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The effects of microgravity and space radiation on cardiovascular health: From low-Earth orbit and beyond

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ABSTRACT

The unique conditions of space harbor considerable challenges for astronauts to overcome. Namely, the ionizing content of space radiation and the effects of microgravity have been implicated in the pathogenesis of cardiovascular disease. Post-flight carotid arterial stiffness was demonstrated in astronaut studies while early arteriosclerosis has been linked with microgravity-induced oxidative stress in cellular studies. Similarly, radiation has been shown to disrupt molecular pathways, enhance reactive oxygen species and increase risk of cardiovascular disease in exposed populations. These results may bear even more significance in space owing to the propensity for microgravity and space radiation to yield synergistic and/or additive interactions. Potential countermeasures such as α-tocopherol and captopril target these oxidative pathways and may help to protect against the effects of microgravity and radiation-induced cardiac damage. However, more research needs to be conducted in this area to facilitate a safe passage for humans to the Moon, Mars and beyond.

Contents

1. Introduction

Initiatives to send man to Mars has long been of interest to national space agencies and corporate entities alike. With the establishment of the International Space Station (ISS), human presence on low-Earth orbit has enabled science to gain a deeper

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understanding of both physiological and molecular alterations in extra-terrestrial environments. However, as the frontiers of space exploration are being tested further, the ever-growing risks of space radiation and microgravity represent a huge concern for long term manned space missions. A few examples include the cardiovascular deconditioning from prolonged exposure to microgravity [1] as well as the detrimental effects of pro-oxidative conditions generated from deep space radiation [2]. Hence, both preventative and therapeutic modalities to safeguard against such stressors have been viewed with mounting interest.

The advent of the first lunar landings from the Apollo spaceflight program had been heralded a great success and represented a huge breakthrough in the scientific community. The ability to perform complex experiments [3] and walk upon a celestial body only consolidated the drive for further innovation and advancements. However, scrutiny into the health of the 24 Apollo lunar astronauts has highlighted increased mortality from cardiovascular disease when compared to astronauts from both low-Earth orbit and those who have never taken part in space flight [4]. These differences may be accounted for by higher levels of exposure to components of galactic cosmic rays and solar particle events outside the Earth's protective magnetosphere [5]. Consequently, focus has heavily accentuated upon the acclimatization and safety of astronauts on future enduring missions.

2. Microgravity

2.1. Effects on cardiovascular physiology

The effects of microgravity represent a unique stressor to humans who have evolved homeostatic mechanisms in a 1 g environment for plenty of millennia. Notable acute effects on cardiovascular physiology include decreased circulatory blood volumes, reduction in arterial blood diastolic pressure, reduced left ventricular size and post-flight orthostatic intolerance [1].

During spaceflight, transient shifts in fluid from intravascular compartments to intracellular spaces cause a reduction in overall circulatory blood volume [6]. Meanwhile, venous return and stroke volumes increase influencing autonomic and endocrine activity [7]. While several researchers have proposed sympathetic activity to dominate in space environments, the actual evidence is conflicting [8]. Though norepinephrine concentrations have found to be increased, there has also been evidence to suggest a reduction in systemic vascular resistance [7,9]. Hence, the actuality of autonomic stressors on the human nervous system may be trivial when in-flight activity has been contrasted against pre-flight control groups.

Similarly, it had been observed that orthostatic intolerance occurred commonly post-flight with many astronauts experiencing syncope and tachycardia [10]. This along with ambulatory blood-pressure variability have long been key determinants of cardiovascular morbidity [11,12] likely owing to increased sympathetic drive and impaired cardiac function [13,14]. However, intensive in-flight training programs as well as landing-day saline resuscitation have helped to mitigate the issues of orthostatic intolerance amongst the latest cohort of astronauts [15].

Cardiac remodeling has been studied to a great degree amongst those in long-term space flights. Owing to the sedentary nature of weightlessness, reductions in metabolic demand and oxygen uptake have led to cardiac atrophy [16] in both microgravity and simulations of it [17]. One study revealed that left ventricular mass of astronauts had decreased by 9.1% on echocardiographic measurements compared to pre-flight measurements but had recovered to normal by third day post-flight [16]. Although this underlines the plasticity of cardiac muscle and a working model of physiological adaptation, potential risks of irreversible structural changes for even longer deep space missions have yet to be explored.

Another important change noticed has been increased carotid arterial stiffness following 6 months of spaceflight as seen in Fig. 1 [18]. These changes were consistent with one to two decades of ageing [19] in the context of the β-stiffness index and carotid distensibility coefficient. Initial mechanisms proposed cephalad fluid distribution and loss of hydrostatic pressure gradients as a proponent of increased arterial pressures and arterial resistance [20]. However, other mechanisms may also play a key part since femoral artery stiffness indices which would have been expected to be lower were in fact also increased. Although carotid artery stiffness recovered four days upon return to Earth, there were

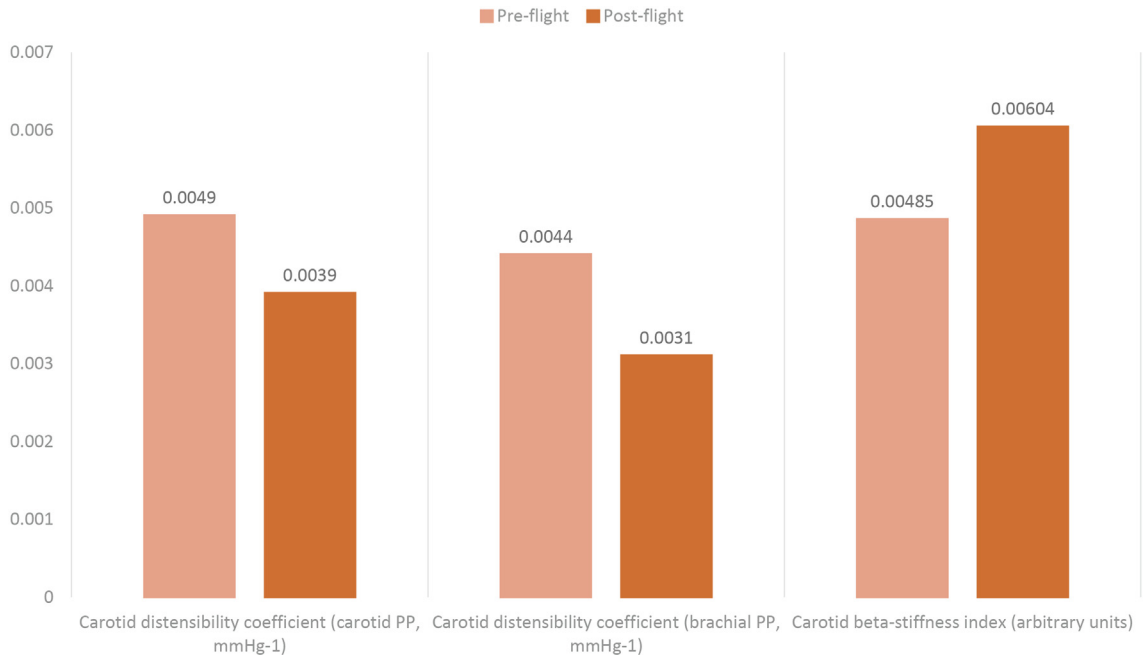

Fig. 1. Cardiovascular markers compared pre- and post-flight as derived from the Hughson et al. study [18].

notable reductions in arterial strain (measured from systolic and diastolic diameters) [21]. This discrepancy questions full recovery of arterial properties post-flight and hence additional studies are required to elucidate longer-term vascular remodeling.

2.2. Pro-oxidative environments

An often overlooked aspect of microgravity is its potential ability to facilitate pro-oxidative environments. Although harder to investigate in actual microgravity conditions, Earth-based simulated microgravity experiments have been conducted to explore this very issue. Wang et al. for example noticed that antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) were decreased in rat PC12 cells exposed to microgravity conditions compared to their counterparts in 1 g [22]. This was also supported by the time-dependent increase in reactive oxygen species (ROS) generated from the cultured PC12 cells in simulated microgravity [22].

Morabito et al. have further investigated the effects of simulated microgravity in human TCam-2 cells and found increased levels of ROS, superoxide anions and anaerobic metabolism following 24 h of exposure [23]. In space-flown mice, it was also noticed that reduced levels of antioxidant enzymes such as CAT were found in the soleus muscle [24].

The implications of these oxidative stress markers for cardiovascular health are far reaching. ROS are chemically reactive species capable of performing insult by oxidizing effects. While natural anti-oxidizing mechanisms exist to scavenge ROS and their products, an abundance can damage cellular components such as lipids, proteins, and DNA [25]. This is especially important in the pathogenesis of arteriosclerosis where early inflammatory responses have been directly linked with increased ROS production via phagocytes [26].

The role of ROS have also been associated with arterial hypertension where superoxide anions ($O_2^{\bullet -}$) derived from NADPH oxidase mop up endothelia-induced nitric oxide (NO) to form peroxynitrite shifting vessels towards a state of vasoconstriction as seen in Fig. 2 [27]. ROS act as secondary messengers and can increase intracellular Ca^{2+} concentrations further promoting vasoconstricting effects [28].

Overall, oxidative stress has heavily been implicated in the pathophysiology of cardiovascular disease. The pathways within the oxidant-antioxidant continuum are complex and highlight the need to further investigate the mechanobiological processes of microgravity. While the above studies emphasize oxidizing agents at a subcellular level, further studies are also warranted to demonstrate the potential long-lasting impacts of microgravity-induced oxidative stress.

3. Space radiation

3.1. Interplanetary space environment

Travel into deeper space presents unique challenges for astronauts in the form of radiation. Beyond low-Earth orbit and Earth's protective magnetosphere, galactic cosmic rays contribute a significant amount towards the overall radiation dose for space travelers as illustrated in Fig. 3. This form of radiation originates from outside the solar system and comprise high linear-energy transfer (LET) particles such as high energy protons and alpha particles [29]. A smaller subset manifest as high charge and energy (HZE) nuclei which move at relativistic speeds [30]. Energies from cosmic rays can reach speeds of 10^{20} eV with nuclear components of particles comprising of 87% hydrogen, 12% helium and 1% of other heavy nuclei [31].

In addition, unpredictable solar particle events (SPE) such as solar flares and coronal mass ejections are responsible for pulses of heavy ion and energetic proton radiation [32]. These solar particles can propagate interplanetary distances at speeds of several GeV nucleon^{-1} and interact with the magnetosphere to form high-energy sub-atomic particles of the Van Allen belts. While rare, this form of radiation is still of significance as five SPE events were recorded on the Mars Science Laboratory spacecraft's mission to Mars [33].

Radiation levels through dosimetry have been detected through various points in space travel history. Onboard the Curiosity rover, for example, a cumulative dose of 466 ± 84 mSv was measured within the shielding of the spacecraft while the silicone detector of the rover averaged 332 ± 23 μGy per day (a large majority of radiation formed from galactic cosmic rays whereas solar particles made up 5% of the remainder) [34]. Hence, deeper space travel presents a hostile environment comprised of the existing dangers of ionizing forms of radiation.

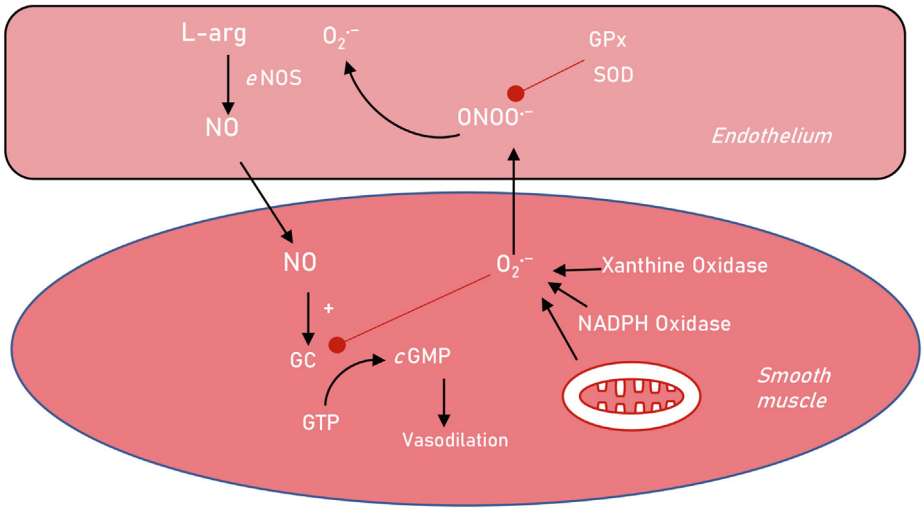

Fig. 2. Physiological and aberrant pathways in endothelial-derived NO formation. Key: L-arg (L-arginine), NO (nitric oxide), ONOO– (perioxynitrite), eNOS (endothelial nitric oxide synthase), GC (guanyl cyclase), GTP (guanosine triphosphate), cGMP (cyclic guanosine monophosphate), NADPH oxidase (Nicotinamide adenine dinucleotide phosphate oxidase), GPx (glutathione perioxidase), SOD (superoxide dismutase).

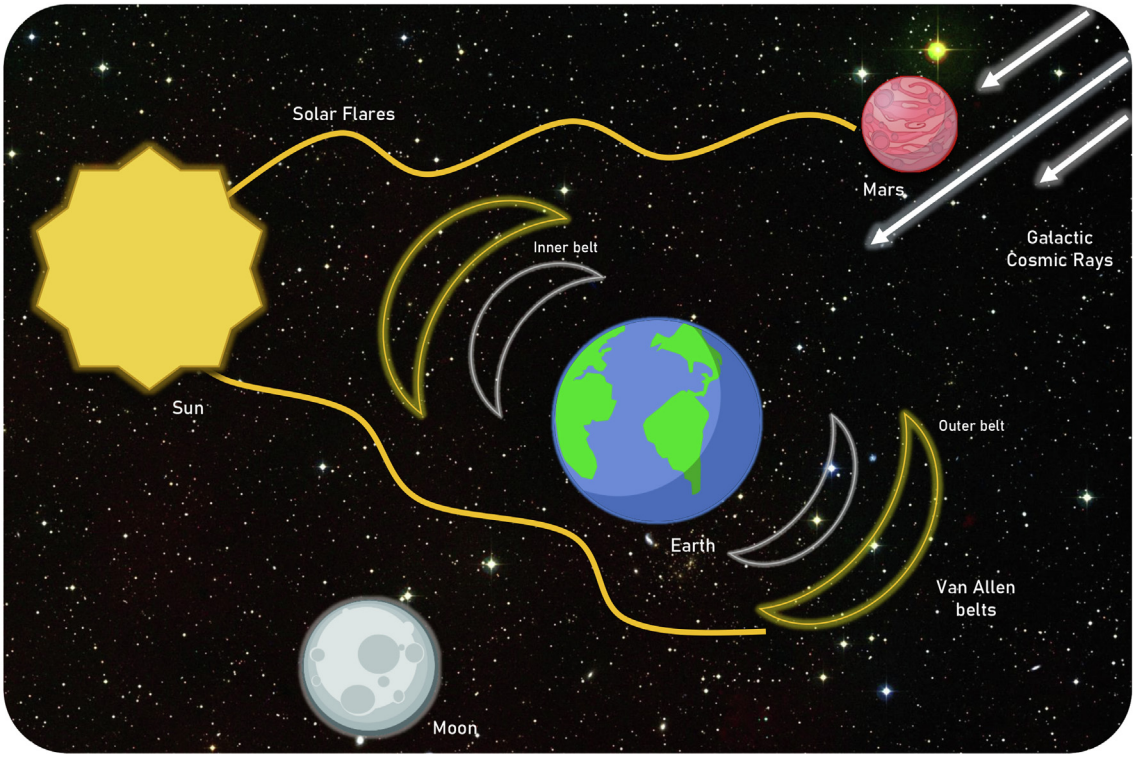

Fig. 3. A visual representation of the various sources of ionizing radiation within the cosmos; galactic cosmic rays, solar particle events and trapped charged particles in Van Allen belts.

3.2. Radiation and cardiovascular disease

The deleterious effects of ionizing radiation have been extensively studied in both human and animal models. Of prominence, data analyzed from the survivors of the atomic bombs in Hiroshima and Nagasaki found an excess relative risk for both stroke and heart disease (9% and 14% respectively) at radiation doses of greater than 0.5 Gy [35]. Similarly, a sub-group analysis of Apollo astronauts found greater proportional mortality from cardiovascular disease compared to both astronauts from low-lying orbits, non-flight astronauts and those of the general population [4]. While the results of this data have been significant from both Earth and space populations, several limitations do exist. For example, confounding variables such as lipid levels and physical exercise were not considered in the Japanese study. This also resonated in the study of lunar astronauts where not only sample size but confounders such as tobacco use and fitness levels may have influenced overall results [36].

Nonetheless, animal models within the literature have repeatedly demonstrated the negative effects of radiating sources. In an interesting study by Soucy et al., rats were exposed to high energy (HZE) Fe^{56}-ion radiation simulating the space environment [37]. The rats exposed to doses of 1 Gy were found to have significantly higher aortic stiffness over a 6-month period. In addition, aortic rings harvested from the irradiated rats revealed greater levels of endothelial dysfunction [37]. Oxidative stress has largely been implicated here as an underlying mechanism of pathophysiology. Enhanced ROS production as well as xanthine-oxidase (XO) species were found in the aortic samples of the rats following HZE Fe^{56}-ion radiation [37]. Thus, reduced bioavailability of NO from superoxide-forming XO and its correlates remain a likely pathway for endothelial dysfunction and vascular stiffness [38,39].

Proton and iron-ion radiation have also shown impaired cardiac function as well as increased cardiac fibrosis in adult male C57Bl/6NT mice with iron-ion radiation producing longer lasting damage [40]. Disrupted cardiac homeostasis appears the result of radiation-induced dysregulation of various intrinsic pathways including the handling of Ca^{2+} by SERCA2a and cardiac hypertrophy signaling via MAP kinases [40] . Aggregates of persistent inflammatory responses were measured by levels of oxidative DNA damage. The increase in genomic injury here may act as both an analogue for ROS and cytokine recruitment as well as a predictor of future cardiovascular disease [41].

Lastly, irradiation of the aortic arches and carotid arteries of apolipoprotein E-deficient ($Apoe^{-/-}$) mice with ^{56}Fe-ion particles demonstrated accelerated progression of atherosclerotic lesions [42]. This in part could be explained by upregulation of transforming growth-factor beta (TGF-β) and nuclear factor kappa B (NF-κB)

Table 1
Table demonstrating common medical exposure types and their estimated radiation dose compared to the risks of space radiation [45].

Exposure type	Cumulative radiation dose (mSv)
Chest radiograph (PA and lateral)	0.05 – 0.24
Pelvis radiograph	0.6
Abdomen radiograph	0.04 – 1.1
CT head	0.9–4
Average background radiation exposure on Earth (per year)	3
CT spine	1.5–10
CT chest	4.0–18
CT abdomen and pelvis	3.5–25
CT angiogram aorta	5.0–32
Average astronaut space radiation exposure in ISS orbit (per year)	182.5
Average astronaut space radiation exposure to Mars (per year)	672

Key: PA (posterior-anterior), ISS (International Space Station), mSv (millisieverts)

following microvascular damage as well as migration of monocytes and macrophages to endothelial structures [43]. Since carotid artery plaques independently predict cardiovascular events, the potential consequences of radiation seem especially pertinent [44].

In effect, the role of space radiation in potentiating cardiovascular disease is still in its infancy where long-term studies are concerned. However, results from existing studies and exposure risk, as seen in Table 1 [45,46], should provide impetus for more research into the crucial role of radiation in cardiovascular pathophysiology as well as prospective countermeasures.

4. Microgravity and space radiation

Only a handful of studies have explored the combination of microgravity and space radiation as a mechanism for disease-causing processes. While both stressors have revealed influential changes at a subcellular level, their interplay is equally important to fully understand the space environment. A study by Mao et al. which analyzed the effects of low-dose radiation (LDR) and simulated microgravity on mice found statistically significant increases in brain lipid peroxidation at 7 days [47]. Although both factors were able to induce these changes alone, the combination of the two produced greater results highlighting a synergistic effect. SOD1, a key antioxidant enzyme, was found to be lowest in mice exposed to both radiation and the effects of microgravity compared to each factor alone [47].

In a similar vein, Hada et al. outlined the additive effects of simulated microgravity and radiation in chromosome aberrations from human fibroblasts [48]. While these studies were conducted in cells of ectodermic origin, there have yet to be definitive experiments focusing on the combination of these influences on cells of cardiovascular origin. However, oxidative stress appears to be a factor largely underpinning the effects of these space phenomena on human biology as well as their synergistic interactions. A caveat worth mentioning here is that stress, disrupted circadian rhythms and factors we may have not yet considered could also form part of the crucial makeup of pathobiology in space.

5. Potential countermeasures

Pharmacological therapies tackling the role of oxidative stress in both microgravity and radiation-induced cardiovascular disease are challenging due to the infancy of this area of research.

However, antioxidants such as pentoxifylline and α-tocopherol have shown early promise in the treatment and prophylaxis of radiation-induced cardiac injury. Significantly improved myocardial fibrosis and left ventricular diastolic dysfunction was observed after a six-month period in locally irradiated rats [49]. The results were obtained following a combination of both pentoxifylline and α-tocopherol ingested both one week before and three months after irradiation [49]. A limitation of this study is that while cells were susceptible to the effects of space radiation simulated on Earth, it remains to be seen whether these can be reproduced under the peculiar radiation of cosmic rays.

Another candidate of interest has been third-generation beta-blockers such as nebivolol. The vasodilator properties of nebivolol have been highlighted in various studies owing to its endothelial-related NO generating effects [50,51]. This may serve as a vital function against oxidative stress mediated endothelial dysfunction. However, further studies are required to validate this.

Captopril, an already established treatment in cardiovascular medicine, has also demonstrated notable effects in radiation-induced cardiac damage. Specifically, the angiotensin-converting enzyme inhibitor (ACEi) ameliorated left ventricular perivascular fibrosis and left ventricular diastolic dysfunction in proton-irradiated rats [52]. As well as its hypotensive properties, captopril appears to be a leader in its drug class for antioxidative effects; a feature likely attributable to its sulfahydryl-scavenging component [53].

No studies have so far been conducted investigating drug actions on the postulated mechanisms of microgravity-induced oxidative stress. This may further be complicated by microgravity effects on pharmacokinetics and pharmacodynamics of drug properties [54]. However, existing preliminary studies conducted on radiation-induced injury certainly pave the way for this paucity of data.

6. Conclusion

To summarize, the cardiovascular system appears inherently susceptible to the complex interplay of space radiation and microgravity. From a molecular to whole organ level, both space phenomena have demonstrated key structural and functional changes of the heart and vasculature. This may in part be explained by their shared propensity to cause oxidative stress and facilitate an 'ageing' environment. However, data surrounding this area of research is limited. Furthermore, only a small number of astronauts have embarked on missions beyond low Earth orbit and the protective magnetosphere. Robotic spacecrafts have served an invaluable tool to assess quantities and depth of radiation aboard extended missions. Thus, the role of technology in evaluating pathogenesis remains key to future space exploration.

While animal and cellular-based studies are important, it is also necessary to understand whether these changes translate to the human condition. The role of preventative medicine, therefore, should also be the focus of plentiful research efforts to mitigate the dangers of space and equip man to the Moon, Mars and beyond.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

SP was involved in the : (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) synthesis of figures (4) final approval of the version to be submitted

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