Volume 18, No 3 | International Journal of Radiation Research, July 2020

Why can COVID-19 fatality in space be significantly higher than on Earth?

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► ***Original article***

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Revised: March 2020
Accepted: April 2020

Int. J. Radiat. Res., July 2020; 18(3): 421-426

DOI: 10.18869/acadpub.ijrr.18.3.421

ABSTRACT

Astronauts are exposed to a wide variety of stressors ranging from radiation and microgravity to persistent fluids shifts, circadian shifts and the psychological stress of prolonged isolation and confinement. On deep space missions, beyond the range of the Earth's magnetosphere, ionizing radiation may increase oxidative stress and DNA damage, immune system dysregulation and alter the effectiveness of the cellular defense mechanisms. By reviewing the health problems reported by astronauts participated in previous space missions, it is evident that viral infections are not rare in space. Recent reports suggest that COVID-19 can last for a long time in communities. Although NASA implements countermeasures designed to limit crew illness during space missions such as a pre-flight quarantine, it is not clear whether an outbreak can be prevented. Currently, it is not likely that astronauts could get a viral infection, but the consequences of potential life-threatening viral diseases such as COVID-19 should be better characterized. In this paper we discuss why COVID-19 fatality in space might be significantly higher than on the Earth. The reasons for such an increased risk include 1) uselessness of social distancing due to microgravity 2) immune system dysregulation 3) possibly higher mutation rates of RNA viruses such as the novel coronavirus (SARS-CoV-2) 4) existence of strong selective pressure and 5) decreased maximum oxygen uptake. Given these considerations, the combined effects of microgravity, space radiation (and possibly other major space stressors) on the immune system of astronauts exposed to SARS-CoV-2 and possible interactions of the virus, space stressors and host should be carefully investigated.

Keywords: *Coronavirus, COVID-19, Immune system, Space, Astronauts, Microgravity, Space radiation, SARS-CoV-2.*

INTRODUCTION

On deep space missions, beyond the protection of Earth's magnetosphere, ionizing radiation may increase oxidative stress, immune dysfunction, DNA damage and alters the effectiveness of the mechanisms involved in cellular defense mechanisms including DNA repair. Besides radiation, astronauts are exposed to other stresses such as microgravity, persistent fluids shifts, space radiation as well as circadian shifts and psychological stress due to prolonged isolation and confinement [1-5]. Immune system deregulation has been reported

[DOI: 10.18869/acadpub.ijrr.18.3.421]

during spaceflight exploration missions [6]. However, it should be noted that deregulation of the immune system can be due to factors other than radiation [7]. Although all organisms living on Earth have evolved strategies to confront ordinary levels of DNA damage [8,9], space stressors can lead to increased DNA lesions, and ultimately these lesions (e.g. double strand DNA breaks, chromosomal aberrations, micronucleus formation, and mutations) can significantly increase the risk for severe adverse health effects [1]. Moreover, during space missions, viral and bacterial infections may occur. The history of influenza in space dates back to 1968, when Apollo 7 crew members grew ill in space and this illness had a significant impact. It's believed that Commander Wally Schirra possibly came aboard with a mild cold and transmitted the disease to other crew. Presumed viral illness was also experienced by Apollo 8 and Apollo 9 astronauts. A review of medical events and recurrences among astronauts of all nationalities on Russian space station Mir from March 14, 1995 through June 12, 1998 showed 3 cases of acute respiratory infections, conjunctivitis and dental infections [10]. Moreover, reactivation of latent herpes virus, an indicator of down-regulation of cellular immunity, has been reported in astronauts participating in space shuttle (10–16 days) and International Space Station (ISS) (≥180 days) missions [11-13]. Some reports indicate journeys beyond low earth orbit (LEO) and into deep space are associated with a growing risk of serious infection for astronauts. How we can treat infections in space may be compromised by significant changes of human physiology [14].

Figure 1 shows the proportion of infectious diseases among 42 reported notable medical events reported in 21 of 46 ISS astronauts [15]. Although United States' National Aeronautics and Space Administration (NASA) now implements countermeasures designed to limit crew illness during space missions such as a pre-flight quarantine and mitigation strategies including microbial monitoring of food, water, vehicles, and cargo, it is not clear whether NASA, The European Space Agency (ESA) and other space agencies are able to fully avert an astronaut disease outbreak.

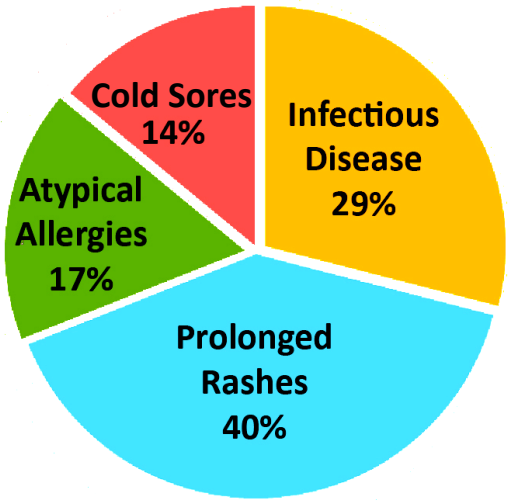

Figure 1. The proportion of infectious diseases among 42 notable medical events reported in 21 of 46 ISS astronauts. (Originally from Crucian et al. 2016 [15]).

In recent years, humans have suffered several severe respiratory infectious disease outbreaks such as SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), avian influenza A(H7N9), and influenza A(H1N1)pdm09 [16]. In December 2019 a new pathogen, firstly named as SARS-CoV-2 was found responsible for pneumonia outbreaks in Wuhan, China. This disease is named and known as COVID-19 pneumonia [17]. Basic reproduction number of COVID-19 was estimated to be 2.68, which means that one infected patient may lead to more than 2 new patients [18]. COVID-19 is a respiratory infection caused by the RNA virus SARS-CoV-2, a novel type of coronavirus that causes a variety of symptoms in infected people. SARS-CoV-2 is highly infectious [19], has an incubation period and the early symptoms of this infection are not typical. However, fever, dry cough, shortness of breath, fatigue, body aches are among the most frequent symptoms [20]. However, some people have reported other symptoms such as headache, abdominal pain, diarrhea, and sore throat indicating that the virus can affect more organ systems than just the pulmonary system. SARS-CoV-2 virus can be spread through respiratory droplets as well as touching contaminated surfaces and then touching one's

[DOI: 10.18869/acadpub.ijrr.18.3.421]

face [20].

The US CDC (Centers for Disease Control and Prevention) believes that a COVID-19 outbreak could last for a long time in communities [20]. The global number of confirmed cases of COVID-19 more than doubled from ~76,000 cases on 20 Feb 2020 to more than 275,680 on 20 March 2020, and a further increase to 2,480,503 on 20 April 2020 indicating a very rapid growth in less than a month [20]. A rapid doubling rate is indicative of a serious public health problem because even developed countries with advanced medical and healthcare systems are apparently overwhelmed by the huge number of patients. This was exactly the case in the Lombardy, Italy, where not only hospitals were overloaded but a growing number of health care providers were under quarantine after they had tested positive. In Lombardy, of COVID-19 patients required intensive care. However, among proven infections, early reports suggested that approximately 5% of the patients required intensive care [21]. Being elderly and having comorbid conditions (particularly diabetes and cardiac disease) are two key factors associated with requiring intensive care in COVID-19 patients [16].

The Scope of Problem

By using measures such as pre-flight quarantine, it is unlikely that astronauts could contract an infection, but the consequences of potential infections such as COVID-19 should be better understood. In this paper we discuss why COVID-19 fatality in space can be substantially higher than on Earth. The rationale for such an increased risk is at least as follows:

1. It is well documented that COVID-19 is mainly transmitted through droplets. These droplets are relatively heavy and hence, where possible, social distancing of 1.5m prevents the infection, thanks to Earth's gravity. On the ISS, everything is experiencing a free fall condition and therefore social distancing will not be practical nor effective. This effect also applies to Mars missions unless the spacecraft are designed to produce a simulated gravitational effect. Moreover, the restricted spacecraft volume and recycled atmosphere most likely increases the probability of transmission of the virus. Figure 2 shows how social distancing can help people prevent the spread of the novel coronavirus (SARS-CoV-2). When a COVID-19 infected person speaks or exhales or coughs or sneezes, the virus-containing droplets travel about 3 to 6 feet (1 to 2 meters) before the Earth gravity pulls them to the ground. In contrast, due to microgravity, social distancing cannot help ISS astronauts avoid such human-human transmission.

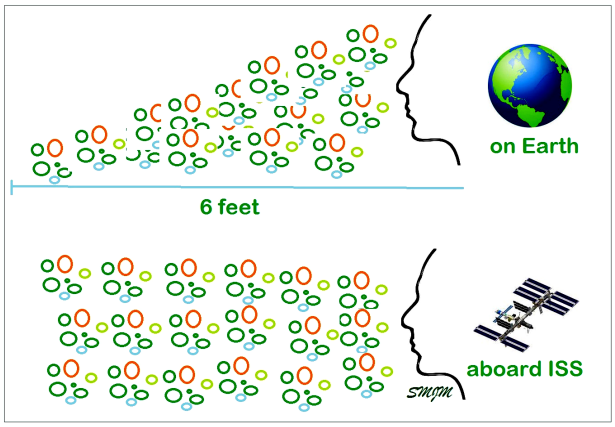

Figure 2. As long as we live on the Earth, when a COVID-19 infected person speaks or exhales or coughs or sneezes, the virus-containing droplets travel about 3 to 6 feet (1 to 2 meters) before the Earth's gravity pulls them to the ground. Due to microgravity, social distancing cannot help ISS astronauts prevent the spread of novel coronavirus (SARS-CoV-2).

2. There is some evidence indicating that the immune system plays a key role in the risk of serious illness due to COVID-19. Given this consideration, as astronauts usually experience different levels of immune dysregulation during long-term space missions, the fatality of COVID-19 in space could be much higher than what we observe on Earth. Crucian *et al*. have previously addressed the dysregulation of the immune system in deep space missions. The immune system seems to be strongly susceptible to space stressors. Crucian *et al.* state that during space missions beyond the reach of our magnetosphere, stressors such as elevated levels of space radiation can lead to increased oxidative stress (leading to alterations in the DNA damage rate and the efficiency of DNA repair mechanisms as well as chronic

[DOI: 10.18869/acadpub.ijrr.18.3.421]

inflammation and immune system dysfunction [2,7,22].

3. Viruses, in particular RNA viruses such as the novel coronavirus (SARS-CoV-2) [23], are always mutating. It is even feared that due to frequent mutations in SARS-CoV-2, development of an effective vaccine could be difficult [23]. Given this consideration, developing more sensitive inspection and effective treatment methods have been suggested as urgent needs [23]. The issue of viral mutations is also of great importance because it can easily explain potential relapses of the viral infectious disease [24]. It is worth noting that genomic analyses suggest that SARS-CoV-2 virus possibly evolved from a strain found in bats. Therefore, an envelope spike mutation in the bat strain has possibly triggered virulence and transmissibility in humans [24]. The crown-like appearance of SARS-COV-2 virus is due to the presence of spike glycoprotein's on its envelope [24]. Thus, due to key stresses such as radiation and microgravity, the rate of mutation in SARS-COV-2 could be higher in space.

4. Early studies on microorganisms showed that by trying to inhibit the growth of bacteria or kill a particular "bug", a very strong selective pressure may be exerted that can induce drug resistance. In a similar pattern, exerting a strong selective pressure on viruses such as SARS-CoV-2 can lead to new mutations. It is worth noting that the combination of antiviral drugs and space stressors (e.g. radiation and microgravity) might augment the selective pressure and increase the rate of mutations.

5. It has been reported that astronauts usually experience a decrease in their maximum oxygen uptake (VO2max) "the majority of astronauts will experience a decrease in VO2max after long-duration space-flight. Interestingly, the two astronauts with the highest preflight VO2max had the greatest loss on R+1/2, and the astronaut with the lowest preflight VO2max increased by 13%. Thus, maintenance of VO2max may be more difficult in astronauts who have a high aerobic capacity, perhaps requiring more intense in-flight exercise countermeasure prescriptions" [25]. It remains possible that a decreased VO2max could make acute respiratory distress syndrome (ARDS) caused by COVID-19 worse than what we would expect on Earth. COVID-19 can occasionally progress rapidly to ARDS causing respiratory failure, septic shock, or multi-organ failure. "Patients develop ARDS in the late stages of the infection when the virus has caused significant damage to the lungs. In the process of trying to fight off the virus, the body sends immune cells to the lungs causing an inflammatory reaction. The reaction can cause small blood vessels in the lung to leak fluid and fill up the alveoli, which are tiny air sacs in the lung, that process oxygen, according to the American Lung Association. That makes it difficult for the oxygen to enter the bloodstream and arrive to the body's organs [26].

6. Recently, a modified method that involves giving COVID-19 patients a single ultra-low dose of X-ray radiation has been discussed. In contrast to antiviral drugs, a single dose of X-rays at these doses (10 cGy to 100 cGy) cannot exert a significant selective pressure on the SARS-CoV-2 virus and hence does not lead to directed accelerated evolution of these viruses that could make them more dangerous and more resistant. Some studies show that low-dose radiation regulates lymphocyte counts, controls bacterial co-infections, and can quell excessive inflammatory responses via M1 to M2 macrophage polarization [27], exactly what is needed for COVID-19 patients. Further studies are needed to clarify whether in case of a possible COVID-19 infection; astronauts can use this treatment method.

7. Recent findings indicate that a fraction of recovered COVID-19 patients still may be carriers of the SARS-CoV-2 [28]. It is worth noting that reactivation of latent herpes virus has been previously reported in astronauts participating in Space Shuttle and ISS missions [11-13]. Given this consideration, it can be hypothesized that reactivation of SARS-CoV-2 in astronauts previously recovered from COVID-19, would be possible.

8. There are also other issues that need attention in space. For example, to have an effective vaccine, we need a virus with a stable genome. But in space, due to multiple key

[DOI: 10.18869/acadpub.ijrr.18.3.421]

stressors, the genome of viruses (in particular RNA viruses like SARS-CoV-2) would be under a strong selective pressure that could cause the virus to undergo more mutations and evolve more rapidly. Thus, it can be hypothesized that vaccines (whether given before take-off or after) would be less effective for astronauts in the space environment.

Given these considerations, the immune system plays a key role in ARDS pathogenesis. Cytokine release syndrome or "cytokine storm" is a well-known phenomenon in many diseases that affect the young and healthy, including the 1918 H1N1 pandemic. Although low levels of space radiation can boost the immune response, through ARDS-like immune-mediated mechanisms, it can lead to a disastrous situation. There is no indication that COVID-19 does not induce ARDS early in the course of most healthy patients (although it can certainly do so later in the disease) nor does the SARS-CoV-2 coronavirus induce a cytokine storm in most cases. However, in serious cases of COVID-19 a cytokine storm may indeed be the proximal cause of death [29].

It should be noted that immune system-related parameters may contribute to the development of the COVID-19-associated complications. Elevated levels of numerous pro-inflammatory cytokines (such as IFN-α, IFN-γ, IL-1β, IL-2, IL-6, IL-7, IL-10, IL-12, IL-18, IL-33, TNF-α, TGF-β) and pro-inflammatory chemokines (such as CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10) were detected in patients with severe COVID-19 [20-31]. This phenomenon (the cytokine storm) can paradoxically promote viral replication and enhance inflammatory-mediated lung damage which lead to other complications such as acute respiratory distress syndrome (ARDS), pneumonia, shock, respiratory failure, organ failure and possibly death [30]. Cytokine storm, is a deadly uncontrolled systemic inflammatory response resulting from the release of great amounts of pro-inflammatory cytokines, which acts as a major etiologic factor for ARDS development [20-31]. The lymphopenia and the reduced number of $CD4^+$ and $CD8^+$ T cells in the peripheral blood of COVID-19 patients were also reported [20-31]. It is thus concluded that, similar to SARS and MERS, lymphopenia and cytokine storm may play a major role in the pathogenesis of COVID-19 [20]. The modulatory effects of low-dose ionizing radiation on the production of the proinflammatory cytokines and chemokines have also been demonstrated [32-33]. Furthermore, it appears possible to prevent lymphopenia and prevent the decrease in the number of $CD4^+$ and $CD8^+$ T cells using suitably low doses of radiation. Although, radiation using appropriate doses may modulate two major damaging factors (lymphopenia and cytokine storm) in COVID-19, the standardization of the radiation concerning its doses, timing and duration need to be clarified through more experiments.

CONCLUSION

COVID-19 fatality in space might be significantly higher than on Earth due to: 1) ineffectiveness of social distancing (due to the effects of microgravity); 2) immune system dysregulation; 3) higher rates of mutation in RNA viruses such as coronaviruses; 4) the existence of strong selective pressure and 5) decreased maximum oxygen uptake (VO2max). Thus, the combined effects of microgravity, low-level (but high-LET) space radiation and other stressors in space on the immune system of astronauts should be thoughtfully investigated.

***Conflicts of interest*:** *Declared none.*

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[DOI: 10.18869/acadpub.ijrr.18.3.421]