Review Article

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ENT and Diseases in Space: From Physiology to Clinical Disorders and Countermeasures

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Abstract

Spaceflight are still very fascinating for us living on Earth. However our full human body is very well adjusted to our Planet Earth, and consequently needs to be protected to travel in the Universe! Since the beginning of the spaceflight area, more than 700 astronauts went to space. Even though we learn a lot; we still need to be vigilant and increase our knowledge. Space is an extreme and hostile environment for three main reasons: the high level of radiations, the microgravity and confinement. The level of radiation is not comparable with what we know on Earth. The change in the gravity level so called microgravity affects the whole body systems. If the impact of radiations is still not fully known, the consequences of the microgravity start to be very well known despite the lack of clear explanations. These consequences of decrease in the gravity level are comparable with ageing, as osteoporosis seen in all type of spaceflight, short (2 weeks) or longer duration (6 months to 1 year), it concern bone lost in bearing bone and among the main obvious consequences of space travel we can give as example, muscle atrophy cardio vascular changes with orthostatic intolerance (directly when astronaut are back to Earth), space motion sickness, impact on the sensory organs like eyes, taste, smell and of course, ENT is not in rest!. The ISS, International space station, is a unique environment which allows the scientist to learn about the behavior of human body, physics and chemistry in space. The benefit is obvious for us on the ground (new technologies developed as well new medications against ageing).. The ISS is an international cooperation build by the two main space agencies: NASA, Russian, with the cooperation of 3 other partners the CSA (Canadian Space Agency), JAXA (Japanese Space Agency) and ESA (European Space Agency). Until now, in case of a major event, the crew on board can still be helped by the ground because we can communicate without delay, and furthermore in case of emergency without physician on board, it is expected that the crew can come back in a reasonable time (few hours-days). The next step for space travelers will be to become autonomous to ensure safe travel not to ISS but to Mars our other planets. In that case the possibility to come back to treat an emergency is not possible and even not foreseen. Pathology linked to the ENT system, could impact the safety of the crew and consequently the safety of the full equipage and might abort the mission, if not clearly identified and treated. This review focus on the main pathology linked to ENT in space environment: from infectious disease as seen on Earth, to barotraumatic accident, hearing loss and vestibular disorders. Finally, some countermeasures will be discussed. Since the beginning of spaceflight the best countermeasure is the exercise which counterbalance the lack of gravity but is not sufficient. Despite 2hours of training per day the astronauts have an impact on their body and the scientist are still working to find the best or probably more realistic the best combination of countermeasures. As seen in this review, ENT system could be a good example to show how space impact the body to simulate aging by an increase of the hearing loss which seems not only connected by microgravity and radiation by mainly by hight level of noise typically seen in the ISS. New technologies and pharmacology should be used and developed to improve the life on board and consequently on Earth.

Keywords: ENT, Space, Vestibular system, Countermeasures

Introduction

Ear, Nose and Throat (ENT) also called Otorhinolaryngology, encompasses a vast disease spectrum. Among those, rhinology disease increases worldwide: about 200 million people worldwide, or approximately 3% of the global population, are estimated to suffer from nonallergic rhinitis (NAR) [1]. Allergic disease has increased as well, at an astounding epidemic rate and is currently estimated to affect 10% to 30% of the world's population [2]. As an example, this trend has been seen in Northern Europe (19.7% to 24.7%) [3], and many other countries (UK, Australia, Italy). The reason is multifactorial and a recent review showed the impact of climate changes [4]. This topic is important on the ground and we can find common reason is space because of the modification of the environment.

The impact of space environment on the ENT system is linked to the three main following factors: radiation, microgravity and confinement. To be complete we need to add the specific condition related to live in space and on board the space station (chronobiology, noise, orbital debris...).

If some pathologies seen in space are common to those on the ground like infectious diseases linked to ear, nose and throat some others are very specific and linked to the modification induced by the new hostile and extreme environment: baro--traumatic events, space motion sickness, headaches. Hearing loss is very frequent and linked mainly to the high level of noise on board the station.

This review focuses on the specificity of space by reviewing the very challenging and extreme environment. The space-related clinical diseases, including common diseases and the most specific ones. Each time feasible the physiological changes induced by space will be presented the clinical presentation with symptoms and the respective treatment.

In the last chapter the countermeasure will be developed: these are the measures proposed by science and medical doctor to counteract the space effect and also avoid major clinical events.

Space Environment an Hostile and Extrem Environment

The ISS (International space station) gravitates at 300-400 km altitude and at this altitude, among the most unusual factors we find a much higher radiation rate than on Earth, the absence of gravity, a new confined environment and finally many other factors directly linked to the space station itself.

Challenges for Radiation Exposure in Space

Exposure to space radiation is one of the main challenges for future long-term space and interplanetary space missions. Many uncertainties remain, especially to quantify the risk of radiation-induced cancer.

Space radiation includes energetic solar particles (emitted during solar flares and coronal mass ejections), GCR (Galactic Cosmic Rays) composed of electrons and positrons (2%), protons (85%), helium nuclei (12%), and heavier ions referred to as high-energy and high-charge particles (HZE 1%) [5].

Despite technical progress, the radiobiological effects and their impact on astronauts is not fully known.

Epidemiological studies on populations exposed to ionizing radiation (primary X-rays or gamma rays) have demonstrated an increase in the incidence of degenerative tissue damage, cataracts, and cardiovascular diseases (atherosclerosis). Although the underlying mechanisms remain unclear, they involve oxidative and inflammatory damage, as well as direct deleterious effects on tissues [6].

Astronauts are exposed to high levels of radiation far exceeding the levels of the normal public. Taking into account that the average exposure per day inside the Space Station amounts to approximately 500 μSv – depending on the shielding conditions and the solar cycle – astronauts would have to return to ground after ~ 100 days in space since the dose limits for occupational workers are reached. Also the best compromised have been taken by the agencies to allow flying longer such 6 or 7 months mission without compromising the health of the astronauts. The National Aeronautics and Space Administration (NASA) has identified four primary biomedical risks that may pose significant health concerns for astronaut crews exposed to the interplanetary radiation environment during exploration missions. These four space radiation risks are carcinogenesis, degenerative tissue effects, CNS (Central Nervous System) decrements and acute radiation syndrome [7].

The Impact of Microgravity

All life on Earth has evolved and adapted to a single downward vector of gravity. In the space environment, this vector is mostly removed, resulting in microgravity conditions. Microgravity also has an impact on all the physiological systems of the human body.

The probably most studied system is the musculoskeletal system. Indeed the most important effects are a muscle atrophy and osteoporosis. The usual bone lost is explained by an increase in osteoblast activity with stable or reduced bone formation [8], the lost in bone is severe, it affects mainly the bearing bone (lumbar spine and hip are the most affected) the lost is about 1% of bone per months. Compared to post menopause it is higher (1% lost per year at menopause). These values of course change depending on the individual and the location.

Effects on the vascular system [9] show among the main ones, stiffness of the vascular wall, atrophy of the heart muscle with some degree of heart failure, and orthostatic intolerance to return to Earth. On the neurological system: first most reported one is sleep disorder [10].

The visual system is affected also in flight. It has been discovered more recently. It is called SANS: Space-Associated Neuro-ocular Syndrome. It is the subject of much current research. The changes most reported are: a flattening of the eyeball and enlargement of the sheath of the optic nerve. Most of the time, astronauts do not suffer from any symptoms, except possibly a certain early presbyopia, which usually reverses on their return to Earth but not in all astronauts. For the moment the mechanisms invoked are multifactorial, among those, modification of the fluid distribution with shift fluid towards the upper part of the skull is the main one [11]. A more recent study indicates the implication of potential dysfunction of the mitochondrial associated with an increase in oxidative stress [12].

On the ENT and vestibular system, space sickness is probably the most studied ones it has a neuro-sensory origin, it will be widely reviewed here. Infectious and baro-traumatic disorders are often reported. Hearing is impacted by space but more by the high level of noise on board. As it will be discussed microgravity can change as well the physiology of the ear. It is difficult to distinguish what part is responsible for the changes: microgravity, radiations something else or/and most likely all together.

The digestive system is affected too in space, the most report symptom is a feeling of fullness in stomach at the beginning of the flight with decrease of the appetite (difficult to extrapolate from the SMS). Constipation and gastroesophageal reflux disease are common symptoms reported. At the moment the digestive flora is the subject of many projects by the scientists. This flora would change mainly because of life in a closed environment [13]. To be complete we can mention the sense of smell and taste, genital, hormonal and immune systems: they are all affected by microgravity but the impact on the human body is not so crucial at a first glance.

Other Challenge inside the Station

Isolation Confinement

One of the third major effect of life aboard the ISS concerns the confinement. It has a psychological impact. Astronauts communicate with families through their iPhone when they ran outside of the experiments. They communicate with ground crews but have no contact outside the teammates and this for 6 months or more, the duration of their mission [14].

Main factors involved in the psychological disturbances are: crew changes, work overloaded, social retract, hazardous atmosphere on board with contaminants, technical deficiency « anxiety or anger » against the ground support, conflict among crew members.

The psychological changes observed could impact the mission, such: irritability, depression and sleep disturbances.

Psychology is among the main challenging topic with radiation and osteoporosis for next step: LEO (Low Earth Orbit) such very long interplanetary mission.

Dark/light: Chronobiological and Biorhythms Changes

The station flies over the globe every 90 minutes, so astronauts will have an alternation day night, which may disturb all hormonal physiology, because the hormones are secreted at specific times of the day (just as an example, cortisol in the morning at 8 am and melatonin at night).

Among Others Changes, Some are Very Important because it Affects the Crew: CO_2 Level, Dust Noise and Orbital Debris

Regarding the CO_2 level, a study from NASA by Law J. et al [15] reported that crewmembers residing in the confined compartment of the International Space Station (ISS) are exposed to elevated ambient CO2 levels averaging 0.5%, which is more than ten times greater than terrestrial levels (0.04%). During their study they showed that each elevation of 1 mmHg of CO_2 level, gives headaches double of normal based. Headaches some years ago were mainly linked to this high level. Following this study which furthermore showed that to see a decrease in less than 1% of headaches, it was necessary to have a level of CO_2 lower than 2 mmHg; a lot of effort was made to really decrease the level on board. Nowadays there is a big improvement even so it is not possible to decrease much more.

The quantity of dust increased considerably on board the ISS, even though each crew member is doing two hours per week of cleaning, on the Saturday. Some new rules and new filter were implemented and were able to reduce the symptoms and improve the way of life on board [16].

Noise is higher than on the normal environment on Earth as already mentioned. This noise comes from many factors, the main one is the noise generated by ECLSS (Environment life Support System), which is a very fundamental system to maintain life in the same conditions as on the Earth. On top of that comes the quantity of computer on board as well the sport exerciser such Treadmill which increase the level of noise. Most of the time, the level of noise reaches the conversational level of 60 dB but can be higher in some part of the modules of the ISS; depending on the activity done! The alarms are another factor generating noise, mentioned here because happen more often than we could expect and usually in the night. Hopefully, most of the time, they are false alarms but wake up the crew [17].

Orbitals Debris are becoming more and more frequent with the high level of space vehicle, and satellites gravitating in the space environment. The impact of orbital debris could be important if it would hurt the station. This requests a high-level of involvement from ground teams to follow and watch the debris carefully. A scale with a level of risk has been defined to monitor in case the risk will increase. At the higher level, it would be requested that the astronauts leave the ISS's modules and go in their vehicle: the Soyuz/Space X and be ready for an evacuation; of course, they have to be fully prepared such wear as well their flight suit …. [18].

Also to conclude the full body is impacted by the new environment as we can see in Figure 1 and table 1. To allow human bodies to stay alive and work in this extreme environment for human, a multitude of actions have been taken and they are called countermeasures. This will be described in the last chapter.

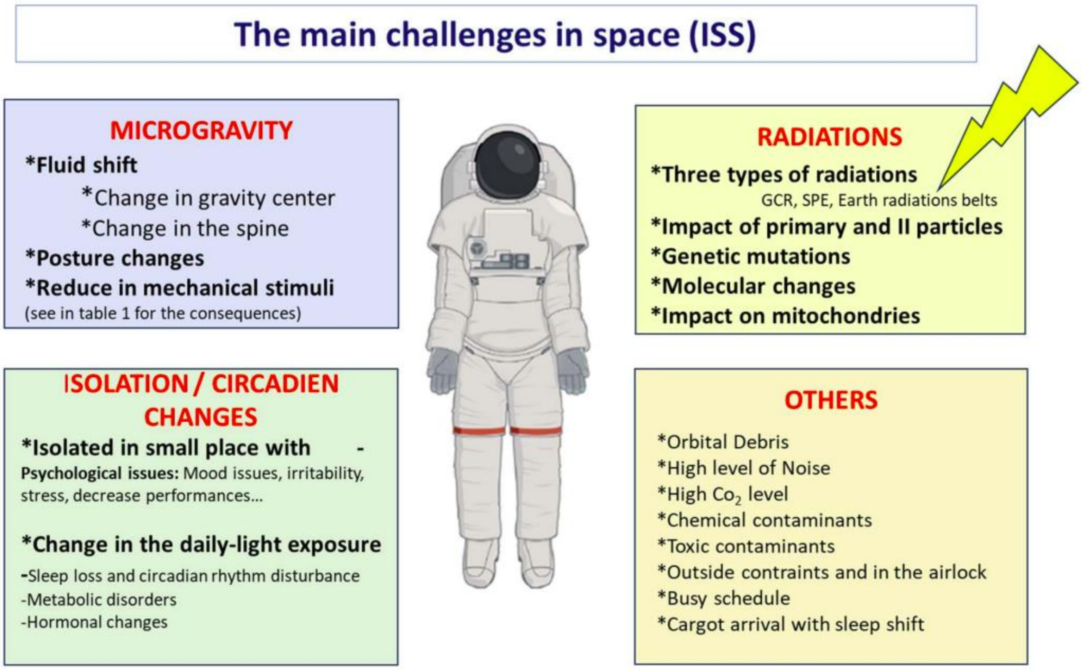


Figure 1: All factors involved on the human body on board the ISS

The three main constraints of spaceflight are the microgravity, the radiations and the confinement. Details are given in the text and in the Table 1 for microgravity and radiations impact on the human body.

The other constraints are mainly due to the live on board the ISS

Table 1: Consequences of the microgravity and of the radiations on the main system in the human body

System\Factor	Microgravity	Radiations
Cardio-vascular	Increase in Heart rate beats and cardio vascular output -ECG Changes -Heart form changes with become sphericity and decrease in muscle mass -Decrease in peripheral vascular resistance-Increase venous stasis -Increase intolerance orthostatique (in post-flight)	-Endothelial dysfunction in arteries -Change in myocardium with increase inflammation and oxidative stress and cellular apoptosis
Musculoskeletal	-Bone changes: Osteoporosis mainly on pelvis and lumbar spine (Due to decrease in bone formation and increase bone osteoclasis) -Muscle changes: Reduce in muscle volume (amyotrophy) and in strengthShift in between fiber fast (decrease) and slow fiber Changes in spine with hyperlordosis with increase heigh and decrease in stabilizer muscles (like multifidusmuscle) Increase risk in disk herniation -Cartilage changes: decrease in cartilage thickness and loss of glycosaminoglycans	-Architecture and density changes -Molecular changes contributing to bone and muscle loss too

Neurology	-Space motion sickness or space adaptation syndrome -Sleep disorders -SANS (Spaceflight Associated Neuro-ocular Syndrome) -Illusion -changes in cognitive performance -reduction in motor function, and psychological disturbances. -Changes in locomotor coordination, in eye-head coordination. And vestibular dysfunction (balance) -Postural and gait changes in post flight	-alteration in cognitive and behavioral functions, - alteration in synaptic integrity, - microglial activation -Neurodegenerative diseases -neuroepigenetic changes which lead to altered gene expression, impacting learning and memory
Digestive system	-Reduced appetite in microgravity Leading to reduce energy intake leading to reduce weight -Changes of the intestinal flora with decrease in varietyHyperacidity (High protein intake might induce low-grade metabolic acidosis) -Metabolism changes with Glucose tolerance ↓ and Insulin sensitivity ↓ and Reduce Vitamin D	-Acute syndrome with nausea, vomiting in case of lethal diseaseChanges in the stability of the food
ENT	-Eustachian tube dysfunction and obstruction -Can lead to barotraumatisms and otitis -Venous sinus congestion -Cochlear hair cells damages (one factor of hearing loss with noise)	-electromagnetic radiation can damage the hair cells of the cochlea leading to hearing loss
Immunology	-cellular and innate immunity display observable changes - Alteration and modification of leukocytes with: Decreased T cell activation and decrease in B cellsIncrease in the Natural Killer fraction Shift from CD4+ to CD8+ memory cells -Changes in cytokine profile reduction in Th1 expression and shift towards Th2 cells significant risk of increase in autoimmune diseases and allergies -Latent Viral reactivation Altogether, could potentially lead to infectious disease with increase virulence of bacteria in flight (expression changes, antibiotic resistance, and increase virulence of microbes).	-Decrease in platelets, lymphocytes and Granulocytes counts
Hematology	-Temporary anemia by fluid shift, decreased red blood cell (RBC) production, and RBC sequestration. Decrease plasma volume	-In case of lethal dose, acute syndrome with necrosis of bone marrow cells
Urology	-Reduction of plasma and extracellular fluid volume Decrease fluid intake, decrease circulating total protein Excessive excretion of calcium Elevated risk of renal stone	-Decrease in anti-oxidant by increase in ROS (reactive oxygen species)Endothelial and mitochondria dysfunctions Could lead to nephrolithiasis

Gynecology	-Changes in cycle length (increase usually) with two concerns first anovulation might occur, resulting in continuous estrogen exposure, endometrial hyperplasia, and possibly menorrhagia. Second, there is some concern that hypothalamic amenorrhea and reduced estrogen levels could occur Increase FSH, decrease LH	-Depleted ovarian folliclesIncrease apoptosis Oxidative damages in oocytesGonades susceptible to cancer

It is very difficult to extrapolate which consequence is really linked to one of the two factors because often both are combine. If microgravity can be studied on the human body without radiation during ground based model we can only study radiations with animals or at the cellular level and it is therefore difficult to extrapolate.

In blue the pathology seen on the organ/system. The consequences are not all detailed but the main one are in the table.

Space Related ENT Diseases

Clinical Pathology Seen in Space

Pathology Reported

It is very difficult to have clinical data from astronauts first of all, because of confidentiality. ESA astronauts are not a large number: « one is flying at a time usually », so it is very difficult to preserve confidentiality and to pool all the information, we need to wait to have enough data.

NASA has of course a bigger number of astronauts which make it probably easier even though it is still very challenging to find such details. Here are the main data on ENT:

During shuttle flight from STS-1 through STS 89 from april 1981 to January 1998

26 number of infectious diseases were reported connected to ENT system.

But more interesting at that time, among a total of 1867 events, 788 were due to SMS

ISS program through Expedition 37/38 on 46 crews

2 allergic reactions, 20 prolonged congestion rhinitis and sneezing, 6 ear related, 1 pharyngitis.

In total 29 events among 70 (almost half of the events) which give us 41,4% ENT cases from the total events [19].

Crucian et al. looked at 46 long-duration ISS crew members, each serving approximately a 6-month mission on board the ISS, constituting 20.57 total flight years. Among all categories, 70 reports of symptoms potentially related to immune dysregulation were tabulated during flight, including both notable and non-notable events. The accumulated incidence rate for these events was found to be 3.40 events per flight year, or averaging approximately 1.7 events per 6-month ISS expedition crew member. By far, the majority of the adverse events observed on board the ISS were skin rashes (23 events), followed by upper respiratory symptoms, including congestion, rhinitis and/or sneezing (20 events). The various types of infectious disease observed during spaceflight (including pharyngitis, skin infection, etc.) indicates at least 13 infectious disease events occurred during the reporting period.

Also, among ENT pathology, we summarize below what is the most usual with the treatment used. Of course this is not exhaustive! It has been decided to describe the main important and interesting ENT disorders specific or not to space. Each disease is divided three main chapter: the physiological changes due to space, symptoms and disease reported and the last one is the treatment. The disease exposed here are: SMS, infections of the ENT, and hearing loss. ENT pathology linked to EVA have been removed because should be the object of another specific review [19].

The Most Frequent Known One with the Impact on the Vestibular System: SMS

Change in the Vestibular system

Introduction on the Vestibular System

Sensory information about motion, equilibrium and spatial orientation is provided by the vestibular apparatus in each ear, which includes the utricle, saccule and three semicircular canals. The utricle and saccule detect gravity (vertical orientation) and linear movement. The semicircular canals, which detect rotational movement, are located at right angles to each other and are filled with a fluid called endolymph. The semicircular canals do not react to the body's position with respect to gravity. They react to a change in the body's position. In another words, the semicircular canals do not measure motion itself but change in motion. This explains that they are not affected by spaceflight.

When the vestibular organs on both sides of the head are functioning properly, they send symmetrical impulses to the brain.

The vestibular system controls various physical functions, including body stability, sympathetic nerve activity, arterial pressure, feeding behavior, body temperature, and muscle and bone metabolism. However, it is highly plastic and its function is altered upon exposure to different gravitational environments.

Abe et al. In 2008 showed that vestibular system regulates both skeletal muscles and bones. Several studies have reported that labyrinthectomy or VL (Vestibular Lesio) reduces bone mass with partial involvement in the sympathetic nervous system in rodents, which indicates that the vestibular system regulates bone metabolism [20]. Clinical studies have reported a relation between benign paroxysmal positional vertigo with the vestibular dysfunction and osteoporosis, high bone turnover, and vitamin D deficiency in patients with osteoporosis [21].

Furthermore from Morita' experience in mice the vestibular system would enhanced osteoblast differentiation partly through the vestibular system, which suggests that the vestibular system might contribute to the adaptive response of bone tissues during gravity change [22]. This is still controversial and need to be confirmed.

Changes in Space

Otoliths and Otoconial Mass Changes

In space, the otoliths are stimulated by head translation, but not by head tilt. Consequently, it is hypothesized that after a period of adaptation, the brain reinterprets all otolith signals as signaling head translation [23].

Clement showed during STS-90 fight (Neurolab centrifuge experiment) that at the beginning of the flight, a 1-g centrifugation in darkness, is perceived as a 45-deg tilt to the side, very much like on Earth. However, as the mission progressed, astronauts felt more and more tilted, until a 90-deg tilt to the side on flight day 16. This simple result indicates that the brain does not continuously calculate the direction of gravity, but uses an internal estimate of gravity whose weighting changes during spaceflight. After a period of adaptation, the internal estimate declines to zero and the astronauts perceive a full body tilt to the side [24].

Accordingly, taken together these findings suggest that the otoconial mass adapts to fluctuations in the gravitational stimulus to maintain a consistent force on the maculae in astronauts during space flight. This has been confirmed on mice by Abe in 2022. Still future work will be required to fully understand the detailed time course of these changes.

Hair Cells Shift in Otoliths

Going in further details: the vestibular receptor cells in all mammalian end organs, including the otoliths, are called hair cells and are divided into two subtypes. These subtypes, termed type I and type II hair cells, occur in nearly equal ratios. Type I hair cells are defined by the presence of calyceal afferent innervation, while in contrast Type II hair cells synapse upon discrete bouton afferent terminals [25]. Intriguingly, prolonged exposure to microgravity (>7 days) increases in the number of type II utricular hair cell synapses in mice after a 9-day space flight using ultrastructural analysis. After 2 weeks in microgravity, an increase in the mean number of presynaptic processes ending on the calyces of type I cells has also been reported [26].

The results of these studies suggest that vestibular hair cells, at least in rodents, can demonstrate adaptative changes in response to altered gravity.

Central Vestibular Processing

Recent MRI studies in astronauts pre- vs. post-flight have provided evidence for vestibular/proprioceptive sensory reweighting and adaptive neuroplasticity at higher levels of processing in the cortex [27]. Indeed, there are evidence from both space- and ground-based studies that such extra-vestibular sensorimotor feedback can rapidly influence the online processing of vestibular information for the control of balance [28] and locomotion [29].

Incidence

Historically, SMS was first reported as an operational issue in 1962 on board the spacecraft Vostok II, the second manned Soviet mission. No SMS was reported in either Mercury or Gemini Project. 35% of the astronauts during Apollo Program and 60% of the Skylab Program developed symptoms of SMS [30]. The incidence of SMS symptoms was 67% among the first time flyers on 24 with Space Shuttle flights.

Historically, the size of space vehicles has increased with the incidence of reported SMS.

Statistically, symptoms occurrence was not different between career versus non career, men versus women, different age group, or first time flyer versus repeat flyer.

Post flight symptoms tend to be more intense than those experienced during flight: 11% of those who had no symptoms in flight experienced SMS post flight.

Symptoms

No correlation was found between SMS and terrestrial motion sickness in term of crew member susceptibility

On Earth, exposure to provocative motion, leads to progressive cardinal symptoms of terrestrial motion sickness, which include: pallor, increase body warm, cold sweating, dizziness, drowsiness, nausea, vomiting.

For SMS in spaceflight, no sweating except palmar sweating, flushing is more common than pallor, more often associated with stomach awareness, vomiting, headache, impaired concentration, lack of motivation and drowsiness. Vomiting is usually sudden and infrequent and often not marked by prodromal nausea.

Universal symptoms are malaise, anorexia or loss of appetite, lack of initiative and increase irritability

Theories and Hypotheses

Many theories and hypotheses have been proposed

The two main theories are the fluid shift theory and the sensory conflict theory. The others ones are less recognized or under investigation like the OTTR (otolith tilt-translation reinterpretation (OTTR).

The Fluid Shift Theory

In first hours of microgravity, the fluid shift going to the upper part of the body increases the central fluid volume, cardiac size (around 20%) and cardiac output. It then leads to a negative fluid balance and reduction of 12-20% in the circulating blood volume, which causes a decreased resting stroke volume of 10-20% and a reduced cardiac output, with an average reduction of 1.5L.min-1 over pre-flight values. These changes are secondary to the reduction in circulating blood volume [31].

This headward fluid shift is also associated with changes in the fluid of the vestibular system, subsequently altering receptor responses in the inner ear. Engorgement of the blood vessels surrounding the endolymphatic duct may restrict the flow of the endolymph sac, resulting in hydrops, or the pressure may act directly on the VIIIth nerve at the internal auditory meatus. This could alter the responses of vestibular receptors, inducing the establishment of SMS. Several mechanisms have been proposed to explain how the headward fluid shift associated with microgravity may produce SMS. The headward fluid shift may change angiotensin activity and produce SMS by altering hormonal or neurotransmitter balance in the chemoreceptor trigger zone, or it may alter the biomechanical properties of the vestibular system

The Sensory Conflict Theory of Motion Sickness

Reason and Brand in 1975 proposed first this theory and a quantitative model was proposed by Oman. It is the most widely accepted theory of motion sickness [32].

Nearly all situations that elicit motion sickness involve some form of sensory motor conflict

Sensory conflict theories typically relate voluntary commands to the musculature (corollary discharge signals) to expected patterns of afferent signals (reafference) from vision, touch, hearing, proprioception and vestibular activity.

However, it is important to realize that whenever arm movements, or virtually, any whole-body activity is executed, the soft tissues of the body are also affected—e.g., lungs, kidneys, viscera, bladder, heart. Sensory compensation occurs when the input from one sensory system is attenuated and signals from others are increased.

On Earth, in a three-dimensional spatial orientation and under Earth's gravitational conditions, sensory inputs are sent to the central nervous system for interpretation. Therefore, the sensory-conflict theory advocates that space motion sickness must be a consequence of the rearrangement of the terrestrial gravity-related relationship between different inputs that are provided by the eyes, skin, joints, muscles, and especially vestibular receptors in the inner ear, when one is exposed to the microgravity environment of space. The interaction of all body systems, commonly used to orient ourselves in relation to the surrounding environment, become disrupted or compromised to some degree. This causes a sensory-motor disturbance that can lead to sensory conflict, which appears to constitute the basic mechanism underlying SMS, an illusion of self-motion associated with spatial disorientation [33]. See Figure 2 below.

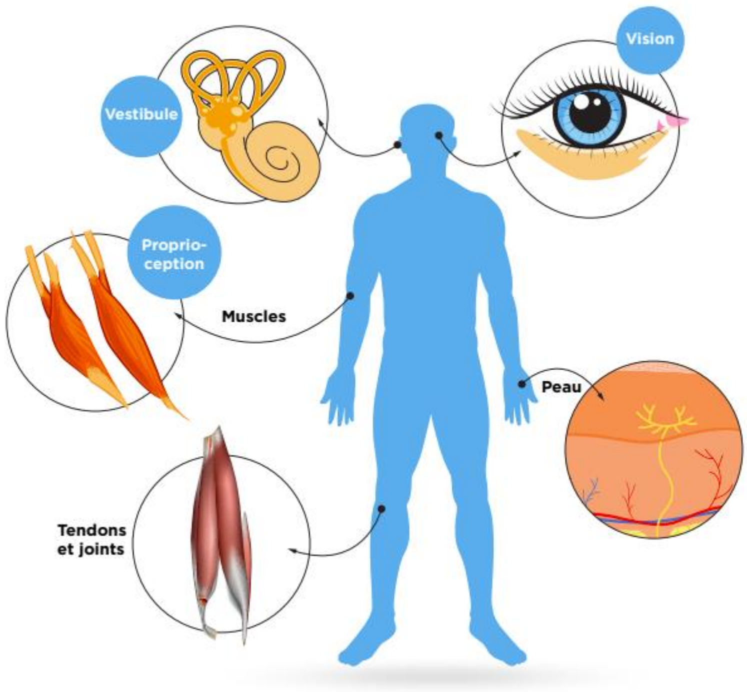


Figure 2: SMS: Space motion sickness

The hypothesis of sensory conflict involves eyes, vestibular system, muscles, cutaneous and joint receptors.

Figure 1 with the permission of the authors, Custaud MA. Blanc S. Gauquelin-Koch, and Gharib C. L'humain dans l'espace. 2020. Edition BoD – Books on Demand, Norderstedt, Germany. Page 90 for Fig 1 and Page 202 for Fig 2

The OTTR Hypothesis; the otolith tilt-translation reinterpretation

The OTTR hypothesis suggest that during adaptation to weightlessness, the brain reinterprets all graviceptor output to indicate translation

This hypothesis has been further refined by Merfeld [34], and Reschke & Clément [35]. It is thought to be the most likely explanation for the SMS.

This hypothesis, named the rotation otolith tilt-translation reinterpretation (ROTTR), suggests that the neural processes resulting in spaceflight adaptation include deterioration in the ability of the nervous system to use rotational cues to help accurately estimate the relative orientation of gravity ("tilt").

NASA classification of space motion sickness (SMS)

None	No signs or symptoms reported
Mild	One or more transient symptomsNo operational impactAll symptoms resolved in 36–48 h
Moderate	Several symptoms of a persistent natureMinimal operational impactAll symptoms resolved in 72 h
Severe	Several symptoms of a persistent natureSignificant performance decrementSymptoms may persist beyond 72 h

NASA classification of space motion sickness (SMS) according to the severity of symptoms. (36)

From Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. Aviat Space Environ Med. 1999 Jul;70(7):705-8.Stangerup S-E, Tjernstrom Ö, Klokker M, Harcourt J, and Stokholm J. Point prevalence of barotitis in children and adults after flight, and effect of autoinflation. Aviat Space Environ Med 1998; 69:45–49.

Treatment

Attempts to prevent space motion sickness have included selection of CM (Crew Member) with a higher tolerance to vestibular stimulation.

Moreover, no correlation has been found with CM who completed pre-flight Coriolis tests and susceptibility to SMS [36].

To note, NASA, JAXA, CSA and ESA astronauts are not screened for SMS although the Russian CM uses this process.

in-flight medication

Many drugs have been tested. Some CM are taken a combination of drugs. An IM injection of 25 mg to 50 mg of promethazine is now the recommended treatment for moderate to severe cases of SMS in the US space program whereas oral and suppository routes are used for less severe symptoms

An analysis of data from STS-1 94 , showed that about 150 of 317 CM experienced SMS. Nearly 90 % of CM affected by SMS took medication with a total of 387 dosing episodes (64). The mean results show:

- Promethazine (Phenergan ™) was taken most often (201 doses) and in most cases resulted in symptom improvement
- 130 CM reported feeling much or somewhat better (65%)
- Although fewer total doses of the combination of promethazine + Dextroamphetamine ware taken (45 doses) slightly more than half of those doses resulted in improvement
- The combination of Scopolamine and Dextroamphetamine ("Scopdex") was reported to be effective in only 37% of cases with 36 of 97 total doses resulting in improvement
- 24% of Scopdex doses was reported to be ineffective compared with Promethazine alone or in combination with dextroamphetamine (10 and 7% respectively).

A recent study from 2023, reviewed 23 peer-studies from based ground studies and spaceflight. It showed that the pharmacological and non-pharmacological tools (Stroboscopic vision and shutter glasses or Autogenic-feedback training exercise (AFTE)) used can mitigate SMS but there is no consensus and lack of a standardized assessment approach to evaluate the most efficient therapy. So, future, standardized testing protocols for spaceflight and ground-based analogs are needed [37].

Upper Respiratory Disorders

Introduction

If symptoms related to changes of the ear/sinus are frequent, diseases and most specifically infections are not so often seen as on earth. Probably one of the most important reason is the fact the crew are leaving together in close environment and due to the quarantine period 15 days before flight, this reduces the risks.

Changes in Space

Eustachian Tube Obstruction Sinusitis and middle and upper respiratory inflammation are known common causes of middle ear effusion, perhaps by blocking the eustachian tube with inflammatory tissue or hypertrophic adenoids or via retrograde flow of secretions through the eustachian tube. Many factors of the ISS environment predispose astronauts to respiratory inflammation and infection. The ISS is an enclosed environment, and air is recirculated after removal of particles by high efficiency air filtration. Sources of particulate matter include cargo, water, experiments, experimental animals, food, crew members, and visitors to the ISS. In microgravity, owing to the lack of gravitational settling, particulates remain airborne until they are trapped by ISS filters. These particulates include bioaerosols created from coughing or sneezing or during speech, increasing the risk of person-to-person transmission of viruses and other microbial agents. In addition, astronauts face many stressors (altered circadian rhythms, strenuous workloads, and radiation exposure) that makes them susceptible to altered immune system function. However, actual infection rates are low, perhaps owing to prelaunch quarantine procedures.

Venous Sinus Pathologic Characteristics

Venous sinus congestion and the consequent lack of adequate venous drainage could generate conditions favorable for the formation of mastoid effusion. The mastoid emissary veins, which drain the posterior auricular veins and the occipital venous plexus, terminate into the transverse and sigmoid sinus system, with the direction of flow normally extracranial to intracranial. Stagnancy of this venous collection system may increase upstream hydrostatic venous pressure and lead to the formation of a transudative fluid edema in the area of the mastoid air cells [38].

Supporting this mechanism, Marshall-Goebel et al recently reported the identification of internal jugular vein thrombosis in 2 ISS astronauts onboard by ultrasonography [39].

Symptoms and Pathology

Symptoms

The nasopharyngeal congestion, barodontalgia, headaches are among the most frequent reported symptoms.

Nasopharyngeal congestion is another common problem for astronauts and cosmonauts in the early period of exposure to microgravity.

Barodontalgia is usually associated with preexisting dental pathology, such as imperfect fillings, pulpitis, and carious teeth; completely normal teeth are not affected. Expansion of trapped air under restorations in the absence of underlying pathology is responsible for only a very small proportion of barodontalgia cases

Ear Barotrauma (Barotitis) is the most common cause of acute ET (Eustachian tube) dysfunction: it is edema or tissue hypertrophy from infection, inflammation, or allergy.

In space flight symptoms of ET dysfunction are generally fullness in the ear, mild intermittent discomfort or pain, and a mild decrease in hearing. On otoscopic examination, the tympanic membrane (TM) shows some retraction with either a normal appearance or slight hyperemia of the vascular strip. The short process of the malleus is prominent or foreshortened, and the malleus may angle more posteriorly than usual.

In chronic cases, there is a "dimple" or retraction of the pars flaccida of the TM, indicating negative pressure. Silent or undiagnosed sinusitis can be associated with ET dysfunction, and barotitis media is directly related to ET dysfunction.

Headaches

From Vein et al, headaches are a common, but rarely voiced, complaint during spaceflights. This is usually attributed as being a part of space motion sickness (SMS). They designed a specific questionnaire based on the International Classification of Headache Disorders, second edition (ICHD-II) criteria, to classify space headache as a separate entity among the secondary headaches, attributed to disorders of homeostasis. Of the 16 male and one female astronaut who participated in the survey, 12 (71%) reported as having experienced at least one headache episode while in space, whereas they had not suffered from headache when on Earth. There were, in total, 21 space headache episodes of moderate to severe intensity in 71% of the sample population. In two (12%) astronauts, the headache and associated symptoms matched the ICHD-II criteria for migraine, and in three astronauts (18%) for tension--type headache. In 12 (71%) astronauts, the headache was nonspecific. The majority of headache episodes (76%) were not associated with symptoms of SMS. Spaceflight appears to trigger headaches without other SMS symptoms in otherwise "super-healthy" male subjects [40].

Of course, headaches can be reported and linked to many diseases and the most important reason in space as proposed by Wilson et al., would be the syndrome of cerebral venous hypertension which explain similarity in between the headache of high altitude and microgravity [41].

To treat efficiently it is better to have the diagnosis. Of course, if not possible a symptomatic treatment might help for short period of time and allow the crew to follow his job. If the treatment is efficient no need to go further; if not efficient at that time the crew will inform his flight surgeon and of course depending on the activities done and the collection of all other symptoms may help to determine what explain this headache. We will not give more details here. The reason for headaches can be: sinusitis, elevated CO_2 as mentioned earlier (15), baro traumatism problem, fever connected to infectious disease: ENT and pneumonitis, congestion (first of all linked to the fluid shift but not only), allergy / dust level as it has been seen frequently in the 2010.

Depending on the reason with tools the crew has on board and with the help of their physician plus the CMO (Crew Medical Officer) the diagnosis should be done easily and treated as such.

Pathology

Sinusitis, although not a prominent disorder among spaceflight crews has to be checked. In a recent study comparing short space flight on board shuttle (<30 days) with a long duration flight (on board ISS, >30 days), Ingelsby et al, in 2020, reported that most astronauts in Long-duration spaceflight (ISS group) had an increased risk of mastoid effusion relative to short-duration spaceflight (relative risk, 4.72; 95%).

This was a retrospective study and we don't have medical details only comparison in both group pre and post flight with MRI measurement (by evaluating changes in the opacification of the paranasal sinuses or mastoid air cells) of the astronauts [42].

Rhinitis, Pharyngitis

Headache and rhinorrhea in spacecraft have multiple causes and are not necessarily suggestive of upper airway infection. Sore throat, cervical lymphadenopathy, and fever are more suggestive of bacterial pharyngitis.

The flight surgeon and the CMO must still consider upper airway inflammation in the differential diagnosis of pharyngitis, however. Since breaches in preflight quarantine are possible, treatment of a crewmember with pharyngitis in the first days of a space flight is similar to that on the ground.

Otitis

Otitis is linked to ET dysfunction. The most common cause of acute ET dysfunction is edema or tissue hypertrophy from infection, inflammation, or allergy. Chronic dysfunction is usually associated with anatomic abnormalities, such as scarring and chronic disease. It could be frequently reported by the crew members but in fact, the CM uses regularly Valsalva Maneuver and prevent such traumatism. Of cause infection is the most frequent reason of otitis. Moreover, microgravity may change the physical presentation of otitis media with effusion, as exudate would not "layer out" behind the tympanic membrane. Otherwise, the principles of clinical diagnosis of otitis media and its treatment are no different in space flight than in terrestrial practice.

The risk of barotrauma increases with EVA and furthermore increases with a history of nasal or middle ear disease, otologic surgery, upper respiratory infection (URI), perforation, cholesteatoma, chronic use of decongestant nasal sprays, and previous barotrauma.

Middle ear pathology, which varies with the rate and magnitude of pressure change, is associated with negative pressure and includes mucosal hemorrhage and congestion, edema, serous and hemorrhagic effusion. TM rupture most commonly occurs in the anterior portion, over the middle ear orifice of the ET. Significant force may also cause an annulus rupture. Otoscopic appearance can range from TM retraction with backward displacement of the malleus, a prominent short process, and anterior and posterior folds, to hyperemia or hemorrhage of the tympanic membrane with varying amounts of serous and sanguineous fluid visible behind the membrane.

The Teed barotrauma classification scheme stages the clinical observations and quantifies sequential damage in 5 Grades [43].

Grade 0 – no visible damage

Grade 1 – congestion redness around umbo (2 psi/100 mmHg differential)

Grade 2 – diffuse congestion redness of TM (2–3 psi/100–155 mmHg differential)

Grade 3 – hemorrhage within the TM

Grade 4 – extensive middle ear hemorrhage with blood and bubbles (air/fluid level) behind TM

Grade 5 – entire middle ear filled with dark blood. Optimally, evaluation techniques would allow identification of susceptible individuals prior to exposure to potentially damaging pressure excursions.

Allergy

We cannot ignore the increased risk of allergies in space as stated by the report made by Wotring in 2015 on the medication used during spaceflight. It showed that rash were mentioned in 46 reports. Half of ISS astronauts and third of astronauts on Space Shuttle reported regular or repeated used of decongestants, and 38% of the astronauts treated these symptoms repeatedly [44]. To clarify often crew report headaches, congestion in the upper respiratory tract which are connected to allergy. See Table 2 below.

Despite the common report of sinus pressure among astronauts, most did not develop or experience worsening of preexisting paranasal sinus mucosal thickening. This finding is inconsistent with reports of medication use by astronauts because head congestion is the most common reason

Table 2 shows the most frequent medication used on board ISS during long duration mission compared to short mission with Shuttle and Submarine from 101 days.

Medication	ISS	Space shuttle	Submarine
NSAID	4.92	1.11	0.123
Acetaminophen	0.924	0.043	0.205
Sleep aids	2.568	1.767	0
Decongestants/antihistamines	2.432	0.808	0.016
Dermatologicals	1.243	0	0.2
SAS treatments	0.784	0.84	0
Gastrointestinal treatments	0.162	0.064	0.066
Ophthalmic treatments	0.162	0	0
Anti-infectives	0.054	0	0

First most used medication is the NSAID followed by almost equally the sleep medication and the decongestants.

With the permission of the author V Wotring VE. FASEB J. Medication use by U.S. crewmembers on the International Space Station. 2015 Nov;29(11):4417-23. doi: 10.1096/fj.14-264838 (44).

Treatment of upper respiratory disorders

Nasal Congestion

Although nasal congestion poses minimal risk to the crew, it can distract from mission tasks and increase insensible fluid loss from mouth breathing. Intranasal oxymetazolone is used most often for this condition, followed by anti-allergenics and diphenyhydramine.

Rhinitis, Pharyngitis, Otitis

Antibiotics are used if clear signs of upper respiratory infection are present. Several classes of oral antibiotics are available in Space Shuttle and ISS medical kits, including penicillins, β-lactamase penicillins, macrolides, and cephalosporins. These antibiotics can be used to reduce the incidence of suppurative complications and perhaps shorten the duration of symptoms. Otitis media suspected during space flight must be aggressively treated with oral antibiotics and decongestants.

Ototoxic antibiotic drops (aminoglycoside antibiotics) should not be used, as there is a possibility of round or oval window rupture. Antibiotics should be used for 7–10 days.

Oral decongestants may be helpful.

Sinusitis

Treatment for acute sinus barotrauma, whether on the ground or in space, is based on decongestants and antibiotics. Repeated barotrauma should be evaluated with computed tomography (CT) scan of the sinuses when available. Functional Endoscopic Sinus Surgery (FESS) may be useful in evaluation of repeated sinus barotrauma in aviators and astronauts.

Hearing Loss

For the past 45 years, temporary and permanent hearing loss has been an outcome of long-duration spaceflight. In 33% of astronauts, the spaceflight environment caused permanent hearing damage, and in some cases astronauts were unable to further pursue spaceflights as a result [17].

Change in the Inner Ear

Hearing/auditory Function

Mechanisms involve microgravity itself of course as seen in previous chapter and mainly connected to fluid shift which may hurt and /or change the inner ear. But on the hearing apparatus itself the changes induced by the spaceflight are unknown. Currently, research has shown sensorimotor and perceptual performance deteriorates after spaceflight. Certainly, the resulting hearing loss may not be caused by a unitary phenomenon, but rather due to a combination of factors endured during space flight. While presumed to be noise induced, no link has been established between hearing loss and noise exposure during spaceflight

Hearing loss in space may then be a result of structural or functional deficits in the peripheral auditory system. But interesting findings in elderly people could be the same explanation because change in space accelerate the process of aging.

Cochlear Hair Cell Damage

We know from earth studies in elderly people that sensorineural hearing loss is caused by the loss of sensory hair cells (HC-s) or a damaged afferent nerve pathway to the auditory cortex. Damage to crucial cochlear structures is mostly irreversible and results in permanent hearing loss.

Wagner et Shin. explain the damage in the sensory hair cells of the inner ear in case of hearing loss in elderly people. Hair cells can accumulate damage stemming from a variety of factors including age, noise, and genetics. 4 major damages have been seen. Some site of a hair cell are vulnerable to damage. First, the tip link breakage. It can be broken by overstimulation or by in vitro calcium chelation, leading to a loss of tension on the MET (mechanical electrical transduction). Second, Stereocilia core damage: Intense noise exposure damages the stereocilia F-actin core. Third, Ribbon synapse: the synapse might be lost due to exposure to loud noise or prolonged exposure to milder noise, even in absence of permanent hearing threshold shift. Their loss can reduce hearing ability in noisy environments, known as “hidden hearing loss”. And fourth, Hair cell death. It has been seen as F-actin scars at the sites of missing hair cells. When hair cells die, they are extruded from the epithelium. This induces holes in the sensory epithelium caused by the extrusion of dying hair cells. Those are sealed by projections from nearby supporting cells to preserve barrier integrity [45].

Alternatively, the gravitational change may impact the mechanistic properties of the peripheral auditory system as changes are seen in vestibular system. Ear bones (ossicles) move fluid inside the ear that, in turn, stimulate hair cells, which send signals to upper areas of the brain. The fluid within the ear will have a different weight (mass*acceleration of gravity) in microgravity relative to Earth which may affect ossicle functionality. Cochlear hair cells, like vestibular hair cells, can change their ribbon synapses, or the mechanosensitive channels in the ear can change affinity. Hearing loss in space may be a result of structural or functional deficits in the peripheral auditory system [45].

A MRI study comparing scans pre- and post-spaceflight showed decreased gray matter in the temporal and frontal regions attributed to neuroplasticity. Collectively, spaceflight studies have shown that sensorimotor and perceptual performances deteriorate in spaceflight conditions.

Other Facter from Space Environment Issue

A number of ototoxic agents such as carbon monoxide and solvents may synergistically interact with noise to produce hearing loss.

Exposure to simultaneous noise and vibration results in temporary and permanent threshold shifts and hair cell loss greater than with noise alone (81). A human study examined combinations of noise (two categories: no noise and stable broadband A-weighted noise of 90 dBA), whole body vibration (three categories: no vibration, sinusoidal whole body vibration of 5 Hz, z-axis and stochastic whole body vibration of 2.8 to 11.2 Hz) and dynamic muscular work (three levels: 2W, 4W, 8W). Noise was the greatest single contributing factor for TTS (temporary threshold shift). TTS increased further as a result of the combinations of noise plus vibration and noise plus muscular work. The combined effect of all three factors (noise, vibration, and work) on the TTS results was greatest when the vibration was stochastic and the dynamic muscular work was light (2W); by increasing the workload the measured TTS levels were attenuated.

Light dynamic muscular work and cardiovascular activity may have enabled the interaction of noise and vibration, while strenuous muscular and cardiovascular activity in some way negated the effects of noise and vibration [46].

Heat stress also appears to play a role; a 10°C ambient temperature increase resulted in 5 to 10 dB greater TTS when subjects were exposed to noise and whole body vibration.

The microgravity environment, dynamic workload, stress, continuous 24-h-a-day moderate noise exposure, electromagnetic radiation, and potential for toxic exposure all may lead to cochlear hair cell damage and greater than expected noise induced hearing loss.

Numerous epidemiological studies have been conducted and showed that hearing levels and longitudinal patterns of hearing change are highly variable. This variability has been attributed to smoking, genetic factors, and cardiovascular risks.

Hearing sensitivity is particularly vulnerable to hazardous noise exposures.

All astronauts benefit from a hearing-monitoring program in which crew members undergo audiometric testing at least once per year during their active astronaut career (and even more frequently when assigned to space missions). From NASA side, later, when participating in NASA's LSAH program, former astronauts may continue to have their hearing tested for the rest of their lives. Female astronauts show no significant differences in hearing thresholds between ears except in those older than 55 (though the sample size for this population is rather small at that age), when the left ear thresholds are slightly better than those in the right ear. Male astronauts show greater hearing loss in the left ear than in the right ear at every age; this finding is consistent with many demographic studies, particularly those in which right-handed subjects have shot shoulder-fired weapons (exposing the left ear to most of the blast wave from the weapon's muzzle). The vocational and avocational activities of many astronauts, military and nonmilitary, often include such firearms.

An important finding from this database (unpublished data) is that although males and females show the expected age-related differences in hearing loss, spaceflight does not seem to affect men and women differently.

Treatment, Prevention

Hearing protection countermeasures include foam ear inserts, passive muff headsets, and active noise reduction headsets. Hearing protection is recommended when the crewmembers' 24-h equivalent noise exposure exceeds 65 dBA or when they are exposed to high levels of noise such as when exercising on the treadmill (TVIS).

Countermeasures

The Best Countermeasure is the Prevention

As usual the most important factor to prevent ENT issues are the selection process and the follow up. Some diseases will be already part of rejection if the candidate has for example, a hearing loss which will be severe enough to interfere with the duties, infections really large and which cannot be treated…

Each year the exam of the astronaut will include tympanometry and audiometry. For all astronauts, some pre-flight hearing assessment will be done by the NASA audiologist. In flight, each astronaut is checking her/his hearing assessment few times and the results will be analyzed and compared with pre flight by NASA audiologist. They prepare as well Custom fitted hearing protection earplugs used by the crew in flight. The Hearing Assessment in flight is usually performed 3 times in 6 months mission [20].

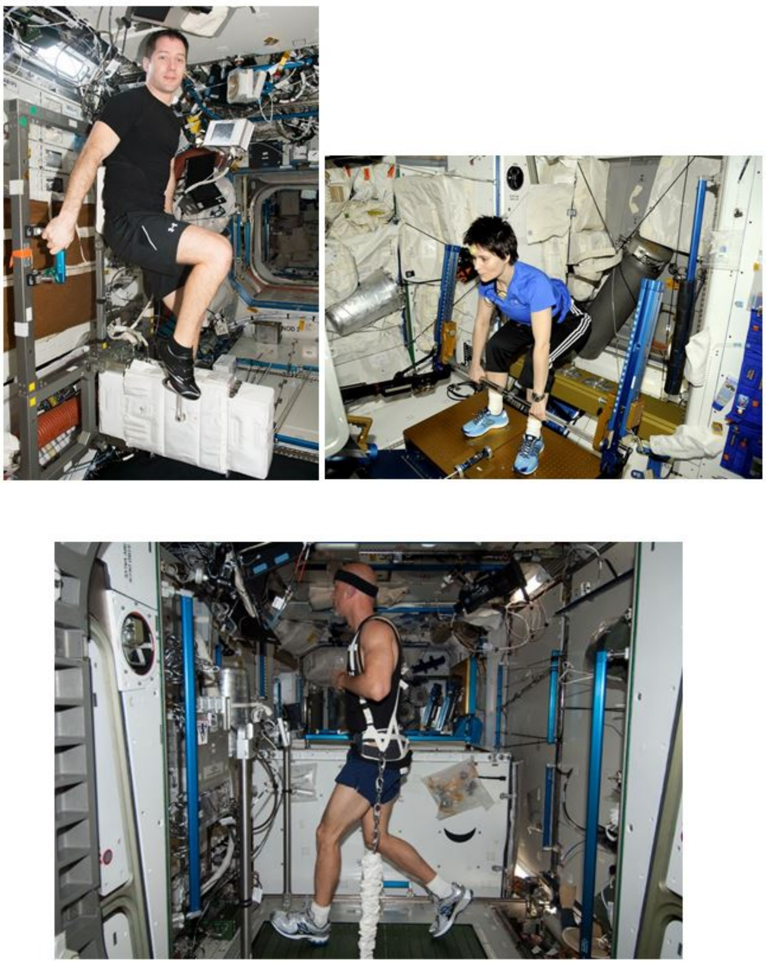
In order to ensure a safe acoustic environment for the crew, noise levels in the ISS modules are routinely monitored. In the Service Module, the primary residence for ISS crews, noise levels have been measured at 69 dBA during ground testing, and 67 to 72 dBA on orbit [47].

Basic Countermeasures on Board Space Station

It would be very good to find one countermeasure acting on all system but until now each team applies countermeasures for each system. But nowadays, two main countermeasures are the most efficient against the microgravity effect: the exercise on board and adequate nutrition. Furthermore, except some preventive measure like the quarantine pre flight to avoid infectious diseases and wearing ear plug to minimize level of noise on board the station, no specific countermeasure is used currently against ENT impairment.

Exercise

Also, the best known countermeasure is the sport.. To avoid to lose too much bone and muscle it has been established since the beginning of the space flight that astronauts have to practise 2h daily sport activity. This activity will be adapted to the phase of the mission and because of the lack of gravity doing treadmill must be performed with a harness to reproduce tension on the body so from the beginning until the end of the mission the goal of the trainer will be to increase regularly the power so that the astronaut after the 6 months in flight has not lose too much. Three types of sport will be done on board the station, the cyclo-ergometer, the treadmill both of those activities will increase or better stabilize the aerobic activity while the new ARED (Advance Resistive Exercise Device) will train the strength [46]. See Figure 6 with all devices used from NASA/ESA side on board the ISS.



Pictures: devices on board the ISS used by NASA and ESA astronauts

With the permission of ESA (ESA picture) The devices on board the ISS, On top on the left side, Thomas Pesquet during his last mission doing CEVIS. On top on the right side, Samantha Cristoforetti during her second and last mission doing ARED exercise. And below, Luca Parmitano during his first mission, doing Treadmill exercise.

Nutrition/Food Prevention Currently on Use

All crew member in the NASA/ESA team receive recommendation with the number of calories intakes, macronutrients and micronutrients adapted to the level of their metabolic rate performed before fight and adjust to their level of exercise (As well if EVA, the level will be adjusted). The MR (Metabolic Rate) is repeated two times on Earth before the flight. They receive Vitamin D for ESA/NASA astronauts, multivitamins on the Russian side. A nutritionist is following and helping the crew by given them recommendations. The ESA astronauts in flight used a tool developed before the first flight of the French astronaut Thomas Pesquet. This tool allows the crew member to follow day by day her/his own nutrition (Diet tracker in space : Every meal on EveryWear https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Astronauts/Diet_tracker_in_space)

As seen in previous chapter to reduce hearing loss, supplementing with an antioxidant combination of L-N- acetyl cysteine and low dose salicylate could be a new combination because was effective in reducing permanent hearing loss as well as hair cell loss in a chinchilla model [47].

Specific Measures for ENT Diseases

Hearing

Countermeasures against spacecraft noise include design engineering controls, sound insulation materials, and hearing protection. Engineering and design controls to reduce noise should be the primary focus of any hearing conservation program, but this is not possible in all situations. Quiet fan technology exists but may act as penalty in weight, power consumption and circulation efficiency, all of which are crucial factors in spacecraft environmental controls.

Advanced composite materials with excellent low frequency attenuation properties could be applied as a barrier protection around noisy equipment or used on personal protective equipment worn by the crew.

Hearing protection countermeasures include foam ear inserts, passive muff headsets, and active noise reduction headsets. Hearing protection is recommended when the crewmembers' 24-h equivalent noise exposure exceeds 65 dBA or when they are exposed to high levels of noise such as when exercising on the treadmill.

However, wearing hearing protection for long periods of time is not an optimal solution because of discomfort, increased risk of ear infections, difficulty with communications, and reduced effectiveness when removed frequently to communicate. Crewmembers should also be aware that playing music over personal headphones or speakers in an attempt to mask noise only increases risk of hearing loss. While noise levels on spacecraft are far below the 110 dBA SPL levels considered necessary for mechanical damage, the continuous nature of this sound environment may cause long term metabolic exhaustion of the inner ear cochlear tissue.

As mentioned earlier in the chapter, periods of quiet rest are needed to allow the cochlea to recover from hearing fatigue. Although most people are able to experience relatively long periods of quiet while sleeping, this was not possible in the environment found on the Mir.

The standard occupational exposure to environmental noise assumes an 8-h exposure with 16 h of acoustic rest. Periods of relative quiet (less than 70 dB) have been suggested for treatment of very high levels of noise exposure, to allow hair cells to repair themselves. Reestablishing a "rest period" through engineering methods, e.g. as with sufficiently quiet sleep quarters or provision of pharmacological protection or repair enhancement may constitute effective countermeasures.

Future Technologies or Pharmaceutical Research in Development

For future long-duration missions, equipment needs to be designed to comply with the limits and to be able to troubleshoot potential noise problems quickly. It is obvious that violating noise regulations, whether for commercial, personal, or any other reason, will have detrimental consequences.

Kadeem notes in his study that changes in the ear fluid's weight would have an impact on ossicle functionality and mechanosensitive processes. Furthermore, compared with separate exposures, simultaneous vibration and noise exposure are more harmful for hearing function. Vibration exposure may damage hair cells and change cochlear blood flow by causing vasoconstriction [47]. So we really need to focus on finding new device more comfortable and reducing the noise which seems really responsible for the hearing loss seen in almost all crew member after a long time exposure to spaceflight.

Another aspect on which we might have an impact would be the pharmaceutical drugs. Nowadays it is clear that anti-oxidant should be helping in all physiological process first of all when radiations are involved but not only because we know that our level of stress will decrease the immune system defends directly acting via the loss of anti oxidant self cells by the subject. Lot of anti-oxidant have been proposed nowadays we still have two challenges in space, find the best drugs for our astronauts but may be we need as well to study the pharmacodynamics and pharmacokinetic in space.

May be as well if we think about interplanetary mission, we will need to have all medications on board but the more material we need to bring the most expansive it is, nowadays lot of researchers are working on new tools to produce, food and/or medications even life tissues like 3D printing.

Conclusions

Physiology and pathology linked to ENT involves few body systems such the vestibular, neurological system including brain and neuro sensory system. And consequently, few organs, ears, nose, sinus, throat vestibule are concerned.

The most frequent ENT symptom in space is the SMS. It is very common as well on earth. In space, nowadays the impact has been reduced due to the increase of flight duration. Despite the fact it has been known and studied since the beginning of space era, it is still not fully understood and is the object of many studies combining scientists from different field such, ENT, neurology, cardiology and even more… probably because the explanation is multifactorial. Up to now, no better countermeasure than the medication has been found to improve it! Furthermore training seems even not helping because if the crew flew few times, we could expect he becomes use to it and less sick but it is not the case. This reinforces the reason why nowadays the hypothesis for SMS is in favour on implication of multiple factors involved. For example since the beginning of their flight the Russian astronauts are doing at least two preventive measures to decrease it, the tilt test starting 5 to 7 days before the flight and the rotation chair … if NASA and ESA used to do it at their beginning of the cooperation they decided to stop it because in some case it was as if the crew were sicker … but of course rotation chair is part of the cosmonaut training and not of the astronaut training which is probably the reason why it seems worst for the astronauts than the Russian astronauts (cosmonauts).

If we excluded the most challenging issue: baro-traumatism due to depressurization during EVA and potential other issues (Orbital debris with the station …), hearing loss has probably the most impact on the crew after long flight. The most frequent issues are linked to the fluid shift impacting the CM with congestion responsible for headaches loss of concentration and can be responsible for URI like parasinusitis, otitis infection. CM are very well trained to the Valsalva maneuver and perform regular acoustic measurement plus send picture of their TM to their flight surgeon before/after EVA and of course each time needed as necessary in case of ear complain.

Regarding hearing loss, many pathological conditions, such as injury, aging, inflammation, ischemia and subsequent reperfusion, excessive production of reactive oxygen species have been postulated to occur and cause cell damage. Evidence has been accumulated indicating that reactive oxygen species play a substantial role in damaging the inner ear secondary to various toxins and noise. Continuous high-level noise is associated with cochlear production of superoxide anion and the hydroxyl radical, both of which are capable of inducing cochlear damage and loss of function. Noise modulates the level and activity of key antioxidant compounds in the inner ear such as glutathione (GSH) and a variety of antioxidant enzymes. Supplanting or reducing inner ear, GSH either ameliorates or intensifies noise induced permanent threshold shift (NIPTS), and a variety of strategies to augment cochlear antioxidant defenses have been shown experimentally to reduce noise related hearing loss. It has recently been shown that an antioxidant combination of L-N- acetyl cysteine and low dose salicylate was effective in reducing permanent hearing loss as well as hair cell loss in a chinchilla model, opening up the very real and exciting possibility of utilizing pharmacological agents to prevent NIPTS [47].

As mentioned in the dedicated chapter it will be interesting to compare at the anatomical/structural level the changes induced by gravitation and what has been found on elderly people by Wagner et Shin. (the damage in the sensory hair cells of the inner ear in case of hearing loss in elderly people).

We already knew at least from the bone/musculoskeletal system that space is “accelerating the aging process”, fortunately CM recover but some recent studies are showing that probably not completely at least 1 to 2 years after the flight [8].

Further studies are needing to check if this hearing loss could be as well a consequence from the multiple factor inside the station but mainly the accelerating aging process. This would be one more reason to say that spaceflight is a good modal for aging and could be used to find new devices or new pharmacological measures to delay aging. This will be important for the next future because the number of elderly people is increasing on Earth and furthermore because we enter in a new era in space with new exploration (longer and deeper space mission as stated by the LEO). Thus, pharmacological strategy with anti oxidant could be a part of the game [48]. We should implement further work to improve our understanding on the role of oxidative stress in NIHL and develop an effective pharmacological strategy to reduce cochlear damage in the spacecraft environment associated with moderate continuous noise. And as mentioned earlier to feel an important gap in space pharmacology we should conduct studies with clinical trials on board space station to improve our knowledge in pharmacokinetics and pharmacodynamics, which remain a vastly unexplored field, we should develop clinical trials on board. Furthermore, it will be necessary to develop technologies that enable and support the on-demand production of medicines or even food in space like three D printing [49].

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