Overview of Space Radiation Health Risks with a Focus on Radiation-Induced Cardiovascular Diseases

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INTRODUCTION

Futured Manned Missions

International Space Station
- ISS ( integrates, IEF, GF, 20yr/normal) 2 yr crew, 360 d in planning
- Approach limits for acceptable radiation risk after 1 to 3 missions

Lagrange Points
- Design Reference Mission currently being formulated
- Design is not approachable

Near Earth Objects
- Design Reference Mission currently being formulated
- Unforeseen mission events
- Galactic cosmic ray risks are major concern
- No human data

Mars
- Post and beyond: Exposed crews, up to 1000 d
- Long-term space missions
- Risks exceed NASA Permissible Exposure Limits (PELs) for cancer, and post significant non-cancer risk

The Space Radiation Problem

- Irradiated cells can be exposed to a high LET radiation environment compared to high energy cosmic and heavy ions (HZE) as well as secondary protons, neutrons, and fragments produced in shielding and debris
- Human cells are quadruply different from 3- to Gamma-rays high LET in low LET
- Ionizing but not identifiable particle tracks
- Chain of events/ DNA damage (aberrations, chromosome aberrations) and biological profiles of clonal damage
- No human data to estimate risk from high LET in space
- Animal and cellular models with simulated exposure radiation must be applied or developed
- Synergistic reactants of risk from other spaceflight factors

Health Risks from Space Radiation

Risk of Radiation Carcinogenesis
- Radiation-induced malignancy, major driver for PELs

Risk of Acute (in flight) & Late Central Nervous System Effects
- Possible in flight; altered cognitive function including short term memory, reduced motor function, and behavioral changes which may affect performance

Risk of Cardiovascular Disease and other Degenerative Tissue Effects
- Degenerative changes in the heart, vasculature, and lens
- Diseases related to aging, including degenerative, inflammatory disease, premature senescence, endocrine, and immune system dysfunction

Risk of Acute Radiation Syndromes due to Solar Particle Events
- Prophylactic effects (trials, vitamins, antioxidants, and fatigue), skin injury, and depilation of the blood-forming organs

Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation

Risk of Degenerative Tissue Effects:
- Osteoporosis: bone density changes, Cataract formation
- Other Health Effects:
  - Diseases related to aging, including digestive, respiratory disease, premature senescence, endocrine, and immune system dysfunction

Driving Evidence:
- Animal Studies
- Radiation, environmental disasters, atomic bomb survivors, data, radiation workers, CVD and others
- Data is confounded by lifestyle factors to a larger extent than cancer, especially in this dose range

Risk Projections:
- Current evidence and models being formulated
- Recent studies suggested may be late dose effects and distinct pathways at low to high dose suggesting mechanistic differences
- Impact of high dose likely unknown

ICRP Recommendations (2012)

Definition of "Threshold Dose":
- Previous ICRP 30 Report defined a "threshold dose" as an exposure below which clinically significant effects do not occur
- ICRP Task Group defined "threshold dose" as ED1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specified, observable effect only 1% of individuals exposed to radiation
- ED1 = a level just starting to raise above the baseline levels in unirradiated, age-matched controls with a variety of systemic diseases (incurable, life-threatening, etc.)
- ED1 does not imply that biological effects occur at lower doses; it merely defines the dose above which a specified effect/cell line or apparent in a small percent of individuals

0.5 Gy may lead to approximately 1% of exposed individuals developing the disease in question 10 years after exposure. This is in addition to the high natural incidence rate (circulatory diseases account for 30-50% of all deaths in most developed countries).

DRIVING EVIDENCE

High Doses > 5 Gy

Radiotherapy Data:
- High doses (>5 Gy exposures) associated with damage to the structures of the heart and to the coronary, carotid, and other large vessels including marked arterial stenosis, damage, especially of the pericardium and myocardium, partial infarction, microvascular damage, and stenoses of the major arteries
- Effects appear in patients receiving RT as well as in experimental animals (Little 2013)
- Deterministic effect (dose reaction)
- Mechanisms involve cell killing or inactivation of large # of cells - functional impairment

Moderate Doses 0.5 - 5 Gy

Life Span Study, Clinical, and Occupational Exposures:
- Moderate doses (0.5 - 5 Gy exposures) associated with attherosclerosis, micro and macrovascular damage
- Possibly a stochastic reaction
- Mechanisms may involve inflammation and oxidative stress, endothelial dysfunction/senescence

Low Doses < 0.5 Gy

Meta-Analysis of Low Dose Studies:
- Low doses < 0.5 Gy associated with systemic effects, microvascular damage
- Possibly a stochastic reaction
- Mechanisms may involve non-targeted effects, kidney dysfunction, monocyte dysregulation
- Confounding effects are large

Although mean cumulative radiation doses were ≤0.2 Gy in most studies, the small number of participants exposed at high cumulative doses (≤0.5 Gy) drive the observed trends in most cohorts with these higher dose groups

- Studies have not been published in a sufficiently uniform format to permit a formal heterogeneity test but still clear that there is substantial heterogeneity between them
- Other challenges for these types of analyses include disease issues, and risk estimation of pathologies/cause of death

Moderate Effects model of 0.15 Gy/gy from the ICRP to the late consequences of the study population. Predicted dose aggregate-genetic effect

Dose Rate Effects
- Radiation exposure dose rate: patients (0.1 Gy, 0.5 Gy, 1000 Gy/yr)

Potential Mechanisms of Radiation-Induced CVD

Risk Mitigation Strategy

Countermeasures

DEGEN RISK SUMMARY

- Association between exposure to high doses of low LET (≤5 Gy) radiation during re-endurance to the chest and increased risk for development of cardiovascular disease at late times post-exposure is clearly established
- Atomic bomb survivors data and analyses of epidemiology data provide evidence for elevation of risk at lower doses than previously identified, with significant risks at doses as low as 0.5 Gy
- Data at low doses is confounded by lifestyle factors, clutching interpretation of epidemiology data below 0.5 Gy
- Results are considered deterministic, with a threshold dose; however recent evidence showing risk at lower doses questions this assumption
- Preliminary risk assessment models being formulated based on recent epidemiology data for lower dose low LET exposures. More risk estimates depend on research results describing the quantitative and qualitative differences between CCR and gamma-rays
- Studies at HZE, with HZE and appropriate animal models are required
- Lack of evidence on radiation quality, disease spectrum, latency and dose rate at low levels of exposures
- The additional morbidity and mortality risks for non-cancer diseases of the cardiovascular system are major concern because they could increase RED values substantially