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

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Future Manned Missions

International Space Station

• 2013-2020: 6-person crews, 180 days (nominal); 2-person crew 360 days in planning
• Approach limits for acceptable radiation risks after 1 to 3 missions

Lagrange Points

• Design Reference Mission currently being formulated
• Outside Earth’s magnetosphere and radiation belts
• Galactic cosmic ray risks are major concern

Near Earth Objects

• Design Reference Mission currently being formulated
• Outside Earth’s magnetosphere and radiation belts
• Galactic cosmic ray risks are major concern

Mars

• 2030 and beyond: 6-person crews, up to 1000 days
• Long deep space transit times
• Risks exceed NASA Permissible Exposure Limits (PELs) for cancer, and pose significant non-cancer risks
Integrated Radiation Protection Strategy Enables Human Mars Exploration

Long-Term Commitment across Research and Technology Required...

Mission and Architecture Systems Analysis

Environmental Modeling, Monitoring, and Prediction

Crew Selection and Operations

Integrated Radiation Protection System Design and Analysis

Radiobiology and Biological Countermeasures

Innovative Multi-Purpose Shield Solutions

Advances benefit homeland security, cancer therapy, Earth observing and communication satellites, and commercial air safety

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The Space Radiation Problem

- Interplanetary crews will be exposed to a high LET radiation environment comprised of high-energy protons and heavy ions (HZE’s) as well as secondary protons, neutrons, and fragments produced in shielding and tissue
- Heavy ions are qualitatively different from X-rays or Gamma-rays: High LET vs. low LET
  - Densely ionizing along particle track
  - Cause unique damage to biomolecules, cells, and tissues
  - Distinct patterns of DNA damage (mutation spectra, chromosome aberrations) and distinct profiles of oxidative damage
- No human data exist to estimate risk from heavy ions found in space
  - Animal and cellular models with simulated space radiation must be applied or developed
- Synergistic modifiers of risk from other spaceflight factors

DNA Damage
\[ \gamma H2AX \text{ foci in EPC2-hTERT cells. (Patel and Huff)} \]

DNA damage: \[ H2AX \text{ foci in EPC2-hTERT cells. (Patel and Huff)} \]

1 GeV/u \[^{56}\text{Fe} \text{ nucleus LET} \sim 150 \text{ keV/\(\mu\text{m}\)} \]

High LET defined as \( \text{LET} > 10 \text{ keV/\(\mu\text{m}\)} \) in tissue

Qualitative differences due to track “core” and correlated tissue damage along a particle path. (Plante, 2011)
Space Radiation Risks

Risk of Radiation Carcinogenesis
• Morbidity and mortality risks; major driver for PELs

Risk of Acute (in flight) & Late Central Nervous System Effects
• Possible in-flight risks: altered cognitive function including short-term memory, reduced motor function, and behavioral changes which may affect performance and human health
• Possible late (post-mission) risks: neurological disorders such as Alzheimer’s disease (AD), dementia, cerebrovascular disease or premature aging

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

Risk of Acute Radiation Syndromes due to Solar Particle Events
• Prodromal effects (nausea, vomiting, anorexia, and fatigue), skin injury, and depletion of the blood-forming organs
Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation

**Risk of Degenerative Tissue Effects:**
- Cardiovascular and circulatory changes
- Cataract formation

**Other Health Effects:**
- Diseases related to aging, including digestive, respiratory disease, premature senescence, endocrine, and immune system dysfunction

**Driving Evidence:**
- Astronaut data (cataracts)
- Radiotherapy, environmental disasters, atomic bomb survivor data, radiation workers (CVD and others)
  - Data is confounded by life-style factors to larger extent than cancer, especially at low doses

**Risk Projections:**
- Preliminary risk assessment models being formulated
- Recent studies suggest there may be low dose effects and distinct pathologies at low vs high dose suggesting mechanistic differences
- Impact of heavy ions largely unknown
Driving Evidence for Radiation-Induced CVD
Main types of circulatory disease:

• Congenital heart disease. Includes a range of abnormalities in heart structure or function that are present at birth. Such conditions could potentially be caused by irradiation of the fetus but obstetric irradiation is carefully controlled.

• Cardiac valve diseases. Include a variety of abnormalities to the heart valves including mitral stenosis and tricuspid regurgitation.

• Hypertrophic cardiomyopathy. Increased muscle density in the heart leading to less effective pumping of the blood.

• Cardiac Arrhythmias. Abnormally slow (bradycardia) or fast (tachycardia) beating of the heart often attributable to abnormalities in the electrical signaling that co-ordinates the beating of the four chambers of the heart.

• Pericarditis. Inflammation of the pericardium, the membrane that surrounds the heart, most frequently attributable to infectious agents but also well established to be caused by high doses of radiation.

• Coronary heart disease/congestive heart disease. Obstruction of the blood flow in the heart due to narrowing of cardiac vessels restricting blood and oxygen supply to the heart. In a mild form, this leads to angina where the reduced blood flow leads to discomfort. When blockage is severe, myocardial infarction (heart attack) occurs leading to acute heart failure.

• Stroke. Interruption of the blood supply to the brain due to blockage or rupture of vessels. Loss of blood and oxygen to areas can lead to cell death and consequently permanent brain dysfunction. Two majors forms of stroke are recognized, ischemic stroke caused by blockage due to blood clots forming locally (thrombotic stroke) or fragments from distant clots lodging in the brain vasculature (embolic stroke).

→ The circulatory diseases subtypes that are considered to be affected by radiation exposure appear in bold text.
**Radiotherapy Data:**

- High doses (>5 Gy exposures) associated with damage to the structures of the heart and to the coronary, carotid, and other large arteries including marked diffuse fibrotic damage, especially of the pericardium and myocardium, pericardial adhesions, microvascular damage and stenosis of the valves—damage observed in patients receiving RT as well as in experimental animals (Little 2013)

- Deterministic effect (tissue reaction)

- Mechanisms involve cell killing or inactivation of large # of cells – functional impairment

*Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.*
Driving Evidence for Moderate Doses 0.5 - 5 Gy

Life Span Study, Clinical, and Occupational Exposures:

- Moderate doses (0.5--5 Gy exposures) associated with atherosclerosis; micro and macrovascular damage
- Possibly a stochastic reaction
- Mechanisms may involve inflammation and oxidative stress, endothelial dysfunction/senescence
### Table 1: Published epidemiological studies reporting on the association between mortality from heart disease and ionising radiation with doses in the range 0.5–5 Gy (or 0.5–5 Sv) and with good power to detect an association. Based on (5) and updated.

<table>
<thead>
<tr>
<th>Population</th>
<th>Relation between mortality from heart disease and ionising radiation</th>
</tr>
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<tbody>
<tr>
<td><strong>Studies finding a significant positive association</strong></td>
<td></td>
</tr>
<tr>
<td>Life Span Study of survivors from atomic bombings of Hiroshima and Nagasaki, Japan</td>
<td>RR for heart disease increased by 17% (90% CI 8%–26%; P = 0.001) per Sv for deaths in period 1968–97, i.e., 23–52 years after exposure.</td>
</tr>
<tr>
<td>Radiologic technologists, USA</td>
<td>RR for heart disease, for deaths in period 1983–1997, 1.22, 1.00, 0.98, 1.00 for those starting work &lt;1940, 1940–49, 1950–59, 1960+: P for trend 0.03. Cumulative doses probably up to 2 Gy for those starting before 1950.</td>
</tr>
<tr>
<td>Patients irradiated for peptic ulcer, USA</td>
<td>RR for heart disease 1.00, 1.00, 1.23, 1.54, 1.51 at 10+ years after exposure for those with average cardiac doses of 0, 1.6, 2.3, 2.8, 3.9 Gy; P for trend 0.01.</td>
</tr>
<tr>
<td>Chernobyl accident emergency workers, Russia</td>
<td>RR for heart disease increased by 41% (95% CI 5%–78%; P = 0.02) per Gy (no lag).</td>
</tr>
<tr>
<td>British Nuclear Fuels, UK</td>
<td>RR for heart disease increased by 70% (90% CI 33%–111%; P &lt; 0.001) per Sv (with 15-year lag).</td>
</tr>
<tr>
<td><strong>Studies not compatible with a positive association based on currently published data</strong></td>
<td></td>
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<tr>
<td>Radiologists, USA</td>
<td>RR for heart disease compared with all male medical practitioners 1.20 and 1.18 for those registering during 1920–39 and 1940–69, respectively. RRs for cancer calculated on a similar basis were 1.54 and 1.22, respectively. Those registered in early period thought to have had lifetime doses of 2–20 Gy.</td>
</tr>
<tr>
<td>Patients with tuberculosis, USA</td>
<td>RR for all circulatory disease: 0.9 (95% CI 0.8–1.00; P = 0.05) in exposed vs unexposed. Mean lung dose 0.84 Gy. Mean heart dose likely to be similar.</td>
</tr>
<tr>
<td>Radiologists, UK</td>
<td>RR compared with other doctors for all circulatory disease 0.79, 0.83, 0.98, 0.59 for those first registered &lt;1920, 1921–35, 1936–54, 1955–79; P for trend &gt;0.10. RRs for cancer calculated on a similar basis were 1.75, 1.24, 1.12, 0.71; P for trend &lt;0.001. The trend for cancer has been interpreted as an effect of radiation. In the 1920s and 1930s doses may have been ~1 Gy per annum.</td>
</tr>
<tr>
<td>Uranium miners, Germany</td>
<td>RR for heart –35% (95% CI –70–0.9%; P &gt;0.10) per Sv for deaths in period 1946–98 (with 5-year lag).</td>
</tr>
<tr>
<td><strong>Other studies</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with ankylosing spondylitis, UK</td>
<td>RR for circulatory disease excl stroke: RR 0.97 (95% CI 0.70–1.33; P &gt;0.10) in exposed vs unexposed. Mean lung dose 2.5 Gy. Mean heart dose likely to be similar.</td>
</tr>
<tr>
<td>Mayak, Russia</td>
<td>RR for all circulatory disease 1.01 (95% CI 0.90–1.15) in those with &gt;1 Gy compared with &lt;1 Gy (no lag).</td>
</tr>
</tbody>
</table>

*RR: Death rate ratio.
Driving Evidence for 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 killing
• Confounding effects are large

Although mean cumulative radiation doses were ≤ 0.2 Gy in most of studies, the small numbers of participants exposed at high cumulative doses (≥ 0.5 Gy) drive the observed trends in most cohorts with these higher dose groups.
Driving Evidence for Low Doses < 0.5 Gy

- Suggests increased risks for IHD and non-IHD heart diseases
- Data suggest that circulatory disease risk is significantly elevated only for acute or cumulative doses of about 0.5 Gy and above; data is not statistically significant at lower doses.

Little 2012 - Environ Health Persp v120 i11 p1503 - Systematic Review and Meta-analysis of Circulatory Disease from Low-Level IR and Estimates of Mortality Risks
Confounding factors in epidemiology studies include (Lifestyle and genetic factors): male sex, family history, cigarette smoking, drinking, diabetes, high blood pressure, obesity, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol plasma levels; shift work.

Risk at lower doses and low dose rates still highly uncertain; existence of threshold dose questionable.

There is also a lack of data on dose rate effects.
Definition of “Threshold Dose”:

- Previous NCRP 2000 Report defined a “threshold dose” as an exposure below which clinically significant effects do not occur.

- ICRP 2012 redefined “threshold dose” as ED1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation.
  - ED1 = effects just starting to rise above the baseline levels in unirradiated, age-matched individuals and, in the case of circulatory disease, to a dose which would increase the already high natural incidence or mortality by only 1%.

- ED1 does not imply that no biological effects occur at lower doses; it merely defines the dose above which a specified effect becomes clinically apparent in a small percentage of individuals.
0.5 Gy may lead to approximately 1% of exposed individuals developing the disease in question \textgreater{}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).

There are notable uncertainties in determining the risks of these diseases at this level of radiation dose. It is \textit{unclear from available evidence whether or not the threshold is the same for acute, fractionated, and chronic exposures}. For the present purposes, the threshold dose is assumed to be the same for all three types of exposure (i.e. approximately 0.5 Gy).
Dose Rate Effects

- Tuberculosis patients in Canadian Fluoroscopy Cohort Study
- 63,707 patients (61% unexposed, 96% <0.5 Gy, mean dose=0.79 Gy)


- ERR/Gy=0.176 for IHD after adjustment for dose fractionation. ERR/Gy=0.149 for doses <0.5 Gy
- Highest risks were for those with fewest fluoroscopic procedures per year

Zablotska 2014) – Am J Epidemiol v79 i1 p120 - Potential increased risk of ischemic heart disease mortality with significant dose fractionation in the Canadian fluoroscopy cohort study.
Potential Mechanisms for Radiation-Induced CVD

**Fig. 6.** Hypothetical mechanisms of radiogenic CVD. Solid arrows represent the inflammation theory. Dashed arrows represent hypotheses discussed here.
Potential Mechanisms for Exposures from Moderate Doses

**FIGURE 6.1** Schematic representation of the most important steps of pathogenesis coronary artery disease. Events that have also been observed after radiation exposure are indicated by flashes. (From Schultz-Hector and Trott, 2007)
Kidney Dysfunction & CVD

- Cohort of atomic bomb survivors in the Life Span Study
- Results show low dose radiation was significantly associated with CKD and severe renal dysfunction independently of hypertension, DM, hyperlipidemia and MetS, suggesting that A-bomb radiation affects the kidney directly.
- Prospective studies are needed to clarify how the association between low-dose radiation and CVD may be mediated by CKD.
Kidney Dysfunction & CVD

The location of the kidneys (yellow) and liver (red) are indicated. The liver lies directly under the diaphragm (blue), which separates the thoracic and abdominal cavities. In this lateral image, the two kidneys are overlapping with the left kidney being the more caudal than the right kidney.

Time-related changes in total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol TBI with and without kidney shielding compared with sham irradiated controls. Data shown as means + SD, n=5-8/group. *=p<0.05, TBI vs. TBI with the kidneys shielded.

Kidney shielding during IR prevents increase in risk factors for heart disease

Lenarczyk and Baker 2013 - Rad Res v180 i3 p247 - Cardiac injury following 10 Gy total body irradiation- indirect role of effects on abdominal organs
Major Risk Questions

- Radiation quality effects?
- Deterministic versus stochastic effects? Existence of thresholds?
- Dose rate effects?
- Validated/appropriate biomarkers?
- Disease spectrum is unclear for doses of interest
  - Necessity for life span studies in an appropriate animal model to determine spectrum of diseases, at low dose rates, with heavy ions
- What are appropriate endpoints?
- What’s the appropriate animal model?
Research Evidence Updates
Late Effects of Heavy Charge Particles on Fine Structure of Mouse Coronary Artery
Yang and Ainsworth 1982

Ultrastructural changes in the coronary artery at 15 months after 0.2 Gy $^{20}$Ne upper body IR. Fragmentation of smooth muscle (SM) with accumulation of matrix material (arrow) and fibrosis (F) are noted. Lumen (L) and elastic lamina (EL). x6480.

- Degenerative changes included smooth muscle degeneration and accumulation of tissue debris and fibrosis
- Low dose, heavy ion radiation accelerated these degenerative changes
- Intimal plaques also observed, but without lipid bodies found in atherosclerosis

Dose-response relationship for damaged smooth muscle cells after heavy charged particle irradiation.
Cardiovascular risks associated with low dose ionizing particle radiation.

Goukassian et al. 2014

- Cardiac fibrosis and hypertrophy still observed at late time points (up to 10 months) after IR with both Fe and protons

Yan and Goukassian 2014 - PLoS One v9 i10 pe110269 - Cardiovascular Risks Associated with Low Dose Ionizing Radiation
Heavy-Ion ($^{56}$Fe) Irradiation Leads to Impaired Aortic Relaxation and Accelerated Atherosclerosis in ApoE-/- Mice.
Kucik et al. 2011, 2014

- Fe irradiation at 2 and 5 Gy doses in 9-week-old apoE-/- mice
- Irradiation *accelerated atherosclerosis at the aortic root* and effects was still seen up to 40 weeks post-irradiation (Kucik et al, Rad Res 2011)

- Fe radiation at 2.6 Gy in 10-week-old apoE-/- mice; 4-5 weeks after IR, saw significantly impaired vascular relaxation in response to acetylcholine (Kucik et al, JRR 2014)

Yu and Kucik 2011 - Rad Res v175 p766 - Iron-Ion Radiation Accelerates Atherosclerosis in Apolipoprotein E-Deficient Mice
White and Kucik 2014 – J Rad Res v55 pi42 - Heavy-Ion ($^{56}$Fe) Irradiation Leads to Impaired Aortic Relaxation prior to Atherosclerotic Plaque Formation in ApoE-/- Mice.
CVD Risk Summary

• Association between exposure to high doses of low-LET (>5 Gy) radiation during radiotherapy to the chest and increased risk for development of cardiovascular disease at late times post exposure is clearly established

• Recent studies of atomic bomb survivor data and analyses of epidemiology data from occupational and medical exposures 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 life-style factors, clouding interpretation of epidemiology data below 0.5 Gy
  − Effects are considered deterministic, with an associated threshold dose; however recent evidence showing risk at lower doses questions this assumption

• Preliminary risk assessment models are being formulated based on recent epidemiology data for lower dose low-LET exposures - future risk estimates dependent on research results describing the quantitative and qualitative differences between GCR and gamma-rays
  − Studies at NSRL with HZE ions and appropriate animals models are required
  − Lack of evidence on radiation quality, disease spectrum, latency and dose rate at low levels of exposures

• The additional mortality and morbidity risks for non-cancer diseases of the cardiovascular system are major concerns because they could increase REID values substantially
STRATEGY
Exposure to Space Radiation
Research Strategy for Risk Mitigation

Evidence
- Human Epidemiology
- Spaceflight
- NSRL Studies

Characterization
- RiskMagnitude
  - Thresholds
  - Dose-rate effects
  - Quality effects
- Risk Mechanisms
  - Functional Biomarkers
  - Surrogate Endpoints

Modeling
- Human Epidemiology
- Risk Transfer
- Systems Biology

Countermeasures
- Operations
- Shielding
- Pharmaceuticals
- Dietary Supplements
- Exercise
- In mission, post mission monitoring

Risk Modifiers
- Individual Sensitivity
- Other stressors
Degenerative Gaps

**Degen - 1:** How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?

**Degen - 2:** What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?

**Degen - 3:** What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors?

**Degen - 4:** How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

**Degen - 5:** What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?

**Degen - 6:** What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?

**Degen - 7:** Are there significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?

**Degen - 8:** Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?
**Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation**

**Three Phase Implementation:**

1. **Phase 1:** Develop biological models, investigate existence of dose thresholds for CVD effects, investigate mechanisms, define radiation quality effects and dose-rate effects
   - Through individual NRAs and the NSBRI CSRR

2. **Phase 2:** Investigate latency periods, progression rates, and individual susceptibility effects
   - Through individual NRAs and the NSCORs

3. **Phase 3:** Identify biomarkers and countermeasures for CVD and investigate potential synergies with other spaceflight factors.
   - Through individual NRAs and a countermeasure NSCOR
Degenerative Risk Summary

Overall, there is a paucity of experimental data related to radiation-induced heart diseases at low doses:

- **Qualitative differences** between GCR and gamma-rays are major concern.
- **Deterministic versus stochastic effects** is unknown at doses <0.5 Gy.
- Impact of **dose rate**
- A concern for **Mars or lunar missions** due to higher GCR and SPE doses with definitive effects.
- Recently established NSBRI **Center for Space Radiation Research** will focus on cardiovascular risk research.
- Can **cataract monitoring in astronauts** provide insight into radiation quality effects, progression, and latency, specifically for space radiation exposure in humans?
- For relevant space radiation doses, can **cataracts and kidney dysfunction be related to other radiation-induced pathologies including CVD**?