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# Physiological Effects of Microgravity & Dry Immersion Model

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**ABSTRACT:** One of the most popular ground models of microgravity is dry immersion (DI). DI quickly and precisely mimics the majority of the physiological consequences of brief spaceflights. The model mimics aspects of space travel like lack of support, mechanical and axial unloading, and idleness. The current publication compiles the findings of physiological research done starting at the time the model was created. In this overview, the effects of DI on the neuromuscular, sensory-motor, cardiorespiratory, digestive, excretory, and immunological systems, as well as on metabolism and hemodynamics, are discussed. These effects can last anywhere from a few hours to 56 days. Practically every alteration that occurs in the bodily systems when exposed to microgravity is replicated by DI. This work provides a summary of the countless publications by Russian researchers that, until recently, were mostly unavailable to scientists from other nations. With the use of these data, DI was proven to be a reliable ground-based model for simulating the physiological impacts of weightlessness. In comparison to previous ground-based microgravity models, this approach is favourable due to the size and rapidity of physiological changes during DI. In the framework of fundamental research and applications for Earth medicine, the model's existing and potential usefulness are described.

**KEYWORDS:** Support Withdrawal, Supportlessness, Gravity Unloading, Dry Immersion, Nervous System,

## I. INTRODUCTION

Weightlessness produces physical deconditioning, which is evidenced by alterations in the majority of physiological systems, according to observations made during space trips of various lengths (Gazenko et al., 1986; Kornilova, 1987; Kozlovskaya et al., 1988, 1990; Berger et al., 1992; Grigoriev and Egorov, 1992; Edgerton and Roy, 1996; Reschke et al., 1998; Clement et al., 2003). The investigation of experimental weightlessness models was prompted by the need to understand the mechanics behind the impact of hypogravitational forces on the human body. The most suitable environment for the physiological studies of hypogravity effects has been suggested to be immersion in a liquid analogous by density to human body tissues (Gazenko et al., 1972; Shulzhenko and Vill-Villiams, 1975); and antiorthostatic hypokinesia (Kakurin, 1968; Genin and Sorokin, 1969). Immersion was decided to be the optimum model for teaching working operations in weightlessness due to support withdrawal, local load reduction, and the proximity of biomechanical circumstances of motor activity organisation to those in weightlessness from the beginning of the space age. Early in the 1960s, researchers began examining the physiological consequences of immersion to see whether it might replicate the effects of weightlessness (Beckman et al., 1961; Graveline et al., 1961). Immersion has been found to mimic the effects of microgravity on the human body's cardiovascular and motor systems as well as other physiological processes (Ovsiyannikov, 1972; Schulzhenko and Vill-Villiams, 1976). The only drawbacks to using immersion as a useful model were pain and potential health hazards from prolonged skin contact with the liquid.

## II. THE NEUROMUSCULAR SYSTEM IMPACTS OF DI

Muscle force-velocity characteristics, as well as muscle tone and composition, dramatically decrease after exposure to DI. Even in very brief space flights, muscle effects, particularly a decrease in force-velocity properties, have been observed (Kakurin et al., 1971; Bryanov et al., 1976; Kozlovskaya et al., 1984, 1988; Bachl et al., 1992); however, their

metrics and temporal dynamics could only be thoroughly investigated under DI conditions. Space missions of the same duration and DI after 7 days have similar depths of alterations, according to comparisons (Grigorieva and Kozlovskaya, 1983; In addition to describing these occurrences, DI trials helped researchers better understand the causes of the up to 30% loss in the force-velocity characteristics of skeletal muscles, which cannot be attributed to muscle atrophy due to significantly longer exposure intervals. Later investigations of the shin muscles' evoked and voluntary maximum contraction (MVC) strength supported this hypothesis (Koryak, 1998, 1999, 2001). According to the study's findings, MVC amplitude declines uniformly following four months of HDBR, seven days of DI, and seven days of spaceflight. However, there was a negligible loss in the amplitude of evoked responses, indicating that the decreased intensity of central efferent command was what produced the reduction in muscle force-velocity characteristics (Koryak, 1998; Koryak, 2001). A flexor posture, which indicates a reduction in the extensor muscle activity necessary to maintain upright posture on Earth, is one of the initial reactions to weightlessness (Thornton, 1987; Reschke et al., 1998; Kozlovskaya, 2007). In reality, neurological examinations of the first space expedition crew members conducted soon after short-term space travels indicated severe extensor atonia (Bryanov et al., 1976). Studies on the transverse stiffness of the shin muscles following seven-day space journeys found that on the second day after landing, the muscular tone in the m. soleus and m. gastrocnemius was reduced by 15-20%. (Kozlovskaya et al., 1988). This phenomenon was thoroughly investigated in ground-based DI experiments, which showed that during the first six hours of exposure, the transverse stiffness of all three heads of the shin extensor—the medial and lateral m. gastrocnemius and, most prominently, the m. soleus—rapidly decreased (up to 40–50%). (Gevlich et al., 1983; Kozlovskaya et al., 1988; Miller et al., 2004, 2005, 2010). After a 7-day DI, it was also shown that the soleus muscle fibres had less transverse stiffness (Ogneva et al., 2011). Studies of the m. tibialis anterior shin flexor's transverse stiffness under DI circumstances failed to detect any appreciable modifications (Gevlich et al., 1983; Kozlovskaya et al., 1988; Miller et al., 2010). Kirenskaya et al. proposed that the loss in muscle tone was reflexive in character and that it was related to changes in the activity of the motor units (1986). This was supported by research on the motor units' (MUs') recruitment order during a task requiring minimal plantar flexion (10–12% of maximum voluntary contraction) after 7 days of DI and 120 days of HDBR (Kirenskaya et al., 1986; Khristova et al., 1988; Kozlovskaya et al., 1988). The findings of these investigations enabled us to draw the conclusion that support unloading alters the recruitment order of the shin extensor MUs by inhibiting the recruitment of tiny (tonic) MUs and facilitating the recruitment of big (phasic) ones. Later, in investigations of DI of various durations, this suggestion was also supported (Shigueva et al., 2015b). It is important to note that disclosed phenomena suggest that the recruitment order predicted by Henneman's law of the MUs is inverted in microgravity. The size principle, or classic Henneman's law, asserts that motor units are recruited in order of size while under stress. This really implies that slower, lower-force, more fatigue-resistant muscle fibres are recruited before faster, higher-force, less fatigue-resistant muscle fibres (Henneman et al., 1965). However, during DI, the recruitment order is not only determined by motoneuron size. An extensive programme of muscle morphology investigations has been carried out under DI circumstances in tandem with the neurophysiological study. After three days and seven days of DI, both slow and fast muscle fibre sizes had shrunk by 5-9% and 15–18%, respectively (Shenkman et al., 1999; Shenkman, 2016; Shenkman et al., 2017). For slow and fast fibre types, respectively, the corresponding changes after 60 days of HDBR were 14.2 and 12.4%. (Shenkman et al., 2004a). Therefore, the extent of the muscle fibres' size loss under short-term DI circumstances was comparable to that under long-term HDBR settings. This fact shows how crucial a part support withdrawal played in the development of hypogravitational muscular atrophy. It is significant to note that several academic studies have addressed the idea of support-dependent regulation of atrophic processes (De-Doncker et al., 2000). However, direct human trials with activation of the support input did not prove this theory. Although these alterations were not as noticeable in HDBR, Oganov et al. (1980) initially showed that the ratio of fast to slow myosin forms shifted in favour of the fast forms under circumstances of gravity unloading (Ilyina-Kakueva et al., 1979; Kuznetsov and Stepantsov, 1989). After three days of DI, more recent experiments carried out under the tight guidelines of maintaining individuals' supine positions revealed considerable atrophy (up to 10%) of type I muscle fibres and a rise in the amount of hybrid, type I/II muscle fibres (Demangel et al., 2013). The early phases of gravity unloading are accompanied by alterations in muscle signalling responses, according to molecular research (Vilchinskaya et al., 2015, 2016). In conclusion, DI has the following neuromuscular effects: reduction in muscle force-velocity characteristics; reduction in extensor muscle tone; suppression of small MU recruitment and facilitation of big MU recruitment; and reduction in the size of both slow and fast kinds of muscle fibres. Gravitational motor physiology is a new area of study in motor physiology that was developed as a result of the DI investigations. Gravity has a significant impact on the motor system, according to studies of its segments and functions at the cellular and systemic levels. It mostly has an impact on the effector system or muscles. Scientists have proposed that gravity is a component that impacts the development of the tonic postural system based on evidence from cell and neurophysiological research. This system, which detects the presence or absence of gravity, is activated by the deep skin sensitivity represented by

groups of Fatter-Paccini bodies (Otelin et al., 1976). Support withdrawal is what drives the abrupt development of both cellular and systemic alterations in DI because there are no other direct afferent changes. The impact of mechanical stimulation of the single support zones in locomotor regimens was examined in order to corroborate the trigger role of support afferentation in the modulation of the structural-functional features of the tonic muscle system. The Compensator of Support Unloading (CSU), which was jointly developed by IBMP, "Zvezda," and "VIT," stimulated subjects by applying alternating pressure of 0.5 kg/cm<sup>2</sup> (40 kPa) to the support zones of the soles (the heel and metatarsal areas). The findings of these studies supported the idea that support afferentation serves as the system's trigger in the postural tonic control system. Participants who received mechanical stimulation of the soles support zones during DI exposure did not experience the aforementioned alterations in their leg muscle functioning (Kozlovskaya et al., 2007a,b). Only on the sixth day of DI did a decrease in transverse stiffness in the m. soleus in this group reach significance; signs of hyperreflexia, changes in MU recruitment order, and decreases in EMG amplitude at rest and maximal isokinetic force of the m. triceps surae, however, were completely unreported (Grigoriev et al., 2004; Khusnutdinova et al., 2004; Miller et al. Kozlovskaya et al., 2007a,b; Shigueva et al., 2015a; Zakirova et al., 2015; Natreba et al., 2004, 2005, 2006). Similar effects of mechanical stimulation of the soles support zones were seen in the architecture of the muscular system: the number of fibres containing slow isoforms of heavy myosin chains did not decline, nor did myofibrils' sensitivity to free calcium ions, which is typically seen under conditions of gravitational unloading (Grigoriev et al., 2004). The method of artificial support stimulation was proposed to be incorporated into the space travel countermeasure system in order to combat the early, acute motor system modifications that occur in weightlessness as a natural outcome of the results outlined above. As a result, the "CSU" gadget, made by IBMP and "Zvezda," which is used to mechanically stimulate the soles support zones, was upgraded to meet ISS specifications and sent to the space station at the end of 2017.

### III. DI & THE SENSORY-MOTOR SYSTEM

The sensory-motor control systems are significantly impacted when unloaded, according to the DI investigations. First, there is a decline in movement control precision (Repin, 1981; Kreidich et al., 1982; Grigorieva and Kozlovskaya, 1985; Kirenskaya et al., 1985; Sosnina et al., 2016). It has also been demonstrated that the systems of posture and locomotion control suffer significantly, and that the cerebral structure of voluntary movements is altered (Kirenskaya et al., 2006; Tomilovskaya et al., 2008). (Melnik et al., 2006; Shpakov et al., 2008; Sayenko et al., 2016; Amirova et al., 2017). Studies of brain activity in the resting state also indicated modifications comparable to those attained during a true space mission, demonstrating that support withdrawal is the primary factor contributing to changes in brain activity and a loss in corticospinal tract function in weightlessness (Kuznetsova et al., 2015; Lazarev et al., 2018). It's interesting to note that support stimulation in DI circumstances also reversed these alterations, but less completely than peripheral ones (Kozlovskaya et al., 2007a,b). Despite the absence of any direct impact on the vestibular system, DI circumstances nevertheless profoundly alter visual-manual tracking and vestibular function (Repin, 1981; Kreidich et al., 1982; Barmin et al., 1983; Kornilova et al., 2004, 2008, 2011a,b, 2013, 2016; Zbova et al., 2008). The thresholds of the oculographic response to galvanic stimulation reduced to 0.68-0.73 mA on the second day after the seven-day DI in contrast to 0.92-1.05 mA before to the DI, indicating a dramatic increase in the sensitivity to vestibular signals (Repin, 1981). Similar results were seen in DI tests carried out on monkeys (Eron et al., 2000; Badakva et al., 2007). It's important to note that throughout DI there were no reports of motion sickness (Tomilovskaya, 2013b). The H-reflex system's sensitivity to proprioceptive signals was also altered as a result of exposure to DI, as shown by a decrease in the soleus H-reflex thresholds and an increase in relative H-reflex amplitudes (Kozlovskaya et al., 2007a; Saenko, 2007; Zakirova et al., 2015). Motion sickness was not seen during DI, as was previously indicated (Tomilovskaya, 2013b). The authors hypothesised that this may be caused by the individuals' largely stationary condition. In order to test this, researchers started looking at a different kind of water immersion called "suit immersion" (SI), which was created by IBMP experts towards the end of the 1980s (Genin et al., 1988a,b). SI differs from DI by excluding rigorous hypokinesia and maintaining a vertical position. SI employed a thin-walled wetsuit called "Forel" (or "Trout" in Russian) coupled with an inflated neck cushion to induce postural, vestibular, and operational demands directly during immersion (Genin et al., 1988a,b; Larina et al., 1999; Larina and Lakota, 2000). While the body positions for DI and SI are different (supine vs. vertical, respectively), it has been demonstrated that hemodynamics and water-salt exchange parameters are comparable (Genin et al., 1988a,b; Larina et al., 1999). However, in the early stages of SI, the emergence of vestibulo-autonomic syndrome—a condition marked by the feeling of body and head rotations—was discovered (Genin et al., 1988b). Additionally, during SI, a wide range of delusions up to a temporary loss of body orientation awareness were seen. After SI, reduced postural control, increased EMG cost of common motor activities, decreased physical and operator capacity, and decreased passive orthostatic probe tolerance were also noted (Kreidich

et al., 2007). In conclusion, the consequences of DI on the sensory-motor system include: Decline in descending regulation of voluntary movements, Decline in movement control accuracy, Increased vestibular sensitivity, decreased visual tracking precision, and increased soleus H-reflex excitability.

#### IV. THE CARDIORESPIRATORY SYSTEM & DI

Studies on respiratory function have revealed modifications in the voluntary control of breathing as well as changes in the thoracic-abdominal ratio, larger inspiratory and lower expiratory reserve volumes, and increased respiratory resistance (Dyachenko et al., 2010; Mikhailovskaya et al., 2011; Popova et al., 2011). Additionally, significant breathing-related heart rate changes have been seen, along with increased amplitude of breathing movements with lower frequency (Semenov et al., 2011). Additionally, after 5 days of DI, a large rise in the oxidative stress indicators such as expired amines, particularly butylamine, 2-cyanacetamide, certain aldehydes, polyols, phenol, phenylacetylene, ketones, and butyl acetate, as well as a considerable decline in fatty acids, have been seen (Mardanov et al., 2011). The aforementioned changes point to changes in metabolism and a deterioration of the antioxidant system. Studies of cardiovascular system changes in DI have revealed the subsequent involvement of electrical (increase in QRS complex amplitude) and then - energy metabolic (decrease in heart rate and changes to the water-electrolyte balance) processes changes in the myocardium; the most notable changes were observed on the fifth day of DI (Ivanov et al., 2011). Additionally, it seems that sympathetic control of the autonomic system is shifting. Even exposure to DI for a short amount of time (7 h) reduces orthostatic tolerance, and when the immersion time is extended, a greater percentage of subjects develop orthostatic hypotension (Iwase et al., 2000). After DI of various durations, all trials showed a rise in heart rate during vertical standing (Navasiolava et al., 2011a,b). Recent research following a 3-day DI period revealed decreased systolic blood pressure, stroke volume, and baroreflex sensitivity, as well as marked tachycardia during the LBNP tilt test (De Abreu et al., 2017). In this study, the time required for orthostatic tolerance decreased from 27 to 9 minutes after DI, and 9 out of 12 participants failed the test. Nine out of twelve participants passed the test at the level of 30 mmHg, while the control study reached 60 mmHg. Only 1 individual out of 12 obtained the LBNP level of 30 mmHg after DI exposure (De Abreu et al., 2017). The correlation between variations in the water-electrolyte balance and cardiovascular responses revealed variations in the electrophysiological propagation of myocardial excitation and an increase in the variability of naturally occurring tiny oscillations of the heart's electric potential (Larina et al., 2011). The brain natriuretic peptide BNP, which is produced by cardiomyocytes in response to stretching following a rise in ventricular pressure, as well as inactive NTproBNP secreted in an equimolar ratio, increased at the same time. The authors contend that the degree of heart deconditioning during DI is indicated by the elevated level of NTproBNP during the recovery phase after DI. The hypothesis of deconditioning-induced increase in heart load during recovery is supported by the observed intense tachycardia during orthostasis after DI, as well as the observed changes in the electrophysiological characteristics of the myocardium and hypovolemia (one of the factors contributing to the development of the cardiovascular deconditioning under microgravity) during DI. Weight loss, a quick loss of fluid and salt, and a rise in the amount of free cortisol in the urine were all seen within the first 24 hours. The variations in the water-electrolyte balance might lead to changes in metabolism and energy levels, which would call for the activation of the appropriate regulatory systems. The inclusion of the central regulation mechanisms in the adaptation processes was an appropriate response intended to compensate for the primary changes in the water-electrolyte balance and hemodynamics, as evidenced by the significant (more than twofold) growth of the centralization index at the conclusion of the experiment. Within the first 24 hours of DI, the alterations were visible, and they continued to show up over the course of the subsequent days of the trial. The myocardium's electrophysiology and autonomic regulation steadily changed during the experiment, reaching their peak at the conclusion of the seventh day of DI. As a result, it has been demonstrated that the structures controlling metabolic processes and, maybe, higher autonomic centres, from the molecular level to the systemic level, may be engaged in the cardiorespiratory response that takes place during the first 24 hours after DI. Further study is necessary in light of the myocardial excitation changes that were observed (Larina et al., 2011). In conclusion, increased respiratory resistance, increased abdominal component during breathing, weakened antioxidant system, increased amplitude of the QRS complex, decreased heart rate, orthostatic hypotension, altered water-electrolyte balance, and changes in cardiovascular responses are all effects of DI on the cardiorespiratory system.

#### OTHER CHANGES

Additionally, exposure to DI has been linked to endothelial dysfunction, including a rise in endothelial microparticles that circulate in the blood. In the course of DI, the linear blood flow velocity along major arteries and low extremity veins slows down, according to ultrasound study of peripheral hemodynamics (Moreva, 2008). During the 5-day DI, it

was also observed that the tissue perfusion intensity was raised and there were more capillaries in the upper extremities (Suvorov et al., 2017). However, other writers found that the jugular vein, thyroid volume, portal vein, and middle cerebral vein all increased within the first two hours after DI (Arbeille et al., 2017). However, internal carotid and vertebral arteries conductance dramatically decreased on the second and third day after DI, contrary to findings from a previous study that found no changes in blood flow in either cerebral artery (Ogoh). It has also been demonstrated that DI has a considerable impact on the blood flow to active muscles. Following DI exposure, the peak bloodstream in the calf muscles drops by 7–20% but post-contraction hyperemia substantially rises (Vinogradova et al., 2002b). It was claimed that exposure to DI increased the contemporaneous associations between local working hyperemia and central vasoconstrictive effects intended to maintain circulatory homeostasis in examinations of the blood flow of the tibia done under physically taxing settings (Stoida et al., 1998). Alterations in energy and metabolism following a 7-day DI were also accompanied by changes in cortisol, triglycerides, insulin, and inorganic phosphate levels in blood plasma, as well as a reduction in creatine phosphokinase activity (Buravkova et al., 2003). However, under the circumstances of local static muscular action, no modifications in metabolic reflex modulation of hemodynamic parameters were noted (Bravy et al., 2008). The following are a few examples of how DI affects hemodynamics: faulty endothelial function, Blood supply to the muscles in the lower extremities is reduced due to a decrease in the linear velocity of blood flow via the major arteries and low extremity veins.

Studies on the kidneys' excretory system along with the traditional rise in diuresis have shown an increase in protein and glucose excretion, albeit not to physiologically abnormal levels (Vorontsov et al., 2011, 2014). There were no changes in tubular reabsorption or glomerular filtration (Nesterovskaya et al., 2008). The impedance measurement also showed that the volume of circulating plasma, extracellular fluid, and total body fluid had decreased concurrently (Larina et al., 2008; Noskov et al., 2011). According to other research, exposure to DI results in a quick loss of fluid and salt, which raises the Na/K ratio in urine. The concomitant body weight loss is brought on by a drop in hydration. Only on the first day of DI did the amount of free cortisol in urine increase; this might be a response to the new circumstances. On the first day of DI, the most obvious alterations were seen. A new level of water-electrolyte equilibrium is developed during the next few days. It was clear that the primary fluid redistribution had been finished by days 3 and 7 since there were no changes in the levels of renin or aldosterone, and the water-electrolyte balance had stabilised. The increased excretion of water but not electrolytes during DI is characterised by a reduction in urine osmolality, which demonstrates that the regulatory systems consider the increased water consumption during DI to be excessive. Additionally, this shows that the kidneys' ability to concentrate has diminished (Larina et al., 2011). Studies on the digestive system have shown evidence of plethora in the abdominal venous system and a slowing of the hepatic venous flow (Solovieva et al., 2016). Pepsinogen, pancreatic amylase, bilirubin total (owing to its unconjugated portion), insulin, and C-peptide were among the compounds whose blood levels were elevated. According to the results of the <sup>13</sup>C-methacetin breath test, the rate of <sup>13</sup>C-methacetin inactivation has slowed and the hepatic metabolic capacity has decreased (Solovieva et al., 2016). Reduced rates of methacetin inactivation and metabolism during immersion could be primarily attributed to a slower assimilation of the preparation and a decrease in the venous blood flow of the liver, as evidenced by the study of liquid food evacuation during immersion, which revealed that its rate did not change significantly. Unconjugated bilirubin's increase in blood concentration may be explained by a decrease in the liver's ability to inactivate harmful compounds during immersion settings, which represents a loss in the liver's metabolic capacity. Additional research has shown that the main factor inhibiting gastrointestinal evacuatory activity in DI is the stability of liquid evacuation from the stomach and acceleration of the chymus transit along the small intestine (Goncharova, 2009; ). The enhanced gastrointestinal electrical activity closely resembled the alterations brought on by caffeine stimulation, prolonged bed rest, or space travel, and may be connected to the increased gastric secretion and raised gut tone in fasting test individuals (Sedova, 2012). The frequency of staphylococcus, yeast microflora, and Gram-negative Bacillus has increased, while faecal lactoflora has significantly decreased and developed variations in the microbial landscape have also been noted. In conclusion, the consequences of DI on the renal and digestive systems include: A decrease in total body water, extracellular fluid volume, and circulating plasma volume, fast salt and fluid loss-related changes, modifications to the abdominal and hepatic venous systems, reduction in the liver's ability to metabolically process digestion-related evacuatory activity inhibition, dysbiotic alterations.

Blood and urine protein content variations were discovered by biochemical assays (Trifonova et al., 2010; Pastushkova et al., 2011; Vorontsov et al., 2014). In particular, there is an increase in insulin and serum NT-proBNP levels, which is a proxy measure for brain natriuretic peptide, and a decrease in the activity of the muscle and cardiac constellation ferments. There is also an increase in the derivatives of lipid metabolism, an increase in erythrocyte concentration, and a decrease in glucose tolerance and hypercholesterolemia (Ivanova et al., 2008; Markin et al., 2008; Navasiolava et al.,

2011c; Coupe et al., 2013; Pastushkova et al., 2014; De Abreu et al., 2017). The examination of the blood plasma proteome was first done in the current wave of DI investigations (Pastushkova et al., 2012). Fragments of complement system proteins C3 and C4, high-molecular kininogen, and fibrinogen all showed development of peak regions on DI days 2 and 3. Changes in the individuals' motor activity can be linked to significant increases in the peak area of apolipoprotein CI (reduced form with segregated threonine and proline), C4 complement system enzymes, and fibrinogen on the first day following the experiment. Although a propensity to decrease in antithrombin III activity (ATIII), protein C, and plasminogen was seen following exposure to 7-day DI, analysis of the hemostasis system did not indicate any significant abnormalities (Kuzichkin et al., 2010). Studies on lipid peroxidation rates and antioxidant defence did not find any evidence of alterations in these parameters after DI adaption. The increase of lipoperoxidation and a decline in the functional activity of the antioxidant defence system, however, show that the restoration to normal activity following DI was linked to the emergence of a major stress reaction (Zhuravleva et al., 2012). In conclusion, alterations in the concentration of protein and lipid derivatives are among the consequences of DI on the biochemical makeup of blood.

Given that the skeletal system is largely inert and alterations after a relatively brief exposure to DI, such as 7 days, are not predicted, it is not unexpected that there are not many research focused on bone marker changes in DI. In the Kopp trial, there were no effects of 7-day DI on bone production or an increase in bone resorption (2008). However, a recent study using a 3-day DI period found that the bone formation indicators total procollagen type I N- and C-terminal propetides and osteoprotegerin had significantly decreased (Linossier et al., 2017).

Studies on the impact of DI on innate and acquired immunity have shown a considerable degree of heterogeneity during DI (Berendeeva et al., 2011; Ponomarev et al., 2013). Congenital immunity abnormalities that were seen after a 5-day DI and throughout recovery point to a greater risk of infectious disorders, such as those brought on by modifications to the normal microbiota, which ordinarily has no pathogenic consequences (Ponomarev et al., 2013). Immunoglobulin (sIgA, IgA, and IgM) levels changed in the gingival fluid, which may indicate a periodontal tissue inflammatory process. Additionally, periodontopathogenic bacteria of the *Prevotella intermedia*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis* types were found in the oral cavity (Nosovsky et al., 2017). Triiodothyronine and cortisol levels during DI were found to be lower, whereas prolactin and thyroxine concentrations were found to be higher, according to research on the neuroendocrine control of DI (Nichiporuk et al., 2011; De Abreu et al., 2017). On day 5 of DI, non-anxious and extraverted individuals showed the highest frequency of immune parameter changes among all participants (Nichiporuk et al., 2011).

After 2.5 months of exposure to short- and long-duration space travel, the body's core temperature gradually rises by 1°C, which was thought to be related to elevated levels of the important anti-inflammatory protein interleukin-1 receptor antagonist (Stahn et al., 2017). Sadly, there are no published research on thermoregulation during DI, with the exception of one article stating that there were no noticeable changes in body temperature on day 3 of DI (De Abreu et al., 2017).

Recent DI investigations looked into the possible causes of the back discomfort that is frequently reported both on Earth and during the start of space missions. Almost all DI research subjects have back discomfort for the first couple of days (Rukavishnikov et al., 2014a,b, 2015, 2017a,b; Kozlovskaya et al., 2015; Treffel et al., 2017). Data from nine of the most recent DI trials at IBMP (2006-2018) were retrospectively analysed, and the results showed that 70 out of 87 volunteers felt back discomfort, with severity ranging from 4-5 to 9-10 points on a ten-mark subjective scale. (Rukavishnikov and colleagues, 2014b) The results also showed a reduction in the stiffness of the back extensor transverse muscles (Rukavishnikov et al., 2017a,b, 2018). The neck, thoracic, and lumbar regions of the spine's vertebral column length rose dramatically, according to data acquired during magnetic resonance imaging (MRI) (Kozlovskaya et al., 2015; ). In addition, the thoracic and lumbar lordosis, as well as the neck and thoracic kyphosis, were flattened at the same time as the height of the intervertebral discs rose and the discs showed signs of swelling. At the level of L4-L5, MRI study of the quadratus lumborum, multifidus, and erector spinae indicated a reduced cross sectional area of mm (Rukavishnikov et al., 2017b). It has been suggested that each of these elements, including intervertebral disc enlargement, spine lengthening, effect on the spine's yellow ligament, and atrophy of the back muscles, might cause hypogravitational back discomfort (Treffel et al., 2016b; Rukavishnikov et al., 2017b).

## V. DI MODEL & THE SPACE FLIGHT COUNTERMEASURE SYSTEM

As was mentioned at the start of this article, DI was created to look closely at the mechanics underlying the impacts of microgravity on the human body. It makes sense that DI has played a key role in the creation of a system of protective measures against the harmful physiological consequences of space travel. The background and scope of research using the DI model that resulted in testing, comparisons, and optimization of several countermeasure techniques need

discussion in a separate review. The main findings that led to the creation of the current countermeasure programmes for use on board the International Space Station are the subject of this section. Studies on the short arm centrifuge were conducted in the late 1970s (Shulzhenko and Vill-Villiams, ). The experiments conducted under 13- and 56-day DI conditions have demonstrated that application of short arm centrifuge (SAC) 0,5-1 Gz rotations during DI was followed by maintenance of the cardiovascular system's backup capabilities and external respiration, as well as an increase in resistance to 5 min + 3 Gz rotations in the "head-pelvis" direction. In this instance, the countermeasure effects were boosted by combining SAC sessions with water-salt supplements and 2340 kg of physical loads (hand and leg workouts with expanders) (Shulzhenko and Vill-Villiams, 1976; Kokova, 1983). Later, a number of DI studies were conducted with the goal of analysing the outcomes of various countermeasure methods. For example, Studies on the effectiveness of bladderless antigravity suits in maintaining orthostatic tolerance have been conducted under 7-day DI (Shulzhenko et al., 1983b; Vil-Villiams et al., 1996). The 20-minute tilt test at 70 degrees caused less fluctuations in blood pressure while wearing the suit "Centaur" than it did without. The minimum stroke volume, pulse pressure, and maximum heart rate were considerably increased. As a result, the authors found that the anti-G suit may be utilised after space travels and helps to boost orthostatic tolerance using the DI model. Early DI research showed that applying a 25 mm Hg negative pressure to the lower body (LBNP) might prevent the loss of orthostatic tolerance. The vascular bed's capacity was improved by the water-salt additions, LBNP, and physical exercise, which helped patients with DI retain bodily fluids, sodium, and chloride ( Shulzhenko, 1979). The length of the break in between hip occlusion sessions had a significant impact on the hip occlusion cuffs' ability to avoid orthostatic intolerance after an 18-hour immersion; the strongest benefit was seen with a 1-min gap (pressure comprised of 25 mm Hg, training session length was 7 h) (Pestov, 1974). The mechanisms of the countermeasure effects of occlusion cuffs revealed in DI experiments are based on the pooling of blood in vessels of the lower extremities as a result of the occlusion of superficial veins and, as a result, the reduction of blood volume that is shifted in a cranial direction. The effectiveness of the separate and combined effects of SAC and veloergometry have been investigated over a 28-day DI trial. According to the study, veloergometry training at a pace of 600 kg/min (10 min of training followed by 10 min of rest) twice daily for 60 minutes resulted in an increase in cardiac output and a decrease in total peripheral resistance. The countermeasure effect was reinforced by veloergometry training combined with SAC (0,8-1,9 Hz twice daily for 60 minutes each session), as measured by cardio-vascular system parameters (Vil-Villiams and Shulzhenko, 1980; Vil-Villiams, 1994). In a series of DI studies, the effects of low- and high-frequency electrostimulation of the leg muscles have been examined (Koryak et al., 2008). These findings showed that low frequency stimulation, especially when applied often and with a high stimulation intensity, can prevent the loss of force-velocity characteristics in the m. triceps surae (more than 13 V). A comparison of the lower limb muscles' response to low-frequency stimulation with high-frequency stimulation over the course of seven days DI shown that low-frequency stimulation is more effective for preventing motor dysfunctions (Koryak et al., 2008; Kozlovskaya, 2008). Positive effects of neuromuscular electrical stimulation during these studies were similarly connected to right heart unloading and were seen in HD ECG parameters and an increase in the "myocardium" index (Eshmanova et al., 2009). High frequency electromyostimulation was used to prevent elevation in pepsinogen, pancreatic amylase, and bilirubin, mostly in its unconjugated fraction, as well as an increase in insulin secretion. It had no effect on the ultrasound patterns of the hemodynamic rearrangement in the liver or abdomen, though (Solovieva et al., 2016). The effects of mechanical stimulation of the plantar mechanoreceptors during locomotor regimens were the focus of a broad programme of DI investigations. These investigations supported the theory that the support (weight bearing) afferentation served as a catalyst for the development of the hypogravitational motor condition (Grigoriev et al., 2004). The negative effects of gravitational unloading on sensory-motor and neuromuscular systems were eliminated by applying plantar mechanostimulation over the course of six 20-minute sessions per day (with stimulation frequency of 75 and 120 steps/min and pressure of 40 kPa). These effects included a decline in extensor muscle stiffness and a decrease in the maximal voluntary force; a significant decrease in the absolute force of the isometric contraction of single skinned muscle fibres; and a prominent (Popov et al., 2003). The rates of mechanical foot stimulation used in the experiment did not modify the amount of energy used by the muscles, but they did moderate the amplitude of angular knee joint movements after 7 days of DI, according to investigations of the biomechanical properties of locomotions (Melnik et al., 2006). Additionally, using the support stimulation to minimise venous compliance rise and orthostatic intolerance was successful (Vinogradova et al., 2002a). The stimulation of the soles' support zones has been shown to have compensatory effects on the vestibular-visual system. The eye tracking parameters in the group of individuals without support stimulation showed significant omnidirectional deviations, but in the group of subjects with support stimulation, these parameters were close to the baseline values. The pursuit function of the eye was stabilised by support stimulation, making it less erratic. However, there was variation in how the participants responded to stimulation, suggesting that individual "moulding" of the strategies for enhancing eye pursuit performance is necessary (Kornilova et al., 2004). In the literature, there aren't

many facts on research of the effects of various pharmaceutical countermeasures using the DI model. No decrease in morning pain sensitivity, which is common under normal circumstances, has been observed in tests evaluating pain sensitivity under DI settings. When evaluating the pain threshold using the thermal algometry approach, an analgesic like ketorolac has no impact on pain sensitivity. The authors discovered that DI significantly changed the pharmacokinetics of ketorolac, causing an increase in the drug's rate of absorption and a decrease in both its relative bioavailability and blood retention duration. These findings suggest that, in comparison to 1G, space flight may require different pain management strategies (Baranov et al., 2015). 22 healthy participants' pharyngeal microbiota was examined in 7-day DI trials. Two probiotic medications were utilised for preventative pharyngeal dysbiosis: oral "lactobacterin dry" and local "lactobacterin immobilised on collagen." Oral probiotic administration was associated with an increase in pharyngeal opportunistic microorganisms that prevented intestinal microbiota from migrating there. Local probiotics, on the other hand, increased gastrointestinal dysbiosis while decreasing opportunistic microorganisms in the pharynx. It was determined that the most effective method of preventing pharyngeal dysbiosis during DI is the combination of topical and oral probiotics (Kryukov et al., 2007; Ilyin et al., 2008). The effects of sydnocarb [3-(beta-phenylisopropyl)-N-phenyl carbamoyl sydnimine] were examined in a different 7-DI investigation. Before and after the individuals were submerged in the water, they worked out on a bicycle ergometer. ECG, heart rate, minute breathing volume, oxygen uptake, carbon dioxide output, cardiac output, and oxygen pulse were all monitored while exercising. The oxygen consumption at maximal exertion significantly decreased in the placebo group of participants. During bicycle ergometry, those who received sydnocarb maintained normal oxygen intake. The medication maintained physical work capacity, increased effort per kilogramme of body weight, and enhanced cardiovascular function following DI exposure (Anashkin and Belyaev, 1982). Amlodipin (a slow calcium channel inhibitor) helped the coronary blood flow, which led to the drug's beneficial impact of reducing myocardial strain; nevertheless, it had a detrimental side-effect on orthostatic stability (Eshmanova et al., 2009). The "Penguin" axial loading suit was developed with active use of the DI model (Barer et al., 1998). Studies on people who exercised on a bicycle ergometer while wearing a Penguin suit have found higher EMG amplitude in the muscles of the lower extremities. The same tests showed that when individuals used Penguin to do the step loading veloergometric test, their heart rates and metabolic rates rose. Other DI investigations revealed that the "Penguin" suit was successful in reducing hypogravitational hyperreflexia, alterations in peripheral microcirculation, height gain, the onset of back discomfort and atonia in the back muscles, and a reduction in force-velocity properties (Barer et al., 1998; Shigueva et al., 2015b; Rukavishnikov et al., 2015; Suvorov et al., 2017).

## VI. DI MODEL'S & MORDERN MEDICINE

Beginning in the 1980s, clinical use was made of the data about the physiological effects of DI on several bodily systems. First, it was seen that DI had benefits on muscular relaxation, reducing skeletal muscle tone and curing spasticity (Kozlovskaya I. B. and Semenova K. A., unpublished observations). The DI has been used in the treatment of edoema, particularly intractable edoema brought on by cardiovascular causes, burns, liver cirrhosis, and renal illness. The benefits of 1.5-3 times diuresis increase after 4-6 h post-DI were maintained for 2 days in those with the aforementioned disorders (Yunusov et al., 1985; Ivanov and Bogomazov, 1988). In the 1990s, a number of trials used DI to treat hypertensive crises (Kirichenko et al., 1988; Evdokimova et al., 1989; Ivanov and Makarova, 1990). After 90 minutes of DI exposure, the results showed a strong and long-lasting hypotensive impact. Two distinct pathways led to the results, either (a) a reduction in the raised total peripheral vascular resistance (TPVR) with no changes in cardiac output, or (b) a reduction in the elevated cardiac output. Sanogenetic processes that improve blood circulation during hypertension were thought to be responsible for these hemodynamic improvements (Evdokimova et al., 1989). Recent research (Meigal et al., 2017) has shown that short-term, up to 6 h, DI sessions had a favourable impact on individuals with Parkinson's disease or parkinsonism. The score of Wein's assessment for autonomic disorders subscale I has fallen by 45%, and subscale II has decreased by 23%. Additionally, the choice reaction time has greatly increased. These results were also seen two weeks after the DI course. The DI is frequently used in paediatrics to regulate hemodynamics and stop cerebral edoema as part of rehabilitation regimens for preterm children. Children with central nervous system problems, such as prenatal encephalopathy and other perinatal pathologies, can also be treated by exposing them to DI (Kazanskaya, 2008; Khan et al., 2015). Due to its effectiveness in reducing hypertonus and hyperactivity as well as in reflex facilitation, the technique is also often employed in children receiving therapy for cerebral palsy (Yatsuk, 2002; Titarenko et al., 2015). In contrast to the detrimental effects of 3–7 days of DI on the immune system (see above), the beneficial benefits of 40–50 minutes of DI on immunological parameters were found. The incidence and severity of newborn infectious and inflammatory disorders have been shown to decrease along with the enhanced normalisation of the functional activity of T-helpers and the decreased sticky characteristics of

lymphocytes (Chasha et al., 2008). Joint Russian-Austrian investigations revealed that DI has a diagnostic utility in the early diagnosis of neurological diseases under normal circumstances. Some healthy volunteers displayed neurological symptoms (such as cerebellar disintegration, decrease in peripheral nerve function, posterior tract, as well as pyramid and extrapyramidal systems) after 24, 48, and 72 hours of DI (Gerstenbrand and Kozlovskaya, 1990; Berger et al., 2001). The central nervous system's strong flexibility usually compensates for these abnormalities, but this phenomena may be explained by the fact that certain persons have latent neurological deficiencies (congenital or acquired as a result of traumas, infections, etc.). By altering the support and proprioceptive afferent intake, DI creates sensory conflict that eliminates compensatory mechanisms that are ineffectual under the new circumstances, exposing concealed neurological abnormalities. DI was also utilised in sports medicine to help athletes recuperate from intense exercise because of its calming properties (Radzievskiy and Radziyevskaya, 2007). The use of DI is also medically contraindicated. Several specialists list myocardial infarction, severe cardiac arrhythmia, chronic respiratory conditions with pulmonary heart decompensation, thrombophlebitis, very shortness of breath at rest, acute inflammatory processes, and widespread skin lesions among them (Ivanov and Makarova, 1990). (Yatsuk, 2002). However, most of these factors are theoretical, with no published quantitative outcomes.

## VII. CONCLUSION

Many of the changes connected with spaceflight can be somewhat replicated by dry immersion. For some systems, DI can be used as a reliable ground-based model to simulate the physiological impacts of weightlessness. In comparison to previous ground-based microgravity models, this approach is favourable due to the size and rapidity of physiological changes during DI. The creation of countermeasure programmes for use in space, particularly passive countermeasures that don't demand a lot of the subjects' motor skills, is greatly aided by DI. DI could possibly have a variety of therapeutic uses that require more research.

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