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Sports Vagotonia as a Result of Increased Synthesis of Non-Neuronal Acetylcholine by Cardiomyocytes

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Abstract

The author's concept is presented, according to which sports vagotonia is a consequence of increased synthesis of non-neuronal acetylcholine (NN-ACh) by cardiomyocytes. It is based on the idea that many cells of the body are capable of producing NN-ACh, among them are cardiomyocytes of the ventricles of the heart, the idea of which, since 2009, has been substantiated by the works of Yoshihiko Kakinuma and other authors. The review provides information about the ability of cardiomyocytes to produce NN-ACh and about its cardioprotective (anti-apoptic) function. In 2023, we proposed a hypothesis about the formation of an anti-apoptic system in athletes training for endurance (for example, in ski racers), the main component of which is the ACh of the vagus terminals, as well as NN-ACh of cardiomyocytes. The paper provides a number of indirect evidence of our hypothesis using the example of a study of heart rate variability (HRV) of elite skiers-riders of the Tatarstan team consisting of 6 masters of sports (MS) and 2 master of sports of international class MSIC), including skier K.D. (master of sports; the first author of the article), which was conducted repeatedly throughout 2019-2020 y.y..Clinostatic 5-minute cardiointervalography was performed using the VNS-Micro medical diagnostic system (Neurosoft). The authors conclude that the values of spectral and temporal HRV- indicators of elite skiers can serve as indicators of intensive synthesis of NN-ACh by cardiomyocytes. Data on these values are proposed to be used in the diagnosis of heart failure and its treatment.

Keywords: Ski racers; Heart rate variability; Periods of the training macrocycle; Non-neuronal acetylcholine; Antiapoptic system

Abbreviations: HRV: Heart Rate Variability; ANS: Autonomic Nervous System; NRSF: Neuron-Restrictive Silencer Factor; NN-Ach: Non-neuronal Acetylcholine; CIG: Cardiointervalography; AR: Adrenoreceptors; ROS: Ractive Oxygen Species; ChAT: Choline Acetyl Transferase; ROS: Reactive Oxygen Species; CHF: Chronic Heart Failure; SD: Sympathetic Department; PD: Parasympathetic Division

Introduction

Common points the phenomenon of sports vagotonia is known to be characteristic of elite skiers specializing mainly in distance and marathon distances, which is confirmed by a huge number of studies of heart rate variability (HRV) [1-14]. At the same time, most authors claim that sports vagotonia is due to an increased influence of the parasympathetic division of the autonomic nervous system (ANS) on the activity of the heart. However, according to A. D'Souza. et al. [2], which was formed on the basis of the results of experiments on the heart of small animals, sports vagotonia develops as a result of changes in the work of the pacemaker (heart rhythm driver), i.e. due to changes in the activity of ion channels, including channels that generate a "wonderful" (fanny) sodium current, which is the basis of heart automation [15,16]. This leads to a slowdown in the pacemaker's own rhythm, i.e., to an increase in the RR interval of the ECG and, as a result, to an increase in HRV, which is usually interpreted as evidence of an increase in the tone of the parasympathetic system. According to A. D'Souza et al. [2], the expression of transcription factor Tbx3 decreases inside the sinus node of animals during training, but the expression of such a transcription factor as NRSF (neuron-restrictive silencer factor) increases, as well as activation of micro-RNA, in particular, miRNA-1.However, according to J. Coote, M. White [1], in humans and large animals (dogs, pigs, horses), the resting heart rate is lower than the frequency of

generation of the pacemaker action potential (PD), and this is due to the influence of acetylcholine (ACh) of the vagal terminals, and therefore in healthy young people atropine blocking, as is known, the effects of vagus, increases heart rate [1]. This does not apply to such small animals as guinea pigs, rats and mice, which have a high sympathetic tone, and the resting heart rate reaches 300-700 beats per minute, while the pacemaker generates only 170-500 beats per minute [2,17]. Therefore, according to J Coote, M White [1], exercise-induced bradycardia in small animals probably involves two mechanisms: 1) an increase in the activity of the parasympathetic ANS and 2) a decrease in the natural frequency of pacemaker cells, but in humans, the main cause of sports vagotonia is an increase in the activity of the parasympathetic division of ANS.

Sharing the view of J. Coote, M. White [1], we assumed [9-14] that athletic bradycardia in ski racers (as in other athletes training for endurance) is the result of an increased effect of Ach on the heart, which is released not only from the vagus terminals, but also from cardiomyocytes of the ventricles of the heart capable of synthesizing non-neuronal ACh (NN-ACh). Therefore, the values of HRV- indicators of elite ski racers are markers of a high level NN-Ach, which is produced by cardiomyocytes.

This article is devoted to the proof of these two assumptions. Briefly, our arguments boil down to the following

a) Many cells in the body produce NN-ACh, which contributes to the realization of their basic functions.

b) Cardiomyocytes of the ventricles of the heart are also able to synthesize NN-ACh, which replenishes the reserves of ACh in the vagus terminals and together with it performs an anti-apoptic, or cardioprotective, function.

c) The cardioprotective function of neuronal Ach and NN-ACh of cardiomyocytes is important for athletes developing endurance, including ski racers, since during prolonged and intensive aerobic and anaerobic training, as well as during competitions, myocardial damage ("sports injury") occurs, requiring repair.

d) Insufficient production ACh by vagal neurone and NN-ACh by cardiomyocytes in humans can lead to the formation of heart failure, and therefore, in its treatment, promising methods that increase the production of neuronal Ach and NN-ACh of cardiomyocytes.

e) Sports vagotonia is typical only for athletes of those sports that require high performance and endurance. The success of athletes in these sports correlates with the severity of their sports vagotonia, and great athletic success is probably achieved only by those athletes whose genome provides the ability to synthesize NN-ACh, metabolize it at a lower rate, and which provides high activation efficiency of M- and H-cholinergic receptors (ChR) of the heart, and in whom the level of the endogenous blocker of M-ChR (EBMChR) has been reduced.

f) In elite ski racers, the values of spectral and temporal HRV indicators, which indicate vagotony, reach maximum values in the preparatory period, decrease slightly in the competitive and transitional periods, but even in these periods they remain much higher than in novice skiers, which indirectly indicates a high rate of synthesis of NN-ACh. which they have it. At the same time, for elite skiers, the value of HRV, which indicate vagotony, directly depends on the volume (duration) of loads performed in aerobic mode. Indirectly, this confirms the literature data that the intensity of NN-ACh- synthesis increases with the activation of beta1–AR, with the activation of M-ChR under the influence of vagal Ach, as well as under the influence of short-term preconditioning anaerobic exercises.

g) Although there is no direct evidence yet that sports vagotonia is a consequence of increased synthesis of NN-Ach in the heart, but a priori it can be assumed that the values of spectral and temporal HRV- indicators recorded in elite skiers during clinostatic cardiointervalography (CIG) in the preparatory period, reflect a high level of production of NN-ACh by cardiomyocytes. and for this reason, they can be used in the diagnosis of heart failure in patients and in evaluating the effectiveness of its treatment. Let's look at these provisions in more detail.

Various Cells of the Body as Producers of NN-ACh

Many cells of the body produce HH-ACh, which contributes to the realization of their basic functions, which is reflected in detail in a number of review articles [18-21]. In particular, in the human and animal body, the NN-ACh system is detected in various components of the skin (keratinocytes, hair, nails, glands), the respiratory system (respiratory epithelium, fibroblasts, ciliary cells, glands), in the epithelium and glands of the digestive tract, in the alpha -cells of the pancreatic islets, in the epithelium renal tubules, collecting tubes, in the epithelium and smooth muscles of the urinary tract, in the endothelium of blood vessels, in osteoblasts, tenocytes and chondrocytes, in immune cells (T- and B-lymphocytes, macrophages), in the components of the female reproductive system (placenta, vaginal epithelium, ovarian granulosa cells, oviduct epithelium) and the male reproductive system (testicular epithelium, spermatozoa, prostate cells). In all non-neuronal (NN-) cells, five variants of M-cholinergic receptors (M-ChR) and a huge number of varieties of N- ChR are expressed. At the same time, many NN cells are able to synthesize NN-ACh, judging by the presence of choline acetyltransferase (ChAT) or carnitine acetyltransferase (CarAT) in them, they are able to store NN-ACh in vesicles, judging by the presence of the vesicular acetylcholine transporter (VAChT), to secrete NN-Ach outside the cell, including with the participation of VAChT or transporters such as OST1 and OST2 as well as to obtain choline from the medium for the synthesis of NN-Ach , judging by the presence of a high-

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affinity choline-1 transporter (CHT1) or choline-transporter-like proteins (CTL1-5) [18-21]. Almost all NN-cells express enzymes that destroy HH-ACh, in particular, acetylcholinesterase (AChE) and/or butyrylcholinesterase [18-21]. It has been shown that NN-Ach acts in an autocrine and paracrine manner, activating M-ChR or N- ChR present on neighboring effector cells [18-21]. In the normal state, NN-Ach plays an important role in many processes, including cell growth, adhesion, migration and differentiation [18-21].

According to the literature [18,19], dysregulation of the NN-ACh system is involved in the pathogenesis of diseases such as atopic dermatitis, vitiligo, psoriasis, pemphigus, skin cancer, bronchial asthma, chronic obstructive pulmonary disease, cystic fibrosis of the lungs and lung cancer, ulcerative colitis, Crohn's disease, pancreatitis, stomach cancer, acute kidney injury in sepsis, hyperactive bladder syndrome, obstruction of the exit from the bladder, rheumatoid arthritis, atherosclerosis, hypertension, autoimmune diseases, immunodeficiency conditions, premature birth, preeclampsia, male infertility. All this points to the important role of NN-ACh in the human and animal body.

Cardiomyocytes of the Ventricles of the Heart as Producers of NN-ACh

The heart, like many other organs, is innervated by sympathetic (adrenergic) and parasympathetic fibers (n. Vagus). At the same time, sympathetic fibers innervate all regions of the heart, including the rhythm driver (sinoatrial node) and atrioventricular node, as well as the left and right ventricles of the heart (LV, RV), while the vagus abundantly innervates the rhythm driver (sinoatrial node), atrioventricular node, but extremely weakly innervates LV and RV [20,22-24]. Proponents of the idea of the presence of an HH-ACh system in the heart attach key importance to this fact and believe that single vagal fibers in the ventricles of the heart cannot cope with the damage that causes the ventricles of the heart, especially LV, excessive activation of beta1- adrenoreceptors (AR) of the heart, hypoxia, reactive oxygen species (ROS) and other factors, but cardiomyocytes of the ventricles of the heart perform a cardioprotective function, producing NN-ACh, which, in conjunction with the ACh of the vagal terminals, helps to preserve the viability of the myocardium even with excessively intensive heart work [20-35].

It has been shown that ventricular cardiomyocytes of adult mice, unlike cardiomyocytes of new born mice [20,27], are able to synthesize NN-ACh, secrete it (with the participation of VAChT, i.e. vesicular transporter ACh) outside the cell, where, interacting with M-ChR or N-ChR, it exerts autocrine or paracrine cardioprotective effects, including enhancing neuronal cholinergic transmission [20]. Cardiomyocytes of the ventricles of the heart of adult mice have been shown to express choline acetyl transferase (ChAT), choline transporter (CHT1), vesicular transporter ACh (VAChT), and acetylcholinesterase (AChE) [20,22, 25,27,28,29,32,33]. In other words, cardiomyocytes of LV and RV express the same set of enzymes, which is used in the synthesis of neuronal ACh. It is important that the same NN-ACh synthesis system is typical not only for rodent cardiomyocytes, but also for cardiomyocytes of adult human [24,28,32].

It has been shown that the synthesis of NN-Ach in cardiomyocytes increases with activation of M-ChR under the influence of Ach of vagal terminals in the heart (due to increased expression of choline acetyltransferase (ChAT) [20,25], Oxytocin, released from oxytocinergic neurons of the hypothalamus, increases the release of ACh from vagal terminals, and thereby increases the synthesis of NN-Ach by cardiomyocytes [36]. Agonists of beta1-AR [22,28] and ischemic preconditioning also increase the synthesis of NN-ACh [31,37].

The Functions of the NN-Ach of Cardiomyocytes of the Ventricles

The NN-ACh of cardiomyocytes performs important functions. It exhibits an antioxidant effect realized upon activation of M2-ChR [38] and/or M3- ChR [38-40], an anti-inflammatory effect that occurs upon activation of M- ChR and alpha-N-ChR and manifests itself in inhibition of cytokine production [20,21,24,27,41,42]. By increasing the production of nitric oxide (NO), NN-ACh exhibits angiogenic and vasorelaxing effects [22,23,43], while preventing impaired myocardial conduction, since NO increases the expression of connexin 43 [33,44]. In addition, NN-ACh, like vagal ACh, reduces oxygen consumption [20,25,26], increases the expression of glucose transporters (GLUT1 and GLUT4) and thereby increases the use of glucose as an energy substrate [20,23,33]. It has been shown that NN-ACh of cardiomyocytes contributes to the function of ACh secreted by the vagus terminals, as it increases the synthesis of ACh in the parasympathetic neurons of the vagus, replenishing its reserves, and enhances the release of ACh from the synapse [20,22,28]. At the same time, ACh and NN-Ach reduce the release of norepinephrine (NE) from sympathetic terminals of the heart (due to activation of presynaptic M2-ChR [24,28,45], and also reduce the activation efficiency of beta1-AR by increasing NO synthesis [46], reducing the intensity Ca current of L-type [46] and by increasing the intensity of potassium currents [46]. All this reduces the damaging effect that occurs when beta1-AR is activated [20,22,24,26,28,29,31,33]. Collectively, all of the above functions lead to the fact that NN-Ach together with synaptic ACh under conditions of excessive stress exhibits cardioprotective effect [20-23,25,27-29,33,35,39,40,43,47-49] Due to such a wide range of action, synaptic ACh and NN-Ach of heart diseases prevent the development of myocardial hypertrophy and heart failure [22-24,29,33,35,50,51], including angiotensin II-induced [50], or intensive activation of beta1-AR [24,51], It also increases survival after myocardial infarction or acute ischemic/reperfusion injury [23] and probably counteracts the formation of hypertension,

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daytime sleepiness and obstructive sleep apnea syndrome in humans [34].

It has been shown that the cardioprotective effect of ACh and NN-ACh, which is realized when M2-ChR, M3- ChR or N-ChR are activated [32,39,50], is based on the ability of ACh and NN-ACh to activate signalling pathways such as the «phospholipase C (PLC)/IP3 pathway» [52], the pathway "PI3K/Akt/HIF-1alpha/VEGF" [23,43], the pathway "PI3K/Akt/HIF-1alpha/GLUT-4" [35]. Also, as Kakinuma Y [20]. Points out, the cardioprotective effect of ACh and NN-ACh is based on an increase in the expression and activity of the transcription factor Nrf-2, which increases the expression of more than 500 genes, including genes of antioxidant enzymes and antioxidants. It was found that the cardioprotective effect of ACh and NN-ACh is based on the ability to increase the expression of cerebral neurotrophic factor (BDNF) [39], inhibit the expression of miRNA-376b-5p [39] and angiotensin II receptor type AT1 [50], as well as reduce the production of atrial natriuretic peptide [50]. It is important to note that according to Kakinuma Y [20], 80% of the vagal fibers are afferent and only 20% are efferent. With an increase in the level of HH-ACh production, the synthesis of nitric oxide (NO) increases, which activates the afferent fibers of the vagus and thereby increases the activity of central nervous system neurons. In mice such afferentation has been shown to have an anti-stress effect, and mice become more calm and resistant to stressors.

Myocardial Damage in Endurance Athletes and Cardioprotective (anti-apoptic) Function of ACh and HH-Ach of Cardiomyocytes

It is known that when beta1-AR is activated (due to a high level of ROS production and due to overload with Ca^{2+} ions), myocardial damage occurs, which leads to cardiomyocyte death and cardio fibrosis [20, 23,26,51,53-55]. In addition, damage to cardiomyocytes, as is well known, occurs under the influence of myocardial hypoxia, or ischemia/reperfusion [20,23-25,37,56,57] and in myocardial inflammation [20,21,27,28,41,42]. Myocardial damage is especially pronounced during intensive and prolonged physical work [37,57-59,60-66], for example, in cross–country skiers [58,61,66], or in athletes of other sports requiring endurance, in particular, in marathon runners [62,64] and stayer athletes [62,65]. So, it is shown that after a long run (at 25, 50, 80 or 160 km) the function of the right (RV|) and left (LV) ventricles temporarily decreases, and this decrease is higher the higher the running speed [62]. According to a number of authors, athletes who train for endurance perform training and competitive loads that exceed 15-20 times the usual recommendations for physical activity [61,67]. At the same time, their sizes of LV and RV increase by 10-20%, and mass of LV increases significantly, and also levels of biomarkers of cardiac damage increase, including levels of troponins and natriuretic peptide B-type [61,67], and dysfunction of LV and RV occurs within 24-48 hours after competition [61,67]. It is noted that prolonged endurance training can be associated with such severe complications as atrial fibrillation, arrhythmogenic cardiomyopathy of RV and hypertrophic cardiomyopathy [57-61,65]. They often develop myocardial fibrosis [61,63] and coronary heart disease [61]. But despite this, elite athletes who train for endurance have an increased life expectancy compared to the general population [61].

In animal experiments it has been convincingly shown that the synaptic ACh and NN-ACh of cardiomyocytes are able to resist damage to cardiomyocytes that occurs during physical exertion, i.e. they exhibit a cardioprotective (anti-apoptic) effect. Thus, in transgenic mice (ChAT tg mice), in which gene of the choline acetyltransferase (ChAT) is overexpressed, it was shown [20,23], that such mice tolerate physical training better, have a higher survival rate after an experimental heart attack, they have less pronounced myocardial hypertrophy and fibrosis after a heart attack, and they have increased resistance to ischemia/reperfusion [20,23,24,56]. At the same time, mice with choline acetyltransferase (ChAT) deficiency had dysfunction of ventricular cardiomyocytes [32], had low resistance to hypoxia [26], and their cardiomyocytes, when isolated, generated higher levels of ROS in response to beta1-AR activation by norepinephrine, were more likely to undergo apoptosis [26] and had reduced expression connexin 43, necessary for intercellular communication [26]. Mice with a knockdown gene of the vesicular transporter ACh (VAChT) had dysfunction of ventricular cardiomyocytes, decreased expression of a number of genes [22,32] and an increased level of cardiac fibrosis after exposure to angiotensin II [32]. Mice with reduced expression of the choline transporter (CHT1) exhibited ventricular dysfunction [68]. When modelling pathological processes in mice (myocardial infarction, heart failure), it was shown that the expression of the vesicular transporter ACh (VAChT) in the ventricles of the heart compensatorily increases [32,53,69] and the production of NN-Ach increases [29,32,48,69,70] So, the literature data prove that the NN-ACh of the heart plays a key role in the conditions of norm and pathology [32].

Heart Failure as a Consequence of a Decrease in the Cardioprotective Function of Synaptic Ach and NN-Ach Cardiomyocytes in Humans. New Principles of Treatment of Heart Failure

In recent years heart failure has been considered as a consequence of a deficiency of vagal terminals ACh and NN-Ach of cardiomyocytes [22,24,30,32,33,36,47,48,53,71-75]. Although beta-AR blockers in combination with e inhibitors of angiotensin converting enzym and blockers of angiotensin receptor are still used as first-line therapy for heart failure, this turned out to be insufficient [36,76]. Therefore, attempts are being made to create clinically acceptable and safe methods to increase the activity of the heart's HH-ACh. Among them are the use inhibitors of AChE, including donepezil [25,32,34,43,77] and pyridostigmine [32,70],

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vagal stimulation [20,21,32,36,44,47-49,53,78], which is probably applicable to humans [36,47,49,78], stimulation of oxytocinergic neurons of the hypothalamus in patients with heart failure [36] or intranasal administration of oxytocin [36], oral administration of choline [32,73], renal denervation [79], as well as the use of physical training [28,53,71,72,74,75,80]. The same methods can probably be used to prevent the development of heart failure in diabetes mellitus-1 [35], as well as for the treatment of hypertension [34] and obstructive sleep apnea syndrome [34,36].

Sports Vagotonia as a Result of the Formation of the NN-Ach Synthesis System in Cardiomyocytes

In our works [9-14] it is shown that vagotonia is typical for athletes of those sports that require high performance and endurance, for example, for ski racers, especially for elite skiers (MS, MSMC, winners of the Olympic Games, world and continental championships). At the same time, success in cross-country skiing correlates with an increase in the degree of sports vagotonia, and overtraining correlates with a temporary decrease of vagotonia. This is confirmed by numerous works by other authors [7,57-66] studying ski racers [58,61,66], marathon runners [62,64], stayer athletes [62,65]. This is due to the fact that endurance athletes perform a huge amount of physical work during training and competitions [61,67].

In 2023, we assumed that athletes who train for endurance, gradually (i.e., as their athletic skills grow, an anti-apoptic (cardioprotective) system is formed, the main component of which is the synaptic ACh and HH-ACh of the heart, and one of the indicators of the formation of the HH-ACh system of the heart is vagotonia, i.e. a significant increase in the effects of the parasympathetic system on the heart, judging by the indicators of heart rate variability [9-13]. In other words, we shared the opinion of the proponents of the concept of the nature of sports vagotonia as a result of endurance training, adding to this concept the idea that the formation of the heart NN-ACh system plays a leading role in this process. Thus, our view does not coincide with the opinion of D'Souza A. et al [2] according to which, as already noted above, sports vagotonia is a consequence of a change in the mechanism underlying the heart pacemaker automation, including due to a change in the activity of the sodium channel, generating the so-called "wonderful" (fanny) incoming current. Our assumption is based on

a) the concept of the existence of the NN-Ch system in the heart of adult rodents and humans, as discussed in detail above.

b) based on the literature data that the complete absence or insufficient development of the heart's HH-ACh system leads to the formation of heart failure.

c) based on literature data on myocardial damage during prolonged endurance training and intense activity of an athlete during competitive races over long distances (20, 50, 70 km).

d) based on literature data on the effectiveness of physical activity in patients with heart failure [71,72,74,80].

Given the importance of these data, we note that A. Coats et al. [80], examining 17 elderly men with moderate to severe chronic heart failure (CHF), showed that training for 8 weeks increases the ejection fraction of LV, reduces systemic vascular resistance, and, judging by HRV indicators such as the value of the RR interval and the power of HF- and LF- waves, increases patients have a parasympathetic effect on the heart. R Fraga et al. [71], examining 27 patients with CHF, in whom the LV ejection fraction did not exceed 35%, and the maximum oxygen consumption (MPC) did not exceed 20 ml/kg/min, showed that 60-minute training on a cycloergometer, conducted once a week, increases the level of MPC. S. Erbs et al. [72], examining 37 patients with CHF, in whom the LV ejection fraction did not exceed 24%, showed that 12-week training increases MPC, LV ejection fraction and skeletal muscle capillary density. K. Haack, I. Zucker [74], in a review article, it is noted that physical exercise in patients with CHF reduces the sympathetic effect on the heart, reduces the production of angiotensin II, reduces the expression of its receptors, reduces oxidative stress, increases the production of nitric oxide and increases survival.

It should be noted that animal experiments also indirectly confirm the formation of an anti-apoptic (cardioprotective) system during physical training [53,75]. Thus, Y Zhang et al. [53] in experiments on dogs that were subjected to high-frequency electrical stimulation of the ventricles for 8 weeks (at 220 beats per minute during the first 4 weeks for the development of heart failure and for another 4 weeks at a speed of 180 beats per minute to maintain heart failure), it was shown that vagal stimulation has a positive effect, judging by to improve HRV indicators and restore the sensitivity of the baroreflex. M Ichige et al [75] in experiments on rats in which heart failure was created by ligation of the coronary arteries, they showed, that after 6 weeks of treadmill training, the expression and activity of choline acetyltransferase (ChAT) in parasympathetic preganglionic neurons were restored, and in general, the tone of the parasympathetic department of the ANS was restored and exercise tolerance increased.

Based on the assumption that athletes who train for endurance gradually develop an anti-apoptic (cardioprotective) system, the main component of which is ACh, including heart NNACh, we assume that in those sports that require high endurance (ski racing, marathon, stayer running) great success is probably achieved only by those athletes, whose genome provides the ability to synthesize of NN-ACh and degrade it at a lower rate, It also provides high efficiency of M2-ChR and M3- ChR activation of the heart. This coincides with the opinion of Joyner M, Coyle E [81], according to which elite performance depends on genetic factors. In this regard, it is noteworthy that US Olympic athletes live 5 years longer than their counterparts from the

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general population [82]. We also assume that a high level of the endogenous M-ChR blocker (EBMChR) in the body, the presence of which we have detected in the blood of a healthy person [83,84], and which is probably Lys phosphatidylcholine by nature [83,84], may hinder the achievement of high results in skiing and other sports requiring high endurance.

Indirect Evidence of the Idea that Sports Vagotonia is the Result of the Formation of a System for the Synthesis of HH-Ach in Cardiomyocytes (According to our own Studies of HRV in Elite Ski Racers)

We have investigated [9-14] the dynamics of the values of a number of spectral and temporal indicators of HRV in 8 elite ski racers, members of the Tatarstan national team (6 MS and 2 MSMC), who had 5-minute clinostatic cardiointervalography (KIG) repeatedly after a night's sleep during two annual seasons (1999 and 2000 y.y.), using the medical diagnostic portable system "VNS-Micro" ("Neurosoft", Ivanovo) and the program "Poly-spectrum" ("Neurosoft"). KIG registration was carried out at training camps (in different regions of Russia, as well as in Bulgaria) in the preparatory (june-november) and competitive (december-march) periods, and for skier K. D., a member of this team, MS, the first author of the article). KIG registration was also carried out in the transitional (april-june) period. At the same time, the skier K. D. recorded the volume of daily training or competitive loads - their duration (minutes per workout, V min) and the length of the distance travelled (km per workout, Vkm), as well as the intensity of the load (Nwp), which was determined by the value of the "working" pulse during training or at competitions, recorded using a POLAR heart rate monitor 430 equipped with a GPS sensor (Finland).

Such spectral parameters of HRV as the total power of the spectrum (TP, ms^2), or total power; the power (ms^2) of High Frequency waves (HF- waves), Low Frequency waves (LF-) and Very Low Frequency waves (VLF- waves); the ratio LF/HF, the relative power of HF-, LF- and VLF-waves were analysed expressed as a percentage of TP, i.e. HF%, LF% and VLF%, as well as time indicators, among which is the stress index, or stress index; the duration of normal intervals RR, or Normal to Normal intervals ((RRNN, ms), analogous to which is heart rate (beats/min), percentage of adjacent NN intervals differing by more than 50 milliseconds (pNN50%), the square root of the mean squared difference of successive RR intervals (RMSSD, мс), standard deviation of normal-to-normal RR intervals (SDNN, ms) and variation range (MxDMn, ms), i.e. the difference between the maximum and minimum RR interval. The results of these studies are presented in (Figure 1) and in (Tables 1 & 2).

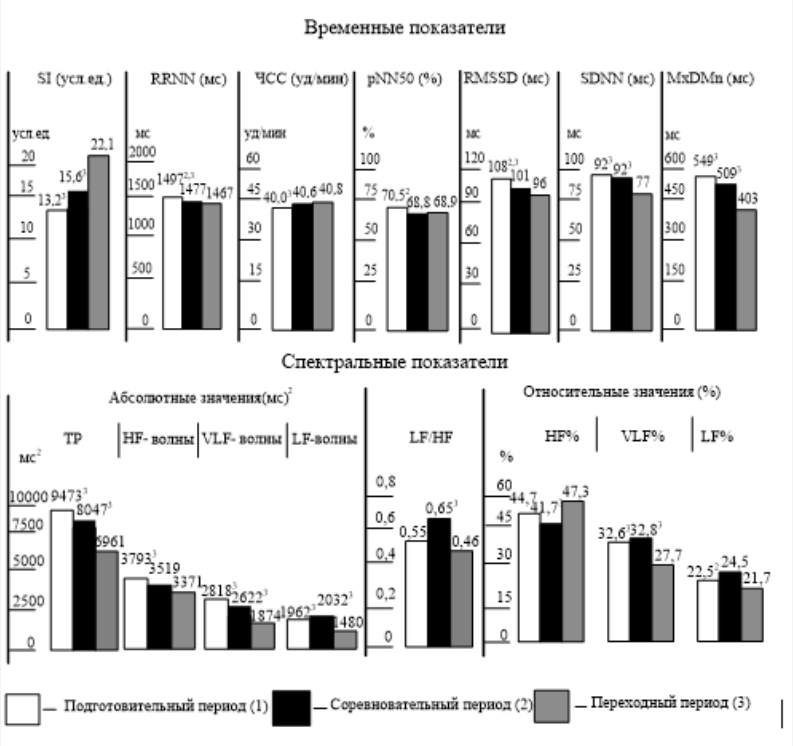

Figure 1: Dynamics of medians of temporal and spectral indicators of HRV in an elite ski racer K.D. during the preparatory (1, white columns), competitive (2, black columns) and transitional (3, gray columns) periods. The numbers in the index (2, 3) indicate the statistical significance of differences with competitive (2) or transitional (3) periods according to the Mann-Whitney criterion, $p<0.05$). The breakdown of the indicators is given in the text.

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Table 1: Median, 25th and 75th centiles of LF/HF indicator (according to cardiointervalography data recorded in clinostasis), as well as volume (Vkm, Vmin) and intensity (Nwp) of training and competitive loads according to months of the annual macrocycle for elite skier K.D.

Month and Year	LF/HF	Volume (V_{km}, V_{min}) and Intensity (N_{wp}) of Training and Competitive Loads		
		V_{km}, km per workout	V_{min}, minutes per workout	N_{wp} working heart rate, beats/min
The competition period				
03.19	0.49 (0.44/0.65)	21.5 (14/25)	93 (65/109)	124 (119/131)
04.19	0.73 (0.44/0.78)	14.8 (9/23)	61 (45/90)	112 (106/123)
The transition period				
05.19	0.36 (0.34/0.61)	15.5 (9/24)	101 (72/146)	124 (112/130)
The preparatory period				
06.19	0.61 (0.44/0.83)	22.5 (18/38)	122 (104/158)	125 (115/130)
07.19	0.49 (0.37/0.61)	25.2 (12/44)	124 (103/166)	122 (111/125)
08.19	0.53 (0.43/0.67)	20.6 (13/31)	129 (90/154)	117 (112/131)
09.19	0.62 (0.54/0.79)	21.7 (12/28)	100 (83/133)	115 (110/124)
10.19	0.34 (0.26/0.52)	15.7 (9/23)	91 (71/120)	122 (109/131)
11.19	0.60 (0.49/0.67)	18.7 (13/23)	84 (63/106)	125 (117/133)
The competition period				
12.19	0.71 (0.54/0.85)	21.5 (14/26)	88 (64/121)	118 (114/128)
01.20	0.64 (0.38/0.78)	18.6 (11/23)	72 (50/101)	124 (113/136)
02.20	0.64 (0.53/0.70)	15.8 (12/22)	79 (53/93)	123 (114/159)
03.20	0.67 (0.50/0.73)	20.2 (15/22)	94 (82/107)	115 (105/123)
The transition period				
04.20	0.42 (0.33/0.58)	13.5 (11/30)	92 (81/117)	113 (104/123)
05.20	0.42 (0.37/0.55)	18.7 (15/60)	119 (87/151)	119 (112/125)
06.20	0.51 (0.41/0.58)	20.4 (16/42)	111 (93/142)	120 (118/125)
In general. for the preparatory (1), competitive (2) and transitional (3) periods				
1	0.55 (0.39/0.66)	21 (13/31)	106 (80/145)	121 (112/130)
2	0.64 (0.46/0.74)	19 (12/25)	82 (61/106)	121 (111/130)
3	0.46 (0.35/0.59)	18 (12/37)	105 (85/142)	120 (112/126)
p< 0.05	2-3	1-2	-	-

Table 2: Median, 25 and 75 cents of HRV indicators for a ski racer K. D. during three training periods and for members of the national team of the Republic of Tatarstan during two training periods (according to cardiointervalography in clinostasis).

HRV-Indicators	The Preparatory Period	The Competition Period	The Transition Period
Ski racer K.D.			
TP, мс^2	9473 (6685/11037)	8047 (6940/9616)	6961 (5349/8416)*#
HF, мс^2	3793 (2860/4579)	3519 (2805/4071)	3371 (2387/3896)*
LF, мс^2	1962 (1307/2814)	2032 (1570/2619)	1480 (1072/2097)*#
VLF, мс^2	2818 (2075/3874)	2622 (2023/3800)	1874 (1374/2582)*#
LF/HF	0.55 (0.39/0.66)	0.64 (0.46/0.74)	0.46 (0.35/0.59)#
HF%	44.7 (35/52)	41.7 (34/48)	47.3 (41/52)#
LF%	22.5 (18/26)	24.5 (20/29)*	21.7 (19/27)

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VLF%	32.6 (24/39)	32.8 (26/40)	27.7 (22/36)*#
SI, acc.unit	13.2 (10/18)	15.6 (12/20)	22.1 (16/25)*#
RRNN, мс	1497 (1453/1540)	1477 (1412/1523)*	1467 (1398/1502)*
Heart rate, beats/min	40.0 (38/41)	40.6 (39/42)	40.8 (39/42)*
pNN50%	70.5 (66/73)	68.8 (62/71)*	68.9 (65/72)
RMSSD, мс	108 (97/120)	101 (94/111)*	96 (91/107)*
SDNN, мс	92 (84/104)	90 (81/101)	77 (73/87)*#
MxDMn, мс	0.549 (0.439/0.609)	0.509 (0.421/0.606)	0.403 (0.348/0.463)*#
The national team of Tatarstan (n=8, including K.D.)			
TP, мс^2	9923 (6658/14428)	7864 (6855/9396)*	-
HF, мс^2	4082 (2576/6335)	3077 (2054/4021)*	-
LF, мс^2	2057 (1119/3202)	1728 (1278/2733)	-
VLF, мс^2	3138 (1818/5611)	2754 (2074/4156)	-
LF/HF	0.50 (0.34/0.65)	0.65 (0.44/0.80)*	-
HF%	43.6 (32/52)	37.2 (28/45)*	-
LF%	19.9 (14/25)	22,7 (17/29)*	-
VLF%	34.1 (24/45)	38.5 (30/48)	-
SI, acc.unit	13.7 (10/20)	17.9 (12/22)*	-
RRNN, мс	1430 (1291/1515)	1490 (1405/1523)*	-
Heart rate, beats/min	42.0 (39/46)	40.2 (39/42)*	-
pNN50%	68.8 (58/75)	65.1 (58/70)*	-
RMSSD, мс	110 (92/135)	96 (86/105)*	-
SDNN, мс	99 (84/123)	87 (79/95)*	-

Note: the national team of the Republic of Tatarstan was not studied during the transition period. * – statistically significant differences with the preparatory period, # – statistically significant differences with the competitive period, p>0.05. The breakdown of the indicators is given in the text.

In particular, Table 1, given as an example, demonstrates the changes in the skier's KD of such parameter of HRV as the LF/HF ratio during each month of the annual macrocycle, and in general, in the preparatory, competitive and transition periods, in comparison with the volume of load (V min, Vkm) and its intensity (Nwp). The data in this table shows that the LF/HF index varies from month to month, which is probably due to the different rate of repair of myocardial damage that occurs after regular training, which in the preparatory and competitive periods took place twice a day (11 workouts per week) and in the transition period-1 workout per day (6 workouts per week); at the same time, the duration of short-term anaerobic loads, which were used for the purpose of myocardial preconditioning, varied.

As can be seen from Figure and Table 2, spectral indicators of HRV and most temporary indicators had maximum values in the preparatory period, or, conversely, minimum values (for example, stress index), which indicates the dominant influence of the parasympathetic division (PD) of the ANS on heart activity. This applies to such indicators as: TP, HF, VLF, VLF%, LF, SI, RRNN, pNN50%, RMSSD, SDNN, Mx DMn, and their change in the competitive period is explained by an increase in the activity of the sympathetic department (SD) of the ANS in this period due to the formation of a sense of anxiety and responsibility for the result, which is reflected in registration of clinostatic CYG. But even in the transition period the HRV indicators of elite ski racers remain much higher than those of beginner skiers.

The analysis of numerous literature data, which we do not provide here, but they are reflected in a series of our articles [9-14], shows that the values of HRV indicators of elite skiers presented in the figure and in Table 2 differ significantly from HRV indicators of athletes of other sports, especially representatives of power sports, as well as from HRV indicators of beginner skiers, and even more so from the HRV indicators of non-athletes, i.e. peers leading a normal (sedentary) lifestyle. This feature of the quantities of HRV values of elite ski racers allowed us to assume that the basis for the gradual change in HRV indicators of ski racers as their skill and athletic performance increase is the formation of NN-ACh system of heart under the influence of endurance training. The fact that a number of spectral indicators can vary from period to period of the annual cycle of elite skier training suggests that such dynamics is a consequence of a change in the intensity of HH-ACh synthesis, and not the result of a change

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in the ionic mechanisms of the heart rhythm driver, as suggested by D'Souza A. et al. [2]. An important argument in favor of the idea of the nature of sports vagotonia as a consequence of the development of the heart system is the data that overtraining is accompanied by a decrease in RMSSD [85-87], and an increase in athletic achievements in 5-time Olympic champion biathlete Martin Fourcade over 11 years correlated with an increase in RMSSD (from 31 ms to 114 ms) [88].

According to NI Shlyk [3,89], the type of autonomic regulation of heart activity (central, or sympathicotonic, and autonomous, or vagotonic) in athletes, including skiers, does not depend on sports specialization and sportsmanship, but depends on innate properties. We have shown [12], that 7 members of the Tatarstan team have the type of autonomic regulation of the heart, according to the classification of NI Shlyk [3,89] belongs to type IV regulation (pronounced autonomous or vagotonic regulation), and only one athlete it belonged to type III (moderate autonomous or vagotonic regulation). At the same time, according to our data, the type of regulation among elite skiers does not change during the annual cycle. The ideas of N. I. Shlyk [3,89], to a certain extent agree with our hypothesis that the formation of the heart's HH-ACh system is the basis of sports vagotonia.

Considering that choline acetyltransferase, the choline-1 transporter, the vesicular transporter ACh, as well as mitochondria as a source of choline and acetyl for the synthesis of ACh are involved in the synthesis of NN-ACh in the heart, and considering also that the effectiveness of ACh (as well as NN-ACh) depends on the intensity of destruction of ACh under the influence of acetylcholinesterase and on the expression of M2- ChR and M3-ChR, as well as, as shown by us [83,84] from the blood level of the endogenous blocker M-ChR (EBMChR), it can be assumed that the rate of synthesis of NN-ACh, the rate of its destruction, as well as the effectiveness of activation of M2-ChR and M3- ChR in humans is individual. Therefore, success in sports requiring high endurance is probably achieved by those athletes who have a high rate of synthesis of HH-ACh in the heart, thanks to which it prevents damage to cardiomyocytes that occurs during intense and prolonged physical exertion.

We have shown [9-14] that in elite ski racers, the value of HRV indicators, which reflect of vagotonia, directly depends on the volume (duration) of loads performed in aerobic mode, i.e. with a "working pulse" equal to 120-121 beats/min. This is proved by the fact that the intensity of HH-ACh synthesis increases with the activation of beta1-AR, with the activation of M-ChR under the influence of vagal ACh, as well as under conditions of preconditioning, i.e. under the influence of short-term myocardial ischemia (hypoxia), which occurs when using short-term loads in an anaerobic regime.

Conclusion

It is obvious that in order to strictly prove the hypothesis about the nature of sports vagotonia as a consequence of the formation of the HH-ACh system in the heart, it is necessary to combine studies of HRV parameters in ski racers with the determination of the activity of enzymes, which are involved in the synthesis of NN-Ach in the heart, , including choline acetyltransferase (ChAT), vesicular transporter AH (VAChT), choline transporter (CHT1), and also the level of ACh in the blood, the activity of acetylcholinesterase (AChE) and the level of endogenous blocker M-ChR (EBMChR). This will answer the question to what extent, in general, the concept is correct, which was proposed in 2009 year by Y. Kakinuma. et al. [25] about the presence of the heart's HH-ACh system and its role in the conditions of norm and pathology.

So far, we can only a priori assert that the values of most indicators of the clinostatic KIG of elite skiers which are registered in the preparatory period, including the power of TR-, absolute power of HF-, LF- and VLF waves, the relative power of VLF-waves, as well as such temporal HRV indicators as SI, RRNN, pNN50%, RMSSD, SDNN and MxDMn, which are presented in Table 2. They are markers of a high level of HH-ACh synthesis in the myocardium Therefore, they can serve as a guide in the study of the role of heart HH-ACh in the development of pathology, in particular, they can be used in the early diagnosis of heart failure and in evaluating the effectiveness of its treatment. In general, the fruitfulness of the idea of the synthesis of HH-ACh in the human myocardium is obvious for the physiology of adaptive processes, for the physiology of sports, as well as for clinical medicine.

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