

REVIEW ARTICLE

Aerospace Cardiology: Historical foundations, physiological adaptation, and future challenges in human spaceflight

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ABSTRACT

Long-duration spaceflight exposes astronauts to unique environmental stressors—primarily microgravity and galactic cosmic radiation (GCR)—that induce profound structural and functional adaptations within the human cardiovascular system. Understanding the pathophysiological mechanisms governing this coordinated deconditioning is critical for ensuring crew safety during future interplanetary exploration missions. This review synthesizes contemporary clinical, histological, molecular, and multi-omic evidence to map the kinetics of spaceflight-induced cardiovascular remodeling and evaluate the efficacy of emerging countermeasure matrices. This review systematically synthesizes physiological data from low Earth orbit missions, terrestrial analogues (head-down bed rest), animal models exposed to high-linear energy transfer (high-LET) heavy ions, and advanced multi-omic datasets (including single-cell transcriptomics) was performed. The elimination of hydrostatic pressure gradients drives an immediate cephalad fluid shift, prompting an acute increase in central blood volume followed by a progressive reduction in total circulating plasma volume. Over time, the myocardium exhibits high plasticity, characterized by left ventricular mass loss and diffuse microstructural remodeling to match decreased volumetric demands. Concurrently, regional vascular beds undergo divergent phenotypic alterations: lower-limb conduit arteries experience low shear stress, inducing inward hypertrophic remodeling, smooth muscle cell phenotypic switching, and matrix degradation, while the vasculature of the upper body and cerebral vasculature undergoes outward hypertrophy. Multi-omic profiles demonstrate that high-LET HZE particles accelerate atherogenesis via irreparable DNA double-strand breaks, endothelial cell senescence, and persistent oxidative stress. Furthermore, continuous venous congestion impairs dynamic cerebrovascular autoregulation and compounds altered cerebrospinal fluid redistribution, contributing to Spaceflight-Associated Neuro-ocular Syndrome (SANS). Traditional exercise regimens fail to mitigate these integrated microstructural and molecular changes completely. Preserving cardiovascular and endothelial integrity during deep-space transit demands a transition toward multi-systemic countermeasure paradigms. The integration of short-radius artificial gravity centrifugation with targeted pharmacogenomics—such as microRNA mimics and specific senolytic or anti-inflammatory cascade inhibitors—may offer a viable biophysical and biomolecular framework to safeguard the cellular architecture of human crews during interplanetary travel.

KEYWORDS

Artificial gravity, cardiovascular deconditioning, endothelial dysfunction, galactic cosmic radiation, multi-omics, Spaceflight-Associated Neuro-ocular Syndrome.

ACRONYMS/ABBREVIATIONS

AG: Artificial Gravity	LEO: Low Earth Orbit
CA: Cerebrovascular Autoregulation	miRNA: MicroRNA
CBF: Cerebral Blood Flow	NF-κB: Nuclear Factor Kappa B
CSF: Cerebrospinal Fluid	NO: Nitric Oxide
DSB: Double-Strand Break	NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide
ECM: Extracellular Matrix	oxLDL: Oxidized Low-Density Lipoprotein
eNOS: Endothelial Nitric Oxide Synthase	PBMC: Peripheral Blood Mononuclear Cell
ET-1: Endothelin-1	RBE: Relative Biological Effectiveness
GCR: Galactic Cosmic Rays	ROS: Reactive Oxygen Species
HFpEF: Heart Failure with Preserved Ejection Fraction	SANS: Spaceflight-Associated Neuro-ocular Syndrome
high-LET: High Linear Energy Transfer	SASP: Senescence-Associated Secretory Phenotype
hs-cTnT: High-Sensitivity Cardiac Troponin T	scRNA-seq: Single-Cell RNA Sequencing
HZE: High Energy and Charge (Z)	SPE: Solar Particle Event
ICAM-1: Intercellular Adhesion Molecule-1	TCD: Transcranial Doppler
ICP: Intracranial Pressure	VCAM-1: Vascular Cell Adhesion Molecule-1
ISS: International Space Station	VSMC: Vascular Smooth Muscle Cell

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I. INTRODUCTION

The adaptation of the human cardiovascular system to Earth's gravity is the result of millions of years of evolution. Space exploration exposes humans to microgravity, ionizing radiation, and prolonged isolation, directly challenges the physiological mechanisms regulating cardiac and vascular function. Within this context, aerospace cardiology emerges as a subdiscipline of aerospace medicine aimed at understanding hemodynamic, autonomic, structural, and molecular changes in the cardiovascular system beyond Earth.

The formal origin of aerospace cardiology can be traced to December 1968, when Mexican cardiologist Ramiro Iglesias Leal interpreted the first electrocardiogram transmitted from space during the Apollo 8 mission. This milestone represented a technological breakthrough and marked the beginning of clinical and physiological analysis of the human heart in the space environment, laying the foundations for remote cardiovascular monitoring and modern telecardiology [1].

Accordingly, this manuscript traces the evolution of aerospace cardiology from its foundational observations to contemporary physiological frameworks. It critically analyzes current mechanistic evidence regarding cardiovascular deconditioning in weightlessness and exposure to cosmic radiation focusing specifically on acute and chronic fluid shifts, myocardial and vascular structural adaptations, autonomic recalibration, and cerebrovascular hemodynamics. Finally, this review evaluates emerging countermeasure platforms designed to mitigate these integrated operational risks during future long-duration lunar and deep-space missions.

II. MATERIAL AND METHODS

This narrative review was conducted to examine the historical evolution, physiological foundations, pathophysiological mechanisms, and future perspectives of aerospace cardiology. A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, complemented by technical reports and official documents from the National Aeronautics and Space Administration (NASA), the European Space Agency (ESA), and the NASA Human Research Program (HRP).

The search strategy combined controlled vocabulary and free-text terms related to cardiovascular adaptation to the space environment, including “aerospace cardiology”, “space medicine”, “cardiovascular physiology”, “microgravity”, “spaceflight”, “cardiac deconditioning”, “orthostatic intolerance”, “heart rate variability”, “space radiation”, “telecardiology”, “International Space Station”, “Apollo pro-

gram”, and “human exploration missions”. Additional references were identified through manual review of the bibliographies of selected articles.

III. HISTORICAL ORIGINS: RAMIRO IGLESIAS LEAL AND THE BIRTH OF AEROSPACE CARDIOLOGY

The origins of aerospace cardiology are closely linked to the earliest efforts to monitor human physiological function during spaceflight. As human exploration expanded beyond Earth's atmosphere during the 1960s, understanding the cardiovascular response to microgravity became a priority for mission safety and operational success. Early space missions demonstrated that the cardiovascular system, which evolved under constant terrestrial gravity, undergoes significant physiological adaptations when exposed to the space environment, creating the need for continuous biomedical surveillance and specialized cardiovascular assessment.

A pivotal milestone occurred during the Apollo 8 mission in December 1968, the first crewed mission to orbit the Moon¹. During the mission, electrocardiographic recordings obtained from astronaut William Anders were transmitted to Earth and analyzed by the Mexican cardiologist Ramiro Iglesias Leal. This event represented one of the earliest documented clinical interpretations of human cardiac electrical activity transmitted during spaceflight and may be regarded as an important early milestone in the development of space-based cardiovascular monitoring and telecardiology. As discussed by Ramiro Iglesias-Leal in his historical account of the development of telemedicine [2], the transmission and remote interpretation of cardiovascular data during human spaceflight illustrated the emerging potential of providing medical assessment across large physical distances, while forming part of a broader evolution of telemedicine rather than representing its sole origin.

The significance of this achievement extended beyond the technical success of transmitting physiological signals across vast distances. For the first time, clinicians were able to evaluate cardiac electrical activity in real time while astronauts operated in an extraterrestrial environment. This capability provided evidence that electrocardiographic monitoring could be reliably performed during space missions and established the conceptual foundations for remote cardiovascular surveillance, a principle that would later evolve into modern telemedicine and telecardiology.

The Apollo program subsequently generated valuable medical observations regarding cardiovascular adaptation to spaceflight. Reports from Apollo missions documented alterations in heart rate reg-

ulation, fluid distribution, and orthostatic tolerance following return to Earth, suggesting that even relatively short-duration missions could induce measurable cardiovascular changes [3]. These early observations stimulated further investigation into the mechanisms governing cardiovascular adaptation to microgravity and highlighted the need for dedicated physiological research during future missions.

Although aerospace medicine encompasses multiple physiological systems, the interpretation of spaceborne electrocardiographic data during Apollo 8 symbolized the emergence of a distinct cardiovascular perspective within the discipline. The work of Ramiro Iglesias Leal therefore occupies a unique place in the history of space medicine, linking the earliest era of lunar exploration with the subsequent development of aerospace cardiology as a field dedicated to understanding cardiovascular physiology, pathophysiology, and clinical monitoring in the space environment.

The historical legacy of these pioneering efforts extends into contemporary human spaceflight programs. Current cardiovascular monitoring aboard the International Space Station employs sophisticated telemetry systems, wearable sensors, and real-time biomedical data transmission technologies that trace their conceptual origins to the first successful electrocardiographic assessments performed during the Apollo era. Consequently, the foundations established during the late 1960s continue to influence modern strategies aimed at protecting astronaut cardiovascular health during long-duration missions to the Moon, Mars, and beyond [4].

IV. EARLY DEVELOPMENT DURING APOLLO AND SKYLAB MISSIONS

The Apollo program provided the first systematic opportunity to evaluate cardiovascular responses during human spaceflight. Although mission durations were relatively short, ranging from several days to approximately two weeks, medical observations obtained during Apollo 7–11 revealed that exposure to microgravity produced measurable physiological adaptations affecting cardiovascular regulation and fluid homeostasis [5].

One of the earliest findings was the redistribution of body fluids toward the thoracic and cephalic regions following entry into microgravity [3, 10]. The absence of the normal hydrostatic gradients generated by Earth's gravity resulted in a central fluid shift that altered cardiovascular loading conditions and initiated compensatory neurohumoral responses. These adaptations were associated with increased diuresis, reductions in plasma volume, and subsequent cardiovascular deconditioning, phenomena

that would later become central topics in aerospace physiology research [6, 10].

Medical reports from Apollo astronauts also documented alterations in heart rate regulation and reduced orthostatic tolerance following return to Earth's gravitational environment [5]. Although the underlying mechanisms were not fully understood at the time, these observations suggested that cardiovascular reflexes adapted rapidly to weightlessness and that re-exposure to gravity posed a significant physiological challenge [8, 9]. Such findings prompted investigators to examine the roles of autonomic regulation, vascular responsiveness, and circulating blood volume in post-flight cardiovascular performance [10].

The transition from Apollo to Skylab represented a pivotal advancement in space biomedical research. Whereas Apollo missions were limited to short durations—typically lasting from a few days to roughly two weeks—Skylab extended continuous microgravity exposure up to 84 days. This extended timeframe allowed investigators to demonstrate that cardiovascular adaptations are not restricted to acute initial fluid shifts, but rather involve progressive physiological remodeling over prolonged spaceflight [6].

Studies conducted during the Skylab revealed sustained reductions in plasma volume and exercise capacity, accompanied by evidence of cardiovascular deconditioning that became increasingly apparent with mission duration [7]. These findings highlighted the importance of maintaining cardiovascular fitness during spaceflight and stimulated the development of in-flight exercise programs designed to mitigate physiological deterioration.

Importantly, the Apollo and Skylab programs established many of the methodological foundations that continue to guide cardiovascular research in space today [3, 4]. Continuous physiological monitoring, serial cardiovascular assessments, and the integration of telemetry systems into mission operations demonstrated the feasibility of conducting sophisticated biomedical investigations beyond Earth [7]. The knowledge gained during these pioneering missions laid the groundwork for subsequent research aboard the Space Shuttle, the MIR space station, and ultimately the International Space Station, where cardiovascular adaptation would become one of the most extensively studied aspects of human space physiology [3, 4, 10].

By the end of the Skylab era, it had become evident that microgravity induced a complex series of cardiovascular adaptations involving fluid regulation, autonomic control, exercise capacity, and orthostatic tolerance. These discoveries transformed aerospace cardiology from an observational discipline into a field increasingly focused on under-

standing the physiological mechanisms underlying cardiovascular adaptation to spaceflight [11].

V. THE INTERNATIONAL SPACE STATION AND THE CONSOLIDATION OF CARDIOVASCULAR RESEARCH

The transition from short-duration orbital flights to extended missions aboard space stations such as MIR and the International Space Station (ISS) necessitated a shift from observational medicine to rigorous mechanistic pathophysiology [4]. Early long-duration studies revealed that cardiovascular deconditioning reaches a relative plateau but continues to cause significant functional impairments [7, 11]. Investigations utilizing Lower Body Negative Pressure (LBNP) during missions lasting up to 14 months aboard the MIR station demonstrated a progressive decline in peripheral vasoconstrictor capacity, which was directly linked to altered baroreflex sensitivity and reduced stroke volume [7, 9]. Furthermore, data collected during the 14-day Antares flight on MIR and subsequent Spacelab missions confirmed that even brief exposures to the space environment initiate rapid neurohumoral and autonomic adaptations, establishing that post-flight orthostatic intolerance is strongly influenced by the duration of microgravity exposure [8].

In the modern era, the ISS has served as a continuous laboratory for evaluating these chronic adaptations. Contemporary multi-omic and organ-level analyses have demonstrated that prolonged weightlessness induces comprehensive microvascular remodeling and macrovascular stiffening [9]. Studies monitoring astronauts over six-month periods have confirmed that systemic arterial compliance decreases while central venous pressures undergo a chronic baseline shift. This body of research has consolidated our understanding of spaceflight deconditioning, proving it is not merely a transient fluid volume phenomenon but a multi-system adaptation involving integrated autonomic, vascular, and structural modifications [11].

VI. FLUID REDISTRIBUTION AND PLASMA VOLUME REGULATION

The immediate entry into microgravity abolishes the hydrostatic pressure gradient that terrestrial gravity exerts on the human body [4]. On Earth, gravity causes a continuous pooling of fluids in the lower extremities; however, in a weightless environment, an acute cephalad fluid shift occurs, redistributing approximately 1.5 to 2 liters of intravascular and interstitial fluid from the lower limbs toward the thoracic and cephalic regions [3, 10]. This acute central fluid shift induces an immediate engorgement of the

jugular veins, facial edema, and a transient increase in early cardiac filling pressures, which is rapidly interpreted by central baroreceptors as a state of relative hypervolemia [10].

In contrast to early conceptual models which hypothesized a sustained rise in central venous pressure (CVP), actual in-flight measurements aboard the International Space Station (ISS) revealed a physiological paradox. Direct intravascular recordings demonstrated that mean CVP rapidly decreases upon exposure to microgravity (falling from pre-flight supine values to approximately 2.5 cmH₂O) [37]. Due to the absence of gravitational forces acting on the chest wall, the compliance of the thoracic cage increases, causing a negative shift in intrapleural pressure that effectively unloads the central veins while maintaining or increasing end-diastolic cardiac filling [3, 37]. Consequently, direct baseline CVP measurements during steady-state spaceflight are lower than or equivalent to pre-flight supine values, despite the persistent cephalad volume overload [9]. (Figure 1.)

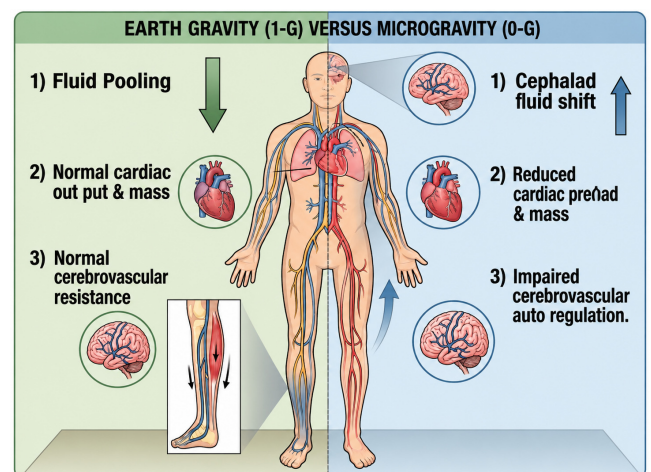


Figure 1. Macrohemodynamics and fluid redistribution: Terrestrial gravity (1-G) vs Microgravity (0-G). Author's own elaboration.

To counteract this perceived redistribution, the central nervous system and endocrinological pathways initiate rapid compensatory neurohumoral resets [8, 10]. These adaptations include the profound suppression of the renin-angiotensin-aldosterone system (RAAS), decreased secretion of antidiuretic hormone (arginine vasopressin), and an increased release of atrial natriuretic peptide (ANP) [6]. This neurohumoral cascade triggers an early operational diuresis and natriuresis during the first days of flight, leading to a profound reduction in total plasma volume [6, 10].

Clinical monitoring of astronauts has confirmed that plasma volume drops by approximately 10% to 15% within the first 48 hours of microgravity expo-

sure and stabilizes at this lower baseline throughout the mission. This intravascular depletion triggers a secondary hematological adaptation known as "spaceflight anemia" [9, 38]. The rapid decrease in plasma volume causes a transient hemoconcentration that suppresses erythropoietin secretion, leading to the selective destruction of newly formed erythrocytes via neocytolysis [38].

Furthermore, according to Starling's forces, the chronic absence of transmembrane hydrostatic pressure alters the physical properties of the vascular endothelium and the surrounding interstitial matrix [4]. Microvascular filtration rates adapt to the local tissue pressures of the upper body, while the lower extremities experience a marked decrease in interstitial fluid pressure [11]. While this systemic hypovolemia and microvascular resetting represent a successful and stable physiological adaptation to minimize central venous congestion while living in space, it constitutes the primary pathophysiological substrate for severe post-flight orthostatic intolerance, baroreflex impairment, and profound cardiovascular deconditioning upon re-entry into a gravitational field [12].

VII. CARDIAC STRUCTURAL REMODELING AND CARDIAC ATROPHY

The chronic unloading of the myocardium induced by the absence of gravitational resistance leads to progressive cardiac structural remodeling and cardiac atrophy. On Earth, the heart continuously performs mechanical work against a hydrostatic column to maintain systemic perfusion; however, the persistent reduction in metabolic demand and the establishment of a lower operational plasma volume in microgravity significantly reduce myocardial workload. Historically, bed rest studies utilizing head-down tilt analogs provided the first robust evidence of this phenomenon, demonstrating that prolonged physical deconditioning and circulatory unloading induce a significant decrease in left ventricular mass [13].

In the modern era of long-duration spaceflight, the integration of advanced imaging modalities has enabled the precise quantification of these changes in astronauts. Assessments using cardiac magnetic resonance imaging (CMR)—the current gold standard for volumetric evaluation—conducted before and after six-month missions aboard the International Space Station have confirmed a measurable loss of myocardial tissue, with reductions in left ventricular mass averaging between 8% for bed-rest missions and 10% for ISS missions [14]. At the cellular and molecular levels, this structural remodeling is driven by altered mechanotransduction. The lack of gravitational loading downregulates focal ad-

hesion kinases and costamere signaling pathways within the cardiomyocyte membrane, shifting the cellular balance toward protein degradation via the ubiquitin-proteasome system. This leads to a global reduction in myofibrillar cross-sectional area and a loss of sarcomeric proteins rather than cellular necrosis, representing a plastic, energetic adaptation to the reduced hemodynamic demands of the space environment [15].

Beyond simple mass loss, the absence of a vertical gravitational vector induces a distinct geometric deformation, causing the heart to become significantly more spherical in flight. This transient change in cardiac sphericity alters the distribution of transmural wall stress and disrupts global ventricular mechanics. Echocardiographic and physiological evaluations during long-duration flights have demonstrated a progressive reduction in left ventricular end-diastolic volume, which directly limits stroke volume during post-flight gravitational stress. This architectural remodeling alters the passive diastolic pressure-volume relationship, resulting in a stiffer, less compliant ventricle upon re-exposure to Earth's gravity [13].

Furthermore, real-time in-flight tissue Doppler imaging and cardiac kinetic analyses have revealed that this spherical remodeling is accompanied by a compensatory redistribution of myocardial velocities. Longitudinal myocardial strain decreases, while radial displacement alters its operational timing to maintain a stable ejection fraction despite the reduced preload [16]. Consequently, while cardiac atrophy and geometric reshaping represent an efficient energetic adaptation for life in weightlessness, the combination of a remodeled myocardium, restricted chamber compliance, and altered contraction kinetics severely compromises the ability of the cardiovascular system to handle acute fluid shifts, creating a critical vulnerability to orthostatic shock upon return to a gravitational field.

VIII. AUTONOMIC NERVOUS SYSTEM AND HEART RATE VARIABILITY

Prolonged exposure to a microgravity environment induces profound alterations in the autonomic nervous system (ANS) architecture and compromises cardiovascular homeostatic reflexes. Under terrestrial conditions, the sympathetic and parasympathetic branches of the ANS exhibit a continuous, dynamic balance to modulate heart rate and vascular tone in response to hydrostatic pressure fluctuations. Upon entry into weightlessness, the persistent cephalad fluid shift and the subsequent reduction in total plasma volume trigger a complex neuroautonomic resetting. Early in-flight assessments utilizing spectral analysis of heart rate variability (HRV) have

demonstrated a significant shift in autonomic balance, characterized by a progressive reduction in parasympathetic (vagal) tone and a compensatory, chronic upregulation of sympathetic nervous system activity [17].

This neurohumoral shift profoundly impacts the microstructural behavior of cardiac rhythm regulation. Quantitative analyses of the high-frequency (HF) component of HRV—which serves as a direct marker of respiratory sinus arrhythmia and vagal modulation—reveal a steady decline during long-duration space missions. Concurrently, the low-frequency (LF) component and the LF/HF ratio exhibit substantial increases, confirming a state of persistent sympathetic dominance. This chronic sympathetic activation occurs as a vital compensatory mechanism to maintain an adequate cardiac output and systemic arterial pressure in the presence of a reduced stroke volume and progressive myocardial remodeling. However, this prolonged autonomic overactivation downregulates beta-adrenergic receptor sensitivity within the sinoatrial node and peripheral vasculature, limiting the functional reserve of the heart [6].

Furthermore, this autonomic dysregulation directly impairs the arterial baroreflex function through both mechanical and central neurophysiological pathways. The chronic absence of gravitational loading blunts the operational sensitivity of both carotid and aortic baroreceptors. Mechanically, local vascular remodeling and changes in extracellular matrix composition within the carotid sinus decrease vessel wall compliance, attenuating the physical stretch required to activate mechanosensitive ion channels in nerve endings. Centrally, the chronic reduction of normal hydrostatic inputs causes a functional resetting at the level of the nucleus tractus solitarius in the brainstem, disrupting the gating of efferent sympathetic discharges. When astronauts are re-exposed to a gravitational vector, this degraded baroreflex loop fails to execute rapid, coordinated peripheral vasoconstriction and tachycardic compensation. The loss of autonomic resonance, evidenced by the blunting of low-frequency arterial pressure oscillations (Mayer waves), prevents the system from counteracting the abrupt caudal pooling of blood, driving the clinical manifestation of post-flight orthostatic syncope [17].

IX. ORTHOSTATIC INTOLERANCE: MICROGRAVITY DYNAMICS, RE-ENTRY PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND COUNTERMEASURES

A. Microgravity Dynamics and Re-entry Pathophysiology

During spaceflight, orthostatic intolerance exists as a latent, subclinical phenomenon due to the absence of a gravitational vector to challenge the circulatory system. However, exposure to Lower Body Negative Pressure (LBNP) devices aboard the ISS serves as an effective diagnostic analog, revealing that cardiovascular reserves are progressively compromised even in flight. Upon re-entry into Earth's gravity, this hidden maladaptation transforms into an immediate pathophysiological deficit. The sudden restoration of a vertical acceleration vector ($+G_z$) drives an abrupt caudal redistribution of intravascular and interstitial fluid, causing approximately 1 to 1.5 liters of blood to pool rapidly within the highly distensible venous capacitance vessels of the lower extremities and splanchnic circulation [18].

The core etiology of this homeostatic failure represents the cumulative intersection of multiple distinct physiological resets. First, total circulating plasma volume remains severely depleted by 10% to 15%, leaving the cardiovascular apparatus with a critically low initial central venous reserve. Second, the chronic lack of gravitational loading increases the mechanical distensibility and compliance of the lower limb vasculature, which significantly exacerbates the volume of venous pooling. Third, when this pooling occurs, the remodeled, atrophied, and geometrically spherical left ventricle cannot expand adequately to maintain an optimal end-diastolic volume, limiting stroke volume via the Frank-Starling mechanism. Finally, peripheral vasoconstriction fails due to the profound blunting of the arterial baroreflex and down-regulated vascular alpha-1 adrenergic receptor sensitivity, preventing the necessary rise in peripheral vascular resistance to meet the gravitational challenge [6].

B. Clinical Manifestations

The clinical presentation of post-flight orthostatic intolerance spans a spectrum of cardiovascular and neurological symptoms that severely impair operational readiness during the critical post-landing phase. Upon assuming an upright posture, the dramatic drop in cardiac output and the failure of compensatory vasoconstriction cause systemic mean arterial pressure to fall below critical cerebral autoregulation thresholds. Astronauts experience immediate prodromal symptoms, including severe dizziness, lightheadedness, generalized weakness, and palpitations driven by a compensatory but ineffective sinus tachycardia.

As cerebral hypoperfusion worsens, visual disturbances such as blurred vision, tunnel vision, or complete gray-outs manifest. If the orthostatic stress is sustained without intervention, the acute

reduction in oxygen delivery to the central nervous system culminates in transient cerebral ischemia, presenting clinically as acute orthostatic syncope or neurogenic shock [19].

C. Countermeasures and Risk Mitigation

To minimize the incidence of post-flight orthostatic intolerance, aerospace medicine relies on an integrated, multi-system countermeasure framework deployed before, during, and after re-entry. Physiologically, the most critical pre-landing intervention is aggressive fluid and electrolyte loading. Astronauts consume specific doses of isotonic saline or water with sodium chloride tablets immediately prior to re-entry to acutely expand plasma volume and restore central venous pressure. Mechanically, the deployment of advanced anti-G garments and specialized lower-body compression garments applies graded external hydrostatic pressure to the lower limbs and abdomen, physically preventing the pooling of blood in venous capacitance vessels during deceleration and initial standing [20].

In-flight physical countermeasures are equally essential to preserve myocardial mass and vascular tone throughout the mission. Long-duration crewmembers engage in intensive daily resistance and aerobic exercise protocols utilizing specialized equipment (such as the Advanced Resistive Exercise Device, ARED, and cycle ergometers) to maintain structural cardiac compliance and skeletal muscle pump efficiency [21]. Furthermore, the periodic use of LBNP devices during the final weeks of flight provides a temporary artificial gravity analog, stimulating the baroreflex arc and preserving microvascular reactivity. Pharmacological adjuncts, including the selective alpha-1 adrenergic agonist midodrine, have also been investigated to artificially augment peripheral vasoconstriction in non-responsive individuals, ensuring that cerebral perfusion remains fully protected during gravitational transitions.

X. ENDOTHELIAL FUNCTION AND VASCULAR REMODELING: SHEAR STRESS, HISTOLOGICAL SHIFTS, AND MOLECULAR SIGNALING

A. Biomechanics of Altered Shear Stress

The chronic elimination of hydrostatic pressure gradients in microgravity profoundly disrupts the local hemodynamic environment, altering the mechanical forces exerted on the vascular wall. On Earth, fluid shear stress—the frictional force generated by blood flow pulling across the apical membrane of endothelial cells—regulates vascular homeostasis and patency. The cephalad fluid shift induces a permanent, regional redistribution of this biomechan-

ical stimulus. Conduit arteries of the upper body and cerebral circulation experience a sustained increase in transmural pressure and flow-induced shear stress, whereas the vasculature of the lower extremities undergoes severe mechanical unloading and a drastic reduction in chronic shear stress baselines.

Endothelial cells act as primary mechanotransducers, utilizing specialized surface structures such as the glycocalyx, integrins, and caveolae to sense these mechanical modifications. In the lower limbs, the drop in laminar shear stress below critical physiological thresholds impairs endothelial mechanotransduction loops [22]. The loss of steady frictional drag deactivates mechanosensitive ion channels, signaling a state of structural redundancy that initiates a coordinated, localized vessel wall remodeling program.

B. Histological Alterations in Conduit and Resistance Vessels

This chronic biomechanical disequilibrium translates into distinct physical and histological structural modifications across regional vascular beds. In response to the persistent transmural pressure drop and low-flow states, the arteries of the lower extremities undergo a process of inward hypertrophic remodeling. Histological evaluations of vascular segments under microgravity-simulation analogs reveal a significant decrease in the internal lumen diameter, accompanied by a paradoxical thickening of the tunica media.

Within the tunica media of these unloaded vessels, vascular smooth muscle cells (VSMCs) exhibit high phenotypic plasticity, shifting from a quiescent, contractile state to an active, synthetic phenotype. This phenotypic switch drives the asymmetric reorganization of the extracellular matrix (ECM), characterized by increased collagen deposition and the structural degradation of internal elastic laminae [23]. Conversely, the cerebral vasculature experiences an outward hypertrophic remodeling with increased medial thickness to buffer the persistent cephalic plethora. This regional divergence in arterial remodeling and medial composition severely dampens systemic arterial compliance and distensibility upon return to a gravitational field.

C. Molecular Cascades and Endothelial Dysfunction

At the molecular level, the downstream consequences of altered shear stress selectively target the endothelial nitric oxide synthase (eNOS) pathway, triggering systemic endothelial dysfunction. Under normal laminar shear stress, the mechanical activation of endothelial cells triggers the phosphorylation of eNOS via the phosphatidylinositol 3-kinase

(PI3K)/Akt pathway, ensuring steady basal synthesis of nitric oxide (NO) to maintain vascular smooth muscle relaxation and suppress inflammation [24]. In the low shear stress environments of the lower body, this pathway is severely downregulated, leading to a profound deficit in bioavailable NO. (Fig. 2.)

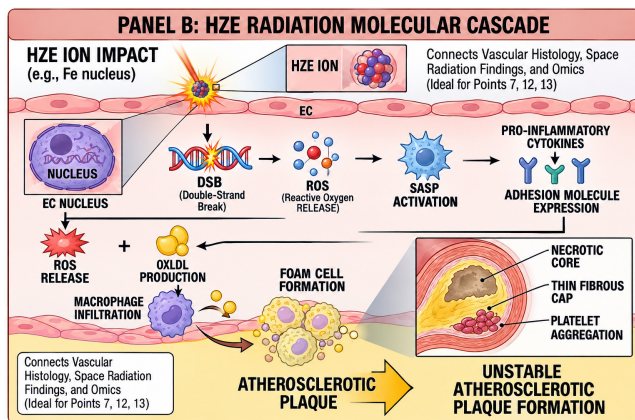


Figure 2. Fig. 2. Radiation-induced atherogenesis. Author's own elaboration.

This impairment in NO bioavailability is further exacerbated by an accelerated accumulation of reactive oxygen species (ROS). The loss of physiological mechanical stimulation upregulates NADPH oxidase and uncouples eNOS, shifting the endothelial enzymatic machinery toward the overproduction of superoxide anions ($O_2^{\cdot-}$). ROS rapidly scavenge remaining NO molecules to form peroxynitrite ($ONOO^-$), a highly destructive reactive nitrogen species. This oxidative microenvironment activates the nuclear factor kappa B (NF- κ B) signaling cascade, promoting the transcription of pro-inflammatory cell adhesion molecules—such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)—along with an increased release of endothelin-1 (ET-1), a potent vasoconstrictor [24]. Cumulatively, this molecular cascade replaces the homeostatic, vasodilatory, and anti-thrombotic endothelial phenotype with a rigid, pro-inflammatory, and highly vasoconstrictive state, cementing structural endothelial dysfunction as a core component of spaceflight-induced cardiovascular deconditioning.

XI. CEREBROVASCULAR AUTOREGULATION AND COGNITIVE IMPACTS: HEMODYNAMIC VOLATILITIES, STRUCTURAL SHIFTS, AND NEUROCOGNITIVE PERFORMANCE

A. Dynamics of Cerebrovascular Autoregulation in Microgravity

The persistent cephalad fluid shift inherent to the microgravity environment imposes a continuous hemodynamic challenge on the cerebral vasculature, testing the limits of intrinsic regulatory mechanisms. Under terrestrial conditions, cerebrovascular autoregulation (CA) maintains a constant cerebral blood flow (CBF) despite wide fluctuations in systemic mean arterial pressure, protecting the brain from both hyperperfusion-mediated edema and hypoperfusion-induced ischemia. In spaceflight, the chronic engorgement of the cranial venous system and the elimination of normal hydrostatic variations disrupt this steady-state balance.

Transcranial Doppler (TCD) ultrasonography and advanced transfer function analyses performed during long-duration missions have revealed that while static CA remains remarkably resilient, dynamic cerebrovascular autoregulation undergoes subtle, progressive impairment. The continuous increase in transmural pressure within the middle cerebral arteries induces an adaptive increase of local vascular resistance; however, the speed and efficiency with which the cerebral vessels damp rapid, systemic pressure oscillations are significantly reduced. This latency in dynamic adaptation leaves the cerebral microcirculation vulnerable to acute pressure surges during intense exercise or microgravity maneuvers [25].

B. Structural Brain Alterations and Fluid Redistribution

This altered hemodynamics, combined with chronic venous congestion, drives profound macroscopic and microstructural modifications within the central nervous system architecture. High-resolution neuroimaging studies utilizing pre- and post-flight magnetic resonance imaging (MRI) have demonstrated a significant upward shift of the brain structure within the neurocranium, characterized by the crowding of sulci at the vertex and the narrowing of the superior sagittal sinus. Concurrently, there is a marked, disproportionate redistribution of cerebrospinal fluid (CSF), with extensive volume expansion in the lateral ventricles and the perimedullary spaces, alongside a restriction of CSF outflow through the arachnoid granulations.

These structural shifts contribute directly to the pathophysiology of Spaceflight-Associated Neuro-ocular Syndrome (SANS) [26], as the localized increase in intracranial pressure (ICP) is transmitted along the optic nerve sheath, resulting in optic disc edema, globe flattening, and progressive hyperopic shifts.

C. Neurocognitive Performance and Operational Impacts

At the functional level, the combination of altered cerebral perfusion kinetics, chronic intracranial congestion, and structural tissue displacement exerts a measurable impact on cognitive performance and operational competence. Longitudinal neurocognitive testing batteries administered to ISS crewmembers [27] indicate that while general intellectual capabilities, logical reasoning, and long-term memory are preserved through robust compensatory cortical networks, specific high-order cognitive domains exhibit transient vulnerabilities.

Spatial orientation, mental rotation, and fine motor tracking performance show noticeable decrements, particularly during the initial adaptation phase to weightlessness and the critical re-entry transition. These neurocognitive fluctuations are closely tied to the disruption of vestibular-visual-proprioceptive integration and are compounded by localized microvascular perfusion changes within the prefrontal and parietal cortices [28]. Consequently, optimizing cerebrovascular health through targeted physiological countermeasures remains imperative to ensure executive function integrity and minimize human-error risks during complex, long-duration deep-space maneuvers.

XII. SPACE RADIATION AND LONG-TERM CARDIOVASCULAR RISK: HZE PARTICLES, ACCELERATED ATHEROGENESIS, AND MYOCARDIAL FIBROSIS

A. Chronic Low-Dose Galactic Cosmic Radiation Kinetics

Beyond the protective magnetosphere of Earth, astronauts executing deep-space exploration profiles are exposed to a complex, unavoidable ionizing radiation environment comprised of Galactic Cosmic Rays (GCR) and potential Solar Particle Events (SPE). While terrestrial radiation risks typically stem from high-dose, short-duration X-rays or gamma-rays, the aerospace environment is characterized by a chronic, low-dose-rate exposure to high-energy protons and highly charged, high-energy (HZE) nuclei, such as iron ^{56}Fe , silicon ^{28}Si , and carbon ^{12}C [29]. These heavy ions possess high linear energy transfer (high-LET) properties, meaning they deposit a dense track of ionization along their trajectory through biological tissues.

An important historical observation supporting a potential cardiovascular effect of deep-space radiation was reported by Delp et al. in a cohort of U.S. astronauts. The authors compared proportional cardiovascular mortality among astronauts

who had never flown, astronauts who had flown exclusively in low Earth orbit (LEO), and Apollo lunar astronauts, who were the only group exposed to the deep-space radiation environment beyond Earth's magnetosphere. Cardiovascular mortality was 9% among non-flight astronauts, 11% among LEO astronauts, and 43% among Apollo lunar astronauts, representing a substantially higher proportion in the latter group. However, this finding should be interpreted cautiously because the Apollo subgroup was very small, consisting of only seven astronauts, and therefore the study cannot establish a causal relationship between deep-space radiation exposure and cardiovascular mortality [30].

To explore a possible biological mechanism, Delp et al., study evaluated vascular function in mice exposed to space-relevant irradiation, with or without simulated weightlessness. Space-relevant irradiation was associated with sustained impairment of endothelium-dependent vasodilation, accompanied by increased vascular xanthine oxidase expression, whereas endothelium-independent vasodilation was not significantly altered. These experimental findings provide a plausible mechanistic link between exposure to high-energy space radiation and vascular endothelial dysfunction, which may contribute to later cardiovascular disease. Nevertheless, the animal model cannot directly establish that radiation was responsible for the excess cardiovascular mortality observed in Apollo astronauts. Taken together, the historical astronaut data and experimental findings support the biological plausibility of radiation-associated vascular injury and reinforce the need for further epidemiological and mechanistic studies of cardiovascular risk during missions beyond low Earth orbit.

Multi-omic analyses from contemporary space biology platforms indicate that deep-space radiation dose equivalents, even when accumulated at low dose rates, exert high relative biological effectiveness (RBE) in damaging quiescent cardiovascular components, initiating a cascade of persistent degenerative pathologies that extend decades beyond mission completion.

B. Molecular Mechanisms of Accelerated Atherogenesis

The primary vascular target of high-LET HZE particles is the endothelial monolayer of large conduit arteries, where radiation exposure triggers an aggressive, accelerated atherogenic process. Unlike traditional age-related plaque development, radiation-induced atherogenesis is driven by immediate, unrepairable double-strand DNA breaks (DSBs) and localized, chronic oxidative stress. The heavy ion track passing through the endothelial cytoplasm causes a massive radiolysis of water, generating

a high, localized concentration of hydroxyl radicals ($\text{OH}\cdot$) and hydrogen peroxide (H_2O_2). This oxidative storm causes immediate lipid peroxidation of cell membranes and chemically modifies low-density lipoproteins (LDL) into highly immunogenic oxidized LDL (oxLDL).

Concurrently, the persistent DNA damage triggers a chronic state of endothelial cell senescence, characterized by the activation of the senescence-associated secretory phenotype (SASP). This phenotype upregulates the continuous expression of pro-inflammatory cytokines (IL-6, TNF- α) and adhesion molecules (VCAM-1, ICAM-1), prompting an unremitting recruitment of circulating monocytes into the subendothelial space. These monocytes differentiate into macrophages, engulf the oxLDL via scavenger receptors, and transform into foam cells, establishing highly unstable, necrotic-core atheromatous plaques that are highly susceptible to spontaneous rupture and subsequent acute ischemic events [31].

C. Microvascular Alterations and Myocardial Fibrosis

Beyond the macrovasculature, chronic high-LET radiation directly damages the coronary microcirculation and the underlying myocardial architecture. Endothelial cells within coronary capillaries exhibit high sensitivity to HZE-induced damage, leading to microvascular rarefaction, compromised capillary density, and chronic localized tissue hypoxia. This persistent hypoxic microenvironment, coupled with radiation-induced activation of the transforming growth factor-beta (TGF- β) signaling cascade, drives the phenotypic transformation of resident cardiac fibroblasts into active, proliferative myofibroblasts [31].

These myofibroblasts orchestrate an excessive, unregulated remodeling of the extracellular matrix, characterized by a massive deposition of interstitial collagen type I and type III. This progressive myocardial fibrosis mechanically stiffens the ventricular walls, altering diastolic filling kinetics and increasing the long-term risk of diastolic heart failure (HFpEF) and ventricular arrhythmias. Consequently, when integrated with spaceflight-induced microgravity deconditioning, the cardiotoxic effects of space radiation significantly elevate the lifetime risk of cardiovascular mortality, highlighting the absolute necessity of developing advanced, biophysical and pharmacological radioprotective countermeasures for interplanetary travel [32].

XIII. FUTURE DIRECTIONS AND INTER-PLANETARY COUNTERMEASURES: ARTIFICIAL GRAVITY, TARGETED PHARMACOGENOMICS, AND BIO-REGENERATIVE MEDICINE

A. Artificial Gravity Infrastructure as a Systemic Countermeasure

As human spaceflight transitions from low Earth orbit (LEO) toward multi-year interplanetary transits, traditional exercise-centric protocols, such as treadmills and cycle ergometers, may prove insufficient on their own to fully prevent the cumulative deterioration of cardiovascular function over extended durations [11, 33]. A potential approach currently under investigation involves the deployment of artificial gravity (AG) through short-radius or large-radius centrifuges [36]. Short-radius centrifuges integrated directly into the transit habitat are designed to generate a controlled centripetal acceleration vector (G_z), establishing a temporary hydrostatic pressure gradient that drives fluid back toward the lower extremities [33].

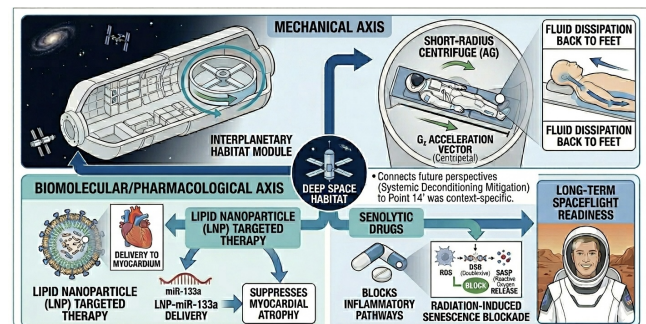


Figure 3. Fig. 3. Interplanetary countermeasure. Author's own elaboration.

Longitudinal validation trials in terrestrial bed-rest analogues suggest that intermittent exposure (e.g., 30 to 60 minutes daily at 1-G to 2-G at the feet) helps attenuate transmural pressure alterations, showing potential to mitigate lower-limb microvascular unloading, counteract adverse remodeling of resistance vessels, and support the dynamic capabilities of cerebrovascular autoregulation [36]. However, the operational feasibility, optimal dosing parameters, and long-term efficacy of continuous or intermittent artificial gravity in deep-space environments remain to be fully established through in-flight clinical validation [33].

B. Pharmacogenomics and Multi-Omic Targeted Therapeutics

To complement mechanical approaches such as artificial gravity, candidate countermeasure frameworks under development explore the potential inte-

gration of personalized, multi-omic-guided pharmacogenomics [29, 34]. Conceptual models suggest that in-flight genomic monitoring and transcriptomic profiling could eventually inform targeted biochemical strategies tailored to an individual astronaut's observed epigenetic alterations [29, 34]. Experimental targets evaluated in cellular and animal models include selective inhibitors of the NF- κ B and JAK-STAT pathways to modulate the senescence-associated secretory phenotype (SASP) triggered by high-LET cosmic radiation, aiming to mitigate radiation-induced vascular damage at the molecular level [31, 32].

Furthermore, pre-clinical investigations into synthetic microRNA candidates (such as miR-133a supplements investigated via nanoparticle delivery systems) represent a novel epigenetic strategy proposed to limit phenotypic switching of vascular smooth muscle cells and attenuate cardiac muscle mass loss [34]. However, while these molecular and genetic interventions show mechanistic promise in laboratory settings and ground-based models, their therapeutic safety, targeted delivery efficacy, and systemic risks in human spaceflight remain unproven prospective hypotheses that require extensive preclinical and clinical validation before consideration for operational deployment.

C. Bio-Regenerative Medicine and Advanced Radioprotection

A theoretical frontier in interplanetary cardioprotection involves the potential integration of bio-regenerative medicine with advanced biophysical shielding [31]. Given the unmitigated nature of Galactic Cosmic Rays (GCR) during deep-space transit, developing biological strategies capable of mitigating cellular radiation damage represents an active area of investigation. Current exploratory research focuses on the evaluation of engineered antioxidant compounds—such as mitochondria-targeted hydrogen sulfide (H_2S) donors—designed to scavenge reactive oxygen species and hydroxyl radicals ($\text{OH}^\cdot$) before they cause irreversible double-strand DNA breaks in the coronary endothelium [32]. Concurrently, conceptual frameworks propose that autologous endothelial progenitor cells, harvested pre-flight and modified via CRISPR-Cas9 gene editing to enhance resistance to oxidative stress, could theoretically serve as an experimental cellular therapy to address microvascular rarefaction and myocardial fibrosis in situ [32]. However, these biotechnological concepts remain in early preclinical stages. While combining physical spacecraft shielding with prospective biological countermeasures aims to support cardiovascular performance, the operational viability and true protective efficacy of these combined strategies for long-duration Martian

missions remain to be demonstrated through rigorous future testing [34].

D. Partial Gravity: Cardiovascular Considerations for Lunar and Martian Exploration

Unlike orbital microgravity, the lunar and Martian surfaces provide persistent gravitational loading of approximately 0.16 g and 0.38 g, respectively. These environments therefore represent distinct physiological conditions rather than simply intermediate forms of microgravity. Partial gravity may partially restore gravitationally driven hydrostatic pressure gradients and reduce cephalad fluid redistribution compared with microgravity; however, the magnitude of these effects and their consequences for plasma volume, baroreflex regulation, vascular remodeling, and orthostatic tolerance remain uncertain [35]. Experimental studies using parabolic flight and terrestrial partial-gravity analogues suggest that cardiovascular responses vary with the gravitational load, but these models cannot fully reproduce prolonged residence on another planetary surface.

Consequently, chronic cardiovascular adaptation to lunar or Martian gravity should not be assumed to mirror a simple mid-point between microgravity and terrestrial gravity [36]. While partial gravity provides a greater degree of continuous physiological stimulus than orbital microgravity, it may still fall below the threshold required to maintain normal 1"-G cardiovascular architecture and autonomic tone over multi-month or multi-year missions [35]. The limited human evidence, particularly for chronic exposure, represents an important knowledge gap. Future investigations using partial-gravity analogues, centrifuge platforms, and other controlled simulation environments will be necessary to characterize the effects of sustained partial gravity on fluid distribution, autonomic regulation, vascular structure, and orthostatic tolerance before definitive cardiovascular countermeasures can be established.

XIV. CONCLUSIONS AND FUTURE PERSPECTIVES

The characterization of cardiovascular deconditioning during human spaceflight has evolved from initial observations of fluid redistribution to a high resolution understanding of dynamic cellular, neuro-humoral and structural remodeling. The elimination of hydrostatic pressure gradients in microgravity initiates an immediate cephalad fluid shift that alters regional transmural pressures and fluid shear stress. As demonstrated across orbital missions, the human cardiovascular system exhibits high physiological plasticity, undergoing adaptations such as cardiac mass adjustments to meet reduced volumetric demands, while regional vascular beds show

distinct remodeling patterns involving microvascular changes in the lower extremities and alterations in macrovascular compliance.

Looking toward deep-space exploration and multi-year interplanetary transits, the cardiovascular risk profile presents novel physiological challenges. Crewmembers will transition from low Earth orbit to face prolonged exposure to high-LET galactic cosmic radiation and solar particle events outside the protective magnetosphere. Preclinical and epidemiological evidence indicates that heavy-ion radiation induces molecular cascades—driven by chronic oxidative stress, endothelial cell senescence, and vascular smooth muscle alterations—that may accelerate vascular aging and promote myocardial fibrosis. These radiation-induced microstructural modifications, when combined with the prolonged mechanical unloading of microgravity, represent important operational concerns for post-flight orthostatic tolerance and long-term cardiovascular health.

Consequently, addressing these integrated physiological impacts will require the continued evaluation and refinement of multi-systemic countermeasure strategies. Physical modalities, such as artificial gravity centrifugation, are under active investigation to assess their capacity to maintain pressure gradients and preserve dynamic cerebrovascular autoregulation. Concurrently, advances in clinical proteomics, transcriptomics, and pharmacogenomics offer promising avenues for exploring targeted biochemical and epigenetic interventions to mitigate oxidative and inflammatory stress at the cellular level. Validating the safety and efficacy of these physical and molecular countermeasures remains an essential priority for operational aerospace medicine to support crew health during future deep-space missions.

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