Report

Issues of health evaluation during simulated space mission to Mars

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

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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

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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>
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<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:

\[
L1 = 0.112 \times \text{HR} + 1.006 \times \text{SI} + 0.047 \times \text{pNN50} + 0.086 \times \text{HF};
\]

\[
L1 = 0.140 \times \text{HR} + 0.165 \times \text{SI} + 1.293 \times \text{pNN50} + 0.623 \times \text{HF}
\]

L1 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. L2, 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 L2 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.

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