https://doi.org/10.47183/mes.2025-301

PROSPECTS OF APPLICATION OF TEAR FLUID ANALYSIS IN AEROSPACE MEDICINE

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Introduction. The improvement of methods for remote health monitoring of astronauts, as well as the search for new noninvasive biomarkers of metabolic adaptation to microgravity conditions, are priority directions in the field of aerospace medicine.
Objective. To assess the possibility of using individual indicators of tear fluid in aerospace medicine.
Discussion. A number of prospects for the application of human tear biomarkers to determine disorders occurring under the influence of spaceflight factors or during their imitation were identified. The use of filter paper is a priority method for collecting lachrymal fluid in spaceflight conditions due to its relative noninvasiveness and simplicity of sample preparation for assay. It was found that the unstimulated tear fluid contains proteins with an antibacterial activity: lysozyme, lipocalin, and secretory immunoglobulin A. The concentration of lysozyme in the tear fluid shows a marked increase relative to pre- and post-flight values. Changes in the concentration of natriuretic peptide, angiotensin II, dopamine, and α2-macroglobulin under conditions of real and simulated microgravity are described. A high diagnostic potential of determining the level of D-dimer in tear fluid under the influence of extreme factors of space flight was established.
Conclusions. The conducted literature review emphasizes the significant theoretical potential for the quantitative determination of natriuretic peptide, D-dimer, and individual components of the dopamine and renin-angiotensin-aldosterone systems in tear fluid for noninvasive diagnostics of pathological processes associated with spaceflight factors.

Keywords: tear fluid; tear fluid collection; tear fluid metabolism; spaceflight; microgravity

For citation: Senchilov M.O., Manko O.M., Vasillieva G.U. Prospects of application of tear fluid analysis in aerospace medicine. *Extreme Medicine*. 2025;27(2):191–196. https://doi.org/10.47183/mes.2025-301

Funding: the study was carried out within the framework of the scientific research topic “The study of the morpho-functional stability of the visual sensory system during the adaptation of the central nervous system to the action of extreme environmental factors” FMFR-2024-0034 (1023022700092-0-3.1.4;3.1.9;5.1.1).

Potential conflict of interest: the authors declare no conflict of interest.

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Received: 14 Nov. 2024 **Revised:** 17 Mar. 2025 **Accepted:** 18 Mar. 2025 **Online first:** 12 May 2025

УДК 613.693

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ АНАЛИЗА СЛЕЗНОЙ ЖИДКОСТИ В КОСМИЧЕСКОЙ МЕДИЦИНЕ

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Введение. Усовершенствование методов дистанционного контроля состояния здоровья космонавтов, а также поиск новых неинвазивных биомаркеров метаболической адаптации к условиям микрогравитации являются приоритетными задачами космической медицины.
Цель. Оценка возможности использования анализа отдельных показателей слезной жидкости в космической медицине.
Обсуждение. Выявлен ряд перспектив применения анализа состава слезы человека для определения биомаркеров различных нарушений организма, происходящих в условиях действия факторов космического полета и при их имитации. Приоритетным методом забора слезной жидкости в условиях космического полета является использование фильтровальной бумаги ввиду относительной атравматичности, простоты метода, более легкой пробоподготовки биообразцов для анализа. Установлено, что в нестимулированной слезной жидкости содержатся белки, обладающие антибактериальной активностью: лизоцим, липокалин и секреторный иммуноглобулин А, причем отмечено выраженное повышение концентрации лизоцима в слезной жидкости относительно до- и послеполетных величин. Описаны изменения концентраций натрийуретического пептида, ангиотензина-II, дофамина и α2-макроглобулина в условиях истинной и моделируемой микрогравитации. Обнаружен высокий диагностический потенциал определения уровня D-димера в слезной жидкости при воздействии экстремальных факторов космического полета.
Выводы. На основании анализа данных литературы подчеркивается существенный теоретический потенциал применения количественного определения натрийуретического пептида, D-димера и отдельных компонентов дофаминовой и ренин-ангиотензин-альдостероновой систем в слезной жидкости для неинвазивной диагностики ассоциированных с факторами космического полета патологических процессов.

Ключевые слова: слезная жидкость; сбор слезной жидкости; метаболизм слезной жидкости; космический полет; микрогравитация

Для цитирования: Сенчилов М.О., Манько О.М., Васильева Г.Ю. Перспективы применения анализа слезной жидкости в космической медицине. *Медицина экстремальных ситуаций*. 2025;27(2):191–196. https://doi.org/10.47183/mes.2025-301

Финансирование: работа выполнена в рамках научной темы НИР «Изучение морфофункциональной устойчивости зрительной сенсорной системы при адаптации центральной нервной системы к действию экстремальных факторов среды» FMFR-2024-0034 (1023022700092-0-3.1.4;3.1.9;5.1.1).

Потенциальный конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Статья поступила: 14.11.2024 **После доработки:** 17.03.2025 **Принята к публикации:** 18.03.2025 **Online first:** 12.05.2025

INTRODUCTION

The habitability of space environments is associated with numerous medical and biological risks. Since the beginning of manned spaceflights, astronauts have shown significant adaptive shifts in water-salt metabolism due to changes in the parameters of the cardiovascular system and neurohormonal regulation. These shifts were shown to be determined by a volume regulatory reflex, manifested by clinically insignificant changes in the concentrations of osmotically active substances in the blood. At the same time, tight correlations between the initial vestibular vegetative stability of astronauts and the specifics of their neurohormonal changes under the influence of spaceflight factors were found [1].

The initial period of weightlessness, due to blood redistribution toward the cranial direction, is associated with jumps in central and renal hemodynamics and is characterized by a decrease in the secretion of hormones of the renin-angiotensin-aldosterone system (RAAS) and antidiuretic hormone during the formation of a new fluid and electrolyte homeostasis with a negative balance of sodium and calcium [2]. The observed hypohydration and hypovolemia, associated with primary adaptive hormonal mechanisms, contribute to an increase in the production of volume and osmoregulatory hormones [3]. These reactions can lead to the development of pathological changes in cardiovascular and hemostatic systems, increase the risk of urolithiasis, and cause demineralization of bone tissue [1].

Monitoring the metabolic adaptation of astronauts to microgravity is an essential aspect in the implementation of space missions. High-precision monitoring of physiological parameters of astronauts using molecular biomarkers is carried out by various methods. However, their analytical performance remains to be problematic, requiring modernization of current diagnostic procedures to minimize errors and facilitate the interpretation of the data obtained. Under conditions of spaceflight, selection of the most noninvasive biomaterial sampling techniques, which allow an informative qualitative and quantitative analysis, is of particular importance.

Tear fluid (TF) is one of the most accessible biological fluids for analysis, characterized by noninvasiveness of sampling and a widely studied composition equivalent to blood plasma [4, 5, 6]. Tear production is regulated by the autonomic nervous system, which allows the glands to rapidly adapt to changing environmental conditions and homeostasis disorders during the development of pathological processes [7].

In this research, our aim was to evaluate the possibility of individual indicators of tear fluid as biomarkers in aerospace medicine.

MATERIALS AND METHODS

The literature search and review was performed using electronic bibliographic databases in the Russian (eLibrary, CyberLeninka) and English (Web of Science, Scopus, PubMed) languages. The search queries included the following key phrases: tear fluid, tear fluid collection, tear fluid metabolism, water-salt metabolism, homeostasis, osmoregulation, glomerular filtration, hormonal regulation, nonspecific protective factors, acute phase proteins, hemostasis system, dopamine system, biomarkers, hypokinesia, immersion, space flight, microgravity. The search depth was 10 years. The inclusion criteria were the availability of structured information on the methods of tear fluid collection, prognostic and diagnostic biomarkers of human body adaptation to the conditions of real spaceflight and during its simulation, qualitative and quantitative methods for their determination.

RESULTS AND DISCUSSION

Methods of collecting tear fluid

The TF sampling method may affect the TF composition. To date, tear collection for biochemical analysis is carried out by two principal methods: using microcapillary tubes with minimal irritation of the conjunctiva and by absorption using an absorbent material (filter paper, polyvinyl acetate sponges) [8].

Sampling with microcapillary tubes without touching the eye provides optimal, unstimulated TF with minimal accompanying components for further research [9]. However, due to the high risk of mechanical injury, this method requires the participation of specially trained personnel, which limits its use in routine practice [4].

The advantage of filter paper in TF sampling consists in its relative noninvasiveness, implementation simplicity, and easier sample preparation [10]. In addition, this method is applicable under the conditions of deficiency of the aqueous component of the tear film observed in microgravity [11, 12].

Antibacterial proteins and natriuretic peptides

Unstimulated TF contains about 20 g/L of proteins, most of which exhibit antibacterial activity, including lysozyme, lipocalin, and secretory immunoglobulin A [7, 13]. Lysozyme, being the leading factor of nonspecific protection of TF, quantitatively prevails over other biological components [14]. Thus, according to [15], crewmembers of the International Space Station (ISS) during spaceflight showed a marked increase in the lysozyme concentration relative to pre- and post-flight values.

Natriuretic peptides (NP_S) are a group of low molecular weight proteins, the main source of which in physiological conditions is atrial tissue [16]. Currently, three types of NP_S and their organic proteolysis products used in clinical diagnostic practice have been identified: atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP), and type C natriuretic peptides (CNP) [17]. The latter are a local regulatory factor of blood vessels and bones, not secreted into the blood [18]. The main physiological effect of NP_S concerns a reduction of the load of hemodynamic factors on the myocardium [19]. In response to increased pressure on the cardiac wall, NP_S cause fluid redistribution to the extravascular sector at the level of the capillary bed, venodilation, and natriuresis stimulation due to increased glomerular filtration rate and RAAS depression [18, 20].

During the initial period of weightlessness and in simulated microgravity, a maximal increase in the NP level in blood plasma under a decrease in sympathetic influence was observed [21, 22].

The researchers in [23] studied the level of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP), secreted in an equimolar BNP ratio and more stable upon release. A high correlation between the concentration of NT-proBNP in blood serum and TF was observed both in normal conditions and during the development of an ophthalmic pathology [23, 24].

Components of the renin-angiotensin-aldosterone system

The RAAS state plays an important role in the adaptation of water-electrolyte metabolism to spaceflight conditions, which significantly affect the kidneys osmoregulatory function [25]. The main RAAS effector is the angiotensin-II (AT2) oligopeptide hormone [26]. AT2 possesses vasoconstrictor properties, stimulates the production of aldosterone and antidiuretic hormone, increasing sodium reabsorption and contributing to the development of hypervolemia [27].

During dry immersion experiments, a significant decrease in the plasma renin activity and serum AT2 concentration was revealed [28, 29].

At the end of the last century, a local renin-angiotensin system was discovered in the human visual system with components (prorenin, renin, angiotensin converting enzyme, AT2) in concentrations exceeding those in blood plasma [30].

At present, convincing data points to the diagnostic significance of AT2 determination in diabetic retinopathy (DR). Thus, according to the authors, in patients with DR, a significant increase in the concentration of AT2 in TF was recorded in close correlation with a similar indicator in the blood serum [31].

Components of the dopamine system

The negative effects of microgravity on the brain dopamine system have also been described. A decrease in the expression of tyrosine hydroxylase during dopamine synthesis in the substantia nigra and a decrease in the expression of the dopamine receptor of the 1st subtype in the hypothalamus were noted [32]. These changes may underlie motor disorders, dyskinesia, and Parkinsonism during and after space flight, which was shown in studies under the Bion-M1 program [33, 34].

The involvement of dopaminergic neurons in the regulation of tear production leads to a higher TF level of dopamine and its metabolites compared to blood plasma [35]. In [36], a more than threefold excess of dopamine levels in tears over its plasma levels was observed, indicating a high diagnostic potential of TF as a noninvasive source of biomarkers of Parkinson's disease (PD) and conditions accompanied by a decrease in the expression of dopamine system genes.

Acute phase proteins

The initial stage of the body's adaptation to microgravity, in addition to the above, is accompanied by an increase in humoral inflammatory factors and changes in the hepatocyte synthesis of acute phase proteins (APPs) induced by inflammatory cytokines (interleukin-1β, interleukin-6, and tumor necrosis factor α) through interaction with liver cells [37, 38].

In an experiment with seven-day dry immersion, the dynamics of APPs in blood plasma corresponding to the response acute phase was demonstrated. On the second day of exposure to simulated microgravity, statistically significant changes in plasma levels of haptoglobin, α1-antitrypsin, and α2-macroglobulin were observed [39, 40].

α2-macroglobulin is an acute phase protein, an inhibitor of proteolytic enzymes with a wide spectrum of action. Upon the development of inflammatory reactions, it reduces damage to structural proteins by proteases released from leukocytes [41]. Over the years, studies have repeatedly been conducted on the diagnostic significance of determining the activity of α2-macroglobulin in TF in ophthalmic and systemic pathologies [42].

It was found that in patients with an early-stage PD and when modeling the preclinical stage of Parkinsonism in mice, the activity of TF α2-macroglobulin significantly exceeded the clinical norm. In addition, the high specificity of α2-macroglobulin activity (>85%) was shown [43], which validates the study of this protein as a biomarker of certain neurodegenerative diseases and conditions of the acute period of body adaptation to spaceflight conditions or during its simulation.

Components of the hemostasis system

Conditions accompanied by shifts in the hemostasis system and coagulation balance also affect the TF composition. In the acute period of exposure to microgravity, as mentioned above, hemodynamic shifts are observed, which in turn lead to changes in the rheological properties of the blood [2, 44]. These changes, along with physical inactivity, may induce abdominal congestion, which increases the risk of developing thrombophilia in astronauts [45]. A striking example is the case of occlusive thrombosis in an ISS crewmember during a recent orbital space flight [46].

The determination of D-dimer (DD), which is a product of the proteolytic degradation of fibrin, is currently a widespread test for assessing the activity of fibrin formation and fibrinolysis processes [47]. A number of studies have described significant changes in blood plasma DD levels during the period of adaptation to gravity unloading, with a tendency to be more pronounced in individuals with signs of vascular endothelial damage [48, 49].

Tear fluid contains components of the hemostasis system. Thus, the researchers in [50] demonstrated a high diagnostic informative value of antithrombin III and plasminogen levels in tears in patients with complicated diabetes mellitus and hypertensive angiosclerosis.

According to the results of a number of studies on determining the DD level in the TF, a statistically significant increase in the DD concentration was revealed in patients with retinal vein occlusion compared to the control group with minor changes in blood plasma [51].

The risk of developing occlusive retinal lesions in real microgravity is probably due to the high level of the homocysteine neurotoxin in blood plasma, recorded in astronauts with ophthalmic pathology before and during a spaceflight mission [52].

The above information justifies further investigation into the diagnostic potential of DD in tear fluid.

The adaptive restructuring of the water-electrolyte balance, recorded at an early stage of weightlessness exposure, may affect the mineral composition of tear fluid. Basal tear is characterized by high concentrations of potassium and sodium ions compared to blood serum, which ensures metabolic processes at the level of the ocular surface through Na, K-ATPase of the lacrimal glands [53]. An increased level of calcium ions in TF is observed during bacterial infections, cystitis, and dry eye syndrome [54, 55].

Pharmacological research

The acquisition of on-board first-aid kits remains relevant to the medical and biological support of manned space flights, taking into account the potential change in the pharmacological properties of individual drugs under the constant influence of extreme factors on astronauts. Pharmacokinetic studies of antiemetic, anti-inflammatory, and antibacterial agents, during flights demonstrated a significant decrease in the bioavailability of active substances relative to similar values on the Earth [56]. To date, the retrospective analysis is limited by the heterogeneity of the conducted experiments [57].

Despite the difficult-to-permeate blood-ocular barrier, a correlation between the concentrations of normothymic agents, macrolide, and beta-lactam antibiotics in blood plasma and TF was established [58, 59]. A deeper understanding of the entry patterns of drugs and their metabolites into tear fluid is a promising task, the solution of which will contribute to optimization and standardization of methods for studying the pharmacokinetic and pharmacodynamic properties of various compounds for more effective formation of medical packages on board spacecraft.

CONCLUSION

The conducted literature review allow us to draw a preliminary conclusion about the high diagnostic and prognostic potential of TF analysis in a wide range of health pathologies and disorders detected under the impact of adverse spaceflight factors. Noninvasive and effortless under appropriate conditions, the study of tear composition appears to be a promising method for monitoring the state of functional systems, as well as for monitoring the correction of deviations in physiological parameters induced during space missions. The practical application of such studies involves the search for specific changes in the TF components, which can be sensitive biomarkers of the body adaptation to microgravity and, subsequently, to other extreme factors of outer space. In the long run, such studies may contribute to successful implementation of interplanetary expeditions.

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Authors' contributions. All the authors confirm that they meet the ICMJE criteria for authorship. The most significant contributions were as follows. Mikhail O. Senchilov — development of the concept of the article, literature review, collection and analysis of literary sources, writing the text; Galina U. Vasillieva — analysis of literary sources, editing of the manuscript; Olga M. Manko — collection and analysis of literary sources, editing of the manuscript, final approval of the manuscript.

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