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21-Day Dry Immersion: Schedule of Investigations and Major Results

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Abstract—The paper describes the main stages of the protocol and results of a unique 21-day experiment undertaken at the Russian Federation State Research Center Institute of Biomedical Problems of the Russian Academy of Sciences (RAS) (IBMP) under the conditions of Dry Immersion. A cohort of participants consisted of 10 healthy male volunteers (the mean age 29.3 ± 3.56 years). The experiment has demonstrated the feasibility and safety of conducting long-duration immersion exposures, confirming the results obtained during previous shorter exposures, as well as allowed us to describe the dynamics of events during extended chronic stays in the conditions of simulated hypogravity. The accumulated experiences are useful for further research into the efficiency of applying the conditions of simulated microgravity and other prophylactic means as countermeasures against negative effects occurring to human body during extended support and weight unloading.

Keywords: dry immersion, support unloading, microgravity models

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The most promising models to study the motor effects of microgravity is immersion (immersion into a fluid medium analogous in density to human body tissues) [1–3] and antiorthostatic hypokinesia [4–6]. The factors of support and body weight unloading and a similarity of biomechanical conditions in the organization of motor activity and those observed in weightlessness were decisive in choosing a procedure of immersion as an almost single testing and training model for the execution of mission tasks in weightlessness.

In the early 1960s, researchers initiated the study of physiological effects produced by immersion with the aim to determine a feasibility of applying the procedure for a ground-based simulation of microgravity effects [7, 8]. Immersion was shown to cause motor [9], cardiovascular [10] and other microgravity-induced changes in human physiological functions. The acceptance of immersion as an adequate simulation model was only restricted by the discomfort and possible unsafety associated with a prolonged contact between a subject's skin surface and water.

In the early 1970s, Shulzhenko and Vil-Villiams, researchers from the Institute of Biomedical Problems (IBMP), developed a method facilitating to conduct a long-duration immersion study based on the principle of dry immersion created by a specific waterproof and high-elastic fabric [11, 12]. In this case, a subject dressed in a vest and swim trunks was placed on a waterproof fabric in the supine position and immersed into water column to the neck level. The surface area of the fabric significantly exceeded the water surface area. The waterproof material folds containing also a portion of immersion medium, met along the subject's body midline, enveloping the body on all sides not tightly. No lodgments were applied to support a subject's body. High elastic properties of the fabric artificially increased the fluid density, creating a level of almost zero buoyancy. As only this model was designed, it became Russia's best one for studying the microgravity effects of a five- to seven-day exposure, which was equal to the duration of so called short-term missions on space stations.

In 1974, Shulzhenko and Vil-Villiams conducted an unprecedentedly long (56-day) immersion experiment with the participation of two volunteer subjects, convincingly proving the feasibility and safety of the model for reproducing the effects of prolonged exposures. The study results had shown that a 56-day immersion reduced the reserve abilities of the circulatory apparatus and caused the whole-body deconditioning. The functional changes in the circulatory system under the immersion conditions demonstrated, on the one hand, the adaptive signs with the

† Deceased.

predominance of parasympathetic tone and, on the other hand, pointed at the signs of reductions in the reserve abilities of the body and in its resistance to the head–pelvis g-overloads and lower body negative pressure [10, 12, 13]. Another two 21- to 28-day experiments with a very humble cohort of subjects and a limited complex of investigations were conducted during the same years. Over the subsequent 40 years, Dry Immersion has been Russia's central model for the study of acute microgravity effects.

Our studies conducted at IBMP over several years with the application of its Dry Immersion (DI) model have allowed us to describe in detail the changes in the dynamics and expression of different body systems during relatively short-term exposures (from 6 h to 7 days) [3]. At the same time, there are still no data on the effects of longer supportlessness (for over 7 days), although this knowledge is necessary in view of future ultra-long space missions.

For example, the results of investigations in the bone system of crew members during long-term missions onboard the Mir Space Station and the International Space Station have shown that one of the most important problems for human beings during a long-duration space mission is constituted by atrophic losses to the bone tissue [14, 15]. At the same time, a relatively small number of model experiments were devoted (there were no studies at all under DI conditions, on the reason of insufficient duration of exposures) to bone changes induced by gravitational unloading, and the mentioned problem was mainly discussed in the studies performed in the conditions of long-duration head down bed rest. In view of the prospects for ultra-long interplanetary missions, the importance of this problem significantly increases, whereas the development of efficient countermeasure means against unfavorable changes in the bone and muscular systems becomes an essential task of providing the feasibility of these missions.

This study was the first stage of the program for experimental studies with the human participation entitled The State of Human Physiological Systems in Simulating Particular Factors of Space Missions under the 21-Day Dry Immersion without Countermeasure Means and with Artificial Gravity Created by a Short Radius Centrifuge.

The objective of the first stage of the program included the integrated study of effects of a long-duration (21-day) support unloading on the state of the body's essential physiological systems and the accumulation of practical knowledge for the further study of artificial gravity in its application as efficient countermeasure. The program of studies was approved by the Commission on Biomedical Ethics of the IBMP RAS/Physiological Section of the Russian National Committee on Bioethics under the Commission of Russian Federation for UNESCO (protocol no. 483 of August 3, 2018).

The battery of studies was based on the recommendations developed for analogous experiments with head-down tilt bed rest (HDBR) (International Academy of Astronautics, IAA, 2014).

METHODS

The battery of standard studies included the study of effects produced by a 21-day support unloading on the sensorimotor, cardiovascular, muscular, bone, and immune systems, as well as on physical and functional capacity, hematological, and psychophysiological parameters. A particular attention was given to important areas in the field of space medicine, including the study of the phenomenon of back pain and changes in intraocular pressure.

The study cohort included 10 voluntary subjects with the mean age 29.3 ± 3.56 years, mean height 175.8 ± 0.03 cm, and the mean body weight 73.24 ± 10.97 kg ($M \pm SD$). The anthropometric parameters of the experiment participants were within the physiological norm. The mass body index (MBI) calculated during the baseline period was equal to 23.2 ± 3.24 kg/m^2 ($M \pm SD$), and the MBI in 3 subjects insignificantly exceeded the normal values: 26.2; 26.9; and 27.4 kg/m^2.

All participants had to pass the medical commission at the IBMP of the RAS, and no pathologies excluding their participation in the experiment have been found. Before their final approval for the experiments, the subjects had to sign the informed consent to their participation in the study.

The experiment was held at the IBMP of the RAS on the Dry Immersion Simulation and Training Facility, a component of the Unique Scientific Installations (USI), Medical and Engineering Complex for Testing Innovational Technologies of Space Biomedicine for the Provision of Orbital and Interplanetary Missions, as well as for the Development of Practical Healthcare. Scientific investigations and medical control measures were conducted during two weeks before the start of immersion and two weeks after its completion, as well as in the course of immersion exposure. During 24 h before the start of immersion, as well as during 34 h after its completion, the subjects were also present in the testing facility under the control of a team on duty. One part of investigations was only performed prior to the start and upon completion of the immersion, whereas the other part of investigations continued through its entire course. After the first investigations on the completion day, the subjects were transported to Clinical Hospital no. 1 (Volynskaya) of the Department for Presidential Affairs of the Russian Federation, where, after the muscle biopsy procedure, they were immersed into immersion baths at the hospital and left there for the night, so the experiment was continued on the next day in the morning at the IBMP of the RAS.

Fig. 1. Dry immersion testing complex at IBMP. Source: O.G. Voloshin (IBMP).

The participants were subjected to Dry Immersion for 21 days (Fig. 1). The immersion bath relatively restricted their movements and they did not perform any physical exercises. The water temperature was kept at a level of 32.5 ± 2°C. Every evening, the subject was lifted out of the bath for 15–20 min, on average, for hygienic procedures, the majority of which the subject fulfilled in a supine position. The medical team on duty, including a physician, a laboratory assistant, and a technician or an engineer, provided the subjects with three meals a day, as well as provided a round-the-clock medical control over the health condition of the subjects and the accuracy of instruments and technical devices. Some investigations were connected with the necessity of lifting the subject out of the bath for a relatively short period of time and keeping him during the procedure in a lying position. During the time free of procedures and methods, the subjects were permitted to read, work at a portative PC, watch TV, and talk on the phone, etc.

Venous blood was sampled for a variety of investigations 4 times before DI (14, 7, and 3 days, as well as 24 h, prior to the immersion into the bath, 4 times during the exposure (on days 3, 7, 14, and 21), as well as twice after the completion of DI (on days 7 and 14 of the recovery period). The total volume of venous blood sampled during a two-month period of investigations per subject was measured at 504.0 mL.

The dietary scheme control was introduced 24 h before the start of the experiment, continued through the whole period under the DI conditions and for 2 days after the completion of the experiment. To develop the dietary scheme and specify its composition and calorie value, the experimenters took into account the study conditions, such as physical inactivity, the elevated temperature of the medium and the reduced energy expenditures of the subjects during the DI period. The indicated dietary scheme was based on dietary table no. 15 (common table) under the medical nutrition scheme specialized by M.I. Pevzner. This diet corresponded to the WHO's recommendations, was balanced in essential nutrients and prescribed for healthy people unengaged in physical labor. The recommended 7-day menu scheme was based on one-day menu with 5 daily food intakes and a 24-h calorie value ratio varying from 2800 to 3000 kcal with the following portions of essential nutrients: protein, 112 g; fats, 88 g; carbohydrates, 380 g. The mineral composition of the nutrition ratios was not calculated. To provide the normal functions of the gastrointestinal tract (GIT), products with increased fatness, hard-processed and gas-forming, and sharp, as well as coffee, were excluded from the diet. Apart from the main nutrition ratio, the menu included some products according to subjects' individual tastes and recommended for supplementary intakes during a day (fruits and dried fruits, cakes, and sweets).

RESULTS AND DISCUSSION

In line with the protocol of the experiment, the investigations on days 7, 9, 14, and 19 of exposure included a passive orthostatic test (tilt test). In view of this, the time spent by the subjects outside the bath on the indicated experimental days significantly exceeded this indicator during the remaining days of exposure ($F(20, 189) = 44.66$; $p < 0.0001$) (Fig. 2). The mean time outside the bath (excluding the days with the orthostatic test) varied from 17.18 ± 4.06 min during the first 24 h of exposure to 30.76 ± 8.04 min on the final days of exposure. The longer time outside the bath on day 21 of exposure was associated with a large number of investigations performed on the day before the completion of immersion.

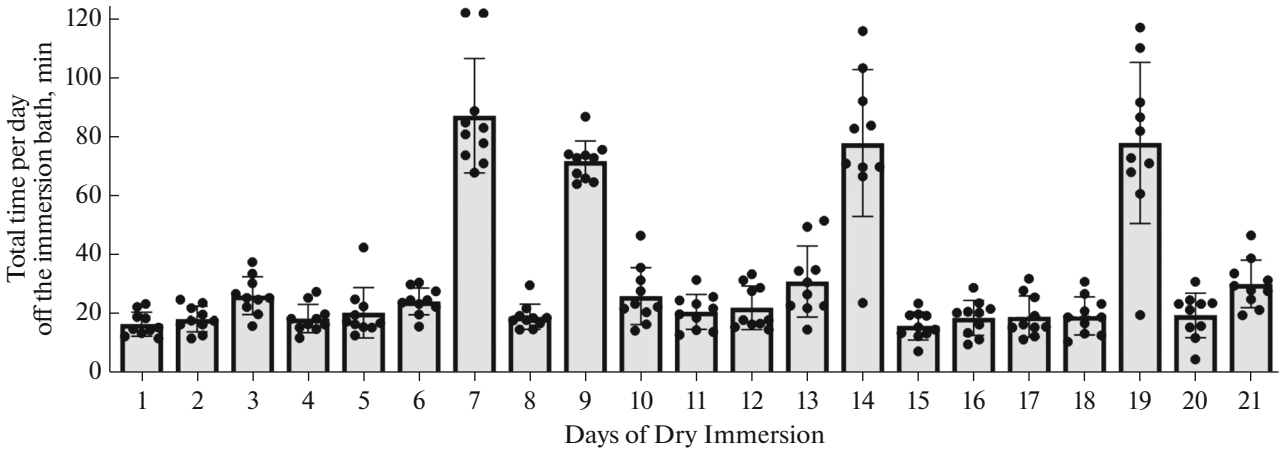

Fig. 2. Time spent by the subjects outside the bath (in both the supine and the vertical position, totally) during the immersion experiment, $M \pm SD$.

During the exposure, as well as 24 h before the start of exposure and during three days after its completion, the body temperature was measured in the subjects on a daily basis with a medical thermometer (at the same time in the morning, in the afternoon, and in the evening) in the area of auxiliary hollows (separately under the right and left armpits). The data analysis has not shown any significant differences between the indicators under the right and left armpits, as well as between the morning, afternoon, and evening recordings. The body temperature did not change significantly during the entire immersion exposure, varying, on average, from 36.21 ± 0.27 to 36.47 ± 0.32°C (Fig. 3a). At the same time, a significant elevation in the body temperature was observed on the next day after the DI completion, which was apparently associated with the effects of muscle biopsy performed on the day of exposure completion ($F(9,225) = 9.155$; $p < 0.0001$).

In the course of DI, the bath water temperature was daily recorded (temperature changes during a day were also recorded under the laboratory control chart). No significant changes in this indicator has been observed in the course of DI exposure, whereas significant individual differences between the desired degrees of water temperature were present ($F(9,180) = 28.18$; $p < 0.0001$). The mean bath water temperature readings varied between subjects from 31 to 34°C (Fig. 3b). At the same time, no dependence has been observed between the mean daily body temperatures and water temperatures in the bath.

In a full correspondence with the observations of short-duration immersion experiments, a significant body length increase was observed on the very first day of exposure ($F(6,061, 54,55) = 30.62$; $p < 0.0001$) (Tomilovskaya et al., 2019). The indicated changes continued to remain during the entire immersion exposure (Fig. 4a). Unlike the short-duration immersion investigations, the return to the initial parameters was observed only on day 2 of the recovery period: significant differences among the body length values were recorded between the sessions on the day of immersion completion and during three days of recovery, as well as between days 1 and 3 of the recovery period (Fig. 4a).

A significant body weight decrease ($F(3,139, 28,25) = 6.115$; $p = 0.0022$) was observed in all subjects during the immersion exposure. Significant differences from the baseline values were recorded in the group during all days of exposure, except days 13, 18, 19, and 20 of DI (Fig. 4b). Individual differences were also highly significant ($F(9,207) = 8.926$; $p < 0.0001$).

Body weight losses could be associated with the loss of liquid by the body. A negative water balance (difference between the consumed water and the 24-h diuresis) was actually recorded during the total 21-day period, but its values did not fall to the body mass reduction values (Fig. 5). The maximum fluid loss was recorded on the initial day of exposure to immersion. A more detailed analysis of changes in the body mass and composition will be given in another separate publication.

As in shorter-term experiments, back and abdominal pain developed within the first few days in all subjects (Fig. 6). The intensity of back pain reached maximum values, i.e., 6–8 points on days 1 and 2 of exposure. Significant differences in this indicator against the baseline data were recorded on DI days 1, 2, and 3. However, unlike shorter DI experiments, back pain continued to be recorded in some individuals even during 6 days of exposure (Fig. 6a).

The intensity of abdominal pain was less expressed, but its duration was limited to the first week of exposure (Fig. 6b). In the majority of cases, abdominal pain was accompanied by meteorism and stool delay.

The medical support team was composed of 18 specialists working as doctors on duty. A third of them participated for the first time in providing a medical

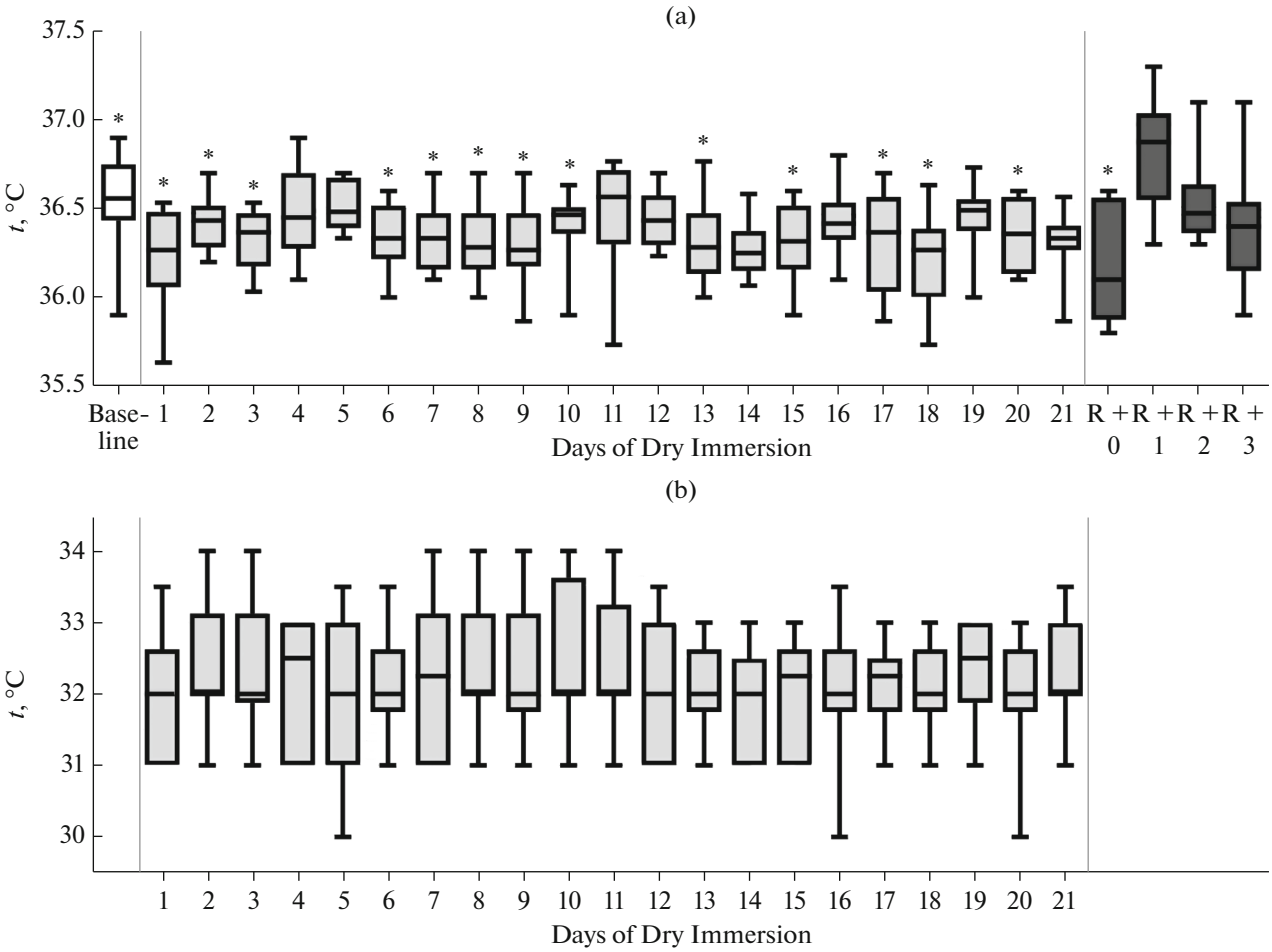

Fig. 3. Body temperature (a) in the group of subjects and the mean per day water temperature in the immersion bath (b) before DI, during and after the completion of 21-day DI, Median ± Max – Min. Abscissa, days of exposure, where the baseline means 24 h before the start of DI; R + 0 is the day of DI completion; (R + 1), (R + 2), and (R + 3) are days 1, 2 and 3 after the DI completion, respectively. * Significant differences from the measures on the next day after the completion of DI (R + 1); $p < 0.05$.

support for experiments with human subjects and worked out the main elements of this support on the operator (subject)–doctor interaction model, which was important for the specialists of IBMP RAS engaged in the medical support of space missions.

When providing the medical support, the team of experimenters successfully collaborated with the clinical base, where the muscle biopsy procedure was performed. The well-coordinated interaction between the medical support team for the experiment from the institute and the colleagues from the Clinical Hospital no. 1 (Volynskaya) of the RF Department of Presidential Affairs allowed the physicians to preserve the effects of the 21-day DI exposure and minimize the time of verticalization and stay outside the bath.

The state of health of the subjects during DI was assessed as good and adequate to the exposure conditions. We should also note individual episodes of temperature elevations in subjects during the initial DI period (on the first three or four days) up to subfebrile levels with cold-related symptoms (nasal congestion or rhinorrhea and sore throat). The symptoms of the process is not characteristic of the classical development and persistence of acute respiratory viral infections (ARVI) or another cold-related disease, since the symptoms were localized and resolved without the temporal dynamics typical of ARVI (or acute respiratory infection, ARI), disappearing within a short period without specific treatment (only with symptomatic correction). Such a state should obviously be discussed within the context of the process of adaptation to new conditions associated with the temporal stress on the defensive mechanisms in the body during its passage from the period of intensive background investigations towards the period of a relatively regular regimen during the DI exposure. The onset of nonspecific cold-like symptoms could be provoked by the conditions of the spring–autumn period, during which the major part of the DI program was being implemented.

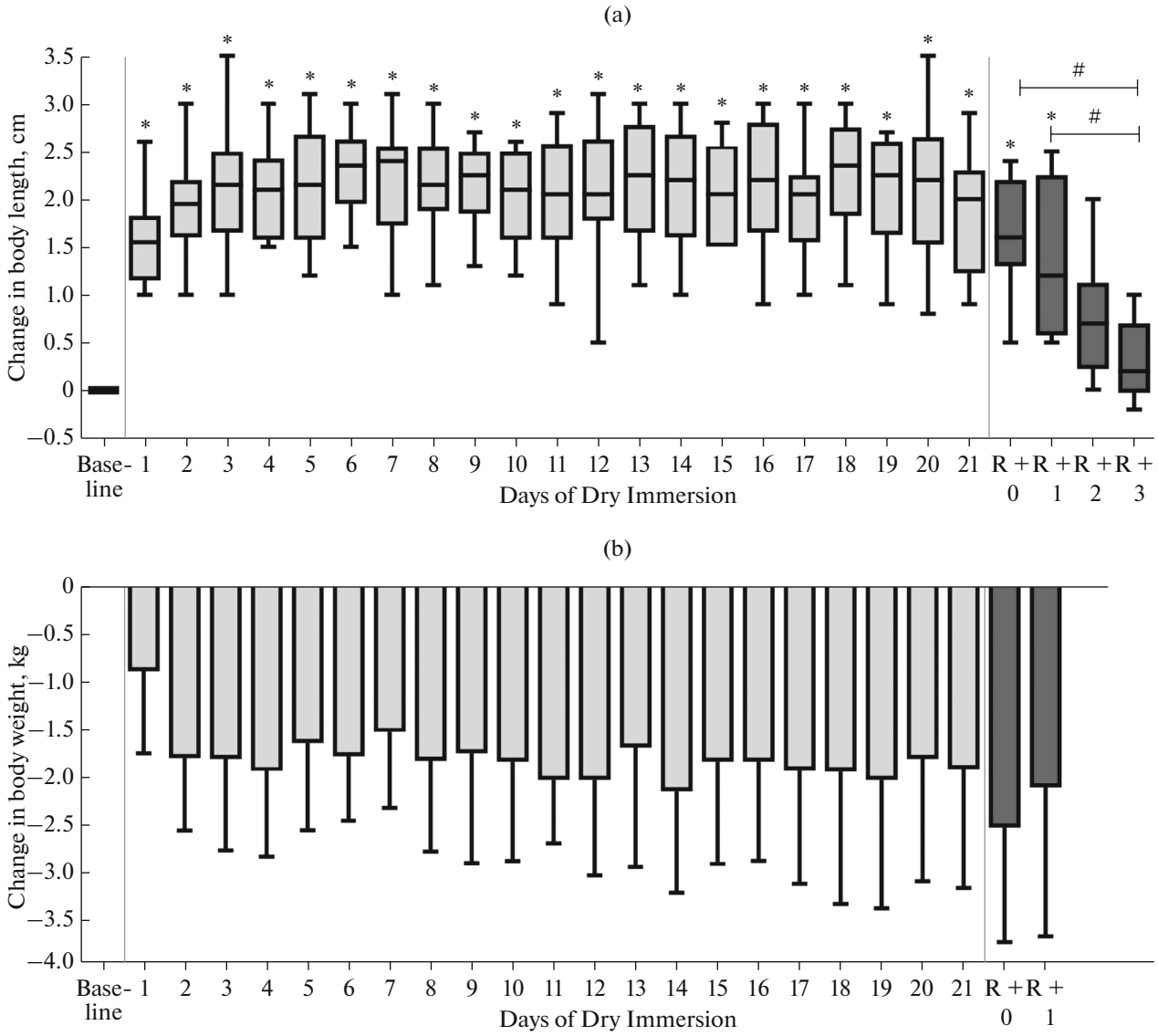

Fig. 4. Changes in the body (a) length and(b) weight in the course of the 21-day Dry Immersion exposure and after its completion, respective to the values recorded 24 h before the start of the immersion exposure. The data are represented as Median ± Max – Min (a) and $M \pm SD$ (b). On the abscissa—days of exposure, where the baseline means 24 h prior to the start of DI; R + 0 is the day of DI completion; (R + 1), (R + 2), and (R + 3) are days 1, 2 and 3 after the DI completion, respectively. * Significant differences from the baseline values before DI, $p < 0.05$; # significant differences from the values on day 3 of the recovery period (R + 3), $p < 0.05$.

Several cases during the experiment were associated with a necessity to manage the post-biopsy injury during the initial six to eight days of immersion. Therefore, the schedule of the preliminary biopsy test was changed: specimens should be collected at least three weeks before the start of DI. The biopsy injury was monitored in one case within the initial period of DI, due to coming out of a suture material from the injury.

One case of acute edema of lower limbs was also recorded during the tilt test performed within the medical support of DI on the next day after the completion of immersion. To exclude the possible complications, the subject was hospitalized on medical indications.

After hospitalization, his state was normalized within 2 h, no pathological changes have been diagnosed by the rheovasography data of the lower and upper extremities, the symptoms were resolved, and the subject was discharged from the hospital on the next day, due to the absence of any pathological changes and complaints. A further observation of the subject's state of health did not diagnose any analogous symptoms. This disorder in the vascular system was possibly of the functional etiology and, therefore, needed further research for diagnosing early signs of

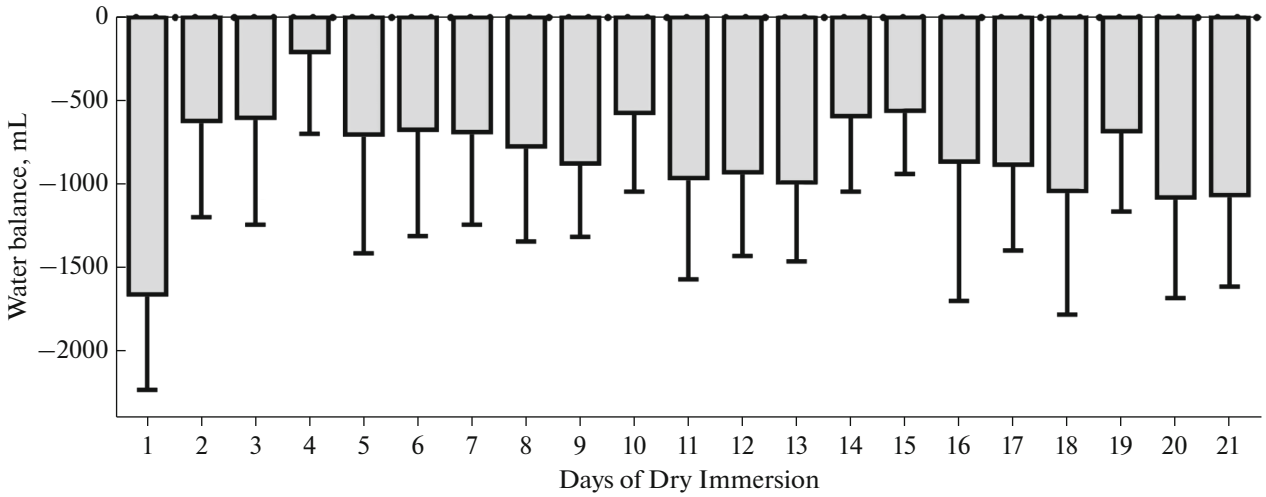

Fig. 5. Values of the water balance during the immersion exposure as the mean per group values ($M \pm SD$).

developing complications during the period of readaptation after a long-duration stay in the conditions of support unloading.

We should note that some symptoms of the microgravity-induced adaptation changes were also observed for the first time in the course of medical support of the experiment. Petechial rash emerged on immersion day 10 after the performance of tilt test and was recorded in the majority of subjects on the distal regions of their lower limbs with its predominant localization on the back surface of the soles, malleolus, and the lower third of the shin. The eruptions were structurally characterized as a diffuse petechial rash without fusion. These symptoms are a signal about possible microgravity-induced changes in the microcirculatory bed. The subsequent observation has shown that subjects felt a mild tingling in lower limbs during a tilt test during the initial 2–3 min after verticalization, which was accompanied by a sensation of leg "overfulness" and a slight leg "burning" sensation.

These changes accompanied almost all tilt tests performed during DI. At the same time, on the next day after the completion of DI, the analogous symptoms were minimal or fully unobservable.

In the course of the DI medical support, maceration-like changes were recorded on the subjects' skin surfaces in the distal compartments of lower limbs with spots of reddening and detachment of upper epidermis, predominantly between toes. These changes were not conjugated with complaints or unpleasant sensations and caused rather a visual discomfort in subjects. The scrapes from the places of changed skin surface have not detected in the first pair of subjects any clinically significant deviations in favor of bacterial and yeast nature of the observed process. According to the dermatologist's consultation, the examination and investigation of the changed skin places evidenced in favor of hyperhydratation-associated skin maceration in lower limbs, which was associated with a long-duration stay of soles in the conditions of increased moisture. Despite the frequent change of underwear, due to natural processes, the skin sweated and moisture was accumulated in places where the body was more surrounded by the film, thus preventing the natural moisture evaporation from the skin surface. Frequent changes of socks and bed sheets did not lead to some characteristic results or could even lengthen the daily interval of staying outside the bath. The application of hydrophobic ointments, beginning from the moment of immersing the subjects into the immersion medium, allowed, in some cases, neutralizing the expression of the skin maceration processes in soles or significantly postponing their onset to the time of DI completion. A possible effect of microgravity conditions and support unloading on the processes of microcirculation regulation, which could contribute to the development of the observed phenomena, is also not excluded.

In total, we should note that the integrated immersion experiment conducted for the first time for 21 days is safe and does not carry any serious medical risks with a properly organized medical control. As to the space mission medical support, some analogous experiments help assess possible medical risks associated with short-term space missions in the conditions of support unloading and physical inactivity, e.g., in the case of a Moon program, where a travel to the Moon and back will take place in a small hermetic volume and for a comparable exposure period. Considering the experience of short DIs, we should now note that a sharp adaptation period takes the first 4 days of exposure to microgravity and may be accompanied by disorders on the part of the gastrointestinal tract (stool delay, abdominal distension, and sensation of extension), which may possibly be associated with its functional atony recorded also in immersion experiments

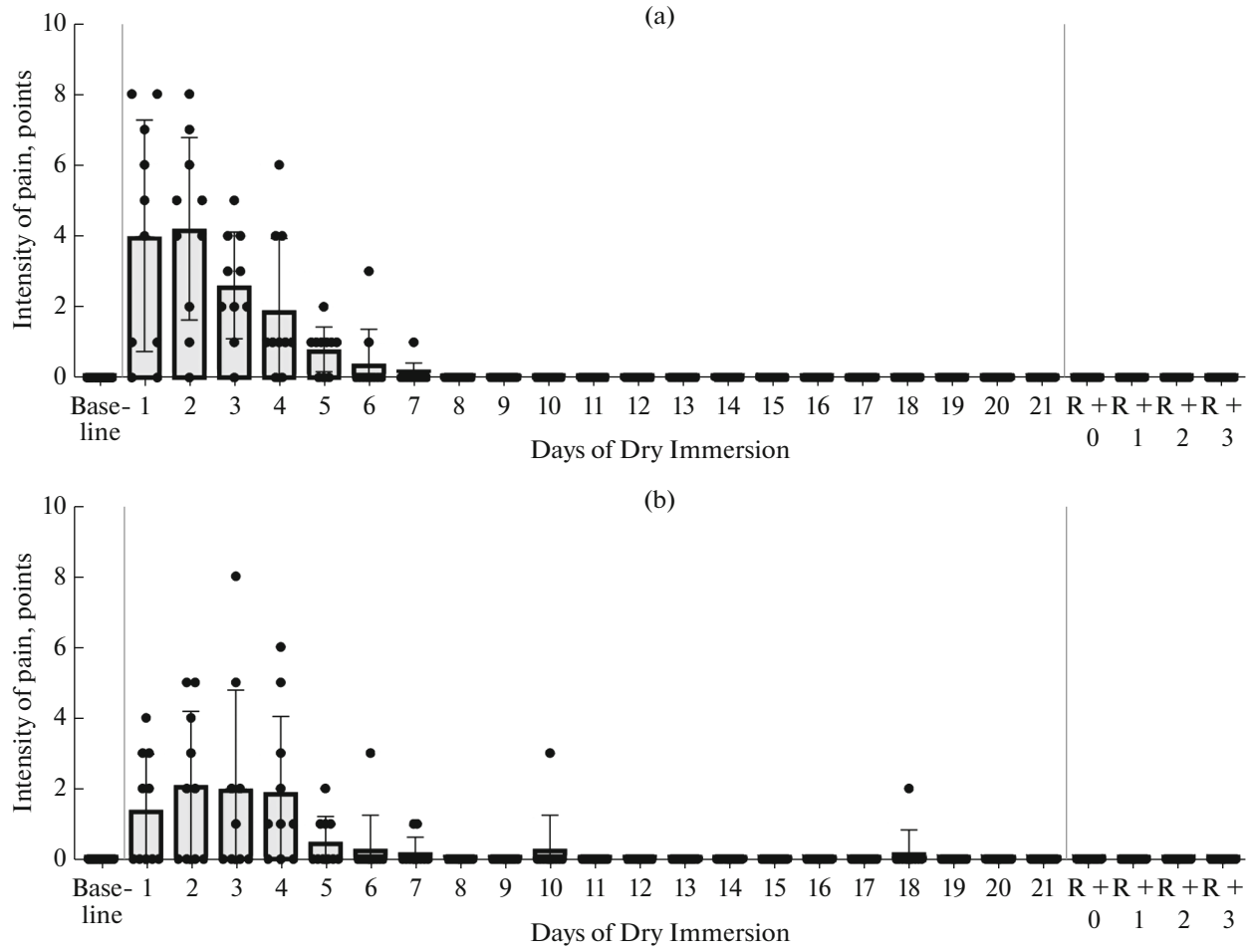

Fig. 6. Intensity of the (a) back and (b) abdominalpain during the immersion exposure as the mean per group values ($n = 10$). On the abscissa—the days of exposure, where the baseline means 24 h before the start of DI; R + 0 is the day of DI completion; (R + 1), (R + 2), and (R + 3) are days 1, 2 and 3 after the DI completion, respectively.

of shorter duration during the spaceflights of monkeys under the Bion program [16]. It should also be noted the emergence and resolution of the back pain syndrome during the first three days, which may also be associated with adaptation to the conditions of support unloading under microgravity. The indicated manifestations were no longer observed during five days of DI up to the DI completion.

Upon completion of DI, the state of health of the subjects remained satisfactory with complaints for sensations of unstable gait, postural instability within the first three days after DI, the swelling of the lower limbs during the first five to eight days after the exit from the immersion, and the signs of body asthenization during one and a half weeks. In addition, in the cases with the post-DI biopsy, the lower limbs were found to be swelled, mainly on the side of biopsy.

CONCLUSIONS

The performed study has shown the feasibility and safety of conducting long-duration immersion experiments. Data have also been accumulated to study the efficiency of applying artificial gravity and other countermeasures against negative effects of long-duration support and weight unloading on the human body.

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geted Increase of Resistance to Unfavorable Conditions) in the research section for visceral systems.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Each study participant provided a voluntary written informed consent signed after explanation of the potential risks and benefits, as well as the nature of the upcoming study.

CONFLICT OF INTEREST

The authors declare no obvious and potential conflicts of interest related to the publication of this article.

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