Experimental Radiation-Induced Heart Disease: Past, Present, and Future

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Abstract

Radiation-induced heart disease (RIHD) is a serious side effect of radiotherapy for intrathoracic and chest wall tumors. The threshold dose for development of clinically significant RIHD is believed to be lower than previously assumed. Therefore, research into mechanisms of RIHD has gained substantial momentum. RIHD becomes clinically apparent ten to fifteen years after radiation exposure. Chronic manifestations of RIHD include accelerated atherosclerosis, cardiomyopathy, and valve abnormalities. Reducing exposure of the heart during radiotherapy is the only known method of preventing RIHD, and there are no approaches to reverse RIHD once it occurs. We use a combination of pharmacological and genetic animal models to determine biological mechanisms of RIHD. Major technological advances in small animal research have made this type of study more valuable. The long-term goal of this work is to identify targets for intervention in RIHD, thereby enhancing the efficacy and safety of thoracic radiotherapy.

It is truly a great honor to receive the Radiation Research Society's 2011 Michael Fry Award, which recognizes the contributions of a junior investigator to the field of radiation research. The main focus of my research has always been radiation-induced heart disease (RIHD). This side effect of radiation therapy captured my attention both as a clinical problem and from a radiation biology standpoint. Here, I am very pleased to have the opportunity to present and describe this line of research, as I hope to convey to you my fascination with it.

Radiation-induced heart disease is a long-term side effect of radiotherapy of thoracic and chest wall tumors when all or part of the heart is exposed to radiation. For instance, RIHD can occur among survivors of Hodgkin's disease (1,2) or breast cancer (3–5) because radiation therapy fields for those patients can encompass the heart. Manifestations of RIHD include accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves (6, 7). Both incidence and severity of the disease increase with higher radiation dose, larger volume exposed, younger age at time of exposure, and greater time elapsed since treatment. From a clinical perspective, the only approach to reduce late complications in the heart is through efforts to reduce cardiac exposure during therapy. Indeed, radiotherapy has undergone many such improvements over the last decades. Nonetheless, recent studies indicate that despite safety advances in radiotherapy some patients with Hodgkin's disease, lung, esophageal or proximal gastric cancers still receive either a high dose of radiation to a small part of the heart or a low dose to the whole heart (8–13). In addition, there is increasing use of concomitant therapies, with the consequences of many combinations yet to be determined. While certain cardio-toxic

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chemotherapeutic agents such as anthracyclines are known to exacerbate radiation injury in the heart, the effects of many other agents are still unknown.

Clinical studies into RIHD are complicated by the fact that the symptoms of RIHD are indistinguishable from those of other forms of heart disease. It is therefore difficult to unequivocally relate injury in the heart to prior radiation exposure, as opposed to radiation injury in certain other organ systems such as the lung or intestine. As a result, most of the time it is impossible to identify the individual patients for whom it is certain that radiation exposure caused their heart disease. Moreover, the incidence and severity of RIHD are influenced by many factors, most of which can be considered general cardiovascular risk factors such as hypertension, smoking, and obesity. To overcome these issues, some studies have compared outcomes between groups of left-sided and right-sided breast cancer patients. The anatomical location of the heart often results in left-sided breast cancer patients being exposed to higher doses to the heart than right-sided breast cancer patients, especially in tangential breast irradiation. Other risk factors are assumed to be evenly distributed between the two groups. Several studies have shown greater morbidity and mortality from cardiovascular disease after treatment for left-sided breast cancer patients compared to those patients treated for right-sided breast cancer, which illustrates the cardiotoxicity of ionizing radiation (5, 14–16).

Analyses of atomic bomb survivors show an increased incidence of cardiovascular disease in populations that have been exposed to low doses of ionizing radiation (17, 18). These outcomes significantly strengthened interest in determining the cardiovascular effects of low-dose ionizing radiation and rekindled debate over the magnitude of the threshold dose (a level below which no effect would be obtained) (19–22). Based on these studies and on studies in other epidemiological cohorts, some researchers have suggested that doses of 1 Gy or lower could result in increased incidence of heart disease (23–25). However, as previously mentioned, the existence of many confounding factors related to cardiovascular disease make it difficult to draw affirmative conclusions about the minimum dose that may cause clinically relevant injury in the heart and vasculature. Nevertheless, these outcomes have raised the issue of possible cardiovascular effects of exposure to ionizing radiation during space flights or other scenarios of low-dose exposure.

Pharmacological methods to prevent or reverse RIHD in humans are not yet available. Therefore, pre-clinical (*in vitro* or animal) studies have been used to unravel biological mechanisms of RIHD, with the ultimate goal of identifying potential targets for intervention (pharmacological or other) that could eventually be translated to human subjects. Studies using these models have shown that local heart irradiation causes long-term changes in cardiac function and adverse myocardial remodeling in dogs, rabbits, rats, and mice (26–30). Spontaneously hypertensive rats or animals on a high-fat diet have been used to study radiation-induced accelerated atherosclerosis in coronary arteries (31, 32). Some of the histopathological changes in pre-clinical models, such as myocardial degeneration and fibrosis, are described in human cases of RIHD after exposure to doses of ~30 Gy and above (1, 2, 33–35). Although clinical and pre-clinical data on the cardiovascular effects of lower radiation doses are growing (9, 18), there is still uncertainty with regard to biological mechanisms and species-specific threshold doses.

I was familiarized with the topic of RIHD during my graduate studies in the laboratory of Jan Wondergem, at the Leiden University Medical Centre in The Netherlands. Dr. Wondergem provided his graduate students much freedom in the design of their experiments, which gave us a positive sense. We determined that histopathological changes in our rat heart model of local heart irradiation could be identified more easily in longitudinal heart sections compared to one midventricular section (36). We observed that a

dose-dependent increase in the number of mast cells in the heart, coinciding with histopathological signs of radiation injury (36). Mast cells are mostly known for their adverse role in allergic reactions, but they also play an important role in tissue homeostasis and remodeling. Hence, the potential role of mast cells in RIHD captured my attention.

Shortly before my graduation, Dr. Wondergem put me in contact with Dr. Martin Hauer-Jensen at the University of Arkansas for Medical Sciences (UAMS), and I was selected to do my postdoctoral studies in his laboratory. Much of what I know today about experimental design and scientific writing I learned during those postdoctoral years. In addition, I realized that I my interest in RIHD remained strong. I was very fortunate that the Department of Pharmaceutical Sciences in the College of Pharmacy at UAMS offered me a faculty position to further develop projects to identify biological mechanisms of and potential interventions for RIHD.

We studied the mechanistic role of mast cells in radiation injury in the heart with the use of a genetic mast cell-deficient rat model (37). After local heart irradiation, mast cell-deficient rats showed more severe changes in *in vivo* and *ex vivo* cardiac function, more pronounced myocardial deposition of collagen III, and less myocardial degeneration than their mast cell-competent littermates (38) (Fig. 1). From these somewhat surprising results we concluded that mast cells played a predominantly protective role in RIHD in the rat. Mast cells may have cardioprotective effects through several mechanisms, one of which involves the kallikrein-kinin pathway. Kinins are peptide hormones that may aggravate the effects of certain cardiac events such as myocardial infarction (39), but they also display several cardioprotective properties, partially through the induction of nitric oxide (40–42). Mast cell-derived proteases enhance the release of kinins from their precursors, which are high-molecular-weight and low-molecular-weight kininogen (43,44). We recently used a rat model deficient in the secretion of kininogens (45, 46) to start investigating the role of the kallikrein-kinin pathway in RIHD. Preliminary results indicated that early cardiac functional events and late changes in inflammatory infiltration after local heart irradiation are less pronounced in kininogen-deficient rats (unpublished data).

Mast cells may also display protective properties by releasing proteases that break down endothelin-1 (ET-1) (47). Interestingly, we found that left ventricular ET-1 gene expression was upregulated after local heart irradiation in mast cell-competent rats, but not in mast cell-deficient rats (48). These results sparked our interest in a potential pharmaceutical intervention in RIHD that would inhibit the effects of ET-1 in the heart. We tested the effects of bosentan, a dual inhibitor of the ET-1 receptors ETA and ETB, in our rat model of local heart irradiation. The effects of bosentan on late cardiac radiation injury in the rat were minimal, which may have been caused by the opposing roles that ETA and ETB are known to play in cardiovascular function and disease (48, 49).

Another pharmaceutical intervention that we are testing is the cyclic AMP phosphodiesterase inhibitor pentoxifylline. Studies by us and others suggest that pentoxifylline in combination with α-tocopherol can improve cardiac function and reduce adverse cardiac remodeling in the rat when administration starts before irradiation, also when administration starts several months after local heart irradiation (50,51) (Fig. 2). Some of our current studies focus on the effects of compounds that are related to pentoxifylline and α-tocopherol.

Small animal models of local heart irradiation have improved greatly. We are now able to perform real-time, image-guided localized irradiation that allows more precise targeting of the organ or tissue of interest (Fig. 3) (52). *Ex vivo* perfused heart preparations have long been used in biomedical research and are continuously updated to provide important insight

into cardiac function and disease including RIHD (Fig. 1) (38, 53, 54). In addition, in the last decade tremendous advancements have been made in the development of noninvasive imaging technologies for use with small laboratory animals. High-resolution ultrasound, magnetic resonance imaging, and single photon emission computed tomography are only a few examples of tools that are now available to closely follow cardiac function in small laboratory animals (55, 56). Several of these technologies have been included in radiobiological studies of cardiovascular radiation injury (50, 57). Future developments will hopefully bring pre-clinical models closer to clinical applications. These are very exciting times to be involved in this type of research.

Once more I would like to end by expressing my deep appreciation for being honored with the 2011 Michael Fry Research Award. These are not the easiest times for junior investigators or those who are considering a career in the research. This award serves as a great motivation for young investigators to continue with their fascinating work in radiation research. One of the highlights since my nomination was an e-mail from Dr. Fry with his congratulations. The Radiation Research Society is one of a kind in this respect.

Acknowledgments

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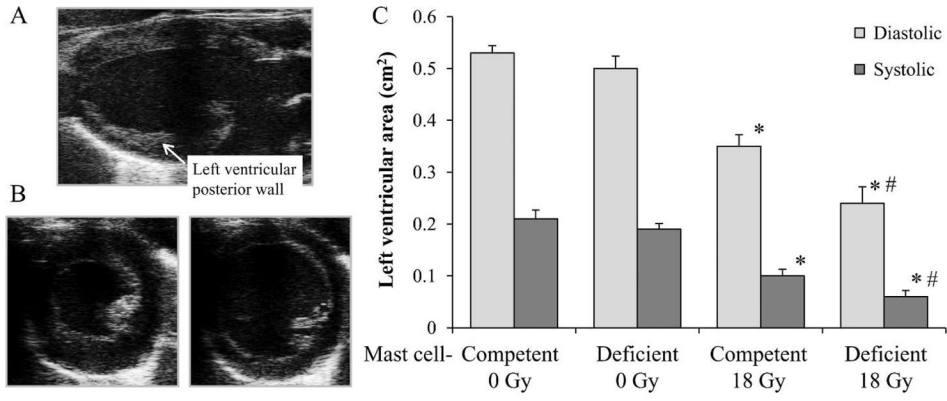
FIG. 1.

In vivo ultrasound at 6 months after local heart irradiation in mast cell-deficient and mast cell-competent rats. Panel A: Long axis view of a rat heart. Panel B: Short axis views of hearts in systole (left) and diastole (right) were used to measure left ventricular area. Panel C: Reductions in left ventricular diastolic area and left ventricular systolic area were more severe in mast cell-deficient rats. Data are shown as average ± SEM, $n = 10$, $*P < 0.05$ irradiated compare to sham irradiation, $\#P < 0.05$ mast cell-deficient compare to mast cell-competent. This figure presents data from (38).
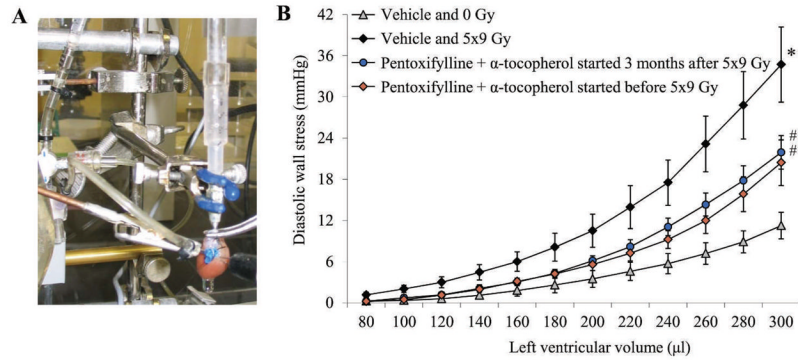
FIG. 2.

Effects of pentoxifylline and α-tocopherol on *ex vivo* cardiac function measurements at 6 months after local heart irradiation. Panel A: The Langendorff *ex vivo* perfused heart preparation is commonly used for investigation of cardiac physiology and disease. The picture reflects a rat heart in a Langendorff apparatus. A left ventricular balloon is connected to a pressure transducer to obtain real-time pressures generated inside the left ventricle. Panel B: Treatment with pentoxifylline and α-tocopherol reduced left ventricular diastolic wall stress at 6 months after local heart irradiation with 5 daily fractions of 9 Gy. Data are shown as average ± SEM ($n = 6–8$). *$P < 0.05$ irradiated compared to sham irradiation, #$P < 0.05$ pentoxifylline + α-tocopherol compared to vehicle. This figure presents data from (50).
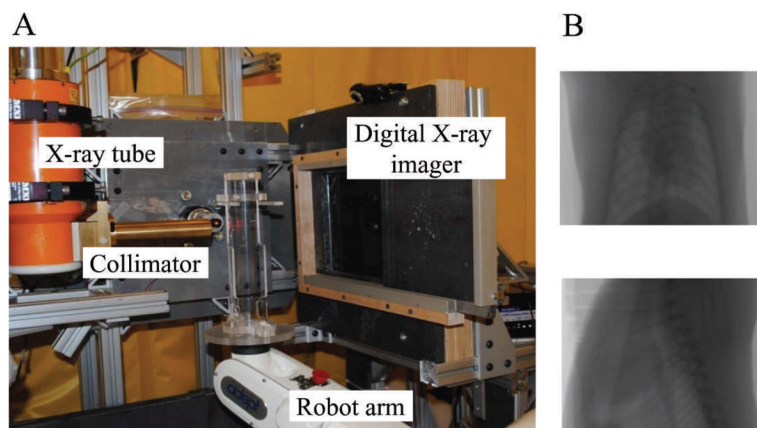
FIG. 3.
The Small Animal Conformal Radiation Therapy Device (SACRTD) (University of Arkansas for Medical Sciences, Department of Radiation Oncology) allows precise image-guided irradiation of the target of interest with minimal exposure of surrounding tissues in small laboratory animals. Panel A: Set-up for localized heart irradiation in the rat. Vertical positioning of the animal allows for X-ray imaging of the chest to delineate the heart. Panel B: Rat chest X rays taken in vertical position at different angles for heart delineation.