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DYNAMICS OF HEPCIDIN, ERYTHROPOIETIN, C-REACTIVE PROTEIN, AND ERYTHROPOIESIS MARKERS IN COSMONAUTS DURING THE EARLY POST FLIGHT PERIOD

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Introduction. Long-duration space flights are accompanied by significant changes in iron metabolism, characterized by accumulation of ferritin, decreased serum Fe³⁺ and transferrin concentrations, and the development of signs of “space anemia”. Excessive iron deposition can impair bone and muscle metabolism, weaken immunity, and increase sensitivity to radiation. Serum iron levels are tightly regulated through modulation of intestinal absorption, macrophage recycling, mobilization of tissue stores, and erythropoiesis, involving key hormones — hepcidin and erythropoietin. Understanding the regulatory mechanisms of iron metabolism and erythropoiesis is necessary to develop measures for anemia prevention in future interplanetary missions.

Objective. Assessment of the dynamics of hepcidin, erythropoietin (EPO), C-reactive protein (CRP), and erythropoiesis markers in the blood of cosmonauts during the early recovery period (RP) after space missions of varying duration on the International Space Station.

Materials and methods. A total of 40 male cosmonauts were examined, divided into three groups according to mission duration: Group A — 8–14 days ($n = 9$), Group B — 125–215 days ($n = 27$), Group C — 340–371 days ($n = 4$). Venous blood was collected 45–30 days before the flight and on days 1 and 7 of the RP. CRP level was determined by immunoturbidimetry; hepcidin and EPO concentrations were determined by enzyme-linked immunosorbent assay. Statistical analysis was performed using the Shapiro–Wilk, Wilcoxon, Friedman, and Spearman correlation tests. Differences were considered significant at $p < 0.05$.

Results. On RP day 1, CRP levels were significantly elevated in all cosmonauts, while hepcidin levels were decreased (statistically significantly in Group A). On day 7, EPO levels were significantly increased in cosmonauts of Group B. Correlation analysis revealed an inverse relationship between erythrocyte count and total time spent in low Earth orbit, as well as positive correlations between mission duration and red blood cell distribution width, and between mission duration and mean erythrocyte volume.

Conclusions. Spaceflight factors and the stress response during post-flight readaptation provoke non-specific inflammation, leading to redistribution and deposition of iron in tissues. Activation of stress erythropoiesis is one of the main factors facilitating the release of iron for hemoglobin synthesis in the early RP. The magnitude of changes in the erythropoiesis system depends on the duration of orbital missions.

Keywords: space flights; C-reactive protein; hepcidin; erythropoietin; stress erythropoiesis; space anemia

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ДИНАМИКА ГЕПСИДИНА, ЭРИТРОПОЭТИНА, С-РЕАКТИВНОГО БЕЛКА И МАРКЕРОВ ЭРИТРОПОЭЗА У КОСМОНАВТОВ В РАННЕМ ПОСЛЕПОЛЕТНОМ ПЕРИОДЕ

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Введение. Длительные космические полеты сопровождаются существенными изменениями метаболизма железа, заключающимися в накоплении ферритина, снижении концентрации сывороточного Fe³⁺ и трансферрина, а также развитии признаков «космической анемии». Избыточное депонирование железа может нарушать костный и мышечный метаболизм, ослаблять иммунитет и повышать чувствительность к радиации. Уровень железа в сыворотке крови строго регулируется за счет модуляции его всасывания в кишечнике, рециркуляции в макрофагах, мобилизации запасов в тканях и эритропоэза, в том числе с помощью ключевых гормонов — гепсидина и эритропоэтина. Понимание регуляторных механизмов обмена железа и эритропоэза необходимо для разработки мер профилактики анемии в условиях будущих межпланетных миссий.

Цель. Оценка динамики содержания гепсидина, эритропоэтина, С-реактивного белка и маркеров эритропоэза в крови космонавтов в раннем периоде восстановления после полетов различной продолжительности на международной космической станции.

Материалы и методы. Обследовано 40 космонавтов мужского пола, разделенных на три группы по продолжительности полетов: группа А — 8–14 сут ($n = 9$), группа Б — 125–215 сут ($n = 27$), группа В — 340–371 сут ($n = 4$). Венозную кровь забирали за 45–30 сут

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до полета и на 1-е и 7-е сут периода восстановления. Концентрацию С-реактивного белка определяли методом иммунотурбидиметрии, гепсидина и эритропоэтина — методом иммуноферментного анализа. Статистическую обработку проводили с использованием критериев Шапиро – Уилка, Вилкоксона, Фридмана и корреляции Спирмена. Различия считали значимыми при $p < 0,05$.

Результаты. На 1-е сут периода восстановления у всех космонавтов достоверно повышался уровень С-реактивного белка, а содержание гепсидина снижалось (статистически значимо — в группе А). На 7-е сут уровень эритропоэтина достоверно увеличивался у космонавтов группы Б. Корреляционный анализ выявил обратную зависимость между количеством эритроцитов и суммарной продолжительностью пребывания на околоземной орбите, а также прямые взаимосвязи длительности полета с шириной распределения эритроцитов по объему и средним объемом эритроцитов.

Выводы. Факторы космического полета и стресс-реакция при послеполетной реадaptации провоцируют неспецифическое воспаление с последующим перераспределением и депонированием железа в тканях. Активация стрессового эритропоэза является одним из основных факторов, обеспечивающих высвобождение железа для синтеза гемоглобина в раннем восстановительном периоде. Выраженность изменений в системе эритропоэза зависит от продолжительности орбитальных экспедиций.

Ключевые слова: космические полеты; С-реактивный белок; гепсидин; эритропоэтин; стрессовый эритропоэз; космическая анемия

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Соответствие принципам этики: все исследования осуществлялись в соответствии с принципами биомедицинской этики, изложенными в Хельсинкской декларации. Исследования проводили на основании Программы биохимических, эндокринологических, иммунологических, гематологических, гемостатических и цитогенетических исследований для членов экспедиций на Международную космическую станцию, утвержденной совместно ФГБУ НИИ ЦПК им. Ю.А. Гагарина и ГНЦ РФ — ИМБП РАН 20.09.2004. Каждый участник исследования дал добровольное письменное информированное согласие после получения разъяснений о потенциальных рисках и преимуществах, а также о характере предстоящих исследований.

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INTRODUCTION

Currently, long-duration expeditions to the International Space Station (ISS) are being carried out regularly, and conducting missions for deep-space exploration, such as flights to the Moon or Mars, is becoming a task of the near future. Spaceflights and their associated stressors — such as microgravity, increased radiation levels, isolation, circadian rhythm disruption, monotony of activities, and hypokinesia — cause muscle atrophy, bone loss, hyper- and hyporeactivity of the immune system, vascular and metabolic changes [1], including disturbances in iron metabolism.

This trace element is essential for many biological processes, including the metabolism of proteins, lipids, carbohydrates, and nucleic acids. When it accumulates abnormally in organs, it contributes to oxidative stress by initiating the Fenton reaction and may play a role in the development of osteoporosis and muscle atrophy. Furthermore, when its distribution in the body is disturbed, iron can also influence the intensity of erythropoiesis and, consequently, contribute to the development of anemia [2].

Trudel et al., in a study of 14 astronauts who participated in ISS missions lasting 136 to 198 days, found increased concentrations of iron and transferrin throughout the flights, with these values decreasing to below baseline on day 4 of the recovery period (RP). Ferritin levels increased during the orbital missions and

decreased below baseline values in the post-flight period [3]. Zwart et al. demonstrated in their work that during both short-term and long-term spaceflights, serum ferritin content increased significantly in the early stages, while transferrin and soluble transferrin receptor concentrations decreased at later stages, indicating that the initial rise in serum ferritin was due to transport of iron into tissues for storage [4].

Iron deposition can contribute to metabolic disorders of bone and muscle tissue, weaken immune function, increase cardiovascular risks, and also enhance the body's sensitivity to radiation [5]. Heparin, a peptide synthesized by the liver, is the main hormone regulating iron metabolism. It binds to ferroportin and induces its degradation, leading to a reduction in the absorption of this trace element in the intestine and its recycling by macrophages [6].

In addition to the physiological changes that can lead to increased iron stores in the human body during spaceflight, an additional factor may be an imbalance in the diet and the intake of nutritional supplements. It should be noted that Russian cosmonauts do not receive special iron-enriched dietary supplements. The food products they consume are balanced in terms of nutrient, vitamin, macro- and microelement content.

The space menu is varied, and the content of major components and the energy value of specially designed diets fully cover energy expenditure and maintain crew members' performance at an optimal level [7]. At the

same time, the iron content in the diet of NASA astronauts is very high: in a standard 16-day diet, it amounts to about 20 mg/day. During long-duration missions, some crew members may consume more than 47 mg of iron per day [8]. By contrast, the recommended dietary allowance for iron is 8 mg/day for men and 18 mg/day for women [9]. In our opinion, it would be inappropriate to directly compare the results of studies conducted with Russian cosmonauts and those conducted with foreign astronauts.

The aim of this work was to assess the dynamics of hepcidin, erythropoietin (EPO), C-reactive protein (CRP), and erythropoiesis markers in the blood of cosmonauts during the early RP after space missions of varying duration on the International Space Station.

MATERIALS AND METHODS

The study was conducted within the framework of the expert program of pre- and post-flight clinical and physiological examinations of ISS expedition crew members. It involved 40 male cosmonauts, who were divided into three groups according to mission duration. The first group (Group A) included 9 individuals (mean age 46.1 ± 3.0 years) who had completed expeditions lasting 8–14 days; the second group (Group B) included 27 individuals (mean age 44.9 ± 1.0 years) who had participated in missions lasting 125–215 days; the third group (Group C) included 4 individuals (mean age 46.8 ± 3.2 years) who had taken part in missions lasting 340–371 days.

Venous blood was collected from the cubital vein on an empty stomach 45–30 days before the start of the flight (baseline examination), as well as on RP day 1 for all three groups, and on RP day 7 for cosmonauts who had completed missions lasting more than 125 days.

In serum, CRP level was measured by immunoturbidimetry using an automatic TARGA BT 3000 biochemical analyzer (Biotechnica Instruments, Italy) with DiaSyS (Germany) reagent kits. Hepcidin and EPO concentrations were determined by enzyme-linked immunosorbent assay using diagnostic kits from Cloud-Clone Corp. (USA). A Stat-Fax-2100 microplate enzyme immunoassay analyzer (Awareness Technology, USA) was used for the measurements.

Red blood cell count, mean corpuscular volume, and red blood cell distribution width were determined as part of the standard complete blood count using a Celltac α -MEK 6318K automated hematology analyzer (Nihon Kohden, Japan).

Statistical analysis was performed using methods from the GraphPad Prism 8.0.2 software package (GraphPad Software, USA). Normality of sample distribution was tested using the Shapiro–Wilk test. Given the small sample sizes and the non-parametric nature of data distribution, the Wilcoxon signed-rank test for

paired samples was used for pairwise comparisons between baseline values and RP values within Group A. Analysis of changes across three time points was performed using the Friedman test with Dunn's correction for multiple comparisons. Differences were considered significant at $p < 0.05$.

Correlation analysis of the obtained data with the values described in previous studies [10, 11] was performed using the non-parametric Spearman rank correlation test. The correlation coefficient was considered significant at a significance level of $p < 0.05$.

Within the framework of the standard expert program of clinical and physiological examination of crew members, the determination of interleukin-6 and other pro-inflammatory cytokines was not provided for; therefore, the role of the inflammatory factor was assessed indirectly — through the dynamics of CRP as an integral marker of non-specific inflammatory response, which is consistent with standard clinical laboratory practice. Direct assessment of the central compartment of the erythron (bone marrow biopsy, enumeration of erythroid precursors) in active cosmonauts was not performed for ethical reasons; the conclusion regarding the activation of stress erythropoiesis was based on a set of indirect signs. The size of Group C is due to the limited number of cosmonauts who have completed ultra-long orbital missions and is a natural limitation of any study of this cohort.

RESULTS

On RP day 1, irrespective of mission duration, CRP levels were statistically significantly elevated in all examined cosmonauts compared to baseline values ($p < 0.05$) (Fig. 1). By RP day 7, CRP values in cosmonauts of Groups B and C had almost returned to pre-flight levels.

Serum hepcidin levels on RP day 1 significantly decreased only in cosmonauts of Group A; however, analysis of individual data revealed that a decrease in hepcidin concentration on the day after landing was also observed in the majority of crew members from Groups B and C. As with the CRP results, hepcidin levels approached or exceeded baseline values by RP day 7.

EPO level on RP day 1 did not change significantly in any of the cosmonauts examined (Fig. 3). On day 7 of the readaptation period, serum EPO levels in crew members who had completed missions lasting 125–215 days increased significantly ($p = 0.05$) relative to baseline values. Regarding cosmonauts who had completed missions lasting 340–371 days, EPO concentration measurements were performed in only two of them. On day 1 after landing, their EPO levels increased sharply compared to baseline data, while by RP day 7 there was a tendency toward a decrease.

It should be noted that the absolute values of hepcidin and EPO at baseline reflect biological interindividual

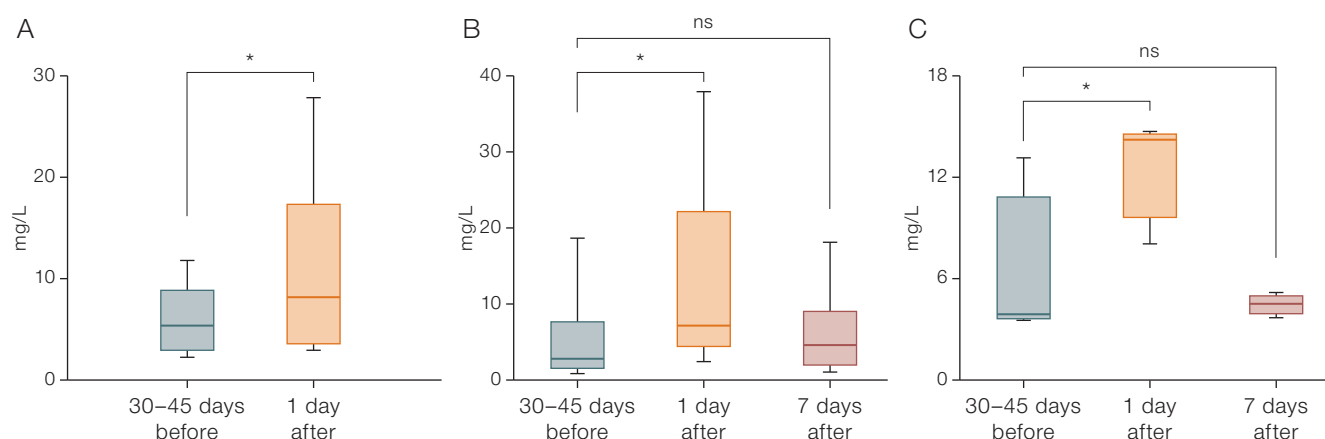


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Fig. 1. Dynamics of serum C-reactive protein levels in cosmonauts following orbital missions. Mission duration (days): A — 8–14, B — 125–215, C — 340–371; * — significant differences from pre-flight values according to the Wilcoxon test, $p < 0.05$ (for Group A) and the Friedman test, $p < 0.05$ (for Groups B and C); ns — no significant differences detected

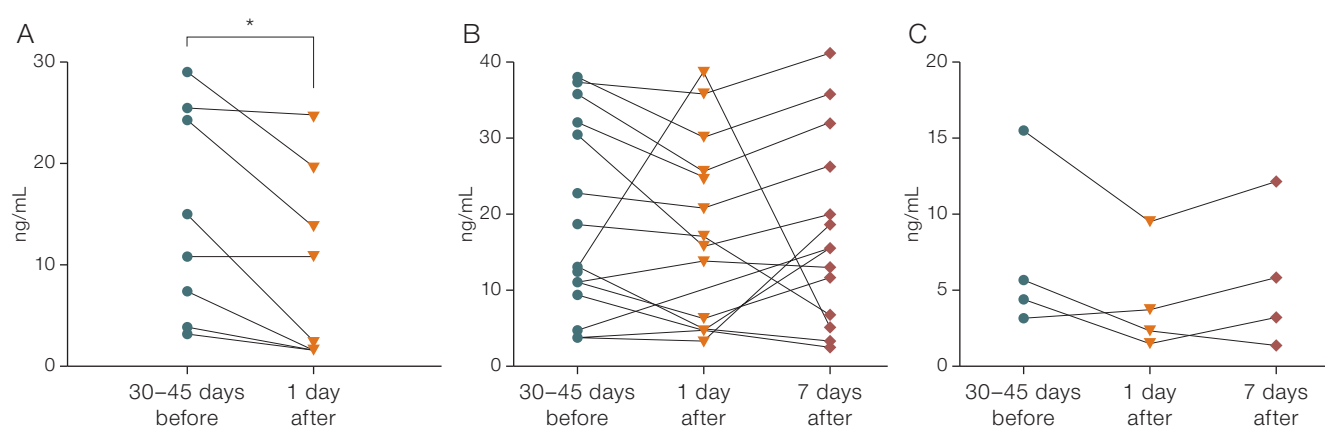


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Fig. 2. Dynamics of serum hepsidin levels in cosmonauts following orbital missions. Mission duration (days): A — 8–14, B — 125–215, C — 340–371; * — significant differences from pre-flight values according to the Wilcoxon test, $p < 0.05$ (for Group A)

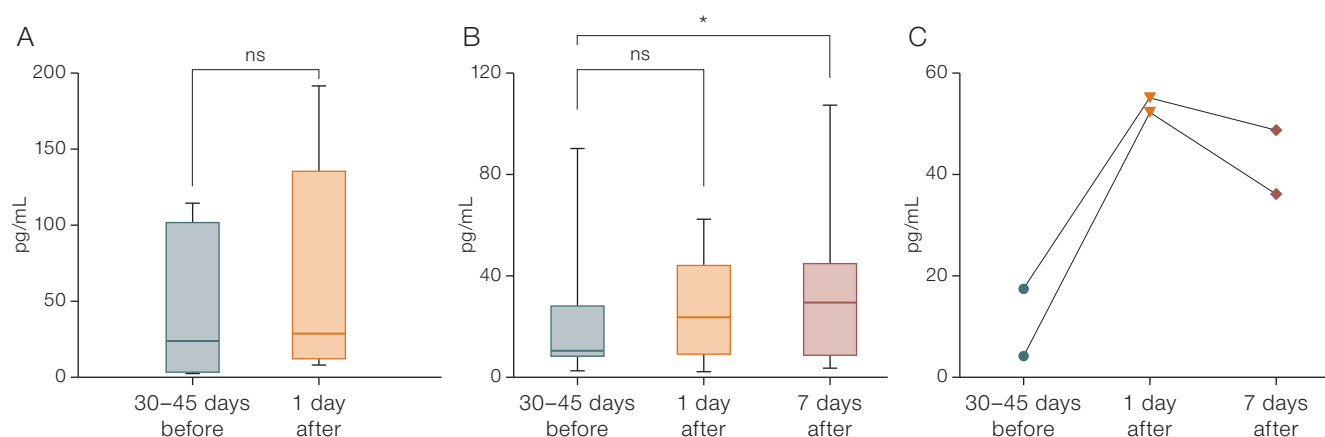


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Fig. 3. Dynamics of serum erythropoietin concentration in cosmonauts after orbital flights. Mission duration (days): A — 8–14, B — 125–215, C — 340–371; * — significant differences from pre-flight values according to the Wilcoxon test, $p < 0.05$ (for Group A) and the Friedman test, $p < 0.05$ (for groups B and C); ns — no significant differences detected

variability of these hormones and are not intended for intergroup comparison. All principal conclusions of the present work are based on within-subject paired comparisons of baseline values with the study time points on days 1 and 7 of the RP within each group.

Correlation analysis of erythropoiesis markers in cosmonauts who had spent varying amounts of time on the ISS did not reveal a significant relationship between the number of flights, the duration of orbital missions, and iron metabolism parameters on day 1 of the readaptation period. However, on RP day 7, an inverse correlation was found between erythrocyte count and time spent in low Earth orbit ($r_s = -0.543$, $p = 0.002$). On this basis, it can be assumed that as the total time spent in microgravity increases, cosmonauts experience a decrease in red blood cell mass, which may negatively affect the efficiency of oxygen transport to tissues during the early post-flight period. Positive correlations were found between mission duration and such parameters as RDW-CV ($r_s = 0.578$,

$p = 0.001$) and MCV ($r_s = 0.447$, $p = 0.008$). This means that the longer the mission, the more heterogeneous the erythrocyte pool will be one week after its completion, and the newly formed red blood cells will be larger.

DISCUSSION

The increase in CRP levels on RP day 1 may be explained by the development of a stress response to the G-forces experienced by crew members during spacecraft descent from orbit and during readaptation to Earth conditions. A study by Buchheim et al. demonstrated significant changes in the levels of regulatory/inhibitory cytokines, such as TGF- β , IL-10, and IL-1ra, which decreased sharply after return to Earth [12], indicating the development of a systemic pro-inflammatory status after landing. Our CRP data are consistent with these results and complement them with a quantitative characterization of the non-specific inflammatory response.

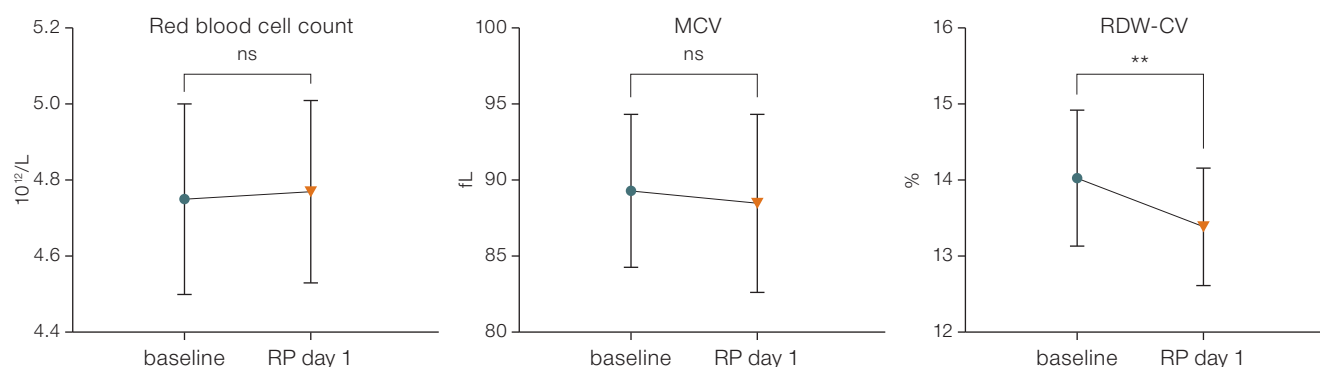


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Fig. 4. Erythropoiesis marker dynamics in cosmonauts' whole blood after 8–14-day orbital flights. MCV — mean corpuscular volume, RDW-CV — red blood cell distribution width; data are presented as median and interquartile range $M_e [Q_1; Q_3]$; ** — significance of differences from pre-flight values according to the Wilcoxon test, $p < 0.01$; ns — no significant differences detected

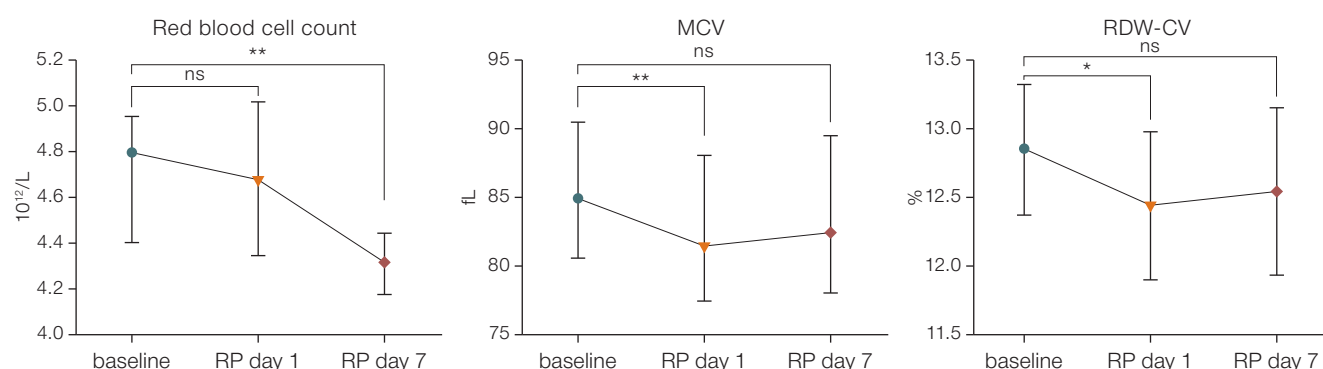


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Fig. 5. Erythropoiesis marker dynamics in cosmonauts' whole blood after 125–215-day orbital flights. MCV — mean corpuscular volume, RDW-CV — red blood cell distribution width; data are presented as median and interquartile range $M_e [Q_1; Q_3]$; * — $p < 0.05$, ** — $p < 0.01$ — significance of differences from pre-flight values according to the Friedman test; ns — no significant differences detected

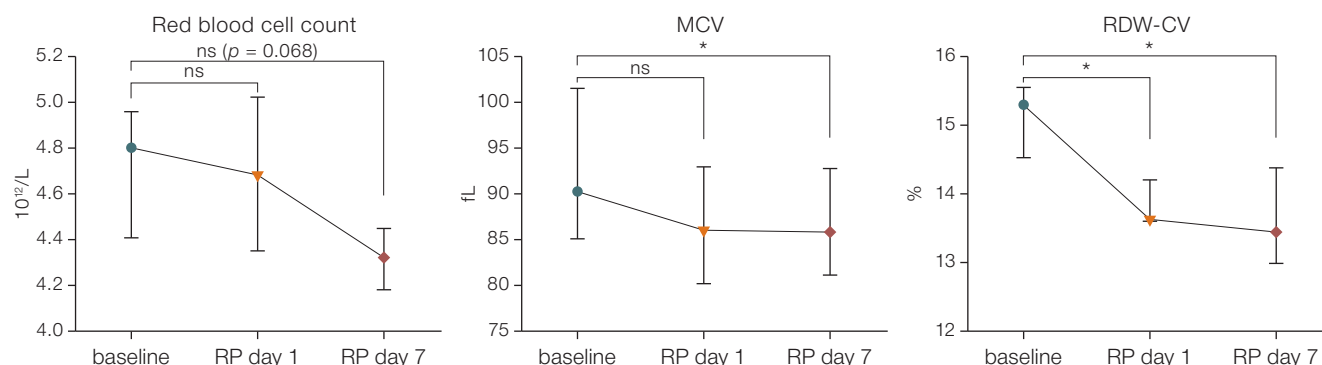


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Fig. 6. Erythropoiesis marker dynamics in cosmonauts' whole blood after 340–371-day orbital flights. MCV — mean corpuscular volume, RDW-CV — red blood cell distribution width; data are presented as median and interquartile range $M_e [Q_1; Q_3]$; * — significance of differences from pre-flight values according to the Friedman test, $p < 0.05$; ns — no significant differences detected

EPO controls red cell mass by regulating the division rate of red blood cell precursors in the bone marrow. Furthermore, there is speculation about its involvement in the process of neocytolysis, in which newly formed red blood cells are selectively destroyed upon entry into microgravity conditions [13]. According to Kunz et al., EPO levels decrease early during flights but increase during the RP after short-duration flights, indicating that homeostatic mechanisms attempt to reduce red cell mass during acute adaptation to weightlessness and restore it upon return to Earth [14]. Our data are consistent with these observations: the delayed increase in EPO by RP day 7 in cosmonauts of Group B reflects the activation of a compensatory erythropoiesis mechanism in response to decreased erythrocyte count and MCV.

There is evidence that hypoxia suppresses hepcidin production [15]. In a study by Grigoriev et al., an increase in the efficiency of oxygen retention by hemoglobin of 34% was found on landing day after long-duration space flights; the authors suggested that this, in the context of decreased Hb and serum Fe^{3+} concentrations, may initiate the development of tissue hypoxia [16]. Hepcidin synthesis in the liver is reduced due to increased production of EPO in the kidneys, erythroferrone in erythroblasts, and other erythroid regulators during erythropoiesis. This enhances iron absorption in the gastrointestinal tract and release of the trace element from stores, ensuring a large supply of iron for hemoglobin synthesis [17]. Furthermore, hypoxia-inducible factors (HIFs), especially HIF2 α , interact with the enhancer region of the HIF-binding element of the EPO gene and increase its expression [16]. The decrease in hepcidin that we found on RP day 1 is consistent with these mechanisms.

Under steady-state erythropoiesis, new red blood cells are produced at a constant rate, replacing aging

cells that are removed by macrophages in the liver and spleen. However, during infections and tissue damage, steady-state erythropoiesis is disrupted. In such cases, stress erythropoiesis is activated to compensate for red blood cell loss [18].

Comparison of the changes in hepcidin and EPO levels described in the present work with the previously published data on iron metabolism [11] from the same three groups of cosmonauts allows a complete physiological picture to be formed. The decrease in serum iron and transferrin concentrations together with an increase in ferritin indicates redistribution of the trace element into stores. At the same time, the hepcidin decrease on RP day 1 promotes activation of ferroportin and ensures release of iron from stores into the blood, while the delayed increase in EPO by RP day 7 supports the demand for this trace element for hemoglobin synthesis by newly formed erythroid precursors. Thus, the regulatory picture obtained is consistent with our own hematological data [10] and does not contradict the concept of stress erythropoiesis.

Pro-inflammatory cytokines suppress steady-state erythropoiesis, shifting hematopoiesis toward myelopoiesis and increasing the production of myeloid effector cells at the expense of steady-state erythropoiesis [19]. Furthermore, interleukin-6, acting as a pro-inflammatory cytokine, increases hepcidin levels, leading to iron sequestration and making iron unavailable for hemoglobin synthesis. In addition, inflammatory processes accelerate erythrocyte turnover, further exacerbating the severity of anemia [20]. To compensate for the disruption of red blood cell production, inflammation activates stress erythropoiesis, which promotes the proliferation of immature precursor cells, resulting in increased production of erythroferrone. Erythroferrone suppresses hepcidin expression, making iron available for hemoglobin biosynthesis during the early stages of precursor cell differentiation.

During stress erythropoiesis, a large number of new red blood cells are produced, which maintain homeostasis until the cause of inflammation is eliminated [21]. Furthermore, it is important to consider that activation of stress erythropoiesis leads to the formation of red blood cells with reduced deformability but anomalously high resistance [22]. These features of stress erythropoiesis may largely account for the increase in erythrocyte population heterogeneity in cosmonauts over the RP course.

It has been shown that in the early RP after long-duration space flights, erythropoiesis is stimulated to enhance the production of normocytes to meet the increased oxygen demand of tissues [23]. Thus, the combination of signs that we found — elevated CRP, decreased hepcidin, delayed increase in EPO, and changes in RDW-CV — is consistent with the concept of activation of stress erythropoiesis in cosmonauts during the early post-flight period.

Our own data, obtained from the same cohort of cosmonauts and published in [10, 11], indicate that in the early post-flight period, regardless of orbital mission duration, cosmonauts exhibit a decrease in red blood cell count, hemoglobin concentration, and iron concentration, a decrease in mean corpuscular volume and hematocrit, an increase in serum ferritin content, as well as a decrease in total iron-binding capacity and transferrin concentration.

Based on the combined hematological and biochemical criteria, the observed changes should be classified as microcytic hypochromic anemia with signs of iron redistribution. In the third group, the severity of these changes is maximal. Comparison of our own data

on erythropoiesis and iron metabolism [10, 11] with the results of the present study allows us to assert that the functional anemia developing in cosmonauts does not fit the classical picture of anemia of chronic inflammation, in which hepcidin is elevated. The observed pattern is more consistent with functional anemia of mixed origin with a predominant stress erythropoiesis component: erythroferrone-mediated suppression of hepcidin prevails over its stimulation by inflammatory cytokines, thereby mobilizing iron for active incorporation into hemoglobin synthesis in precursor cells. A schematic representation of the proposed changes in iron metabolism and erythropoiesis in cosmonauts during the early RP is presented in Figure 7.

When comparing our own data with the results obtained from examinations of NASA astronauts, several fundamental differences must be considered. According to Trudel et al. [3], a decrease in iron and transferrin concentrations below baseline levels is observed in astronauts on RP day 4. Furthermore, Zwart et al. [4] described an increase in serum ferritin levels in the blood of crew members during the early stages of orbital flights, interpreting this as a sign of iron redistribution into tissues. Kunz et al. [14] found a EPO decrease at the beginning of the flight, followed by an increase in its concentration during the early post-flight period in astronauts after short-term ISS missions. Our own data obtained from Russian cosmonauts generally confirm the direction of these changes; however, there are several distinctive features: a delayed, rather than early, increase in EPO, peaking by RP day 7 of the predominantly in cosmonauts with medium-duration flights, as well as a pronounced decrease in hepcidin on RP day 1.

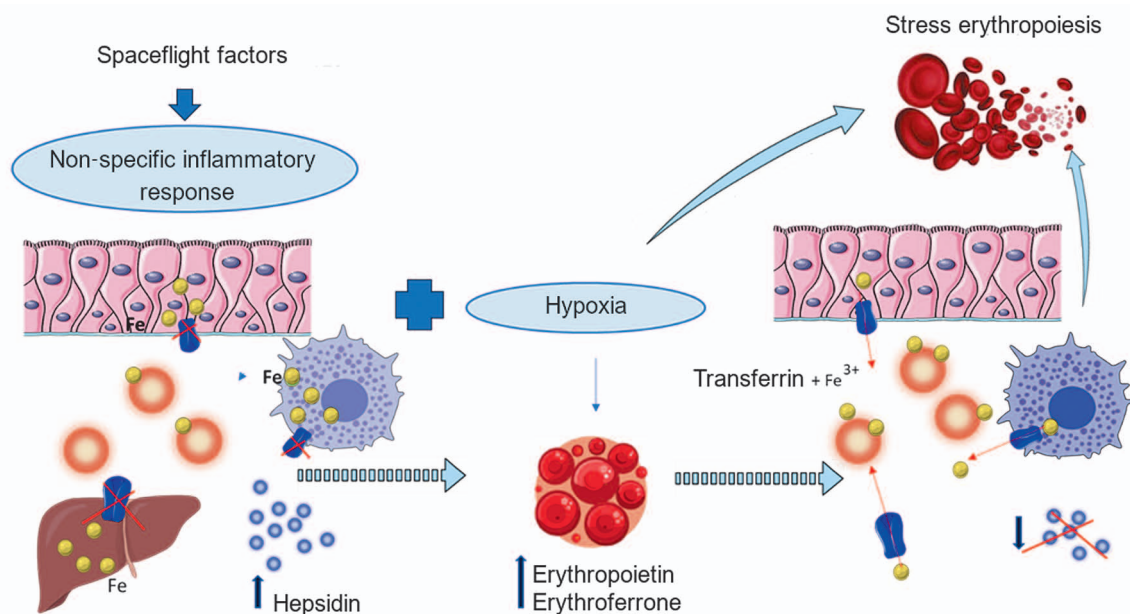


Figure prepared by the authors

Fig. 7. Iron metabolism changes in cosmonauts during the early recovery period after flights of varying duration to the International Space Station

These differences may be due to fundamentally different dietary structures and differences in the timing of biosample collection.

CONCLUSIONS

Thus, in cosmonauts who have completed orbital missions of varying duration on the International Space Station, changes in iron metabolism are observed against the background of a non-specific inflammatory response. This inflammatory response likely triggers the redistribution and storage of this essential trace element in tissues, followed by its release for hemoglobin synthesis due to the activation of stress erythropoiesis in the early RP. Furthermore, the changes in the erythron system are directly dependent on the duration of the space mission. The heterogeneity of the erythrocyte pool is more pronounced in cosmonauts who have completed longer orbital flights. Studies of iron metabolism changes and the mechanisms of stress erythropoiesis under

spaceflight conditions represent one of the most promising directions in space medicine. Their implementation will allow progress to be made in understanding the biochemical and molecular foundations of these physiological responses of the body.

The practical significance of the results obtained is as follows. The identified correlations between total time spent in microgravity and erythrocyte count, MCV, and RDW-CV can be used to predict the severity of post-flight changes in the erythron system and to identify crew members who require priority medical support during the readaptation period.

The results obtained provide a scientific basis for the development of preventive measures, including possible nutritional correction of diets in light of the identified iron redistribution patterns. This is particularly relevant for planned interplanetary missions, during which medical evacuation to Earth is impossible and the necessary comprehensive post-flight rehabilitation will be technically challenging.

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