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

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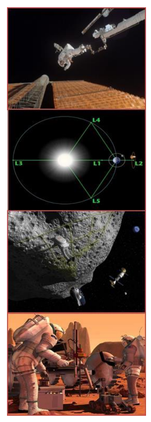
INTRODUCTION

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

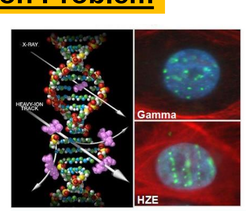
Lagrange Points
- Design Reference Mission currently being formulated
- Outside Earth's magnetosphere and radiation belts
- Galactic cosmic ray risks are major concern

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

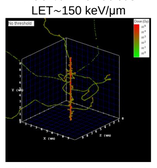
The Space Radiation Problem

- Interplanetary crews will be exposed to a high LET radiation environment comprised of high-energy protons and heavy ions (HZEs) 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

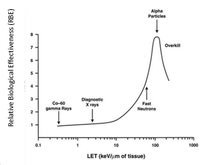


DNA Damage
γH2AX foci in EPC2-hTERT cells.
(Patel and Huff)

1 GeV/u ^{56}Fe nucleus
LET~150 keV/μm



High LET defined as
LET > 10 keV/μm in tissue

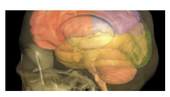


Qualitative differences due to track "core" and correlated tissue damage along particle path. (Plante, 2011)

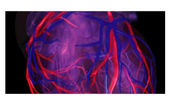
Health Risks from Space Radiation

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

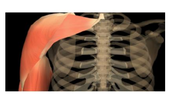
Risk of Acute (in flight) & Late Central Nervous System Effects
- Possible in-flight risks: altered cognitive function including short-term memory, reduced motor function, and behavioral changes which may affect performance and human health
- Possible late (post-mission) risks: neurological disorders 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



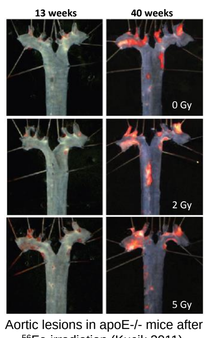
Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation

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



Aortic lesions in apoE-/- mice after ^{56}Fe irradiation (Kucik 2011).

ICRP Recommendations (2012)

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 >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 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

Darby 2013

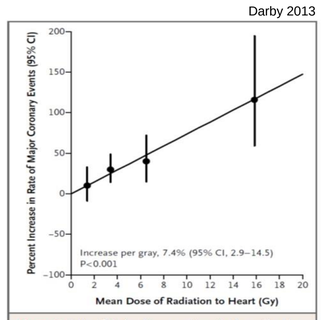


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

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

Shimizu 2010

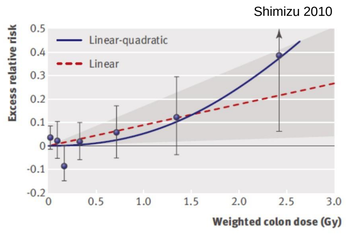


Fig 1| Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

McGale and Darby 2008

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

Population	Relation between mortality from heart disease and ionising radiation
Studies finding a significant positive association	
Life Span Study of survivors from atomic bombings of Hiroshima and Nagasaki, Japan[8]	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.
Radiologic technologists, USA[10]	RR for heart disease, for deaths in period 1983–1997, 1.22, 1.00, 0.98, 1.00 for those starting work <1940, 1940–49, 1950–59, 1960+; P for trend 0.03. Cumulative doses probably up to 2 Gy for those starting before 1950.
Patients irradiated for peptic ulcer, USA[6]	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.
Chernobyl accident emergency workers, Russia[7]	RR for heart disease increased by 41% (95% CI 5–78%; $P=0.02$) per Gy (no lag).
British Nuclear Fuels, UK[9]	RR for heart disease increased by 70% (90% CI 33–111%; $P<0.001$) per Sv (with 15-year lag).
Studies not compatible with a positive association based on currently published data	
Radiologists, USA[11]	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.
Patients with tuberculosis, USA[12]	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.
Radiologists, UK[13]	RR compared with other doctors for all circulatory disease 0.79, 0.83, 0.98, 0.59 for those first registered <1920, 1921–35, 1936–54, 1955–79; P for trend >0.10. RRs for cancer calculated on a similar basis were 1.75, 1.24, 1.12, 0.71; P for trend <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.
Uranium miners, Germany[8]	RR for heart ~35% (95% CI ~70–0.9%; $P>0.10$) per Sv for deaths in period 1946–98 (with 5-year lag).
Other studies	
Patients with ankylosing spondylitis, UK[14,15]	RR for circulatory disease excl stroke: RR 0.97 (95% CI 0.70–1.33; $P>0.10$) in exposed vs unexposed. Mean lung dose 2.5 Gy. Mean heart dose likely to be similar.
Mayak, Russia[16]	RR for all circulatory disease 1.01 (95% CI 0.90–1.15) in those with >1 Gy compared with <1 Gy (no lag).

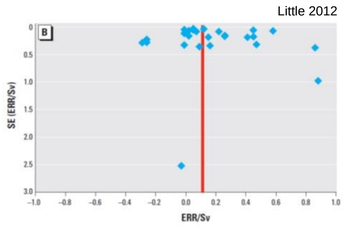
[a]RR: Death rate ratio.

- Still, there is conflicting data even at moderate dose ranges
- The results of these 11 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 dosimetry issues, and misclassification of pathologies/cause of death

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

Little 2012



Funnel plot of ERR/Sv versus SE of ERR for 4 main circulatory disease subtypes. Red line shows aggregate random-effects ERR estimate.

➢ **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**

Table 2. ERR coefficients for circulatory diseases as a result of exposure to low-level radiation ≥ 5 years earlier, by disease.

Disease	References	Fixed-effect estimate of ERR/Sv (95% CI)	Random-effect estimate of ERR/Sv (95% CI)	1-sided significance, p-value (fixed effect/ random effect)	Heterogeneity χ^2 (df)/p-value
IHD (ICD-10 I20–I25)	Azizova et al. 2010a[a], Ivanov et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.10 (0.05, 0.15)	0.10 (0.04, 0.15)	< 0.001/< 0.001	7.20 (7)/0.408
Non-IHD (ICD-10 I26–I52)	Ivanov et al. 2006, Shimizu et al. 2010[b], Vrijheid et al. 2007[c]	0.12 (–0.01, 0.25)	0.08 (–0.12, 0.28)	0.031/0.222	4.65 (3)/0.199
CVA (ICD-10 I60–I69)	Azizova et al. 2010b[d], Ivanov et al. 2006, Kreuzer et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.20 (0.14, 0.25)	0.21 (0.02, 0.39)	< 0.001/0.014	34.28 (8)/< 0.001
Circulatory disease apart from heart disease and CVA (ICD-10 I00–I19, I53–I59, I70–I99)	Ivanov et al. 2006[e], Shimizu et al. 2010[f], Yamada et al. 2004[g]	0.10 (0.05, 0.14)	0.19 (–0.00, 0.38)	< 0.001/0.026	66.83 (7)/< 0.001

Values are from Table 1, unless otherwise indicated.
[a]Analysis based on morbidity from IHD, with a 10-year lag. [b]Analysis based on mortality from heart failure and other heart disease. [c]Analysis based on mortality from heart failure. [d]Analysis based on morbidity from CVA, with a 10-year lag. [e]Analysis based on morbidity from hypertension, disease of arteries, arterioles and capillaries, veins, lymphatic vessels, and lymph nodes. [f]Analysis based on mortality from rheumatic heart disease and circulatory disease apart from heart disease and CVA. [g]Analysis based on morbidity from hypertension, hypertensive heart disease, and aortic aneurysm.

➢ **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**

Low Dose Confounders & Uncertainties

- **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**

Dose Rate Effects

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

Zablotska 2014

Table 6. Excess Relative Risks per Gy for Noncancer Causes of Death by Categories of Dose Fractionation, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	Dose Fractionation, Gy/year[a]										P Value[b]
	0	0.0004–0.14			0.15–0.29			0.30–7.30			
	No. of Deaths	No. of Deaths	ERR/Gy[c]	95% CI	No. of Deaths	ERR/Gy[c]	95% CI	No. of Deaths	ERR/Gy[c]	95% CI	
All noncancer[d]	8,299	810	0.168	−0.179, 0.617	940	0.069	−0.017, 0.173	2,886	0.034	−0.006, 0.080	0.569
All CVDs	5,696	569	0.281	−0.139, 0.848	650	0.089	−0.017, 0.219	1,962	0.021	−0.025, 0.077	0.241
Ischemic heart disease	3,716	391	0.592	0.004, 1.400	442	0.145	0.007, 0.320	1,269	0.010	−0.043, 0.078	0.022
Hypertensive and other (nonstroke) CVDs	1,078	106	0.381	<−0.198, 1.953	120	−0.069	<−0.099, 0.187	393	0.035	−0.059, 0.177	0.447
All respiratory diseases	1,694	179	0.645	<−0.200, 2.114	186	−0.0002	<−0.117, 0.225	599	0.093	0.006, 0.214	0.299

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ERR, excess relative risk.
[a] The 4 dose fractionation groups are equivalent to the following numbers of fluoroscopic procedures per year: 0, >0–11, 12–23, and 24–584.
[b] P for heterogeneity from the likelihood ratio test.
[c] All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification.
[d] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.

➢ **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**

Potential Mechanisms of Radiation-Induced CVD

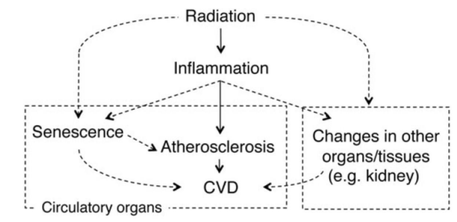


Fig. 6. Hypothetical mechanisms of radiogenic CVD. Solid arrows represent the inflammation theory. Dashed arrows represent hypotheses discussed here. Hamada 2014

Potential Mechanisms for Exposures at Moderate Doses

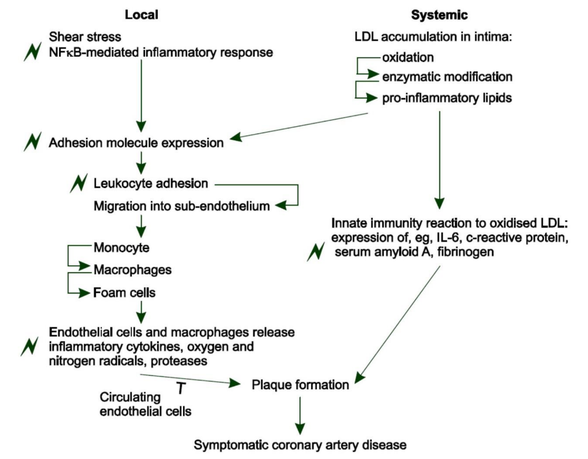
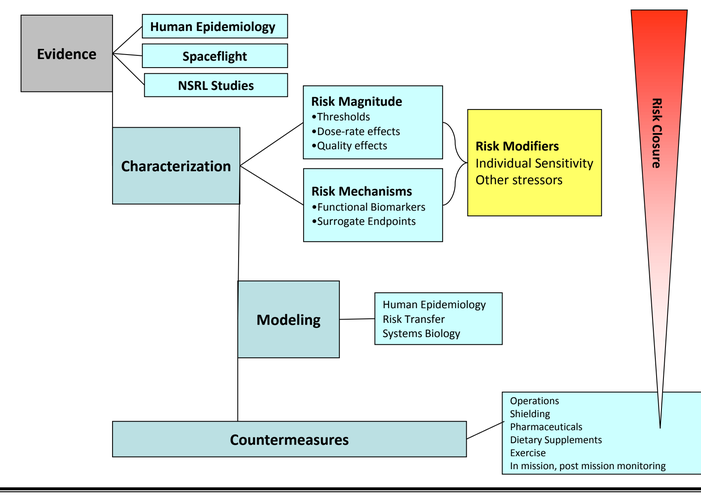


FIGURE 6.1 Schematic representation of the most important steps of pathogenesis coronary artery disease. Events that have also been observed after radiation exposure are indicated by flashes. (From Schultz-Hector and Trott, 2007) Health Protection Agency 2010

Risk Mitigation Strategy



DEGEN 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
- Atomic bomb survivor 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 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 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**