Space medicine: releasing return tickets for a human mission to Mars?
CARDIOMETRY
Basic and applied research.
Theory, practice, therapy, engineering, philosophy & methodology
ISSN 2304-7232 e-Journal
www.cardiometry.net

Editorial board

EDITOR-IN-CHIEF
Prof. Y Guliaev, RU

EXECUTIVE EDITORS
Prof. V. Zernov, RU
Prof. M. Rudenko, RU

EDITORIAL ADVISORY BOARD
Prof. R.Baevsky, RU
Prof. S.Chefranov, RU
Dr. S.Kolmakov, FI
Dr. K.Mamberger, RU
Prof. J.Moreno-López, SE
Prof. V.Polikarpov, RU
Prof. G.Stupakov, RU
Prof. V.Tyutyunnik, RU

Prof. H.R.Horvitz, US
Prof. P.Mansfield, GB
Dr. D.Makedonsky, RU
Dr. C.Müller, AT
Dr. S.Rudenko, RU
Dr. V.Skakov, RU
Dr. O.Voronova, RU
Prof. V.Vecherkin, RU

Founded and published by
Russian New University

www.rosnou.ru
Editorial Front Office: Radio Street, 22 Moscow Russia 105005
Phone/Fax: +7 (495) 925-03-83,

Editorial Back Office: Alexandrovskaya Street, 47 Taganrog Russia 347900
Phone/Fax: +7 (8634) 31-24-03 E-mail: journal@cardiometry.net


Design developer: T. Fedosova. Content manager: K. Kamyshev

© All rights reserved.
BASIC RESEARCH

Issues of health evaluation during simulated space mission to Mars
Part 1. Research methodology and methods used in experiment Mars-500
Roman M. Baevsky, Evgenie Y. Bersenev, Anna G. Chernikova

ECG periodic table: a new ECG classification based on heart cycle phase analysis
Mikhail Y. Rudenko, Olga K. Voronova, Vladimir A. Zernov

A new point on ECG: point L as identifier of rapid and slow ejection phases boundary
Sergey M. Rudenko

On conditions of negativity of friction resistance for non-stationary modes of blood flow
and possible mechanism of affecting of environmental factors on energy effectiveness of
cardiovascular system function
Sergey G. Chefranov

PRACTICE

History of space medicine: Academician Vasily V. Parin, founder of space cardiology
Anatoly I. Grigoriev, Roman M. Baevsky

Issues of health evaluation during simulated space mission to Mars
Part 2. Vegetative regulation of blood circulation in the Martian crew individuals in the
Mars 500 project
Evgenie Y. Bersenev, Vasily B. Rusanov, Anna G. Chernikova

Issues of health evaluation during simulated space mission to Mars
Part 3. Assessment of adaptation reactions in the participants of the long-term medical
& ecological investigations during the experiment Mars-500
Roman M. Baevsky, Azalia P. Berseneva, Irina N. Slepchenkova, Anna G. Chernikova

Glomus caroticus, environment, time parameters of cardiac and pathogenic mechanisms
of formation of somatogenic depression and mixed encephalopathies on the
methodological grounds of non-invasive hemogram analyzer
Anatolii N. Malykhin, Nataliia N. Malykhina, Anatolii N. Pulavskyi

Cardio-eigenoscopy: significance of this new method in prognosis of risks of fatal
arrhythmia progression in AMI patients
Dmitry V. Issakevich, Vladimir V. Chepenko, Mikhail Y. Rudenko,
Konstantine K. Mamberger

Study of effects of simulated space flight factors and use of infusion liquids on human
hemodynamics with the use of the Cardiocode method
Olga K. Voronova, Mikhail Y. Rudenko, Vladimir A. Zernov

A new method of effective training of crew members for long-term space mission
Victor N. Skakov

Chronobiological methods of human body self-regulation reserve evaluation
Sergey N. Zaguskin, Yuriy E. Gurov, Gina N. Bakuzova, Irina D. Svishcheva,
Svetlana N. Zaguskina
LATEST NEWS

In honor and remembrance of Vladimir Borisovich Alekseyev 147

Conference report. 38th Annual Conference of International Society for Computerized Electrocardiology. April 17-21, 2013 148

Cardiometry webinar 157

We recommend attending the following meetings 162
Dear readers!

We are pleased to offer a new issue of our journal to your kind attention. It covers medical aspects of the issue of manned mission to Mars. Taking into account that our journal deals with cardiology, based on the principles of accurate cardiovascular system parameter measurements, the articles inserted herein were selected according to the said basic principles. We think it is not a mandatory requirement for our articles to contain a lot of hemodynamic mathematics. It is more important that effects of using new methods described in the latest articles hereof can be successfully applied in practice, and that the new methodology can be used to predict solutions of some problems that may occur during a long-term space manned mission.

The solution of the problems should reflect not only diagnostics, but also the treatment. Therefore, an analysis of methods for the treatment of various pathologies affecting the phase mechanisms of the cardiac performance is very promising. The study of biochemical reactions connected with hemodynamics is important as well.

The issue of a manned mission to Mars requires not only evidence-based recommendations of preparation and monitoring of crew members health state, but the prediction of therapy problem solutions in case of emergency as well. This issue is also addressed herein. Cardiometry is a very young science. But it has already answered many fundamental questions in cardiology. It’s really a great success! But at the same time, it gives a rise to new challenges to be met. The quest of their solutions requires strict adherence to the methodology of scientific research. A solution cannot be treated true if it exists only as a scientific hypothesis. A true methodology of scientific research is valid only in the case if it is reproducible in practice under different conditions.

The journal will cover some issues allowing readers to better recognize the true scientific methodology in research. The evolution of society has reached the border line in its development, where design and development of precise noninvasive measuring methods in medicine is required. Some of them are already available but their wide use is constrained by the existing paradigm of the scientific community. Overcoming this barrier promotes the scientists not only to solve tasks of development of fundamentally new noninvasive measuring technologies, but it also contributes to the refinements of the existing methods and technologies by making their application in practice as simple as possible even by intuitive users. An example is a widespread use of noninvasive blood pressure measurement devices.

Our journal would like to encourage the discussion of the above mentioned issues. You can find herein information on educational courses in cardiometry. Our videos are downloadable. This allows to better visualize results of the research of our authors.

The first issue of our journal has attracted considerable interest in the scientific community. The journal’s Editorial Board hopes that the second issue will outperform the first one and enable our readers to find answers to questions and challenges they face in their current
research. Of course, we hope that the methods of diagnostics and treatment presented in this issue of our journal will take another step on the way to make the human dream of a successful mission to the charming and mysterious planet Mars come true.

Editorial Board
Cardiometry
Report

Issues of health evaluation during simulated space mission to Mars

Part 1. Research methodology and methods used in experiment Mars-500

Roman M. Baevsky¹, Evgenie Y. Bersenev¹, Anna G. Chernikova¹*

¹ State Scientific Center of the Russian Federation, Institute of Biomedical Problems of the Russian Academy of Sciences, 123007, Russia, Moscow, 76A Khoroshevskoye Ch.
* Corresponding author: Phone: +7 (499) 193-62-44. E-mail: anna.imbp@mail.ru
Submitted: 27 December 2012
Accepted: 23 January 2013
Published online: 30 May 2013

Abstract
Research methodology and methods used in experiment Mars-500 held at the Institute of Biomedical Problems of the Russian Academy of Sciences in 2009-2011 are considered. 6 volunteers were isolated during 520 days in a sealed ground-based facility simulating space ship. Along with studies of the Martian crew, a number of satellite research were also carried out, which were devoted to the long-term program of medical and ecological investigations. This program was aimed at the study of the dynamics of adaptation abilities of the organism during its long stay in the natural social, living and industrial environments. For physiological investigations in experiment Mars-500, including the main experiment in a sealed ground-based facility and parallel long-term medical and ecological investigations in different regions of the world, the specialized hardware-software complex "Ecosan-2007" was used. The methodology was based on the principles of prenosological diagnostics that have been further developed in the concept of adaptation risks and in the probabilistic approach to their evaluation. For evaluation of various components of the autonomous regulation state the method of heart rate variability (HRV) was used. It was concluded that the most important field in experiment Mars-500 was the investigation of the methodology of prenosological diagnostic in the preparation of a space mission to Mars.

Keywords
Mars-500 • Prenosological diagnostics • Adaptation abilities • Heart rate variability • Medical & ecological investigations

Imprint
Roman M. Baevsky, Evgenie Y. Bersenev, Anna G. Chernikova. Issues of health evaluation during simulated space mission to Mars. Part 1. Research methodology and methods used in experiment Mars-500; Cardiometry; No.2; May 2013; p.7-18; doi: 10.12710/cardiometry.2013.2.718
Introduction

In recent years, some projects related to the possibility of a manned mission to Mars are developed intensively. One of such projects, Mars-500 was carried out by the Institute of Biomedical Problems, Russian Academy of Sciences in 2009-2011 [1]. In three articles published in the present issue of Cardiometry, the materials of that project concerning health evaluation during a simulated mission to Mars are presented. An important prerequisite for the success of the Mars mission is the human body's ability to adapt to a prolonged space flight. According to the research carried out on board the space station "Mir" and the International Space Station (ISS), the homeostasis of the organism main vital systems is maintained owing to active regulatory systems performance [2, 3]. Therefore, an important place in the future medical monitoring systems should be given to the information technologies, aimed at the regulatory system state evaluation, since it is just the regulatory mechanisms that are overstrained and the decline of the functional reserves associated therewith is one of the main risk factors for disease [2, 4]. As a result, we put forward the concept of adaption risk with regard to long-term human space mission [5]. An adaptation risk is a probabilistic characteristic of adaption abilities of the organism and its functional state at different stages of adaptation. The adaptation risk increases due to the rising of regulatory systems tension and the reduction of functional reserves. A several months' space mission is a chronic stress, which, at reduced functional reserve, can lead to depletion of regulatory mechanisms and development of adverse pre-pathological states.

The main purpose of the experiment Mars-500 was obtaining the experimental data on health and the performance capacity of a human, isolated for a long time in a sealed confined space modeling the main features of the Martian mission (extremely long duration, autonomy, modified terms of communication with the Earth, communication delay, limited consumable resources). The experiment’s duration was 520 days. Among the main objectives of the experiment a great attention was paid to the study of the effect of simulated conditions of the manned Mars mission on the health and performance of the crew and the working out of the principles, methods and means of control, diagnosis and prognosis of health state. Along with studies of the Martian crew, a number of so-called satellite research were also carried out, where the focus of the attention was the program of long-term medical and ecological investigations. This program was aimed at the study of the dynamics of adaptation abilities of the organism during its long stay in the natural social, living and industrial environments. The obtained data were compared with the results of similar studies carried out in isolation and specific conditions of life and work of a small group that simulate the activities of the Martian
crew. Such studies were organized with a certain approximation to the experimental design Mars-500 with the participation of volunteers carrying out their normal work and living in their usual social conditions. The duration of parallel experiments was similar to the main experiment.

Materials and methods

Research methods

For physiological investigations in the experiment Mars-500, including the main experiment in sealed confined space and parallel long-term investigations carried out in different regions of the world, the specialized hardware-software complex "Ecosan-2007" made by "Medical Computer Systems" (Russia) specially for this project was used [6]. When developing "Ecosan-2007" a principal attention was paid to the selection of informative set of recorded parameters best suited for early revealing of organism regulatory systems tension developing and their functional reserve reduction and promising for use in future space exploration. Prenosological diagnostics, studying the functional states on the norm-pathology boundary [7] shows that the cardiovascular system and its regulatory mechanisms are the most sensitive to a variety of stress influences [8]. In a large number of publications it is shown that the evaluation of the state of various parts of the autonomous regulation on the basis of the analysis of heart rate variability (HRV) is the most commonly used method in the study of the various contingents of people working in conditions of chronic stress [9]. High information value of HRV methods during stress is also confirmed by space medicine. [3] In recent years, the ECG dispersion mapping method is applied along with the heart rate variability for the early revealing of stress-related myocardial damage, which allows estimating the initial, not identifiable with standard electrocardiographic study, metabolic and energy disorders in myocardium by micro fluctuations of heart electric potential [10]. Finally, an estimation of the psychomotor actions speed, as a measure of reactivity, which plays an important role in complex stress situation, is important for functional state evaluation for people working under stress. Table 1 presents a list of selected research methods.
### Table 1. Research methods selection for functional state evaluation for people working under chronic stress

<table>
<thead>
<tr>
<th>Functional state evaluation criteria</th>
<th>Research methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system performance</td>
<td>Heart rate and arterial pressure measurement</td>
</tr>
<tr>
<td></td>
<td>Electrocardiography</td>
</tr>
<tr>
<td></td>
<td>ECG dispersion mapping</td>
</tr>
<tr>
<td>Regulatory systems tension</td>
<td>Heart rate variability analysis</td>
</tr>
<tr>
<td>Regulatory systems functional reserves</td>
<td>Fixed breathing rate (6 breaths per min.)</td>
</tr>
<tr>
<td></td>
<td>Breath-holding during inspiration</td>
</tr>
<tr>
<td>Psychophysiologic state</td>
<td>Psychomotor actions speed.</td>
</tr>
</tbody>
</table>

All the methods presented in the Table are described in numerous sources and widely used in different fields of medicine and physiology.

Ecosan-2007 consists of three units: 1) electrocardiograph Kardi-2, 2) cardiopolygraph Pneumocard, 3) psychophysiological tester SKUS (stress monitoring system). Kardi-2 registers ECG in three standard and three unipolar leads. It is also used to program Cardiovisor-06s (ECG dispersion mapping, ECG DM). In addition to computation of the common ECG parameters, Kardi-2 analyzes low-amplitude oscillations of cardiac potentials (dispersion) displaying the results in the form of “heart portrait”. An integral parameter of this analysis is the myocardium index that normally does not rise above 15% [10]. Cardiopolygraph Pneumocard was developed specifically for investigations on board the International Space Station, where it was used from 2007 since 2012 [11]. The "Ecosan-2007" complex is shown on Figure 1.

In experiment Mars-500 four functional tests were carried out with Pneumocard: 1) fixed breathing rate test, 2) breath-holding during inspiration (Stange test) and expiration (Gench test), 3) mental test combined with measurement of simple and integral sensomotoric reaction 4) static manual ergometry. The heart rate variability (HRV) analysis was performed in all periods of the investigation, and during functional load tests. This approach provides a possibility to assess results of the functional tests and also their “cost”, i.e., the level of tension of the regulatory systems necessary for test implementation (the “adaptation cost”) [3, 12]. In addition to ECG and HRV, impedance cardiogram (IC), seismic cardiogram (SC), photoplethysmogram finger (FPG) and pneumotachogram (PTG) were registered during functional testing.

The HRV analysis played the leading role in assessing the results of studies, which was conducted in accordance with Russian and international standards [9,17] for autonomous regulation evaluation using HRV. The commonly accepted characteristics of HRV were calculated as follows: heart rate (HR), standard deviation of normal-to-normal beats (SDNN), i.e., the cumulative effect of regulatory influences, and the difference between the minimum
and maximum cardiac interval (MxDMn) as the maximum amplitude of regulatory influences, coefficient of variation (CV) as a normalized integrated activity of regulatory systems, the number of pairs of consecutive cardiac intervals, differing by more than 50 ms (pNN50) as an indicator of the degree of predominance of parasympathetic regulation over the sympathetic, index of tension of regulatory systems (SI), total spectral power (TP) and the spectral power in high-frequency (HF), low frequency (LF) and very low frequency (VLF) bands of the HRV spectrum. Index of centralization (IC) and the ratio of very low and high frequency components of the spectrum (VLF / HF) as an indicator of the degree of centralization of heart rate control were also calculated.

The protocol of the investigation incorporates two types of monitoring:

A) Monthly ECG recording over 10 minutes combined with the breath-holding tests, blood pressure measurement, determination of time for simple and integral sensomotoric reactions, and filling out a questionnaire about day-to-day life, stresses and possible upsets of the past month.

B) Quarterly evaluation of the complex of cardiorespiratory parameters during implementation of physical, mental and orthostatic tests.

Figure 1. Polycardiographic investigation during psychophysiological test using Ecosan-2007.
Research methodology. Prenosological approach

One of the important conditions of experiment Mars-500 was the comparability of the obtained data and uniformity of the methods used. The methodology and technology of investigation common to all the surveyed groups were created [13]. The methodology was based on the principles of prenosological diagnostics [12]. Prenosological diagnostics is a new theoretical and practical field, evaluating the functional states on the norm-pathology boundary. Functional states, when adaptation is maintained at the cost of considerable regulatory systems tension, are called prenosological [14], since they precede the development of pathological states in different nosological forms of disease. Prenosological diagnostics principles have been developed in the concept of adaptation risks and in a probabilistic approach to their evaluation, developed and tested during numerous space missions [12].

The health monitoring of the crew members in manned interplanetary missions should be based on different principles than that on modern spaceships and orbital stations. Nowadays the health monitoring is based on the traditional for terrestrial medicine approach when the goal is to determine the presence and severity of pathological abnormalities in organs and systems, and to diagnose the disease. However, the experience of medical support in long-duration space mission shows that the symptomatology of the observed deviations was caused mainly by insufficient adaptation ability of the organism, that is, almost all of the observed deviations can be rated as prenosological.

The concept of health, developed in space and preventive medicine considers the transition from health to disease as a process of gradual organism adaptation abilities reduction and prenosological states development, which occurs as a result of functional reserve reduction of organism regulatory systems [3,15]. Prenosological diagnostics distinguishes four types of organism functional states: normal, prenosological, premorbid, and pathological.

One of the most important issues of the experiment Mars-500 was evaluation of pathology development risk during long interplanetary missions. In such missions failure or reduced ability to carry out the responsibilities of any crew member can lead to the failure of entire expedition. Therefore, reliable methods of determining the abnormalities risk long before they can appear as the first symptoms of disease are needed. The probabilistic approach for predicting pathological state, developed on the basis of a mathematical model describing norm-pathology transition, was proposed to solve the issue as offered in [16]. In the mathematical model of organism functional state the degrees of regulatory systems tension (DT) and their functional reserve (FR) are used, being calculated using data of heart rate variability (HRV) analysis.
For the mathematical modeling of functional states a step-by-step discriminant analysis was applied [18]. The equations of the discriminant function in a standardized format for the first two canonical variables L1 and L2 are as follows:

\[ L_1 = 0.112 \times HR + 1.006 \times SI + 0.047 \times pNN50 + 0.086 \times HF; \]
\[ L_1 = 0.140 \times HR + 0.165 \times SI + 1.293 \times pNN50 + 0.623 \times HF \]

\( L_1 \) is an indicator of the regulatory mechanisms mobilizing function (SI and HR have maximum importance in it), so it can be considered as an indicator of functional reserves (FR), which are mobilized and can be quickly consumed, when growing of the sympathetic activity. \( L_2 \), connected with the parasympathetic activity indicators (pNN50, HF), reflects the protective function of the regulatory mechanisms and the state of autonomous balance according to changes of autonomous nervous system parasympathetic activity, i.e., we can consider that \( L_2 \) characterizes the degree of regulatory systems tension (DT).

FR and HF values were considered as coordinates of the phase plane, which forms the space of functional states. Geometric centers of subgroups with different functional states are shown in Figure 1. The results of testing of the model developed examining 34 crew members of the orbital station "Mir", as well as on the basis of the ground-based experiments on a 120-day antiorthostatic hypokinesia and 8-month isolation are also presented here. Geometric centers of the subgroups with different functional states are shown in Fig. 2. The subgroups are located in the phase plane in such a way that the physiological norm is characterized by positive FR values and negative CH values. The center of this subgroup is in the lower right quadrant of the phase plane. Other subgroups are located in the other quadrants: prenosological states are in the upper right quadrant, premorbid states are in the upper left, pathological states are in the lower left one. The averaged values of DT and FR for different experimental groups are also marked there. It is shown that health state of the cosmonauts during space mission and the volunteers at various stages of ground-based experiments is changing mainly due to increase in the degree of regulatory systems tension and its shift towards prenosological states.

Further development of mathematical modeling of functional states was the probabilistic approach for predicting abnormalities and diseases and calculating the risk category [18]. Risk evaluation of disease development is based on the calculation of posterior probability of each of the four possible states existence (normal, prenosological, premorbid, pathological).
Figure 2. Space of functional states formed by mathematical model according to HRV analysis results. DT and FR average values for each class of norm group, for group of cosmonauts during real space missions (SM), and for different stages of ground-based 8-month isolation and 120-day antiorthostatic hypokinesia (AH) experiments.

The calculations are carried out using the heart rhythm variability values taking into account the autonomous regulation type. At the probabilistic approach a probability of the certain functional state can be considered as its quantitative measure. The higher is the functional state probability, the greater is its intensity. The growth of prenosological state probability is a prognostically unfavourable factor that should be taken into account. Prenosological state with a significant reduction of functional reserves and evident regulatory systems tension becomes premorbid state, which is the sign of a high probability of developing of pathological state transforming into a concrete disease.

Research organization

To organize the investigations parallel to experiment Mars-500 in different regions of the world, a special project "Long-term medical and ecological investigations" was developed, it was supported by the Presidium of Russian Academy of Sciences and included in the program "Fundamental sciences to medicine". 12 research institutions and companies from Russia, Belarus, Kazakhstan, Germany, the Czech Republic, Canada and the United States took part in this project. Thus, 125 testers (13 groups) were involved, including 6 members (the first
group) in the model of interplanetary spaceship sealed ground-based facility and other 12 groups (5-15 people in each group) in the 12 cities of the world (see Figure 3). Rather simple but highly informative methods providing 15-20 minutes examination were used for operative functional state evaluation. The result was an operative conclusion and formation of special file with the results of the investigations in the individual database with its subsequent transfer to the analytical center. The conclusion of investigation was automatically generated.

To control the investigations carrying out simultaneously in a sealed ground-based facility and in different regions of the world, a special website (www.iki.rssi.ru/mars500) was developed [1]. This site was a joint project of the Institute of Biomedical Problems (IBMP), the Institute of Space Research (IKI) and "Medical Computer Systems' Corp. IKI collected and displayed the ecological information and MCS Corp. carried out technical support of the investigations as a developer and manufacturer of the "Ecosan-2007" device (see Figure 4).

Figure 3. 520-days experiment Mars-500 participants.
Conclusions

The most important issue in experiment Mars-500 was to study the possibility of using the prenosological diagnostic methodology in Mars mission preparation. Such preparation should solve not only the issues of revealing the primary and latent forms of disease, but also of their prediction. The 520-day stay of 6 members of the Martian crew in a sealed ground-based facility isolation shows that prenosological diagnostic methods allow carrying out reliable medical monitoring of the functional state of practically healthy people, promptly identifying the probability of increasing of transition to premorbid and pathological states. It is shown that the dynamics of the crew members functional state was within the physiological norm during the whole examination period. A weak tendency for the prenosological states probability increasing was found with the probabilistic approach. «Long-term medical and ecological investigations» project provided important experimental data necessary for the development of criteria for prenosological and premorbid states risk evaluation in practically healthy people during long-term examination.

In the future Mars missions it becomes necessary to shift from nosological medical monitoring principle to prenosological one, not excluding the many years’ experience of space missions medical support, oriented to pathology revealing and treatment. The prenosological approach provides a reliable prediction of potential adverse changes in crew members health state. With this approach, medical monitoring is proceeded from the risk of prenosological and premorbid states preceding the disease rather than the possibility of specific diseases.
appearance during mission. The methodology and research methods described herein were approved in the experiment Mars-500 and can be recommended for use in future projects dedicated to manned Mars mission preparation.

**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**
R.M.B., E.Y.B. and A.G.C. developed the concept, prepared the manuscript and analyzed the data, A.G.C. drafted the manuscript, A.G.C. read and met the ICMJE criteria for authorship. All authors read and approved the final manuscript.

**References**
1. www.imbp.ru/mars500
# Original research

## ECG periodic table: a new ECG classification based on heart cycle phase analysis

Mikhail Y. Rudenko\(^1\)*, Olga K. Voronova\(^1\), Vladimir A. Zernov\(^1\)

\(^1\)Russian New University, 105005, Russia, Moscow, 22 Radio St.

* Corresponding author: Phone: +7 (8634) 31-24-03. E-mail: cardiocode.rudenko@gmail.com

Submitted: 17 April 2013
Accepted: 08 May 2013
Published online: 30 May 2013

### Aims

The article considers the development of the periodic table of ECG phase changes which should reflect the variety of the ECG curves and can be used as reference system for diagnostics purposes.

### Materials and methods

More than 5,000 ECG records were studied. They were recorded as original single-lead ECG of the ascending aorta. This fundamentally new ECG lead system reflects all processes in cardiovascular system. It was named by its developers the “ECG – HDA”. Basing on the theory of cardiac cycle phase analysis, the authors defined deviations from the normal ECG curve. Clinical tests were conducted and descriptions based on the laws of cardiometry were provided.

### Results

A fundamentally new system of the ECG curve evaluation has been developed.

### Conclusion

It is stated that all the variety of the actual ECG curves can be divided into 10 groups. Each group contains 4 levels of characteristic changes, starting from the norm up to and including critical deviations from the norm. The results are presented in the “ECG phase changes periodic table”. The table can be used for very precise diagnostics. The periodic table enables assessing the capabilities of the practical application of electrocardiography from a new point of view.

### Keywords

Cardiometry • Cardiovascular system diagnostics • Cardiac cycle phase analysis • ECG–HDA

### Imprint

Mikhail Y. Rudenko, Olga K. Voronova, Vladimir A. Zernov. ECG periodic table: a new ECG classification based on heart cycle phase analysis; Cardiometry; No.2; May 2013; p.19-28; doi: 10.12710/cardiomery.2013.2.1928
Introduction

Cardiovascular system diagnostics based on the ECG curve analysis has never taken into account the processes of the cardiac cycle phase structure. According to the existing standards [1,2,3], the ECG was treated as a set of segments, intervals and waves. Herewith, the functional interrelation of the above elements was not proved. Examination and establishing diagnosis were based on the practical description of the ECG in every individual case. It was assumed that the more ECG channels recorded in every medical case, the more probable is the reflection of the process under diagnosis in the ECG curves. Herewith, the methodological error and systematic error were not taken into account. This approach became conventional. It consists in collecting the descriptions of the medical cases. The collected data enabled creating a global ECG data base [4]. However, none of the cases from the above mentioned data base as well as the cases mentioned in the standards, was described from the point of view of the laws of natural science which provide the logics of evidence basing on the cause-and-effect relations of the observed phenomenon and the factors causing its occurrence. There existed no fundamental theoretical models of hemodynamics which could provide the proper mathematical description of the blood flow through the vessels. Consequently, no concepts of the reference ECG curves and their functional relationships were offered. It means that fundamental classical measurement principles were not included in the existing standards. The practical use of the standards was limited to statement of facts, and the possibility of modeling the diagnosis was not used. The existing standards show a number of inconsistencies. Practicing physicians need much time to compare the real multi-channel ECG recording in order to trace its agreement with the existing standards. However, in most cases precise diagnosis can not be guaranteed.

Materials and methods

For development of a fundamentally new system of the ECG analysis the method of cardiac cycle phase analysis and hemodynamic equations by G. Poyedintsev and O. Voronova were used5. The ECG of the ascending aorta should be recorded. Unlike the already known ECG leads, it contains information about all phase processes in every cardiac cycle5. The location points of the ECG electrodes are shown in Fig.1. The new single-channel lead system enables the ECG signal recording reflecting all processes occurring in the cardiovascular system. The shape of the single-lead ECG can be seen in Fig.2 herein. As opposed to the standard multi-channel ECG leads, it can be provided with metrology that guarantees a minimum methodological error [5, 6, 7].
Figure 1. Location points of the electrodes for recording the ECG of the ascending aorta.
Amplitude of every of the 10 cardiac cycle phases reflects the relationship between the amplitude of the muscle contraction and the respective anatomic part of cardiovascular system [5]. The process of the amplitude change can be shown by identifying conditional zones of the norm, its limits and pathologies [6]. The mentioned zones are shown in Fig.3.
**Figure 3.** Color-marked ECG – HDA wave amplitudes relative to isoelectric baseline: the green-bar field indicates the norm, the yellow one indicates the norm boundary, the white field is used to indicate pathological cases.

**Table 1. Coefficients of the ECG wave amplitude increase**

<table>
<thead>
<tr>
<th>ECG waves</th>
<th>P</th>
<th>R</th>
<th>S</th>
<th>L</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>The amplitude which compensates the decreased contractile function of the heart adjacent segment</td>
<td>+2,0</td>
<td>+2,0</td>
<td></td>
<td>+2,0</td>
<td>+2,0</td>
</tr>
<tr>
<td>The amplitude is within the norm</td>
<td>+1,5</td>
<td>+1,5</td>
<td>-0,5</td>
<td>+1,5</td>
<td>+1,5</td>
</tr>
<tr>
<td>The norm</td>
<td>+1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>The amplitude is within the norm</td>
<td>+0,5</td>
<td>+0,5</td>
<td>-1,5</td>
<td>-0,5</td>
<td>-0,5</td>
</tr>
<tr>
<td>The muscle contraction amplitude is below the norm (except for wave S)</td>
<td>+0,25</td>
<td>-1,5</td>
<td>-2,0</td>
<td>-1,5</td>
<td>-1,0</td>
</tr>
</tbody>
</table>

The processes responsible for changing the ECG curve may be divided into ten function groups, namely:

1. Natural changes caused by physical activity.
2. Cardiac insufficiency:
   2.1. Septal contraction.
   2.1. Myocardial contraction.
   2.3. Septal and myocardial contraction.
3. Synchronization of systemic and pulmonary circulation hemodynamics:
   3.1. Arrhythmias.
   3.2. Sudden cardiac death signs and symptoms.
4. Heart valve function:
   Aortic valve opening.

5. Anatomic continuity of septum:
   Ventricular septum defect (VSD).

6. Coronary flow performance:
   6.1. Thrombus formation.
   6.2. Sclerosis development.

Results

The “ECG phase changes periodic table” is a result of a long-term research work (see Fig.4).

![Figure 4. ECG phase changes periodic table.](image-url)
The ECG phase changes periodic table covers the ECG – HDA curves that are used to detect the pathologies of the cardiovascular system function. With the help of the ECG it is possible to trace 10 functions mentioned above. Each of the functions can be traced within the norm as well as within the critical limits of deviations from the norm. The ECG phase changes periodic table includes 30 characteristic ECG – HDA curves. The other curves that can be practically observed are regarded as transitional ones, and can be classified depending on the phase changes characteristic of definite functions.

Let us consider the changing of the ECG – HDA phase amplitudes and the values of the blood volumes that are characteristic of evaluation of the septal contraction function (see Fig.5).

**Figure 5.** ECG – HDA phase changes characteristic of mitochondrial cardiomyopathy in the septum.
Mitochondrial cardiomyopathy is the most frequent pathology of the septum. This pathology is caused by abnormality in operation of the mitochondria in the septum that can lead to water metabolism disturbance and cell swelling. The pathology can be detected only in orthostatic test. Comparing ECG – HDA in both tests it is possible to trace the difference in R-wave amplitudes which is characteristic of the septal contraction.

During the orthostatic test not only the R-wave amplitude is changed, the phase blood volumes are changed as well. Thus, in supine position the minute volume MV=4,9 l/min whereas in standing position MV=6,3 l/min. These characteristics are considered as minor deviations from the norm. The people having these changes do not experience any specific problems in their everyday life. However, in case of development of this type of pathology, the symptoms of cardiac insufficiency can be observed. Herewith, the heart pumps smaller volumes of blood. In standing position MV=3,9 l/min whereas in supine position MV=5,6 l/min. The amplitude of the septal contraction becomes smaller and is on the level of the isoelectric baseline (Fig.5) which is characteristic of significant deviations from the norm.

In case of further pathology development the ECG – HDA curve is characteristic of the known in classical electrocardiography Brugada syndrome. There is no R-wave, and phases S – L and L – j have high amplitude. It is defined by the compensatory mechanism. It maintains the tension of the phases due to the weakness of the heart muscle. The weakness of the heart muscle contributes to the low value of the minute volume MV=3,0 l/min, that is characteristic of the critical limit of deviations from the norm.

The norm is MV=3,6 l/min. It is shown in the upper left corner of the Table.

The other system segments shown in the Table were systematized according to the same principles.

**Discussion and conclusions**

Creation of the presented system is a logical development of the research of the cardiac cycle phase characteristics [5]. Considering a huge volume of the conducted significant research work and a great variety of recorded signals, the objective laws of formation of the cardiac signals phase characteristics have been traced. Thus, it becomes possible to trace and systematize the most characteristic ECG – HDA curves typical for different stages in pathology development for different functions of the cardiovascular system.

The study of the existing classical standards raised many questions. The attempt of using them for the system creation did not prove to be a success. The existing inconsistencies within the standards appear significant.
But it should be noted that the present research work follows the certain issues that have been treated in the papers by Marek Malik, Jose Jalife, Peter W. Macfarlane and Nikus K.

The newly developed system can not be regarded as an absolutely complete table. The cases of the function of the aortic valve, the influence of the coronary artery atherosclerosis and the cases of a discontinuity of the septum require further study. However, the system proved to be effective in its practical application. Thus, the practicing physician using the single lead ECG – HDA will be capable of making diagnosis and monitoring the further treatment process.

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
M.Y.R., O.K.V. and V.A.Z. developed the concept, analyzed the data and prepared the manuscript and, M.Y.R. drafted the manuscript and read the ICMJE criteria for authorship. All authors read and approved the final manuscript.

References
2. ECG learning centre. http://ecg.utah.edu/


XXI century.
Mars exploration with the American rovers.
Reprinted with the written consent of NASA
## Original research

### A new point on ECG: point L as identifier of rapid and slow ejection phases boundary

**Sergey M. Rudenko**

1 Russian New University, 105005, Russia, Moscow, 22 Radio St.

* Corresponding author: Phone: +7 (8634) 31-24-03. E-mail: tagbox2011@rambler.ru

Submitted: 01 May 2013

Accepted: 26 May 2013

Published online: 30 May 2013

### Aims

Description of rapid and slow ejection phases in the cardiac cycle.

### Materials and methods

The theory of cardiac cycle phase analysis and mathematical equations of hemodynamics were used in the paper. The equations were employed to verify the balance of the phase-related diastolic and systolic blood volumes reliant on phase durations, and the identification of boundaries of the cardiac cycle phases on the ECG. Further, synchronous ECG & RHEO recording was used. Aortic blood filling was studied in the stated phases.

### Results

The location of boundaries of rapid and slow ejection phases is traced. The boundaries did not have a precise definition before. Thus, a new symbol, the L point, on the ECG has been introduced to identify the boundaries of phases S - L, L - j.

### Conclusion

Previously the location of point j on the ECG was impossible to identify. It was considered as a hypothermic wave on the ECG that could not always be traced. Point j was defined as the j (Osborn) wave. Thereby the location of boundaries of rapid and slow ejection phases, where volumetric parameters were equal to the stroke volume, was not accurately identified. The research enabled detecting the ECG recording criteria of the rapid and slow ejection phases. The results of the present research are published for the first time.

### Keywords

Cardiometry • Cardiology • Hemodynamics • ECG • Rheogram • Point j

### Imprint

S. Rudenko. ECG periodic table: a new ECG classification based on heart cycle phase analysis; Cardiometry; No.2; May 2013; p.30-39; doi: 10.12710/cardiometry.2013.2.3039

Available from: [http://www.cardiometry.net/issues/no2-may-2013/new-point-on-ecg.pdf](http://www.cardiometry.net/issues/no2-may-2013/new-point-on-ecg.pdf)
Introduction

The clinical interpretation of the ECG has an important function in the classical theory of electrocardiography. It is based on the analysis of the ECG intervals, segments, points and waves [1,2]. Despite the long period of practical application of the present analysis, no unique criteria for beginning and end of the intervals and waves existed. Numerous contradictions contributed to understanding of the ECG systolic cardiac cycle structure.

This is true for the S-T segment which structure is poorly known. The reason is its research complexity. Ambiguous and irregular variations of the S-T segment form have not enabled its accurate analysis yet.

To study the S-T segment the high resolution electrocardiography was recommended [3]. However, the aims have not been achieved and the S-T segment is regarded as Terra incognita by the researchers.

The controversial aspect is the j point location on the ECG. The uncertainty of its recording criteria led to refer to it as wave j following the QRS complex on the ECG curve [4, 5]. A number of researches consider wave j to appear close to wave T [6]. Hypothermia is considered to be a clinical cause for its appearing [7].

Since the S-T segment takes a half of the systole in the cardiac cycle, it becomes apparent that there is much to be studied in electrocardiography. Dissenting opinions confirm the existence of invisible zones on the ECG curves [8].

Studies on cardiac cycle phase analysis [9] appeared in the early 2000s. The research results on the noted problem became the subject for two theses [10,11]. To find out the truth of biological processes appropriate for the ECG systolic segment, the author of the present paper had to introduce new electrocardiological notions determining clear boundaries of the phase structure of the systolic part of the cardiac cycle.

Materials and methods

The theory of cardiac cycle phase analysis [9] was applied in this paper. The goal of the research was to identify the recording criteria of the cardiac cycle phases in the S-T segment on the ECG. Since there had been no boundary criteria of the cardiac cycle phases described in the literature, hemodynamics equations by G.Poyedintsev – O.Voronova [9] were applied in the paper. The present equations are based on the phase blood volume calculations by the indirect method. The cardiac cycle phase durations serve as volume characteristics for calculation functions. The S-T segment phase structure includes several phases: the load phase, rapid and slow ejection phases. Considering the fact that boundary recording criteria of these phases were not determined, the comparison principle of the known and unknown was
employed. Thus, the hemodynamics equations by G.Poyedintsev – O.Voronova enable calculating phase-related diastolic and systolic blood volumes. The boundaries of diastolic cardiac cycle phases are clearly identified on the ECG curve. The criteria of identification of early atrial diastole and systole in the theory of electrocardiography are absolutely true. The equation is based on the law of conservation of energy, i.e., the amount of blood entering the heart is the same as the amount of blood ejected from the heart. Thus, setting up the equation of blood volumes of systolic and diastolic phases it is possible to find the causes for equation discrepancies and avoid them.

The equation is as follows:

\[ PV1 + PV2 = PV3 + PV4 \]

where:
PV1 is the volume of blood entering the ventricle in the early diastole (ml);
PV2 is the volume of blood entering the left ventricle in the atrial systole (ml);
PV3 is the volume of blood ejected by the ventricle during the rapid ejection phase (ml);
PV4 is the volume of blood ejected by the ventricle during the slow ejection phase (ml).

The first stage was to verify the recording criterion of point S, i.e., the load phase beginning. The recorded ECGs showed the S point was at the deflection point of the right part of the S wave. It conformed to the logic of biophysical processes creating the ECG form [9]. The first order derivative helped to identify it with 100% of the actual ECGs.

As a result the equality of diastolic and systolic blood volumes was obtained. It pointed out the validity of the S point identification criteria.

Further it was necessary to obtain individual components of systolic blood volume, namely PV3+PV4. The criterion of identification for boundaries of rapid and slow ejection phases should be identified. The load phase of the S-T segment was to be considered as well.

Within this phase the aortic valve is closed with no blood entering the aorta.

Thus, the second stage was to establish the identification criterion of the time of the beginning of the aortic valve opening procedure. It was more complicated. The synchronous ECG & RHEO recording was used (Fig. 1).
Figure 1. The synchronous ECG & RHEO recording. The beginning of the aortic valve opening procedure corresponds to the beginning of rapid ejection phase. To denote this moment on the ECG, a new symbol, the L point, was introduced.

Figure 1 shows the small ECG wave corresponding to the beginning of the RHEO curve elevation. The studies revealed it in every ECG recording. Scientific research was not capable both identifying its boundaries and its significance, so it was important to introduce a new notion for this wave. It was marked with L which is the beginning of the rapid ejection phase. The next stage was to specify the identification criterion of the rapid ejection phase end being at the same time the beginning of the slow ejection phase. Actually, the location of the j point was to be specified. The synchronous ECG & RHEO recording was used as well (Fig.2).
Figure 2. The synchronous ECG & RHEO recording. The j point corresponds to deflection point of the RHEO curve elevation segment and is identified with the maximum of the first order RHEO derivative. It represents the end of the small ECG wave before the T wave.

Figure 2 represents the deflection point of the RHEO curve elevation segment clearly defined with the maximum of the first order derivative. However, it reflects the end of the small ECG wave located before the T wave. The approximate location of the point j corresponding to its registered location is described in the existing studies. Substituting the S-L and L-j phase durations into the G.Poyedintsev – O.Voronova hemodynamics equations, we obtain phase-related systolic blood volumes with their sum equal to the sum of diastolic blood volumes.

Further research completely confirmed that the use of S-L and L-j phase identification criteria proved to be true, and the equation mentioned above holds in 100% of cases.

Results

The main result is the identification of registration criteria of the boundaries of the rapid and slow ejection phases in cardiac cycle phase structure.

The second significant result is practical use of the mathematical model of hemodynamics that enables calculating the phase blood volumes.
The third result is the acquired possibility to measure the rapid and slow ejection phases in clinical trials.

**Discussion and conclusions**

The paper describes classical scientific approaches to research. Statistical approaches applied in medicine did not allow the researchers to avoid a concept crisis on significant cardiac cycle phases. It resulted in possibility of applying a single-channel ECG lead. This channel records a signal in the aorta where the function of the whole cardiovascular system is reflected [9]. It was essential to compare the ECG & RHEO aortic phase relations.

Earlier the ECG & RHEO recording was employed. But there was a multi-lead system ECG and chest rheography to cover blood filling of the chest organs.

Not knowing the location of the S wave as one of the key points, the RHEO was synchronized by fixing its minimum with respect to isoelectric baseline.

In the present paper the RHEO baseline was fixed in the point of the S wave [9]. The exact S point location enabled analyzing the mechanism of the regulation of the diastolic arterial pressure by the RHEO [9]. It was measured by the availability or deficit of blood filling with the RHEO curve up to point S, as Figure 3 shows. We are pioneers in solving this problem.

![Figure 3. The possibility of qualitative evaluation of changing in aortic blood filling with the aortic valve closed. The RHEO curve elevation to the S point shows the blood volumes entering the aorta through the closed aortic valve.](image-url)
Figure 3 demonstrates the RHEO curve elevation to the S point. When comparing with Figures 1 and 2, the blood penetration through the closed aortic valve is observed. If the RHEO was fixed on the isoelectric baseline by the RHEO minimum, it would be hard to define this elevation being a criterion of significant changes in the aortic valve functioning.

New solutions are opened up in the evaluation of the rapid and slow ejection phases. Figure 4 shows no elevation of the RHEO in the L-j phase. This entails significant clinical effects, namely, the impossibility of formation of the blood flow structure showing the elevated fluidity properties [9]. This can result in the large vessel thrombosis.

Figure 4. No normal growth of the rapid ejection phase. There is a negative slope in the L-j phase of the RHEO curve.
The definition of the Osborn wave can be treated from a new viewpoint. Figure 5 shows the ECG recording indicating the Osborn wave. However, the "wave" and "point" are to be separated. Point j reflects the rapid ejection phase end marked with a vertical stripe in Fig. 5. It is a middle portion of elevation of the RHEO curve. The Osborn wave is to the left of the phase.

\[ \text{Figure 5. Point j location reflects the rapid ejection phase end marked in the Figure. It is verified by the middle of the RHEO leading edge.} \]

The cardiac cycle phase analysis based on the mathematical models of hemodynamics by G.Poyedintsev – O.Voronova exposed Terra incognita in ECG hiding the structure of three systolic cardiac cycle phases, namely, the load, rapid and slow ejection phases. Indisputably, the research results will contribute to the electrocardiographic notions [12-17].

Awakening of the phase formation will enable experts to hold the key to the yet unknown functioning mechanisms of the cardiovascular system that remains enigma. If only there had been no Terra incognita in ECG, an artificial heart would have been created. But its creation is still ahead.

**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.

References
2. ECG learning centre. http://ecg.utah.edu/
Report

On conditions of negativity of friction resistance for non-stationary modes of blood flow and possible mechanism of affecting of environmental factors on energy effectiveness of cardiovascular system function

Sergey G. Chefranov¹*

¹ Obukhov Institute of Atmospheric Physics of RAS, 119017, Russia, Moscow, Pijevskaya str.3
* Corresponding author: E-mail: schefranov@mail.ru
Submitted: 21 February 2013
Accepted: 24 March 2013
Published online: 30 May 2013

Abstract

It is shown that initiated by action of molecular viscosity impulse flow, directed usually from the moving fluid to limiting it solid surface, can, under certain conditions, turn to zero and get negative values in the case of non-stationary flow caused by alternating in time longitudinal (along the pipe axis) pressure gradient. It is noted that this non-equilibrium mechanism of negative friction resistance in the similar case of pulsating blood flow in the blood vessels, in addition to the stable to turbulent disturbances swirled blood flow structure providing, can also constitute hydro-mechanical basis of the observed but not explained yet paradoxically high energy effectiveness of the normal functioning of the cardiovascular system (CVS). We consider respective mechanism of affecting on the stability of the normal work of CVS by environmental variable factors using shifting of hydro-dynamic mode with negative resistance realization range boundaries and variation of linear hydro-dynamic instability leading to the structurally stable swirled blood flow organization.

Keywords

Non-stationary flow ● Non-equilibrium mechanism ● Friction resistance ● Blood flow structure

Imprint

Sergey G. Chefranov. On conditions of negativity of friction resistance for non-stationary modes of blood flow and possible mechanism of affecting of environmental factors on energy effectiveness of cardiovascular system function; Cardiometry; No.2; May 2013; p.40-50; doi: 10.12710/cardiometry.2013.2.4050
Introduction

Investigations of non-stationary flow of viscous incompressible fluid in the pipes with elastic and rigid walls are widely used for modeling of pulse blood flow in arteries [1-3]. The problem of observed mysteriously high energy effectiveness of CVS functioning is not yet solved. It can’t be explained based on usual assumptions on rapid increase of resistance to the blood flow with successive branching of vessels and their narrowing [4]. Actually, according to the Poiseuille law, viscous flow friction on walls of blood vessels must grow as the fourth power of the value of relative decrease of the vessel’s radius [4,5]. Hence, to pump the blood through the CVS (where the vessels diameter ranges from 10 mm to 1 mm) it would be necessary pressure difference dozens times greater than that is character for CVS artery-vein pressure difference (about 100 mm mercury column).

However, from the other side, Poiseuille law itself is applicable to already stationary flows only, to which in the general case, non-stationary mode of real blood flow in CVS does not belong. It is also known that even for non-stationary modes in the pipes with rigid wall observed value of volumetric rate of flow can significantly differ from pre-calculated values and rate of its change in time grows with the decrease of the used in experiments pipe diameter [6].

J. Womersley (see [3] and referenced there his previous works) was one of the first who theoretically considered peculiarities character for very non-stationary modes in relation with modeling of artery blood flow in CVS. He introduced a dimensionless parameter (further – Womersley number), value of which characterizes extent of deviation of the viscous fluid flow under consideration from a stationary mode. Here $R$ is the radius of a pipe along which the fluid with kinematical viscous coefficient $\nu$ flows, and value $\alpha$ is defined by the character time scale of variability of longitudinal (along the pipe axis) pressure gradient providing existence of the fluid flow in the pipe. In particular, for the case of periodic variations in time of the longitudinal pressure gradient this time scale corresponds to the period of such variability [3].

As noted in [3], the parameter is a modification of existed before this only one dimensionless parameter being a ratio of the width of the blood vessel wall to its radius. Also it is set in [3] that for some values of the parameter $\alpha$, relationships between the pressure gradient and stream velocity for elastic and rigid pipe walls are practically the same. It is considered that the Womersley number shows how much velocity profile for laminar flow in a long pipe differs from the Poiseuille’s one when the fluid is subjected to variable in time longitudinal pressure gradient [1]. In the CVS values of $\alpha$ (calculated for the character heart beat rate) vary in the wide range. So, in aorta, can be more than 10, whereas in capillaries it is about $10^{-2}$ [1].
In [3], however, there were not considered the modes of the pressure gradient change character for relatively short time intervals lying inside a heart cycle when only monotonic change (in the most part of the cycle it is monotonic decreasing) of this value takes place.

In the present work, it is made in particular in assumption of exponential monotonic pressure gradient decreasing with time that allowed defining explicit analytical conditions of existence of the flow modes with negative value of the viscous friction force for a flow with respect to the pipe walls with circular cross-cut of radius $R$. Womersley numbers are estimated for which conditions of linear instability of non-stationary Hagen-Poiseuille flow are met and it is possible emergence of the resulting spiral flow relatively more stable with respect to turbulent disturbances than a laminar non-swirled mode of the fluid flow in the pipe. Applications of the obtained conclusions to explaining of the observed paradoxically high energy effectiveness of CVS normal work are considered. Possible hydro-mechanical mechanism explaining impact of the varying environmental factors on emergence of weather induced pathologies level of which depends on the individual features of stable CVS work and other integrative organism systems in the whole.

Materials and methods

Exact solution of non-stationary hydro-dynamic equations for a circular pipe

Let us consider the flow of viscous incompressible fluid in stationary straight pipe of the unbounded length having circular cross-section (constant for the whole pipe) with radius $R$. We assume that longitudinal along the pipe axis pressure gradient causing the fluid flow is as follows:

$$\frac{\partial p}{\partial z} / \rho_0 = -a_r \exp(-\lambda t) = -a(t) \quad (1)$$

Where in cylindrical reference frame $(z, r, \varphi)$, coordinate $z$ is directed along the pipe axis, and $\rho_0$ is the constant fluid density. We consider flow in the pipe caused by (1) when it is possible to count values of radial and tangent components of the velocity field in the pipe equal to zero, i.e. $V_r = V_\varphi = 0$.

For the longitudinal component of the velocity field $V_z$ taking into account (1), we have the following expression for evolutionary equation followed from nonlinear non-stationary three-dimensional Navie-Stokes equations [5]:
\[
\frac{\partial V}{\partial t} = a(t) + \frac{v}{r} \frac{\partial V}{\partial r}, \quad (2)
\]

where the function \(a(t)\) is defined in (1).

It is not difficult to show that an exact solution of the equation (2), meeting natural boundary condition of non-slipping (when on the solid boundary due to the action of viscous forces fluid flow velocity turns to zero, i.e. \(V_z = 0\) for \(r = R\)) has the following form:

\[
V_z = -\frac{a_0}{\lambda} \exp(-\lambda t) \left[ 1 - \frac{J_0(r\alpha / R)}{J_0(\alpha)} \right], \quad (3)
\]

where \(a_0 > 0, \lambda > 0, \ J_0\) is the Bessel function of the zero order, and the value of \(\alpha = R\sqrt{\lambda / v}\) corresponds to the defined above Womersley number \([3]\). Contrary to \([3]\), here value of \(\lambda\) is real (i.e. it has zero imaginary part), whereas in \([3]\) it is considered as purely complex with zero real part. In the rest, solution (3) coincides with formula (12) of the work \([3]\) in the variant corresponding to the problem of finding an expression for a longitudinal velocity field component via longitudinal pressure gradient. Note that the specified variant is a particular case of the formula (10) from \([3]\), taking into account also elastic features of the pipe wall when modeling artery blood flow.

Using (3) and definition of the tangent friction force per boundary surface square unit,

\[
\sigma = \rho_0 v \left( \frac{\partial V}{\partial r} \right)_{r=R}, \quad [5]\]

(see also in \([5]\) the formula (15.17) for the component \(\sigma_{zz}\) of the viscous stress tensor), we get an exact expression:

\[
\sigma = -\rho_0 a_0 \exp(-\lambda t) \frac{J_1(\alpha)}{\alpha J_0(\alpha)}, \quad (4)
\]

where \(J_1\) is the Bessel function of the first order and the sign of \(\sigma\) characterizes the direction of the impulse flow. So, for the negative values \(\sigma < 0\), the impulse flow is directed as usually from the flowing fluid to the pipe wall causing the flow deceleration due to the positive force of the friction force with respect to the pipe wall. Conversely, from (4), it follows that for the values of \(\alpha > 0\), for which the Bessel function of the first order turns to zero and then gets negative values, friction force also turns to zero and gets negative values when \(\sigma > 0\) in (4). In particular, in the limit of large values \(\alpha >> 1\) in (4) the function \(\frac{J_1(\alpha)}{J_0(\alpha)} \cdot \tan(\alpha)\). In this limit, positivity \(\sigma > 0\) in (4) takes place under condition of meeting the following inequalities (following from the condition \(\tan(\alpha) < 0\)): 
\[ \pi / 2 + \pi n < \alpha < \pi + \pi n, \quad (5) \]

where \( n \) is an integer value and in (5) it must be \( n \gg 1 \). In the general case, for \( \alpha \), instead of (5), the following restrictions defined by the conditions of negativity of \( J_1(\alpha)/J_0(\alpha) < 0 \) are obtained:

\[ \gamma_{0,n} < \alpha < \gamma_{1,n}, n = 1, 2, \ldots, \quad (6) \]

where for any integer \( n \) by definition \( J_1(\gamma_{1,n}) = 0; J_0(\gamma_{0,n}) = 0 \) (in particular, \( \gamma_{0,1} \approx 2.4; \gamma_{1,1} \approx 3.8 \) и т.д.). Thus, scale invariance of the condition (6) takes place related with the possibility of its realization for finite and arbitrary large values of the Womersley number (the latter when selecting sufficiently large integer value of \( n \) in (6)).

When as in [3], value \( \lambda = i\omega \) in (1)-(4), already in the general there are no such simple conditions of negativity of the friction force as (5), (6). However, in the limit of large values of the Womersley number (in the form just considered in [3]) \( \alpha_0 = R\sqrt{\omega/\nu} >> 1 \) it is already not difficult to get instead of (5) the following condition (when replacing in (4) \( \lambda \) by \( i\omega \))

\[ -\pi / 4 + \pi (2k - 1) < \omega < -\pi / 4 + \pi 2k, k \gg 1, \quad (7) \]

where \( k \) is an integer. Inequalities (7) define finite intervals of time corresponding to the negative friction force per the pipe square unit. Condition (7), contrary to (5), (6), is already independent from the pipe radius. It is obtained from the inequality

\[ \sigma \not\sim -\rho_0 a_0 \sqrt{\nu / 2\omega}(\cos \omega t + \sin \omega t)(1 + O(e^{-R\sqrt{2\omega\nu}})) > 0, \quad (8) \]

The condition (7) shows possibility of realization of energy effective mode with negative friction force (and impulse flow directed from the pipe wall to the stream) only for some time intervals but not for all time instances as in (5) и (6). However, such a mode with oscillating pressure gradient is more energy effective than stationary Poiseuille mode because on average for the period of the pressure gradient varying value of (8) turns to zero and losses on the friction have exponentially small value corresponding to the terms neglected in (8).

Note that the obtained conclusions about possibility of the sign change of the impulse flow on the pipe boundary under conditions (5) - (7) are not reflected on the estimate of the value of corresponding energy flow value of which on the boundary for the flow (3) in any case is zero.

Consider also an estimate of the value of hydro resistance that generalizes Poiseuille law for the case of stationary flow (3). Rate of the fluid in the pipe is defined by the volumetric velocity \( Q = 2\pi \int_0^R drV_z \), which for the flow (3) has the following form:
In the limit of small Womersley numbers, from (9), it follows
\[ Q = \frac{\pi a_0 R^4 \exp(-\lambda t)}{\nu\alpha} \left[ 1 - \frac{2J_1(\alpha)}{\alpha J_0(\alpha)} \right]. \]

In the limit of small Womersley numbers, from (9), it follows
\[ Q = \pi a_0 R^4 \exp(-\lambda t)(1-\frac{\alpha^2}{6}+O(\alpha^4))/8\nu, \]
that for \( \lambda \to 0, \alpha \to 0 \) exactly coincides with the well
known dependency stated empirically by Hagen (G. Hagen, 1839) and Poiseuille (J.L.M.
Poiseuille, 1840) and explained theoretically by Stokes (G.G. Stokes, 1845) [5]. It follows that
in the considered limit nonstationarity of the fluid flow itself leads only to the increase of the
hydro resistance \( 1/(1-\frac{\alpha^2}{6}+...) \) times. In the general case of arbitrary Womersley numbers,
hydro resistance changes (decreases) \( \frac{2J_1(\alpha)}{\alpha J_0(\alpha)} - 1 \) \( \frac{\alpha^2}{1} \) times with respect to the case of zero
Womersley number. For example, in the case of large Womersley numbers, when
\( \alpha \to \pi/2 + \pi n, n \gg 1 \), hydro resistance tends to zero. Moreover, if conditions (5) or (6) are
met, the value of this resistance becomes negative that leads to the necessity of qualitative
change of the notion of hydro resistance for such modes of the fluid flow.

Specified above wide range of variability of the Womersley number \( \alpha \) for the blood flow in
CVS in [1] is estimated based on the assumption that for artery vessels of different caliber the
value of \( \lambda \) is one and the same and is defined only by the heart rate (HR). In the present
work, vice versa, the value of the parameter \( \lambda \) (characterizing rate of monotonic exponential
decay with time for the value of longitudinal pressure gradient) may in principle depend also
on the radius of the corresponding vessel in the hierarchy of artery vessel system, not on HR
only, coinciding with it by the order of value only for the largest arteries. In particular, we can
suppose scale invariance of the Womersley number \( \alpha = \) const, under fixing which the value
\( \lambda \rightleftharpoons O(1/R^2) \) can significantly grow with the decrease of radius of the blood vessel \( R \). For such
case, in inequalities (5) or (6), values of \( n \) may be fixed and the inequalities themselves can
have one and the same form for any vessel of artery vessel system independently on their
radius.

Under conditions (5) or (6) direction of the impulse flow changes sign and it corresponds
now to the transfer of impulse from the pipe wall to the flow. In the result, the flow can get
additional acceleration but only during a finite time interval proportional to the value of \( \lambda^{-1} \).
Real wall of an artery vessel has not only passive elastic-resilient features but also its own
muscular system regulated due to nervous and humoral factors. In the norm, it may provide
longer support of the considered undamped blood flow mode thanks to the viscous friction forces and corresponding energy effective mode of CVS work. Really, in the case of the specified prolongation of the mode with negative friction resistance, it is possible its joining with the next heart cycle. Initial part of such a cycle (exhibiting before the start of the phase of monotonic decrease of longitudinal pressure gradient) can be modeled by more short time phase of sharp exponential monotonic increase of the value of longitudinal pressure gradient.

Note that change of sign near $\lambda$ (i.e. for negative values of this parameter $\lambda < 0$) in (1) leads to the same structured solution of type (3), but in which it is necessary to replace $\lambda$ by $-\lambda$ and Bessel function $J_0$ by the modified Bessel function of zero order $I_0$. Meanwhile value (4) is negative for any value Womersley parameter $\alpha$.

Thus, only in the phase of monotonic decrease according to (1) and only under condition (6), it takes place the energy saving effect of realization of negative friction resistance leading to the transfer of impulse from the wall to the flow additionally accelerating it. In engineering practice similar energy saving effects for pulsating modes of the fluid flow (associated even with "super-fluidity") are known for a long time. They were used already in the development of energy optimal system of the fuel feeding for FAU missiles in 1941 and they are also used in the base of empirical equations of G. Poyedintsev-O. Voronova [7], used in the software of the device CARDIOCODE [8, 9] (certified in RF and states of EU). This device is used for complex cardio-metering (synchronized recording and analysis of ECG and rheography) for setting normal mode of functioning of CVS and for quantitative defining of deviations from the normal energy effective work of ECG.

In the result, conclusion about possibility of hydro-dynamic mechanism of sustaining in norm observed phenomenal efficiency of CVS providing by correlation of hydro-mechanical and nervous-humoral factors defining opportunity of the prolongation of the mode with negative friction resistance and its sequential joining in conjugated heart cycles. And, conversely, the problem of observed individual sensitivity to variable environmental factors gets new understanding on the base of the suggested mechanism that joins expressions of such sensitivity with particular individually defined reasons of disruptions of the pointed correlation in the work of CVS and other organism systems

**Stability of non-stationary hydro-dynamic mode**

It is interesting to consider the question of stability of flow mode (3) to arbitrary small by amplitude disturbances on the base of respective generalization of the investigation of linear stability of the Hagen-Poiseuille (HP) flow. It is possible to use results obtained in [10,11], where it was suggested a new linear theory of hydrodynamic stability of the HP flow and the
first time conditions of instability are obtained for very arbitrary small on amplitude axial-symmetrical disturbances already for above threshold Reynolds numbers Re>124. Contrary to the classical hydrodynamic stability theory [5], we consider not pure periodic along the pipe axis disturbances but quasi-periodic with two character incommensurable longitudinal periods each of which describes longitudinal periodic variability of one out of two independent radial Galerkin’s modes of tangent velocity field disturbance.

Let us consider opportunity of generalization of that theory on the case of non-stationary modification of HP flow (3). We use (3) as the main disturbed flow instead of known (see [5]) classical exact stationary solution of Navie-Stokes equations

\[ V_{0z} = V_{max0} \left(1 - \frac{r^2}{R^2}\right), V_{max0} = \frac{R^3}{4\rho_0 \nu} \frac{\partial p_0}{\partial z}. \]

Actually, in the limit of small \( \alpha << 1 \) from (3) it follows that

\[ V^i = V_{0z} \exp(-\lambda \xi) \cdot V_{0z} \left(1 - \alpha^2 \tau + ...\right), \tau = \nu / R^2. \]

In cylindrical reference frame \((z, r, \phi)\) the equation for extremely small on amplitude disturbance of tangent velocity field component (in axially symmetrical case, i.e. when \( \frac{\partial V_\phi}{\partial \phi} = 0 \)) has the form [10,11]:

\[
\frac{\partial V_\phi}{\partial t} + V_z(r,t) \frac{\partial V_\phi}{\partial z} = \nu (\Delta V_\phi - \frac{V_\phi}{r^2}), \quad (10)
\]

where \( V_z \) is the main flow from (3), which is affected by the disturbance \( V_\phi \) so that the resultant flow is already spiral.

Let us find a solution of the equation (10), which satisfies the boundary non-slipping condition on the solid boundary of the pipe (i.e., the condition \( V_\phi(r=R,z,t)=0 \) must hold). The solution is represented in the following form:

\[ V_\phi = V_m \sum_{n=1}^{N} A_n(z,t) J_1(\gamma_{1,n} \frac{r}{R}), V_m = \frac{a_n}{\lambda}, \quad (11) \]

where \( J_1 \) is the Bessel function of the first order, and \( \gamma_{1,n} \) are its zeroes, i.e.. \( J_1(\gamma_{1,n}) = 0 \).

After substitution of (11) in (10), multiplication by \( r J_1(\gamma_{1,n} \frac{r}{R}) \) and integration over \( r \) in the limits from 0 to \( R \), we get (in the result of application of this standard procedure of Galerkin’s approximation of the solution of the equation (10)) in dimensionless form a closed system of equations for \( N \) unknown radial amplitudes \( A_n, m = 1...N \):
\[
\frac{\partial A_m}{\partial \tau} + \gamma_{1m}^2 A_m - \frac{\partial^2 A_m}{\partial x^2} + \frac{4}{\alpha^2} \text{Re} \exp(-\alpha^2 \tau) \sum_{n=1}^{N} p_{nm} \frac{\partial A_n}{\partial x} = 0, 
\]

\[
p_{nm} = -\delta_{nm} + 2 \frac{J_2^2(\gamma_{1m})}{J_2(\gamma_{1m})} \int_0^{\infty} dy J_0(\alpha y) J_1(\gamma_{1m}, y) J_1(\gamma_{1m}, y). 
\]

(12)

In (12) \( \text{Re} = V_{\max} R / \nu \), \( V_{\max} = \frac{\alpha R^2}{4 \nu} \) is Reynolds number, \( J_\alpha \) is the Bessel function of the second order, \( \delta_{nm} \) is the Kronecker symbol, \( x = z/R \), \( \tau = t \nu / R^2 \). The system (12) exactly coincides with the system (3) in [11] when Womersley number tends to zero or equals zero \( \alpha = 0 \), when in (12) there must be made substitution \( J_0(\alpha y) \rightarrow (1 + \alpha^2(1 - y^2) / 4) \), and also \( V_m \) must be replaced by \( V_{\max \alpha} \) in the definition of Reynolds number Re.

Thus, in the limit of small Womersley numbers \( \alpha \ll 10^{-3} \) character for arteries of small caliber, conclusions obtained in [10,11] about linear instability leading to spiralization of the resultant flow for \( \text{Re} > 124 \), actually are remained true also for the non-stationary main flow (3), considered here instead of the stationary mode of the HP flow. At the same time, for aorta, where the value of Womersley number \( \alpha \ll 10 \), conclusions [10, 11] already need substantial refinement since in (12) the term proportional to the Reynolds number Re is found extremely small even for short times \( \tau \ll 10^{-1} \). Obviously realization of the mode of linear exponential instability is found out to be difficult for the flow (3), modeling blood flow in aorta and other large vessels of the arterial system. However when considering time scales including not one but many heart cycles (when the pressure gradient in (1) is described by a periodic function of time, and using substitution \( \lambda \rightarrow i \omega \) in (1)), there appear already qualitatively new opportunities for realization of instability of the main flow related with the effect of parametric resonant instability [12]. In that case it might be reasonable to use Krylov-Bogolyubov method of averaging in the region of the main demultiplicative resonance of frequencies (see [12]). More detailed investigation of stability of the flow (3) might be conducted in a separate work but already now there are grounds state that solution of the problem of stability of the flow (3) with respect to small disturbances and possibility of respective transformation of (3) in a flow with finite spirality substantially depends on the Womersley number.
Conclusions

Results obtained in the present paper point on important features of unsteady non-stationary modes of viscous incompressible fluid flow in the pipe with circular cross-section and solid walls. We show that in principle energy effective hydro-dynamic modes are possible that practically do not have losses due to friction on pipe walls under defined above conditions on Womersley number for such a flow. We obtained conditions of realization of stable to turbulent pulsations spiral swirled flow in the pipe emerging already for not large Reynolds numbers in the result of linear hydro-dynamic instability of the main non-stationary flow generalizing well known mode of the HP flow for the case of unsteady flow. In its turn, relative (compared to a pure laminar flow) energy efficiency of the swirled structural flow organization is caused by minimality of the rate of viscous dissipation of kinetic energy and by extremum of this flow energy [13, 14]. Actually, swirled spiral blood flow structures are observed in CVS and are found to be important for sustaining of it its normal function efficiency [14, 15, 16].

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.

References


XX century.
The first photo of the surface of Mars taken from the Soviet interplanetary space station "Mars"
Review

History of space medicine: Academician Vasily V. Parin, founder of space cardiology

Anatoly I. Grigoriev¹, Roman M. Baevsky¹*

¹ State Scientific Center of the Russian Federation, Institute of Biomedical Problems of the Russian Academy of Sciences, 123007, Russia, Moscow, 76A Khoroshevskoye Ch.
* Corresponding author: Phone: +7 (499) 193-62-44. E-mail: baevsky.imbp@mail.ru
Submitted: 03 March 2013
Accepted: 29 March 2013
Published online: 30 May 2013

Abstract

Russian Academician Vasily V. Parin was one of the leading world scientists in the field of physiology of blood circulation. In this article his role in the development of the space cardiology, an important area of space medicine, is considered. The development and use in space flights of such methods as the analysis of heart rate variability and seismocardiography, creation of the onboard medical equipment is connected with the name of Vasily V. Parin. The monography “Space cardiology” issued in 1967 by Vasily V. Parin with co-authors has dictated and governed the development of this key area in science for many years ahead. The article presents the basic results of cardiological researches in space in the 70-90-s and in the beginning of the 2000s when the space cardiology made its progress keeping the tendencies and traditions created by Vasily V. Parin in the 60s.

Keywords

Space cardiology • Heart rate variability • Seismocardiography • Ballistocardiography • Mars-500

Imprint

Anatoly I. Grigoriev, Roman M. Baevsky. History of space medicine: Academician Vasily V. Parin, founder of space cardiology; Cardiometry; No.2; May 2013; p.52-61; doi: 10.12710/cardiometry.2013.2.5261
Available from: http://www.cardiometry.net/issues/no2-may-2013/history-of-space-medicine.pdf
On the 18th of March, 2013 we celebrated the 110th anniversary of the birth of Vasily Vasilievich Parin, an outstanding Russian physiologist and one of the world-top scientists who made a great contribution to the development of blood circulation physiology. This article is dedicated to one of the principal research activities conducted by Vasily Parin, to the creation and development of space cardiology as a new research area in space medicine.

The 60s marked the beginning of the era of human space missions. The birth and rapid development of space medicine was the necessary condition for successful manned space navigation. New scientific space data on the human health effects of the space flight factors, and, in particular, the effect of weightlessness on the cardiovascular system was analyzed profoundly. In conditions of the weightless, blood is redistributed to the upper body, and the specific circulatory changes trigger various adaptive reactions in the organism. Studying the reactions resulted in the creation of a special space medical area that is known today under the name of the space cardiology.

The new space medicine area was clearly defined in the summary paper by V.V. Parin, R.M. Baevsky and O.G. Gazenko “The Heart and Blood Circulation in Space” published in Cor et Vasa in 1965. And in the same year, in 1965, the “Cardiology” Journal presented his article “Achievements and Success in Space Cardiology” considering issues of the blood circulatory system responses under adaptation of the organism to the weightlessness conditions. It has been shown there that it is just the vegetative nervous system that plays the leading role in
the adaptation and that it is just the analysis of heart rate variability (HRV) as basic method that is capable of studying the vegetative regulation of blood circulation. And it was actually the space medicine that gave birth to the HRV analysis method which is now widely used in various fields of cardiology [1,2].

The first studies of vegetative regulation of blood circulation in the space flight applying the HRV analysis were performed in 1960 for dog space flights on the third earth satellite vehicle, later in 1963-64 for the Vostok -3, Vostok-5 and Voskhod-1 space flights. It have made possible to obtain valuable data in support of the suggestion that the vegetative balance shifts towards the dominance of the activity of parasympathetic regulation member at the first stage of the adaptation to the weightlessness conditions. At the 18th International Astronautic Federation Congress (1967) V.V. Parin (collaborated with R.M Baevsky and G.A.Nikulina) presented the paper “Heart Rate Rhythm as Indicator of State of Neuroendocrine Regulation of Organism in Space Flight Environment”.

In 1967 the monograph “Space Cardiology” by V.V.Parin, R.M.Baevsky, Yu.N.Volkov and O.G.Gazenko was published. That work summarized a broad array of problems associated with impacts and effects of space flight factors on the circulatory system. And the cardiovascular system was presented there as an indicator of adaptive reaction of the organism as a whole. A number of essential scientific and theoretical conceptual principles determining the later development of the space cardiology were formulated there by summarizing the results of the first space flights of the Vostok and Voskhod space crafts [3,4].

The HRV analysis played the key role in studying the vegetative regulation of blood circulation in a space flight. The HRV analysis revealed the mechanisms responsible for re-configuration and re-adjustment of different vegetative regulation members under the weightlessness conditions. It has been found that first the mechanisms of the vegetative regulations are involved into the adaptation process, since the weightlessness leads primarily rather to underloading than overloading of various systems of the organism. The central mechanisms are actuated at subsequent space flight stages. A survey of the HRV analysis application cases in space medicine was introduced in a number of reports at the First All-Union Symposium on the mathematical analysis of heart rhythm guided by V.V.Parin held in Moscow, 1966. About 50 papers on the use of the above method in various areas of clinical and preventive medicine, sport and experimental physiology were discussed at that Symposium.

The analysis of cosmonaut’s heart rate variability during their space flights was one of the important scientific and technical achievements in space medicine in the 60s last century. But it should be noted that almost all the components of orbit medical support system for manned
space missions were developed and designed under the guidance of V.V.Parin. Salyut 1, the first orbital space station, was placed into orbit in the Parin’s lifetime (April 19, 1971). The medical equipment, instrumentation and systems of that station were structurally similar to those used in the contemporary orbital stations. The medical control system was based on ECG, respiration and seismocardiogram recording. The Polynom 2M medical research equipment enabled recording of a great number of cardiac and respiratory parameters. The pioneered program design concept for on board systems was applied to in-depth medical studies and investigations. The preventive health care system was supported by a bicycle ergometer, running simulator, gravity simulating suits and a vacuum vessel to provide a LBNP chamber. It is of course clear that the current IT solutions have made a significant progress and become an integral part of the modern space ship equipment, so that the engineering capabilities which existed in the 1960s at present seems to be at least primitive. But the general principles of data acquisition, processing and analysis applied to the first manned space flights remain valid today. The past years can be regarded as the period of experience accumulation, but today we are expecting a qualitative breakthrough accompanied by a transition to a fundamentally new stage in the development of information technology in space medicine [5,6,7,8].

Our concepts of the human adaptation to the weightlessness conditions have been considerably changed and extended for more than thirty years’ space science experience gained after V.V.Parin’s death. The engineering systems of the manned cosmonautics have been cardinally changed, too, and now we are approaching very closely to the borderline of preparation for interplanetary missions. But the progress and achievements of the 1960s, the age of the progress made owing to V.V.Parin’s academic career and organizational activity, are considered by us as the reference point for evaluating the current advances and developments in space medicine and physiology. Now we are meeting true revolutionary changes over the past three decades in the areas of space medicine and physiology which were the topics of Parin’s keen interest. The case in point is the space cardiology, the use of electronics and computer-assisted equipment for monitoring and control in cosmonauts, the issues of medical prediction and medical support for long-term space missions. We would like to offer herein a comprehensive survey on the key advancements in one of the major space medicine areas which is the space cardiology that is always associated with the name of Vasily Vasilevich Parin who gained wide recognition as the founder of the said science.

In the early 80's, the space cardiology took new important steps to develop new research methods for investigations of blood circulatory system in space. A 24-h ECG recording (Holter-monitoring ECG recording) was first performed during a prolonged space flight. Thereupon,
that method was included into the scope of medical continuous monitoring methods. At that
time, the HRV analysis was first used in the orbital stations to assess the actual functional state
of the organism during physical conditioning exercises on board.

Particular attention should be given to the method of the ballistocardiography that is
capable of examining the heart contractile function by capturing pulse micro movements of the
human body. It was one of the Parin’s favourite methods. He pioneered in its development and
application in the mid 50s in Russia, and it has been just Parin who has translated the
monograph “Ballistocardiography” written by V.Dock and G.Mandelbaum from English into
Russian and who has constructed the first Russian ballistocardiograph. His dream was to
record a weightlessness ballistocardiogram. But it became possible only after the first orbital
stations appeared, so that the first ballistocardiogram was recorded in 1977 on board the
orbital station Salyut-6. But by Parin’s initiative the method of the seismocardiography, closely
related to the ballistocardiography, was employed already during the very first space missions.

The 90s were featured by an intensive international cooperation in the space cardiology.
First of all, a collaboration project in space medicine with Austria should be mentioned, when
the joint scientific experiments Pulstrans and Night were conducted on board the orbital station
MIR. The experiment Pulstrans was aimed at studying vascular responses under conditions of
weightlessness (recording of upper and lower limb sphygmograms). The first contactless
ballistocardiogram was recorded in the experiment Night in the cosmonaut’s sleep with a
sensor positioned in his space sleeping bag. An extensive scientific program with Holter-
monitoring ECG recording during prolonged space flights was successfully implemented in
collaboration with the USA scientists. Valuable data on arterial blood pressure variability were
first obtained in joint researches with scientists from France, and a baroreflex component of
the weightlessness adaptation reactions was analyzed therewith. And the circadian arterial
blood pressure dynamics was a subject of the joint studies as well [9,10,11].

By the early 2000s, the cardiac research results of long-term space missions on board the
orbital station MIR have been summarized (R.M. Baevsky, G.A.Nikulina, I.I.Funtova,
A.G.Chernikova, 2001). The activation regularities of various members in the vegetative
nervous system at different stages of long-term space flights were identified. It has been
shown that usually the tone of the parasympathetic regulation member is enhanced within the
first two flight months. During the space flight months 3-4 noted is the simultaneous
strengthening of the tone both of the parasympathetic and sympathetic systems. The space
flight months 5-6 show a clear shifting of the vegetative homeostasis towards the activation of
the sympathetic regulation member. A pronounced growth of the VLF (Very Low Frequency)
spectral components connected with the activation of the over-segmental brain parts was
observed during an extended space mission months 7-8 due to exposure to the weightlessness. Those fluctuations should be considered as a reliable indicator of the energy and metabolic process control, and they reflect energy-deficit states in the organism. The essential growth of the VLF-component of the HRV spectrum shows a development of the next adaptation stage and involving of the higher vegetative centers into the organism adaptation to the weightlessness conditions. It means that the long-term weightlessness conditions induce a supplementary mobilization of the functional resources. Results from an analysis of ultraslow (circahoralian) heart rate oscillations obtained in a super-long 14-month space mission completed by Valery Polyakov, a cosmonaut-physician, have validated the above staged-adaptation theoretical concept. The period from the 5th to the 9th months of the space flight showed the sequential activation of the higher vegetative centers with a gradual increase both in the amplitude and the circahoralian wave periods.

A new phase in the studies of the adaptation reactions of the blood circulatory system commenced with the start of the operation of the International Space Station (ISS). The emphasis was on individual evaluation of the degree of tension of the regulatory system and the functional reserves of the organism. Since 2003 the scientific experiment Pulse, the scope of which includes recording of ECG, finger photoplethysmograms and respiration rates, has been conducting on the ISS [10].

Further expansion and extension of the said experiment was undertaken in collaboration with German experts. The new Pnevomokard device was developed and designed with their participation to record an impedance cardiogram and a seismocardiogram added thereto. Since 2007 the Pnevomokard scientific experiment has been monthly performing on board the ISS that covers functional tests with fixed respiration rate, with inspiratory and expiratory breath holding technique, with an active orthostatic test before the space mission and after it (A.I. Grigoriev, R.M. Baevsky, 2007)

The Pulse and Pnevomokard experiments held within semiannual flights in 25 crew members on the ISS enabled us to produce a huge amount of scientific material on individual features of the adaptation of the cardiovascular system to long-term microgravity conditions. It has made possible to identify 4 types of the vegetative regulation differing in the patterns of their adaptation reactions. On the basis of generalization of the materials obtained therein, a mathematical model to evaluate the functional states of cosmonauts in space flights by the HRV analysis data was developed (R.M. Baevsky, A.G. Chernikova, 2002). The mathematical model allows differentiating of four types of the functional states which are as follows: the state of physiological norm, the prenosological state, the premorbid state and the pathological state. This classification of the functional states was offered in the 70-80s and enjoyed great
popularity as the “Traffic Light” Rating System (Green indicates: everything is O.K.; amber indicates: attention!; red indicates: danger!). It was presented as a “status step stair”, where the level of the functional reserves (FR) was linearly connected with the degree of tension (DT) of the regulatory systems. The said mathematical model has shown that the dependence between the FR and the DT is not linear and is determined by the individual type of the vegetative regulation. Based on the described mathematical model, the probabilistic approach to an assessment of risks of pathology progression was developed. The offered new approach showed its effectiveness in analysis of the research results received from the ISS.

A new line of investigation in the space cardiology became studying of the vegetative regulation of blood circulation during night’s sleep based on contactless physiologic signal recording. Upon completion of the first experiments in this area, the new Sonocard device was designed in the 90s within the framework of the joint Soviet-Austrian scientific program, and since 2007 it has been using on a regular basis during the ISS flights. The obtained experimental materials made it possible to establish that in case of absence of day operating loading for cosmonauts there is a gradual shifting of the vegetative homeostasis towards the dominance of the sympathetic regulation member with an involvement of the above-segmentary levels of the regulatory mechanism in months 5-6 of the space flight for long-term space missions. By this means additional evidence has been furnished in support of the previously offered conclusions on the multi-stage nature of the adaptation of the organism to the long-term weightlessness conditions. Besides, the Sonocard device is also capable of assessing the quality of the cosmonaut’s sleep that is of great importance for the monitoring and control of the functional states of crew individuals, especially when they undertake high stress activities, for instance, operations in the outer space.

The development of the space cardiology is considerably promoted by ground-based experiment results where impacts and effects of space flight factors are simulated. Pioneering methodological approaches and instrumentation are tested in such experiments under conditions of long-term hypokinesia, isolation and dry immersion; the experiments of this kind reveal new factors which are utilized for elaboration of operational scientific hypothesis. So, in the experiments in 2009 with 7-day dry immersion, a novel method of evaluation of myocardial energetic and metabolic processes, namely, the dispersion ECG mapping was verified. It was shown there that the redistribution of blood and water-electrolytic shifts in the organism cause changes in the electrophysiological characteristics in the myocardium. Those data were utilized for the scientific justification for preparation for new special experiments on the ISS (the Cosmocard experiment).
A large series of cardiologic tests were included into the Mars-500 experiment simulating the space mission to Mars. For the said project used was the complex of cardiologic methods and techniques (the Ecosan-2007 device), that was applied to monitoring and control in 6 individuals of the international crew under conditions of the 520 day isolation and confinement in a sealed ground-based simulation facility, accompanied by the similar monitoring and control of 10 reference groups (each consisting of 10-15 subject) in different parts of the world. The huge experimental database resulted from the project in question enables us not only to prepare medical and technical requirements for the future interplanetary space ship equipment and refine our understanding of the issues on the physiological norm and transitional states, but to offer also the scientific justification of innovative methodology and equipment intended for use in space researches and health care.

An introduction of space technologies in the health care practice has always a significant place in the space cardiology. As early as in the 80s, the Autosan-82 lab as a portable automated laboratory was designed for preventive health examinations of population. The lab was equipped with the devices and applied the methods which were identical to those utilized in the Salyut-6 orbital station. Besides, there a medical computer was provided that was absolutely exclusive in its space medicine application. At the beginning of 2000s, the Stressmeter clinical device based on the Pulse device was created, and commercial production of the Varicard HRV analysis device was started. Before its space application, the Ecosan-2007 complex mentioned above had successfully completed clinical and physiological trials and tests in health examinations of bus drivers and civil pilots. The space device Sonocard was a pilot product for the development of its Earth-used analogue, namely, the device Cardioson-3 that is capable of conducting contactless investigations of sleep that is of great importance for critical patients in intensive care units.

So, the space cardiology, a new research area, born in the 60s, has been making a good progress in the context of space medicine, in a close cooperation with the conventional clinical and preventive cardiology. In this case, the innovative nature of the space cardiology progression should be noted. It applies the latest and the most advanced scientific achievements modifying them in order to solve its specific issues. Innovative original concepts and solutions of methodical and scientific problems are intensively conveyed for their use to conventional health care practice and applied physiology. Such doubled feedback promotes further successful advancements of the space cardiology as a separate area in science and practice.
Conclusions

The space cardiology is a new research area that was formed in the 60-70s last century under the guidance of V.V. Parin and that demonstrates its intensive development nowadays. In 2011, within the framework of 14th Congress of the International Society for Holter and Noninvasive Electrocardiology (14-th ISHNE, Moscow, 2011), a special symposium on space cardiology was held, which was dedicated to the 50th anniversary of the first human space flight. 8 reports on top priority issues of the space cardiology were presented at the symposium. Their publication is devoted to the 110th anniversary of Russian Academician Vasily Vasilevich Parin, the founder of the space cardiology, the contemporary advancements of which are intimately linked with the name of the Russian prominent scientist.

Statement on ethical issues

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

Author contributions

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

Conflict of interest

None declared.

References


7. Parin VV, Baevsky RM, Nikulina GA. Heart contraction rhythm as indicator of the neuroendocrine regulation state of organism in space flight. XVIII Congr Inter Astronaut Feder; Belgrade, Sept. 25-30, 1967.


Report

Issues of health evaluation during simulated space mission to Mars
Part 2. Vegetative regulation of blood circulation in the Martian crew individuals in the Mars 500 project

Evgenie Y. Bersenev¹, Vasily B. Rusanov¹*, Anna G. Chernikova¹

¹ State Scientific Center of the Russian Federation, Institute of Biomedical Problems of the Russian Academy of Sciences, 123007, Russia, Moscow, 76A Khoroshevskoye Ch.
* Corresponding author: Phone: +7 (499) 193-62-44. E-mail: vasilyrusanov@gmail.com
Submitted: 12 March 2013
Accepted: 05 April 2013
Published online: 30 May 2013

Abstract

In order to evaluate the vegetative regulation of blood circulation and assess individual health risks under conditions of the 520 day isolation, used was an analysis of the heart rate variability (HRV). The most significant changes in the HRV values against the background data were reported in the second half of the said experiment. At that time, the heart rate (HR) values showed some reductions, the standard deviation of normal-to-normal beats (SDNN) was increased, and the simultaneous activation of all regulation members (pNN50 – parasympathetic regulation, IC and VLF – the sympathetic and neurohumoral regulation) occurred. The period of “the Mars orbiting”, the time of the crew dividing and “the landing to Mars” featured the highest level of the tension of the regulatory systems and the significant increase in the health risks. An assessment of the functional state of the organism and the adaptation level according to the degree of the tension (DT) of the regulatory systems and their functional reserve (FR) made it possible not only to confirm the presence of the changes identified by the commonly used HRV, but to make them more apparent as well. An assessment of group risks of adaptation disorders at all stages of the experiment provided support that on the average the risk category did not exceed the safe levels, and the functional state of the crew individuals remained within the zone of the physiological norm.

Keywords

Regulation of blood circulation • Space mission to Mars • Isolation • Functional reserves • Degree of tension • Heart rate variability

Imprint

Evgenie Y. Bersenev, Vasily B. Rusanov, Anna G. Chernikova. Vegetative regulation of blood circulation in the Martian crew individuals in the Mars 500 project; Cardiometry; No.2; May 2013; p.62-73; doi: 10.12710/cardio.2013.2.6273
Introduction

Among the main tasks of the ground-simulated experiment Mars-500, the task of obtaining experimental data on the health state and the operational capability of an individual staying for a long time under conditions of the isolation and confinement, with simulating the major specific features of the space mission to Mars, came to the forefront. The information of this sort is required for a better understanding of the dynamics of the adaptation abilities of the human organism affected by various factors, including isolation and staying of the crew in a confined space for a long period of time. In the circumstances, the mechanisms of regulation of physiological functions, which are responsible for setting and adjustment of different systems of the organism to a functioning level that fits the environment adequately, are gaining in importance. The experience of long-term studies in the field of space medicine shows that it is just the method of the heart rate variability analysis that is capable of delivering the most valuable information with respect to the investigation of the regulatory systems being in response to space flight factors [1,2,3]. Space medicine is one of the first areas both in science and in practice where the HRV analysis has been successfully applied to produce new scientific data and solve problems of medical monitoring and control over a human who performs his work under extreme conditions [4]. At present, the HRV analysis has found a wide use in a great diversity of the areas in medicine and applied physiology [5].

The studies were conducted before starting the isolation and every month in the morning hours in a sealed ground-based isolation facility simulating a space ship. The simulated mission crew was international. The crew was composed by 6 individuals (males). Their average age was 32±3,7 years. The occupations of the experiment participants were as follows: physicians, engineers and computer science experts. Every research participant signed his informed written consent. The study & research reports were duly approved by the authorized Bioethics Board. The experiment duration was 520 days. The work and rest schedule of the crew was chosen similar to that used in the orbital space flights (a 7 day week with two days-off). The scope of the activity of the crew included the following: the normal operations and procedures (medical monitoring & control over the health, physical training procedures, inspection and maintenance of the equipment systems, control of the Mars landing module, etc.), conduction of scientific investigations, completion of sanitary and hygienic procedures, etc. The experiment covered 4 main stages as listed below: background studies, the beginning of the isolation (June to November 2010), preparation and implementation of “landing to Mars”, dividing of the crew into groups (December 2010 to February 2011), the return journey to Earth, finishing of the experiment (March to November 2011). During the experiment, two off-nominal situations were simulated (1 - 2 December 2010: imitation of an onboard fire
emergency, 18-25 April 2011: simulated loss of communication with the Earth with an absolutely autonomous space flight).

The menu of food items for the crew members’ nutrition was identical to that usually consumed by cosmonauts in the International Space Station. The crew operated in the artificial atmospheric environment at normal barometric pressure.

The studies of the HRV were conducted with use of the hardware & software system Ecosan in the crew individuals at rest. The HRV analysis was carried out in accordance with the relevant Russian national and international standards [5,6] applied for evaluation of autonomous regulation by the HRV parameters. For an assessment of individual risks of adaptation disorders, utilized were methods which had been previously developed for an application in the space flight environment, based on the HRV analysis. In accordance with the said analysis, the level of adaptation should be evaluated by the ratio between the functional reserves (FR) and the degree of tension (DT) [3,7,8,]. The results were also analyzed with use of classification of the functional states by the HRV data applying the probabilistic approach in order to calculate the probability of occurrence of one of the four probable functional states which might be as follows: the state of physiological norm, the prenosological state, the premorbid state and the pathological state. An individual functional state was identified to belong to a certain class of the above functional states by the maximum likelihood, considering at the same time the likelihood to belong to any other classes. Probabilities of occurring of the prenosological and premorbid states (or a reduction in the probability of occurring of the physiological norm state) serve as a quantitative measure of an assessment of the risk of the adaptation disorder. For that purpose, used were 10 conventional risk categories.

A comparison of the dynamics of the data obtained in the experimental group due to a small sample size was carried out with an application of non-parametric Friedman test and Wilcoxon’s criterion. Kendall's coefficient of concordance was used for assessing an intra-group agreement of changes in the separate HRV values in their dynamics. The data given in the tables below are presented with indicated mean values (M) and mean square errors (m).

**Results and discussion**

Table 1 offers monthly-based mean values of basic statistics and spectral HRV parameters related to 6 crew members that were taken before the experiment and during the latter. The application of the Friedman test made it possible to detect the presence of significant changes in the following parameters: HR, pNN50 and SI (p≤0,02). The Kendall's coefficient of concordance related to the above parameters was at a level of 0,3 and showed statistical significance bearing witness to the intra-group concordance of the changes of the parameters.
in question. On days 56-58 in the experiment, a moderate increase in the heart rate with the significant reduction in the heart rate variability (the TP and parasympathetic activity indicator pNN50) was observed. It could be treated as a moderate tension of the regulatory systems connected with an adaptation to a new environment. The same tendency was revealed in other studies, too [9]. Later on, (on days 89-91), an activation of the parasympathetic member of the regulation was reported: a reduction in the SI parameter was significantly identified that might be considered as a response to the completion of the period of the initial (acute) adaptation. At a later time, starting with days 115-117, an increase in the heart rate was observed (p≤0,05) followed by a reduction in the parasympathetic activity (p≤0,05 for parameter pNN50) (on days 148-150).

The most significant changes in the HRV parameters were reported in the second half of the experiment (the return journey period). During the said period of time, it was significantly established that periodically a decrease in the heart rate (HR) occurred, the parameter of the standard deviation of normal-to-normal beats (SDNN) was increased, and the simultaneous activation of all members of the regulation (pNN50 – parasympathetic regulation, and IC – sympathetic and neurohumoral regulation) took place.

**Table 1. Mean values of HRV parameters for the group during the 520 day isolation.**

<table>
<thead>
<tr>
<th>Day / month of isolation</th>
<th>HR, beats/min.</th>
<th>pNN50, %</th>
<th>SDNN, µsec.</th>
<th>SI, conventional units</th>
<th>IC, conventional units</th>
<th>TP, µsec.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before isolation</td>
<td>63,5±2,4</td>
<td>23,19±6,63</td>
<td>69,6±9,5</td>
<td>45,6±8,82</td>
<td>4,3±1,37</td>
<td>3648±1013</td>
</tr>
<tr>
<td>29-31 June 2010</td>
<td>62,4±4,3</td>
<td>22,26±9,72</td>
<td>70,4±10,9</td>
<td>60,6±22,2</td>
<td>3,3±0,82</td>
<td>5824±2214</td>
</tr>
<tr>
<td>56-58 July 2010</td>
<td>66,5±4,2</td>
<td>*18,72±7,28</td>
<td>62,7±8,9</td>
<td>73,3±21,6</td>
<td>3,9±1,3</td>
<td>*3490±1285</td>
</tr>
<tr>
<td>89-91 August 2010</td>
<td>59,3±3,5</td>
<td>25,30±11,09</td>
<td>70,8±13,3</td>
<td>*55,2±16,3</td>
<td>3,3±0,86</td>
<td>5670±1870</td>
</tr>
<tr>
<td>115-117 September 2010</td>
<td>*62,2±3,9</td>
<td>24,57±9,02</td>
<td>65,1±8,1</td>
<td>54,8±12,4</td>
<td>3,7±1,36</td>
<td>3307±735</td>
</tr>
<tr>
<td>148-150 October 2010</td>
<td>*70,3±3,6</td>
<td>*12,28±7,78</td>
<td>57,8±9,6</td>
<td>*77,1±17,5</td>
<td>5,3±1,61</td>
<td>4828±2388</td>
</tr>
<tr>
<td>180-182 November 2010</td>
<td>64,2±4,6</td>
<td>21,11±6,28</td>
<td>61,4±8,6</td>
<td>66,7±20,5</td>
<td>5,1±1,37</td>
<td>3986±1727</td>
</tr>
<tr>
<td>217-219 December 2010</td>
<td>67,3±3,6</td>
<td>15,35±6,96</td>
<td>61,0±9,9</td>
<td>72,2±21,9</td>
<td>4,8±1,30</td>
<td>3290±1033</td>
</tr>
<tr>
<td>235-237 January 2011</td>
<td>*68,1±3,9</td>
<td>15,20±8,22</td>
<td>58,2±10,1</td>
<td>85,1±22,8</td>
<td>5,3±1,45</td>
<td>4203±1768</td>
</tr>
<tr>
<td>274-276 March 2011</td>
<td>63,4±5,7</td>
<td>*26,17±10,7</td>
<td>63,2±12,1</td>
<td>*79,6±26,2</td>
<td>*2,7±0,81</td>
<td>4063±1837</td>
</tr>
<tr>
<td>303-305 April 2011</td>
<td>*58,0±3,8</td>
<td>*31,01±10,1</td>
<td>*85,3±15,4</td>
<td>*47,1±15,8</td>
<td>*4,4±1,02</td>
<td>6920±3173</td>
</tr>
<tr>
<td>333-335 May 2011</td>
<td>*59,4±4,9</td>
<td>29,96±13,17</td>
<td>83,32±15,1</td>
<td>*40,2±12,2</td>
<td>8,0±5,03</td>
<td>5884±1838</td>
</tr>
<tr>
<td>373-375 June 2011</td>
<td>*63,8±4,9</td>
<td>30,44±10,28</td>
<td>79,72±15,3</td>
<td>63,3±33,3</td>
<td>5,5±1,63</td>
<td>5614±2377</td>
</tr>
<tr>
<td>401-403 July 2011</td>
<td>61,9±3,8</td>
<td>26,52±11,08</td>
<td>83,11±13,2</td>
<td>39,26±10,8</td>
<td>5,5±1,16</td>
<td>6823±1779</td>
</tr>
<tr>
<td>431-433 August 2011</td>
<td>62,8±4,2</td>
<td>26,01±13,35</td>
<td>*64,0±12,1</td>
<td>*75,0±31,8</td>
<td>6,0±3,2</td>
<td>*3969±1739</td>
</tr>
<tr>
<td>507-509 October 2011</td>
<td>60,9±4,1</td>
<td>27,62±9,56</td>
<td>86,36±13,3</td>
<td>48,19±15,8</td>
<td>4,56±0,76</td>
<td>6062±1614</td>
</tr>
</tbody>
</table>

Note: * - significant differences (p<0,05) from one of the two previous measurements.
It is common knowledge that the HRV spectrum reflects the state of various members of the HRV regulation and permits of judging which of the regulatory mechanisms is dominating at every stage of the adaptation; therefore, an analysis of individual components of the said spectrum is of great importance for different stages of the isolation.

In the above experiment, it was reported that the relative power of the high-frequency oscillations of the spectrum (HF%) was reduced since the end of October 2010 (days 148-150 in isolation). That was in correspondence with the growth of activity of the over-segmentary parts of the regulatory mechanism involved in the regulation of energetic-metabolic processes (VLF%), and the ratio VLF/HF, as of on days 180-182, differed significantly from the background values that was an evidence in support of the growth of the activity of the sympathetic member of the regulation (the reaction of tension). In the described case, the activity of the centers of the blood vessel tonicity regulation (LF%) was stepped down, that resulted likely from the reduced physical activity of the crew (s. Fig. 1 below herein).

The revealed dynamics of the HRV parameters confirms the known facts about the multi-stage nature of the process of a long-term adaptation: upon an acute period of the adaptation to the space flight environment, there comes the period of re-arrangement or re-configuration of all vital functions (space flight months 1 to 3), thereupon the period of a relatively stable adaptation begins (from space flight month 4) with a progressive enhancement of the activity of the regulatory systems, especially the activity of the central loop of the regulation [10, 11]. Upon the period of the relatively stable adaptation (from space flight month 3 till space flight month 5), in order to preserve an acceptable adaptation of the organism to the microgravity environment, it is required for the organism to provide an additional mobilization of the
functional reserves and a supplementary activation of the regulatory systems. In the experiment with the 520 day isolation it took place after starting the simulated return journey to the Earth (April 2011).

The applied phase plane method capable of evaluating the functional state of the organism and the level of the adaptation by plotting a coordinate plane with axes being the values of the degree of the tension of the regulatory systems (DT) and their functional reserve (FR) enabled us not only to lend credence to the changes revealed by the commonly accepted HRV parameters, but to display them more apparently as well (s. Fig. 2).

![Phase tracking of functional state of the Martian crew under conditions of isolation and confinement.](image)

From June 2010 till February 2011 the functional state of the members of the Mars mission crew under conditions of the isolation remained within the physiological norm. There was a tendency for a DT growth accompanied by a gradually decrease in the FR and moving of the functional state closer to prenosology zone, particularly in the period from December 2010 till the end of February 2011. From March 2011 till the end of the isolation, the functional state was optimized within the zone of the physiological norm. In the probabilistic assessment of the functional state of the crew individuals it was detected that the mean probability of the prenosological state throughout the experiment (except for January 2011) did not exceed 20%, and the group risk of the adaptation disorder was reported to be under category 2.

The mechanisms of adaptation, particularly the hearth rhythm regulation, show their high plasticity and mutual dependence. The aim of the adaptation is not only a mere adjustment or “a new setting” to the changed environment, but the maintenance of the required homeostatic equilibrium of the organism to be consistent to the external environment as well, that may be
achieved by activation of different regulatory mechanisms. As compared with the conditions of the real space mission, the 520 day isolation experiment was a simulation only, where human subjects did not experience such a powerful factor like exposure to real or artificial microgravity, that was noted by other researches, too [11]. From the very beginning of the isolation, the intra-group dispersion of all HRV parameters was almost doubled (s. Table 1). It indicated a high individualization of the adaptation processes considering both the time requirement and the response intensity that might hinder an evaluation of common tendencies.

In order to analyze the specific features of the adaptation of the crew individuals at different stages of the 520 day isolation experiment, the HRV analysis data were grouped by formal criteria of the experiment management as follows: 1) background studies, 2) the beginning of the isolation (June - November 2010), 3) preparation and implementation of “landing” to Mars, dividing the crew into groups (December 2010 – February 2011), and 4) the return journey to Earth, experiment finishing (March - November 2011).

The most pronounced changes were reported to be associated with the preparation and implementation of the simulated landing to the Red Planet and the final stage of the experiment (s. Table 2 below herein). The identified tendencies of the month-by-month dynamics of the HRV parameters became more clear-cut.

**Table 2. Dynamics of some HRV parameters at main stages of the experiment (M±m)**

<table>
<thead>
<tr>
<th>HRV parameters</th>
<th>Stage 1, before the experiment</th>
<th>Stage 2, June – November 2010, simulated traveling to Mars</th>
<th>Stage 3, December 2010 – February 2011, landing to Mars</th>
<th>Stage 4, March – November 2011, return journey to Earth</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats per min.</td>
<td>63,25±2,45</td>
<td>64,18±1,65</td>
<td>66,32±2,48</td>
<td>61,12±1,68***,***</td>
</tr>
<tr>
<td>SDNN, µsec.</td>
<td>69,63±9,48</td>
<td>64,75±3,87</td>
<td>60,83±5,85</td>
<td>80,78±5,51**,<strong>,</strong>*</td>
</tr>
<tr>
<td>CV, %</td>
<td>7,30±0,87</td>
<td>6,65±0,27</td>
<td>6,40±0,43</td>
<td>7,92±0,45***</td>
</tr>
<tr>
<td>VLF/HF</td>
<td>1,35±0,39</td>
<td>1,57±0,18</td>
<td>1,94±0,36</td>
<td>2,74±0,63*,***</td>
</tr>
<tr>
<td>RSAI, conventional units.</td>
<td>3,50±0,71</td>
<td>3,97±0,30</td>
<td>3,89±0,48</td>
<td>4,47±0,25**</td>
</tr>
<tr>
<td>Risk, scored</td>
<td>1,00±0</td>
<td>1,31±0,96</td>
<td>1,72±0,21*</td>
<td>1,11±0,68***</td>
</tr>
</tbody>
</table>

Note: significant differences (p<0,05) *difference from stage 1, **difference from stage 2, ***difference from stage 3.

The changes occurred in the initial period of the isolation (June - November 2010), as described above, are primarily related to the adaptive re-configurations of the regulatory mechanisms and fluctuations in the autonomous balance. Therefore, the changes in the
vegetative regulation of the hearth rhythm within the entire group in general were falling short of the significance. It might depend on the fact that the probable adverse effect of the entire complex of the experiment conditions (isolation and confinement, social and cultural differences, changes in nutrition, loading, etc.) was not substantial, and it was balanced out by such an important factor as the work-and-rest scheduling, i.e., by more stable conditions as compared with the usual way of life.

During the period of simulation of orbiting Mars, dividing the crew into groups and landing to the Mars surface, observed was a tendency for the vegetative regulation to be shifted towards strengthening of the sympathetic activity and decreasing that of the parasympathetic (an increase in the VLF/HF index as the ratio between the low-frequency and the high-frequency components of the spectrum; they were the highest HR values on record within the whole experiment period). Hence, even such not appreciably remarkable shifts of the vegetative regulation produce a significant increase in the mean group category risk of the adaptation disorders.

As mentioned above, the most pronounced changes of this sort were recorded in the final period of the experiment. Significantly identified was the following: the heart rate (HV) values were falling, the integrated variability of the heart rhythm (SDNN, CV) was increasing, and observed was the simultaneous activation of the parasympathetic regulation (a decrease in the HR and an increase in the variability) and the sympathetic and neurohumoral regulation (an increase in the VLF/HF ratio). As against the simulated traveling time, the preparation and the landing to the Mars surface, the functional state of the system of the vegetative regulation of the heart rhythm at the final stage of the experiment was the most favorable, and the risk of the adaptation disorder was reported to be at its minimum, but it was achieved due to strengthening of the activity of all members of the regulatory mechanism (the significant growth of the RSAI, the regulatory system activity indicator), most notably the central loop of the control (a significant increase in the VLF/HF). A similar dynamics of the mechanisms of the homeostasis regulation was demonstrated by other researches, too [12,13].

Some individual peculiarities of the processes of the adaptation of the crew members during the simulated space mission to Mars were described by us before [14]. The said peculiarities should be analyzed in more details, considering the nature of the activity and psychological reactions of every crew individual. It is important to note in this case that an individual assessment of the adaptation risks at different stages of the 520-day isolation experiment has not only confirmed the presence of the individual specific features in the adaptation for every crew member, but it also has made possible to evaluate the adaptation burden and the actual physiological “cost” thereof at every stage in the experiment. Figure 3 displays some individual
category cases of the risk of adaptive health changes for each crew member separately, covering the entire experiment.

Figure 3. Changes of individual risk categories in their dynamics under conditions of the Martian crew isolation (1, 2, 4, 6 – the Nos. of crew individuals, the risks of crew individuals Nos. 3 and 5 were reported to be under category 1).

Prior to the experiment, the risk category of all crew members was the least (category 1). Within the first half of the simulated space mission, before approaching the Red Planet, an increase in some individual risks was reported for two members of the crew only: they were individuals under Nos.1 and 6, whereby No.1 was the crew Commander. During the period of the simulated landing to the Mars surface, an increase in the individual risks was reported even for four crew individuals of the six, and at the final stage it was just the crew Commander only who showed an increase in his individual adaptation risk.

The individual risk distribution of this sort is an important fact in support of a series of our hypotheses at once, which were formulated by us before the experiment and which were used as the basis for the definition of the problems of the study of the vegetative regulation of the heart rhythm under conditions of the 520-day isolation and interplanetary expedition simulation.

Conclusions
In the first place, high informativity of the HRV analysis methodology for the assessment of the functional state and the adaptability of a human under changed conditions has been
successfully demonstrated. The data obtained thereon allow judging not only the group-related dynamics of the functional state that is of prime importance for extended space expeditions, but the individual adaptive reactions as well, along with the individual risks of the adaptation disorders. The observed dynamics of the vegetative regulation and the adaptive abilities according to the HRV data are consistent with the experiment’s results related to the blood system, human immunity, metabolic changes, adaptive and psychological states of the crew members [9, 11, 13, 14-19].

In the second place, the HRV analysis under conditions of the long-term isolation in simulated space mission to Mars has revealed that, in general, no serious changes in the functional state are available, and the adaptive reactions of the crew individuals have been adequate in most cases. The group assessment of the functional state dynamics has demonstrated that the functional state throughout the period of the survey has been found to be within the physiological norm. When applying the probabilistic approach, a weak tendency for a growth of the prenosological states has been detected. The methodology of the assessment of the adaptation risks to health shows that the above prenosological state growth tendency does not lead to an increase in the risk above risk category 2. When applying the risk classification scored from 1 to 10, the foregoing category should be treated as a very weak risk of progression of adaptive disorders for health.

In the third place, the analysis of the results of the studies confirm the presence of some individual specific features of the adaptation to the experiment environment that might be associated with typological, specific traits of personality and some other features, including the job functions assigned in the crew.

As a result of the conducted studies, unique materials have been obtained which describe the effects of the long-term isolation and confinement on the status of the vegetative regulation of blood circulation. An efficiency of the application of the HRV analysis method and the probabilistic approach to the assessment of the obtained data in particular for this purpose has been reinforced. The study has made apparent that during the simulated space mission to Mars, the 520-day isolation has not caused any serious changes in the functional state of a human, and the risk of progression of any pathological deviations has not exceeded the safe limits.

The experience acquired in the studies with use of the sealed ground-based facility simulating the space ship mission enables us to carry out new long-term investigations in further experiments in a more efficient way. New technologies approved during the 520-day isolation and confinement study can be effectively used in researches of effects of space mission factors on the organism. The outcomes of the completed studies can be applied to
preparation of medical and technical requirements for a medical support system to be provided for future interplanetary space missions, specifically for an individual prenosological control system and an assessment of the of adaptation disorders in interplanetary space flights.

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

Author contributions
V.B.R., E.Y.B. and A.G.C. developed the concept, prepared the manuscript and analyzed the data, V.B.R. drafted the manuscript, read and met the ICMJE criteria for authorship. All authors read and approved the final manuscript.

Conflict of interest
None declared.

References
of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
11. Pasekova OB, Stepanova GP, Skedina MA. Spectral characteristics of EEG alpha-rhythm and results of myocardium dispersion mapping in the experiment with 520-day isolation. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
12. Novikov VE, Oganov VS. Investigation of bone system and body composition in the participants of the Mars-500 project. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
13. Stepanova GP, Pasekova OB, Degterenkova NV. Dynamics of the cardiovascular parameters and bioelectrical activity of the brain during the bicycle test performed before and after 520-day isolation. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
15. Morukov BV, Kuzichkin DS, Markin AA. Studies of hemostasis system during 520-day isolation and confinement. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
16. Nichiporuk IA, Vassilieva GY, Noskov VB, Morukov BV. Comprehensive dynamic evaluation of human neurohumoral, immunological and psychophysiological status, body liquids and mass. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
18. Skedina MA, Chanieva MI, Ivanova SM, Pogorelov VM. Investigation of the erythron peripheral component of the test subjects during 520-day isolation. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
19. Sorokin OG. Dynamics of adaptation in the Mars-520 crew members. International Symposium on the results of the experiments, simulating manned mission to Mars (MARS-500); Moscow; 23-25 April 2012.
Report

Issues of health evaluation during simulated space mission to Mars
Part 3. Assessment of adaptation reactions in the participants of the long-term medical & ecological investigations during the experiment Mars-500

Roman M. Baevsky¹, Azalia P. Berseneva¹, Irina N. Slepchenkova¹, Anna G. Chernikova¹*

¹ State Scientific Center of the Russian Federation, Institute of Biomedical Problems of the Russian Academy of Sciences, 123007, Russia, Moscow, 76A Khoroshevskoye Ch.
* Corresponding author: Phone: +7 (499) 193-62-44. E-mail: anna.imbp@mail.ru
Submitted: 16 March 2013
Accepted: 10 April 2013
Published online: 30 May 2013

Abstract

The paper presents the results of the long-term medical & ecological investigations conducted during the experiment Mars-500. Methodology of conducting the long-term medical & ecological investigations and the applied methods are considered. The results are presented in the materials of the research conducted in Russian Federation and Republic of Belarus (Moscow, Syktyvkar, Yekaterinburg, Izhevsk, Magadan and Minsk). For comparative evaluation of the functional state of different reference groups the notion of “ecological stress” was introduced. It depends upon the degree of dominance of the activity of the sympathetic member of the regulatory system over the parasympathetic member. Application of probabilistic approach to the assessment of the functional state and adaptation level with the FR (functional reserve) and the DT (the degree of tension) of the regulatory mechanisms proved the detected peculiarities of the heart rhythm vegetative regulation. Clear dependency of the functional state of the volunteers on geographic location of regions and climatic parameters is observed. Almost every HRV indicator is characterized by seasonal dynamics. Seasonal dynamics data is exemplified by the research conducted in Yekaterinburg and Syktyvkar.

Keywords

Medical and ecological investigations • Research • Adaptation • Prenosological diagnostics • Functional state • Heart rate variability • Ecological stress

Imprint

Roman M. Baevsky, Azalia P. Berseneva, Irina N. Slepchenkova, Anna G. Chernikova. Assessment of adaptation reactions in the participants of the long-term medical & ecological investigations during the experiment Mars-500; Cardiometry; No.2; May 2013; p.74-87; doi: 10.12710/cardiometry.2013.2.7487
Introduction

During the experiment “Mars-500” flight conditions to Mars and space crew life were simulated. Simultaneously satellite investigations of the reference groups of volunteers living and working in natural social and work environment were conducted. These investigations were important for scientific analysis of the health changes in the crew of Mars-500 experiment. The group of people spent almost two years being isolated and experiencing the influence of different factors (isolation, hypomobility, psychological and emotional tension, etc.). These factors produced significant influence on the human body, its adaptive abilities and regulatory mechanisms. Test experiments are to be conducted where similar groups of people would be under natural conditions influenced by different environmental factors, e.g., climatic and geographical, working, social and living conditions. Health criteria and pathology risks can be identified only when comparing the adaptive reactions of the groups of people being put under simulated and regulated environmental conditions, with the reactions of the similar groups under natural conditions.

In this connection the project “Long-term medical and ecological investigations” supported by General Committee of the Russian Academy of Science was developed. As in case of the basic experiment conducted with the participation of the European Space Agency, parallel international investigations were conducted in Russia, in Europe (the Czech Republic and Germany) and in America (Canada and the USA). Thus, a set of adaptive reactions determined by climatic, ethnical, geographical, working and social differences was obtained. The conducted investigations can be called medical & biological as both the inner risk factors and environmental stress influence are considered. One of the main objectives of the present research work was the development and scientific rationale of the evaluation criteria of health and health risks with practically healthy people under different social and ecological conditions. Of great importance in the conducted investigations is examination of the novel methods of assessment and forecasting of health and adaptive abilities. These methods are developed in cosmic medicine with regard to problems of practical healthcare and applied physiology. Investigations with groups of practically healthy people in different climatic and geographical regions provides information for future application of the results of MARS-500 experiment.

In the present paper the main attention is given to the results of medical & ecological investigations conducted in the cities of Russian Federation and Republic of Belarus (Moscow, Yekaterinburg, Syktyvkar, Izhevsk, Magadan and Minsk).
Materials and methods

152 volunteers (13 groups) participated in the investigations. 6 participants (the first group) were put in a sealed ground-based facility. The other (satellite) groups (6 – 18 people in each group) were situated in 12 cities around the world (s. Table 1). The groups included mainly the intellectual workers (research laboratory staff, engineers, economists, teachers).

Table 1. Participants of experiment MARS-500

<table>
<thead>
<tr>
<th>City</th>
<th>Number of participants</th>
<th>Number of investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moscow (MARS-500)</td>
<td>6</td>
<td>120</td>
</tr>
<tr>
<td>Moscow</td>
<td>16</td>
<td>139</td>
</tr>
<tr>
<td>Voronezh</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>Syktyvkar</td>
<td>17</td>
<td>232</td>
</tr>
<tr>
<td>Yekaterinburg</td>
<td>12</td>
<td>146</td>
</tr>
<tr>
<td>Magadan</td>
<td>20</td>
<td>254</td>
</tr>
<tr>
<td>Izhevsk</td>
<td>11</td>
<td>103</td>
</tr>
<tr>
<td>Minsk (Republic of Belarus)</td>
<td>10</td>
<td>127</td>
</tr>
<tr>
<td>Almaty (Kazakhstan)</td>
<td>18</td>
<td>221</td>
</tr>
<tr>
<td>Berlin (Germany)</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>Prague (Czech Republic)</td>
<td>8</td>
<td>61</td>
</tr>
<tr>
<td>Toronto (Canada)</td>
<td>6</td>
<td>98</td>
</tr>
<tr>
<td>Poulsbo (USA)</td>
<td>4</td>
<td>114</td>
</tr>
</tbody>
</table>

Similarity of investigations in all regions was provided by application of the hardware and software complex Ecosan-2007 [1]. Only in Canada and the USA the “Heart Wizard” device (product of the American company “Bicom Technologies”) was applied instead [2]. The device is used for analysis of HRV using the photoplethysmographic ear sensor with the application of Internet technology. The computer software of the device was modified to obtain the results answering the data recorded with the hardware and software complex Ecosan-2007.

Research report of the investigations of all reference groups covered monthly ECG recording during 5 minutes at rest and 15 minutes with respiratory tests, filling the special question form concerning lifestyle, loads and possible complaints during the month. Arterial pressure, height and weight were measured. All experiment participants signed the informed consent statement. The research reports were approved by Commission on Bioethics. To provide the uniformity of the investigations in all regions a special procedure manual was prepared [3].

The examination resulted in preliminary findings and formation of the file containing the results of the conducted investigation in the individual database with its further communication to Analytical Center. For exchange of the information as well as methodological and technical support a special website was designed [4]. During the investigations the average results for the cities and weather conditions were displayed.
Prenosological approach described in publications [5, 6, 7] was used when assessing the results.

Results and discussion

Figure 1 shows distribution of the satellite groups from several regions of Russia and Republic of Belarus according to age and body mass index (BMI). We can observe minor but significant (p<0.001 according to F-ratio test) differences of age (from 28.9 in Minsk to 35.1 in Moscow) and body mass index (from 23.6 in Minsk to 26.4 in Moscow). When comparing the results of physiological and medical investigations these differences should be taken into account. The exception is the group from Izhevsk which is younger and has minor age differences (its participants are students).

Average group values of certain indicators of functional state evaluation in the groups are represented in Table 2. It can be observed that in Minsk, Syktyvkar and Moscow heart rate variability tends to rise. The highest arterial pressure rate (systolic and diastolic) is observed in Magadan and Moscow.

In Yekaterinburg the lowest heartbeat rate and arterial pressure values are observed. When comparing the data on functional state of cardiovascular system with age and body mass index it can be supposed that the observed differences in cardiovascular homeostasis are connected...
not only with age and body peculiarities. This speculation can be proved when comparing the indicators of self-regulation in the examined groups. Index of stress reflects the sympathetic regulation level and degree of tension whereas pNN50 reflects the parasympathetic level. The most favourable state of regulatory mechanisms is observed with the group from Yekaterinburg (the group has average indicators of age and BMI - body mass index), the most unfavourable state is with the group from Magadan (its indicators of age and BMI are the second among the groups). The group from Minsk shows the highest stress index values but activity of parasympathetic regulatory member remains (pNN50). The group from Izhevsk showed quite high stress-index, the parasympathetic regulation indicator was the highest.

Table 2. Basic indicators of the operational evaluation of functional state of volunteers in different regions

<table>
<thead>
<tr>
<th></th>
<th>Izhevsk n=103</th>
<th>Minsk n=129</th>
<th>Magadan n=251</th>
<th>Yekaterinburg n=146</th>
<th>Syktyvkar n=232</th>
<th>Moscow n=140</th>
</tr>
</thead>
<tbody>
<tr>
<td>heartbeat rate, BPM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.5±1.2</td>
<td>79.3±1.1</td>
<td>72.8±0.7</td>
<td>70.4±0.6</td>
<td>74.0±0.5</td>
<td>74.1±0.8</td>
</tr>
<tr>
<td>systolic arterial pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>117.9±1.9</td>
<td>123.2±0.9</td>
<td>129.4±0.6</td>
<td>118.5±0.7</td>
<td>121.0±0.6</td>
<td>124.4±0.6</td>
</tr>
<tr>
<td>diastolic arterial pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76.0±0.9</td>
<td>79.11±0.7</td>
<td>80.6±0.6</td>
<td>76.5±0.6</td>
<td>75.9±0.4</td>
<td>78.8±0.7</td>
</tr>
<tr>
<td>load index, c.u.</td>
<td>108.3±9.2</td>
<td>135.6±11.6</td>
<td>135.0±5.7</td>
<td>82.6±5.1</td>
<td>127.0±4.3</td>
<td>125.3±8.6</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>22.7±2.3</td>
<td>13.8±1.3</td>
<td>8.7±0.7</td>
<td>20.9±1.4</td>
<td>11.4±0.8</td>
<td>10.7±0.9</td>
</tr>
<tr>
<td>ecological stress</td>
<td>37.5±7.6</td>
<td>70.6±12.4</td>
<td>67.2±6.3</td>
<td>18.8±3.9</td>
<td>27.2±2.9</td>
<td>38.9±7.2</td>
</tr>
</tbody>
</table>

For comparative evaluation of functional state of different reference groups the notion "ecological stress" (ES) was introduced. It is identified by degree of dominance of activity of sympathetic member of regulatory system over parasympathetic member. Correlation of pNN50 and SI, concentration index as well as heartbeat rate and arterial pressure values enable considering ecological stress. Ecological stress is the body’s response to combined influence of environmental factors, it is the result of the body’s adaptability to environmental conditions. Table 3 shows the average values of some indicators in 6 reference groups studied in Russia and Republic of Belarus, as well as the values of ecological stress indicators calculated from the formula SI/pNN50. Significant differences between the cities with different environmental conditions can be observed. Thus, in Minsk and Magadan the highest ecological stress level is observed. These cities have the highest average values of systolic and diastolic arterial pressure and SI whereas Magadan has the lowest pNN50 value. Probably the degree of ecological stress depends not only on geographical location of the studied group but on the complex of social, working, psychological and living conditions. Thus, Izhevsk, Syktyvkar and especially Yekaterinburg which are situated in the northern part of Russia differ from Magadan...
in many parameters, whereas in Minsk which is situated southward diastolic arterial pressure and SI values hardly differ from those recorded in Magadan. It is well illustrated by the ecological stress data presented in table 2. Comparing the average SI data in the groups it is observed that the differences are determined mainly by the pNN50 value, i.e., by the degree of activity of parasympathetic member of regulatory system.

Application of probabilistic approach for evaluation of functional state and adaptability level according to FR and DT data proved the revealed peculiarities of vegetative regulation of heart rhythm and allowed to make a conclusion about the revealed differences.

Figure 2. Functional state in satellite groups during experiment Mars-500.

Figure 2 shows the averaged points of functional state in functional reserve (FR) and degree of tension (DT) data recorded in different regions over a 1.5-year monitoring period. At first three zones can be identified where the functional states of regions are grouped. The first is physiological standard zone (Yekaterinburg and Izhevsk), the second is the upper limit of the norm zone and prenosological state zone (Moscow and Minsk), the third is the lower limit of prenosological state zone and physiological standard zone. The main differences are connected with increase of regulatory mechanisms tension, the exception is the group from Yekaterinburg where the lowest tension of regulatory systems was recorded whereas the FR indicator was higher compared with the other groups. During pair-wise comparison of groups using these parameters, differences (p≤0.001) by F-criterion are significant. The exceptions are groups from Syktyvkar and Magadan (p=0.20) and to some extent groups from Syktyvkar and
Moscow (p=0.06) as well as from Minsk and Izhevsk (p=0.03). We can assume that agreeing closely functional states recorded with groups from Syktyvkar and Magadan are due to influence of unfavourable environmental factors such as long severe winter, short summer, short daylight hours in winter and white nights in Magadan in summer. Magadan is situated in the permafrost zone. The functional states of the Moscow and Syktyvkar groups are comparatively similar. This fact can be explained by the similar age range (this indicator is the highest among the groups) and body mass index (s. Fig.1). On the contrary, groups from Minsk and Izhevsk are the youngest.

Table 3 offers the averaged probability estimate of functional states and risks of adaptation disorders in different cities. It is not surprising that the highest probability of prenosological states and adaptation health risks are observed in groups from Magadan and Syktyvkar. The second is the group from Minsk which participants are younger. In can be connected with reduction of functional reserve (the lowest FR value among all groups) due to high level of ecological stress.

Table 3. Probability estimate of functional states and risks of adaptation disorders of volunteers in different regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Izhevsk n=103</th>
<th>Minsk n=129</th>
<th>Magadan n=251</th>
<th>Yekaterinburg n=146</th>
<th>Syktyvkar n=232</th>
<th>Moscow n=140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of prenosological state, %</td>
<td>24±3</td>
<td>24±2</td>
<td>36±2</td>
<td>16±2</td>
<td>32±2</td>
<td>24±2</td>
</tr>
<tr>
<td>Probability of normal state, %</td>
<td>74±3</td>
<td>73±3</td>
<td>63±2</td>
<td>83±2</td>
<td>68±2</td>
<td>75±2</td>
</tr>
<tr>
<td>Average risk category</td>
<td>1,99±0,14</td>
<td>2,04±0,13</td>
<td>2,41±0,09</td>
<td>1,55±0,08</td>
<td>2,16±0,08</td>
<td>1,91±0,10</td>
</tr>
</tbody>
</table>

The participants of the research were divided into 4 risk groups according to their average individual risk evaluation recorded during 1.5 years. The average value of the risk category (M) scores 2.09, standard deviation (SD) scores 1.34. Value 0.5 SD was taken as classification interval.

The average risk category value for the first group of people was M-0.5 SD, for the second group – up to M+0.5 SD, for the third group – up to M+1.0 SD, for the fourth group – higher than M+1.0 SD.

Estimation of the average risks of adaptation disorders in different regions proved that the most unfavourable distribution of people according to risk categories (s. Fig.3) is observed in Magadan and Syktyvkar. If in Yekaterinburg more than a half of the studied volunteers refer to the 1st risk group, in Magadan and Syktyvkar more than 70% of the volunteers refer to the
second risk group with prenosological states dominating, and probability of development of premorbid states is high.

**Figure 3. Disposition of the participants of satellite investigations from different regions in experiment Mars-500 according to risk categories.**

Thus, dependency of functional states of volunteers on geographical location of the regions and climatic conditions is revealed. In this connection seasonal changes of the basic functional indicators should be considered. Figure 4 represents the graphs of average monthly values of the basic anthropometric and cardiological data for all investigations conducted in Russia and Republic of Belarus (1006 investigations). There can be observed a trend of autumn increase of arterial pressure indicators (in October and November) as well as increase of stress index and “myocardium” index. Body weight and pulse rate increase in October and July. In winter time increase of systolic arterial pressure, body weight and total power of HRV spectrum is observed. In July increase of the stress index value is observed. Thus, we should note that almost every indicator is characterized by seasonal dynamics.

Let us consider the results of investigations in certain cities. The data from Yekaterinburg (ecological stress=18.8, the average risk category = 1.55) and Syktyvkar (ecological stress=27.2, the average risk category = 2.16) are presented below. Dynamics of changes of physiological parameters in groups in these cities reveals seasonality of functional state.
Figure 4. Graphs of average monthly values of anthropometric and cardiological parameters.

Investigation results in Yekaterinburg

Table 4 provides average monthly values of the parameters of cardiovascular system functional state from June 2010 to September 2011. Changes of average values of all
parameters were within the physiological norm. Changes of heartbeat rate during the year were insignificant (within 67-74 BPM) and reached maximum values in winter months (December). They decreased in summer and autumn months (from June to November).

Table 4. Results of medical and ecological investigations in Yekaterinburg

<table>
<thead>
<tr>
<th>Month, year</th>
<th>heartbeat rate</th>
<th>pNN50</th>
<th>SI</th>
<th>TP</th>
<th>myocardium</th>
<th>RSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2010</td>
<td>68.67</td>
<td>19.99</td>
<td>83.35</td>
<td>2699.44</td>
<td>14.58</td>
<td>3.67</td>
</tr>
<tr>
<td>July 2010</td>
<td>69.75</td>
<td>21.09</td>
<td>75.60</td>
<td>4227.56</td>
<td>13.08</td>
<td>5.33</td>
</tr>
<tr>
<td>August 2010</td>
<td>69.55</td>
<td>25.05</td>
<td>68.14</td>
<td>3912.33</td>
<td>14.55</td>
<td>4.36</td>
</tr>
<tr>
<td>September 2010</td>
<td>70.25</td>
<td>20.93</td>
<td>91.68</td>
<td>4017.11</td>
<td>14.92</td>
<td>4.75</td>
</tr>
<tr>
<td>October 2010</td>
<td>69.90</td>
<td>17.40</td>
<td>73.78</td>
<td>2759.98</td>
<td>13.30</td>
<td>4.00</td>
</tr>
<tr>
<td>November 2010</td>
<td>69.89</td>
<td>22.37</td>
<td>68.58</td>
<td>3807.65</td>
<td>14.22</td>
<td>4.44</td>
</tr>
<tr>
<td>December 2010</td>
<td>74.40</td>
<td>17.44</td>
<td>111.42</td>
<td>3407.14</td>
<td>13.90</td>
<td>4.90</td>
</tr>
<tr>
<td>January 2011</td>
<td>70.80</td>
<td>24.65</td>
<td>78.70</td>
<td>3811.98</td>
<td>13.40</td>
<td>4.70</td>
</tr>
<tr>
<td>February 2011</td>
<td>68.00</td>
<td>27.99</td>
<td>61.15</td>
<td>4219.91</td>
<td>14.10</td>
<td>4.40</td>
</tr>
<tr>
<td>March 2011</td>
<td>73.80</td>
<td>17.97</td>
<td>89.35</td>
<td>3233.73</td>
<td>14.30</td>
<td>3.60</td>
</tr>
<tr>
<td>April 2011</td>
<td>71.50</td>
<td>18.52</td>
<td>79.89</td>
<td>3189.21</td>
<td>13.70</td>
<td>3.50</td>
</tr>
<tr>
<td>May 2011</td>
<td>67.40</td>
<td>27.19</td>
<td>64.54</td>
<td>3524.88</td>
<td>14.40</td>
<td>3.80</td>
</tr>
<tr>
<td>June 2011</td>
<td>71.25</td>
<td>21.45</td>
<td>88.19</td>
<td>2949.67</td>
<td>14.25</td>
<td>4.00</td>
</tr>
<tr>
<td>August 2011</td>
<td>71.13</td>
<td>24.09</td>
<td>83.99</td>
<td>2969.34</td>
<td>14.50</td>
<td>4.50</td>
</tr>
<tr>
<td>September 2011</td>
<td>69.78</td>
<td>22.48</td>
<td>95.00</td>
<td>3402.22</td>
<td>13.22</td>
<td>4.11</td>
</tr>
</tbody>
</table>

It should be noted that in December increase of activity of sympathoadrenal member of regulatory system was noted (increase of stress index, increase of RSAI and decrease of pNN50). In spring (March) and autumn (September) activity of this member of regulatory system was less significant. We should note that RSAI as an integral indicator changed its values smoothly from the summer period to winter period and vice versa. Besides, there was sharp increase of RSAI in July 2010 which was probably caused by extremely hot weather for that period.

Dynamics analysis of pNN50 appears to be of interest. It mainly reflects the state of the parasympathetic member of regulatory system and characterizes protective and restoring role of regulatory mechanism. As can be seen from the table, increase of pNN50 was noted in May, August and February. These are the months preceding the beginning of summer, autumn and winter seasons. There may exist two explanations of the mentioned phenomenon. We either observe the defense reaction of the body as a response to energy consumption necessary for changing the functions during the preceding season, or the body “foresees” its change to the new function level and prepares for the forthcoming loads.

“Myocardium” index is an integrative indicator of energy and metabolic changes in myocardium. It monitors seasonal changes of the functional state. Its minimum values in July, September (2011), October (2010), January and April characterize the optima of seasonal adaptive body reactions.
Results of investigations in Syktyvkar.

In Fig. 5 annual dynamics of the basic indicators HRV are shown. These indicators are used to calculate the FR (functional reserve) and DT (degree of tension) for phase plane construction. An increase in the heart rate during the autumn months and reduction during the winter months is observed.

![Figure 5. Annual dynamics of the average group values of heartbeat rate, SI, pNN50 and HF.](image)

In October and November increase in activity of the sympathetic member of regulatory system is observed. It is evident as increase in stress index (SI), decrease in RMSSD and relative power of high-frequency content of the spectrum (HF). In January and February the stress index decreases and RMSSD and HR increase.

Figure 6 shows the phase plane constructed with the results of mathematic modeling with calculation of monthly DT and FR values presented by the points on the phase plane. Series-connected average monthly group indicators of the functional state create the phase tracking. It reflects the seasonal functional state changes. Four loops can be distinguished: autumn loop (on the right), winter loop (on the left), spring loop (in the center), summer loop (it is partly laid on the winter loop).
Figure 6. Phase tracking of the 1.5-year dynamics of the functional state of the reference group participants in Syktyvkar constructed according to results of the monthly HRV analysis.

In Fig. 6, geometric centers of the seasonal loops of the solution curve are shown. The centers of all loops (except autumn 2010) are situated in prenosological state zone. They differ in DT and FR values. Spring and autumn centers differ in DT values. In spring the degree of tension of regulatory systems is higher than in autumn. Centers of the summer and winter loops are similar to DT in coordinates. Though in winter the degree of tension of regulatory systems is slightly higher in case the level of functional reserves is high.

Conclusion

The results of the long-term medical and ecological investigations conducted simultaneously with the earth-bound experiment Mars-500 showed that health changes with the practically healthy people usually remain within the prenosological state zone. Although, risk of pathology development with different people changes significantly. It follows that within the same functional state of the body, the higher is the probability of pathology development, the more serious should the precautionary measures be. One of the important results of the Mars-500 experiment is successful testing of prenosological diagnostics which is a new trend in modern medicine and physiology [7].

Prenosological diagnostics studies the states on the boundary of norm and pathology, and is aimed mainly at studying healthy people having no signs of pathology. This scientific field developed in cosmic medicine to evaluate the degree of the body adaptability to spaceflight.
conditions. The methods of prenosological diagnostics came into operation in 1980s during preventive examinations [8, 9], and in recent years are used to evaluate the risks of pathology development in bus drivers and pilots [1, 10]. Experiment Mars-500 offered a unique opportunity to verify effectiveness of prenosological approach for evaluation of the long-term dynamics of the functional state of healthy people living in different environmental conditions. As a conventional reference group the Martian crew was considered. The volunteers lived in controlled ecological environment. The investigations results showed that despite differences in sensitivity to ecological factors with different populations, in all cases there was observed a correlation of prenosological and premorbid state development and changes in social and working environment, seasonal changes or health problems.

Results of the long-term medical & ecological investigations prove that prenosological state zone is a place where the body interacts with environment, and problems of further development are considered [7]. Prenosological state is an unstable equilibrium between health and pathology supported by tension of regulatory mechanisms and utilization of information, energy and metabolic body reserves. Consequently further development of prenosological approach for evaluation of health and pathology development is an upcoming trend both for cosmic and preventive medicine.

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

Author contributions
R.M.B., A.P.B., I.N.S. and A.G.C. developed the concept, prepared the manuscript and analyzed the data, A.G.C. drafted the manuscript. All authors read and met the ICMJE criteria for authorship. All authors read and approved the final manuscript.

Conflict of interest
None declared.

Acknowledgments
Authors are thankful to teams of scientists, participating in medical-ecological researches under the project “Mars-500”: Е.R. Bojko, Y.G. Solonin, A.L. Markov from Institute of Physiology (Syktyvkar), A.L. Maximov, I. V. Suchanova, S.A. Vdovenko from Scientific Center “Arktika” (Magadan), Y.L. Gabinsky, S.A. Raengulova from Ural Cardiological Institute, (Yekaterinburg), A.M. Merzliy, T.A. Zenchenko from Institute of Space researches (Moscow),
A.S. Medvedev, T.N. Lisok from Institute of Physiology (Minsk), Z. Trefny, E. Filatova from Cardiological laboratory (Prague), D. Zenke from company “Strategieteam” (Berlin), O.M. Baevskaya from company “Autosun Health Technology Inc“. (Toronto,Canada), V.I. Pougatchev from company “Biocom Technologies” (Poulsbo, USA), N.I. Shlyk, E.N. Sapozhnikova, T.G. Kirillova from Udmurt’s State University (Izhevsk), E.V. Minakov, G.N. Streletskaia, T.P. Kuchkovskaya from Voronezh Medical Academy (Voronezh), A.K. Yeshmanova from Kazachstan Medical University (Almaaty), N.K. Smagulov from Medical institute (Karaganda). Many thanks to Academician of RAS and RAMS Prof. Anatoly Grigoriev, who was initiator of these studies and supported them over all time their development by grant of Russian Academy of Sciences “Fundamental sciences to medicine”.

References

Original research

Glomus caroticus, environment, time parameters of cardiac and pathogenic mechanisms of formation of somatogenic depression and mixed encephalopathies on the methodological grounds of non-invasive hemogram analyzer

Anatolii N. Malykhin¹, Nataliia N. Malykhina¹, Anatolii N. Pulavskyi¹*

¹ Biopromin LTD, 61038, Ukraine, Kharkov, 50 Khalturina Street, office 2
* Corresponding author: Phone: +38 (057) 755-43-35. E-mail: bioluch@yahoo.com
Submitted: 21 March 2013
Accepted: 08 April 2013
Published online: 30 May 2013

Aims
The aim is to determine interaction of risk factors (volume of ingested food and exogenous alcohol) and their effects on thermal regulation of a body due to the changed activity of biochemical reactions of neuromediator regulatory systems, related to the synthesis of endogenous alcohol.

Materials and methods
Based on study of neurological status, biochemical and instrumental methods of precordial mapping, urine specific gravity and thermometry of five biologically active points, 1200 males were examined for pathogenic mechanisms of endogenous alcohol synthesis and formation of time parameters of cardiac and clinical manifestation of somatogenic depression.

Results
The amount of endogenous alcohol determines disorders in the bradykinin-acetylcholine and dopamine-noradrenalin systems and formation of clinical syndromes in the continuum of somatogeny-psychogeny (according to the international classification of diseases (ICD-10)).

Conclusion
Changes in thermal regulation were accompanied with changes of functional mechanisms of Glomus Caroticus, affecting erythrocyte and its receptors, related to atomic oxygen and hydrogen in atmosphere, with formation of relevant pH values of arterial and venous blood, amount of endogenous alcohol.

Keywords
Non-invasive analyzer • Time parameters of cardiac • Encephalopathies

Imprint
Anatolii N. Malykhin, Nataliia N. Malykhina, Anatolii N. Pulavsky. Glomus caroticus, environment, time parameters of cardiac and pathogenic mechanisms of formation of somatogenic depression and mixed encephalopathies on the methodological grounds of non-invasive hemogram analyzer; Cardiometry; No.2; May 2013; p.88-102; doi: 10.12710/cardiometry.2013.2.88102
Introduction

In recent years, problems of pathogenesis of depressions and encephalopathies are indissolubly related to the issues of energy metabolism of a cell and vascular body homeostasis. These issues are a major focus of research clinical and experimental studies. They are based on defining symptoms on the ground of external manifestations of metabolic syndrome (MS), including a classic triad: overweight, high blood sugar level and elevated blood pressure. Alcoholic encephalopathies (due to alcohol abuse (AA) are considered in terms of alcohol consumption and addition to alcohol without studying a connection between energy and metabolism aspect of this issue. In our opinion, studying of common pathogenic mechanisms of metabolic disorders, such as MS and AA should be based on scientific theoretical foundation of the present-day typology of metabolic disorders. These disorders include analysis of exogenous and endogenous risk factors in their connection to basic factors (genetic make-up of metabolism and blood circulation), reflected in continuum of somatogeny and psychogeny of continuum classification of P. Kielholz, 1969. Formation of somatogeny-psychogeny is syndromologically embodied in the ICD-10, chapter F-30-39, where connections in somatogeny-psychogeny system is established depending on etiologic factor. Authors of continuum classification found the casual connection between AA and alcohol, but there is no connection between ingested food and MS.

MS and AA, as well as mechanisms of their development are considered in respective articles and monographs using various methodological approaches. Typically, there are no generalization of findings, reflecting common natural factors and mechanisms of influence of ingested food and exogenous alcohol on formation of energy metabolism and role of endogenous alcohol [1, 3, 8, 13, 14, 22, 24-26, 28-31, 33, 36, 38-40] in the structural and functional energy regulation of the central nervous system (CNS) at the neuromediator and hormone levels. Also, those papers lack analysis of temporal factors of interaction of the acetylcholine-, adren- and dopaminergic systems, based on relation of leptin with PPAR receptors (Peroxisome Proliferator Activated Receptor) [2, 10-12, 15, 16, 20, 21]. Practically, when studying energy metabolism, such papers lack data on effects of exogenous alcohol and ingested food (risk factors) on body temperature, pulse rate and respiration rate. There are no description of their relation to the energy supply for a reaction of lipid peroxidation (LPO) and metabolism of vitamins A, B and D.

LPO reaction occur at the different regulatory levels: CNS, gastro-intestinal tract (GIT), cardiorespiratory and renal systems, combined in a single regulatory mechanism by blood circulation. System of blood circulation regulation is based on receptor activity of skin and cells of hematopoietic and immunologic systems. Supposedly, these cells involve methanol in the
metabolism of enkephalines and regulatory neuropeptides at the neuromediator and hormone levels by changing activity of leptin, PPAR and insulin receptors. System of blood circulation regulation combines regulatory haemodynamic and metabolic mechanisms by changing activity of metalloenzyme systems (oxidases and catalases being a part of erythrocytes and blood cells). The latter determine metabolic regulatory connection at the level of neuromediator systems (synthesis and breakdown of acetylcholine, serotonin, dopamine and bradykinin, adrenaline and noradrenaline, insulin and glucagon, as well as icosanoids, which determine local blood flow in the brain and internal organs). Blood flow in the brain and internal organs determines thermometric and related energetic and metabolic specific features of regulation in the system pituitary-hypothalamic-hippocampal controlling mechanisms and definition of clinical, behavioral and emotional aspects of a personality [4, 17, 21-23, 25, 32, 34, 37-39].

**Goal of research**

To determine interaction of risk factors (volume of ingested food and exogenous alcohol) and their effects on thermal regulation of a body due to the changed activity of biochemical reactions of neuromediator regulatory systems and changes in blood flow in the brain and internal organs, as well as synthesis of endogenous alcohol.

**Materials and methods**

**Research tasks**

1. Based on analysis of changes in thermal regulation due to food and alcohol ingestion, to determine limits of time range of interaction of choline- and serotonergic systems, which determine structural and functional potential initiating mechanisms of food factor and exogenous alcohol effect on genetic structures of the regulatory neuropeptides with determination of a volume of endogenous alcohol.

2. Based on analysis of changing of endogenous alcohol volume and its interrelation with time parameters of cardiac, to determine disorder of synthesis of enkephalines and endorphines, causing disorder of dopamine "turnover", which determines mental, emotional and organic neurological disturbances, typical for metabolic syndrome (ICD-10 F4 31,32,33) [6, 7]) and alcohol withdrawal syndrome of varying severity according to ICD-10 (F10.2.4.2.) with formation of clinical syndromes in the somatogeny-psychogeny system.
Data for research

1200 males with AA, average age 40±10 years, average weight 70±30 kg, were studies on the clinical base of the 13-th Regional Psychiatric Hospital of Kharkov (Ukraine) for 10 years. Anamnestically, it has been established that people, consuming more than 500 ml of alcohol per day, are admitted to hospital at least twice a year.

Control group (outpatient) consisted of 200 people, consuming up to 500 ml of alcohol per week and not having been admitted to hospital even once. A weight-to-age ratio and a ratio between heart rate and accumulated temperature index in the carotid arteries have been determined in all examined subjects.

20 persons from control group at the age of 25±5 years with weight 70±30 kg (volunteers) consumed 450 ml of vodka (40%) during 2 hours with 40-minute interval (75 ml or 7 ml/kg on the average). The same group has been examined 24 hours after vodka consumption and 1 hour after food ingestion: 200 g pork, 2 patty cakes and 200 ml grape juice.

Research methods

Clinico-neurological, instrumental, and biochemical (with blood sampling) for: alcohol, metalloenzymes, bilirubin, cholesterol, glucose, urea, proteins and creatinine. EKG was studied, as well as urine specific gravity, heart rate (HR) and respiratory rate (RR).

Thermometry was conducted 3 times per day for 5 points: 2 carotid arteries (in bifurcation region), 2 axillary points (in left and right armpits) and in abdominal region (near navel).

USPIH-based non-invasive blood formula analyzer was taken as a methodological foundation for studying alcohol metabolism in the body. USPIH software functioning is based on Dalton’s law, Henry’s law and fluid mosaic model of the structure of cell membranes (Singer S. Nicolson G., 1973), low-density lipoprotein model (M. Brown G. Goldstein, 1984) and organelle model [2-5]. Based on these methods, a temperature-dependent biotechnological model of correlation between temperature and lipid metabolism [29-32] was developed. This model is based on interaction of hemoglobin, bilirubin and cholesterol, occurring at the neuromediator, regulatory level (level of interaction of somatotrophic pituitary hormone (STPH), transforming growth factor (TGF), thyrotropic pituitary hormone (TTPH), leu- and methionine-enkephalins, specialized ubiquitin-proteolytic system, and leptin). Along with retinol, rhodopsin and vitamins В1 and D, these regulators change mass transport of hydrogen in the acetylcholine hydrolysis system with producing of choline and acetaldehyde. Such regulatory metabolic mechanism is associated with interaction system of the ratio between molar weights of adenosine triphosphoric acid (ATP), glucose, glutamic acid, γ-aminobutyric acid (GABA), palmitic acid, angiotensin converting enzyme (somatic), dopamine, and
adrenaline and molar weights of lactic acid, carnitine, serotonin, reproductive fragment of angiotensin converting enzyme, and noradrenaline. These weight ratios determine synthesis of endogenous alcohol and changes in the structure of cell membranes and organelles (peroxisomas, in particular), volume of incoming oxygen, related to the ratio between molar weight of glucose and lactic acid in cells.

The ratio between molar weight of glucose and lactic acid in cells is determined by regulatory function of limbic and hypothalamic systems, which is based on factor of the ration between acidic proteins and basic proteins, and constitutes 14.4. The ratio between this factor and molar weights of lactic acid and glucose determines basic value of arterial blood pH. pH value of arterial blood depends on the regulatory metabolic reactions of cholesterol, leptin and choline. In its turn, the ratio between molar weights of secretin, glucagon, insulin and dopamine and molar weights of ubiquitin, acetylcholine, gastrin and noradrenaline affect course of the regulatory metabolic reactions. Molar weight ratios determine H₂O₂ synthesis and metabolic cost of peptide bond breaking in the cell membranes and peroxisomas.

The ratio between molar weight of acetylcholine and dopamine is regulated by PPAR receptors, which are connected with cell pore complexes (PC) and ratio between molar weights of acidic and basic proteins (factor 14.4).

This factor is associated with molar weight (115 kD; Gerondakis, 1998) of lymphocyte transcription factor NF-kB (consisting of two proteins with molar weight 50 kD and 65 kD, forming 15 dimmers), through a value of the ratio between molar weight of specialized protein ubiquitin and molar weight of leptin, as well as a value of the ration between molar weight of dopamine and molar weight of glucose and quantitative change of dopamine and glucose in one minute, value 7.424 (correlating with genetically determined pH value of venous blood).

The ratio between molar weights of phospholipids, forming a part of chylomicrons, and molar weight of amino acids is 5. The product of factor 14.4 by 5 equals a total accumulated temperature in two active points (in armpits).

Sequence of the regulatory biochemical processes is determined by the ratio of the above said factors and ratio of molar weights of intestinal synthetases, bilirubin, and cholesterol, and determines molar weight of ethyl alcohol, as well as total accumulated temperature in five active points and pH of arterial blood [5, 18, 18, 25, 27, 28-31, 35, 38, 39].

With regard to the above mentioned, a rate of interaction of major chemical environment components [28-31], occurring in the cell membranes, at the liquid-gaseous interface (alveoles) [4, 19, 25, 38, 39] takes place with obligatory involvement of bilirubin-hemoglobin complex, ethanol, E. coli synthetase (70% of membrane of which consists of phosphatidylethanolamine), vitamins A, B₁ and D, as well as with involvement of universal
proteolytic regulators of cholesterol and lipid metabolism (ubiquitin-proteolytic system, \(\alpha\)-trypsin, nitrogen oxide and calcium oxide) [19, 35, 9].

This structural and functional organization of biochemical reactions provides for the body thermal regulation, being implemented in thermometrical dependency of temperature factors of five points (2 carotid, 2 auxillary and 1 abdominal) [28-31]. Temperature component of these reactions is associated with neuromediator choline- and adrenergic systems, which are primarily connected with glomus caroticus [28-31], with formation of charge-carrying interaction at the level of thyroxin and imidazole protein receptor of erythrocytes, and PPAR (Shinizky, 1968). Along with erythrocytes, PPR forms pH value of arterial blood in accordance with temperature parameters of interaction of opiate receptors (\(\alpha, \beta, \gamma\)) in the choline- and adrenergic regulatory mechanisms of endogenous alcohol synthesis, determined by interaction of the metabolic processes of cholesterol, vitamins \(\text{B}_1\) and \(\text{D}\), glucose, lactic acid, ubiquitin, intestinal synthetase and \(\alpha_1\)-trypsin.

Based on data, obtained using non-invasive Hemogram Analyzer and USPIH software, 1200 persons with AA and 200 persons from control group (consuming no alcohol or small amount of alcohol) were divided into three groups taking into account correlation of temperature indicators in various points:

1. Group 1 (control group, 200 people) - total sum of temperature indicators of 5 points: \(168\leq T_{\text{sum}}\leq 173\), total sum of temperature indicators of 3 points (carotid and abdominal): \(102\leq T_3\leq 105\), the ratio between total sum of temperature indicators of carotid arteries and abdominal temperature: \(2<T_{\text{car/abd}}\leq 2.05\).

2. Group 2 (consuming up to 500ml alcohol) - total sum of temperature indicators of 5 points more than \(174\leq T_{\text{sum}}\leq 178\); total sum of temperature indicators of 3 points \(100\leq T_3\leq 101\); the ratio between total sum of temperature indicators of carotid arteries and abdominal temperature: \(1.9\leq T_{\text{car/abd}}\leq 2.00\).

3. Group 3 (consuming more than 500-1000 ml alcohol, when admitted to hospital) - total sum of temperature indicators of 5 points more than \(175\leq T_{\text{sum}}\leq 180\); total sum of temperature indicators of 3 points \(102\leq T_3\leq 105\); the ratio between total sum of temperature indicators of carotid arteries and abdominal temperature less than \(T_{\text{car/abd}}<1.9\).

In the control group, the ratio between accumulated temperature of 5 points and abdominal temperature has made up \(5\pm 0.05\), and the ratio between accumulated temperature of two carotid arteries and abdominal temperature has made up \(2\pm 0.05\).

It has been proved on the volunteers, that intake of 100 g vodka causes changes in temperature of the right carotid artery in 15 minutes (increase by 0.03°C), as well as decrease in temperature in the armpits by 0.02°C and increase in abdominal temperature by 0.025°C.
Accordingly, the ratio between accumulated temperature of the carotid arteries and abdominal temperature is changed (T_{car/abd} < 2), and heart rate is elevated by 10 heartbeats per 100 g alcohol. The said changes persist for 12-14 hours. With further alcohol consumption, abdominal temperature is increased by 0.03°C; accordingly the ratio between accumulated temperature of the carotid arteries and abdominal temperature (T_{car/abd}) is decreased.

As opposed to alcohol consumption, food ingestion increases temperature in the carotid arteries and abdominal region without changing the ratio between accumulated temperature of the carotid arteries and abdominal temperature (T_{car/abd}) and heart rate. (See Table 1 and Figure 1).

<table>
<thead>
<tr>
<th>Groups and temp. indicators</th>
<th>Ceruloplasmin, mg/dl</th>
<th>Transferrin, g/l</th>
<th>pH*</th>
<th>Cholinesterase, mmol/l</th>
<th>LDH, mmol/l</th>
<th>Bilirubin, mcmol/l</th>
<th>Endogenous Alcohol</th>
<th>Energy of peptide bond breaking 1 g - 200 ml.∑</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g - 200 ml.∑ 168±5</td>
<td>285.6±1.16</td>
<td>2.5±0.47</td>
<td>0.074±0.025</td>
<td>307.02±17.68</td>
<td>2.01±0.17</td>
<td>12.08±0.92</td>
<td>0.0260</td>
<td>1308.66 kJ/sec</td>
</tr>
<tr>
<td>2-group up to 500∑175.5±2</td>
<td>439.2±3.89</td>
<td>1.7±0.61</td>
<td>0.082±0.025</td>
<td>278.03±21.19</td>
<td>2.47±0.19</td>
<td>18.53±1.49</td>
<td>0.0258</td>
<td>1302.55 kJ/sec</td>
</tr>
<tr>
<td>3 group ≥550∑179±15</td>
<td>526.7±4.77</td>
<td>1.4±0.29</td>
<td>0.102±0.025</td>
<td>229.61±20.05</td>
<td>3.35±0.27</td>
<td>31.06±2.73</td>
<td>0.0256</td>
<td>1287.42 kJ/sec</td>
</tr>
</tbody>
</table>
Figure 1. Major Pathogenic Mechanisms of Metabolism and Hemodynamics Regulation.
Thus, obtained parameters of cerebrospinal fluid pressure by groups (1 gr - 120±10 mm Hg, 2 gr. - 140±10 mm Hg, 3 gr. - 150±10 mm Hg) enable to estimate pH values of arterial and venous blood, and accordingly, and accordingly arteriovenous difference by groups: 1 group– pH of arterial blood -7.35±0.04, pH of venous blood - 7.424±0.03, arteriovenous difference - 0.074±0.025; 2 group – pH of arterial blood -7.32±0.025, pH of venous blood - 7.424±0.03, arteriovenous difference - 0.082±0.025; 3 group – pH of arterial blood -7.31±0.025, pH of venous blood - 7.424±0.03, arteriovenous difference - 0.102±0.02. (Table 1)

Important mechanisms of metabolic and hemodynamic aspects of regulation include energy processes, related to the ratio between age and weight, as well as the ratio between accumulated temperature in the carotid arteries and heart rate, and their changes per time unit. It has been established that value of arteriovenous pH difference is closely correlated with values of time intervals of QRS complex, PQ and urine specific gravity.

Quantitative indicators of basal glucose level depend on the interaction of various parameters, being defined as the ratio between product of molar weights of hemoglobin, dopamine, carnitine, atomic oxygen, sum of insulin subunits of receptors α and β (located on the surface of membrane and transmembrane), ubiquitin and PC and product of molar weights of E.coli synthetase, glutamic acids, palmitic acid, PPAR-receptors, catalase and quantitative indicators of arteriovenous difference. Basal glucose level changes depending on the temperature indicators in five points, the ratio between temperature indicators of carotid and abdominal area, the ratio between accumulated temperature in axillary and abdominal, heart rate and respiratory rate (basal glucose levels at 36,06°C is 4.09mmol/l). Moreover, basal glucose level is affected by contents of cholinesterase.

Quantitative reference indicators of cholinesterase (E.Sh. Shatilina and V.V. Prikhozhan method), lactic acid, bilirubin, transferrin (by spectrophotometric method 2.81±0.73 g/l) and ceruloplasmin (by immunoturbometric method 300±18 mg/l) have been compared with quantitative data of glucose and endogenous alcohol, obtained by computational non-invasive method, using non-invasive blood formula analyzer, with further statistic analysis of correlation ratio, defined by means of Spearman's rank correlation coefficient. Spearman's rank correlation coefficient is in the range of 0.7-0.9, which indicates of high correlation ratio between the selected parameters: temperature in the left and right carotid arteries, age and weight, arteriovenous pH difference, level of cholinesterase and glucose, level of lactic acid and glucose, level of glutamic acid and γ-aminobutyric acid.
Discussion and conclusions

1. General pathogenic mechanisms of formation of endogenous depressions and MS are related with the course of regulatory metabolic and hemodynamic LPO reactions. LPO reactions are related to the functioning of Glomus Caroticus and time parameters of cardiac, and regulated by the ratio between molar weights of transferrin and ceruloplasmin at the level of hepatocytes, angiotensin converting enzyme, PO and catalase, and difference of amino acids - components of gastrin and secretin (which is 14, since gastrin comprises 27 amino acids, and secretin consists of 13 amino acids), and factors 14.4 and 4.75 (ratio between molar weights of ubiquitin and leptin). These reactions result in temperature indicators in carotid arteries and abdominal region (sum of which makes up 102.36°C), pH of arterial blood (7.326) and pH of venous blood (7.351). Arteriovenous difference determines volume of endogenous alcohol (0.026).

2. Volume of endogenous alcohol is inversely related with energy of peptide bond breaking (1308 kJ/sec) and molar weight of lactic acid through the synthesis of leu-enkephalins (molar weight 554 mmol/l). Synthesis of methionine-enkephalins (molar weight 572 mmol/l) is determined by the same processes, but activity of synthesis is regulated by the ratio between molar weight of leptin and molar weight of ubiquitin and is related with amount of cholinesterase, atomic oxygen and the ratio between molar weight of glucose and molar weight of adrenaline. In its turn, the ratio between difference of molar weights of methionine- and leu-enkephalins with molar weight of glucose and volume of cholinesterase, leptin and ubiquitin determines activity of lactic dehydrogenases and oxygenases in the hemoglobin-bilirubin reaction at the level of PPAR-receptors and PO, as well as quantitative indicators of glucose level.

3. Reactions of atomic oxygen generation are important link in the PLO regulatory metabolic reactions and formation of time parameters of cardiac. Process of atomic oxygen production is regulated by the following interaction: the ratio between molar weights of γ-aminobutyric acid, transferrin, palmitic acid, carnitine with difference of molar weights of methionine- and leu-enkephalins and product of molar weight of ceruloplasmin, amount of amino acids and difference of molar weights of palmitic acid and carnitine. By affecting structure and molar weights of contractile proteins of the cell membranes and glycoporphin (structural protein of an erythrocyte membrane), atomic oxygen determines necessary energy for breaking of chemical element bonds (H, C, O, NO, NH, N). Energy value is regulated by molar weight of catalase, pH of arterial blood, the ratio between molar weights of ubiquitin and leptin and factor 2.03 (the ratio of temperature indicators of carotid arteries to abdominal region temperature). This ratio is also related with thermal and temporal factors of interaction of LPO and PO, arteriovenous
pH difference, the ratio between molar weight of acetylcholine and pH of venous blood and molar weight of glutamic acid, factor 153.2, which is equal to molar weight of dopamine.

4. Initial mechanisms of somatogenic depressions, MS and encephalopathy pathogenesis are time relationship between bradykinin and acetylcholine, dopamine and serotonin, based on functioning of Glomus Caroticus. Glomus Caroticus functioning determines temperature indicators in five points, functions of surface cutaneous, muscle and PPAR receptors. Receptors are located in the cell membranes and intracellular compartment. They function synchronously with palmitin-carnitine complexes, signal temperature G-proteins, receptors of transforming growth factor (TGFb) and bone morphogenetic protein (BMP2). TGFb and BMP2 determine growth and growth inhibition of sympathetic neurons through photoreceptor molecule of retinol (286.5 g/mol), associated with metabolism of vitamins B1 and D (265.4 g/mol, 397.5 g/mol). Metabolism of vitamins determines thermal dependent function of α- and β-adrenoreceptors with cholinoreceptors, included in their structure. Cholinoreceptors and α- and β-adrenoreceptors are associated with calcium metabolism (calnexin, 88 kDa), calreticulin (46 kDa) and calmodulin (16.4 kDa). They combine regulatory mechanisms in one single structural and functional system by the course of LPO at the level of PPAR-receptors, related with temporal parameters of cardiac cycle.

5. MS and encephalopathy pathogenesis in AA is related with the course of reductive-oxidative proton-dependent proteolytic biochemical processes, occurring at the level of receptors of erythrocytes, monocytes, and lymphocytes, as well as in the extra cellular fluid compartment. Proton mechanisms determine time of acetylcholine hydrolysis and cholinesterase activity. Cholinesterase activity is associated with interaction reactions of serotonin, adrenaline and bradykinin. These reactions, occurring at the organ level, are related with functional activity of the brain, metabolism of regulatory neuropeptides and enkephalines, determining clinical syndromes, behavior, and emotions through regulatory functions of hypothalamo-pituitary-hippocampal-renal systems.

6. Pathogenic mechanisms of formation of clinical syndromes in MS and alcohol withdrawal in AA are related with disorders in biologic laws of cellular compartmentalization of the functions based on the phenomenon of targeted delivery of informational molecules to the cell membranes and organelles. Targeted delivery is based on the interaction mechanism of acidic and basic amino acids, thyreotrophin-releasing factor (TRF), growth hormones and transforming growth factor, gastrointestinal hormones, participating in the transmission of external signals through the cell membrane structures with the involvement of dopamine, NF-kB, specialized proteins rhodopsin and retinol, vitamins B1 and D, determining location of arginine in the 117th location of 7th chromosome and location of glutamic acid in the 292nd
position of 14th chromosome with formation of relevant pH values of arterial and venous blood, volume of endogenous alcohol and serotonin-dopamine and dopamine-noradrenalin interaction in the regulatory system of LPO reactions, related with PPAR function and insulin receptors by means of accumulated temperature indicator in five biologically active points.

7. Proton mechanism of formation of time parameters of cardiac, clinical syndromes of depressions and encephalopathies is associated with degenerative changes of nervous system, which are determined by disorders in the regulatory processes of formation of pH values of arterial and venous blood. Interaction of ATP and iodineperoxidase at the level of molar weights of TTF, photoperceptive protein - retinol, PO, mannose-6-phosphate, serotonin and dopamine, glucose, and TTPH is related with amount of endogenous alcohol, energy of peptide bond breaking, arteriovenous pH difference of the blood, correlating with temporal parameters of the QRS complex. In the somatogeny-psychogeny context, manifestation rate of clinical symptoms depends of the regulation of neuropeptides and enkephalines. The latter are related with activity of angiotensin converting enzyme, determined by arteriovenous pH difference, amount of endogenous alcohol, and the ratio between molar weight of glucose and molar weight of dopamine. Angiotensin converting enzyme and time relations between bradykinin and acetylcholine are the major ones in the formation of urine specific gravity, blood pressure, and greater lesser and circulation time, determining synthesis of enkephalines and dopamine.

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

Author contributions
A.M., N.M. and A.P. developed the concept, prepared the manuscript, analyzed the data and drafted the manuscript. All authors read and met the ICMJE criteria for authorship. All authors read and approved the final manuscript.

Conflict of interest
None declared.
References


Automatic Noninvasive Express Screening Analyzer (ANESA)

Biopromin Ltd.
Ukraine 61038 Kharkiv,
Khalfurina str. 50
tel.: +38-057-732-52-05, 755-43-35
e-mail: bioluch@yahoo.com
Report

Cardio-eigenoscopy: significance of this new method in prognosis of risks of fatal arrhythmia progression in AMI patients

Dmitry V. Issakevich¹, Vladimir V. Chepenko¹*, Mikhail Y. Rudenko², Konstantine K. Mamberger²

¹Vladimir State University, Faculty of Applied Mathematics and Physics, 600026, Russia, Vladimir, Stroiteley av. 3/7
²Russian New University, 105005, Russia, Moscow, 22 Radio St.

* Corresponding author: E-mail: chepenko.vladimir.49@mail.ru
Submitted: 28 March 2013
Accepted: 20 April 2013
Published online: 30 May 2013

Abstract

The aim of the study was to evaluate the significance of cardio-eigenoscopy method for the prognosis of risks of fatal arrhythmia (the primary and secondary VF) progression in AMI individuals. The study was performed with the use of the PC-assisted hemodynamic analyzer Cardiocode. The cardio-eigenoscopy was developed as a methodology that is capable of presenting all ECG changes in the basis of eigenvectors of a covariance matrix of ECG amplitudes and providing an analysis of a spectrum of eigenvalues. The ECG analysis software is implemented as a real-time monitoring of a set of parameters that makes possible to evaluate the therapy effectiveness.

The cardio-eigenoscopy method is capable of assessing the risk of progression of fatal arrhythmia events in MI patients. The major markers of the possible progression of fatal arrhythmia were identified. The cardio-eigenoscopy provided the maximum expressibility of an ECG curve at any specified EVE values.

Keywords

Arrhythmia • Cardiovascular system • ECG • Cardio-eigenoscopy • Myocardial infarction

Imprint

Dmitry V. Issakevich, Vladimir V. Chepenko, Mikhail Y. Rudenko, Konstantine K. Mamberger. Cardio-eigenoscopy: significance of this new method in prognosis of risks of fatal arrhythmia progression in AMI patients; Cardiometry; No.2; May 2013; p.104-123
doi: 10.12710/cardiometry.2013.2.104123
Available from: http://www.cardiometry.net/issues/no2-may-2013/cardio-eigenoscopy.pdf
Introduction

Cardiac insufficiency (CI) is a clinical manifestation of various cardiac diseases. This is a condition when compensatory mechanisms of the cardiovascular system are no longer capable of maintaining the normal homeostasis. Nowadays there are more than 22 million CI patients throughout the world. According to different estimations, a sudden stoppage of blood circulation is annually reported for 200 000 to 450 000 subjects in the United States, and it is the cause of 95% of the cases of sudden cardiac death (SCD). In the developed European countries sudden cardiac death accounts for 2500 deaths per day, with only 2% to 5% of the SCD statistics referred to patients’ stay registered upon their admission to medical institutions. The world-covering predicted SCD rate is about 3 000 000 deaths per year with the 1.0% chance of survival only. The chance of a successful outcome upon intensive care does not exceed 5% in the economically developed countries. 40% of sudden cardiac death cases cannot be identified at all, or are reported as occurred in sleep. It should be noted that 80% of the SCD cases occur at home or other places of permanent residence. The well-known Framingham heart study (1970) has shown that the survival coefficient with the initial CI diagnosis accounts for 62% of males and 42% of females. The share of the SCD cases in the total mortality rate was 40% to 50% [1, 2].

The main nosological cause of SCD progression is ischemic heart disease (IHD) that is reported in 80% to 85% of the SCD cases, including more than 65% which are connected with an acute stoppage of blood flow in the coronary arteries. Further 5% to 10% of the SCD cases are caused by dilated cardiomyopathy (DCM), and the remaining 5% to 10% of the SCD cases are induced by other cardiac diseases. In the circumstances, arrhythmias are treated to be the direct mechanism of the circulation stoppage, with 90% of ventricular tachyarrhythmias among them. Electromechanical dissociation and bradyarrhythmia lead to the circulation stop in 10% of all SCD cases.

In accordance with the modern concepts, etiology and pathogenesis of ventricular arrhythmias (VA) in IHD subjects imply that there is an interaction of numerous factors we have to deal with, which are as follows: structural cardiac changes [3,4,5], myocardial electrical instability (MEI), neurohumoral mechanisms [6,7], circadian biorhythms [8,9] and genetic defects [10,11].

It is reported that about 20% of the patients survived upon intensive care show no signs of myocardial ischemia, but almost without exception they have an apparent ventricular dysfunction that takes place after previous myocardial infarctions. With respect to these patients, it should be noted that the predictor of their mortality in general, including the SCD mortality, is a reduction in the pumping function in the cardiovascular performance, but not
the accompanying arrhythmias. In case of insufficient pumping function of the left ventricle, extrasystole being correlated with the degree of the LV function reduction is observed in 80% of the cases for the said patients.

A reduced cardiac output and a nonsustained ventricular tachycardia (VT) recorded by Holter-monitoring ECG and identified during an electrophysiological study of post-AMI patients remain currently to be used as the main prognostic markers of a high risk of the SCD [12,13]. One of the latest studies in subjects with Implantable Cardioverter Defibrillators (ICD) demonstrates that sudden occurrence of the ventricular tachycardia (VT) or ventricular fibrillation (VF), as a rule, is found in patients showing an unchanged cardiac output; a gradual growth of ventricular ectopic activity accompanied by the lowered contractility is observed in the above patients before the VT or VF attacks. The lowered left ventricular contractility increases the SCD risk not only for the IHD subjects, but also for patients suffering from other heart diseases [14,15]. An apparent atherosclerotic narrowing (over 50%) of the coronary arteries is found in 90% of the SCD cases. The degree of damage of the coronary arteries plays an important role in VA and SCD progression [10,11]. According to a great number of clinical investigations, both symptom-accompanied and symptom-free myocardial ischemia types are considered as an informative SCD risk marker for the patients suffering from different IHD forms [16,17,18]. Known is the so-called SCD triangle of IHD patients which is constructed by myocardial ischemia, myocardial electrical instability (MEI) and left ventricular dysfunction [19]. It should be noted that the most unfavorable combination is produced by two SCD risk factors which are as follows: the frequent ventricular extrasystole and the left ventricular dysfunction with a reduced cardiac output < 40 %. According to the GISSI-2 research studies, under the said conditions, a 16-fold increase in the risk of sudden arrhythmic death is reported [3]. A life threatening VA (stable VT, VF) occurs when a combination of several MEI predisposing factors appears which are as follows: a substrate (a structural disease of the heart) modulating the dysfunction of the vegetative nervous system and some VA trigging factors. The morphological substrate producing the post-MI inhomogeneity of impulse conductivity is a myocardial area which is a boundary area being located in the vicinity of necrotic tissues of myocardium and which is formed by interlaced islets made of viable myocardial fibers and conjunctive tissue. The impulse conductivity path is extended there due to conjunctive tissue islets hindering the cardiac impulse traveling, and the conductivity speed falls due to disorders in muscle fibre parallel orientation. Besides, known are some other SCD risk factors, in particular, a disturbance in the vegetative regulation of the heart with the dominance of the sympathetic activity. The most important marker of this abnormality is a reduced variability of sinus rhythm [20], along with an extended Q-T interval and a dispersion
of the latter [21,22]. The reduced rhythm variability and the extended Q-T interval are
deemed to be supplementary MEI indicators [21]. An apparent left ventricular hypertrophy,
especially in subjects suffering from arterial hypertension [23,24,25,26,27] and hypertrophic
cardiomyopathy [28,29], is considered to be one of the SCD risk factors. The discussion on
what antecedents of the VF are available is still in progress, and so far there is no consensus of
opinion among the experts. The commonly accepted risk factors of life-threatening VA
progression for IHD patients do not show the proper sensitivity and the specificity, and life sets
us a challenge to find some absolutely new MEI markers [27,28].

The cardio-eigenoscopy method makes possible to provide an analysis of real-time cardiac
signal shape changes with an assessment of risks of progression of fatal arrhythmias.

Materials and methods

The aim of our study was to evaluate the significance of cardio-eigenoscopy method for the
prognosis of risks of fatal arrhythmia (the primary and secondary VF) progression in AMI
individuals. 56 MI-diagnosis individuals with different MI localizations, on hospital days 1 to 10,
were covered by the study. The test cohort included 13, 6% of females and 86,4% of males.
The mean age was 63 years. Group 1 comprised 42 patients survived. Group 2 comprised 14
subjects with lethal outcome. The study was conducted on hospital days 1, 3, 5 and 7–9 in the
dynamics.

The study was performed with the use of the PC-assisted hemodynamic analyzer
Cardiocode. The cardio-eigenoscopy has been developed as a methodology that is capable of
presenting all ECG changes in the basis of eigenvectors of a covariance matrix of ECG
amplitudes and providing an analysis of a spectrum of eigenvalues. The ECG analysis software
is implemented as a real-time monitoring of a set of parameters that makes possible to
evaluate the therapy effectiveness.

In the offered methodology, a covariance matrix is computed with the utilization of a matrix
of an ensemble of cardiac oscillations. The ensemble is created by a segment of a cardiac
signal which refers to several tens of cardiac contractions. Every ensemble element represents
a portion of a signal with a certain length, containing the respective signal generated by a
single cardiac contraction.

Processed are the successive discretized and digitalized cardiac signal segments which have
an N discrete length and which comprise several tens of the cardiac oscillations, as mentioned
above. The signal in each segment is specified by a series of discrete counts $S_{i,i} = \frac{I}{N}$. An
example of a cardiac signal with the dominance of peaks is illustrated in Fig.1.a herein. This
signal is of infrequent occurrence. Fig.1.b displays another cardiac signal which is relevant to
fibrillation (a coma patient). As the figure suggests, no dominance of peaks is available in the case illustrated in the said figure.

![Figure 1: Examples of a cardiac signal segment for the following cases: a) shows the case of the dominance of the peaks, b) shows the case with no peak dominance.](image)

Each of the successive length part of the N length is centered and brought to "the normal form" (with positive peaks if they dominate). If we deal with the peak dominance (that is determined by the R wave amplitude), locations of the peaks and an averaged period of their recurrence $T_{cp,N}$ are identified, and then the respective ensemble of the cardiac oscillations is created. If no dominance of the peaks is observed, an averaged period is identified immediately, and thereafter an ensemble is created. Each element of such an ensemble represents a matrix row describing a separate segment of a cardiac signal on an interval which is equal to the averaged period. In case of the dominance of the peaks, the cardiac oscillation peak is located in the center of the above matrix row, and the full length of the matrix row is equal to the discrete value of the averaged period $T_{cp,N}$. Fig.2.a offers us an illustration of
such ensemble for the peak dominance case, and Fig. 2.b indicates another case, when no peak dominance is observed.

**Figure 2.** Examples of an ensemble of the cardiac oscillations for the following cases:
a) shows the case of the dominance of the peaks, b) shows the case of no-peak-dominance.
The ensemble is a rectangular matrix $T_{K \times T_{cp,N}}$ with a dimension of $K \times T_{cp,N}$, where $K$ is the number of elements of the ensemble that is equal to the number of the cardiac oscillation integers with a dimension of $T_{cp,N}$ which are presented along the analysis interval $N$.

With the use of the matrix $T_{K \times T_{cp,N}}$, a covariance matrix of the cardiac oscillations is calculated from a formula as given below:

$$K_{T_{cp,N}} = \frac{T_{K \times T_{cp,N}} \cdot T_{K \times T_{cp,N}}}{K-1}, \quad (1)$$

where $(...)'$ is the matrix transpose.

For the covariance matrix (1) we can find the eigenvectors (EVEs) and the eigenvalues (EVAs) which satisfy the relation as follows:

$$K_{T_{cp,N}} \cdot \psi_i = \lambda_i \cdot \psi_i, \quad i = 1 \div T_{cp,N}, \quad (2)$$

The dimensionality of the covariance matrix for the case of cardiac signal discretization with the $10^{-3}$ second period is usually less than 700. The time required for the calculation of the covariance matrix described by the relation (1) for $K \leq 50$ and the calculation of the matrix EVE and EVA for $T_{cp,N} \leq 700$, using standard computation tools, is 1 to 5 seconds. Therefore, it is possible to trace the EVEs and the EVAs of the covariance matrix under the real-time conditions.

An averaged energy of the signal observed on the interval $T_{cp,N}$ is described by the relation given below:

$$\bar{\mathcal{E}} = \sum_{i=1}^{T_{cp,N}} \lambda_i. \quad (3)$$

This implies that the series

$$\bar{\mathcal{E}}^{(i)}_{OTH} = \frac{\lambda_i}{\sum_{j=1}^{T_{cp,N}} \lambda_j}. \quad (4)$$

which will be further referred to as the normalized spectrum of eigenvalues (NSEVA) determines the relative share in the average energy (3) that belongs to the corresponding EVE. Further, as it is the case with [1], the NSEVA will be arranged in a descending order. Since every NSEVA parameter expresses the relevant information on the energy share which is “credited” to the relative EVE, the NSEVA value of the respective EVE will be referred to as the
expressibility of the said EVE. The expressibility can be evaluated in percent, so that the total expressibility of all EVEs is 100%. The higher the expressibility of an EVE is, the more information it contains and the greater energy the respective cardiac signal component possesses.

It can be shown that the NSEVA for the covariance matrix (1) constructed with the use of $T_{K \times T_{p,N}}$ possesses such a number of non-zero EVAs that is equal to $K$. A screen-shot presented in Fig.3.a herein (s. top right window) demonstrates the typical NSEVA (4) constructed for the case $K = 35$ and $T_{p,N} = 680$. As will be seen from the plot in the above window, the first 35 NSEVA values only exceed the level of $10^{-5}$.

**Figure 3.** Screen-shot visualizing NSEVA (expressibility of an EVE as percentage) for the following cases: a) shows the case of the peak dominance, b) shows the case of the absence of peaks dominance.
But even the above mentioned number of the NSEVA values is redundant for the analysis. The top left window in a screen-shot presented in Fig.3.a displays the first 10 NSEVA values, where only the 4 of them demonstrate their expressibility exceeding 1%, and only the 7 of them show their expressibility higher than 0.1%. Therefore, it may be concluded that for the purposes of diagnostics it is quite sufficient to visualize the first 10 of the NSEVA values. The bottom windows in the screen-shot in Fig.3.a contain some plots of the cumulative expressibility. Every plotted point is the sum of the number of the first NSEVA values specified on the abscissa. So, the bottom left plot indicates that the first 4 NSEVA values provide their cumulative expressibility (the credited averaged energy) at a level of 99%. This parameter is typical for the healthy heart.

In case when fibrillation is available, we deal with another condition: the expressibility of the first EVE is considerably reduced, while the expressibility both of the first and the second EVE becomes comparable. It is displayed in the respective screen-short given in Fig.3.b. In case of the absence of the peak dominance, the first 10 NSEVA values might be insufficient for the analysis of the expressibility. Therefore, it should be recommended to utilize all NSEVA parameters higher than $10^{-5}$.

A screen-shot shown in Fig.4.b offers a typical example of the first four EVEs for the no-peek-dominance case.
Figure 4. Screen-shot visualizing the first four eigenvectors for the following cases: the peak dominance case is illustrated in a), and the no-peak-dominance case is indicated in b). The windows above the plots indicate the No. of each EVE and the respective expressibility in %.
The EVE expressibility may vary with time. A screen-shot shown in Fig.5 depicts a plot in the top right window to demonstrate how the expressibility of the first four EVEs is varying throughout 11 analysis intervals; the left top window presents the initial cardiac signal on the last analysis interval, and the bottom windows display the first 10 NSEVA values for the last analysis interval (left) and the cumulative NSEVA for the same analysis interval (right).

![Picture](image)

**Figure 5.** Screen-shot showing an analysis of a temporal row of expressibility.

The NSEVA analysis suggests that it is reasonable to analyze the first EVEs only, which demonstrate their highest expressibility. A screen-shot in Fig.4.a gives us an illustration of the first four EVEs for a specified interval of the analysis used for the peak-dominance case. It is evident from the figures that the first EVE shows actually the maximum expressibility (over 88%). The other three EVEs might have significance to be applied to the analysis in some specific cases only. For instance, it might be done when we deal with a weakened level of the cardiac signal being below the harmonic noise level, the first (and eventually the second) EVE would contain some noise, then the next EVEs would express the cardiac signal.

The EVEs given under Nos. 2 to 4 in the above figure are less expressible than the first EVE, and, as a rule, they contain information on noises affecting the cardiac signal and the
fluctuations of the latter. To identify zones of instability of the cardiac oscillations, an approach is offered as described below. For the EVE modules under Nos. 2-4, the geometric mean should be found (an example is shown in the left window on a screen-shot in Fig.6).

![Image](image.png)

**Figure 6. Screen-shot for analysis of variations of the first EVE.**

The top right window (Fig.6) shows the first EVE with instability areas indicated (marked with vertical viewers). In order to identify instability zones, the geometric mean value plot is used, in this case for the 2-5 EVE modules (given in the left window). A quantile in the specified order is computed from this geometric mean value plot (left side indication: a quantile of the 97% level), thereafter areas, where a quantile is exceeded by the geometric mean values, are computed which are indicated as instability zones in the right window.

On those time intervals where all above mentioned EVEs (under Nos. 2-4) show their high values, the geometric mean is also high. For the geometric mean, a quantile according to a specified order can be computed (the said figure shows an example for the percentile $X_{0.97}$), and the time interval boundaries, where the geometric mean exceeds the quantile, can be determined. It is precisely these boundaries that clearly identify the instability zones of the cardiac oscillations and that can be visualized by plotting of the first EVE, as it is illustrated in
the right window in the screen-shot in Fig.6 herein. Such way of identifying the instable zones of the expressibility considerably facilitates the diagnostics procedure.

Finally, the obtained EVEs can be used to reconstruct or restore cardiac oscillations. In this case we use a formula as follows

$$T_{\text{assoc},L} = T_{K_{T_{cp},N}} \cdot \psi_{L,L} \cdot \psi_{L,L}$$, \hspace{1em} (5)

where

- $T_{\text{assoc},L}$ is an ensemble consisted of the $K$ cardiac oscillations reconstructed or restored with $L$ EVEs,
- $T_{K_{T_{cp},N}}$ is an initial ensemble of the cardiac oscillations to construct or to restore the EVE,
- $\psi_{L,L}$ is the EVE matrix utilized for the said reconstruction or restoration (the EVEs are written as columns in this matrix).

Fig.7 and 8 illustrate an example of the reconstruction or restoration with the use of the formula (5) for the cases $L = 4$ and $L = 2$, accordingly.

**Figure 7.** Screen-shot visualizing reconstruction of cardiac oscillations. The last 9 cardiac oscillations are presented (on the specified analysis interval containing 13 oscillations) reconstructed with the use of the first 4 EVEs.
Figure 8. Screen-shot visualizing reconstruction of cardiac oscillations. The last 9 cardiac oscillations are presented (on the specified analysis interval containing 13 oscillations) reconstructed with the use of the first 2 EVEs.

It should be noted that there are several options how to provide the proper visualization of the data produced by the analysis performed by the hemodynamic analyzer Cardiocode. The most effective way of the visualization is an application of a two-window visualization interface that is illustrated in Fig.9 and 10 showing two cases described earlier: the peak-dominance case and the no-peak-dominance case.
Figure 9. Analyzer screen-shots displaying a cardiac signal with the peak dominance.
The top left window indicates the first EVE (Fig.9 a). The bottom left window shows EVE expressibility. The top right window shows temporal rows of expressibility of the first EVE (the top plot) and cumulative expressibility of the other EVEs (the lower plot). The bottom right window indicates an asymmetry coefficient temporal row.

The top window in Fig.9.b) displays a cardiac signal on the analysis interval reconstructed with the first four EVEs. The bottom window is a cardiac signal on the analysis interval reconstructed with the first two EVEs.

**Figure 10.** Analysis displaying a cardiac signal in case of absence of peaks dominance.
The first screen-shot is given in Fig.10.a). The top left window indicates the first and the second EVE, respectively. The bottom left window shows expressibility. The top right window indicates temporal rows of expressibility of the first EVE (the top plot) and cumulative expressibility of the other EVEs (the lower plot). The bottom right window indicates an asymmetry coefficient temporal row.

The second screen-shot is given in Fig.10.b). The top window displays a cardiac signal on the analysis interval reconstructed with the first two EVEs. The bottom window indicates the following procedure: the components corresponding to the first four EVEs are excluded from the cardiac signal, next an EVE basis is constructed for the signal newly produced, and by using the first two of the newly constructed EVEs a high-frequency component is identified.

As indicated in Fig.10 b), if necessary, the reconstruction or the restoration of cardiac signal components can be undertaken many times. A screen-shot presented in Fig.10 b) demonstrates the reconstructed cardiac signal (top window) upon the completed reconstruction procedure which is as follows: initially, the first 4 components of the signal are removed, thereafter, for the remainder an ensemble is created once again, on the basis of which new EVEs are obtained, and with the use of the first two newly produced EVEs the reconstruction is performed.

The cardiac oscillation ensemble for the cases of the peak dominance and no-peak-dominance are created, as discussed earlier, on an interval equal to the averaged period of the cardiac oscillations (that corresponds to the heart rate). But there are differing algorithms which are utilized for measuring of the averaged period in the above mentioned cases. The above mentioned hemodynamic analyzer is capable of automatically differentiating the type of the signal to be analyzed on any specified interval of the analysis.

According to the conducted surveys, the best quality in the proper differentiation of the cases of the peak dominance and no-peak-dominance is provided with the use of the criterion applying the asymmetry coefficient \( \gamma_1 \), calculated by a standard formula as follows:

\[
\gamma_1 = \frac{1}{N} \sum_{i=1}^{N} (S_i - m_s)^3 / \sigma^2, \quad \text{where} \quad m_s = \frac{1}{N} \sum_{i=1}^{N} S_i \quad \text{is the sample average}, \quad \sigma^2 = \frac{1}{(N-1)} \sum_{i=1}^{N} (S_i - m_s)^2
\]

is the sample dispersion, \( S_1, \ldots, N \) is the cardiac signal sampling on the analysis interval.

In this case, the best threshold value of the dominance criterion employing the asymmetry coefficient is value 2. Therefore, it should be offered to apply to the analysis performed by the hemodynamic analyzer the following decisive rule:

if \( \gamma_1 \geq 2 \), the dominance of peaks is available,
if $\gamma_1 < 2$, the dominance of peaks is not available.

We dwell on the issue on how the ensemble of the cardiac oscillations is created by the Cardiocode device that is used to calculate the respective covariance matrix including the EVEs and EVAs of the latter. The selection of an averaged period to be used as an interval in the analysis (covering both cases: with peak dominance and no-peak-dominance) has the advantage (as the special surveys has demonstrated) that, under such conditions, the EVE maximum expressibility is observed. It is applicable to a greater extent to the case when the dominance of the peaks is available.

**Conclusions**

The cardio-eigenoscopy method is capable of assessing the risk of progression of fatal arrhythmia events in MI patients within 6 to 7 hospital hours by automatic analyzing the degree of variation of the specific ECG records in 97,5% of cases (showing the sensitivity of 88% and the specificity of 93,6%).

It has been found that the major markers of the possible progression of fatal arrhythmia are as follows: a share of the first vector was reported to be reduced to 80% and an ECG asymmetry coefficient was recorded to fall to 2,2. So, it should be noted that the cardio-eigenoscopy provides the maximum expressibility of an ECG curve at any specified EVE values. To provide an efficient analysis, it would suffice to use no more than 3 eigenvectors.

**Statement on ethical issues**

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

**Author contributions**

All authors prepared the manuscript and read the ICMJE criteria for authorship, V.V.C. drafted the manuscript. All authors read and approved the final manuscript.

**Conflict of interest**

None declared.
References

Original research

Study of effects of simulated space flight factors and use of infusion liquids on human hemodynamics with the use of the Cardiocode method

Olga K. Voronova¹, Mikhail Y. Rudenko¹*, Vladimir A. Zernov¹

¹ Russian New University, 105005, Russia, Moscow, 22 Radio St.
° Corresponding author: Phone: +7 (8634) 31-24-03. E-mail: cardiocode@mail.ru

Submitted: 02 April 2013
Accepted: 28 April 2013
Published online: 30 May 2013

Aims
The aim is to study the effect of simulated space flight factors on the human central hemodynamics and evaluate the effectiveness of colloid and crystalloid infusions in microgravity simulation using the Cardiocode method.

Materials and methods
Test subjects were six men aged 20 to 35 without chronic somatic diseases. Antiorthostatic hypokinesia with an angle of 15 ° (ANOH-15) simulated the weightlessness was used. Diuretics were used to simulate hypovolemia in the test individuals. During ANOH-15 the colloid and crystalloid intravenous infusions were applied. Central hemodynamics parameters were measured by Cardiocode method.

Results
Background quantitative and qualitative central hemodynamics parameters were obtained, several individual characteristics of blood flow regulation were identified. The effects of space flight factors, ground-based simulated with antiorthostatic hypokinesia, on the human hemodynamics were investigated.

Conclusion
The Cardiocode method allowed obtaining the information about the effects of simulated space flight factors and different infusion fluids on the human central hemodynamics. The efficacy of crystalloid and colloid infusions for the correction of central hemodynamics abnormalities in test subjects in microgravity was positively evaluated.

Keywords
Cardiocode • Hemodynamics • Simulated space flight • Antiorthostatic hypokinesia • Hypovolemia • Microgravity

Imprint
Olga K. Voronova, Mikhail Y. Rudenko, Vladimir A. Zernov. Study of effects of simulated space flight factors and use of infusion liquids on human hemodynamics with the use of the Cardiocode method; Cardiometry; No.2; May 2013; p.124-135; doi: 10.12710/cardiometry.2013.2.124135
Available from: http://www.cardiometry.net/issues/no2-may-2013/simulated-space-flight-factors.pdf
Introduction

The further progress in cosmonautics, the prospects for long-term interplanetary missions dictate us today the necessity of the development and improvement of the system of medical services for orbital flights. Prolonged space missions require further adjustments and corrections of the preventive measure system, improving the system of medical selection of cosmonauts and astronauts, elaboration of absolutely new methods of diagnostics and treatment of cosmonauts both during their space missions and their adaptation to new tasks of the existing medical equipment systems already admitted to be used in space medicine (1).

One of the biggest challenges for the nearest future, which has been discounted up to the present day, is devising of new methods of intensive therapy and eventual surgical treatment to be used on board a space ship during long-term space missions in case of emergency. As to the orbital flights, in case of necessity of a surgical treatment, or in case some critical health conditions occur, there exists always the possibility to interrupt the space flight and return the critically ill person to the Earth within the possible shortest time. But it is just another case with interplanetary missions: there is no way of doing the same. Therefore, this makes the elaboration of a new reliable medical service system all the more important for its use during long-term space flights, including creation of new concepts and development of new methods of on-board surgical treatment of cosmonauts or astronauts in critical cases, if any.

One of the most significant components of surgery and intensive therapy during a space flight is infusion therapy. The existing equipment systems and facilities make possible to use the infusion therapy even under the weightlessness conditions. But at the same time, it should be noted that there are no data on impacts of various infusion liquids on parameters of the central and the peripheral hemodynamics, including data on their impacts on blood microcirculation and tissue gas exchange processes in the microgravity environment during a space flight.

There is a huge amount of data collected by experts which are related to issues on re-distribution of liquids in the body under the microgravity conditions (2), changes in water-salt exchange in the organism (3,4), tissue metabolism, effects of weightlessness both on the central and the peripheral hemodynamics (5). An efficiency of the use of infusion liquids under the space flight conditions has not been studied until now.

In the microgravity environment, when the parameters of the central and the peripheral blood circulation, the volumes of circulated blood and microcirculation indices are changed and when liquids in the cosmonaut’s body are re-distributed, the effects of the use of infusion liquids might differ significantly from those expected. This factor should be considered in specifying tactics of infusion therapy under the space flight conditions.
Upon investigations of effects of colloid and crystalloid intravenous infusions on various parameters of the central and peripheral hemodynamics, we are able to optimize to a large extent all algorithms of intensive therapy in some surgical cases and some cases of critical health states under the weightlessness conditions.

In this connection it should be noted that it is advisable to carry out a number of ground-based experiments in order to identify some impacts of a simulated space flight on the efficiency of different infusion liquids used there.

The ground-based simulation of the microgravity is widely used both for training of cosmonauts and conducting of medical and technological experimentation under the microgravity conditions. There exist some different ways of how to imitate and simulate the weightlessness conditions on ground.

In medical studies, for the purpose of the microgravity simulation, most commonly used are methods simulating a lack of blood hydrostatic pressure in the organism. In particular, one of the microgravity models is restricting of test subjects to head down tilt bed rest which is called antiorthostatic hypokinesia (ANOH).

This article is presenting some results of an experimental study on the effects of factors of a space flight with the use of a ground-based simulation on the organism, with the utilization of the antiorthostatic hypokinesia (ANOH) at a tilt angle of 15°.

For conducting of such studies, the issues on methods of assessment, control and monitoring of the state of the cardiovascular system are of great importance.

In pursuing these aims, obtaining of reliable measurement data on the central hemodynamics by noninvasive technologies is really a very challenging idea.

In the above ANOH studies, in order to evaluate the responses of the human cardiovascular system to the simulated space flight conditions in combination with the support of the infusion liquids, we applied a new diagnostics method based on an application of the Cardiocode device (6).

The Cardiocode device offers an innovative noninvasive measuring technology that delivers noninvasively volumetric parameters of hemodynamics, based on the heart cycle phase analysis. This technology has its origin in a new theoretical model of blood flow via blood vessels in the organism.

This noninvasive technology makes possible to obtain not only values of phase-related parameters of hemodynamics, but to provide qualitative assessments of functional and structural changes, including hemodynamic changes in various parts of the cardiovascular system, as well.
Materials and methods

The aim of the experimental study with the use of the Cardiocode device & technology was to reveal and assess impacts and effects of a simulated space flight on the human cardiovascular system and evaluate the efficiency of the use of colloid and crystalloid intravenous infusions under the microgravity conditions.

Issue 1 was to reveal changes in the central hemodynamics of a human due to exposure factors of the simulated space flight (during a short-term ANOH and under conditions of in case of intentionally produced loss of fluid); Issue two was assessing the efficiency of the use of colloid and crystalloid intravenous infusions in test subjects with hypovolemia in order to correct abnormalities of the central and peripheral hemodynamics under conditions simulating microgravity effects (antiorthostatic hypokinesia at a tilt angle of 15° (ANOH -15°).

Six individuals (males) without any chronic somatic diseases, aged from 20 to 35, participated in the experimental study.

The antiorthostatic hypokinesia at a tilt angle of 15° (ANOH-15°) during 21 hours was taken as the model simulating the weightlessness conditions (microgravity).

The state of hypovolemia in the hypokinetic subjects was produced with the use of diuretics (furocemide).

During the ANOH-15° test, the above test subjects received colloid (infucol 10%) and crystalloid (glucose 5%) infusions via intravenous therapy.

The study comprised three sets of the experiment as follows:

• Set 1 of the 21 hour ANOH-15° test, no infusions were received. The liquid loss state was simulated with the use of the diuretics within the ANOH 14th hour.

• Set 2 of the 21 hour ANOH-15° test, when the test subjects received the colloid infusion (infucol 10%) via intravenous therapy within the ANOH 17th hour (500 ml during 1 hour). The liquid loss state had been produced with the use of the diuretics within the ANOH 14th hour.

• Set 3 of the 21 hour ANOH-15° test, when the test subjects received crystalloid infusion via intravenous therapy (glucose 5%) within the ANOH 17th hour (500 ml during 1 hour). The liquid loss state had been produced with the use of the diuretics within the ANOH 14th hour.

It should be noted that all test subjects were involved in the above three sets of the experiment. An interval between the tests for each individual was 5 to 7 days.

All test participants were subjected to orthostatic tests both before the ANOH-15 and after it covering all 3 sets of the experimental study (orthostatic test is referred to as the OT – passive vertical position on tilt table).
Changes in the central hemodynamic parameters during the experiment were recorded and evaluated with the utilization of the device Cardiocode. The experimental studies were carried out in line with the following testing schedule.

1. Set 1, no infusion received:

<table>
<thead>
<tr>
<th>Time</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background recumbent position</td>
<td>Minute 1, OT upright position</td>
</tr>
<tr>
<td>Minute 1</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 4</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 8</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 12</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 15</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 30</td>
<td>ANOH-15°</td>
</tr>
<tr>
<td>Morning hours, ANOH-15°</td>
<td>Day hours, ANOH-15°</td>
</tr>
<tr>
<td>Evenings hours, ANOH-15°</td>
<td>Horizontal recumbent position, before OT</td>
</tr>
<tr>
<td>Minute 1</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 4</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 8</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 12</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 15</td>
<td>OT upright position</td>
</tr>
</tbody>
</table>

2. Sets 2 and 3, infusion receiving:

<table>
<thead>
<tr>
<th>Time</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background recumbent position</td>
<td>Minute 1, OT upright position</td>
</tr>
<tr>
<td>Minute 1</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 4</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 8</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 12</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 15</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 30</td>
<td>ANOH-15°</td>
</tr>
<tr>
<td>Morning hours, ANOH-15°</td>
<td>ANOH-15° before receiving infusion</td>
</tr>
<tr>
<td>ANOH-15°, minute 15 of receiving infusion</td>
<td>ANOH-15°, minute 30 of receiving infusion</td>
</tr>
<tr>
<td>ANOH-15°, minute 45 of receiving infusion</td>
<td>ANOH-15°, minute 60 of receiving infusion</td>
</tr>
<tr>
<td>Evenings hours, ANOH-15°</td>
<td>Horizontal recumbent position, before OT</td>
</tr>
<tr>
<td>Minute 1</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 4</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 8</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 12</td>
<td>OT upright position</td>
</tr>
<tr>
<td>Minute 15</td>
<td>OT upright position</td>
</tr>
</tbody>
</table>

In the test subjects recorded were ECGs and Rheograms at times specified by the above experiment schedule (s. Fig. 1 herein).
On the basis of the recorded ECG and Rheo curves, the appropriate heart cycle phase structure for every individual was automatically identified and the relevant parameters of the central hemodynamics were calculated (6).

**Results**

The basic (recorded before the experiment) quantitative and qualitative characteristics of the cardiovascular system performance in all test subjects were within the norm. Certain individual peculiarities of blood flow regulation not referring to pathology were noted.

**Influence of simulated space flight factors and infusion liquid injection on hemodynamics of the test subjects**

Before evaluating the influence of infusion of colloid and crystalloid solutions on central hemodynamics, it is necessary to understand how hemodynamic parameters change under the influence of the simulated space flight factors. Analysis of parameters of central hemodynamics in the test subjects calculated with the Cardiocode device showed that the most significant changes during the experiment can be observed in the following parameters:

- **SV** – stroke volume, ml;
- **MV** – minute volume, l;
PV1 – volume of blood entering the ventricle in the early diastole, which is the characteristic property of the suction function of the ventricle, % of SV;

PV2 – volume of blood entering the left ventricle in the systole phase, which is the characteristic property of the contraction function of the atrium, % of SV;

PV5 – volume of blood (SV fraction) pumped by the ascending aorta as peristaltic pump which is the characteristic property of the aortic tonus, % of SV.

Heart rate, HR

Hemodynamic parameters the values of which are given as percentage of stroke volume provide a better understanding of cardiac output formation than the absolute values. Thus, percentage ratio of volumes PV1 and PV2 shows the process of the heart filling with blood, in particular, whether the ventricle or the atrium are to a greater degree responsible for diastole. Volume PV5 characterizes the contribution of the aorta to blood ejection from the ventricle in the systole phase.

The diastole contributes to formation of cardiac output significantly. Without heart relaxation and diastole there would be no contraction and systole phase. An increase in the heart rate serves as a protection tool of the human body and assists in maintaining sufficient blood supply of body organs and tissues under conditions of increased loads. The inner structure of the cardiac cycle changes as well, and the functions are redistributed among the atria, ventricles and large vessels which take part in cardiac output formation. As investigations showed, under these conditions the interrelation of diastolic phase volumes changes, volume PV2 increases significantly and the atrium load on myocardium increases as well. In case of high pulse rate the ventricles are filled with blood only during the systole phase. Thus, the compensation mechanism works.

We will pay attention to the analysis of diastolic heart function considering the interrelation of volumes PV1 and PV2 as diagnostic criterion. The subject whose ventricles are filled in bed rest position during the early diastole phase possesses greater compensation capabilities.

Let us consider the general scheme of the dynamics of the central hemodynamic parameters of the test subjects during the experiment. Then we shall consider some individual characteristics.

It should be noted that the mentioned scheme can be observed in practically every test subject with only minor deviations. It is only the intensity of changes that is different.

A clear-cut response to orthostatic load preceding and following antiorthostatic hypokinesia (ANOH) as well as preceding and following the infusion therapy is typical for all test subjects.
Let us consider the scheme of dynamics of central hemodynamic parameters. The most significant changes during all three sets of the experimental study in all test subjects are as follows.

1. **Position: recumbent bed rest.**
   Volume $PV_1$ is larger than volume $PV_2$ in absolute terms as well as in relative values. This means that the heart is filled mostly by means of the ventricle activity.

2. **Orthostatic test before the ANOH-150 and after it**
   Stroke volume $SV$ decreases, minute volume $MV$ rises compared with the background. The heart rate increases significantly. The interrelation of diastolic phase volumes $PV_1$ and $PV_2$ change, $PV_2$ increases significantly. That means that the ventricle is filled with blood due to the atrial systole. The myocardium load of the atrium occurs whereas the influence of the ventricle on cardiac output formation decreases. The ECG curves of certain test subjects show negative T waves. The Rheo curve changes as well (a diastolic wave rises).

3. **Antiorthostatic hypokinesia at an angle of 15° (ANOH-15°)**
   Stroke volume $SV$ decreases compared with the orthostatic test, minute volume $MV$ rises, the heart rate decreases. The interrelation of diastolic blood volumes changes, $PV_1$ increases and $PV_2$ decreases. With bed rest position of the subjects the heart is filled with blood easily, and an active function of the atrium is not necessary.
   The use of furosemide during the 14th hour of the ANOH does not lead to significant changes of central hemodynamic parameters. The volume of the venous bed increases at the same time decreasing blood supply to lesser circulation. This can soothe the condition of the subject experiencing the antiorthostatic hypokinesia during several hours.

4. **Blood volume $PV_5$ (% of $SV$) changes ranging from 11% to 16% in all test subjects.**
   Thus, aorta constantly contributes to cardiac output under the influence occurring in the process of experiments.

5. **Infusion therapy.**
   In the course of colloid and crystalloid intravenous infusions the changes of values of central hemodynamic parameters are not significant. However, during infusion colloid infusion an increase in the minute volume $MV$ against the infusion background is observed in all test subjects. It can indicate increase in volume of blood circulation as a result of the infusion. In the process of glucose crystalloid infusion an increase in the $MV$ is observed in four test subjects, test subjects No 4 and No 5 being exception. The reason of this difference can be explained as follows. Colloid infusions are kept better in vascular bed than crystalloid infusions. Thus, colloid infusion influences the central hemodynamics.

6. **Orthostatic test after the ANOH-150.**
Table 1 presents values of the central hemodynamic parameters in all test subjects during the orthostatic test following ANOH in the course of three sets of the experimental studies. Thus, it is easier to evaluate the influence of infusions upon acceptability of the orthostatic test following the zero-G-conditions simulation.

Table 1.

<table>
<thead>
<tr>
<th>Test subject No</th>
<th>hemodynamic parameters</th>
<th>Set 1 without infusion</th>
<th>Set 2 colloid intravenous infusion</th>
<th>Set 3 Crystalloid intravenous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MV, l</td>
<td>6,7 - 7,2</td>
<td>6,0 - 6,6</td>
<td>5,9 - 6,6</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>37 - 44</td>
<td>48 - 55</td>
<td>30 - 53</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>56 - 63</td>
<td>44 - 52</td>
<td>47 - 70</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>121 - 132</td>
<td>108 - 116</td>
<td>111 - 123</td>
</tr>
<tr>
<td>2</td>
<td>MV, l</td>
<td>6,3 - 6,9</td>
<td>6,1 - 6,7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>15 - 40</td>
<td>37 - 55</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>60 - 85</td>
<td>45 - 63</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>105 - 115</td>
<td>87 - 100</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MV, l</td>
<td>5,4 - 6,2</td>
<td>7,8 - 8,1</td>
<td>5,5 - 5,9</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>49 - 58</td>
<td>41 - 54</td>
<td>52 - 59</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>42 - 51</td>
<td>46 - 59</td>
<td>41 - 48</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>98 - 109</td>
<td>104 - 111</td>
<td>91 - 102</td>
</tr>
<tr>
<td>4</td>
<td>MV, l</td>
<td>5,1 - 5,8</td>
<td>4,8 - 5,4</td>
<td>4,9 - 5,3</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>57 - 69</td>
<td>63 - 71</td>
<td>65 - 72</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>31 - 43</td>
<td>29 - 37</td>
<td>28 - 35</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>93 - 107</td>
<td>79 - 96</td>
<td>79 - 89</td>
</tr>
<tr>
<td>5</td>
<td>MV, l</td>
<td>5,1 - 7,3</td>
<td>6,8 - 7,3</td>
<td>5,4 - 7,1</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>16 - 51</td>
<td>8 - 20</td>
<td>23 - 61</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>49 - 84</td>
<td>80 - 92</td>
<td>39 - 77</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>102 - 130</td>
<td>123 - 136</td>
<td>90 - 129</td>
</tr>
<tr>
<td>6</td>
<td>MV, l</td>
<td>5,5 - 6,8</td>
<td>6,5 - 6,9</td>
<td>5,7 - 6,6</td>
</tr>
<tr>
<td></td>
<td>PV1 %</td>
<td>35 - 56</td>
<td>32 - 41</td>
<td>26 - 49</td>
</tr>
<tr>
<td></td>
<td>PV2 %</td>
<td>44 - 65</td>
<td>59 - 68</td>
<td>51 - 74</td>
</tr>
<tr>
<td></td>
<td>heart rate</td>
<td>99 - 125</td>
<td>116 - 129</td>
<td>107 - 121</td>
</tr>
</tbody>
</table>

The criteria for selection of test subjects best prepared to adaptation to the conditions of a space flight and re-adaptation upon return to the Earth

When selecting the candidates for a space flight it is reasonable to take into account at least three criteria as listed below:

- an acceptable ability to bear overloads during the start;
- an acceptable ability of adaptation to weightlessness;
• availability of a body compensatory reserve required for return to the Earth and re-adaptation to the normal gravity conditions.

This is certainly a very difficult task. Much more information is needed to solve it. We can only offer a sort of prognostication, when using the results of the analysis of circulatory system response to the effects of simulated space flight factors in the above mentioned completed experiment.

The ability of every test individuals to be adapted to the weightlessness conditions is beyond any doubt. But their ability of re-adaptation to the Earth normal gravity conditions after a space flight raises far more questions.

Antiorthostatic hypokinesia at an angle of 15° (ANOH-15°) is a model of weightlessness in these experiments. The analysis of the data on hemodynamics changes during the ANOH showed that the ratio of diastolic phase volumes changes towards an increase in the PV1 blood volume and a decrease in the PV2 blood volume, i.e., the atria are discharged.

The orthostatic test carried out after the ANOH can be considered as a model of return to the normal gravity on the Earth after the weightlessness conditions. It is evident that it leads to a sharp increase in the heart rate and the PV2 parameter. It also implies a sudden overloading of atrial myocardium.

After a long-term stay in the weightlessness environment in a real space flight, the fact described above can play a significant role in the re-adaptation of a cosmonaut to the Earth gravity.

Taking it into account, a better ability to tolerate the orthostatic test under conditions of the simulated ground-based weightlessness can be considered as one of the criteria for the selection of test subjects for a real space flight.

This study allows drawing some general conclusions only and tracing some tendencies of the human cardiovascular system response to the space effects simulated in the experiment.

**Discussion and conclusions**

In conclusion, we would like to summarize the results of the conducted experimental study.

First, the Cardiocode method used for the experimental study allowed us to obtain most valuable qualitative and quantitative data on the effects of simulated space flight factors and infusion fluids on the human central hemodynamics. It has been found that the use of colloidal and crystalloid infusions in the test subjects with hypovolemia in the microgravity environment is a very effective measure for coping with undesirable space flight effects.

Second, despite the complex theoretical concept of hemodynamics, the new noninvasive method of measuring phase-related volumetric parameters of hemodynamics has been successfully implemented in a very easy way, with the use of the small-sized portable PC-
assisted device Cardiocode. So, this device can be used to obtain information not only during a cosmonaut preflight training, but also during a real space flight.

Third, the Cardiocode technology can be successfully used to evaluate and monitor the effectiveness of the developed preventive measures to avoid hemodynamic abnormalities in cosmonauts in the weightlessness environment.

Fourth, the possibility of obtaining a complete set of quantitative and qualitative parameters featuring the performance of the various circulatory system segments allows using the Cardiocode method developed by the authors hereof for evaluating the effects of various external factors, including those of a space flight, on the human cardiovascular system.

List of abbreviations
ANOH - a definite position of the person in bed, when the upper part of the body is located below the horizontal line, the so-called antiorthostatic position or antiorthostatic hypokinesia (weightlessness simulation);
OT - orthostatic test (passive vertical position on a tilt-table);
ECG - electrocardiogram;
Rheo - rheogram.

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

Author contributions
All authors prepared the manuscript and read the ICMJE criteria for authorship, M.Y.R. drafted the manuscript. All authors read and approved the final manuscript.

Conflict of interest
None declared.

References


Original research

A new method of effective training of crew members for long-term space mission

Victor N. Skakov

Aim

The aim of the study is to select an effective method of system recovery of the organism for space pre-flight training to provide the normal long-term human stay in space.

Materials and methods

For this purpose, the method of acupuncture is used. Its distinctive feature is the needle acupuncture technique based on the fundamental knowledge of the classical Chinese Book of Changes. This technique was developed by Master of Traditional Chinese Medicine A.I. Falev (1953-2005) and improved by his followers. The above method allows awakening the energy of Chi in the human organism that in its turn initiates the therapeutic & health improving programs stored in the deepest layers of the human body nature.

Results

As a result of the Chi energy awakening, a complex of therapeutic & health improving reactions stored in the human body nature initiates. During the treatment, uncontrolled movements of the body and limbs appear, and the patient involuntarily performs some elements of point and remote energetic massage, self-manual therapy, yoga exercises, health-improving breathing exercises. The health-improving reactions appearing thereafter restore the proper circulation of Chi energy in the organism that leads to true recovery and full health restoration.

Conclusion

This method of treatment based on the ancient techniques of acupuncture, aimed at awakening the Chi energy in the organism, can be effectively used in an integrated program of systematic health improvement of crew members during long-term space missions. This method is very efficient, does not require expensive equipment and is based exclusively on releasing hidden reserves stored in the human body.

Keywords

Long-term space mission • Pre-flight training • Acupuncture • Chi energy

Imprint

Original research

Chronobiological methods of human body self-regulation reserve evaluation

Sergey N. Zaguskin\(^1\)*, Yuriy E. Gurov\(^1\), Gina N. Bakuzova\(^2\), Irina D. Svishcheva\(^2\), Svetlana N. Zaguskina\(^1\)

\(^1\) Research Institute physics of Southern Federal University, 344006, Russia, Rostov-on-Don, Bolshaya Sadovaya st, 105/42
\(^2\) Rostov State Medical University, 344022, Russia, Rostov-on-Don, 29 Nahichevansky Lane

* Corresponding author: Phone: +7 (863) 200-08-46. E-mail: zaguskin@gmail.com
Submitted: 28 April 2013
Accepted: 24 May 2013
Published online: 30 May 2013

Aims
Chronodiagnostical methods for evaluating reserve and unfavourable responses of human cardiac function and under prolonged stress load.

Materials and methods
24-h ECG R–R interval recording of Holter-monitoring ECG recording and 1-h IPI and RespI recordings of healthy young and elderly subjects, post-MI patients, subjects suffered from chronic cerebral ischemia leading to a cognitive decline, healthy subjects following post-stress load, as well as R–R intervals recordings of the AHA ECG database of heart failure and AF.

Results
Self-regulation reserve reduction of oxygen transfer body systems and increase in unfavourable response probability under stress load are accompanied by the amplitude and fluctuation increase of redundancy quotient in the ECG IPI, RespI and R–R intervals, as well as increase of hierarchical desynchronosis with dominating sympathicotonia and vagotonia, decrease in cellular immunity.

Conclusion
Symbolic dynamics method provides distinction between age-related and abnormal changes in hierarchy of cardiac rhythms. The amplitude and fluctuation increase of redundancy quotient indicates the increase of control intensity with oxygen transfer body systems and predicts the reduction of self-regulation reserve in cardiac rhythms.

Keywords
Stress • Self-regulation reserves • Cardiac rhythms • Redundancy • Symbolic dynamics • R–R intervals

Imprint
Sergey N. Zaguskin, Yuriy E. Gurov, Gina N. Bakuzova, Irina D. Svishcheva, Svetlana N. Zaguskina. Chronobiological methods of human body self-regulation reserve evaluation; Cardiometry; No.2; May 2013; p.137-146; doi: 10.12710/cardiometry.2013.2.137146
Available from: http://www.cardiometry.net/issues/no2-may-2013/chronobiological-evaluation-methods.pdf
Introduction
Planning long duration space missions and performing complex work under stress load requires an evaluation of the human body self-regulation and adaptability reserve, probability of unfavourable responses in cardiac and respiratory function. Despite the existence of numerous indirect evaluation methods for body self-regulation reserve and adaptability to environmental unfavourable conditions [1], their prediction capabilities are not conclusively proved. The crucial task is to develop quantitative methods for predicting unfavourable responses and the risk of pathological abnormalities. The successful transient process appears to be significant for the evaluation of human adaptability to changing environmental conditions rather than maintenance of stable homeostasis. The transient process requires energy costs, and its effectiveness depends upon initial coordination of the body system performance. So the evaluation of the body sub-system activity coordination proves to be more efficient [8,10] than observations of solitary homeostasis criteria in predicting the ability to adaptability success. Today, the development of synergetics fostered a number of methods to evaluate adaptability parameters and transient performance. Fractal dimension in cardiac rhythm and respiration ratio [3,4] is shown to be a predictor for successful adaptability to changing or unexpected environmental conditions. The contemporary systemic approach requires consistency and correlation of various parameters in adaptability dynamics. The crucial task is to implement modern systematic non-linear dynamics approaches in evaluation of human adaptability and success of transient process, considering various changing criteria.

Materials and methods
For a 24-h ECG R-R interval recording, the Valenta Holter monitor (NEO scientific production association, Russia) was used. Recordings of 20 patients, aged 50 to 70, who suffered from arterial hypertension, and recordings of 20 healthy subjects of the same age range were analyzed. Besides, 24-h heart rate recordings of PhysyoNet database [15] were analysed, namely, 54 recordings of healthy subjects with normal sinoatrial rate (30 males aged 54 to 76, and 24 females aged 58 to 73), 44 recordings of subjects suffered from congestive cardiac failure (the 34 to 79 age range), 84 recordings of subjects suffered from long-term or paroxysmal atrial fibrillation and atrial fibrillation.
We designed a Family Doctor and Teacher device and implemented it for 1-h IPI and RespI recordings. The series received with the output signals from pulse and respiration sensors and entered into the computer were analyzed in healthy young (20 individuals) and elderly subjects (20 individuals), patients suffered from myocardial infarction (30 individuals), patients suffered from chronic cerebral ischemia leading to a cognitive decline (10 individuals) and
healthy subjects after stress loads (10 individuals). Deviations from circahoralian and circadian vegetative rhythms of Kérdö's index, individual minute and heart rate variability (scatter plot, ratio of low to high frequencies, Baevsky’s tension index) of all healthy and sick individuals were analyzed. Non-linear symbolic dynamics methods [2] and redundancy quotient rate parameters [9] were applied to evaluate self-regulation, adaptability reserve and unfavourable response prediction. Additionally, with the same purpose, the cellular immunity of healthy and sick subjects was evaluated with differential temperature survey method [6]. Computerized automatic respiratory gymnastics [5] and biocontrolled laser therapy [11,12] were used to normalize vegetative status and reconstitute cellular immunity rehabilitating post-stress patients.

**Results**

Comparison of various chronodiagnostical factors of healthy subjects of various age and subjects suffered from cardiac insufficiency, atrial fibrillation, arterial hypertension and myocardial infarction showed the dynamics of fractality features and redundancy quotient to be the most informative indicator of stress loads. Redundancy quotient R was calculated from formula (1), where $E_{\text{exp}}$ – experimental entropy, and $E_{\text{max}}$ – maximum entropy, taken to be homogeneous distribution of IPI or ECG R–R intervals:

$$ R = 1 - \frac{E_{\text{exp}}}{E_{\text{max}}} \quad (1) $$

While analyzing retrospectively redundancy quotient dynamics of the post-MI patients and patients suffered from arterial hypertension, general regularity was revealed. The amplitude and fluctuation of redundancy quotient increased immediately prior to maximum arrhythmia or maximum ischemia, and in some patients that increase commenced an hour or even two hours before the unfavourable response. Those factors enabled us to assume that the fluctuation parameters of redundancy quotient can be used to evaluate the self-regulation reserve of oxygen transfer body systems and tolerance to stress load for healthy individuals. To prove this assumption, the analysis of redundancy quotient fluctuation parameters has been performed in healthy individuals under stress loads (temporary duty trip to the zone of anti-terror activities).

Fig. 1 demonstrates redundancy quotient dynamics for two healthy patients suffered from that stress load. Subject (a) shows no changes in parameters of redundancy quotient dynamics, neither before nor after the stress load or rehabilitation. Maximum recorded amplitude is within 0.04 and 0.14. Subject (b) suffered from the stress load showed rhythmical
increase of redundancy quotient fluctuation amplitude (maximum peak is within 0.05 and 0.45). Recovery and reflection period has reduced rhythmical amplitude increase and rate time of redundancy quotient to initial values of stress starting point (curve c) for two weeks. Those patients had no essential individual differences in redundancy quotient before the beginning of stress loads. These factors suggest fluctuation parameters of redundancy quotient being used to predict individual organism resistance to stress or other negative loads, i.e., evaluating reserves and intensity of oxygen transfer body system self-regulation. The amplitude increase and fluctuation time increase of IPI and RespI redundancy quotient dynamics prove this suggestion, though the increase is less intense with healthy individuals during thinking process and emotional responses.

Redundancy quotient delivers more detailed information when analyzing 24-h ECG R–R interval recordings with different averaging, i.e., at varying length of sampling of redundancy quotients in the ECG R–R intervals sequencing. Fig. 2 demonstrates the rate hierarchy difference of this parameter in sick and healthy subjects. The use of different sample periods shows frequency and length of regulation intensity periods of oxygen transfer body systems, their association with day time and decrease moments of self-regulation reserves and adaptability to stress and other environmental loads in particular patients.

![Figure 1](image1.png)

**Figure 1.** IPI redundancy quotient dynamics for the patient after the long-term stress load (a, high resistance) and for the patient before (b, low self-regulation reserves) and after (c) recovery and reflection period.
Another method to evaluate human self-regulation reserve can be based on non-linear symbolic dynamics method [2,3]. Functional dynamics of regulatory subsystem was discussed as the interchange of two phases, and the number of activities in each phase was estimated. Heart beat dynamics can be divided into phases of the rise in heart rate (sympathetic tonus prevailing), and the drop in Deflate Rate (parasympathetic tonus prevailing). In each phase the number of heart beats (commonly from 1 to 4) should be counted. Transition from one phase to another can be encoded with a symbol depending on the beat quantity counted in the previous and following phases (Fig.3, to the right). For heart beat dynamics 25 symbols will be enough. In this case the subsystem functional dynamics will be described by one word composed of these symbols. The research of this subsystem functional language appears to be a sustainable method and allows for chronodiagnostics. With a number of features of symbolic dynamics (sizes of vocabularies, conventional entropy and similarity indices) we could reveal specific characteristics of different body states, namely, ageing or pathologies [2, 12]. It turned out that young healthy individuals were characterized with a large variety of vocabulary in comparison with the elderly healthy and the sick ones, and the primary role in the subsystem functional dynamics is played by shorter words (Fig. 4).
**Figure 3.** Left: scatter plot of phase length (in milliseconds) of sympathetic or parasympathetic tonus prevailing with one of the subjects, and its coding. You could see the most frequent symbols. Right: coding table depending on the number of heart beats in the current and following phases. For instance, «R» symbol means that the current phase included 4 beats and the following one had 2 beats.

<table>
<thead>
<tr>
<th>( b_i )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>&gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>O</td>
<td>I</td>
<td>U</td>
<td>E</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>F</td>
<td>H</td>
<td>C</td>
<td>J</td>
</tr>
<tr>
<td>3</td>
<td>L</td>
<td>M</td>
<td>K</td>
<td>N</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>Q</td>
<td>R</td>
<td>S</td>
<td>P</td>
<td>T</td>
</tr>
<tr>
<td>&gt;4</td>
<td>V</td>
<td>X</td>
<td>G</td>
<td>Z</td>
<td>D</td>
</tr>
</tbody>
</table>

**Figure 4.** Symbolic dynamics method of ST–diagram for 25 lines describing cardiac rhythm dynamics from left to right as follows: a young healthy individual, an elderly healthy individual, an individual suffered from cardiac insufficiency, an individual suffered from atrial fibrillation and a patient suffered from sudden cardiac death. Black squares mark transitions with frequency more than 0.1, black circles – with frequency more than 0.01 but less than 0.1. Empty circles indicate transitions with nonzero frequencies, less than 0.01.
Prediction capabilities of the symbolic dynamics method are shown in Fig. 5. This figure demonstrates the range of coordinates corresponding to values of young and elderly healthy subjects and individuals suffered from cardiac insufficiency and atrial fibrillation. Chronodiagnostics of these two patients describes that Patient 1 (red field) appears to have some signs of cardiac insufficiency in the early preclinical stage, and Patient 2 (green field) has no pathology, but it is expectable (on dispersion boundaries).

![Figure 5. IPI symbolic dynamics (1-h recordings).](image)

Fig. 6 shows sizes of vocabularies of two-symbol words for a 24-h recording of apparently healthy groups (e and y) and the sick (c and l) groups. The general quantity decrease of two-symbol words with heart diseases determines more simplified cardio rhythm dynamics [2-4, 16].

![Figure 6. shows sizes of vocabularies of two-symbol words for a 24-h recording: y - young healthy individuals; e - elderly healthy individuals; c - individuals suffered from congestive heart failure (of all ages); l - individuals suffered from atrial fibrillation (of all ages) [15].](image)
Discussion and conclusions

For individuals suffered from arterial hypertension and post-MI patients, the amplitude and fluctuation increase of redundancy quotient is estimated as the decrease of adaptive abilities and self-regulation reserve, and preliminary figures indicate they can be used to evaluate tolerance to stress of the healthy individuals. It is necessary to predict unfavourable responses and the decrease of resistance to stress loads by assessing a set of indicators. We showed that dynamics evaluation of IPI and RespI redundancy parameters and their interrelations can be an efficient predictor of adaptability and describe self-regulation reserves [3,8,9]. The prime analysis tool will be the well-proven (see above) non-linear dynamics tool [16] according to the method designed by us [2].

Two central problems remain to be relevant in diagnostics of cardiovascular response to stress loads. The first problem is connected with the lack of early disease diagnostics to detect abnormalities in human body performance before pathological abnormalities occur. Symbolic dynamics method, as our researches described, obtains prediction capabilities. The second problem is the following: today establishing accurate diagnosis requires long-lasting (24-h and more) ECG recordings, and it complicates surveying. Implementation of redundancy quotient and symbolic dynamics proved that some problems require only a 1-h recording. Our research implemented non-linear symbolic dynamics method [16] with coding words varying in their length for the first time, which includes applying scattering diagrams of ECG R–R interval minimum and maximum peaks [10]. As our research revealed [3,4,12], diagnostic methods of abnormality in subsystem consistency are highly informative. The first class of system disruption in coordination can be detected while comparing rhythms of various periods of the same organization level. For instance, for human organs and body systems disruption can be detected with features of relationship dynamics of rate of heart contraction and respiratory rate. This disruption in coordination characterizes precursory symptom of heart and respiratory diseases, as well as predicts unfavourable vegetative human responses under stress loads, development of resistant sympathicotonia or vagotonia. The second class of system disruption in timing is determined as the disruption of optimum ratio and coordination for rhythms of various periods, in our case it is the ratio of cardio rhythms of various periods.

To restore self-regulation reserve and improve adaptability to unfavourable environmental conditions, stress loads in particular, it is necessary to estimate and restore, when required, circahoralian and circadian vegetative rhythms for protection and rehabilitation. Chronodiagnostics of their abnormality should be combined with respiratory gymnastics [5]. By increasing the time of inhaling against the exhalation time the tonus of sympathetic control can be enhanced against the tonus of parasympathetic control, and vice versa in the case of
vagotonia. Another essential component to evaluate self-regulation reserve and its regeneration is the cellular immunity evaluation method with the developed differential temperature survey [6], and immune reconstitution by applying biocontrolled laser vein-area treatment of blood, lien and thymus gland [11,14]. The important post-stress rehabilitation component is normalization of calcium metabolism with the help of biocontrolled electrophoresis [13], and normalization of blood microcirculation and blood venous return with the help of biocontrolled pneumomassage [7].

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

Author contributions
S.Z., Y.G., G.B., I.S. and S.Z. developed the concept, prepared the manuscript and analyzed the data, G.B. and I.S. drafted the manuscript, S.Z. read and met the ICMJE criteria for authorship. All authors read and approved the final manuscript.

Acknowledgements
The research is performed with financial support from Russian Humanitarian Science Foundation (RHSF) within Research and Development Project of RHSF «Development of Evaluation Methods and Restitution of Human Body Reserve», project №12-06-00018а.

Conflict of interest
None declared.

References
2. Gurov YV. Development of the methods of symbolic dynamics for systemic analysis of cardiological processes Rostov-on-Don2012
5. Zaguskin SL, inventorDevice for respiratory gymnastics. SSSR28.06.90.


Editorial
In honor and remembrance of Vladimir Borisovich Alekseyev (19.08.1933 - 01.03.2013)

Vladimir Borisovich Alekseyev died. Cosmonaut and researcher, he was a legend. He came to the Cosmonaut Training Center on April 12, 1967 to the first group of cosmonauts. The group, he worked at, was focused on the performance of certain special tasks in space. However, it must be such a fate, his personal space mission was not on agenda. Having great experience and knowledge in all problems of cosmonaut training, Alekseyev realized that the key issue is the physical training of a human at a space mission. Despite a lot of institutions were involved in solving this issue, he, as an engineer, has made a great contribution to the understanding of the problem of the human presence in space.

When the programs he participated in were postponed, and later even cancelled, he took an active part in the study of problems of human survival under extreme conditions and the rehabilitation of cosmonauts returning from orbit. The intuition of a scientist allowed him to understand the systemic issues of the organism performance and realize in practice the electropunctural diagnostics and correction of cosmonauts functional state. One of the devices developed by him was used in the space station. It was used unofficially, but it was just the case with the use of that device that made possible to save several human space mission programs, being on the brink of collapse because of the cosmonauts’ health problems.

Following the initiative by V. Alekseyev and under his personal participation, in 1980, a group of scientists was formed and created a new scientific field, the theory of hemodynamics. Later they developed the theory of heart cycle phase analysis. Both theories became the basis of CARDIOMETRY, a science of measurements in cardiology. It is precisely the science our journal is dedicated to.

Alekseyev’s scientific talent and energy of his enthusiasm were not fully used on the work in the cosmonauts’ group. And in the film, which was shot in his memory, he was called "a scientist whose life was classified top secret".

The team of scientists created CARDIOMETRY will always remember that the founder of this field of science was a fine man, a researcher and intellectual, Vladimir Borisovich Alekseyev.

A group of friends
Conference report

38th Annual Conference of International Society for Computerized Electrocardiology
April 17-21, 2013
San Jose, California, USA

by Ljuba Bacharova, International Laser Center, Bratislava, Slovak Republic
Konstantin Kamyshev*, Russian New University, Moscow, Russia

*Corresponding author: Phone +7 (908) 183-34-98 E-mail: costyan21@yahoo.com

The 38\textsuperscript{th} Annual Conference of International Society for Computerized Electrocardiology (ISCE) was successfully held during April 17-21, 2013 in San Jose, California, USA. Over 100 delegates participated in the five day Conference, which brought together medical doctors, medical equipment engineers and R&D sectors, businessmen, scientists and researchers involved in all aspects of electrocardiology, which issues were discussed in depth to provide up-to-date information to the world. The meeting provided a great information platform for researchers to communicate with each other and resulted in great exchange of knowledge. Delegates came from USA, Finland, Denmark, Israel, Italy, Slovak Republic, Russia, UK, Holland, Switzerland, Canada, Brazil, Germany and other countries.

The conference theme was \textit{"Engineering aspects of automated rhythm analysis during 12-lead electrocardiography"}. Sessions included \textit{J wave syndromes}, Telecardiology, ECG databases, Sudden cardiac death, T-wave variability.

The scientific program was a rich mix of formats, ranging from keynote sessions featuring many well-known speakers to highly interactive discussion sessions. Presentations defined and analyzed the most important ideas and opportunities and were thought-provoking and stimulating. Adequate time for discussion was allowed. The conference included 7 keynote sessions and 2 poster sessions. Scientific session’s established active contribution from researchers and principal investigators, and the Poster presentations were phenomenally excellent.

A series of lectures by Honorable guests and members marked the commencement of the event. We were honoured to have Kjell Nikus, M.D., Tampere University Hospital and Paul Kligfield, M.D., Weill Cornell Medical College, officially opened the conference and held the first session. The main speakers were Richard Gregg, Philips Medical Systems, Andover MA USA; Charles Antzelevitch, Masonic Medical Research Laboratory, Utica NY USA; Peter Macfarlane,
University of Glasgow, Glasgow Scotland UK; Roger Abächerli, Schiller AG, Baar, SWITZERLAND; Larisa Tereshchenko, Johns Hopkins University, Baltimore MD USA; Raimond Winslow, Johns Hopkins University, Baltimore MD USA; Mikkel Schoos, Rigshospitalet, Copenhagen DENMARK; Marek Malik, St. George's University of London, London UK; Barbara J. Drew, UCSF, San Francisco CA USA; and many others.

However, the main focus and benefit of the ISCE conference is on the discussion at the posters. Sufficient time is devoted for each poster session and there are no other parallel activities or sessions. The authors and participants really utilize the time devoted to the posters presentations. These vivid discussions provide qualified feedback to authors, create a basis for exchanging of ideas, for developing new ideas and potentially for future collaboration. A lot of posters were presented at ISCE conference this year. Among them were posters of Deodato Assanelli, University of Brescia, Brescia ITALY; Jose Vicente, US Food and Drug Administration, Silver Spring MD USA; Dimitrios Poulikakos, St. George's University of London, London UK; Vincent Jacquemet, Hôpital du Sacré-Coeur de Montréal, Montreal CANADA; Massimo Rivolta, Università degli Studi di Milano, Milan ITALY; and others.

ISCE 2013 gave great opportunity for investigators from all over the world to share their ideas cause this year there were a lot of universities becoming members of ISCE and participating in the conference for the first time. Russian New University was among them. It was also the only organization from Russian Federation attending the ISCE conference 2013. The poster describing the latest scientific achievements of university Laboratory of Human Cardiovascular System (Russian New University, Moscow, Russia) was displayed and appreciated by all attendees. "I want to express our pleasure at having Konstantin Kamyshev attend the recent Annual Meeting of the International Society for Computerized Electrocardiology in San Jose, California. His participation in ISCE was greatly appreciated and we hope to see him and/or other representatives of Russian New University and Cardiometry attend future Meetings” said Rory Childers, President of ISCE.
SCIENTIFIC PROGRAM

WEDNESDAY, 17 APRIL 2013

Engineering aspects of automated rhythm analysis during 12-lead electrocardiography

Organizers: Paul Kligfield, Weill Cornell Medical College, New York NY USA

Eric Helfenbein, Philips Medical Systems, Andover MA USA
Paul Kligfield, Weill Cornell Medical College, New York NY USA
Robert M. Farrell, GE Healthcare, Wauwatosa WI USA

Basic engineering issues for rhythm detection

Richard Gregg, Philips Medical Systems, Andover MA USA

Sensitivity-specificity tradeoff for arrhythmia detection

Johan de Bie, Mortara Instrument, Milwaukee WI USA

Detection of atrial flutter and tachycardia in a 10-second 12-lead ECG

Shen Luo, Mindray Biomedical, Mahwah NJ USA

Evaluation of rhythm and pacemaker performance for 12-lead electrocardiographs

THURSDAY, 18 APRIL 2013

Session I: Papers from submitted abstracts

Chair: Paul Kligfield, Weill Cornell Medical College, New York NY USA
Co-chair: Kjell Nikus, Tampere University Hospital, Tampere FINLAND

Paul Kligfield, Weill Cornell Medical College, New York NY USA
Jørgen Kanters, University of Copenhagen, Copenhagen DENMARK

T-wave morphology combination score, heart rate and the QT interval as risk predictors for all-cause-mortality in the general population

Reza Firoozabadi, Philips Healthcare, Thousand Oaks CA USA

Predicting defibrillation success in sudden cardiac arrest patients

Phyllis Stein, Washington University School of Medicine, St. Louis MO USA

24-hour Holter-derived VPC counts and incident outcomes in older adults: The cardiovascular health study
Jean-Philippe Couderc, University of Rochester Medical Center, Rochester NY USA

Combination of T-wave alternans and QT variability predicts ICD discharge in MADIT II patients

Session II: J wave syndromes and sudden cardiac death. From cell to bedside
Chair: Charles Antzelevitch, Masonic Medical Research Laboratory, Utica NY USA
Co-chair: Peter Macfarlane, University of Glasgow, Glasgow Scotland UK

Charles Antzelevitch, Masonic Medical Research Laboratory, Utica NY USA
Peter Macfarlane, University of Glasgow, Glasgow Scotland UK
ECG distinctions, prevalence and nomenclature

Charles Antzelevitch, Masonic Medical Research Laboratory, Utica NY USA
Genetics, cellular and ionic mechanisms and approach to therapy

Arnon Adler, Tel Aviv Medical Center, Tel Aviv ISRAEL
Risk stratification of early repolarization

Poster Session 1
Salah Al-Zaiti, University at Buffalo, Buffalo NY USA
Predicting mortality using heterogeneity of ventricular repolarization: A metaanalysis. Findings from a global population of 362,816 patients

Deodato Assanelli, University of Brescia, Brescia ITALY
T-wave axis deviation and left ventricular hypertrophy interaction in the MOLI SANI project

Ljuba Bacharova, International Laser Center, Bratislava SLOVAK REPUBLIC
The effect of periinfarction block on the QRS complex and ST segment patterns: A model study

Said Yama Fakhri, University Hospital, Copenhagen DENMARK
Novel electrocardiographic pre-hospital salvage score outperforms reperfusion delay for prediction of left ventricular function in patients with ST elevation myocardial infarction

Arzhang Fallahi, Beth Israel Medical Center, New York NY USA
EKG and angiographic correlation in patients with acute anteroseptal versus extensive anterior STEMI
Konstantin Kamyshev, Russian New University, Moscow Russia

Fundamental research on the mechanism of cardiovascular system hemodynamics self-regulation. Determination of the norm-pathology boundary for the basic hemodynamic parameters and analysis of the compensation mechanism as a method of revealing the underlying causes of the disease

Michele M Pelter, University of Nevada, Reno Nevada USA

Transient myocardial ischemia among Non-STEMI and unstable angina patients treated with invasive versus conservative treatment

David Pickham, University of California, San Francisco CA USA

Development of ECG abnormalities in the first year after heart transplantation

Dimitrios Poulikakos, St. George's University of London, London UK

T wave morphology descriptors during haemodialysis

Autumn Schumacher, Georgia Regents University, Augusta GA USA

Defibrillation threshold testing does not cause acute electrocardiographic changes in cardiomyopathy patients undergoing insertion of an implantable cardioverter defibrillator

Jose Vicente, US Food and Drug Administration, Silver Spring MD USA

Gender differences in the evolution of spatial QRS-T angle and ventricular gradient with age

Sofieke Wijers, University Med. Center Utrecht, Utrecht THE NETHERLANDS

Proposing a new ECG parameter for risk stratification in repolarization dependent ventricular arrhythmias: STVQT

SESSION III: Telecardiology

Chair: Roger Abächerli, Schiller AG, Baar, SWITZERLAND

Co-chair: Peter Clemmensen, Rigshospitalet, Copenhagen DENMARK

Roger Abächerli, Schiller AG, Baar, SWITZERLAND

Lemuel Cunha, Federal University, Belo Horizonte BRAZIL

Main features of a Brazilian large scale telecardiology network

Richard Gregg, Philips Healthcare, Andover MA USA

Comparing ST-segment elevation myocardial infarction criteria for left bundle branch block
Salah Al-Zaiti, University at Buffalo, Buffalo NY USA  
*Novel technical solutions for ECG transmission: Clinical perspectives*

Peter Clemmensen, Rigshospitalet, Copenhagen DENMARK  
*Prehospital diagnosis and transfers of patients with acute coronary syndrome*

**FRIDAY, 19 APRIL 2013**

**Session IV: ECG databases/Sudden cardiac death**

Chair: Larisa Tereschchenko, Johns Hopkins University, Baltimore MD USA  
Co-chair: Konrad Brockmeier, University of Köln, Köln GERMANY

Larisa Tereschchenko, Johns Hopkins University, Baltimore MD USA  
Raimond Winslow, Johns Hopkins University, Baltimore MD USA  
*A web-based tool for managing and analyzing ECG data*

Larisa Tereschchenko, Johns Hopkins University Baltimore MD USA  
*ECG as a screening tool in the general population*

Adriaan van Oosterom, Radboud University, Nijmegen THE NETHERLANDS  
*Repolarization features as detectable from electrocardiograms and electrograms*

Joseph E. Marine, Johns Hopkins University, Baltimore MD USA  
*ECG features suggesting a potentially life-threatening arrhythmia as the cause for syncope*

Mathias Baumert, University of Adelaide, Adelaide AUSTRALIA  
*Symbolic analysis of coupling between heart rate, blood pressure and respiration*

**Poster Session 2**

Roger Abächerli, SCHILLER AG, Baar SWITZERLAND  
*Is it possible to reduce the false positive diagnostic statements in young athlete ECG screening?*

Deodato Assanelli, University of Brescia, Brescia ITALY  
*T-wave axis deviation and left ventricular hypertrophy interaction in diabetes and hypertension (MOLI SANI project)*
Han Chengzong, Philips Healthcare, Andover MA USA
Comparison of QT heart rate correction methods during drug-induced QT prolongation in rabbit

Simon Chien, Philips Healthcare, Andover MA USA
A software algorithm for detection of biventricular pacemaker pulses in the surface ECG

Dirk Feild, Philips Healthcare, Thousand Oaks CA USA
Evaluation of a real-time automated algorithm for ST measurement

Patricia Harris, University of California, San Francisco CA USA
Heart rate turbulence in patients with respiratory failure

Vincent Jacquemet, Hôpital du Sacré-Coeur de Montréal, Montreal CANADA
Consistency of QTc measurements in atrial flutter patients before and after catheter ablation

David Pickham, University of California, San Francisco CA USA
Association between endomyocardial tissue biopsies and right ventricular conduction delays

Mads Riemann, University of Copenhagen, Copenhagen DENMARK
Absence of potassium channel interacting protein 2 delays conduction in the mouse ECG

Massimo Rivolta, Università degli Studi di Milano, Milan ITALY
Quantification of ventricular repolarization heterogeneity during sotalol administration using the V-index

John J Wang, Philips Healthcare, Andover MA USA
On transformations for estimating body-surface potential maps from the standard 12-lead electrocardiogram

Sofieke Wijers, University Medical Center Utrecht, Utrecht, THE NETHERLANDS
Acute, short, and long term ‘reverse’ electrical remodeling after biventricular pacing in patients with cardiac resynchronization therapy

Wojciech Zareba, University of Rochester, Rochester NY USA
ECG parameters and cardiac resynchronization therapy
**Session V: Jos Willems Young Investigators Competition**

Chair: Mary G. Carey, University of Rochester Medical Center, Rochester NY USA
Co-chair: Shen Luo, MindRay Biomedical, Mahwah NJ USA

Mary G. Carey, University of Rochester Medical Center, Rochester NY USA
Mikkel Schoos, Rigshospitalet, Copenhagen DENMARK

*A novel pre-hospital electrocardiogram score predicts myocardial salvage in patients with ST segment elevation myocardial infarction, evaluated by cardiac magnetic resonance*

Michael Daly, Royal Victoria Hospital, Belfast Northern Ireland UK

*Epicardial potentials derived from the body surface potential map using inverse electrocardiography improve diagnosis of acute myocardial infarction: A prospective study*

Lars Johannesen, US Food and Drug Administration, Silver Spring MD USA

*Going beyond QT: Integrated electrocardiographic and vectorcardiographic analysis of 20 QTc-prolonging drugs*

Peter van Dam, University of Nijmegen, Nijmegen THE NETHERLANDS

*Quantitative spatial cardiac localization of PVCs and pacemakers using the 12 lead ECG*

**SATURDAY, 20 APRIL 2013**

**Session VI: T-wave variability**

Chair: Marek Malik, St. George's University of London, London UK
Co-chair: Robert Lux, University of Utah, Salt Lake City UT USA

Marek Malik, St. George's University of London, London UK
Richard Verrier, Harvard Medical School, Boston MA USA

*Electrophysiology of T-wave alternans: Cellular mechanism and insights derived from large animal models*

Marek Malik, St. George's University of London, London UK

*QT interval and T wave variability during provocative test*

Joel Xue, GE Healthcare, Wauwatosa WI USA

*T wave variation detection, an industrial perspective of research and development*

Derek Exner, University of Calgary, Calgary CANADA

*Clinical application of T-wave alternans*
Georg Schmidt, Technische Universität, München GERMANY
Low frequency oscillations of T-wave vector predict mortality in post-infarction patients

David G. Strauss, U.S. Food and Drug Administration, Silver Spring MD USA
Going beyond QT interval in the assessment of electrocardiographic drug effects

Yochai Birnbaum, Baylor College of Medicine, Houston TX USA
High risk ECG patterns in ACS – need for guideline revision

Session VII: Patient monitoring alarm fatigue: Potential device based solutions
Chair: Barbara J. Drew, UCSF, San Francisco CA USA
Co-chair: John Wang, Philips Healthcare, Andover MA USA

Barbara J. Drew, UCSF, San Francisco CA USA
Alex Chen, Mortara Instrument, Milwaukee WI USA
Reduction of false alarms in the detection of lethal arrhythmias in patient monitoring

Xiao Hu, UCLA, Los Angeles CA USA
Integrated utilization of monitor alarms to detect patients at risk for sudden cardiac arrest in hospital

Mikko Kaski, GE Healthcare, Helsinki FINLAND
Reduction of false and irrelevant ECG alarms in monitoring

John Wang, Philips Healthcare, Andover MA USA
Alarms for real-time ECG/arrhythmia monitoring: Review of potential device solutions

On the whole, the 38th Annual Conference of ISCE was a great success. The delegates built professional networks to share knowledge and made friends with each other. Informal interactions contributed strongly to the quality of the meeting. Conference business was conducted in an open and democratic fashion.

Thanks to all the attendees of the 38th Annual Conference of International Society for Computerized Electrocardiology
April 17-21, 2013
San Jose, California, USA
Dear colleagues!
Mikhail Rudenko holds online seminar on the theory and practice of Cardiometry. The exact date and time will be announced soon on our journal website.

1. Role of cardiometry in cardiology.

2. Theoretical basis of cardiometry. (45 min).
2.1. Existing contradictions in cardiology.
2.2. Biophysics of hemodynamics. A specific blood flow mode in blood vessels.
2.3. Using the specific fluidity mode in engineering & technology.

3. Fundamentals of electrocardiography (45 min).
3.1. The mechanisms of the heart performance control. Important nodes of control: SA - baroreceptor, AV - baroreceptor, Aortic baroreceptor (pulmonary artery).
3.2. Relationship between the nerve impulses generation in baroreceptors and blood pressure on them.
3.3. Phase structure of the cardiovascular system performance.
3.4. ECG and Rheo are the electrical cardiac signals completely reflecting the phase mechanism of the heart performance and sufficient for accurate analysis of hemodynamics and cardiovascular system functions.

4. Cardiac cycle phase analysis (45 min).
4.2. Hemodynamic parameters most accurately reflecting the cardiovascular system performance. Blood phase volumes.
4.3. The principal functions of the cardiovascular system.
4.4. Aerobic and anaerobic biochemical processes in heart. Their effect on the cardiovascular system functions.

5. The practical implementation of the hemodynamics theory. (45 min).
5.1. ECG recording technology development.
5.2. Technology of ECG and Rheo recording of the ascending aorta.
5.3. Algorithms for automatic processing of ECG and Rheo of the ascending aorta.

6.1. Self-regulation mechanism maintaining the normal hemodynamics. The norm-pathology boundaries.

7. Diagnostics by cardiac cycle phase analysis method. Periodic system of ECG phase changes. (75 min).
7.1. Capabilities and scope of ECG diagnostics.
7.2. Periodic system of ECG phase changes. Diagnosed functions and levels of their change as a basis for ECG shapes classification and systematization.
7.3. Practical implementation of the ECG periodic table. Decision-making in diagnostics.

8. Formation of a new way of thinking in terms of cause-effect analysis (causality). Natural science laws applied to medical practice (45 min).
8.1. The need for practical use of the cause-effect relationship analysis by physicians. Conflicts between the diagnosis and legal liability.
8.2. Scientific progress and the system of medical personnel training. The existing system of the scientist rating system.
8.3. The journal "Cardiometry"
8.4. Manuals.
8.5. Internet resources.

9. Cardiovascular system biochemistry. (45 min).
9.1. The biochemical mechanism of myocardial and septal contraction function maintaining.
9.2. Tryptophan, serotonin, L-carnitine and endorphins as the principal biochemical components in the energetic system of heart performance and their relationship with hemodynamics.
9.3. Aerobic, glycolytic and phosphocreatine reaction.
9.4. Acid-alkaline balance (pH) in cardiovascular system. The capabilities of acid-alkaline balance registration by ECG phase analysis of and its practical value.

10.2. The basic elements of nutrition for the proper hemodynamics maintaining.

11. Practice. How to use the device Cardiocode: training (45 min).
11.3. Case reports.
Theoretical Principles of Heart Cycle Phase Analysis
Read the guidelines on cardiac cycle phase analysis

At [amazon.com](http://amazon.com)

At [buchhandel.de](http://buchhandel.de)

At [lob.de](http://lob.de)
We recommend attending the following meetings

ESC Congress 2013
31 Aug 2013 - 04 Sep 2013
Amsterdam - Netherlands
http://www.escardio.org/congresses/esc-2013/

The 40th International Congress on Electrocardiology
August 7-10, 2013
Glasgow, Scotland
http://www.electrocardiology.org/
Computing in Cardiology
CinC 2013 Zaragoza
22-25 September 2013
http://www.cinc.org/board.shtml
The best recreation is offered in the resort area hotel Buran!

86 км from Moscow, 33 км from Sergiev Posad
tel. (495) 972-75-35 • sp.buran@mail.ru • www.panburan.ru