VEGETATIVE REGULATION OF BLOOD CIRCULATION AND BIOELECTRIC PROCESSES IN THE HUMAN MYOCARDIUM UNDER SIMULATED HYPOMAGNETIC CONDITIONS

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Today, the prospect of long-term interplanetary missions becomes relevant, that is why it is necessary to understand the changes in the cardiovascular system (CVS) that would occur in hypomagnetic environment. The study was aimed to assess the changes in the CVS mechanisms underlying formation of heart rate variability and bioelectric processes in the myocardium under conditions the 350-, 650-, and 1000-fold reduced Earth's magnetic field. The experiment (2023) involved 6 male volunteers aged 26–37 years, in whom electrocardiography was continuously performed throughout 32 h. The data obtained were assessed by cluster analysis and analysis of variance. It was found than male volunteers, who belonged to the group showing predominance of parasympathetic effects, had enough functional reserve for critical values (exposure to the up to 1000-fold reduced magnetic field). In volunteers showing predominance of sympathetic modulatory effects, the adaptive response maintenance was ensured by the metabolic regulatory circuit. In this group, the response to the reduced magnetic field exposure was quite pronounced at the threshold of its 350-fold reduction. Our pilot experiment reflecting the effect of the reduced Earth's magnetic field on the CVS is crucial for development of the concept of further experimental exposures related to magnetic field reduction benefiting space physiology and medicine.

Keywords: hypomagnetic conditions, cardiovascular system, bioelectric processes, heart rate variability, dispersion mapping

Funding: the study was conducted within the framework of the RAS core themes, FMFR-2024–0042.

Author contribution: Popova OV — manuscript writing, data acquisition and analysis; Rusanov VB — manuscript writing, data analysis; Orlov OI — scientific advisor for the experiment.

Compliance with ethical standards: the study was approved by the Ethics Committee of the State Scientific Center of the Russian Federation – Institute for Biomedical Problems RAS (Moscow) (protocol No. 641 dated 14 June 2023). All subjects submitted the informed consent to study participation.

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Received: 22.05.2024 **Accepted:** 02.06.2024 **Published online:** 21.06.2024

DOI: 10.47183/mes.2024.019

ВЕГЕТАТИВНАЯ РЕГУЛЯЦИЯ КРОВООБРАЩЕНИЯ И БИОЭЛЕКТРИЧЕСКИЕ ПРОЦЕССЫ В МИОКАРДЕ ЧЕЛОВЕКА В МОДЕЛИРУЕМЫХ ГИПОМАГНИТНЫХ УСЛОВИЯХ

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На сегодняшний день становится актуальной перспектива длительных межпланетных полетов, поэтому необходимо понимание изменений в сердечно-сосудистой системе (ССС), которые будут происходить в гипомагнитных условиях. Целью исследования было провести анализ изменений механизмов ССС, которые представляют собой основу для формирования вариабельности сердечного ритма и биоэлектрических процессов в миокарде, в условиях сниженного в 350, 650 и 1000 раз магнитного поля Земли. В эксперименте (2023 г.) участвовало 6 мужчин-добровольцев в возрасте 26–37 лет, у которых непрерывно в течение 32 ч регистрировали электрокардиограмму. Анализ полученных данных проводили при помощи кластерного и дисперсионного анализа. Было обнаружено, что у мужчин-добровольцев, относящихся к группе с преобладанием парасимпатических влияний, функционального резерва хватает для критических значений (воздействия сниженного магнитного поля до 1000 раз). У добровольцев с преобладанием симпатических моделирующих влияний поддержание приспособительных реакций осуществляется метаболическим регуляторным контуром. В этой группе реакция на воздействие сниженного магнитного поля достаточно выражена при пороге его снижения от 350 раз. Проведенный нами пилотный эксперимент, отражающий влияние сниженного магнитного поля земли на ССС, имеет определяющее значение для разработки концепции последующих экспериментальных воздействий, связанных с редукцией магнитного поля, для интересов космической физиологии и медицины.

Ключевые слова: гипомагнитные условия, сердечно-сосудистая система, биоэлектрические процессы, вариабельность сердечного ритма, дисперсионное картирование

Финансирование: работа была выполнена в рамках базовой тематики РАН FMFR-2024–0042.

Вклад авторов: О. В. Попова — написание статьи, сбор и анализ данных; В. Б. Русанов — написание статьи, анализ данных; О. И. Орлов — научный руководитель эксперимента.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБУН ГНЦ РФ — ИМБП РАН (Москва) (протокол № 641 от 14 июня 2023 г.). Все участники подписали добровольное информированное согласие на исследование.

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Статья получена: 22.05.2024 **Статья принята к печати:** 02.06.2024 **Опубликована онлайн:** 21.06.2024

DOI: 10.47183/mes.2024.019

The changes in geomagnetic conditions (GMCs) definitely affect the living organisms [1]. Each cell of the biological system incorporated in the magnetic fields MF of the Sun and Earth is continuously exposed to their fluctuations in a broad frequency range [2].

In recent years, the studies were conducted focused on assessing the relationships between magnetic activity and biological systems of various living organisms. These demonstrate the effects of geomagnetic and solar activity on various physiological rhythms, as well as on the possible synchronization of such rhythms, for example the effects of geomagnetic disturbances on the cardiac and vegetative nervous system (VNS) function [3]. Such effects occur, when human physiological systems are affected by various changes in geomagnetic dynamics. The geomagnetic field line resonances and the Schumann resonances emerging in the space between the Earth's surface and the ionosphere produce the resonant frequency range overlapping frequencies of the human brain, VNS, and cardiovascular system. Rhythms generated by the brain and the heart are more susceptible to the influence of changes in geomagnetic conditions, than other physiological systems investigated so far [4].

Artificial simulation of geomagnetic storm has shown that geomagnetic activity can evoke a pronounced cardiovascular response [5]. Furthermore, there is evidence suggesting the relationship between the short-term geomagnetic disturbances and the number of deaths from cardiovascular disorders and myocardial infarction [6].

At the same time, the geomagnetic field (GMF) changes can modify the cardiovascular system (CVS) functional state related to the physiological process of aging [7].

In the near future, there will be a prospect of flights into deep space, however, the following question remains: how will reduction of the GMF, which is 10^3–10^5 times smaller in space relative to the Earth's magnetic field, affect human physiological systems? Furthermore, hypomagnetic conditions (HMCs) will become an essential part of the complex of factors influencing the austronauts during the long lasting interplanetary missions, outside the Earth's magnetic field, and the human body adaptation to HMCs will interfere with the regulatory processes in various physiological systems.

Animal studies demonstrate the effects of reduced GMF on the mammalian organism. Disorders of lymph and blood flow were revealed in mice after spending 3 h under HMCs (80–120-, 300-, and 1000-fold GMF attenuation). Cardiomyocyte structural alterations were observed after the 6 h-exposure to HMCs. Lysis of the sarcoplasmic reticulum myofibrils, sarcoplasmic matrix, and mitochondrial matrix was activated. Disruption of the mitochondrial cristae and enlargement of vesicles in the smooth and rough endoplasmic reticulum were also observed. The process of protein biosynthesis in cardiomyocytes was impaired or completely suppressed under HMCs. All the above are indicative of the ultrastructural restructuring similar to apoptosis.

The effects of GMF on the blood vessel tone have been repeatedly confirmed in human studies [8–11]. Changes in blood vessel tone modulate the changes in blood pressure (BP) independently of other geomagnetic climatic factors. It has been noticed that geomagnetic storms resulting from solar flares [9] that force the adaptive mechanisms to get out of balance and cause severe adaptive stress responses affect the CVS regulatory mechanisms. This is manifested in the decreased heart rate variability (HRV) and blood flow, increased platelet aggregation activity, blood coagulation and viscosity even in healthy people [11, 12].

Physiological processes following the changes in magnetic and solar activity occur with a lag. This phenomenon is referred to as the "lag phase" lasting from several hours to 2–3 days after the GMF alteration [10, 12, 13]. It is noted that cardiovascular disorders significantly decrease the subjects' sensitivity to GMF changes, which can results in critical health issues [14].

It has been shown that HMCs affect capillary blood flow, blood pressure, and heart rate (HR), increase the activity of the heart rhythm regulation parasympathetic segment [15].

Continuous CVS hemodynamics (HR, blood pressure (BP), Kerdo Vegetative Index) monitoring was performed in eight healthy adult males at rest. The experiment conducted for 8 h consisted of two acquisition series: under HMCs (1000-fold reduction of the Earth's magnetic field induction) and under exposure to the Earth's natural magnetic field. The decrease in HR (on average by 4 bpm) and BP relative to the control group was revealed. Furthermore, systolic BP decreased on average by 16 mm Hg, while diastolic BP decreased by 16 mm Hg. The Kerdo Vegetative Index, in contrast, increased by 20% during the 8 h stay in hypomagnetic environment [16].

Clinical assessment revealed functional changes in the major body systems of the individuals, who had been working under exposure to the 3–10-fold reduced GMF for a long time, such as vegetovascular dystonia syndrome, abnormal myocardial repolarization, essential hypertension, dystonia of the brain with the regulatory interhemispheric asymmetry, significant increase in biological age by 4.2 years relative to chronological age [17].

In this regard, the study was aimed to assess systemic changes in the CVS resulting from the mechanisms underlying HRV and reflecting the regulatory component of this physiological system, as well as bioelectric processes in the myocardium under conditions of n-fold magnetic field reduction.

METHODS

The experimental study was conducted in 2023 using the Arfa stand (State Scientific Center of the Russian Federation — Institute for Biomedical Problems RAS) for simulation of magnetic fields being a part of the unique scientific installation "Medical and technical complex for the development of innovative technologies of space biomedicine in the interests of ensuring orbital and interplanetary flights, as well as the development of practical healthcare" (Fig. 1).

The design and technical characteristics of the Arfa magnetic field simulation system have been reported earlier [18].

The study sequence diagram represented a randomized blind four-series study. The baseline testing was conducted before the beginning of each series. The first session included the subject's 8 h stay in the installation (morning–afternoon) followed by the 3 h controlled break. Second session: the subject stayed in the installation for 8 h (nighttime – sleep), which was also followed by the 3 h controlled break. Third session: the subject was placed in the installation for 8 h (daytime), which was followed by the tests performed within the 3 h period of aftereffect (Fig. 2).

The experimental exposure included four 37 h series that included baseline tests, stay under HMCs, and the periods of aftereffect. Under HMCs, GMF was reduced 350-, 650-, and 1000-fold; there was also a placebo series. The experimental exposure and placebo were randomized. To ensure the subject's adaptation to the unfamiliar condition of stay in the Arfa installation, hypokinesia, and the experimental program methods, a 4 h training series was previously launched for each subject. The volunteer stayed in the Arfa installation in a sitting position with the limited motion (not leaning, not moving his hands in various directions, not standing up).

The experiment with HMCs involved 6 male volunteers aged 26–37 years (body length 178 ± 7 cm, body weight 76.5 ± 15.5 kg, body mass index 24.77 ± 2.99), in whom electrocardiography (ECG) was continuously performed throughout 32 h. Inclusion criteria: all the volunteers underwent medical examination and were allowed to take part in the experimental studies by the expert medical committee of the State Scientific Center of the Russian Federation — Institute for Biomedical Problems RAS. In addition to the medical expert committee examination, medical examination was performed 2 days before the exposure to antiorthostatic hypokinesia, based on which the subjects were allowed to take part in the experiments by the responsible physician. The Cosmocard ECG monitor (State Scientific Center of the Russian Federation — Institute for Biomedical Problems RAS; Russia) designed for testing at the International Space Station was used. ECG was recorded using four chest leads. The lead II recording was analyzed. The previously recorded ECG was edited by visual inspection and manual adjustment of certain RR intervals. After that the recording was processed using the Iskim-6 software ("Ramena" Institute for Introduction of New Medical Technologies; Russia).

To assess regulatory processes in the CVS, we determined and calculated the HRV values associated with the VNS parasympathetic and sympathetic modulatory effects on the sinoatrial (SA) node. The state of the mechanisms underlying blood circulation regulation was estimated in accordance with the guidelines developed by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [19]. The ECG dispersion mapping (DM) based on the analysis of microfluctuations characterizing myocardial electrophysiological processes were used to estimate bioelectric processes in the myocardium [20].

Statistical analysis of the acquired dataset was performed using the STATISTICA 13.0 software package (IBM; USA) using cluster analysis and analysis of variance [21].

RESULTS

The Ward's method was used for classification based on the predominant type of the SA node activity autonomic regulation (Fig. 3). The integrated analysis of all the HRV parameters recorded during the experiment was performed. As a result, two groups were allocated:

1) group 1 — volunteers, who took part in the experiment, showing predominance of parasympathetic modulatory effects (*n* = 4, volunteers 1, 2, 4, and 5);

2) group 2 — volunteers, who took part in the experiment, showing predominance of sympathetic modulatory effects (*n* = 2, volunteers 3, 6).

The cluster and discriminant analysis were used to determine the classification functions including the indicators that were most informative under experimental conditions and reflected the balance of autonomic effects, primarily parasympathetic activity and the extent, to which it predominated over sympathetic modulatory autonomic effects: HR (physiologically reflecting the systemic circulation homeostasis), RMSSD (ms, square root of the mean squared difference of successive ECG intervals, indicator of parasympathetic effects on the heart rhythm), pNN50 (%, the number of pairs of successive intervals that differ by more than 50 ms as a percentage of the total number of ECG intervals, reflects the relative extent, to which parasympathetic modulatory autonomic effects in the CVS predominate over sympathetic ones), SDNN (ms, standard deviation of the entire set of ECG intervals, indicator of the overall effect of autonomic blood circulation regulation), HF

Fig. 1. Arfa magnetic field simulation system and the experimental procedure

(ms2, spectrum power of the HRV high-frequency component from the total oscillation power, characterizes parasympathetic activity and the extent of its predominance over sympathetic activity).

The dynamic changes of these parameters in various phases of the experiment are provided in Fig. 4.

In volunteers showing parasympathetic modulatory effects, the RMSSD and HF parameters significantly decreased compared to the placebo series during the session conducted under exposure to the up to 1000-fold reduced magnetic field; a similar decrease was observed under conditions of up to 650- and 350-fold magnetic field reduction (Fig. 4). In volunteers showing sympathetic modulatory effects, the values

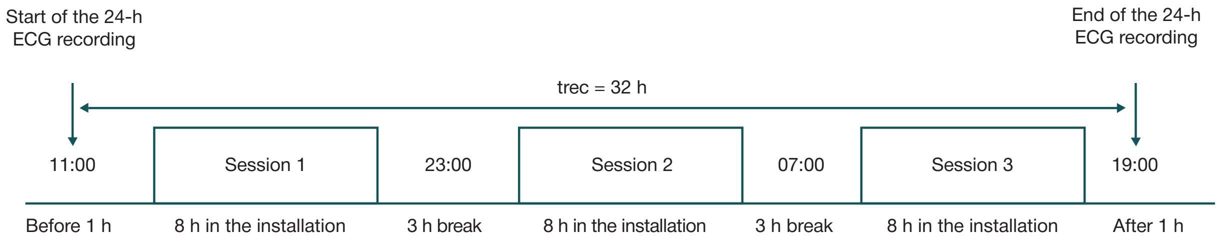

Fig. 2. Sequence diagram of a single experimental session

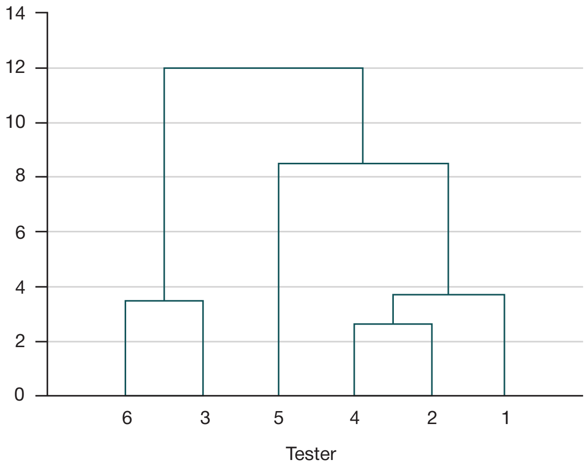

Fig. 3. Dividing volunteers into groups

of these parameters increased after the 24 h stay (session 3) under exposure to the up to 650-fold reduced magnetic field. However, it should be noted that a significant decrease in this indicator relative to placebo was observed during the first 8 h of stay in the installation under exposure to the 1000-fold reduced magnetic field.

The pNN50 and SDNN values decreased in the volunteers showing parasympathetic effects on the heart rhythm compared to placebo during sessions 2 and 3 under conditions of 1000- and 650-fold reduced magnetic field, while in patients showing sympathetic effects a significant decrease in these indicators was observed throughout their stay under exposure to HMCs with the 1000-, 650-, and 350-fold reduced magnetic field.

The dynamics of HR (indicator reflecting the CVS function stability at the systemic level) in the group of volunteers with parasympathetic modulation of the SA node increased throughout the period of experimental exposure without going outside the normal physiological range. In the group with sympathetic modulation, there was a significant increase in this indicator under exposure to the 1000- and 350-fold reduced geomagnetic field during the 8 h (session 1) and 24 h (session 3) stay, respectively (Fig. 5).

The ECG DM analysis showed that the indicator reflecting the right ventricle depolarization (G3) significantly increased throughout the series with the 650-fold reduced magnetic field in the volunteers with parasympathetic effects (Fig. 6). In the group of patients with sympathetic modulation of the heart rhythm, the increase in the indicator under exposure to the 1000- and 350-fold reduced magnetic field was observed.

The G7 (ventricular depolarization symmetry) indicator of the volunteers with parasympathetic effects significantly increased in the series with the 1000- and 659-fold reduced magnetic field; the increase in the indicator was also observed in the series with the 1000-fold reduced magnetic field in the individuals with sympathetic modulation of heart rhythm, however, the indicator also increased under exposure to the 350-fold reduced magnetic field.

As for the emergence of arrhythmias during the experiment, their number increased, which was indicated by the NArr (quantitative parameter characterizing the overall number of arteries) values (%). The indicator values increased in the series with the 1000- and 350-fold reduced magnetic field in the volunteers with parasympathetic regulatory effects. In the group of patients with sympathetic regulatory effects, the NArr

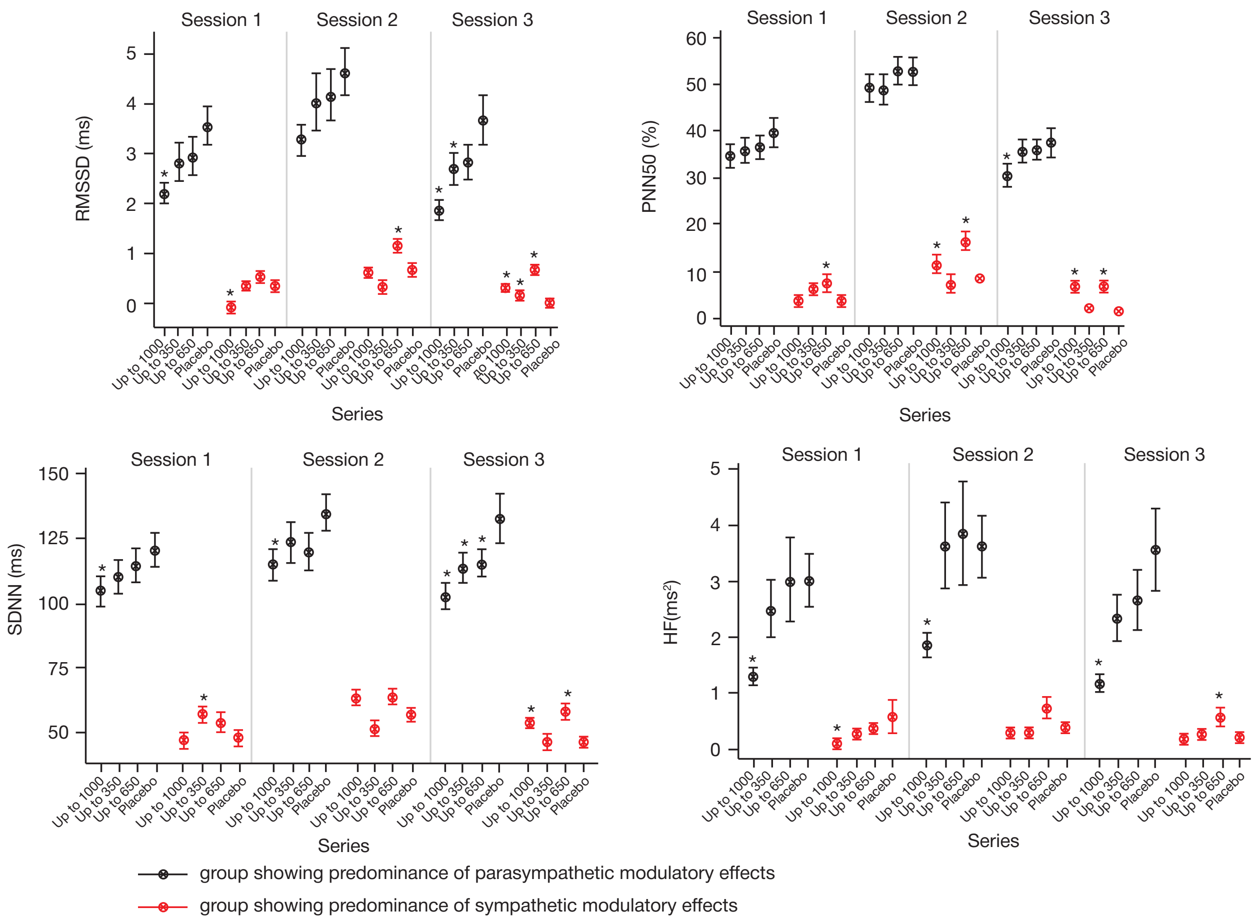

Fig. 4. The most informative parameters characterizing the predominant type of autonomic regulation and their dynamics during the experiment. * — significant difference compared to placebo

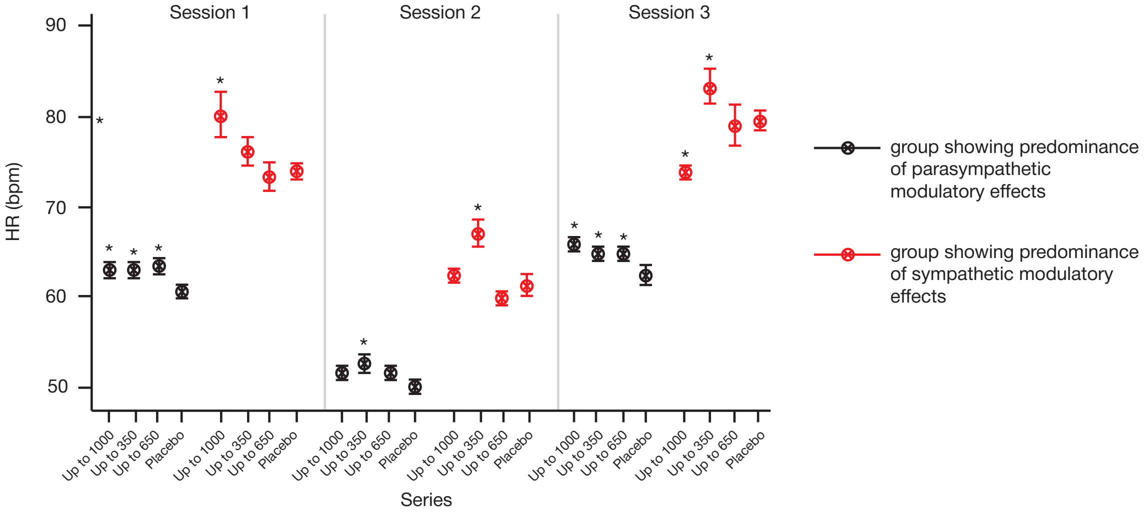

Fig. 5. HR dynamics. * — significant difference compared to placebo

values increased only by the experimental session, in which the magnetic field was reduced 1000-fold (Fig. 7).

DISCUSSION

HRV characterizes the changes of the time windows between the successive heart contractions and serves as an important indicator reflecting the dynamics of the VNS activity and its effects on the circulatory system [22]. The HRV patterns observed show the functional state of the co-dependent regulatory systems that operate at different time scales in order to adapt to the environmental and psychological problems. The lower degrees of the age-adjusted HRV that suggest chronic stress, disorder or functional insufficiency of the regulatory

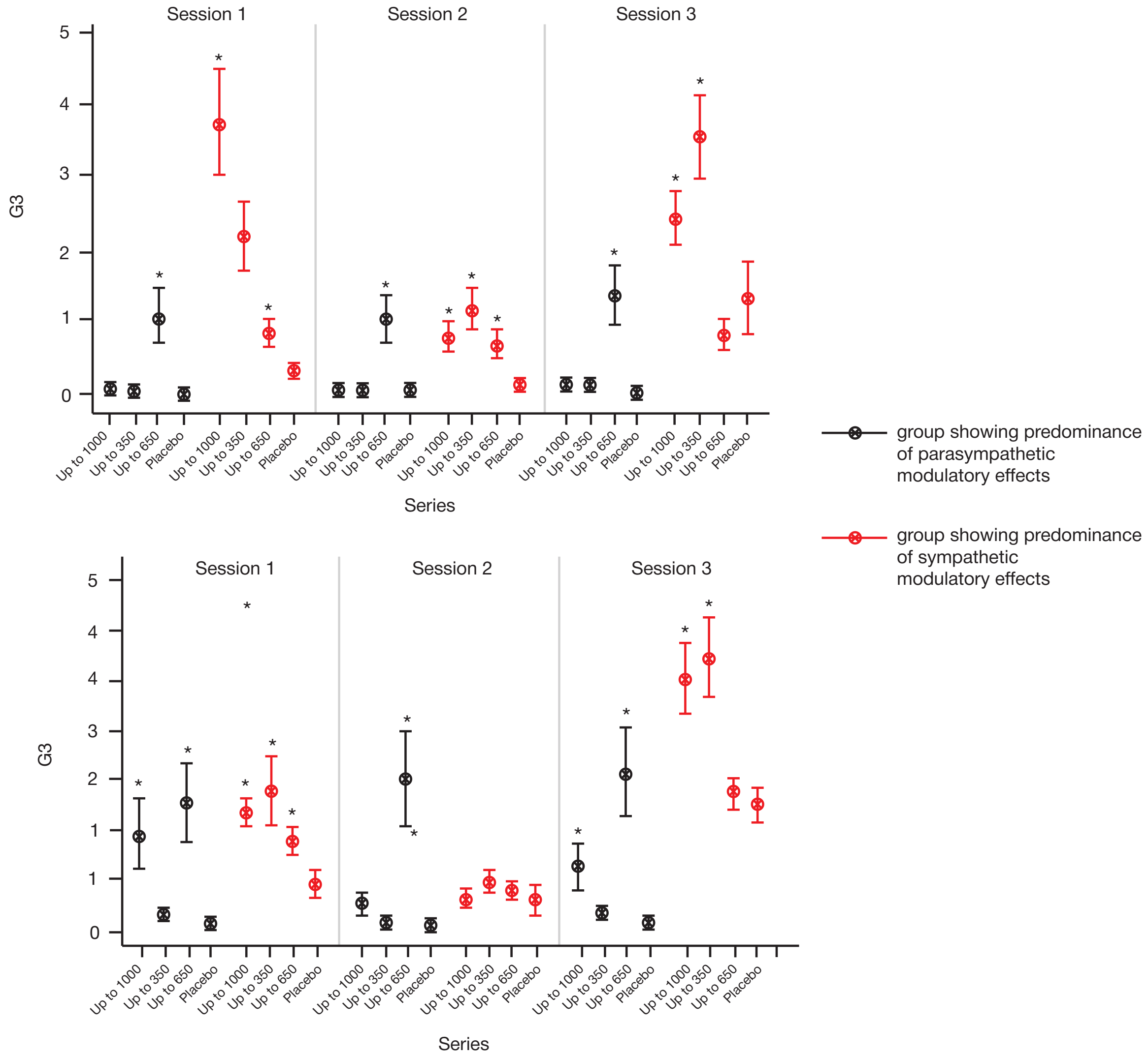

Fig. 6. ECG DM dynamics. * — significant difference compared to placebo

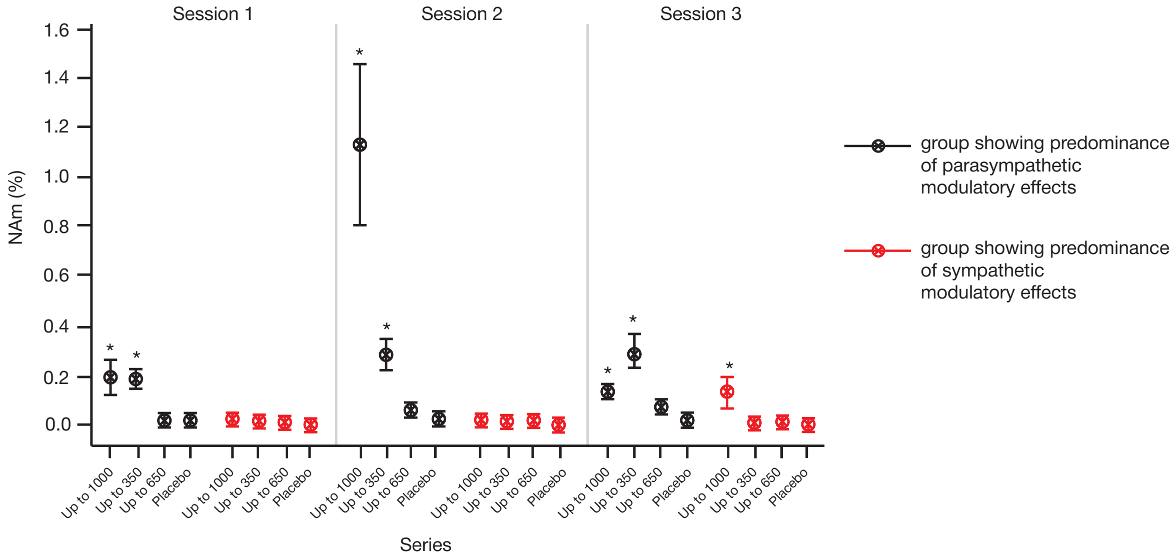

Fig. 7. NArr dynamics. * — significant difference compared to placebo

systems in the nervous system, are associated with all-cause mortality, while higher degrees of variability suggest stability and capacity for self-regulation and adaptation to the changing demands [23].

Since the adaptation processes in volunteers showing predominance of parasympathetic effects are maintained by means of the neural regulatory circuit, the functional reserve is enough for critical values (exposure to the 1000-fold reduced magnetic field). In volunteers showing predominance of sympathetic modulatory effects, the adaptive responses are maintained by the metabolic regulatory circuit. In this group, the response to the reduced magnetic field exposure is rather pronounced at the reduction threshold of 350 times.

The significantly changing ECG DM parameters G3 and G7 constitute parts of the aggregate indicator G3+G4+G7, where G4 represents an indicator reflecting the left ventricular depolarization, which can be indicative of ischemic disorders: probable disturbances of blood flow and myocardial perfusion [20].

The indicator characterizing the number of arrhythmias increased in the group showing predominance of parasympathetic regulation during the nighttime session under the exposure to the 1000-fold decreased magnetic field, however, it was within normal range (1–2%). When reviewing individual recordings, we found ventricular extrasystoles (VEs) in one volunteer; no VEs were reported under placebo conditions.

VE is the most common form of ventricular arrhythmia [24]. It has been reported that VE in patients having no structural heart disease can represent the so-called “arrhythmic” form of the essential hypertension onset, various clinical variants of the onset of coronary heart disease, myocarditis, various forms of cardiomyopathy, stroke and other cerebrovascular disorders. VE can be also an independent predictor of the development of life-threatening ventricular arrhythmias, atrial fibrillation, and sudden death [25].

It is well known that the detection rate of VE increases in organic heart diseases associated with hypoxemia, myocardial damage, and the increase in the VNS sympathoadrenal activity. It was noted that in healthy individuals the number of VEs was higher in the morning, than during the night. Nocturnal VEs were described. Furthermore, it was shown that the emergence of VEs during the night could be associated with the mainly nocturnal type of circadian distribution in patients with sleep apnea syndrome [26].

The GMF strength fluctuations resulting to the decrease in HRV and increase in HR can provoke cardiac arrhythmia [27]. This trend is especially strong in the group of hypertensive patients [28]. It has been found recently that the GMF increased activity in the low-frequency ranges is associated with the higher incidence of acute atrial fibrillation and flutter [29]. Apparently, the higher GMF intensity in the low-frequency ranges is associated with the emergence of arrhythmia, while that in the high-frequency range is associated with the cardiac ischemic events [30].

CONCLUSIONS

Thus, during the experiment involving magnetic field reduction we acquired unique data on the mechanisms underlying autonomic regulation of blood circulation and bioelectric processes in the myocardium. However, the study had an important limitation: relatively low number of participants. Nevertheless, one of the pilot experiments with the GMF effects on the physiological processes in the human body at the systemic level we have conducted is crucial for the development of the concept of further experimental exposures related to magnetic field reduction benefiting space physiology and medicine. The complexity of developing such concept is to the great extent determined by the bioethical issues related to investigation of the effects of poorly understood factors (such as HMCs) on the human body.

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