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How is hematology involved in the era of aerospace medicine?: Systemic and hematological changes in the astronaut

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ABSTRACT

One of the most important successes of the human being in the last decades is the extent of their knowledge of space through research to keep the human body in microgravity during the spaceflight. In this article we review the literature on organic regions affected in an astronaut to continuous exposure that is involved, making a special emphasis on the cellular and molecular damage of their blood elements as there is the possibility of reproducing the effects of exposure to microgravity for evaluating the innate immune response and the condition of the bone marrow to study the neocytolysis (selective hemolysis of neocytes) and the presence of schistocytes and stomatocytes, occurring due to high levels of glutathione increases the rigidity of the erythrocyte membrane, which is favored by hidrostatic pressure changes, microviscosity and permeability, which may influence the transfer of oxygen. High concentrations of lactate contribute to an anaerobic condition, symptoms such as headache, nausea and malaise. In the process of readaptation to Earth occurs a stimulation of erythropoiesis aimed to maintain the optimal level of blood erythrocytes, necessary for the increased demand of oxygen in the tissues under the conditions of gravitation.

Key words: microgravity, spaceflight, neocytolysis.

La hematología en la era de la medicina aeroespacial: cambios hematológicos en los astronautas

RESUMEN

Uno de los éxitos más importantes del ser humano en las últimas décadas es la extensión de su conocimiento del espacio mediante las investigaciones realizadas para mantener al cuerpo humano en condiciones de microgravedad durante el vuelo espacial. En este artículo realizamos una revisión de la bibliografía acerca de las regiones orgánicas afectadas en un astronauta ante la exposición continua que experimenta y hacemos especial insistencia en el daño celular y molecular de sus elementos sanguíneos porque existe la posibilidad de reproducir los efectos de la exposición a la microgravedad para evaluar la respuesta inmunitaria innata y el estado de la médula ósea para estudiar la neocitólisis (hemólisis selectiva de neocitos) y la exis-

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tencia de esquistocitos y estomatocitos que se producen debido a altas concentraciones de glutatión que aumenta la rigidez de la membrana eritrocitaria, favorecida a su vez por cambios de presión hidrostática, microviscosidad y permeabilidad, que pueden influir en la transferencia de oxígeno. Las concentraciones elevadas de lactato contribuyen a un estado anaerobio, así como a cefalea, náuseas y malestar general. En el proceso de readaptación a la Tierra se estimula la eritropoyesis que está dirigida a mantener la concentración óptima de eritrocitos en la sangre, necesaria para incrementar la demanda de oxígeno en los tejidos en las condiciones de gravitación.

Palabras clave: medicina aeroespacial, astronautas, cambios hematológicos.

The organic effect of microgravity in humans

Human spaceflight has facilitated many key discoveries about our universe, as well as medical insight into human physiology. From all the forces that have a direct consequence on human health and that control everything in the cosmos, gravity has been a constant one throughout evolutionary history, at least, on Earth.[1,2] As a derivative presentation of gravitational force, weightlessness is the state in which a body having a certain weight is balanced by another force or remains in free-fall without feeling the effects of the atmosphere, equivalent to the situation faced by an astronaut aboard a spaceship. On the other hand, microgravity means that gravity is not absolutely zero, is only negligible.[3] Now we know that the two major factors that may influence astronaut's health in space environment are space radiation and weightlessness.[4]

Almost all systems in the human body are affected by gravity and weightlessness, and among these the cardiovascular system in particular is altered.[5] The human adaptive response to weightlessness encompasses numerous conditions that may affect the possibility of long-term flight missions, including space motion sickness, cardiovascular deconditioning due to reduced blood volume, and prolonged gastrointestinal transit time.[6] In fact, the biggest problem for space missions of several years in duration is the harmful effects of microgravity on the human body. Such reactions by the body might be appropriate for zero-gravity flight but are inappropriate in landing on the surface of any planet.[7] Also, aside from microgravity astronauts in the space environment are subjected to other factors such as cosmic radiation and altered magnetic fields.[8] Ionizing radiation in out-of Earth represents an environmental mutagen to which humans are daily exposed on Earth. Crewmembers of space mission are more exposed to it because the cosmic radiation field is different from that experienced on Earth.[9]

The physiology of microgravity has been studied extensively since the first human space flight of Yuri Gagarin in 1961.[5] During spaceflights, microgravity induces many adaptations within the human body that are similar to those that may occur with aging or some diseases, and all physiological systems are challenged.[1,7] Microgravity directly affects the vestibular, cardiovascular, musculoskeletal, hematologic and immune systems. It produces an effect of accelerated evolution in muscle atrophy caused by the least effort and the least blood supply, as well as progressively loss of bone density caused by demineralization which increases the susceptibility to nephrolithiasis. In fact, during spaceflight bone mineral is constantly being lost from the weight-bearing sites of the skeleton at an average of 2-3% per month, accompanied by increases in urine excretion of Ca^{2+} and hydroxyproline expressing the net bone loss at the tissue level.[6,7]

In space, the body has mass but not weight. Without gravity, blood supply to the legs is reduced. An astronaut does not walk as on Earth so that neuromuscular innervation to the legs is minimally used. Leg muscles do not have to bear the body's load or contract as much with the result that they atrophy, which is particularly true for postural muscles like soleus, but all leg muscles are affected. Astronauts in space lose about 1% of muscle a month and generally about 1.8-2% of bone during that same period.[10]

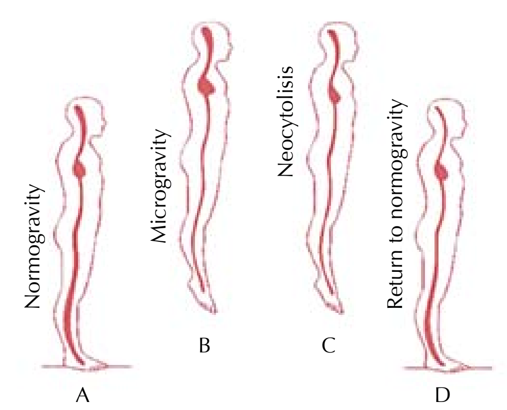

Figure 1. Effects of microgravity respect in upright position and changes in central blood pooling in space: Upon transition from normogravity (**A**) to microgravity (**B**) the blood of peripheral vascular space shifts to central space, causing central acute plethora, accompanied by peripheral vessel constriction. An adjustment is obtained by reduction of plasma volume and red blood cells mass through neocytolisis and erythropoietin reduction (**C**) over the first days of spaceflight. Then, upon return to normogravity (**D**), the normal redistribution of blood volume and the augmentation of blood fluid reduce the hematocrit (space anemia). Adapted from Charles et al, 1994.[14]

Hypergravity tends to exert hypertensive effects on circulation, while microgravity exposure relaxes the circulation. The increased thoracic blood volume and rapid rise in pulse pressure entering microgravity stimulate cardiopulmonary volume receptors and arterial baroreceptors together, which induces a cardiovascular depressor reflex, manifested initially by a fast bradycardia response.[5]

There are metabolic changes like weight, fluid and electrolyte loss. There could be certain endocrine disorders, such as sleep disturbances and disrupted circadian rhythm. Most astronauts experience problems with balance and orientation, fainting, damage in proprioception, and loss of cardiovascular functional capacity. Living in space for as little as 9 days accelerates problems of equilibrium on standing, walking and coordination to Earth. Re-adaptation to Earth after flights of 4-9 days began immediately on landing.[7,10]

The National Air and Space Agency (NASA) has reported that astronauts aboard the International Space Station exposed to prolonged to zero gravity for a mean 6 months have an increased incidence of papilledema. Also, astronauts in the zero gravity environment present on the International Space Station that have returned to Earth and have been found to have optic nerve head edema.[11] Also, it has been seen that during spaceflights or very soon after returning to the Earth, astronauts of the Apollo missions suffered from bacterial and viral infections, while latent viruses such as varicella zoster were reactivated.[2]

Patients with a disease on Earth can be described as living in a normal environment and having an abnormal physiology. In contrast, astronauts are people living with normal physiology but they live in the abnormal environment called space, which causes physiological changes that require the attention of physicians and scientists.[12]

Searching for a model of spaceflight in Earth

There has been slow progress in space research because of the small numbers of astronauts and the operational difficulties of conducting research in microgravity. However, lying continuously in head-down bed rest (HDBR) at -6 ºC is used as the model of choice. Physiological changes in space and HDBR are similar; as HDBR induces the spectrum of adaptations associated with microgravity such as a head-ward shift of fluids and precludes changes in posture.[10] In this position, the subjects experience a rapid decline in aerobic capacity due primarily to decreased circulating blood volume that occurs in response to the head-ward body fluid shift. During exposure to microgravity, gravitational blood pressure gradients are lost, and blood volume is redistributed towards the head. This may contribute to the early discomforts of space travel, such as the headaches, nausea, and malaise.[1]

Spaceflights and head-down bed rest are characterized by diminished cardiac function and mass. The initial trigger is the fluid shift from the lower to the upper body that results in upper body blood volume expansion. This stimulates central volume carotid, aortic and cardiac receptors inducing a transient increase in diuresis and natriuresis with sustained 2-4% reduction of body mass and 6-15% of plasma volume, which is followed by decreased heart size, cardiac filling, stroke volume, cardiac output, and aerobic capacity.

In healthy students immobilized in bed it has been seen that inactivity causes severe calcium and bone loss. Also, it has been hypothesized that astronauts would show similar bone and calcium loss in space, where without gravity their bodies would become virtually inactive.[10]

On the other hand, parabolic flight of an airplane is a unique opportunity that creates fast gravity transitions between normo- (1 Gz = 9.81 m/s^2), hyper- (1.8 Gz) and micro-gravity (0 Gz), with duration of 20 s.[5] The subjects fasten a seat belt maintain a sitting position and fix their upper and lower limbs during the flight. It has been seen that during acute microgravity induced by parabolic flight, cardiac output increases as much as 29% without increasing the mean arterial pressure and[13] despite a decrease in central venous pressure, even under the extreme gravitational challenges in the upright position.[5] Also, the antigravity slow muscles and high-oxidative fibers have more capillaries and receive adequate blood flow.[13]

Intervention of Hematology in Aerospace Medicine

The initial adaptation to space can be attributed to a redistribution of body fluids toward the head. The spatial position prior to launch in supine position with the legs raised above the thoracoabdominal coronal plane initiates a fluid movement that continues in the journey into orbit.[12]

Charles *et al* raised the representation of the central accumulation of blood in the space. In the transition from Earth to space in normal gravity to microgravity several peripheral vascular changes occur, favoring its collapse[14] because the weight of the blood at that time does not get the necessary force to maintain vascular permeability, and thus a central redistribution can be achieved where the blood volume has a less dependence in gravity, creating a pseudo hypervolemia in a normoxic environment, which triggers a series of events in where a fluid redistribution is achieved.[15] Baroreceptors of central vasculature, which acts through suppression of the renin-angiotensin-aldosterone system, leads to increase renal excretion of sodium and water, and a net reduction in plasma volume. Furthermore, there is a decreased blood flow that may be more pronounced in the lower limbs, with a potentially muscular atrophy, under microgravity conditions because of fluid shifts toward the upper body and due to the diminished venous return of blood to the heart.[13] It causes facial swelling, generating the "swollen face-bird leg syndrome".[12] Therefore, the fluid adjustment is obtained by reducing plasma volume and red cell mass through erythrolysis and the reduction of erythropoietin in the earliest days of space flight.[14] Subsequently, hemoconcentration is generated with an increase in hematocrit, which is favored by the rapid decrease in the erythrocyte count and selective hemolysis.[15] On the return to normal gravity it occurs again a redistribution of blood volume and an increase in blood flow to lower the hematocrit, causing "anemia of the space".[14,15] In fact, spaceship crewmembers lose around 15% of their red blood cell mass over the course of a few weeks.[6]

It has been seen that returning astronauts of spaceflight missions exhibited immediately after landing a strong increase of neutrophil granulocytes, and neutrophil chemotactic assays has showed a ten-fold decrease in the optimal dose-response after landing. However, phagocytosis and oxidative burst capacity of neutrophil granulocytes has been reported to be not significantly altered after a 5-days mission in space,[8] but T cell activation upon landing after spaceflight is significantly depressed.[16]

Microgravity and blood cells at molecular level

Microgravity is now considered one of the major causes of the severely immune cell dysfunction during space fight.[2,8,16] The changes of immune system during short- or long- duration of spaceflights include altered leukocyte distribution, altered serum cytokine levels, reduced functions of natural killer cell, granulocyte, and monocyte, reduced leukocyte proliferation following activation, decreased delayed-type hypersensitivity to recall antigens, and latent viral reactivation.[17-19]

Factors contributing to decreased lymphocyte numbers and function during and post-spaceflight include exposure to microgravity, stress and radiation.[4,16] Gravity-sensitive functions of T lymphocytes comprise cell cycle regulation, epigenetic regulation, chromatin regulation, expression profile of microRNA, cell motility, and regulation of apoptosis.[2] In fact, it has been shown that changes in gravity inhibited lymphocyte motility through type I collagen, whereas activated T cells cultured in hypergravity became earlier motile than cells cultured at normal gravity,[8] and cell apoptosis is increased by simulated microgravity. Also, radiation induces intracellular generation of reactive oxygen species, which can be lethal to several cell types in blood.[4] There is gradual decrease in the number of INF-γ-producing T cells and Cytomegalovirus- and Epstein-Barr virus-specific T cells. There is significant reduction of IL-17A, suggesting a weakened T helper as well as Th17 types of response. T cells exposed to microgravity have defects in early T cell activation, which is featured by decreased IL-2/IL-2 receptor expression, down-regulated NF-κB and protein kinase A activity. There is up-regulation of IL-18, which is associated with chronic inflammatory diseases, including atopic eczema, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome.[17]

Of the blood cell types, lymphocytes are the most sensitive to ionizing radiation exposure.[16] In peripheral blood lymphocytes, the expression of miRNAs involved in the DNA-damage response to γ-radiation is affected by modeled microgravity incubation during the repair time, enhancing the biological effects of ionizing radiation.[9]

Circulating monocytes are also increased in number. However, the phagocytic capacity and oxidative burst potential of neutrophils and monocytes are reduced. Also, the matured B cell fraction is significantly suppressed in rodents exposed to spaceflight, and it is accompanied by an increase in the natural killer cell fraction.[6]

Under simulated microgravity, there are no effect on numerical chromosome instability of human peripheral blood cells, but it enhances the structural chromosome instability through the inhibition of DNA replication and the reduction of DNA repair. Also, the expression rate of chromosome fragile sites is enhanced and the expressions of DNA replication as well as the DNA repair genes are down regulated.[20]

As can be seen, the immune system is suppressed but bacterial pathogens appear to be unaffected by, if not benefiting from, spaceflight conditions. Bacterial cells may not be affected at all by the weightlessness environment. In fact, *Salmonella enterica* and *Escherichia coli* has been benefited from spaceflight. Also, bacterial resistance to antibiotics is increased, as well as the rate of mutation accumulation.[6]

Neocytolysis in microgravity

Erythropoiesis lasts approximately 10 days and the half-life of an erythrocyte is considered to be of 120 days. Circulating reticulocytes become neocytes, and later mature erythrocytes. After 10 days in space, erythrocytes reduction is close to 10% approximately, and that's how the term "neocytolisis" arises, with the "selective hemolysis of neocytes" in which the larger erythrocytes are destroyed, and they have a shorter half-life of 10 days, without alteration of erythropoiesis, as a result of the adaptation to environmental conditions and microgravity, affecting the amount of hematocrit in response to a negative stimulus for erythropoietin secretion by the kidneys due to an accelerated fall in levels of hematocrit, as well as the total number of red blood cells and hemoglobin. This model shows that selective hemolysis *in vivo* allows the establishment of the erythropoietin function in the erythrocyte plasmatic maturation and it allows the progression of the neocyte to erythrocyte in the senescence process, which starts in response to stress and injury to the erythrocyte, being an alternative path in response to programmed cell death and it is vitally important to suppress the formation of cancer cells, as well as having angiogenic and antiapoptotic power which are essential in the process of ischemia and acute inflammation at endothelial, retinal, cardiac, neuronal, and nephron cellular levels.[6,18,21]

Analyzes were performed on blood samples in Russian cosmonauts before, during and after the journey to the International Space Station and in the morphologic study there was determined the presence of schistocytes and stomatocytes, as well as lactate concentrations which increased at the end of the trip, indicating dominance of an anaerobic state. Glutathione, which has antioxidant properties, was reduced at the beginning and increased at the end of the trip. During the voyage there was an increase in the percentage of phosphatidylcholine associated with the increase in membrane rigidity. Changes in physicochemical properties of the plasma membrane of erythrocytes (microviscosity and permeability) can influence the efficiency of oxygen transfer, the state of the hemoglobin and some changes in the conformation of the hematoporphyrin molecule.[21,22] However, with re-adaptation to Earth there appears a stimulation of erythropoiesis which is aimed at maintaining the optimal level of red blood cells, necessary for the increased demand of oxygen in the tissues under the conditions of gravitation of the Earth.[21,23,24]

Concluding remarks

The extent of knowledge of space has been made possible thanks to the exploration by astronauts, however exposure to microgravity during space flight is associated with various health risks, which potentially affect the body multisystem and make vulnerable to secondary conditions such as the effects of radiation and physiological consequences as neocytolysis, muscle atrophy, hydrostatic pressure changes, and metabolic changes position. Consequently, microgravity is the most profound aspect of the space environment on human physiology. Aerospace medicine aims to develop research to help the recognition of relationships and trends of these critical processes to propose strategies aimed at maintaining optimal health status of space crews and security throughout the flight path, thanks to this have been generated contributions to global knowledge and promoting partnerships between research groups with common fundamental goal towards the Air Health.

This article is dedicated to all Mexican medical doctors, pilots and engineers that have contributed to the knowledge of the Space in the National Aeronautics and Space Administration (NASA) and in the International Space Station (ISS).

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