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Effects of ionizing radiation on the heart

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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 non-invasive 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.

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-

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

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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]

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 $\geq$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