Delayed effects of acute radiation exposure on the cardiovascular system using a murine model of the hematopoietic acute radiation syndrome

Beatrice Thungu[1], Miguel Ortiz[1], Joseph L. Unthank[1, 2], Christie M. Orschell[3], Steven J. Miller[1, 2]
Departments of [1]Surgery, [2]Cellular and Integrative Physiology, and [3]Medicine
Indiana University School of Medicine
Indiana University-Purdue University Indianapolis

Introduction. Exposure to high level radiation from accidents or belligerent activities results in acute and chronic organ damage. The hematopoietic system is the most sensitive organ to radiation damage (2-10 Gy) and results in the hematopoietic acute radiation syndrome (H-ARS). Survivors of H-ARS are plagued months to years later with delayed effects of acute radiation exposure (DEARE), characterized by chronic illnesses affecting multiple organ systems. Previous results using the murine H-ARS model showed numerous kidney and heart DEARE-related pathologies similar to humans, including tissue fibrosis and elevated blood urea nitrogen. The goal of this study was to utilize the murine H-ARS model to determine possible roles for abnormal iron metabolism, inflammation, oxidant stress, and senescence in the development of cardiac DEARE.
Methods. Mice (C57BL/6; 12 week-old) received total body irradiation (TBI: ~8.5-8.7 Gy, ^{137}Cs, $LD_{50}$to LD_{70}) and hearts were harvested at various times post-TBI from H-ARS survivors. Paraffin tissue sections were stained with hematoxylin/eosin or Perls Prussian Blue, or reacted with a macrophage-specific antibody (F4/80). Total RNA was purified from fresh tissue and changes in mRNA expression were assessed by real-time PCR for the senescence marker p16 and NADPH oxidase subunits Nox2, Nox4, or p47phox.
Results/Significance. Compared to age-matched non-irradiated controls (NI), tissue iron deposits were increased in irradiated (IR) hearts at 4 months, and progressively declined with time post-TBI. Numbers of macrophages were greater in IR vs. NI sections at all time points and decreased with time post-TBI. Nox2 and Nox4 mRNA expression was increased at both 9 and 21 months post-TBI, but p47phox increased only at 21 months. Expression of p16 in IR heart was increased at 7, but not at 22 months post-TBI. Taken together, the results indicate abnormal iron metabolism, inflammation, oxidant stress, and early senescence may contribute to development of cardiac DEARE.