

Space radiation and cardiovascular disease risk

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Abstract

Future long-distance space missions will be associated with significant exposures to ionizing radiation, and the health risks of these radiation exposures during manned missions need to be assessed. Recent Earth-based epidemiological studies in survivors of atomic bombs and after occupational and medical low dose radiation exposures have indicated that the cardiovascular system may be more sensitive to ionizing radiation than was previously thought. This has raised the concern of a cardiovascular disease risk from exposure to space radiation during long-distance space travel. Ground-based studies with animal and cell culture models play an important role in estimating health risks from space radiation exposure. Charged particle space radiation has dense ionization characteristics and may induce unique biological responses, appropriate simulation of the space radiation environment and careful consideration of the choice of the experimental model are critical. Recent studies have addressed cardiovascular effects of space radiation using such models and provided first results that aid in estimating cardiovascular disease risk, and several other studies are ongoing. Moreover, astronauts could potentially be administered pharmacological countermeasures against adverse effects of space radiation, and research is focused on the development of such compounds. Because the cardiovascular response to space radiation has not yet been clearly defined, the identification of potential pharmacological countermeasures against cardiovascular effects is still in its infancy.

Key words: Space radiation; Cardiovascular disease risk; Experimental models; Countermeasures; Ionizing radiation

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Core tip: This review article provides an overview of studies in experimental models that have begun to shed light on the potential risks of damage in heart and blood vessels after exposure to space radiation.

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INTRODUCTION

Participants of future long-distance space missions will be exposed to significant doses of ionizing radiation in space, and the health risks of these exposures need to be assessed. Because the cardiovascular system has recently been shown to be more sensitive to ionizing radiation than was previously thought, there is current concern that exposure to radiation during long-distance space travel may be associated with a cardiovascular disease risk. This review article provides an overview of studies in experimental models of ionizing radiation exposure relevant to that found in space that have started to shed light on the potential risks for heart and blood vessels.

Characteristics of ionizing radiation

Exposure of living cells and tissues to ionizing radiation, forms of radiation that can remove electrons from the atoms in these cells or tissues, may result in molecular damage, which can eventually lead to early and late injury. Exposure of cells or tissues to ionizing radiation causes DNA damage, which has long been considered as the primary cause of cellular injury and cell death. However, additional mechanisms are now recognized as important in normal tissue radiation injury^[1]. Doses of ionizing radiation are indicated in Gray (1 Gy equals 1 Joule of absorbed energy per kilogram of mass, e.g., tissue). Because equal doses of different types of ionizing radiation may not have equal biological effects, one can express radiation exposure as equivalent dose in Sieverts (Sv), which is the absorbed dose multiplied by a unit-less radiation weighting factor and accounts for difference in the biological response^[2].

Ionizing radiation can take many forms, including electromagnetic waves and high energy charged particles; the latter deposit their energy along densely ionizing cylindrical tracks. These forms of radiation can be distinguished, among other characteristics, by the

amount of energy the radiation transfers to the target material per unit of track length, or linear energy transfer (LET)^[2]. Ionizing radiation in the form of electromagnetic waves, such as X-rays or γ -radiation, are considered forms of low-LET radiation and deposit their energy uniformly in target volumes, while high energy charged particles release their energy along dense tracks of ionization and are considered high-LET radiation. Space travel is associated with low-dose-rate exposure to high-LET radiation in the form of galactic cosmic rays (GCR) and occasional high dose rate solar particle events (SPEs)^[3].

IONIZING RADIATION AND THE CARDIOVASCULAR SYSTEM

Ionizing radiation has long been known to cause injury in heart and blood vessels. These effects first became apparent from follow-up of patients after radiation therapy, which delivers high doses of low-LET radiation locally to the tumor but in some cases also exposes normal (non-cancer) tissues such as the heart and blood vessels^[4-8]. Several previously published review articles^[9-11] have provided a comprehensive overview of the effects of low-LET radiation on the cardiovascular system. In short, manifestations of radiation-induced heart disease as a result of exposure to high doses of ionizing radiation include accelerated atherosclerosis, myocardial fibrosis, and cardiac conduction and valve abnormalities. Most deleterious effects in heart and blood vessels are observed years to decades after exposure to ionizing radiation. Therefore, long post-radiation follow-up is required for a full assessment of cardiovascular risk. Mechanisms by which ionizing radiation has its effects in the cardiovascular system are not yet fully known.

Recent reports of health assessments in atomic bomb survivors^[12-15] have shown an increased incidence of cardiovascular disease, including ischemic heart disease and stroke, in people several decades after exposure to doses of γ -radiation as low as 2 Gy. Moreover, other epidemiological studies in occupational exposure and low-dose exposure due to medical treatments indicate that cardiovascular disease may occur after lower doses of ionizing radiation than was previously thought^[16-20]. The main cardiovascular effects seen in atomic bomb survivors include hypertension and ischemic heart disease, suggesting that after low-dose radiation exposure a vascular component may play a central role in the cardiovascular disease risk.

These recent reports on health effects from exposure to low doses of low-LET radiation have raised the concern about potential risk of cardiovascular disease from exposure to ionizing radiation during space travel^[21]. However, care should be taken when the results of terrestrial radiation exposures such as those from atomic bombs are used to support the potential for a cardiovascular disease risk from space radiation, since certain conditions such as dose rate are different

between atomic bomb events and radiation exposure in space. The remainder of this review is focused on studies in experimental models that have aimed to shed light on the cardiovascular risk of exposure to space radiation.

SPACE RADIATION

Characteristics of space radiation

While astronauts in the International Space Station are somewhat protected from exposure to space radiation due to the earth's magnetosphere, future long-distance space travel (beyond low-Earth orbit) will be accompanied by exposure to higher cumulative doses of space radiation, and short-term and long-term health risks need to be assessed^[22,23].

GCR and solar emissions are dominated by protons and iron, silicon, oxygen, and carbon that are highly energetic. The greatest particle abundance is found for particles with energies ranging from hundreds of MeV per nucleon (MeV/n) up to about 1 GeV/n^[24]. Practical levels of current shielding materials cannot easily protect against these particles^[25]. Chronic exposure occurs at a dose rate of 1.3 mGy/d, or the dose equivalent of 4.8 mSv/d, when assuming the radiation weighting factors of the International Commission on Radiological Protection Publication 60 outside the earth's magnetosphere^[26,27]. The exposure is characterized by the traversal of most cells in the body by one or more protons and electrons per day, with infrequent traversals (days to weeks) by ions of higher atomic number (Z).

SPEs consist predominantly of protons, and exposure to the largest SPEs occurs at dose rates up to 0.5 Sv/h over hours to a few days^[28]. Energies of SPE protons are less than those for GCR and therefore have shorter ranges in material, which may enable effective shielding inside a spacecraft but not inside a thin spacesuit. These higher dose rate exposures may put an astronaut at risk for acute radiation effects, sometimes collectively called acute radiation sickness^[29]. Both SPEs and GCR may also cause long-term degenerative disease in various tissues, including the heart and blood vessels.

Experimental data obtained from animal and cell culture models play an important role in estimating health risks from exposure to space radiation. Appropriate simulation of the space radiation environment, including the long-term low-dose rate exposures to various charged particles and the appropriate energy of these particles, and the choice of the most relevant animal or cell culture model are challenging but key to providing relevant estimates of health risks^[30-32]. The concern of adverse cardiovascular effects of exposure to space radiation is relatively new, and studies on the cardiovascular effects in animal models of space radiation exposure are not yet abundant. An overview of existing studies on heart and blood vessels is given below. Since much of this work is ongoing, we have had to occasionally refer to proceeding abstracts, but hope to find the results in peer-reviewed publications in the near future.

Cardiac response in animal models of charged particle exposure

Studies in animal models of charged particle exposure have shown cardiovascular effects at doses lower than those required to cause cardiovascular changes if low-LET radiation is used. This may not be surprising, since high-LET radiation typically causes more damage per unit of absorbed dose. Among studies with charged particles, some previous research has focused on the cardiac response to fission spectrum neutrons in animal models^[33-36]. More recently, studies were designed to provide answers about the cardiovascular risk from exposure to high-LET radiation in space. Exposure of male C75Bl/6NT mice at 8-10 mo of age to protons (1 GeV, 0.5 Gy) or iron ions (1 GeV/n, 0.15 Gy) induced cardiac infiltration of CD68-positive cells (monocytes and macrophages), increased DNA oxidation, myocardial fibrosis, and modified cardiac function, both at baseline and in response to myocardial infarction, in a radiation-type specific manner^[37-39]. Exposure of male CBA/CaJ mice at 10-12 wk of age to silicone ions (300 MeV/n) at doses between 0.1 and 0.5 Gy caused prolonged apoptosis and increased expression of the common pro-inflammatory cytokines interleukin (IL)-1 β , IL-6, or tumor necrosis factor- α in the heart^[40]. Low doses of high-LET radiation have been shown to cause long-term alterations in DNA methylation in various organ systems *in vivo* and cells in culture^[41-43]. Similarly, we recently found changes in cardiac DNA methylation in male C57BL/6J mice exposed at 10 wk of age to protons (150 MeV, 0.1 Gy) or iron ions (600 MeV/n, 0.5 Gy) (Figure 1), suggesting that epigenetic alterations may contribute to the cardiac radiation response^[44]. Analysis of the response in individual cardiac cell types is also ongoing^[45].

Vascular response in animal models of charged particle exposure

Whole-body exposure of rats to iron ions at doses of 0.5 and 1 Gy induced long-term indications of endothelial dysfunction and increased aortic stiffness^[46]. It is difficult to assess the effects of ionizing radiation on atherosclerosis when using regular rodent models, due to the low prevalence of atherosclerosis in these animals. Targeted exposure of the atherosclerotic-prone apolipoprotein E-deficient (Apo^{-/-}) mouse model to iron ions (600 MeV/n) at doses of 2 and 5 Gy caused accelerated atherosclerosis in the exposed parts of the aorta^[47]. Additional studies with lower doses of particle irradiation may provide a more comprehensive estimate of cardiovascular risk in this mouse model. Studies on adhesiveness of endothelium in charged particle-exposed animal models are also underway^[48].

The microvasculature also plays an important role in normal organ function, degenerative tissue effects, and tissue injury from ionizing radiation^[49,50]. Exposure of 10-wk old male C57BL/6 mice to iron ions (600 MeV/n) at doses between 0.5 and 2 Gy caused a long-term loss of endothelial cells in the hippocampus^[51].

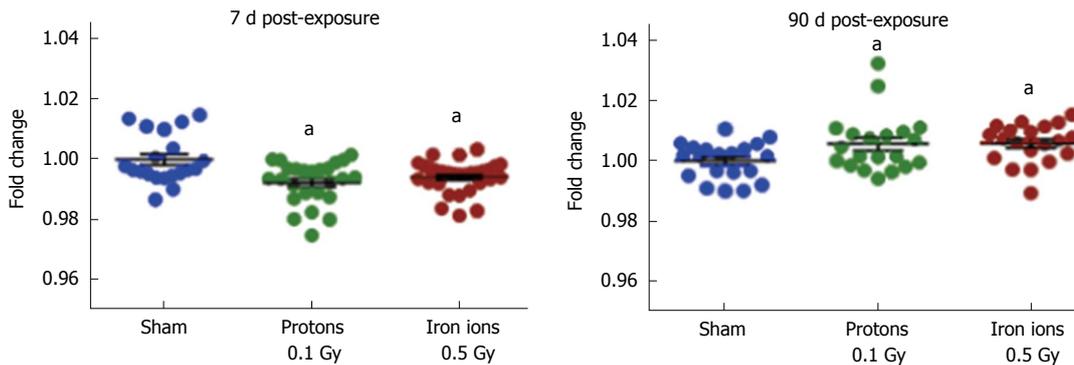


Figure 1 Methylation of genomic DNA isolated from hearts of male C57Bl/6 mice at 7 d and 90 d after exposure to protons (150 MeV, 0.1 Gy) or iron ions (600 MeV/n, 0.5 Gy). DNA methylation of the open reading frame 1 of long interspersed nuclear element-1, a transposable element that comprises about 20% of the mouse genome, as assessed by pyrosequencing and indicated as fold change compared to sham-irradiated controls. Each group contained 4-5 animals. Horizontal lines indicate average \pm standard error of the mean. ^a $P < 0.05$ vs the sham-irradiated control group.

More research is required to assess the effects of space radiation on the microvasculature.

Studies on charged particle exposure in cells culture models

Endothelial cells are considered to play a central role in the cardiovascular response to ionizing radiation. Endothelial dysfunction, which is characterized by a pro-inflammatory and profibrogenic phenotype of endothelial cells, is a critical contributor to the patho-physiological manifestations of radiation injury^[52-54]. Experimental models of exposure to low-LET radiation have shown that ionizing radiation can cause prolonged endothelial dysfunction, thereby sustaining a detrimental tissue environment that leads to chronic inflammation and adverse remodeling^[55,56].

Because of the central role of endothelial cells in the radiation response, studies are addressing the effects of space radiation on endothelial cells in cultures^[57]. Various tissue-relevant cell culture models are being used^[58]. For instance, in three-dimensional culture models of human endothelial cells, protons (1 GeV) and iron ions (1 GeV/n) at doses up to 3 Gy caused alterations in vasculogenesis and endothelial cell death in a radiation-type specific manner^[59,60]. These results raise the concern of damage of the human vasculature from exposure to charged particles *in vivo*.

Potential countermeasures against the cardiovascular response to space radiation

Astronauts could potentially be administered pharmacological countermeasures against adverse effects of space radiation, when the countermeasure is safe, stable during long-term space flight, and has a relatively light weight. Therefore, research is focused on the development of countermeasures against various biological effects of space radiation^[29]. Interestingly, pharmacological countermeasures are being developed for low-LET radiation in exposure scenarios on earth and may point to potential countermeasures against adverse effects of space radiation. Neupogen [filgrastim,

recombinant human granulocyte colony stimulating factor (G-CSF)], for instance, was recently approved by the American Food and Drug Administration as a countermeasure against acute injury from accidental radiation exposure. G-CSF has also been shown to protect animal models against acute injury from exposure to SPE-like protons^[61].

Because the cardiovascular response to space radiation has not yet been clearly defined, the identification of potential pharmacological countermeasures against cardiovascular effects is still in its infancy. Nonetheless, similar to the acute response scenario, potential countermeasures against cardiovascular effects of terrestrial radiation exposure, albeit not yet approved for clinical use, may be pursued in space radiation models. For example, the angiotensin converting enzyme (ACE) inhibitor captopril has been shown to reduce cardiac injury in animal models of localized irradiation of the heart^[62,63]. In addition, the vitamin E analog γ -tocotrienol is one of the most potent dietary countermeasures to radiation injury currently known. It is safe and nontoxic and has no known drug interactions. It is commercially available, requires no specific storage conditions, and is currently in advanced stages of development for terrestrial applications in radiation protection^[64,65]. In addition, γ -tocotrienol has several beneficial effects in the cardiovascular system. It is a potent inhibitor of the cholesterol biosynthesis pathway, thereby reducing the isoprenylation of Rho proteins that modify a wide range of cellular functions, including stress fiber formation, hypertrophy, regulation of NOS, and production of cytokines and growth factors^[66]. Indeed, γ -tocotrienol reduces vascular oxidative stress and protects against vascular radiation injury at least in part *via* HMG-CoA reductase inhibition^[67,68]. The protective properties of agents such as ACE inhibitors or γ -tocotrienol against cardiovascular effects of space radiation need to be assessed.

CONCLUSION

The cardiovascular system may be more sensitive

to ionizing radiation than was previously thought, which raises the concern of a cardiovascular risk from exposure to ionizing radiation during long-distance space missions. Animal and cell culture models have started to shed light on risk of cardiovascular complications from exposure to charged particle irradiation. Additional studies, including those that employ low radiation doses/dose rates and mixed particle fields to mimic GCR are required to aid in assessing the cardiovascular risk of space radiation.

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