenomenon has been explained and allowed to use the dynamics of the area as a marker for the initiation of the heart enabling a central (brain) rhythm.

4. Gradient of rhythmogenesis levels in intact body.

It is logical to assume that the heart rhythm when enabling the signals along the vagus nerves, the sino-atrial node automaticity is suppressed and subordinated to a higher level of machine, i.e. shows the principle of the gradient of automaticity, the established Gaskell (19). Fact checking the suppression of automaticity of the sino-atrial node in heart rhythm when playing the signals in vivo via the vagus nerves in chronic experiments performed with one-stage bilateral blockade of the excitation of the vagus nerves in dogs (Fig. 4).

In 13 dogs under general anesthesia was performed prior operation: both the vagus nerve strengthened platinum electrodes connected to the anode of direct current. The cathode is located

under the skin in the neck. Points for connections for direct current are displayed on the dorsal surface of the animal's neck.

Through the femoral vein with the probe led up to six electrodes of the sinus node of the heart for recording electrograms, which allowed to evaluate the cross section of the initial focus of excitation in the sino-atrial region of the heart. Bilateral blockade of the vagus nerves was carried out on the field in the anode direct current during anesthesia and 3-5 days after surgery. The action of direct current on excitable tissue, in accordance with the law Pfluger (20), in the anode, which is fixed on the nerve, at the time of closing the circuit and the current flow-conduction block develops.

Logic and experimental techniques have made it possible for the same dog, but in its various functional states perform the same effect - the blockade of the excitation of the vagus nerves. In the first case the blockade was performed in an animal that is in anesthesia, in the second - after the surgery in 3-5 days (in an intact animal that is in adequate relationship with the environment). It is crucial that in both states, the estimate focal initiation of excitation in the sino-atrial node, which allows to determine whether the heart rhythm reproduced, coming to him from the brain of the vagus nerves, or primary source of rhythm generation was the sino-atrial node (see Section 3).

The blockade of excitation of both vagus nerves in the anesthetized animals resulted in increased heart from 102.4 ± 3.2 to 123.8 ± 4.4 min, while at the same dogs after 3-5 days in the waking state blockade caused a brief cardiac arrest (Fig. 5).

Duration of the stop was 2.0 ± 0.2 s and depended on the cross section area of the source of excitation in the initiation site at the time of the siege. In dogs with a greater cross-sectional

area in a developing chamber blockade stop was prolonged. The correlation coefficient between the cross section area scale and duration of pause was 0.95.

Analysis of short-term nature of cardiac arrest at blockade of conduction in the vagus nerves has shown that it is a pre-automatic pause. Prior to the initiation of excitation blockade hearth covered several points, indicating that the heart of the central rhythm enabling, and when resuming after stopping heartbeat hearth initiation was localized only at one point, indicating that the generation of excitation in the sino-atrial node (Fig. 5).

The data presented confirm the fact that reproduction in the wild heart rhythm signals coming to it from the central nervous system via the vagus nerves. They show that the sino-atrial node in the intact organism serves as a latent pacemaker. The ability to perform the role of the sino-atrial node latency driver is shown in electrophysiological studies (21). When imposing a heart beat rhythm through electrical stimulation, it learns the rhythm and reduced in this rhythm. Cessation of electrical stimulation is always accompanied by a brief cessation of rhythmic activity of the site - develops pre-automatic pause. Recovery of activity after a pause, sino-atrial node demonstrates the manifestation of his latent properties of the pacemaker.

Thus, the fact that the possibility of the sino-atrial node pacemaker function of the latent and identifying the time and conditions necessary for its transition to its own machine, got a decent confirmation in clinical electrophysiology. This phenomenon is used to determine functional recovery of the sino-atrial node by trans-esophageal electrical stimulation. In our study law, as expressed in the sino-atrial node of the manifestation of the latent properties of the pacemaker was demonstrated in real conditions of formation of cardiac rhythm in the body. In connection with the facts presented the concept of gradient automaticity "left" outside the heart and extends to the whole system of rhythmogenesis in the body. It was found that the

dominant - subordinating to itself and maps the sino-atrial node to the role of the latent pacemaker - may be the source of the currently more frequent rhythm, whether brain levels of rhythmogenesis or artificial pacemaker in the form of electro stimulation. In both cases, the immediate cessation of income to the sino-atrial node of this rhythm results in transient cardiac arrest, which is pre-automatic pause (21). It is important to note that the duration of the pre-automatic pause more, than more pronounced role of brain levels of a hierarchical system of rhythmogenesis in the formation of heart rate (Fig. 5). As shown in Section 3, the rate of incorporation of a cerebral level rhythmogenesis hierarchical system shows an area of focus of the initiation of excitation in the sino-atrial node - the larger the area, the significant role of brain-level systems.

Consequently, the more pronounced suppression of the sino-atrial node higher in the hierarchical system rhythmogenesis rhythm generator, the longer the recovery function of the sino-atrial node rythmogenical who carried out under these conditions, the latent function of a pacemaker. Consequently, the area of focus in the initiation site reflects the degree of suppression of automaticity in it, and characterizes the cerebral dominant level of rhythmogenesis hierarchical system.

Thus, the presented system of scientific facts, including:

- 1. reproduction by the heart rate signals arising in the vagus nerves during stimulation of their groups ("bursts") pulse;
- 2. reproduction of the natural heart rate signals in efferent vagus nerves in the cardiorespiratory synchronism;
- 3. fundamentally different-sized zones of initiation of excitation in the field when playing sino-atrial heart rhythm signals received from the brain (the area projected by cross section area),

and the generation of excitation directly into the sino-atrial node of the heart (area projected by point);

4. sino-atrial node implementation functions of the latent pacemaker.

Totality of the evidence suggests that in vivo activity of the organism by the formation rate of multilevel hierarchical system, including brain and heart.

The hierarchical principle of organization of rhythmic functions in the body is one of the fundamental principles of life. If the organization of circadian rhythms, the rhythms of breath and other mechanisms of the principle of hierarchy is no doubt that the heart rhythmogenesis hierarchical principle, including the structure of the brain, is shown for the first time. The reason is that, in the heart of a powerful level of rhythmogenesis, historically attracted the attention of researchers and has become subject to multilateral examination. Investigation of heart rhythmogenesis integrated system require development of specific methodological approaches.

Their implementation has revealed hidden before the attention of naturalists laws rhythmogenesis heart. The facts presented on the integration of the two hierarchical levels of rhythmogenesis make clear reliability and functional perfection of cardiac rhythm generation in the intact organism (1). Intracardiac generator is a life supporting factor. He maintains the pumping function of the heart when the central nervous system is in a deep state of inhibition. The central generator provides the adaptive responses of the heart in vivo. However, the weight of the methodology of scientific research goes beyond the establishment of mechanisms for organizing a system of life and raises the question of interpolation of the path of knowledge to other systems of the body and the body itself, which integrates all of its components.

The idea of changing the strategy of scientific research in this direction overdue. It is suggested by the natural evolution of cognitive processes. A key role in physiological research strategy is to study the nature of regulation of individual processes to ensure the activities of the intact organism as a whole.

Figure legends:

- Fig. 1. Activity dynamics of interneuron of the vagal complex in the medulla oblongata depending on the respiration phase.
- 1 electromyogram of the diaphragm, 2 electrocardiogram, 3 impulse activity of the neuron.
- Fig. 2. Partial recording of cardiorespiratory synchronism.

Vertical lines: long – correspond to the frequency of stimulator's signals on the display and correspond to the frequency of arbitrary breathing during the test, short – correspond to the heart rhythm. The fact of synchronization is established based on the equality of intervals between long and short lines.

- Fig. 3. Dynamics of early depolarization focus in the sinoatrial node in humans (explanation given in the text).
- A during the surgery (under anesthesia); B day after surgery; C second day (morning); D second day (afternoon); E second day (evening). Scheme: AD right atrium; VCI inferior vena cava; VCS superior vena cava; VD right ventricle.
- Fig. 4. Scheme of the experiment with one-step bilateral blockade of innervation conduction in vagus nerves in dogs in a chronic test.

A⁺ and K⁻: constant current anode and cathode, respectively.

- Fig. 5. Pre-automatic pause in a conscious dog during one-step blockade of innervation conduction via vagus nerves.
- 1 synchronous electrocardiogram recording, 2 electrograms of the right atrium from the endocardial probe, 3 contours of the sinus node region with the localization of innervation initiation focus registered with a 6-electrode probe.

References and Notes:

- 1. Pokrovskii V.M. Formirovanie ritma serdtsa v organizme cheloveka i zhivotnikh. //Krasnodar. Kuban-Kniga. 2007. P. 143.
- 2. Pokrovskii V. Alternative View on the Mechanism of Cardiac Rhythmogenesis. Heart, Lung Circ., 2003. V. 12, № 1, P. 18-24;
- 3. Pokrovskii V. Integration of the Heart Rhythmogenesis Levels: Heart Rhythm Generator in the Brain. Journal of the Methodist DeBakey Heart Center, 2006. V. 2, № 2, P. 19-23;
- 4. Pokrovskii V. M., Abushkevich V. G., Gurbich D. V., Klykova M. S., Nechepurenko A. A. Interaction of Brain and Intracardiac Levels of Rhythmogenesis Hierarchical System at Heart Rhythm Formation Journal of Integrative Neuroscience, V. 7, No. 4 (2008). P. 457- 462.
- 5. Zubkov A.A. Usvoenie serdtsem ritma razdrazheniya bluzhdayuschikh nervov // Byul. eksperim. biologii i medicini. 1936. V. 1 P. 73-74.
- 6. Levy M.N., Martin P.J., Iano T., Zieske H. Paradoxical effect of vagus nerve stimulation on heart rate in dogs. Circ. Res. 1969. V. 25, N 3. P. 303 314.
- 7. Reid J.V.O. The cardiac pacemaker: effects of regularly spaced nervous input // Reid Amer. Heart. J. 1969. V. 78, N1. P. 58 64.
- 8. Suga H. Periodic variation of heart rate caused by repetitive electric stimulation of cardiac vagus nerve / H. Suga, M. Oshima // J. Physiol. Soc. 1969. V. 31, N 1. P. 33-34.
- 9. Iaizzo Paul A. (editor). Handbook of Cardiac Anatomy, Physiology and Devices. Springer 2009.

- 10. Koepchen H.P. Respiratory and cardiovascular "centres" functional entirety or separate structures // Central neuron environment and the control systems of breathing and circulation.-Berlin: Springer, 1983. P. 221-237.
- 11. Pokrovskii V.M., Bobrova M.A. Impulsnaya aktivnost neyronov prodolgovatogo mozga, svyazannaya s serdechnim i dykhatelnim ritmami. Fisiol. zhurn. (Ukr.) − 1986. − V. 32, №1. − P. 98 -102.
- 12. Pokrovskii V.M. Serdechno-dykhatelniy sinkhronizm v otsenke regulyatorno-adaptivnikh vozmozhnostey organizma. Krasnodar. «Kuban-Kniga», 2010. P. 244.
- 13. Pokrovskii V.M., Potyagaylo E.G., Abushkevich V.G., Pokhotko A.G. Serdechnodykhatelniy sinkhronizm: viyavlenie u cheloveka, zavisimost ot svoystv nervnoy sistemi i funktionalnikh sostoyaniy organizma. Uspekhi fiziolog. nauk. 2003. V.34, № 3. P. 68-77.
- 14. Pokrovskii V.M. et al. Sinkhronizatsiya serdechnikh sokrascheniy i dikhaniya pri termoregulyacionnom polipnoe u sobak. DAN SSSR. -1986. V. 287, № 2. P. 479 481.
- 15. Pokrovskii V.M., Ponomarev V.V., Artyushkov V.V., Fomina E.V., Gritsenko S.F., Polischuk S.V. Sistema dlya opredeleniya serdechno-dykhatelnogo synkhronizma u cheloveka // Patent № 86860 ot 20 sentyabrya 2009.
- 16. Pokrovskii V.M., Abushkevich V.G., Fedunova L.V. Elektrofiziologicheskiy marker upravlyaemoy bradikardii. DAN. -1996. V. 349, № 3. P. 418 420.
- 17. Hariman R.J., Krongrad E., Boxer R.A., Bowman F.O., Malm J.R., Hoffman B.F. Methods for recording electrograms of the sinoatrial node during cardiac surgery in man. Circulation. 1980. V.6, N 5. P.1023-1029.

- 18. Hoffman B.F., Naylor R.E. Electrical activity from the sinus node region in conscious dogs. Circ Res. 1980 Nov; V. 47 N5 P. 775-791.
- 19. Gaskell, W.H. On the innervation of the heart, with especial reference to the heart of the tortoise, J Physiol V. 4:43-127, 1883.
- 20. Pflüger E.W. Untersuchungen über die Physiologie des Electrotonus. Berlin: A. Hirschwald, 1859.
- 21. Fogoros R. N. Electrophysiologic Testing // Blackwell Publishing. Pittsburgh, 2006. P. 64.









