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Heart rate variability analysis: physiological foundations and main methods

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Abstract

The article presents the main provisions of the methodology for the analysis of heart rate variability (HRV), which is now actively and widely implemented in many fields of medicine and applied physiology. This methodology was first developed in space medicine, where, already during the first manned spaceflights, there was a need in operative assessment of the person's reactions and abilities to maintain high performance and good level of health under different stress conditions.

The HRV analysis methodology is based on the measurement of a consecutive series of cardiac cycle durations, for which electrocardiography, rheocardiography, ballistic cardiography, etc., can be used. The resulting numerical series are subjected to mathematical analysis using statistical, spectral and other methods. The results are interpreted as medical and physiological criteria of the functional state of the organism. Based on the mathematical model, a probabilistic approach to the prediction of pathological conditions was proposed. Indicators of the stress degree of regulatory systems and their functional reserve, which are calculated from the HRV analysis data, are used in the mathematical model of the functional states. In order to obtain the decision rules for the recognition of identified classes of functional states the stepwise discriminant analysis has been applied.

Equations of the discriminant function were obtained. This article examines in detail this new probabilistic approach to the HRV analysis and provides examples of its use for assessing the functional state of cosmonauts at various stages of long space flights.

Keywords

Heart rate variability, Space medicine, Stress, Discriminant analysis

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Introduction

Heart rate variability analysis (HRV) is a universally accepted methodology and technique of investigating and evaluating the functional state of organism and, specifically, components of the autonomic nervous system. At present, this is one of the most popular methods of functional diagnostics worldwide. In many respects it was initiated by the pioneering spirit of space medicine that worked up and implemented a number of complex indices to characterize functioning of the regulatory systems of organism [1]. On the first symposium on cardiac rhythm mathematical analysis in 1966 V.V. Parin presented a large report and noted that the source of this method was space cardiology where it had been first used to study circulation regulation during space flight.

Structure of heart rate as a diagnostic criterion was first applied in the USSR in 1960s. Originally, V.V. Parin and R.M. Baevsky proposed HRV as a method for evaluation of autonomic regulation and states of human organism in space flights [2].

"In the condition of microgravity, animals exhibited profound variations of cardiac contractions, depth and frequency of respiration. The considerable variability of the length of RR segments on the electrocardiogram was observed in Yu.A. Gagarin during his orbital flight. All these changes can be viewed as disorders in the feedback within the system of autonomic regulation where the brain is commander. This concept opens up the opportunity to investigate these phenomena experimentally with the help of electronic computing machines report titled "Heart rate as an indicator of neuroendocrine regulation" by academician V.V. Parin in co-authorship with R.M. Baevsky and G.A. Nikulina was presented at the 18th congress of the International Astronautic Federation in Beograd in 1967. In late 1960s, I.G. Nidekker and R.M. Baevsky proposed heart rate spectral analysis as a tool of evaluating periodic components of heart rate [3, 4].

Advances of space medicine in HRV analysis stimulated further development of the method. The first symposium on heart rate variability took place in 1966. In the USSR, investigations into HRV peaked in 1970s-80s. In Russia, interest to the HRV investigations decayed at the end of 1980s and beginning of 1990s but has revived in recent years.

Since 1970s, the number of HRV studies has increased sharply in Western Europe and the US. B.M. Sayers described rhythms present in changed HR [5]. In 1981 S.D. Akselrod et al. used power spectrum analysis of heart rate fluctuations to quantify cardiovascular parameters beast-to-beat [6–8]. Clinical advantages of HRV were accepted in 1965 after the observation made by Hon and Lee in their studies of intrauterine damages. They noticed that bad disturbances of fetal heart rate were preceded by changes in the HR structure [9–13].

HRV assimilation in cardiologic diagnostics was complicated because of the need for standards of measurement, physiological interpretation and clinical procedures.

In 1996, the Task force of the European Society of Cardiology and American Society of stimulation and electrophysiology prepared and published guidelines "Heart rate variability. Standards of measurement, physiological interpretation and clinical use". In 2001, methodical recommendations on HRV analysis were published by a group of Russian investigators [14]. In the past 10–15 years these basic documents have been supplemented by more recent experimental and clinical findings and methodical approaches. The explosive development of microelectronics, hard- and software made it possible to design innovative, more refined HRV devices and techniques.

At present, thousands of papers on the subjects are published annually. HRV has gained footing in cardiology, surgery, physiology of labor and sport, experimental physiology. Particularly often HRV is used in stratification of the risks of cardiac and arrhythmic deaths in consequence of myocardium infarction (MI) and diagnostics of autonomic neuropathy in diabetic patients. It was established that HRV reduction increases significantly the risk of cardiovascular diseases.

Physiological nature of cardio interval fluctuations is still far from clarification and causes many questions; that is why HRV remains essentially a research procedure but not a routine clinical tool [15].

Goal of this section in monograph "Devices and methods of space cardiology" is to propound the key principles of HRV methodology and new technologies that have been developed for the purpose of individual pre-nosology monitoring of space crews during long stay in microgravity. The technologies have been introduced in some areas of preventive medicine and applied physiology.

Physiological foundations of heart rate variability

The major information about the HR regulating is contained in the "ejection function" of interval duration. Sinus arrhythmia was discovered by Karl Ludvig in 1847. It reflects complex interactions of various loops of heart rate regulation. HRV is based on the theory that variability of RR duration or sinus rhythm frequency is controlled by the autonomic nervous system and catecholamines circulating in blood.

Own or inherent frequency of the sinus node varies between 95 and 110 beats per a minute and is age-dependent [16]. Sympathetic influences increase pulsation rate, while parasympathetic, on the contrary, decrease. In the norm, resting heart rate is within the range of 60-70 beats/min which implies an obvious domination of parasympathetic influences on the sinus node. Rhythmic variations of the rate of pulses conducted via the vagus nerve are modulated by respiration rate and depth, which leads to RR changes known as sinus arrhythmia [17,18]. RR duration can also be affected by mental or physical activities and posture which reduce the average rate of pulses conducted via the vagus and, as stress grows, intensify the sympathetic nervous activity.

Literary data drive us to the conclusion that interval variability is largely neurogenic by nature, i.e. it is controlled by commands of different CNS levels to the segmental apparatus of the autonomic nervous system. Rhythm of cardiac contractions is a sensitive indicator of changes in nervous and humoral regulation. Due to nervous regulation HR is capable to react momentarily to changes in body demand in blood supply. Characteristics of interval variability carry information about functioning of the regulatory systems of organism [19–30].

However, as it was mentioned in the Introduction to this section, we still cannot tie up heart rate varibality to frequency characteristics and underlying regulatory mechanisms.

Some clarity has been reached only with regard of high-frequency HRV or respiratory waves associated with breathing movements and pointing

to vagus involvement in regulation. As for slow fluctuations, their origin remains unclear.

In the opinion of some authors, slow HR waves with the period of 7-20 seconds are associated with sympathetic (adrenergic) control of the autonomic nervous system [31-34]. The waves were first detected by Mayer et al. (1931) and this explains why they are called Mayer waves. Power of the 1st order slow waves describes activity of the vasomotor center. It is also believed that these variations reflect involvement of both parasympathetic and sympathetic regulation [35]. At the same time, the parasympathetic activity reveals itself indirectly through baroreflex regulation of the vascular tone [36]. Normally, sensitive receptors of the sinocarotid zone perceive changes in blood pressure. Afferent nervous pulses are transmitted to the vasomotor center in medulla oblongata where, following afferent synthesis (information processing and analysis), control signals (efferent nervous pulses) are sent to the vascular system. The process of vascular tone regulation with a feedback to vessels in smooth muscles is executed by the vasomotor center continuously.

Physiological correlates of power of 2nd order slow waves with a period of 20-70 seconds are still unknown and a subject of debate. Most of the authors hold it that the waves are linked with the sympathetic activity, and with influences of the cerebral ergotropic activity on subjacent structures. By and large, they characterize influences of higher autonomic centers on the cardiovascular subcortex center and can be viewed as a reliable marker of how tight is the link of autonomic (segmental) regulation with suprasegmental, including the pituitary-hypothalamic and cortical levels.

A two-loop model of heart rate regulation was proposed in 1968. It utilizes the cybernetic approach, i.e. the sinus node regulation is presented in the form of two interconnected loops – central and autonomic or controlling and controlled with feedward and feedbackward (Fig.1).

The sinus node, vagus nerves and their nuclei in medulla oblongata are working organs of the controlled (lower, autonomic) loop. Respiratory sinus arrhythmia is an indicator of the controlled loop activity; the respiration system can be considered to be a feedback element within heart rate autonomic regulation. The controlling (higher, central) loop is characterized by various slow-wave components of heart rate. Its indicator is non-respiratory sinus arrhythmia. Feedforward between the controlling and control loops is implemented via nervous (mainly sympathetic) and humoral channels. Feedback is also implemented via these channels; however, an important role is played by afferent pulsation from cardiac and vascular baroreceptors, chemoreceptors, vast receptor areas in other tissues and organs. At rest, the controlled loop functions in the autonomic mode accompanied by marked respiratory arrhythmia. Respiratory waves grow high during sleep or under anaesthetic when the central effect on the autonomic loop weakens. Involvement of the central loop in heart rate control to support stressed organism slackens the respiratory component of sinus arrhythmia and intensifies the non-respiratory one. The general rule is that higher levels of control brake lower levels. Heart rate may respond to stresses in different ways. Provided regulation is optimal, control runs with minimal participation of higher levels or minimal centralization of control. Otherwise, activation of higher control levels will be necessary. The higher control level is activated, the longer periods of respective slow waves are. This appears as strengthening of the non-respiratory component of sinus arrhythmia and emergence of slow waves of increasingly greater orders.

On our own and literary data [37–40] we developed a model of neuroautonomic HR regulation. The model was built about the theory of R.M. Baevsky et al. supplemented with some inputs detailing the origin of cardio interval waves. Considering HR fluctuations as a result of activities of different CNS levels and HNS components, Kurianova E.V. maintains that frequency of HR waves or the chronotropic function of the heart is controlled at CNS levels, whereas wave amplitudes at all frequencies are dependent on both the sympathetic and parasympathetic HNS components, on whether their activities are balanced or one of the components prevails.

Main HRV methods and results evaluation

Quantitative evaluation of the nervous and humoral effects on the sinus node is made by calculating indices of RR variability. Methods of its description can be divided into time and frequency analyses [41–46].

Statistical methods are used for HRV quantitative evaluation within time periods under study. To this end, intervalogram is treated as a totality of sequential time intervals, i.e. RR intervals (Fig. 2).

Statistical characteristics of the cardio intervals dynamic sequence are: SDNN, CV, RMSSD, PNN5O.

SDNN – is a cumulative index of RR variability over the period under study (NN – normal to normal series without extra systoles).

SDNN is expressed in milliseconds (ms). Normal SDNN values lie within the range of 40 to 80 ms. However, these values are age- and gender dependent which must be taken into account during evaluation of the results of investigation.

SDNN rise and reduction can be caused as by autonomic regulation, so central (equally sympathetic and parasympathetic). In short records, as a rule, a SDNN rise points to activation of autonomic regulation, i.e. growth of the respiration effect on heart rate, typically observed in sleeping people.

SDNN reduction suggests activation of sympathetic regulation that inhibits the autonomic loop. Sharp SDNN reduction is a result of critical straining of regulatory systems and involvement of higher levels of control; consequently, the autonomic loop is almost completely inhibited. Similar physiological information can be learnt from the index of total power (TP). Specifics of the index is that it describes only periodic HR processes and does not contain the so-called fractal part, i.e. nonlinear and nonperiodic components.

CV is a variation factor. It is very practical, as this is actually a normalized SDNN estimate, CV = SDNN /M*100, where M is mean RR duration.

To describe fluctuations with cycles measured in seconds, two indices estimating difference between adjacent NN intervals are used: RMSSD and pNN50. They evaluate high-frequency NN variability due to the vagus modulation of sinus node frequency.

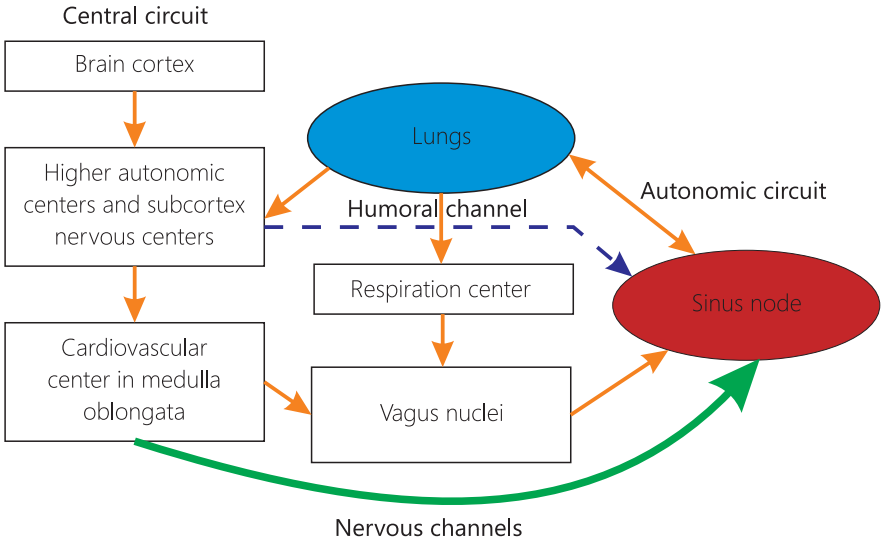

Figure 1. Two-circuit model of heart rate regulation

RMSSD is a square root from the sum of squared differences of sequential NN pairs (normal RR intervals). RMSSD is an index of parasympathetic activity within the autonomic regulation and does not contain HR slow-wave components. It reflects the autonomic activity. The higher RMSSD, the more active parasympathetic regulation. Index normal values are within the range of 20–50 ms. Similar information can be obtained by pNN5O that shows in percent the number of differences greater than 50 ms.

NN5O is a number of pairs of sequential NN with difference greater than 50 milliseconds in all record;

pNN5O (%) is percent of NN50 from the total number of sequential pairs of intervals differing in more than 50 seconds over the whole record time;

Geometric methods assess RR forms and distribution over the period of investigation. For the purpose, variation curve (histogram of interval distribution) is built and main characteristics

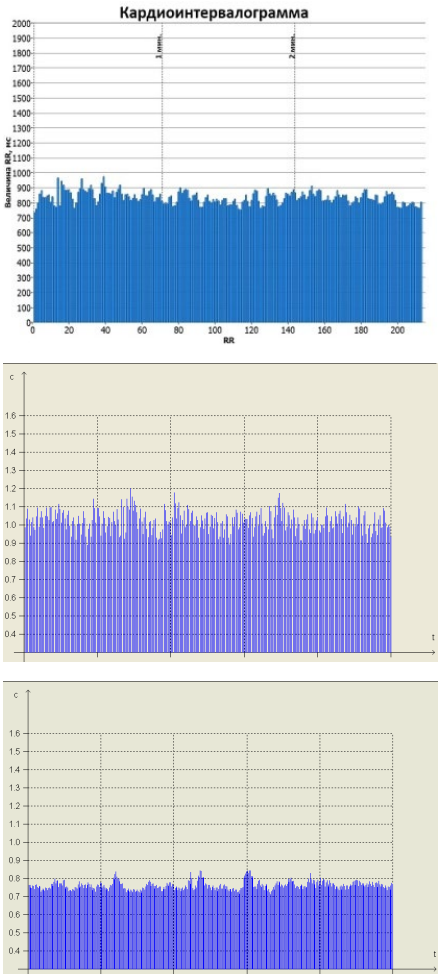

Figure 2. Cardiointervalogram

are determined including Mo (mode), AMo (mode amplitude), MxDMn (variation range) (Fig. 3).

Mode is the most common interval value in a given dynamic series. In case of normal distribution and high process stationarity, Mo differs little from mathematical expectation (M).

AMo (mode amplitude) is a number of intervals corresponding to mode value in % to sample size.

Variation range (MxDMn) shows the degree of interval variativity in a given dynamic series. It is calculated from the difference of maximum (Mx) and minimum (Mn) intervals and, therefore, can be distorted by arrhythmias or artifacts.

Data of variation pulsimetry are used to calculate the widespread in Russia index of regulation straining or stress-index.

$$IS = AMo/2Mo^* MxDMn.$$

Index of regulation strain (SI) characterizes the activity of sympathetic or central regulation. Activation of the central loop or sympathetic regulation during mental or physical stresses manifests itself by rhythm stabilization, decrease of the range of interval duration, and increase of the number of intervals with similar duration (AMo growth). Histogram form changes, i.e. it gets narrow and grows in height. In stressful situations and in the event of pathology, the diagram will have a narrow base and a sharp peak (excessive). Asymmetric diagram can be associated with a transitory process and impaired stability of process. Multimodal diagram is indicative of a non-sinus rhythm (extrasystole, ciliary arrhythmia).

Digitally it can be represented by the ratio of histogram height to width (see above). The parameter was termed the index of regulation strain (SI). Normal SI fluctuates within 80-150 conventional units. It is very sensitive to the sympathetic tone rise. A mild physical or emotional stress increases SI in 1.5-2 times. Strong stress increases SI in 5 to 10 times. In resting patients with permanently strained regulatory systems SI is equal to 400-600 conv.units. In resting patients afflicted with attacks of angina pectoris and cardiac infarction SI reaches 1000-1500 conventional units.

West-European and US investigators use triangular approximation of the interval distribution curve and calculate the so-called triangular index, i.e. the distribution density integral (overall number of intervals) referred to maximum distribution density (AMo). The index is abbreviated as TINN (triangular interpolation of NN intervals).

Another method to evaluate HRV is determination of spectral indices. The case in point is calculation of spectral power of NN fluctuations with the help of nonparametric (Fourier fast transform) and parametric (autoregression) techniques. Spectral methods are used to quantify frequency components of heart rate; they demonstrate graphically the ratios of different HR components representing specific regulation activities [47–52].

Spectral analysis in Fig. 4 estimates contributions of these or other periodic components to dynamic changes in RR duration. They can be [53]:

– high-frequency range (HF) representing largely the parasympathetic influence on heart rate;

– low frequency range (LF) characterizing generally the sympathetic nervous activity and its effects on heart rate;

– very low frequency range (VLF) conditioned, first and foremost, by the humoral influence on heart rate.

Spectral analysis typically includes computation for each component of

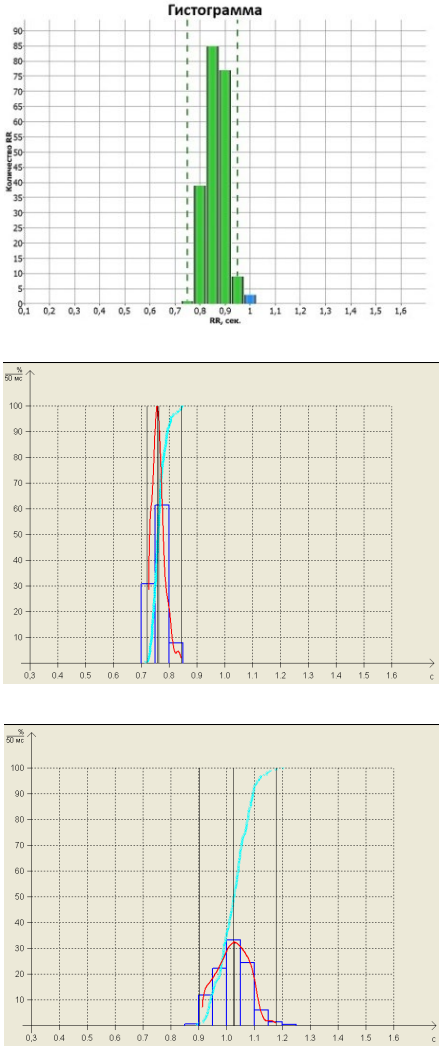

Figure 3. Histogram

absolute total power within a range, mean power within a range, maximal harmonic and relative harmonic values in percent of total power (TP) (within all ranges). TP is a sum of power in the HF, LF and VLF ranges.

Vagal activity is a basic HF component. This is evident from absolute and relative (% of total power) values of respiratory wave power. Extent of autonomic regulation inhibition driven by the parasympathetic segment gives insight into the sympathetic nervous activity as one of the autonomic balance components.

As a rule, respiratory HF constitutes 15–25 % of total power. Percentage reduction to 8–10 % points to the au-

tonomic balance shift towards sympathetic dominance. If HF falls below 2–3 %, we may infer about a sharp sympathetic dominance. In this case, RMSSD and pNN50B also decrease drastically.

Low-frequency power (slow waves of the 1st order or vasomotor waves, LF) characterize the sympathetic nervous activity and, specifically, the vascular tone regulating system. Time for the vasomotor center to receive, process and transfer information varies from 7 to 20 seconds; typically, it is 10 to 12 seconds. This explains the appearance of waves with a frequency close to 0.1 Hz (10 s) which were termed vasomotor.

Transition from the supine to upright position leads to a considerable power rise within this range of HR fluctuations. The vasomotor center activity weakens with age; in senior people its effect virtually fades out. Instead of the 1st order slow waves, power grows in slow waves of the 2nd order. This means that blood pressure is controlled with participation of nonspecific mechanisms by activation of the sympathetic segment of the autonomic nervous system. In the norm, percentage of vasomotor waves in supine position varies between 15 and 35–40 %. Noteworthy is also the dominating frequency in the vasomotor range. Usually it is in the range of 10–12 seconds and its extension to 13–14 seconds may imply a lowered vasomotor activity or slowed baroreflex regulation.

Very low frequency power (slow waves of the 2nd order). Normally, relative VLF power is 15–35 %. Increase in percent suggests a more intensive sympathetic activity and suprasegmental regulation. Dedicated investigations of A.N. Fleishman (1999) demonstrated HRV significance in the VLF power range. His classification of HRV spectral components gives consideration to the ratio of HF, LF and VLF amplitudes and includes 6 classes of spectrogram. A.N. Fleishman also showed that VLF power is a sensitive indicator of metabolism regulation and a good representative of energy-deficient states well.

Besides, spectral methods are instrumental in determining the balance of sympathetic and parasympathetic influences and resulting autonomic nervous effects on heart rate [54, 55]. That is why practice took up various indices that reveal ratios of HR spectral components.

Spectral analysis allows calculation of the index of centralization (IC = (HF+LF)/VLF) and index of vagosympathetic interaction LF/HF. In the norm, this index is equal to 0.5 – 2, while IC varies from 2 to 8.

In spectral power calculated for a 24-hour interval we may single out one more range (ULF) between 0.0033 Hz and 0.00003 Hz. Physiological correlates of this spectrum has not been established; however, some facts evidence that it is modulated by the renin-angiotensin system [53].

Autocorrelation analysis is used to explore heart rate as a stochastic process. The autocorrelation function is a diagram of correlation coefficients dynamics; data of this qualitative analysis makes it possible to judge about central influences on the cardiac autonomic system [56]. Computation and construction of the autocorrelation function of interval series has the goal to look into the internal structure of the series as a stochastic process (Fig. 5). The autocorrelation function is a diagram of correlation coefficients dynamics obtained by displacement of

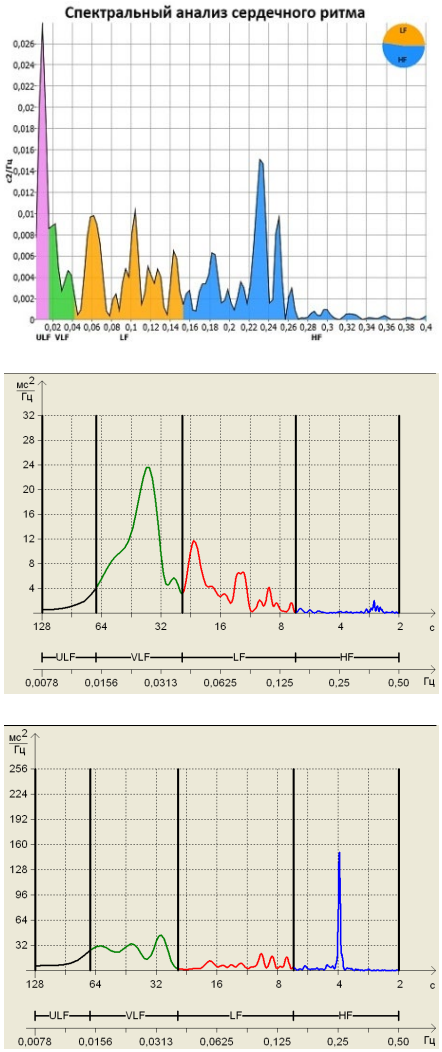

Figure 4. Spectral analysis of heart rhythm

the series under study at one number relative to own series. Autocorellogram allows conclusions about hidden HR periodicity. Quantitative indices in the autocorellogram are C1 – correlation coefficient after the initial displacement and C0 – number of displacements resulting in the zero correlation coefficient.

Correlation rhythmography (scatterography). In essence, correlation rhythmography is graphic representation of sequential pairs of intervals (previous and successive) in a two-dimensional coordinate plane. R-Rn is plotted on the abscissa and R-Rn+1 is plotted on the ordinate. The diagram and the domain of acquired points (Poincare or Lo-

rentz spots) are named the correlation rhythmogram or scatterogram (Fig. 6). This HRV technique falls in the category of nonlinear analysis and is particularly useful in cases when rare and sudden deviations (ectopic contractions and/or beat drop-outs) occur on the background of HR monotony. For arrhythmias when statistical and spectral HRV analyses are uninformative or unacceptable, it stands to reason to examine correlation rhythmograms. This technique enables evaluation of sympathetic nervous involvement in HR regulation. On scattergram constructed for healthy human the ellipse will be prolated along the bisector.

Digital filtration. Digital filtration has been proposed for rapid analysis of short ECG episodes (less than 5 minutes) and quantitative evaluation of HRV periodic components. There are several options of digital filtration as, for instance, moving averaging over a number of sequential intervals. First order slow waves are determined by averaging over 5 or 9 intervals. Second order slow waves are isolated by averaging over 23 or 25 intervals.

Methods of nonlinear dynamics. Multiple influences on HRV, including neurohumoral mechanisms of higher autonomic centers, are responsible for the nonlinear character of HRV changes that can be described with the help of special methods. In recent years this issue has been in the spotlight of investigators abroad and in Russia [57, 58]. Nonlinear properties of variability were described using the Poincare section, spectral clustering, attractor graphics, singular decomposition, Lyapunov exponent, Kolmogorov entropy etc. All these techniques are interesting only to researchers, as their application is limited. We should also mention the procedure of functional state evaluation based on the chaos theory embodied in device Vita-Ritm (Neirosoft, Ivanovo, Russia).

For investigators and clinicians of great importance is physiological and clinical interpretation of HRV data. However, at present there is no unanimity on the subject. The majority of publications hold more or less common clinical and physiological views on the main HRV parameters. Some of the indices have original and still debatable interpretation awaiting a more precise substantiation.

Difficulties with evaluation and interpretation of HRV data often stem from the fact that separate HRV parameters closely correlate with one another remaining relatively independent from others. As a result, there are three groups within which parameters correlate at r>0.9. The first group consists of SDNN and total power (TP). The second group includes VLF and LF powers. The third group combines such indices as RMSSD, pNN50 and HF power. This ratio suggests that indices belonging to a group represent processes of common origin and can be, possibly, interchangeable [59].

For this reason, of particular significance is an HRV-based complex evaluation of the functional state of organism for functional diagnostics or nonspecific non-nosologic diagnostics. One of the approaches is computation of the index of regulation system activity (IRSA). The index is using a special algorithm comprising statistical indicators, data of histogram and interval spectral analysis calculated. IRSA allows differentiate levels of regulation straining and assess adaptive potential of organism.

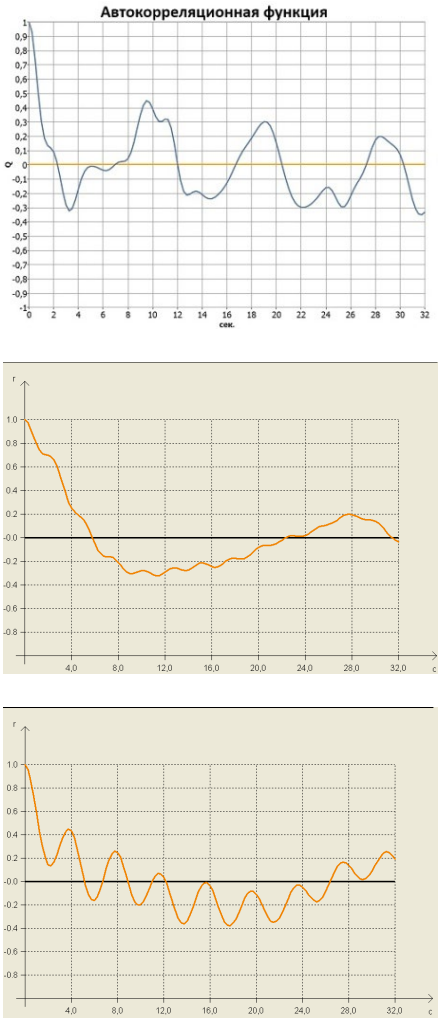

Figure 5. Autocorrelation analysis

IRSA algorithm incorporates the next five criteria:

A. Total regulation effect – HR

B. Overall regulatory activity - standard deviation (SD) or total power (TP).

C. Autonomic balance – complex of indices: SI, RMSSD, HF, IC.

D. Vasomotor center control of vascular tone - power of 1st order slow waves (LF).

E. Activity of the cardiovascular subcortex nervous center or suprasegmental regulation – power of 2nd order slow waves (VLF).

IRSA values are expressed in numbers between 1 and 10. Different functional states can be diagnosed by dint of IRSA value analysis.

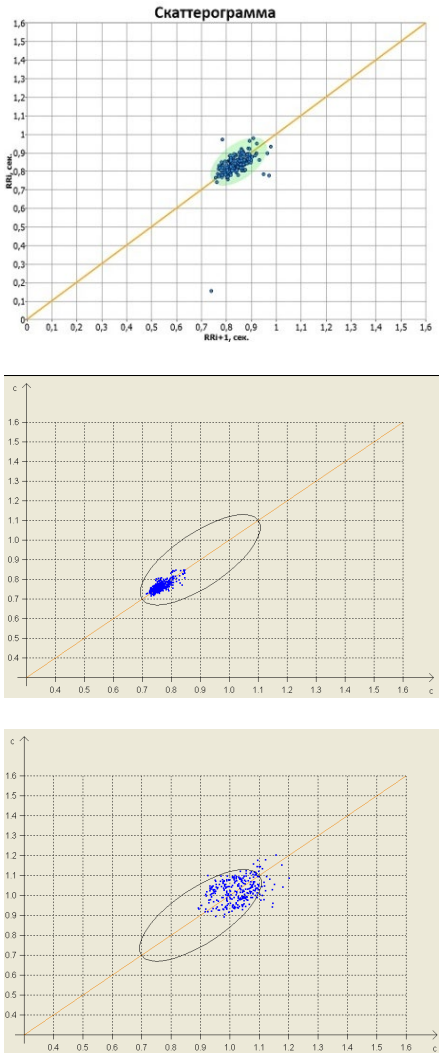

Figure 6. Correlation rhythmogram

One more integrative indicator of regulation strain is the straining index (SI) that shows level of HR control centralization. Consistent SI growth not only points to alteration of HR regulation but also helps identify a variety of unfavorable states: compensated stress in case of a slight excess of normal values to functional disorders, and even damage of organs, first of all, the heart by the stress-fighting systems.

Recently, space medicine investigators have proposed a probabilistic approach to evaluation of the functional state of humans and level of adaptation risks based on the HRV data [60] and consisting of computation of integrative indices of the functional reserve and straining. The approach will be detailed in the chapter below.

It is important to compare data of investigations with normal values. The norm as a statistical population acquired through examination of a reference group of selected healthy people needs reconsideration to be applicable in HRV analysis. Since the subject of evaluation is not parameters of relatively stable homeostasis but rather changeable autonomic regulation, we maintain that it is proper to speak of the norm as a functional optimum [61].

It should be kept in mind that individual optimum of organism does not necessarily coincide with the average statistical norm, as similar adaptation reactions take on different patterns depending on conditions one lives in, and individual functional reserve. Space medicine has developed the concept of physiological norm and maintenance of a sufficient level of functional capabilities of organism [62, 63]. Homeostasis of the main systems is retained with minimal straining of regulation. Accordingly, for the most part, HRV parameters must not overstep the thresholds defined for specific age, gender, occupational and regional groups. This stipulation is best satisfied by thorough study of the HRV results (see below). There is also a concept of clinical norm applied to people who do not exhibit symptoms of a disease. However, it is common knowledge that the nosology approach consists primarily of evaluation of structural, metabolic or energy-metabolic shifts in organism and gives little consideration to the functioning of regulation systems. Apparently, the HRV-based norm concept calls for more scrupulous investigation.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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