



Radiosensitivity of the Heart



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Abstract

Epidemiological and clinical evidence confirm that hearts are sensitive to ionizing radiation (IR). They are even more radiosensitive than formerly believed. Mechanistic studies show that the radiosensitivity is not due to the heart muscles but mainly to the cardiovascular system (CV). In fact, endothelial cells of the CV appear to be particularly affected by doses much lower than those used in radiation therapy. Also, low dose rate IR has been shown to induce premature senescence in endothelial cells. Thus, even relatively low « out-of-site » radiation doses in the treatment of breast tumours by radiation therapy may affect regular heart functions and cause heart disease. The present mini-review recalls recent findings suggesting that radiation protection of the heart even to relatively low radiation doses remains an important issue.

Keywords: Cardiovascular disease; Ionizing radiation; Low dose; Low dose rate; Radiation therapy; Epidemicology; Nuclear workers; Patients

Abbreviations: IR: Ionizing Radiation; RT: Radiation Therapy; LNT: Linear no-Threshold; ICRP: International Commission on Radiation Protection

Introduction

It is known from epidemiological and clinical studies that the heart is an organ at risk when exposed to ionizing radiation (IR). For example, long-term outcomes of radiotherapeutic treatments of Hodgkin's disease and breast cancers (typically 10-15 years after exposure) may include cardiovascular disease (CVD) as a consequence of radiation damage to the, the, coronary arteries, valves and the vascular system of the heart [1-3] noted that high radiation doses (>5Gy) increase the risk of CVD. The gravity of the IR-induced tissue damage depends on the heart volume exposed and the total dose (> 30-35 Gy) applied in radiation therapy (RT) [4].

Epidemiological findings

In recent years, epidemiological analysis during the Life Span Study of Hiroshima-Nagasaki A-bomb survivors 1950-2003 [5] as well as studies on nuclear workers revealed that even low and moderate radiation doses below 0.5Gy may be responsible for CVD [6-8]. In line with this, ICRP considers that in humans a dose of 0.5Gy may cause in 1% of the individuals cardiovascular and cerebrovascular diseases > 10 years after exposure to IR, and this in a population in which already 30 and 50% suffer from these diseases [9,10]. Available epidemiological data point to a linear no-threshold (LNT) response for CVD [2, 8]. Indeed, significant increases in the risk of CVD have been found for IR doses of 0.5Gy and above. Below these doses, epidemiological studies have difficulties to provide significant data because of statistical limitations. Thus, for doses below 0.5Gy, the risk is not yet well established, and the

dose response may include non-linearities and thresholds (below 0.5mGy), as supported by recent fundamental and mechanistic studies [2,8,11].

Mechanisms involved in CVD

For the induction of CVD the heart itself is not the most radiation sensitive structure. The adult heart counts mainly non-proliferating cardiomyocytes (around 70%) together with slowly dividing endothelial cells covering the inner surface of the vascular system and the heart [2,3]. Thus, endothelial cells appear to be clearly the most critical targets for radiation-induced CVD [2,7,8]. Studies in mice and rats suggest that IR-induced cardiotoxicity involves the cardiomyocytes, smooth muscle cells, endothelial cells and leukocytes [2]. High total body doses (10Gy) increases the risk of coronary sclerosis, degeneration of heart structure and function in rats [12]. In mice, IR induces persistent alterations in cardiac mitochondrial functions [13,14]. In addition, also high LET radiation at 0.5, 2 and 5Gy induces a persistent DNA damage response with down regulation of cell cycle genes and upregulation of some genes involved in oxidative stress, DNA repair, apoptosis and cell-cell signaling in endothelial cells [15]. In mice, unrepaired single-strand breaks (related to XRCC1 deficiency) appear to be associated with the up-regulation of inflammatory cytokines and an increase in inflammatory cells in the heart causing cardiac failure [16]. Primary human vascular endothelial cells (HUVEC) show apoptosis after exposure to 0.5Gy [17], and also RhoGDI and NO signaling pathways are affected leading to longterm premature endothelial dysfunction

[18]. This seems to fit also to epidemiological data indicating a risk of CVD at 0.5Gy [8]. At low doses of IR the metabolic pathways of p53/p21 (inhibition of replication), PI3K/AKT/mTOR and IGF1R are involved in the radiation response of endothelial cells [19,20]. Chronic low dose exposures (at dose rates from 1.4 to 4.1mGy/h) and total doses from 0.7 to 4.13Gy lead to premature senescence of endothelial cells in vitro due to the inactivation of PI3K and MAP kinase signaling pathways [19]. In this process, also non-coding miRNAs are involved [21]. IR induced senescence is clearly non-linearly related to changes in dose rate [19]. Single doses of X-rays (0.05, 0.5 and 2Gy) have been shown to induce dose- and time dependent transcriptional changes in immortalized human coronary artery endothelial cells connected with atherosclerosis-related processes [22]. This suggests that also low doses of 50mGy may be detrimental for heart function. Interestingly, DNA double strand breaks, reactive oxygen species and the antioxidant enzyme SOD are induced in a non-linear fashion in the low dose range (0.5 and 0.7Gy) [23].

Considering mouse and human data, a model has been proposed [2]: IR is thought to affect important biological pathways concerning cardiomyocytes (inactivation of PPAR alpha, reduced fatty acid oxidation, increased inflammatory response and mitochondrial ROS production), smooth muscle cells (IR affecting paxillin/integrin, actin signaling, cytoskeletal organization and intercellular junctions) and endothelial cells (inactivation of PI3K, MAP kinase and Rho signaling pathways, cytoskeletal disorganization), decreased NO production and bioavailability as well as enhanced leukocyte migration associated with increased expression of cell adhesion molecules (ICAM1, VCAM-1 and E-selectin) and interruptions of cell-cell junctions (see for review 2).

Discussion

This brief review recalls some recent findings concerning the radiosensitivity of the heart. As outlined above, the heart mainly consists of cardiomyocytes that are in their adult state non dividing and thus relatively radioresistant, whereas endothelial cells are proliferating cells and more radio-sensitive. Endothelial cells belonging to the cardiovascular system are also sensitive to low dose chronic radiation, mostly leading to premature senescence but not to apoptosis [17]. They are thought to contribute to the formation of atherosclerotic plaques after RT [24]. The mechanisms of IR induction of CVD are clearly multifactorial and several important pathways are already known to be involved. However, suitable biomarkers and knowledge on low dose and low dose rate effects of IR also in epidemiological cohorts are still very scarce [2,8].

Conclusion

As shown above, proper heart function is not so much affected by the radiation damage inflicted on cardiomyocytes but much more so by the damage inflicted on the endothelial vascular cells. Some of the results reported here suggest that dysfunctions of the heart may well be induced by much lower IR doses (50mGy) than previously thought (0.5Gy). Thus, out-of-field effects in RT

and Hadron therapy as well as exposures during space missions are likely to be responsible for the occurrence of long-term late effects such as CVD. Extrapolations from high to low dose IR effects do not seem to be fully applicable because the dose dependency of IR-induced heart disease is not necessarily linear at low doses and low dose rates [2,8]. Clearly, more knowledge is needed on the mechanisms involved. More interdisciplinary and well-integrated epidemiological and mechanistic studies are essential to further elucidate CVD induction by low doses of IR [25]. From such studies, new protective measures against CVD induction are likely to emerge for IR-exposed populations such as nuclear workers and patients.

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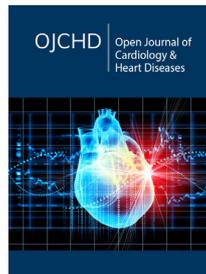
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