HHS Public Access

Author manuscript

Mutat Res. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Mutat Res. 2016 ; 770(Pt B): 319–327. doi:10.1016/j.mrrev.2016.07.003.

Effects of Ionizing Radiation on the Heart

Marjan Boerma[1], **Vijayalakshmi Sridharan**[1], **Xiao-Wen Mao**[2], **Gregory A. Nelson**[2], **Amrita K. Cheema**[3], **Igor Koturbash**[4], **Sharda P. Singh**[5], **Alan J. Tackett**[6], and **Martin Hauer-Jensen**[1,7]

[1]University of Arkansas for Medical Sciences, Division of Radiation Health, Little Rock, AR

[2]Loma Linda University, Department of Basic Sciences, Loma Linda, CA

[3]Georgetown University Medical Center, Departments of Oncology and Biochemistry, Molecular and Cellular Biology, Washington, DC

[4]University of Arkansas for Medical Sciences, Department of Environment and Occupational Health, Little Rock, AR

[5]University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, Little Rock, AR

[6]University of Arkansas for Medical Sciences, Department of Biochemistry and Molecular Biology, Little Rock, AR

[7]Central Arkansas Veterans Healthcare System, Surgical Service, Little Rock, AR

Abstract

This article provides an overview of studies addressing effects of ionizing radiation on the heart. Clinical studies have identified early and late manifestations of radiation-induced heart disease, a side effect of radiation therapy to tumors in the chest when all or part of the heart is situated in the radiation field. Studies in preclinical animal models have contributed to our understanding of the mechanisms by which radiation may injure the heart. More recent observations in human subjects suggest that ionizing radiation may have cardiovascular effects at lower doses than was previously thought. This has led to examinations of low-dose photons and low-dose charged particle irradiation in animal models. Lastly, studies have started to identify noninvasive methods for detection of cardiac radiation injury and interventions that may prevent or mitigate these adverse effects. Altogether, this ongoing research should increase our knowledge of biological mechanisms of cardiovascular radiation injury, identify non-invasive biomarkers for early detection, and potential interventions that may prevent or mitigate these adverse effects.

Correspondence: Marjan Boerma, PhD; University of Arkansas for Medical Sciences; Division of Radiation Health; 4301 West Markham, Slot 522-10; Little Rock AR 72205; Phone: 501-686-6599; mboerma@uams.edu.

Conflicts of Interest statement

The authors declare that there are no conflicts of interest.

Keywords

Heart; Radiation therapy; Low-dose radiation; Radiation-induced heart disease; Intervention

1. Introduction

Exposure of the heart to high doses of ionizing radiation has long been known to cause cardiac injury. Although some pathology can be observed early after irradiation, the heart is considered a late responding organ with the appearance of most manifestations of radiation injury a decade or more after exposure. More recently, clinical, epidemiological, and experimental studies have provided evidence that the cardiovascular system may also be injured by ionizing radiation at low doses.

This review article describes clinical and preclinical studies on cardiac effects of cancer therapy-induced high doses local to the heart, and potential cardiovascular risks of low doses of radiation exposure that may occur on Earth and in space. Lastly, we summarize recent research aimed at identifying non-invasive methods for the detection of cardiac radiation injury and interventions that may prevent or mitigate these effects. Because vascular alterations play a central role in the cardiac response to radiation, when appropriate we have included research into vascular radiation effects. Table 1 provides an outline of the article and its main points.

2. Cardiac injury of high-dose radiation

2.1. Clinical studies of high-dose local irradiation as associated with radiation therapy

Exposure of the heart to ionizing radiation during radiation therapy of intrathoracic and chest wall tumors has long been known to cause radiation-induced heart disease, a mostly late and sometimes severe side effect [1–3]. While high doses of radiation can cause acute pericarditis, most manifestations of radiation-induced heart disease are observed more than a decade after radiation therapy and include accelerated atherosclerosis, adverse myocardial remodeling, conduction abnormalities, and injury to cardiac valves [4–6]. Atherosclerotic plaques in high-dose exposed arteries are described as fibrous and rich in proteoglycans [7;8]. Since most injury in heart and blood vessels is observed years to decades after exposure to ionizing radiation, long post-radiation follow-up is required for a full assessment of deleterious effects.

Survivors of childhood cancer are at high risk of developing late side effects of radiation therapy [9,10]. For instance, in a French cohort of 3162 childhood cancer survivors, in those patients who did not receive anthracyclines, at median follow-up of 26 years after estimated average doses to the heart ≥30 Gy, the risk of heart disease was increased several fold compared to patients who had received doses to the heart <0.1 Gy [11].

Population studies in patients treated with tangential irradiation of breast cancer have also been used to determine cardiac disease risk in response to X-ray exposure. With this treatment modality, treatment of left-sided breast cancer typically leads to a higher dose to the heart compared to the treatment of patients with right-sided breast cancer, although right-

sided breast cancer treatment can also be associated with some radiation exposure of the heart [12;13]. A significant increase in cardiac mortality rate is observed in patients with left-sided breast cancer compared to right-sided breast cancer at 10 years or more after diagnosis [14]. Since other cardiovascular risk factors can be assumed to be the same in both patient groups, these studies confirm that cardiac radiation exposure is associated with increased risk of heart disease. A limitation is that in many of these patients the radiation dose to the heart was not determined at the time of treatment. The group of Sarah Darby performed a study in which the mean radiation dose to the whole heart and to the left anterior descending coronary artery of individual patients was determined from the original treatment planning documents and applied to a computed tomography scan of a woman of typical anatomy. The rate of coronary events increased by 7.4% per Gy mean dose to the heart [15]. Additional studies on the cardiac effects of high-dose radiation exposure have been described in many previous reviews, of which we here can only list a few [16–18].

From a clinical perspective, the only available approach to reducing late cardiac complications is through efforts to reduce cardiac exposure during therapy. Indeed, radiation therapy has undergone many improvements in treatment planning and radiation delivery. Nonetheless, a significant subset of patients with thoracic cancers, including those of the lung, esophagus, and proximal stomach, still receive considerable doses of radiation to the heart [19–21]. Moreover, radiation therapy is often combined with chemotherapeutic agents that have their own side effects in the heart. With improved cancer detection and treatment, more patients will survive longer and may be at risk for late side effects of radiation therapy and other cancer treatments.

2.2. Cancer cachexia and heart disease

In addition to radiation and chemotherapeutic agents, cancer-related metabolic alterations can contribute to atrophy and adverse remodeling in the heart. Although underlying mechanisms are not yet fully understood, there seems to be a contribution of an imbalance between cardiac protein synthesis and degradation [22;23]. To better understand heart failure due to cachexia, animal models are being designed [24;25]. Heart disease in cancer cachexia and interactions with adverse cardiac effects of cancer treatment should be investigated further, to aid in improving the safety of cancer therapy.

2.3. Interaction between radiation therapy and other cancer treatments

Radiation therapy is commonly combined with chemotherapeutics. Since several of these agents, for example anthracyclines, adversely affect cardiac function [18], there may be a concern for cardiac toxicity of combined treatment. Although some studies show no interaction between radiation therapy and anthracyclines [10], other reports in both human subjects and animal models indicate that the adverse cardiac effects of these two cancer treatments are at least additive [26–29]. Radiation therapy is increasingly combined with targeted cancer therapies such as biological and small molecule inhibitors of growth factor receptors and tyrosine kinases. Some of these therapies have their own cardiotoxic effects and may require close monitoring of cardiac function during and after treatment [30–32]. However, mechanisms of cardiotoxicity of targeted therapies are largely unknown, and the long-term effects of combination treatments with classical chemotherapeutics and radiation

therapy have yet to be determined [30;33–37]. In time, cardiovascular outcome of radiation in combination with targeted cancer therapies will become apparent as the number of patients receiving this treatment regimen grows. In the meantime, studies in animal models may provide first indications about potential interactions between cardiac radiation exposure and targeted therapies.

2.4. Experiments with high-dose irradiation in animal models

Clinical studies of cardiac toxicity of cancer treatments are complicated by common confounding cardiovascular risk factors. Preclinical studies in animal models in which the cardiac radiation dose is known and confounding factors are mostly controlled, may shed light on the risk of cardiac injury from exposure to ionizing radiation and biological mechanisms by which radiation causes cardiac injury. While it can take 10–15 years for cardiovascular radiation effects to become apparent in human subjects, because of the shorter life span of (small) experimental animals, long-term follow-up can usually be achieved within a year. Radiation-induced accelerated atherosclerosis is not commonly found in regular laboratory animal models, but myocardial alterations in response to local exposure to high doses of radiation are similar to those observed in human subjects [38;39]. Most pre-clinical studies thus far have used (young) adult male animals. As described in sections 3.1 and 3.2, there is still uncertainty about myocardial effects of low doses of ionizing radiation in both human subjects and experimental animal models.

Radiation therapy is typically administered in 30 one-a-day fractions of ~2 Gy. The response of tissues to fractionated radiation is generally described by the linear quadratic model, in which the ratio of the parameters α and β is an indication of the sensitivity of the tissue or organ to radiation dose per fraction. A low α/β ratio (below ~4 Gy) indicates that an organ or tissue shows enhanced injury particularly with increased dose per fraction. Early experiments with fractionated local heart irradiation in dog and rat models resulted in calculations of α/β ratios between 2.5 and 3.7 Gy, depending on the nature of the cardiac endpoint [40–42]. These relatively low α/β ratios are typical for late radiation responding organs and, as described above, suggest that cardiac injury is dependent on dose per fraction. However, most research into mechanisms by which radiation modifies the heart has been performed mostly with a high-dose rate single high dose of radiation to the heart, or a limited number of fractions [43–46]. While these radiation protocols seem to cause comparable late cardiac remodeling, there is insufficient data available from animal models to determine whether fractionation schedules as used in the clinic cause cardiovascular effects similar to single high-dose exposures. Since sensitive techniques for the measurement of cardiac function and molecular alterations have become available, this seems to be the appropriate time to assess the cardiovascular effects of clinically relevant radiation fractions in animal models in long-term follow-up.

We here give some examples of the many studies in rodent models designed to identify potential biological mechanisms by which radiation may cause cardiac injury. Several months after local heart irradiation with a single dose or a limited number of fractions, an increase is seen in the deposition of both perivascular and interstitial collagen in the myocardium, which become progressively worse in time [47–49]. This radiation-induced

fibrosis is preceded by changes in the density and function of the microvasculature in the myocardium [50–53]. Interestingly, a mouse model with an endothelial cell-specific deletion of p53 showed increased myocardial necrosis and cardiac dysfunction in response to local heart irradiation with a single dose of 12 Gy [54], confirming the importance of the myocardial vasculature in maintaining cardiac function and structure after irradiation. While whole body irradiation of the rat (15 Gy single dose) caused a significant reduction in cardiac vascular density, this effect was not observed after irradiation of the thorax alone [55], indicating that alterations elsewhere in the body may enhance the effects of radiation in the heart. Follow-up experiments by the same group of investigators suggest that these indirect effects may be mediated by the kidney [56]. These results are in agreement with recent reports in human subjects that also suggest a connection between kidney radiation exposure and adverse cardiovascular effects [57].

Increases in collagen deposition also coincide with local increases in growth factor expression [58;59], and pharmacological induction of transforming growth factor beta 1 enhances cardiac radiation fibrosis, confirming that increased growth factor signaling may worsen radiation-induced heart disease [60].

Single dose local heart irradiation in rodent models causes long-term alterations in the function, morphology, and protein expression of cardiac mitochondria [43;61–63]. Sequestered on the mitochondrial membrane in its inactive form is nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf2), a transcription factor that regulates the expression of various anti-oxidant enzymes [64]. While the Nrf2 pathway is linked to reduced radiation injury in several organs including the heart [43;65–67], the exact role of mitochondrial alterations and the Nrf2 pathway in radiation-induced heart disease has not yet been determined.

Local heart irradiation in rodent models (15–21 Gy single dose or 5 daily fractions of 9 Gy) leads to an increase in cardiac mast cell numbers that coincide with the development of radiation fibrosis [43;47]. However, contrary to what may be expected, experiments in a mast cell-deficient rat model suggest that mast cells play a predominantly protective role in radiation-induced heart disease [68]. Mast cells may mediate these effects via their close interactions with the sensory nervous system in the heart [49;69].

Work with targeted single dose proton irradiation of the rat heart and lung has shown that the lung and heart interact in their response to ionizing radiation [70;71]. The angiotensin converting enzyme (ACE) inhibitor captopril reduced pulmonary radiation injury, but only in those rats in which the heart was included in the radiation field [72]. Moreover, the reduction in pulmonary radiation injury was associated with a reduction in cardiac damage, again suggesting that heart and lung radiation injury are influenced by each other.

To study radiation-induced accelerated atherosclerosis, animal models with one or more additional vascular risk factors are required, such as genetically modified mouse models with enhanced susceptibility to atherosclerosis. Localized irradiation of the neck (single dose of 8 or 14 Gy, or 20 fractions of 2 Gy) in apolipoprotein E (ApoE) knockout (KO) mice caused increased macrophage-rich atherosclerotic plaques in the carotid artery [73–75]. In

addition, upon local heart irradiation these mice showed increased microvascular damage and atherosclerotic lesions in the coronary arteries [76]. These studies in small animals corroborate observations in clinical tissue specimens that show increased intima-media thickness and other artery wall lesions upon external beam irradiation [8;77].

In addition to rodents, larger animal models such as rabbits, dogs, and non-human primates have been used for many years to study radiation effects in both the heart and vasculature [78–80]. For instance, cardiovascular pathology after localized single-dose exposure in rabbit models has been described as very close to the pathology observed in cardiac tissue specimens of human subjects [28;38]. Moreover, radiation-induced accelerated atherosclerosis is observed in rabbits given a high lipid diet [81]. These types of studies in addition to work in rodent models should aid in the translation of preclinical results into understanding cardiac radiation injury in human subjects.

3. Cardiac alterations after exposure to low-dose ionizing radiation

3.1. Epidemiological studies

Japanese atomic bomb survivors who were exposed to high-dose rate γ-radiation at single doses, mostly up to ~2 Gy to a large part of their body have been followed closely to identify short-term and long-term health effects [82–84]. Some of the recent reports have shown an increased incidence of cardiovascular disease in these people several decades after exposure [84–88]. Additional epidemiological studies in low-dose exposure due to occupation or medical treatment confirm that cardiovascular alterations may occur after lower doses of ionizing radiation than was previously thought [89–93]. Some of the main cardiovascular effects are ischemic heart disease and stroke, potentially enhanced by an increased rate of hypertension [87].

While it is likely that different biological mechanisms underlie heart disease after high doses compared to low doses of radiation, these mechanisms are largely unknown. The outcomes of ischemic heart disease and stroke in atomic bomb survivors suggest that vascular alterations may play a prominent role in the response to low-dose radiation. There is still uncertainty about potential direct effects of low doses of ionizing radiation on the myocardium and cardiomyocytes.

3.2. Determination of the cardiac response to low-dose radiation in animal models

The recent observations of potential adverse cardiovascular effects of low doses of ionizing radiation have led to further investigations in animal models to aid in identifying the risks and underlying mechanisms. Single low doses of ionizing radiation (0.025 – 2 Gy) administered to the heart or whole body may cause inflammatory responses in ApoE KO mice [94;95]. Hence, a potential role of inflammatory responses in low-dose radiation induced cardiac injury deserves further investigation. In addition, proteomics analysis of primary human coronary artery endothelial cells exposed to a single dose of 0.2 Gy revealed a dysregulation of pathways involved in cellular organization and molecular transport [96], which may contribute to an adverse microenvironment in the vasculature.

4. Cardiovascular effects of space radiation

4.1. Does exposure to space radiation cause adverse effects in the cardiovascular system?

Space travel is associated with exposure to protons due to solar particle events, and protons and heavy charged particles in the form of galactic cosmic rays. While proton exposure due to solar particle events can occur at dose rates as high as 1.5 Gy/hour [97], galactic cosmic ray exposure occurs at low dose rates (1.3 mGy/day) [98]. Most of space travel thus far has been within low-Earth orbit. In this environment, doses of ionizing radiation, although higher than those found on the Earth's service, may not be of concern for biological effects such as cardiac radiation injury. However, plans are being made for space travel beyond low-Earth orbit, and in that scenario larger doses of ionizing radiation will be encountered. Since both men and women travel in space, it is important to determine radiation risk in both sexes. While recent reports on human populations exposed to low doses of radiation have raised the concern about potential adverse cardiovascular effects of ionizing radiation during long-distance space travel [99], types of ionizing radiation in space (mostly charged particles) are different from photons encountered on Earth, and as described above, exposures in space generally occur at much lower dose rates. As a result, biological effects of low doses of space radiation may be different from low doses of ionizing radiation encountered on Earth. Determination of short-term and long-term health risks of exposure to space radiation depends largely on research in animal models.

4.2. Animal models of exposure to space-like radiation

The concern of adverse cardiovascular effects of exposure to space radiation is relatively new, and experimentation has only recently begun. Studies are performed with cell cultures and animal models exposed to high energy charged particles to model space radiation. Although most studies are performed with appropriate doses of 1 Gy and below, practical considerations thus far have limited most studies to administering these doses within minutes, while it takes up to a year for galactic cosmic rays to provide these doses. Cardiovascular effects have not yet been studied in animal models of low-dose rate charged particle exposures.

Among studies with charged particles, some previous research has focused on the cardiac response to fission spectrum neutrons at a mean energy of 0.8 MeV [100–103]. In these experiments, both a single dose (0.8 or 2.4 Gy) and protracted exposure regimens (24 weekly fractions to a total of 0.2 – 2.4 Gy) induced significant radiation injury in the myocardium, coronary arteries, and aorta in a mouse model.

Targeted exposure of ApoE KO mice to iron ions (600 MeV/n) at single doses of 2 and 5 Gy caused accelerated atherosclerosis in the irradiated parts of the aorta [104]. Additional studies with lower doses of particle irradiation may provide a more comprehensive estimate of cardiovascular risk in this mouse model. More recently, studies were designed to determine the effects of protons and heavy ions at doses up to 1 Gy on cardiac function and structure. In a mouse model of single-dose exposure to protons (1 GeV, 0.5 Gy) or iron ions (1 GeV/n, 0.15 Gy) caused cardiac infiltration of monocytes/macrophages, increased DNA oxidation, myocardial fibrosis, and modified cardiac function in a radiation-type specific

manner. These effects were observed both at baseline and after the induction of experimental myocardial infarction [105;106]. Moreover, in a mouse model of single dose exposure to silicon ions (300 MeV/n, 0.1 – 0.5 Gy), increased cardiac apoptosis and expression of pro-inflammatory cytokines were observed [107].

At 1 week and 3 months after exposure of mice to 0.1 Gy of protons (150 MeV), no detectable structural or molecular changes had occurred in the heart. However, when administered 24 hours before a subsequent exposure to iron ions (0.5 Gy, 600 MeV/n), proton exposure prevented iron ion-induced markers of inflammatory infiltration, cardiac remodeling, and formation of cleaved caspase 3 [108]. These results suggest that proton exposure induced an as of yet unknown response in the heart that provided protection against further charged particle exposure. Proteomics analysis has started to reveal potential signaling pathways induced by low-dose particle irradiation in the heart [109].

It is becoming increasingly evident that ionizing radiation can cause epigenetic alterations. Among epigenetic parameters, DNA methylation has received most attention in the context of radiation biology. Low doses of charged particle have been shown to induce changes in DNA methylation in various cell types and tissues [110–112]. Recently, alterations in DNA methylation have been described in the heart in response to protons and iron ions [113;114]. The role of DNA methylation in cardiac function and disease has only recently started to emerge [115–117]. For instance, changes in gene-specific methylation were reported in dilated cardiomyopathy, arrhythmia and in heart failure [118–122]. The role of epigenetic alterations in the cardiovascular response to ionizing radiation is not yet known. Further research is required to identify whether charged particle-induced epigenetic alterations contribute to an altered physiology in organs such as the heart.

5. Detection of radiation-induced heart disease and non-invasive biomarkers

Studies in both animal models and human subjects have shown that manifestations of radiation-induced heart disease can be detected relatively early with non-invasive imaging techniques such as conventional echocardiography and strain rate analysis [123;124]. In addition, molecular markers in body fluids such as plasma or urine may aid in the early detection and monitoring of cardiovascular radiation injury. Common circulating markers of cardiac injury from various causes, such as troponins, atrial natriuretic peptide, and brain natriuretic peptide have been tested as early identifiers of cardiac radiation injury in patients, with varying results [125–131]. Studies are increasingly focused on finding molecular markers that can specifically indicate radiation injury [132], and new sensitive high-throughput technologies prove to be useful [133]. The goal of these studies is to identify biomarkers that can distinguish cardiovascular radiation toxicity from cardiovascular disease due to other causes. Hence, the ideal biomarker is upregulated in individuals with radiation-induced cardiovascular injury, but is unaffected in individuals with cardiovascular disease who have not previously been exposed to ionizing radiation.

6. Methods to intervene in the adverse effects of ionizing radiation on the heart

6.1. Pharmacological interventions in radiation-induced heart disease are required

Clinical treatment of radiation-induced heart disease currently consists of standard interventions, including cardiac transplantation and other surgical procedures [134–136]. The only available approach to prevent cardiac complications is through efforts to reduce cardiac exposure during radiation therapy. However, ongoing research efforts are aiming at identifying safe pharmacological countermeasures that may prevent or mitigate the adverse effects of radiation in the heart.

6.2. Testing of anti-oxidants in experimental animal models

Radiation-induced heart disease in animal models appears to be associated with long-term oxidative stress [36;43;46]. Hence, some of the interventions that have been tested in animal models of radiation-induced heart disease act via anti-oxidant mechanisms.

Amifostine is one of the few clinically approved compounds that may be administered as radiation protector in cancer patients. Upon administration, amifostine is metabolized into its active compound, WR-1056 that is thought to act at least in part by scavenging free radicals [137]. Amifostine was shown to protect against cardiac fibrosis and function loss when administered before local irradiation with high single doses in the rat [138–140]. However, although approved for clinical use, amifostine is not in wide use because of side effects.

Other protective treatments in animal models of radiation-induced heart disease may act via anti-oxidant properties. Black grape juice, for instance, when administered starting one week before irradiation in a rat model, reduced adverse cardiac effects [141]. Moreover, administration of water saturated with molecular hydrogen starting 24 hours before single dose local heart irradiation reduced chronic myocardial injury in a mouse model, and the main suggested mechanism of action was free radical scavenging [142]. On the other hand, when administered 24 hours before local heart irradiation (21 Gy single dose), the vitamin E analog and anti-oxidant γ-tocotrienol prevented radiation-induced alterations in cardiac mitochondria but did not protect against late cardiac fibrosis [46].

Altogether, while anti-oxidant strategies alone may not suffice in fully preventing cardiovascular radiation injury, they may contribute to radiation protection when administered in combination with other radioprotective compounds.

6.3. Testing of potential countermeasures with non-antioxidant biological mechanisms

In addition to anti-oxidant strategies, certain interventions with known beneficial effects in heart disease have been tested in animal models of cardiac radiation injury. The common cholesterol-lowering drugs statins, for instance, have shown promising effects in mouse and rat models of single dose local heart irradiation [143;144] and whole body irradiation [145]. On the other hand, atorvastatin did not modify radiation-induced accelerated atherosclerosis in the carotid artery upon a single dose of 14 Gy to the neck of ApoE KO mice [146]. Since some of the intermediates of the cholesterol signaling pathway are used to modulate

signaling molecules such as Ras-like proteins, statins have various anti-inflammatory and anti-coagulant effects on endothelial cells [147]. Hence, their mechanisms of action in the cardiovascular system may go beyond improving cholesterol levels.

Besides some gene and protein expression data [148], there is no evidence of activation of the renin angiotensin system (RAS) in the irradiated rat heart. Nonetheless, the ACE inhibitor captopril has shown to reduce cardiac radiation injury in the rat [149]. However, captopril has various other effects not related to ACE inhibition, and the beneficial effects on the irradiated heart may be mediated in part by its non-ACE inhibitory properties. Moreover, the effects seem to rely on modifying the lung and/or the interaction between the heart and lung [72].

The anti-platelet agent clopidegrol did not modify radiation-induced accelerated atherosclerosis in the carotid artery of ApoE KO mice [146]. Moreover, a nitric oxide releasing aspirin reduced age-related atherosclerosis but not atherosclerosis associated with a single local dose of 14 Gy in this mouse model [150].

Even though radiation-induced heart disease in animal models is associated with cardiac inflammatory infiltration [60;93;151], a strategy to inactivate macrophages with the use of thalidomide did not alter late cardiac radiation injury from a single dose of 16 Gy in a mouse model [152].

The rheological agent pentoxifylline has been tested as a potential radiation mitigator that may be administered after irradiation, at a time when late effects have become apparent. When administered in combination with α-tocopherol from 3 until 6 months after local heart irradiation with 5 fractions of 9 Gy in a rat model, pentoxifylline reduced cardiac fibrosis and improved cardiac function [153]. However, when administered after a single dose of 21 Gy using an image-guided protocol with reduced lung radiation exposure, pentoxifylline caused increased bradycardia and arrhythmia that seemed to offset its beneficial effects in the heart [154]. We speculate that the single dose irradiation and/or the reduced lung radiation exposure in the second study revealed the adverse chronotropic effects of pentoxifylline in the irradiated rat heart.

6.4. Countermeasures against adverse effects of space radiation

Experiments involving pharmacological countermeasures against the effects of space radiation, including those in the heart and vasculature, have been reviewed in detail elsewhere [155]. Some of these interventions may eventually prove to be safe in reducing early or late adverse effects of both photon and charged particle irradiation in the heart.

7. Conclusions and future directions

While high doses of ionizing radiation have long been known to cause injury in the heart, recent studies suggest that low doses may also have adverse cardiovascular effects, possibly via different mechanisms. With recent developments in radiation delivery to small animals and high-resolution *in vivo* imaging, future preclinical studies can include clinically relevant radiation schedules and close monitoring of animals to increase our knowledge of biological

mechanisms of cardiovascular radiation injury and test potential interventions that may prevent or mitigate these effects. As is the case for most animal experiments in the biomedical sciences, the majority of experiments focused on cardiovascular effects of ionizing radiation have been performed in male animals. Since cardiovascular disease risk is known to be sex-dependent, future studies will have to include both male and female animals. Moreover, since childhood cancer survivors are at higher risk of developing radiation-induced heart disease, experimental models that mimic childhood radiation exposure may enhance our understanding of the role of age at exposure in cardiovascular radiation injury. Lastly, high-throughput small molecule analysis will contribute to the identification of novel non-invasive biomarkers for early identification of patients at risk.

Acknowledgments

This work was supported by the National Institutes of Health [CA148679], the American Cancer Society [RSG-10-125-01-CCE], and the National Space Biomedical Research Institute [RE03701 through NCC 9-58].

List of Abbreviations

ACE	Angiotensin Converting Enzyme
ApoE	Apolipoprotein E
KO	knockout
Nrf2	Nuclear factor erythroid 2 [NF-E2]-related factor 2
RAS	Renin angiotensin system

References

1. Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, Greenbaum N, Mauch P, Lipshultz SE. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol. 2004; 22(15):3139–3148. DOI: 10.1200/JCO.2004.09.109 [PubMed: 15284266]
2. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005; 6(8):557–565. DOI: 10.1016/S1470-2045(05)70251-5 [PubMed: 16054566]
3. Early Breast Cancer Trialists Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet. 2000; 355(9217):1757–1770. [PubMed: 10832826]
4. Heidenreich PA, Kapoor JR. Radiation induced heart disease: systemic disorders in heart disease. Heart. 2009; 95(3):252–258. DOI: 10.1136/hrt.2008.149088 [PubMed: 19144884]
5. Martinou M, Gaya A. Cardiac complications after radical radiotherapy. Semin Oncol. 2013; 40(2): 178–185. DOI: 10.1053/j.seminoncol.2013.01.007 [PubMed: 23540743]
6. Mill WB, Baglan RJ, Kurichety P, Prasad S, Lee JY, Moller R. Symptomatic radiation-induced pericarditis in Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1984; 10(11):2061–2065. [PubMed: 6436206]
7. Brosius FC, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med. 1981; 70(3):519–530. [PubMed: 6782873]

8. Russell NS, Hoving S, Heeneman S, Hage JJ, Woerdeman LA, de BR, Lohuis PJ, Smeele L, Cleutjens J, Valenkamp A, Dorresteijn LD, Dalesio O, Daemen MJ, Stewart FA. Novel insights into pathological changes in muscular arteries of radiotherapy patients. Radiother Oncol. 2009; 92(3): 477–483. DOI: 10.1016/j.radonc.2009.05.021 [PubMed: 19541382]

9. Akam-Venkata J, Franco VI, Lipshultz SE. Late cardiotoxicity: issues for childhood cancer survivors. Curr Treat Options Cardiovasc Med. 2016; 18(7):47.doi: 10.1007/s11936-016-0466-6 [PubMed: 27230282]

10. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guerin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, de Vathaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010; 28(8):1308–1315. DOI: 10.1200/JCO.2008.20.2267 [PubMed: 20142603]

11. Haddy N, Diallo S, El-Fayech C, Schwartz B, Pein F, Hawkins M, Veres C, Oberlin O, Guibout C, Pacquement H, Munzer M, N'Guyen TD, Bondiau PY, Berchery D, Laprie A, Scarabin PY, Jouven X, Bridier A, Koscielny S, Deutsch E, Diallo I, De Vathaire F. Cardiac diseases following childhood cancer treatment: cohort study. Circulation. 2016; 133(1):31–38. DOI: 10.1161/CIRCULATIONAHA.115.016686 [PubMed: 26487757]

12. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, Darby SC. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys. 2008; 72(2): 501–507. DOI: 10.1016/j.ijrobp.2007.12.058 [PubMed: 18374500]

13. Taylor CW, Nisbet A, McGale P, Goldman U, Darby SC, Hall P, Gagliardi G. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiother Oncol. 2009; 90(1):127–135. DOI: 10.1016/j.radonc.2008.09.029 [PubMed: 19008005]

14. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005; 6(8):557–565. DOI: 10.1016/S1470-2045(05)70251-5 [PubMed: 16054566]

15. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013; 368(11):987–998. DOI: 10.1056/NEJMoa1209825 [PubMed: 23484825]

16. Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 2003; 45(1):55–75. [PubMed: 12482572]

17. Fajardo LF, Berthrong M. Vascular lesions following radiation. Pathol Annu. 1988; 23(Pt 1):297–330. [PubMed: 3387138]

18. Lipshultz SE, Cochran TR, Franco VI, Miller TL. Treatment-related cardiotoxicity in survivors of childhood cancer. Nat Rev Clin Oncol. 2013; 10(12):697–710. DOI: 10.1038/nrclinonc.2013.195 [PubMed: 24165948]

19. Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA. Comparison of Heart and Coronary Artery Doses Associated with Intensity-Modulated Radiotherapy Versus Three-Dimensional Conformal Radiotherapy for Distal Esophageal Cancer. Int J Radiat Oncol Biol Phys. 2012; 83(5): 1580–1586. DOI: 10.1016/j.ijrobp.2011.10.053 [PubMed: 22284687]

20. Tillman GF, Pawlicki T, Koong AC, Goodman KA. Preoperative versus postoperative radiotherapy for locally advanced gastroesophageal junction and proximal gastric cancers: a comparison of normal tissue radiation doses. Dis Esophagus. 2008; 21(5):437–444. DOI: 10.1111/j.1442-2050.2007.00794.x [PubMed: 19125798]

21. Wu WC, Chan CL, Wong YW, Cuijpers JP. A study on the influence of breathing phases in intensity-modulated radiotherapy of lung tumours using four-dimensional CT. Br J Radiol. 2009; 83(987):252–256. DOI: 10.1259/bjr/33094251 [PubMed: 19723769]

22. Zheng Y, Chen H, Li X, Sun Y. Pay attention to cardiac remodeling in cancer cachexia. Support Care Cancer. 2016; 24(7):3253–3259. DOI: 10.1007/s00520-016-3222-2 [PubMed: 27108265]

23. Murphy KT. The pathogenesis and treatment of cardiac atrophy in cancer cachexia. Am J Physiol Heart Circ Physiol. 2016; 310(4):H466–H477. DOI: 10.1152/ajpheart.00720.2015 [PubMed: 26718971]

24. Sala V, Gatti S, Gallo S, Medico E, Cantarella D, Cimono J, Ponzetto A, Crepaldi T. A new transgenic mouse model of heart failure and cardiac cachexia raised by sustained activation of met tyrosine kinase in the heart. Biomed Res Int. 2016; 2016 9549036. doi:1155/2016/9549036.
25. Molinari F, Malara N, Mollace V, Rosano G, Ferraro E. Animal models of cardiac cachexia. Int J Cardiol. 2016; 219:105–110. DOI: 10.1016/j.ijcard.2016.05.071 [PubMed: 27317993]
26. van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Petersen EJ, Raemaekers JM, Kok WE, Aleman BM, van Leeuwen FE. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med. 2015; 175(60):1007–1017. DOI: 10.1001/jamainternmed.2015.1180 [PubMed: 25915855]
27. Fajardo LF, Eltringham JR, Steward JR. Combined cardiotoxicity of adriamycin and x-radiation. Lab Invest. 1976; 34(1):86–96. [PubMed: 1246126]
28. Eltringham JR, Fajardo LF, Stewart JR. Adriamycin cardiomyopathy: enhanced cardiac damage in rabbits with combined drug and cardiac irradiation. Radiology. 1975; 115(2):471–472. DOI: 10.1148/115.2.471 [PubMed: 806934]
29. Aleman BM, van den Belt-Dusebout AW, de Bruin ML, van 't Veer MB, Baaijens MH, de Boer JP, Hart AA, Klokman WJ, Kuenen MA, Ouwens GM, Bartelink H, van Leeuwen FE. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007; 109(5):1878–1886. DOI: 10.1182/blood-2006-07-034405 [PubMed: 17119114]
30. Ky B, Vejpongsa P, Yeh ET, Force T, Moslehi JJ. Emerging paradigms in cardiomyopathies associated with cancer therapies. Circ Res. 2013; 113(6):754–764. DOI: 10.1161/CIRCRESAHA.113.300218 [PubMed: 23989717]
31. Sivagnanam K, Rahman ZU, Paul T. Cardiomyopathy Associated With Targeted Therapy for Breast Cancer. Am J Med Sci. 2016; 351(2):194–199. DOI: 10.1016/j.amjms.2015.11.014 [PubMed: 26897275]
32. Murtagh G, Yu Z, Harrold E, Cooke J, Keegan N, Fukuda S, Addetia K, Kim JH, Spencer KT, Takeuchi M, Kennedy J, Ward RP, Patel AR, Lang RM, DeCara JM. Monitoring Ionizing Radiation Exposure for Cardiotoxic Effects of Breast Cancer Treatment. Am J Cardiol. 2016; 117(10):1678–1682. DOI: 10.1016/j.amjcard.2016.02.047 [PubMed: 27040573]
33. Magne N, Chargari C, MacDermed D, Conforti R, Vedrine L, Spano JP, Khayat D. Tomorrow's targeted therapies in breast cancer patients: what is the risk for increased radiation-induced cardiac toxicity? Crit Rev Oncol Hematol. 2010; 76(3):186–195. DOI: 10.1016/j.critrevonc.2010.01.012 [PubMed: 20138541]
34. Witteles RM, Telli M. Underestimating cardiac toxicity in cancer trials: lessons learned? J Clin Oncol. 2012; 30(16):1916–1918. DOI: 10.1200/JCO.2011.40.4012 [PubMed: 22454419]
35. Belkacemi Y, Gligorov J. Concurrent trastuzumab–internal mammary irradiation for HER2 positive breast cancer: "It hurts to be on the cutting edge". Radiother Oncol. 2010; 94(1):119–120. DOI: 10.1016/j.radonc.2009.04.009 [PubMed: 19410315]
36. Sridharan V, Thomas CJ, Cao M, Melnyk SB, Pavliv O, Joseph J, Singh SP, Sharma S, Moros EG, Boerma M. Effects of local irradiation combined with sunitinib on early remodeling, mitochondria, and oxidative stress in the rat heart. Radiother Oncol. 2016; 119(2)doi: 10.1016/j.radonc.2016.03.027
37. Seemann I, te Poele JA, Song JY, Hoving S, Russell NS, Stewart FA. Radiation- and anthracycline-induced cardiac toxicity and the influence of ErbB2 blocking agents. Breast Cancer Res Treat. 2013; 141(3):385–395. DOI: 10.1007/s10549-013-2707-7 [PubMed: 24091769]
38. Fajardo LF, Stewart JR. Pathogenesis of radiation-induced myocardial fibrosis. Lab Invest. 1973; 29(2):244–257. [PubMed: 4724850]
39. Schultz-Hector S. Experimental studies on the pathogenesis of damage in the heart. Recent Results Cancer Res. 1993; 130:145–156. [PubMed: 8362084]
40. Gillette EL, McChesney SL, Hoopes PJ. Isoeffect curves for radiation-induced cardiomyopathy in the dog. Int J Radiat Oncol Biol Phys. 1985; 11(12):2091–2097. [PubMed: 4066441]
41. Gillette SM, Gillette EL, Shida T, Boon J, Miller CW, Powers BE. Late radiation response of canine mediastinal tissues. Radiother Oncol. 1992; 23(1):41–52. [PubMed: 1736331]
42. Schultz-Hector S, Sund M, Thames HD. Fractionation response and repair kinetics of radiation-induced heart failure in the rat. Radiother Oncol. 1992; 23(1):33–40. [PubMed: 1736330]

43. Boerma M, Singh P, Sridharan V, Tripathi P, Sharma S, Singh SP. Effects of Local Heart Irradiation in a Glutathione S-Transferase Alpha 4-Null Mouse Model. Radiat Res. 2015; 183(6):610–619. DOI: 10.1667/RR13979.1 [PubMed: 26010708]
44. Gao S, Wu R, Zeng Y. Up-regulation of peroxisome proliferator-activated receptor gamma in radiation-induced heart injury in rats. Radiat Environ Biophys. 2012; 51(1):53–59. DOI: 10.1007/s00411-011-0390-9 [PubMed: 21997460]
45. Ferreira-Machado SC, Salata C, Rocha NN, Correa AF, Corte-Real S, Peregrino AA, Campos VM, Andrade CB, Bernardo-Filho M, Cabral-Neto JB, Dealmeida CE. Caspase-3 activation and increased procollagen type I in irradiated hearts. An Acad Bras Cienc. 2013; 85(1):215–222. [PubMed: 23460445]
46. Sridharan V, Tripathi P, Aykin-Burns N, Krager KJ, Sharma SK, Moros EG, Melnyk SB, Pavliv O, Hauer-Jensen M, Boerma M. A tocotrienol-enriched formulation protects against radiation-induced changes in cardiac mitochondria without modifying late cardiac function or structure. Radiat Res. 2015; 183(3):357–366. DOI: 10.1667/RR13915.1 [PubMed: 25710576]
47. Boerma M, Zurcher C, Esveldt I, Schutte-Bart CI, Wondergem J. Histopathology of ventricles, coronary arteries and mast cell accumulation in transverse and longitudinal sections of the rat heart after irradiation. Oncol Rep. 2004; 12(2):213–219. [PubMed: 15254680]
48. Schultz-Hector S. Radiation-induced heart disease: review of experimental data on dose response and pathogenesis. Int J Radiat Biol. 1992; 61(2):149–160. [PubMed: 1351901]
49. Sridharan V, Tripathi P, Sharma S, Moros EG, Zheng J, Hauer-Jensen M, Boerma M. Roles of sensory nerves in the regulation of radiation-induced structural and functional changes in the heart. Int J Radiat Oncol Biol Phys. 2014; 88(1):167–174. DOI: 10.1016/j.ijrobp.2013.10.014 [PubMed: 24331664]
50. Lauk S. Endothelial alkaline phosphatase activity loss as an early stage in the development of radiation-induced heart disease in rats. Radiat Res. 1987; 110(1):118–128. [PubMed: 3562789]
51. Schultz-Hector S, Balz K. Radiation-induced loss of endothelial alkaline phosphatase activity and development of myocardial degeneration. An ultrastructural study, Lab Invest. 1994; 71(2):252–260. [PubMed: 8078304]
52. Boerma M, Kruse JJ, van Loenen M, Klein HR, Bart CI, Zurcher C, Wondergem J. Increased deposition of von Willebrand factor in the rat heart after local ionizing irradiation. Strahlenther Onkol. 2004; 180(2):109–116. DOI: 10.1007/s00066-004-1138-0
53. Fajardo LF, Stewart JR. Capillary injury preceding radiation-induced myocardial fibrosis. Radiology. 1971; 101(2):429–433. DOI: 10.1148/101.2.429 [PubMed: 5114783]
54. Lee CL, Moding EJ, Cuneo KC, Li Y, Sullivan JM, Mao L, Washington I, Jeffords LB, Rodrigues RC, Ma Y, Das S, Kontos CD, Kim Y, Rockman HA, Kirsch DG. p53 Functions in Endothelial Cells to Prevent Radiation-Induced Myocardial Injury in Mice. Sci Signal. 2012; 5(234):ra52.doi: 10.1126/scisignal.2002918 [PubMed: 22827996]
55. Baker JE, Fish BL, Su J, Haworth ST, Strande JL, Komorowski RA, Migrino RQ, Doppalapudi A, Harmann L, Allen LX, Hopewell JW, Moulder JE. 10 Gy total body irradiation increases risk of coronary sclerosis, degeneration of heart structure and function in a rat model. Int J Radiat Biol. 2009; 85(12):1089–1100. DOI: 10.3109/09553000903264473 [PubMed: 19995235]
56. Lenarczyk M, Lam V, Jensen E, Fish BL, Su J, Koprowski S, Komorowski RA, Harmann L, Migrino RQ, Li XA, Hopewell JW, Moulder JE, Baker JE. Cardiac injury after 10 gy total body irradiation: indirect role of effects on abdominal organs. Radiat Res. 2013; 180(3):247–258. DOI: 10.1667/RR3292.1 [PubMed: 23919311]
57. Adams MJ, Grant EJ, Kodama K, Shimizu Y, Kasagi F, Suyama A, Sakata R, Akahoshi M. Radiation dose associated with renal failure mortality: a potential pathway to partially explain increased cardiovascular disease mortality observed after whole-body irradiation. Radiat Res. 2012; 177(2):220–228. [PubMed: 22149958]
58. Gao M, Shirato H, Miyasaka K, Kuwabara M, Koyama T. Induction of growth factors in rat cardiac tissue by X irradiation. Radiat Res. 2000; 153(5 Pt 1):540–547. [PubMed: 10790275]
59. Kruse JJ, Bart CI, Visser A, Wondergem J. Changes in transforming growth factor-beta (TGF-beta1), procollagen types I and III mRNA in the rat heart after irradiation. Int J Radiat Biol. 1999; 75(11):1429–1436. [PubMed: 10597916]

60. Boerma M, Wang J, Sridharan V, Herbert JM, Hauer-Jensen M. Pharmacological induction of transforming growth factor-beta1 in rat models enhances radiation injury in the intestine and the heart. PLoS One. 2013; 8(7):e70479.doi: 10.1371/journal.pone.0070479 [PubMed: 23936211]
61. Barjaktarovic Z, Schmaltz D, Shyla A, Azimzadeh O, Schulz S, Haagen J, Dorr W, Sarioglu H, Schafer A, Atkinson MJ, Zischka H, Tapio S. Radiation-induced signaling results in mitochondrial impairment in mouse heart at 4 weeks after exposure to x-rays. PLoS One. 2011; 6(12):e27811.doi: 10.1371/journal.pone.0027811 [PubMed: 22174747]
62. Barjaktarovic Z, Shyla A, Azimzadeh O, Schulz S, Haagen J, Dorr W, Sarioglu H, Atkinson MJ, Zischka H, Tapio S. Ionising radiation induces persistent alterations in the cardiac mitochondrial function of C57BL/6 mice 40 weeks after local heart exposure. Radiother Oncol. 2013; 106(3): 404–410. DOI: 10.1016/j.radonc.2013.01.017 [PubMed: 23522698]
63. Sridharan V, Aykin-Burns N, Tripathi P, Krager KJ, Sharma SK, Moros EG, Corry PM, Nowak G, Hauer-Jensen M, Boerma M. Radiation-induced alterations in mitochondria of the rat heart. Radiat Res. 2014; 181(3):324–334. DOI: 10.1667/RR13452.1 [PubMed: 24568130]
64. Lo SC, Hannink M. PGAM5 tethers a ternary complex containing Keap1 and Nrf2 to mitochondria. Exp Cell Res. 2008; 314(8):1789–1803. DOI: 10.1016/j.yexcr.2008.02.014 [PubMed: 18387606]
65. Chute JP. NRF2 mitigates radiation-induced hematopoietic death. J Clin Invest. 2014; 124(3):960–961. DOI: 10.1172/JCI74143 [PubMed: 24569364]
66. Mathew B, Jacobson JR, Siegler JH, Moitra J, Blasco M, Xie L, Unzueta C, Zhou T, Evenoski C, Al-Sakka M, Sharma R, Huey B, Bulent A, Smith B, Jayaraman S, Reddy NM, Reddy SP, Fingerle-Rowson G, Bucala R, Dudek SM, Natarajan V, Weichselbaum RR, Garcia JG. Role of migratory inhibition factor in age-related susceptibility to radiation lung injury via NF-E2-related factor-2 and antioxidant regulation. Am J Respir Cell Mol Biol. 2013; 49(2):269–278. DOI: 10.1165/rcmb.2012-0291OC [PubMed: 23526214]
67. Travis EL, Rachakonda G, Zhou X, Korhonen K, Sekhar KR, Biswas S, Freeman ML. NRF2 deficiency reduces life span of mice administered thoracic irradiation. Free Radic Biol Med. 2011; 51(6):1175–1183. DOI: 10.1016/j.freeradbiomed.2011.05.038 [PubMed: 21712086]
68. Boerma M, Wang J, Wondergem J, Joseph J, Qiu X, Kennedy RH, Hauer-Jensen M. Influence of mast cells on structural and functional manifestations of radiation-induced heart disease. Cancer Res. 2005; 65(8):3100–3107. DOI: 10.1158/0008-5472.CAN-04-4333 [PubMed: 15833839]
69. Arizono N, Matsuda S, Hattori T, Kojima Y, Maeda T, Galli SJ. Anatomical variation in mast cell nerve associations in the rat small intestine, heart, lung, and skin. Similarities of distances between neural processes and mast cells, eosinophils, or plasma cells in the jejunal lamina propria. Lab Invest. 1990; 62(5):626–634. [PubMed: 2342332]
70. Ghobadi G, van der Veen S, Bartelds B, de Boer RA, Dickinson MG, de Jong JR, Faber H, Niemantsverdriet M, Brandenburg S, Berger RM, Langendijk JA, Coppes RP, van Luijk P. Physiological interaction of heart and lung in thoracic irradiation. Int J Radiat Oncol Biol Phys. 2012; 84(5):e639–e646. DOI: 10.1016/j.ijrobp.2012.07.2362 [PubMed: 22975617]
71. van Luijk P, Faber H, Meertens H, Schippers JM, Langendijk JA, Brandenburg S, Kampinga HH, Coppes RP. The impact of heart irradiation on dose-volume effects in the rat lung. Int J Radiat Oncol Biol Phys. 2007; 69(2):552–559. DOI: 10.1016/j.ijrobp.2007.05.065 [PubMed: 17869668]
72. van der Veen SJ, Ghobadi G, de Boer RA, Faber H, Cannon MV, Nagle PW, Brandenburg S, Langendijk JA, van Luijk P, Coppes RP. ACE inhibition attenuates radiation-induced cardiopulmonary damage. Radiother Oncol. 2015; 114(1):96–103. DOI: 10.1016/j.radonc.2014.11.017 [PubMed: 25465731]
73. Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Russell NS, Daemen MJ, Stewart FA. Single-dose and fractionated irradiation promote initiation and progression of atherosclerosis and induce an inflammatory plaque phenotype in ApoE(−/−) mice. Int J Radiat Oncol Biol Phys. 2008; 71(3): 848–857. DOI: 10.1016/j.ijrobp.2008.02.031 [PubMed: 18514779]
74. Stewart FA, Heeneman S, Te Poele PJ, Kruse J, Russell NS, Gijbels M, Daemen M. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE$^{-/-}$ mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. Am J Pathol. 2006; 168(2):649–658. DOI: 10.2353/ajpath.2006.050409 [PubMed: 16436678]

75. Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Visser N, Cleutjens J, Russell NS, Daemen MJ, Stewart FA. Irradiation induces different inflammatory and thrombotic responses in carotid arteries of wildtype C57BL/6J and atherosclerosis-prone ApoE(−/−) mice. Radiother Oncol. 2012; 105(3): 365–370. DOI: 10.1016/j.radonc.2012.11.001 [PubMed: 23245647]

76. Gabriels K, Hoving S, Seemann I, Visser NL, Gijbels MJ, Pol JF, Daemen MJ, Stewart FA, Heeneman S. Local heart irradiation of ApoE(−/−) mice induces microvascular and endocardial damage and accelerates coronary atherosclerosis. Radiother Oncol. 2012; 105(3):358–364. DOI: 10.1016/j.radonc.2012.08.002 [PubMed: 22959484]

77. Gianicolo ME, Gianicolo EA, Tramacere F, Andreassi MG, Portaluri M. Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. Cardiovasc Ultrasound. 2010; 19(8):8.doi: 10.1186/1476-7120-8-8

78. McChesney SL, Gillette EL, Powers BE. Radiation-induced cardiomyopathy in the dog. Radiat Res. 1988; 113(1):120–132. [PubMed: 3340716]

79. Wondergem J, Persons K, Zurcher C, Frolich M, Leer JW, Broerse J. Changes in circulating atrial natriuretic peptide in relation to the cardiac status of Rhesus monkeys after total-body irradiation. Radiother Oncol. 1999; 53(1):67–75. [PubMed: 10624856]

80. DeBo RJ, Lees CJ, Dugan GO, Caudell DL, Michalson KT, Hanbury DB, Kavanagh K, Cline JM, Register TC. Late Effects of Total-Body Gamma Irradiation on Cardiac Structure and Function in Male Rhesus Macaques. Radiat Res. 2016; in press. doi: 10.1667/RR14357.1

81. Tiamson E, Fritz KE, Campana H, Anzola E, Zgoda A, Daoud AS. Studies in rabbits of cellular mechanisms accounting for enhancement of diet-induced atherosclerosis by x-irradiation. Exp Mol Pathol. 1970; 12(2):175–184. [PubMed: 5434755]

82. Wong FL, Yamada M, Sasaki H, Kodama K, Akiba S, Shimaoka K, Hosoda Y. Noncancer disease incidence in the atomic bomb survivors: 1958–1986. Radiat Res. 1993; 135(3):418–430. [PubMed: 8378535]

83. Yamada M, Naito K, Kasagi F, Masunari N, Suzuki G. Prevalence of atherosclerosis in relation to atomic bomb radiation exposure: an RERF Adult Health Study. Int J Radiat Biol. 2005; 81(11): 821–826. DOI: 10.1080/09553000600555504 [PubMed: 16484151]

84. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res. 2003; 160(4):381–407. [PubMed: 12968934]

85. Stewart AM, Kneale GW. A-bomb survivors: factors that may lead to a reassessment of the radiation hazard. Int J Epidemiol. 2000; 29(4):708–714. [PubMed: 10922349]

86. Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958–1998. Radiat Res. 2004; 161(6):622–632. [PubMed: 15161358]

87. Ozasa K, Takahashi I, Grant EJ. Radiation-related risks of non-cancer outcomes in the atomic bomb survivors. Ann ICRP. 2016; 45(1 Suppl):253–261. DOI: 10.1177/0146645316629318 [PubMed: 26956675]

88. Adams MJ, Grant EJ, Kodama K, Shimizu Y, Kasagi F, Suyama A, Sakata R, Akahoshi M. Radiation dose associated with renal failure mortality: a potential pathway to partially explain increased cardiovascular disease mortality observed after whole-body irradiation. Radiat Res. 2012; 177(2):220–228. [PubMed: 22149958]

89. Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, Chumak VV, Cucinotta FA, de VF, Hall P, Harrison JD, Hildebrandt G, Ivanov V, Kashcheev VV, Klymenko SV, Kreuzer M, Laurent O, Ozasa K, Schneider T, Tapio S, Taylor AM, Tzoulaki I, Vandoolaeghe WL, Wakeford R, Zablotska LB, Zhang W, Lipshultz SE. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect. 2012; 120(11):1503–1511. DOI: 10.1289/ehp.1204982 [PubMed: 22728254]

90. Carr ZA, Land CE, Kleinerman RA, Weinstock RW, Stovall M, Griem ML, Mabuchi K. Coronary heart disease after radiotherapy for peptic ulcer disease. Int J Radiat Oncol Biol Phys. 2005; 61(3): 842–850. DOI: 10.1016/j.ijrobp.2004.07.708 [PubMed: 15708264]

91. Ivanov VK, Maksioutov MA, Chekin SY, Petrov AV, Biryukov AP, Kruglova ZG, Matyash VA, Tsyb AF, Manton KG, Kravchenko JS. The risk of radiation-induced cerebrovascular disease in

Chernobyl emergency workers. Health Phys. 2006; 90(3):199–207. DOI: 10.1097/01.HP.0000175835.31663.ea [PubMed: 16505616]

92. Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P. A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. Radiat Res. 2008; 169(1): 99–109. DOI: 10.1667/RR1070.1 [PubMed: 18159955]
93. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys. 2007; 67(1):10–18. DOI: 10.1016/j.ijrobp.2006.08.071 [PubMed: 17189062]
94. Monceau V, Meziani L, Strup-Perrot C, Morel E, Schmidt M, Haagen J, Escoubet B, Dorr W, Vozenin MC. Enhanced sensitivity to low dose irradiation of ApoE$^{-/-}$ mice mediated by early pro-inflammatory profile and delayed activation of the TGFbeta1 cascade involved in fibrogenesis. PLoS One. 2013; 8(2):e57052.doi: 10.1371/journal.pone.0057052 [PubMed: 23451141]
95. Mathias D, Mitchel RE, Barclay M, Wyatt H, Bugden M, Priest ND, Whitman SC, Scholz M, Hildebrandt G, Kamprad M, Glasow A. Low-dose irradiation affects expression of inflammatory markers in the heart of ApoE$^{-/-}$ mice. PLoS One. 2015; 10(3):e0119661.doi: 10.1371/journal.pone.0119661 [PubMed: 25799423]
96. Barjaktarovic Z, Anastasov N, Azimzadeh O, Sriharshan A, Sarioglu H, Ueffing M, Tammio H, Hakanen A, Leszczynski D, Atkinson MJ, Tapio S. Integrative proteomic and microRNA analysis of primary human coronary artery endothelial cells exposed to low-dose gamma radiation. Radiat Environ Biophys. 2013; 52(1):87–98. DOI: 10.1007/s00411-012-0439-4 [PubMed: 23138885]
97. Parsons JL, Townsend LW. Interplenatary crew dose rates for the August 1972 solar particle event. Radiat Res. 2000; 153(6):729–733. [PubMed: 10825747]
98. Cucinotta FA, Wu H, Shavers MR, George K. Radiation dosimetry and biophysical models of space radiation effects. Gravit Space Biol Bull. 2003; 16(2):11–18. [PubMed: 12959127]
99. National Council on Radiation Protection & Measurements. Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit. 2006NCRP Report No.153
100. Stearner SP, Yang VV, Devine RL. Cardiac injury in the aged mouse: comparative ultrastructural effects of fission spectrum neutrons and gamma rays. Radiat Res. 1979; 78(3):429–447. [PubMed: 451165]
101. Yang VV, Stearner SP, Tyler SA. Radiation-induced changes in the fine structure of the heart: comparison of fission neutrons and 60Co gamma rays in the mouse. Radiat Res. 1976; 67(2): 344–360. [PubMed: 948560]
102. Yang VV, Stearner SP, Dimitrievich GS, Griem ML. Radiation damage to the microvasculature in the rabbit ear chamber. An electron microscope study. Radiat Res. 1977; 70(1):107–117. [PubMed: 850725]
103. Yang VV, Stearner SP, Ainsworth EJ. Late ultrastructural changes in the mouse coronary arteries and aorta after fission neutron or 60Co gamma irradiation. Radiat Res. 1978; 74(3):436–456. [PubMed: 684161]
104. Yu T, Parks BW, Yu S, Srivastava R, Gupta K, Wu X, Khaled S, Chang PY, Kabarowski JH, Kucik DF. Iron-ion radiation accelerates atherosclerosis in apolipoprotein E-deficient mice. Radiat Res. 2011; 175(6):766–773. DOI: 10.1667/RR2482.1 [PubMed: 21466380]
105. Sasi SP, Yan X, Lee J, Sisakyan H, Carrozza J, Goukassian DA. Radiation-associated degenerative cardiovascular risks during normal aging and after adverse CV event 10 months post-initial exposure. J Radiat Res. 2014; 55(Suppl 1):i111–i112.
106. Yan X, Sasi SP, Gee H, Lee J, Yang Y, Mehrzad R, Onufrak J, Song J, Enderling H, Agarwal A, Rahimi L, Morgan J, Wilson PF, Carrozza J, Walsh K, Kishore R, Goukassian DA. Cardiovascular risks associated with low dose ionizing particle radiation. PLoS One. 2014; 9(10):e110269.doi: 10.1371/journal.pone.0110269 [PubMed: 25337914]
107. Tungjai M, Whorton EB, Rithidech KN. Persistence of apoptosis and inflammatory responses in the heart and bone marrow of mice following whole-body exposure to ^{28}Silicon (^{28}Si) ions. Radiat Environ Biophys. 2013; 52(3):339–350. DOI: 10.1007/s00411-013-0479-4 [PubMed: 23756637]

108. Ramadan SS, Sridharan V, Koturbash I, Miousse IR, Hauer-Jensen M, Nelson GA, Boerma M. A priming dose of protons alters the early cardiac cellular and molecular response to ^{56}Fe irradiation. Life Sci Space Res. 2016; 8:8–13. DOI: 10.1016/j.lssr.2015.12.001

109. Coleman MA, Sasi SP, Onufrak J, Natarajan M, Manickam K, Schwab J, Muralidharan S, Peterson LE, Alekseyev YO, Yan X, Goukassian DA. Low-dose radiation affects cardiac physiology: gene networks and molecular signaling in cardiomyocytes. Am J Physiol Heart Circ Physiol. 2015; 309(11):H1947–H1963. DOI: 10.1152/ajpheart.00050.2015 [PubMed: 26408534]

110. Aypar U, Morgan WF, Baulch JE. Radiation-induced epigenetic alterations after low and high LET irradiations. Mutat Res. 2011; 707(1–2):24–33. DOI: 10.1016/j.mrfmmm.2010.12.003 [PubMed: 21159317]

111. Lima F, Ding D, Goetz W, Yang AJ, Baulch JE. High LET ^{56}Fe ion irradiation induces tissue-specific changes in DNA methylation in the mouse. Environ Mol Mutagen. 2013; 55(3):266–277. DOI: 10.1002/em.21832 [PubMed: 24723241]

112. Nzabarushimana E, Miousse IR, Shao L, Chang J, Allen AR, Turner J, Stewart B, Raber J, Koturbash I. Long-term epigenetic effects of exposure to low doses of ^{56}Fe in the mouse lung. J Radiat Res. 2014; 55(4):823–828. DOI: 10.1093/jrr/rru010 [PubMed: 24585548]

113. Koturbash I, Miousse IR, Sridharan V, Nzabarushimana E, Skinner CM, Melnyk SB, Pavliv O, Hauer-Jensen M, Nelson GA, Boerma M. Radiation-induced changes in DNA methylation of repetitive elements in the mouse heart. Mutat Res. 2016; 787:43–53. DOI: 10.1016/j.mrfmmm.2016.02.009 [PubMed: 26963372]

114. Impey S, Pelz C, Tafessu A, Marzulla T, Turker MS, Raber J. Proton irradiation induces persistent and tissue-specific DNA methylation changes in the left ventricle and hippocampus. BMC Genomics. 2016; 17(1):273.doi: 10.1186/s12864-016-2581-x [PubMed: 27036964]

115. Gornikiewicz B, Ronowicz A, Krzeminski M, Sachadyn P. Changes in gene methylation patterns in neonatal murine hearts: Implications for the regenerative potential. BMC Genomics. 2016; 17(1):231.doi: 10.1186/s12864-016-2545-1 [PubMed: 26979619]

116. Napoli C, Grimaldi V, De Pascale MR, Sommese L, Infante T, Soricelli A. Novel epigenetic-based therapies useful in cardiovascular medicine. World J Cardiol. 2016; 8(2):211–219. DOI: 10.4330/wjc.v8.i2.211 [PubMed: 26981216]

117. Recchioni R, Marcheselli F, Antonicelli R, Lazzarini R, Mensa E, Testa R, Procopio AD, Olivieri F. Physical activity and progenitor cell-mediated endothelial repair in chronic heart failure: Is there a role for epigenetics? Mech Ageing Dev. 2016; in press. doi: 10.1016/j.mad.2016.03.008

118. Duygu B, Poels EM, da Costa Martins PA. Genetics and epigenetics of arrhythmia and heart failure. Front Genet. 2013; 4:219.doi: 10.3389/fgene.2013.00219 [PubMed: 24198825]

119. Haas J, Frese KS, Park YJ, Keller A, Vogel B, Lindroth AM, Weichenhan D, Franke J, Fischer S, Bauer A, Marquart S, Sedaghat-Hamedani F, Kayvanpour E, Kohler D, Wolf NM, Hassel S, Nietsch R, Wieland T, Ehlermann P, Schultz JH, Dosch A, Mereles D, Hardt S, Backs J, Hoheisel JD, Plass C, Katus HA, Meder B. Alterations in cardiac DNA methylation in human dilated cardiomyopathy. EMBO Mol Med. 2013; 5(3):413–429. DOI: 10.1002/emmm.201201553 [PubMed: 23341106]

120. Movassagh M, Choy MK, Goddard M, Bennett MR, Down TA, Foo RS. Differential DNA methylation correlates with differential expression of angiogenic factors in human heart failure. PLoS One. 2010; 5(1):e8564.doi: 10.1371/journal.pone.0008564 [PubMed: 20084101]

121. Movassagh M, Vujic A, Foo R. Genome-wide DNA methylation in human heart failure. Epigenomics. 2011; 3(1):103–109. DOI: 10.2217/epi.10.70 [PubMed: 22126157]

122. Movassagh M, Choy MK, Knowles DA, Cordeddu L, Haider S, Down T, Siggens L, Vujic A, Simeoni I, Penkett C, Goddard M, Lio P, Bennett MR, Foo RS. Distinct epigenomic features in end-stage failing human hearts. Circulation. 2011; 124(22):2411–2422. DOI: 10.1161/CIRCULATIONAHA.111.040071 [PubMed: 22025602]

123. Bordun KA, Premecz S, daSilva M, Mandal S, Goyal V, Glavinovic T, Cheung M, Cheung D, White CW, Chaudhary R, Freed DH, Villarraga HR, Herrmann J, Kohli M, Ravandi A, Thliveris J, Pitz M, Singal PK, Mulvagh S, Jassal DS. The utility of cardiac biomarkers and echocardiography for the early detection of bevacizumab- and sunitinib-mediated cardiotoxicity. Am J Physiol Heart Circ Physiol. 2015; 309(4):H692–H701. DOI: 10.1152/ajpheart.00172.2015 [PubMed: 26092985]

124. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, Voigt JU, Weltens C. Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. 2013; 85(5):1172–1178. DOI: 10.1016/j.ijrobp.2012.09.022 [PubMed: 23149005]

125. Skytta T, Tuohinen S, Boman E, Virtanen V, Raatikainen P, Kellokumpu-Lehtinen PL. Troponin T-release associates with cardiac radiation doses during adjuvant left-sided breast cancer radiotherapy. Radiat Oncol. 2015; 10:141.doi: 10.1186/s13014-015-0436-2 [PubMed: 26159409]

126. Kuo AH, Ancukiewicz M, Kozak KR, Yock TI, Padera TP. Cardiac and inflammatory biomarkers do not correlate with volume of heart or lung receiving radiation. Radiat Oncol. 2015; 10:5.doi: 10.1186/s13014-014-0324-1 [PubMed: 25573181]

127. Gomez DR, Yusuf SW, Munsell MF, Welsh JW, Liao Z, Lin SH, Pan HY, Chang JY, Komaki R, Cox JD, McAleer MF, Grosshans DR. Prospective exploratory analysis of cardiac biomarkers and electrocardiogram abnormalities in patients receiving thoracic radiation therapy with high-dose heart exposure. J Thorac Oncol. 2014; 9(10):1554–1560. DOI: 10.1097/JTO.0000000000000306 [PubMed: 25521400]

128. Cheung YF, Yu W, Cheuk DK, Cheng FW, Yang JY, Yau JP, Ho KK, Li CK, Li RC, Yuen HL, Ling AS, Li VW, Wong WK, Tsang KC, Chan GC. Plasma high sensitivity troponin T levels in adult survivors of childhood leukaemias: determinants and associations with cardiac function. PLoS One. 2013; 8(10):e77063.doi: 10.1371/journal.pone.0077063 [PubMed: 24204736]

129. D'Errico MP, Grimaldi L, Petruzzelli MF, Gianicolo EA, Tramacere F, Monetti A, Placella R, Pili G, Andreassi MG, Sicari R, Picano E, Portaluri M. N-terminal pro-B-type natriuretic peptide plasma levels as a potential biomarker for cardiac damage after radiotherapy in patients with left-sided breast cancer. Int J Radiat Oncol Biol Phys. 2012; 82(2):e239–e246. DOI: 10.1016/j.ijrobp.2011.03.058 [PubMed: 21640499]

130. Kozak KR, Hong TS, Sluss PM, Lewandrowski EL, Aleryani SL, Macdonald SM, Choi NC, Yock TI. Cardiac blood biomarkers in patients receiving thoracic (chemo)radiation. Lung Cancer. 2008; 62(3):351–355. DOI: 10.1016/j.lungcan.2008.03.024 [PubMed: 18462828]

131. Wondergem J, Strootman EG, Frolich M, Leer JW, Noordijk EM. Circulating atrial natriuretic peptide plasma levels as a marker for cardiac damage after radiotherapy. Radiother Oncol. 2001; 58(3):295–301. [PubMed: 11230891]

132. Jacob NK, Cooley JV, Yee TN, Jacob J, Alder H, Wickramasinghe P, Maclean KH, Chakravarti A. Identification of sensitive serum microRNA biomarkers for radiation biodosimetry. PLoS One. 2013; 8(2):e57603.doi: 10.1371/journal.pone.0057603 [PubMed: 23451251]

133. Menon SS, Uppal M, Randhawa S, Cheema MS, Aghdam N, Usala RL, Ghosh SP, Cheema AK, Dritschilo A. Radiation Metabolomics: Current Status and Future Directions. Front Oncol. 2016; 6:20.doi: 10.3389/fonc.2016.00020 [PubMed: 26870697]

134. Saxena P, Joyce LD, Daly RC, Kushwaha SS, Schirger JA, Rosedahl J, Dearani JA, Kara T, Edwards BS. Cardiac Transplantation for Radiation-Induced Cardiomyopathy: The Mayo Clinic Experience. Ann Thorac Surg. 2014; 98(6):2115–2121. DOI: 10.1016/j.athoracsur.2014.06.056 [PubMed: 25443015]

135. Barbetakis N, Xenikakis T, Paliouras D, Asteriou C, Samanidis G, Kleontas A, Lafaras C, Platogiannis D, Bischiniotis T, Tsilikas C. Pericardiectomy for radiation-induced constrictive pericarditis, Hellenic. J Cardiol. 2010; 51(3):214–218.

136. Al-Kindi SG, Oliveira GH. Heart Transplantation Outcomes in Radiation-Induced Restrictive Cardiomyopathy. J Card Fail. 2016; 22(6):475–478. DOI: 10.1016/j.cardfail.2016.03.014 [PubMed: 27084524]

137. Grdina DJ, Kataoka Y, Murley JS. Amifostine: mechanisms of action underlying cytoprotection and chemoprevention. Drug Metabol Drug Interact. 2000; 16(4):237–279. [PubMed: 11201306]

138. Kruse JJ, Strootman EG, Wondergem J. Effects of amifostine on radiation-induced cardiac damage. Acta Oncol. 2003; 42(1):4–9. [PubMed: 12665324]

139. Dragojevic-Simic VM, Dobric SL, Bokonjic DR, Vucinic ZM, Sinovec SM, Jacevic VM, Dogovic NP. Amifostine protection against doxorubicin cardiotoxicity in rats. Anticancer Drugs. 2004; 15(2):169–178. [PubMed: 15075674]

140. Tokatli F, Uzal C, Doganay L, Kocak Z, Kaya M, Ture M, Kurum T, Alkaya F, Karadag H, Kutlu K. The potential cardioprotective effects of amifostine in irradiated rats. Int J Radiat Oncol Biol Phys. 2004; 58(4):1228–1234. DOI: 10.1016/j.ijrobp.2003.09.071 [PubMed: 15001267]

141. de Freitas RB, Boligon AA, Rovani BT, Piana M, de Brum TF, da Silva JR, Rother FC, Alves NM, Teixeira da Rocha JB, Athayde ML, Barrio JP, de Andrade ER, de Freitas BL. Effect of black grape juice against heart damage from acute gamma TBI in rats. Molecules. 2013; 18(10): 12154–12167. DOI: 10.3390/molecules181012154 [PubMed: 24084019]

142. Qian L, Cao F, Cui J, Wang Y, Huang Y, Chuai Y, Zaho L, Jiang H, Cai J. The potential cardioprotective effects of hydrogen in irradiated mice. J Radiat Res. 2010; 51(6):741–747. [PubMed: 21116102]

143. Zhang K, He X, Zhou Y, Gao L, Qi Z, Chen J, Gao X. Atorvastatin Ameliorates Radiation-Induced Cardiac Fibrosis in Rats. Radiat Res. 2015; 184(6):611–620. DOI: 10.1667/RR14075.1 [PubMed: 26579943]

144. Monceau V, Pasinetti N, Schupp C, Pouzoulet F, Opolon P, Vozenin MC. Modulation of the Rho/ROCK pathway in heart and lung after thorax irradiation reveals targets to improve normal tissue toxicity. Curr Drug Targets. 2010; 11(11):1395–1404. [PubMed: 20583978]

145. Lenarczyk M, Su J, Haworth ST, Komorowski R, Fish BL, Migrino RQ, Harmann L, Hopewell JW, Kronenberg A, Patel S, Moulder JE, Baker JE. Simvastatin mitigates increases in risk factors for and the occurrence of cardiac disease following 10 Gy total body irradiation, Pharmacol. Res Perspect. 2015; 3(3):e00145.doi: 10.1002/prp2.145

146. Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Pol JF, Gabriels K, Russell NS, Daemen MJ, Stewart FA. Anti-inflammatory and anti-thrombotic intervention strategies using atorvastatin, clopidogrel and knock-down of CD40L do not modify radiation-induced atherosclerosis in ApoE null mice. Radiother Oncol. 2011; 101(1):100–108. DOI: 10.1016/j.radonc.2011.09.019 [PubMed: 22001104]

147. Wolfrum S, Jensen KS, Liao JK. Endothelium-dependent effects of statins, Arterioscler. Thromb. Vasc Biol. 2003; 23(5):729–736. DOI: 10.1161/01.ATV.0000063385.12476.A7

148. Ferreira-Machado SC, De Novaes Rocha N, Mencalha AL, De Melo LD, Salata C, Ribeiro AF, Da Silva Torres T, Mandarim-De-Lacerda CA, Canary PC, Peregrino AA, Magalhães LA, Cabral-Neto JB, Dealmeida CE. Up-regulation of angiotensin-converting enzyme and angtiotensin II type 1 receptor in irradiated rats. Int J Radiat Biol. 2010; 86(10):880–887. DOI: 10.3109/09553002.2010.492489 [PubMed: 20695764]

149. Yarom R, Harper IS, Wynchank S, van Schalkwyk D, Madhoo J, Williams K, Salie R, Genade S, Lochner A. Effect of captopril on changes in rats' hearts induced by long-term irradiation. Radiat Res. 1993; 133(2):187–197. [PubMed: 8438060]

150. Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Bolla M, Pol JF, Simons MY, Russell NS, Daemen MJ, Stewart FA. NO-donating aspirin and aspirin partially inhibit age-related atherosclerosis but not radiation-induced atherosclerosis in ApoE null mice. PLoS One. 2010; 5(9):e12874.doi: 10.1371/journal.pone.0012874 [PubMed: 20877628]

151. Seemann I, Gabriels K, Visser NL, Hoving S, te Poele JA, Pol JF, Gijbels MJ, Janssen BJ, van Leeuwen FW, Daemen MJ, Heeneman S, Stewart FA. Irradiation induced modest changes in murine cardiac function despite progressive structural damage to the myocardium and microvasculature. Radiother Oncol. 103(2):143–150. DOI: 10.1016/j.radonc.2011.10.011

152. Hoving S, Seemann I, Visser NL, te Poele JA, Stewart FA. Thalidomide is not able to inhibit radiation-induced heart disease. Int J Radiat Biol. 2013; 89(9):685–691. DOI: 10.3109/09553002.2013.788797 [PubMed: 23527854]

153. Boerma M, Roberto KA, Hauer-Jensen M. Prevention and treatment of functional and structural radiation injury in the rat heart by pentoxifylline and alpha-tocopherol. Int J Radiat Oncol Biol Phys. 2008; 72(1):170–177. DOI: 10.1016/j.ijrobp.2008.04.042 [PubMed: 18632215]

154. Sridharan V, Tripathi P, Sharma S, Corry PM, Moros EG, Singh A, Compadre CM, Hauer-Jensen M, Boerma M. Effects of late administration of pentoxifylline and tocotrienols in an image-guided rat model of localized heart irradiation. PLoS One. 2013; 8(7):e68762.doi: 10.1371/journal.pone.0068762 [PubMed: 23894340]

155. Kennedy AR. Biological effects of space radiation and development of effective countermeasures. Life Sc Space Res. 2014; 1:10–43. DOI: 10.1016/j.lssr.2014.02.004

Table 1

Key points of this article.

Section	Main outcomes	Reference
2.1	Exposure of the heart to high doses of ionizing radiation causes radiation-induced heart disease.	1–3
	A study in 2168 breast cancer survivors estimates that the rate of coronary events increases by 7.4% per Gy mean dose to the heart.	15
2.2	In addition to treatment, the cancer itself can cause metabolic alterations, cachexia, with an adverse impact on the heart.	22;23
	Work in animal models has recently begun to investigate mechanisms of heart failure due to cachexia.	24;25
2.3	The adverse cardiac effects of ionizing radiation and anthracyclines appear to be at least additive.	26–29
	There is a concern about potential interactions between ionizing radiation and recently developed targeted chemotherapies.	33–35
2.4	Experiments with local heart irradiation in animal models have resulted in calculations of α/β ratios of 2.5 – 3.7 Gy.	40–42
	Animal models indicate that the myocardial (micro)vasculature contributes to the development of radiation-induced heart disease.	50–57
	Animal models indicate that radiation injury in the heart and lung influence each other.	70–72
	Genetically modified atherosclerotic-prone mouse models are used to assess radiation-induced vascular alterations.	73–77
3.1	An increased incidence of cardiovascular disease is reported in various populations decades after low doses of photon radiation to a large part of the body.	84–93
3.2	Low-dose radiation exposures in animal models are associated with cardiac inflammation and endothelial cell alterations.	94–96
4.2	Mouse models of exposure to protons, iron ions, or silicon ions (0.15 – 0.5 Gy) show cardiac inflammatory infiltration, DNA oxidation, myocardial fibrosis and apoptosis. Effects of lower dose rates remain to be determined	104–107
	While charged particle exposures cause alterations in DNA methylation in the heart, their role remain to be determined.	113;114
5	Common circulating markers of cardiac injury have been tested to identify cardiac radiation injury in patients, with varying results.	125–131
	Current studies are focused on using high-througphut –omics technologies to identify novel biomarkers of radiation injury.	132;133
6.2	Anti-oxidants have been tested as potential countermeasures in animal models of radiation-induced heart disease, with varying results.	46;138–142
6.3	Both statins and ACE inhibitors reduce myocardial injury in animal models of radiation-induced heart disease.	143–146; 72;149