Task Book Report Generated on: 04/16/2024

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Project Title: Indizing Radiation and its Effects on Cardiovascular Function in the Context of Space Fight Program/Discipline: IIUMAN RESEARCH Program/Discipline: HUMAN RESEARCH Program/Discipline: HUMAN RESEARCH Frogram/Discipline: HUMAN RESEARCH Frogram/Discipline: HUMAN RESEARCH Frogram/Discipline: HUMAN RESEARCH Frogram/Discipline: HUMAN RESEARCH Frogram Riscoarch Program Elements: (1) SR-Space Radiation health Frogram Research Program Riscoarch Ul Sardiovascular-Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes Space Biology Element: None Space Biology Element: None Pl Famall: Space Biology Element: None Pl Famall: Space Biology Special Category: None Pl Famall: Space Biology Space In None Pl Famall: Space Biology Special Category: None Pl Famall: Space Biology Special Category: None Pl Famall: Space Biology Special Category: None Pl Famall: Space Biology Space In None Pl Famall: Space Space Pl Famall: Space Biology Space Research Ford Mission Performance and Health Space Biology Space Research Ford Mission Performance and Health Research Ford Mission Performance Adaptations Contributing to Adverse Fyelogy Balance Research Ford			Task Last Opuateu:	F1 0//24/2007
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An appropriate examination of the health risks associated with manned space flight necessitates an understanding of the molecular consequences of exposure to the radiations encountered in space. Human radio-epidemiologic data and animal studies indicate that irradiation of the heart can cause a spectrum of cardiovascular complications. The mechanisms suggested for these alterations are chronic inflammation induced by oxidative stress. It is well known that ionizing radiation (IR) produces biological damage by direct effect on DNA and indirectly by generation of reactive oxygen species (ROS) in the cellular milieu. The xanthine oxidoreductase (XOD) system is one of the major sources of free radicals in biologic systems. Since the XOD system is present primarily in the reduced XDH form in normal tissue, the production of free radicals is negligible. However, emerging data demonstrates that IR irreversibly converts the xanthine dehydrogenase (XDH) to xanthine oxidase (XO) leading to amplification and persistence of IR induced, ROS dependent cell damage. It is well known that ROS interferes with cellular signaling (nitrosylation and phosphorylation) and is pro-apoptotic (releases mitochondrial cytochrome-C and activates apoptotic pathways). One of the postulated mechanisms of radiation related tissue injury is endothelial cell damage. However little is known regarding other cellular and molecular targets in the pathophysiology of radiation-induced cardiovascular system dysfunction. Furthermore, little is known regarding the response of endothelial cells and cardiac myocytes to high LET (linear energy transfer) radiation. In this proposal we intend to use established in vivo and in vitro bioassays to characterize the radiation response to charged particle exposure. Furthermore, mechanistically we will focus on the interaction between ROS and nitric oxide (NO) pathways in the regulation of myocardial and vascular structure and function following oxidative stress (OS) induced by high LET radiation. Our group have demonstrated the important reciprocal interaction between NO and O2- (derived from XO) in the regulation of myocardial contractility and endothelial function. We will utilize our expertise to determine the effect of radiation on these important signaling pathways in the cardiovascular system. We hypothesize that charged particles will produce an acute oxidative stress event with cellular injury and possible death with early and late consequences that are dose, LET, and time-dependent. Endothelial and myocardial dysfunction represent integrated cumulative indicators of this cellular injury. We further hypothesize that radiation-induced endothelial and myocardial contractile dysfunction results from the specific imbalance in NO signaling induced by increased ROS production. In addition, we hypothesize that the XO, NOS (Nitric Oxide Synthase), arginase pathways play a critical role in the response to radiation-induced OS. Therefore, our Specific Aims are:

Hypothesis 1: Charged particles (iron ions) will produce an acute oxidative stress event characterized by cellular and tissue injury expressed by endothelial and myocardial dysfunction.

Specific Aim 1: Time- and dose-responses for multiple indices of endothelial and myocardial function will be established in adult Wistar rats exposed to 600 MeV/n Fe (iron) beams at the NASA Space Radiation Laboratory, Brookhaven National Laboratory (BNL). Animals will studied non-invasively and tissues will be collected for histological, functional and molecular analyses using methods established in our laboratory at different time points. Indices of normal tissue function and homeostasis to be investigated include:

a) Endothelium: 1) vascular stiffness by Doppler effect using pulse wave velocity; 2) endothelial function in isolated vascular ring tissue and microvessels; 3) markers of apoptosis in vascular tissue.

b) Heart: 1) myocardial contractile function and contractile reserve in vivo; 2) contractility and contractile reserve in vitro in isolated cardiac myocytes; 3) markers of apoptosis in cardiac tissue (as above).

Hypothesis 2: Iron irradiation-induced endothelial and myocardial contractile dysfunction results from the specific imbalance in NO signaling induced by increased ROS production.

Specific Aim 2: To determine the whether low-fluences of iron ions alter the balance in NO signaling as a function of increased ROS production thereby impairing endothelial and myocardial function. Radiation doses will be selected based on results of Aim 1 and animals will be sacrificed for detailed analyses at various time points as in Aim 1. Vascular and heart tissues from adult Wistar rats exposed to 600 MeV/n Fe ions will be collected and we will measure:

1) NO bioavailability in vascular rings and NOx in plasma, 2) NOS activity using fluorescent dye in heart and blood vessels, 3) ROS levels using chemiluminescence and fluorescence bioassays, 4) Nitroso-tyrosine expression in vascular and cardiac tissue using Western blot analysis.

Hypothesis 3: XO, NOS, and arginase pathways play a critical role in the cardiovascular response to HZE particle radiation

Specific Aim 3: Rats will be exposed to 600 MeV/n iron ions to determine the specific roles of XO, NOS and arginase in modulating cellular and tissue response to charge particle-induced oxidative stress. Radiation doses will be selected based on results of Aims 1-2 and animals will be sacrificed for detailed analyses at various time points as in Aim 1 for the following endpoints:

1) expression and activity of NOS, Arginase and XO at an RNA and protein level using quatitative PCR, Western blot and immunohistochemistry in heart and blood vessels; 2) Enzyme activity using specific inhibitors of each of the enzymes both alone and in combination with our in vitro vascular ring bioassay and isolated cardiac myocytes; 3) The effect of specific inhibitors on bioassays of ROS and NO (as in Aim 2). Hypothesis 4: Enzyme inhibitors and ROS scavengers will modulate early and late cardiovascular toxicity of low-fluences of iron ions.

Specific Aim 4: To determine if enzyme inhibitors and ROS scavengers can modulate the cardio-vascular effects of iron ions, Wistar rats and/or tissue preparations will be treated with enzyme inhibitors or ROS scavengers prior to and following 600 MeV/n Fe beam irradiation. We will use in vivo and in vitro bioassays of endothelial and myocardial function to test whether the XO inhibitor allopurinol, and the arginase inhibitors S-(2-boronoethyl)-L-cysteine (BEC), or difluoromethylornithine (DFMO) will attenuate radiation-induced cardiovascular effects.

While IR may have parallel effects on peripheral vasculature endothelium and cardiac contractile tissue, the interaction between the blood vessels and heart (ventricular-vascular coupling) has further profound effects on each of these systems. It is for this reason that an approach which incorporates both in vivo (integrated cardiovascular measures such as PWV and P-V loops), as well as isolated cellular and tissue measures of function is so important. Our methodologies will allow us to assess the contribution of each component (heart and vasculature) to the integrated system response to charged particle exposure.

Task Description:

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Rationale for HRP Directed Research	
Research Impact/Earth Benefits:	
Task Progress:	Our data strongly supports the hypothesis that a single, high-dose gamma-irradiation can induce endothelial dysfunction. We have confirmed that this phenomenon is observed. The effects observed two-weeks post-radiation include: increased in vivo aortic stiffness and impaired endothelial-dependent vasorelaxation. In addition, we demonstrate a substantial increase of XO activity and a restoration of vasorelaxation after XO-specific inhibition. Furthermore, we have demonstrated that ROS production is increased in irradiated rats and that the source of the ROS is most likely XO. Finally, and most importantly, administration of Oral Oxp, the XO inhibitor results in a significant attenuation of endothelial dysfunction and prevents the development of increased vascular stiffness in irradiated rats. Thus, radiation insult can produce endothelial dysfunction and vascular stiffening, with the XO upregulation system being a probably contributory mechanism. More importantly, xanthine oxido-reductase appears to be a valuable target for radiation-induced vascular pathology. In summary, we have demonstrated that: 1) Both conventional gamma and Fe56 ion radiation results in significant endothelial dysfunction. 2) This endothelial dysfunction results in a significant increase in vascular stiffness. 3) Endothelial dysfunction results in part from an increase in ROS production. 4) The source of the ROS is predominantly but most likely not exclusively xanthine oxidase. 5) Inhibition of XO prior to following radiation with Oxp results in a significant improvement in endothelial function and a decrease in vascular stiffness in irradiated rats. Thus, XO appears to be a critical target in countermeasure design for radiation-induced cardiovascular dysfunction.
Bibliography Type:	Description: (Last Updated: 01/13/2014)
Articles in Peer-reviewed Journals	Soucy KG, Lim HK, Benjo A, Santhanam L, Ryoo S, Shoukas AA, Vazquez ME, Berkowitz DE. "Single exposure gamma-irradiation amplifies xanthine oxidase activity and induces endothelial dysfunction in rat aorta." Radiat Environ Biophys. 2007 Jun;46(2):179-86. Epub 2007 Jan 26. PMID: 17256177 , Jun-2007
Articles in Peer-reviewed Journals	Berkowitz DE. "Myocyte nitroso-redox imbalance in sepsis: NO simple answer." Circ Res. 2007 Jan 5;100(1):1-4. Review. PMID: 17204656 , Jan-2007