An introduction to space radiation and its effects on the cardiovascular system

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Abstract

While the Earth's magnetic fields deflect most of the radiation that is found in space, space travel beyond low Earth orbit such as missions to Mars, will be associated with significant exposures to radiation. Therefore, the health risks of exposure to space radiation during these type of missions need to be assessed. The cardiovascular system is one of the organ systems that is of concern for potential adverse effects of space radiation. Because these effects cannot be determined in human subjects, ground-based studies with animal and cell culture models have been designed to estimate the risks. This article provides an introduction to space radiation characteristics, followed by an overview of the indicators that suggest to us that the cardiovascular system may be at risk, and lastly the results of animal and cell culture studies that have been performed to test what the risks may be.

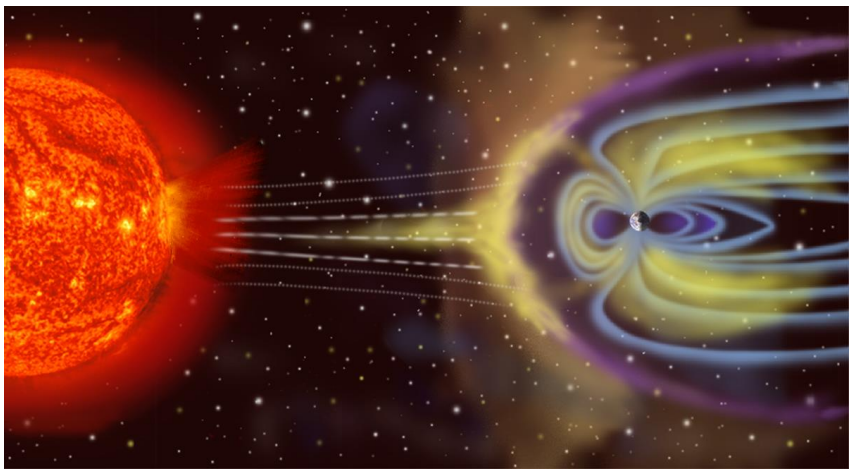
What is space radiation?

Space radiation is among the many types of ionizing radiation, each capable of removing electrons from the atoms in materials or cells that are exposed. While ionizing radiation on Earth is often found as electromagnetic waves such as X- or γ-rays, ionizing radiation in space is predominantly in the form of high energy charged particles. All ionizing radiation leaves a track of ionizations as they deposit their energy in materials or cells. While electromagnetic waves leave relatively little energy per unit of track length, and are therefore considered low linear energy transfer (LET) radiation, charged particles deposit their energy along densely ionizing tracks and are considered high-LET radiation [1,2]. The unit of **absorbed dose** of ionizing radiation is the Gray (1 Gy equals 1 Joule of absorbed energy per kg of material or tissue). However, because different forms of ionizing radiation can have different biological effects, one cannot always compare them by using absorbed dose. For this purpose, the **equivalent dose** is used, the absorbed dose multiplied by a radiation

weighting factor that should take into account differences in biological effects. Equivalent dose is given in Sieverts (Sv) [see also https://www.remm.nlm.gov/dose_animations.htm].

Ionizing radiation in space is predominantly high-LET radiation as galactic cosmic rays (GCR) and also due to solar emissions and solar particle events (SPEs). SPEs consist mostly of protons, and current efforts are aimed at predicting their occurrence several hours to days in advance [see also the National Space Weather Prediction Center: http://www.swpc.noaa.gov/].

The largest SPEs have dose rates up to 0.5 Sv/hour and can last for hours to a few days [3]. GCR and solar emissions, on the other hand, are dominated by protons and high energy ions such as iron, silicon, oxygen, and carbon. The Earth's magnetic fields exert forces on moving charged particles. As a result, levels of space radiation on the surface of the Earth are low, while charged particles are trapped in the Earth's magnetic fields leading to regions of higher charged particle irradiation surrounding the Earth, the Van Allen belts.



Artist's rendition of Earth's magnetic fields that deflect the majority of the charged particle irradiation in space.
Source: NASA (http://sec.gsfc.nasa.gov/popscise.jpg)

Since the International Space Station is located within the Earth's magnetic fields, astronauts are somewhat protected from space radiation, although exposures are higher than on the surface of the Earth. Long-distance space travel, however, is associated with much higher cumulative doses of radiation. Chronic radiation exposure occurs at a dose rate of 1.3 mGy/day, or the dose equivalent of 4.8 mSv/day [4,5]. While the shielding materials that are currently used cannot easily protect against GCR, SPE protons have shorter ranges in

material, and the wall of a spacecraft may provide effective shielding against this radiation. A thin spacesuit, on the other hand, may not provide protection against GCR or SPEs [6].

Health risks of space radiation: acute and degenerative tissue effects

Exposure of cells to ionizing radiation leads to molecular damage. While most cells have strong molecular repair mechanisms, some radiation damage can remain. Exposure to ionizing radiation is therefore associated with an increased risk of carcinogenesis. Studies have long been focused on the risk of carcinogenesis from space radiation [7]. In addition, exposure to ionizing radiation at high dose rates can cause acute injury to cells and tissues. Several organ systems, including the gastrointestinal and the hematopoietic system, are sensitive to high dose rate radiation. Acute effects in these types of organs can collectively lead to acute radiation sickness within hours to days after exposure. Because of the relatively high dose rates of some SPEs, exposure to larger SPEs can put an astronaut at risk for these and other acute health effects [8]. Other organ systems do not show significant acute effects after radiation doses encountered in space, but adverse effects may appear months or years after exposure. These are collectively called degenerative tissue effects and can be caused by both SPEs and GCR. Currently, degenerative effects in the central nervous system, eye, and cardiovascular system are considered to be of main concern [see also https://humanresearchroadmap.nasa.gov/] [9,10].

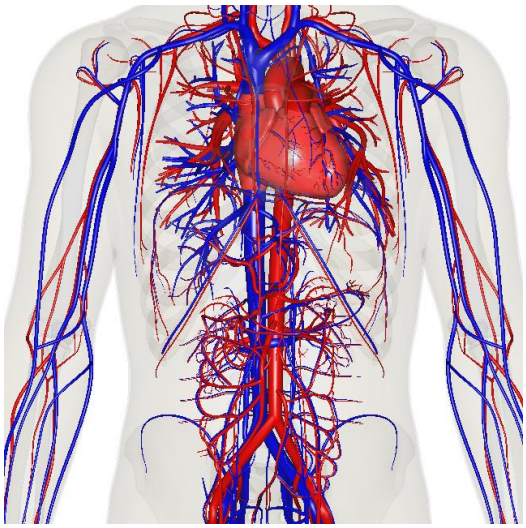
Effects of ionizing radiation on the cardiovascular system

Several decades ago, when radiation therapy first became a common cancer treatment, radiation fields included large volumes of non-cancer (normal) tissues surround the tumors. As a result, the cardiovascular system became one of the organ systems that showed sometimes severe side effects of cancer treatment. The side effects include accelerated atherosclerosis, myocardial fibrosis, and cardiac conduction and valve abnormalities, and most of these became apparent many years to decades after exposure [11-15]. Although some cancer patients still receive a high dose of radiation to a small part of the heart, general improvements in treatment planning and delivery of radiation therapy have greatly reduced

the doses of radiation to normal tissues. The biological mechanisms by which ionizing radiation has its effects in the cardiovascular system are not yet fully understood.

Many of the survivors of the atomic bombs in Japan in 1945 were exposed to low-LET radiation at doses up to 2 Gy to a large part of their body. These survivors have been followed closely for many decades to identify short-term and long-term health effects [16-18]. Some of the recent reports have shown an increased incidence of cardiovascular disease, including ischemic heart disease and stroke [19,20]. These observations have led to additional epidemiological and clinical studies in people exposed to low doses of ionizing radiation such as from nuclear accidents, medical, or occupational exposure. Most studies conclude that cardiovascular disease may occur after exposure to ionizing radiation at lower doses than was previously thought [21-26].

The recent reports on health effects from exposure to low doses of low-LET radiation have raised the concern about the risk of cardiovascular disease from ionizing radiation during long-distance space travel [27]. However, some of the characteristics of space radiation (high-LET radiation at mostly low dose rates), are very different from the above examples of ionizing radiation on Earth (low-LET radiation at high dose rates). Therefore, research is needed to better understand the risk of degenerative tissue effects from space radiation. Because data in human subjects are nearly non-existent, and humans almost always come with additional cardiovascular risk factors that can complicate the interpretation of study results, research in animal and cell culture models should help in estimating the health risks of space radiation.



All parts of the cardiovascular system are affected by ionizing radiation. Source: BodyParts3D, The Database Center for Life Science (http://lifesciencedb.jp/bp3d/)

Charged particle exposure: mimicking space radiation

To investigate biological effects of space radiation, animal and cell culture models are exposed to high energy charged particles. Proton radiation therapy facilities, for instance, can be used to model proton exposures from an SPE [28]. Particle accelerators such as at Brookhaven National Laboratory (Upton, NY) are used to perform high energy charged particle exposures [see also https://www.bnl.gov/nsrl/]. In these types of experiments it is important to provide the best possible simulation of the long-term low-dose rate exposures to a variety of charged particles, at the most appropriate energies. Below is a brief description of animal and cell culture studies that have been performed in the recent years.

Effects of charged particle exposure on the heart in animal models

Most studies of cardiac effects of simulated space radiation have used male mice. Since astronauts are mostly 40-60 years old during their space travel, it is important to expose animals to space-like radiation when they are at comparable "middle age", relative to their life span. In addition, since some cardiovascular disease risks are known to be sex-dependent, female animals will hopefully be included in future studies.

Exposure of male mice to protons (0.5 Gy) or iron ions (0.15 Gy) induced cardiac infiltration of CD68-positive cells (monocytes and macrophages), increased DNA oxidation, myocardial fibrosis, and modified cardiac function, both in normal animals and in response to experimentally induced myocardial infarction, in a radiation-type specific manner [29,30]. Exposure of male mice to silicon ions at doses between 0.1 and 0.5 Gy caused prolonged apoptosis and increased expression of pro-inflammatory cytokines in the heart [31]. While exposure of male mice to protons at a dose of 0.1 Gy did not cause detectable changes in the heart at the fairly short follow-up times of 2 weeks and 3 months, a dose of 0.5 Gy of iron ions induced protein markers of inflammatory infiltration and cell death. However, when mice were administered proton irradiation 24 hours before the dose of iron ions, all iron ion-induced changes were prevented. [32]. Hence, the proton exposure must have induced an as of yet unknown response in the heart that provided protection against further charged particle exposure. High throughput proteomics has started to reveal potential signaling pathways

induced by low dose particle irradiation in the heart [33], and analysis of the response in individual cardiac cell types is also ongoing [34].

Effects of charged particle exposure on the vasculature in animal models

All components of the vasculature, from the larger arteries to the smallest capillaries show their own unique response to ionizing radiation, and these responses play a role in the overall radiation injury observed in tissues and organs [35,36]. It is therefore important to understand how the vasculature responds to space radiation. Exposure of male mice to iron ions at doses between 0.5 and 2 Gy caused a long-term loss of endothelial cells in the hippocampus [37], and exposure of male rats to iron ions (0.5 and 1 Gy) induced long-term indications of endothelial dysfunction and increased stiffness of the aorta wall [38]. Studies on adhesiveness of endothelium in charged particle-exposed animal models are also underway [39].

It is difficult to assess the effects of ionizing radiation on atherosclerosis when using regular rodent models, because at baseline these animals show very low rates of atherosclerosis. Therefore, genetic animal models are used that are more prone to developing atherosclerosis. For instance, targeted exposure of the aorta of apolipoprotein E-deficient mice to iron ions at fairly high doses of 2 and 5 Gy caused accelerated atherosclerosis [40]. While animals in this particular study received a standard chow diet, studies without radiation typically require for these mice to be on a high-fat diet to induce a high rate of atherosclerosis. Additional experiments are required to define the response of larger blood vessels and the microvasculature to space radiation.

Studies on charged particle exposure in cell culture models

In line with the role of the vascular system in normal tissue radiation injury, endothelial cells are considered to play a central role in the cardiovascular response to ionizing radiation, and endothelial dysfunction contributes to the pathophysiological manifestations of radiation injury in many organs [41-43]. Therefore, studies are addressing the effects of space radiation on endothelial cells in cultures. Various tissue-relevant cell culture models are being used to simulate all biological and physical properties of the vasculature [44]. In one

of those three-dimensional culture models of human endothelial cells, protons and iron ions at doses up to 3 Gy caused endothelial cell death and changes in vasculogenesis in a radiation-type specific manner [45,46]. Studies in cultures of endothelial cells will help us understand the biological mechanisms of vascular injury from charged particle exposure.

Interaction of radiation with other environmental factors in space

Travel in space is associated with other stressors, such as exposure to microgravity, which are known to influence the cardiovascular system [47]. While small experimental animals are sometimes flown into space to examine the effects of space environmental factors [48], studies on Earth are designed to determine how radiation may interact with other cardiovascular risk factors in space. The hindlimb unloading model of mice and rats is currently the most used model to simulate fluid shifts, and muscle and bone atrophy due to weightlessness. This model can be combined with radiation exposure to test the interaction between these two factors [49]. As for the cardiovascular system, both radiation (2 Gy γ-rays) and 15 days of hindlimb unloading caused a reduction in endothelium-dependent and –independent vasodilation in arteries that feed one of the calf muscles in a mouse model, but radiation and unloading did not enhance each other's effects [50].

While studies with cells in culture can be done in space [51], cells can also be subjected to simulated microgravity by placing them in a rotating vessel that constantly changes the vector of gravity, so that on average the gravity factor is close to zero. Stem cells grown in rotating vessels showed enhanced formation of cells with endothelial cell properties [52], and endothelial cells grown in rotating vessels showed a change in their growth pattern and the production of nitric oxide, a mediator that influences vasodilation [53]. As already performed with other cell types [54, 55], we can now combine endothelial cell cultures in rotating vessels with radiation to further characterize the interaction between these two factors in space.

Summary of recent findings and future directions

Studies in human populations have shown that the cardiovascular system may be more sensitive to ionizing radiation than was previously thought. This has made the risk of

degenerative cardiovascular effects one of the main concerns of exposure to radiation during long-distance space travel. Studies using animal and cell culture models have started to shed light on risk of cardiovascular complications from exposure to charged particle irradiation. Future studies, including those that employ low radiation doses/dose rates and mixed particle fields to further simulate GCR will enhance our knowledge of the risks of exposure to space radiation.

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