DIVERSE SEQUENCE AND FRACTIONATION OF ^{1}H VS. A SINGLE ^{56}FE-IR INDUSES DRAMATICALLY DIFFERENT BIOLOGICAL RESPONSES IN THE HEART

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BACKGROUND: Astronauts will be exposed to IR composed of a spectrum of low-fluence protons (^{1}H) and high charge and energy (HZE) nuclei iron (^{56}Fe). During GCR each cell in an astronaut's body is being traversed by a ^{1}H about every 3 days and HZE nuclei about every few months. Hence, the traversal sequence of cells with an ion in space is random and 99% of the space IR environment consists of ^{1}H and helium (^{2}He). Therefore, a scenario that a cell in human body may be hit first with several ^{1}H particles then with HZE or an HZE then several ^{1}H should be equally probable. The effect of cosmic IR during and after space flights on cardiovascular (CV) system is unknown. Therefore it is important to evaluate the effects and potential CV risks caused by space IR. We hypothesized that: ***(1)*** the effects of the fractionated/sequential ^{1}H- and ^{56}Fe-IR regimens may be long-lasting and are IR type, fractionation and sequence-dependent; and ***(2)*** fractionated/sequential IR regimens may increase CV risks in the aging heart (**IR+AGING**) and affect the processes of recovery after a possible adverse CV event, such as acute myocardial infarction (AMI), commonly known as a heart attack (**IR+Aging+AMI**). Accordingly, we present here the data on the effects of the fractionated-sequential ^{1}H- and ^{56}Fe-IR regimens in the hearts of 8-9 months old C57BL/6 mice over 1 and 3 months after initial exposure.

METHODOLOGY: We evaluated the effect of low-dose fractioned and sequential IR dose regimens in 8-9 month old C57BL/6 male mice in the following groups: **Group 1**- control; **Group 2** - ^{1}H 17 cGy x 3 every 2 days; **Group 3** - ^{1}H 17 cGy x 3 every 2 days/^{56}Fe 15 cGy; **Group 4** - ^{56}Fe 15 cGy/^{1}H 17 cGy x 3 every 2 days at the energy of 1 GeV/n, for both ions. Cardiac function was assessed by echocardiography (ECHO) and hemodynamic measurements (HEMO). AMI was induced by ligation of left anterior descending (LAD) coronary artery 1 and 3 months post-IR. IR-induced cardiac fibrosis and cardiac remodeling (formation of post-AMI scar in the heart tissue), was assessed by H&E and Masson's Trichrome staining on day 28 post-AMI.

RESULTS: In **IR + 1 and 3 months of mouse AGING** group, fractionated ^{1}H-IR alone or fractionated ^{1}H-IR followed by a single ^{56}Fe-IR *DID NOT* have any negative effect on post-IR mice survival and cardiac function, in contrary, mix ion fractionated/sequential IR regimens *DECREASED* cardiac fibrosis, at least 1 month post-IR. However, when a single ^{56}Fe-IR was followed by a fractionated ^{1}H-IR, there were several *NEGATIVE* developments: ***(a)*** post-IR survival was *DECREASED* >20% at 1 and 3 months; ***(b)*** left ventricular end diastolic pressure (LV EDP) was *INCREASED* at 3 months (suggesting reduced relaxation function) and Max LV pressure was *DECREASED* at 1 month (reduced contractile function), both are indicative of negative hemodynamic developments in the heart of the surviving fraction of mice in **^{56}Fe/^{1}H+^{1}H+^{1}H-IR** group.
In **IR + 1 month of mouse AGING + AMI** group, fractionated ^{1}H-IR alone or ^{56}Fe-IR followed by fractionated ^{1}H-IR *DID NOT* have significant negative effect on post-AMI survival and cardiac function at 1 month post-IR. However, when fractionated ^{1}H-IR was followed by a single ^{56}Fe-IR, there were several *NEGATIVE* developments – ***(a)*** a 24% decrease in post-AMI survival at 1 month; ***(b)*** LV EDP was *DECREASED* at 1 month (altered relaxation function); ***(c)*** post-AMI cardiac fibrosis was *INCREASED*. These findings are indicative of significant negative effects for post-AMI recovery after **^{1}H+^{1}H+^{1}H/^{56}Fe-IR** regimen in the surviving fraction of mice in this group

SUMMARY. Taken together, our findings in mix ion fractionated/sequential IR groups strongly suggest dramatically different biological responses due to diverse sequence and fractionation of ^{1}H vs. single ^{56}Fe-IR. In **IR + AGING** group - **^{56}Fe/^{1}H+^{1}H+^{1}H-IR** had significant negative effects on the heart during aging, whereas ^{1}H+^{1}H+^{1}H/^{56}Fe-IR and ^{1}H+^{1}H+^{1}H-IR had no negative effect, at least up to 3 months post-IR. In **IR + AGING + AMI** group, in contrary to IR + AGING group **^{1}H+^{1}H+^{1}H/^{56}Fe-IR** regimen presented significant degenerative CV risk for the recovery of the heart after AMI, whereas both ^{56}Fe/^{1}H+^{1}H+^{1}H-IR and ^{1}H+^{1}H+^{1}H-IR had no negative effect on AMI recovery at least up to 1 month post-IR. These findings emphasize the necessity to determine underlying molecular mechanisms responsible for this significant mix ion fractionation and sequence-dependent divergent responses in the heart during aging and in case of a possible adverse cardiovascular event.