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REVIEW – OPEN ACCESS

Adverse Effect of the Neuronal Cells and the Coronary Artery Endothelium in Extreme Environments—Roles of Advanced Molecular Imaging Markers

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ABSTRACT

Extreme environment is an inhabitable ambience affecting the normal physiology of the human body. Radiation personnel who travel to low earth orbit for long space journey may face a detrimental effect of the influx of radiation source during extravehicular activities that lead to chronic endothelial injury of the underlying cells. In addition, the low pressure oxygen (hypobaria) of the space station environment could potentially underpin cellular changes in sensitive organ, i.e., the brain cells. These factors could pose a threat to the reconditioning of the vital functioning organs. Spatial oxygen concentration will decrease to >20% to a higher altitude of 5300 m, whereas insulin and C-peptide concentrations are increased by 200% during the endurance stay at the altitude for 2 weeks. Therefore, the potential increase in fasting insulin, homeostatic model assessment of insulin resistance, and glucagon influences the elevation of markers of oxidative stress and the inflammatory markers. The use of advance molecular imaging biomarkers that range from the inflammatory markers, hybrid imaging markers, such as functional magnetic resonance imaging, and genetic markers could discover the early changes of the cellular reprogramming in cells that could avert the ongoing process of oxidative stress injury via mitigation programs and preventive measures. In this review, specific documentation on the various ambiences of the physiological environment, i.e., hypobaria, chronic ionizing radiation, and hypergravity pull, would be discussed with the potential molecular imaging markers used to exploit the early physiological, inflammatory, and genetic deconditioning that underpin the cellular changes leading to the untoward effect on oxidative stress.

Keywords: Endothelium, extreme environment, molecular markers, 82Rb, spygmomanometer

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Radiation in LEO

Galactic cosmic rays (GCR) and solar emissions are mostly protons and iron, silicon, oxygen, and carbon that are of high-energy elements. They are abundant of particles with energies ranging from 100 MeV/nucleon up to approximately 1 GeV/n (1). In low earth orbit (LEO), astronauts are exposed to GCR and high-energy nuclei, protons, and electrons in Earth's radiation belts, and the low to medium energy protons are found during the solar particle events.

Chronic radiation exposure in space occurs at a dose rate of 4.8 mSv/day for which heavier high atomic number and energy (HZE) ions, such as 56Fe, yield a complex tissue damage to DNA molecules that challenges cellular repair and recovery (2, 3). Charged particles traversing the spacecraft shielding and thence the nuclear interactions occur as they traverse the varied physical substance of the built material. These will lead to the fragmentation of particles of dampened energy but higher linear energy transfer (LET) that contributes to the spacecraft background radiation (range 0.18–1.14 cGy) (4). Astronauts in LEO would receive 50–100 mSv over a 6–12-month stay that is predominantly attributed to the GCR (5).

Dose rates to the blood forming organs are deemed to be exposed by the course of the solar cycle at a dose rate ranging from 0.4 to 1.1 mSv/day. HZE ions could cause a detrimental effect on the DNA molecules with deconditioning of the cellular repair and recovery. The search on the potential molecular biomarkers, such as microRNA (miRNA), and their role in cardiovascular diseases (CVDs) during the space flight requires more discoveries on the radiation burden exposed to the in-flight astronauts. The expression and correlation of novel biomarkers in angiogenesis could contribute to the understanding of the early diagnosis and prognosis of the development of atherosclerosis associated with radiation exposure especially during extravehicular activities or during space flight at the deeper orbital altitude. The understanding of the pathway of biogenesis and the regulation of CVDs by existing biomolecular, such as protein, enzyme on metabolomics associated with novel biomolecular markers will enhance the current intervention in the treatment of ischemic heart disease (IHD) among the astronauts during the different space flight durations.

Radiation-Induced Endothelial Injury

Hypercholesterolemia is an important predictor for metabolic syndrome. The prevalence of IHD ensues from the orchestration of cellular changes in oxidative stress that underpin the activation of lipid peroxidation and chronic inflammatory markers (6). There are common oxidative stress precursors that are responsible for the development of atherosclerosis that include inflammatory mediators, such as nitric oxide, prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), cytokines (tumor necrosis factor-α, interleukin (IL)-4, and IL-8), cyclooxygenase-1 and -2 (COX-1 and COX-2), and nuclear factor-kappa B (NF-κB) in human monocytic cells. These markers are the potential measurable blood markers to be analyzed.

There were epidemiological studies that had correlated the increasing risk for IHD and ionizing radiation exposure (7–9). In this context, the exposures are largely attributed to LET radiation exposures, such as X-rays or gamma rays. Therefore, the radiation leak through the spacecraft shielding would risk the space crews on CVD during the long space flight. On the other hand, HZE ions cause genetic alterations and perturbations to redox metabolism with resultant persistent activation of oxidative stress (10, 11).

The number of deaths due to IHD in the deeper space orbits was almost five times greater than that in the non-flight astronauts and four times higher than that in LEO astronauts with all the mortality seen in male astronauts (12).

Radiation Effect on Biogenetic Markers

The impairment of oxidative energetic reactions is resulted from the decrease in oxygen flux diffusion of the reduced $BiFeO_3$ cellular oxygen concentration (13). Prolonged tissue hypoxia induces the induction of reactive oxygen species, inflammatory adipokines, and adipose tissue macrophage infiltration. In addition, chronic hypoxia may affect the glucose–insulin homeostasis via increased endothelial permeability resulting from inflammation and alteration of pancreatic β-cell function (14, 15).

Inflammatory mediators, i.e., PGE2, COX-2, and iNOS, are the predicting markers for the anti-inflammatory effects of therapeutic products (16, 17). NF-κB is a transcription factor that regulates the expression of cascaded immune and inflammatory genes when there are external stimuli that trigger the inflammatory responses (18). miRNAs are important regulators of gene expression with a potent impact on cardiovascular pathophysiological function. Patients with IHD have elevated plasma cathepsin-S and cathepsin-B miRNA, for which genes are responsible in the formation and destabilization of the atherosclerotic plaque (19).

There are concerns among the space crews on the influence of chronic exposure to low doses of low LET radiation on IHD during long space travel (20). The expression and correlation of novel biomarkers in angiogenesis could contribute to the understanding of the early diagnosis and prognosis of CVDs. The understanding of the novel molecular pathway of biogenesis and the regulation of CVDs by existing biomolecular, such as protein, enzyme on metabolomics associated with novel biomolecular markers will enhance the current intervention in the treatment of CVDs and new lead in therapeutics.

Molecular Imaging Marker of Endothelial Injury: IMT

The measurement of the progression of the carotid artery wall thickness using an ultrasound imaging is a popular choice of noninvasive examination. It is a reliable method for assessing early morphological arterial changes known to be associated with

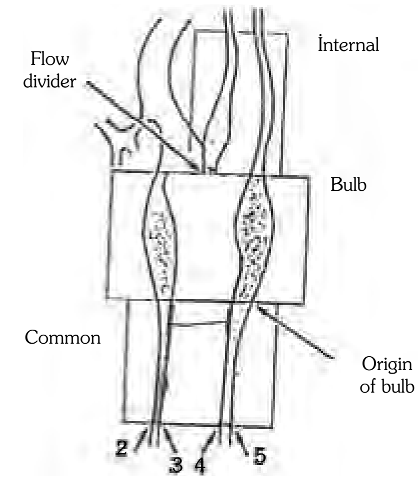

Figure 1. Diagrammatic structure of a carotid artery. The 2–3 interfaces indicate the intima-media thickness of the near carotid wall, and the 4–5 interfaces indicate the far carotid wall

arthrosclerosis and suitable for the long-term investigation of the artery (21). The subject rests in supine position with the head being positioned toward the examiner. The scanning protocol is performed by using an ultrasound carotid b mode scan device equipped with a high-resolution annular array scanner (L11-3) with display image monitoring at 39 frames/s acquisition rate. These images provide a comprehensive view of the carotids and define the maximum arterial intima-media thickness (IMT) in the entirety of the carotid arteries. The available dedicated ultrasound system is allowed for the automatic measurement of the IMT using QLAB IMT plug-in. The measurement of the IMT is performed after the completion of the scanning series using the recorded continuous data in the hard drive. IMTs are the automated quantification by measuring the linear distance at the perpendicular angle between the two points of the ultrasonic interfaces (Fig. 1).

Hypergravity Effect on Central Hemodynamic Pressure

The central blood pressure that determines the intracardiac blood pressure is more reliable as a tool in assessing human cardiovascular physiology especially when the peripheral hemodynamic parameters are insensitive in detecting the early changes of IHD.

Using a molecular marker of the arterial pulse wave velocity (PWV) that measures the elasticity of the peripheral arterial blood vessels would enable the estimation of the central aortic pressure. The sphygmogram is a novel technique that quantifies the changes in the central aorta endothelial elasticity and pressure in the development of hypertension. Pulse wave analysis (PWA) is a complementary system for estimating the ascending aortic blood pressure waveform and central aortic hemodynamic.

The SphygmoCor system is a device used to assess pulse waveform, augmentation index (Ai), and central aortic pressure via a pencil-tip sonography called an applanation tonometry. The radial–carotid artery pressure waves and amplitude are recorded noninvasively by this technique whereby a point at the base of the neck for the right common carotid artery and over the left radial artery is indicated. Arterial PWV is determined by the foot-to-foot flow wave velocity method with the flow wave recording performed at the sharp systolic up-stroke. The time delay was measured between the feet of the flow waves recorded as pulse transmit time. The distance traveled by the pulse wave is measured over the surface of the body. PWV is measured using a formula stated as the distance:transit time ratio and is expressed as m/s. PWA consists of Ai (22). The Ai is defined as the proportion of the central pulse pressure due to the late systolic peak, which in turn is attributed to the reflected pulse wave of the difference between early and late pressure peaks divided by pulse pressure. Subendocardial velocity ratio or Buckberg ratio is a measure of propensity for myocardial ischemia that is equal to the ratio of diastolic time by the pressure over the systolic time by time.

In a study encompassing military personnel who were exposed to high G-pull at 5 g/ms, it was revealed that the Ai index was not significantly changed during the 5g pull probably due to the efficient reconditioning of the baroreceptors following the simulation study and hence indicating that the endothelial integrity and the arterial elasticity were competent (23).

Molecular Imaging Marker of Hypobaric Effect on the Cardiovascular System

In potentially mild hypobaric oxygen saturation in the International Space Station (ISS) capsule, chronic exposure to the cardiovascular system may risk the onboard crews to the development of IHD. Alexander et al. reported that normal subjects who are exposed for 3 weeks at 3100 m altitude show a compromise of the maximal oxygen uptake by 25% during the first day of exposure (24, 25). In this regard, the measurable parameters to ascertain chronic myocardial perfusion deficit may include advance hybrid imaging modalities, i.e., positron emission tomography–computed tomography (PET–CT), single-photon emission computed tomography–CT, or magnetic resonance imaging (MRI)–PET. The assimilation of such myocardial viability measurement was studied by Fathinul et al. (25). The study revealed that 82Rb PET–CT image analysis is a valuable molecular probe in evaluating the ventricular flow reserve (VFR; ml/g/m) of the left ventricle. The low VFR was a sole predictor for a patient with non-insulin-dependent diabetes mellitus (Fig. 2, 3).

Hypobaria-Induced Neuronal Cell Injury

Chronic hypobaric-mediated hypoxia at an altitude of 5000 m would result in irreversible neuronal damage to the human brain. The changes persist for ≥1 year, following the return to sea level. At high altitude, there is a decrease in barometric pressure that leads to the reduction of partial pressure of oxygen. The mechanisms are commonly occurring in an extreme environmental condition, i.e., during military training or space travel. A pilot study on eight subjects who underwent repeated high altitude training disclosed that the inflammatory marker of peak systolic velocity of the right common carotid artery was significantly higher among the chronic-exposed subjects, and that there was a strong correlation with functional MRI brain signal intensity of the right superior temporal gyrus that affects cognitive function (Fig. 4) (26).

As a result, there are potential adverse effects of hypobaria on cognitive functions and performance, specifically learning, memory, mood, and cognitive performance (27, 28). Titus et al. suggested

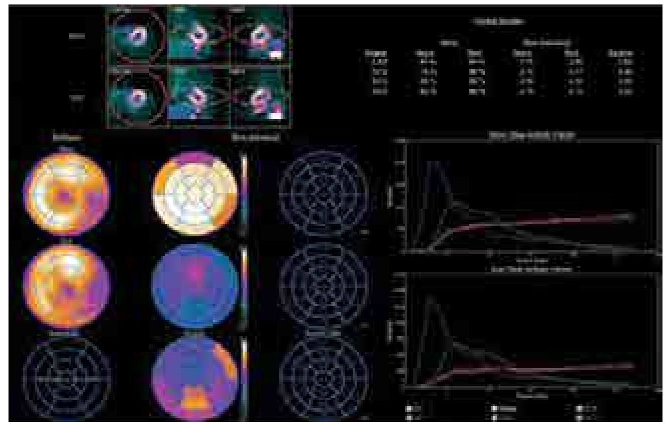

Figure 2. The dual-phase camptothecin was performed during 5 min of ice cube emersion for the stress phase and at rest to underpin the physiological changes of the left ventricular reserve flow being evaluated by the 82Rb PET–CT. Utilizing the acquisition of the list mode CT in static and dynamic phases to reconstruct CT images for attenuation correction and the dynamic data acquisition were processed to obtain the quantification value of VFR of the left ventricle using FlowQuant software (Ottawa, Canada) on the PET polar map

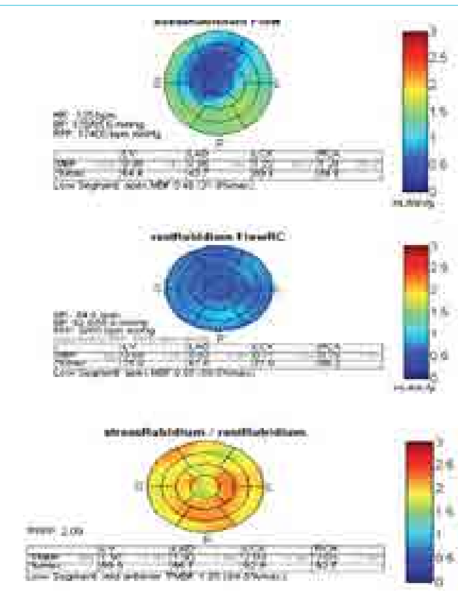

Figure 3. The polar map showing the quantification of the coronary blood perfusion during rest and stress with grid color spectrum showing the intensity of the perfusion from adequate (blue) to reduced (red)

that hippocampal dendrite atrophy following exposure to hypobaria can represent a potential mechanism underlying these cognitive deficits (29). Exposure to acute hypobaria potentially leads to cognitive deficits, along with the activation of oxidative stress (30). Muthuraju et al. reported that the effects of exposure to hypobaria for 7 days on relearning and memory retrieval depend on the impairment of the cholinergic systems (31). In addition, there were studies that revealed that the regional brain oxygen saturation at rest

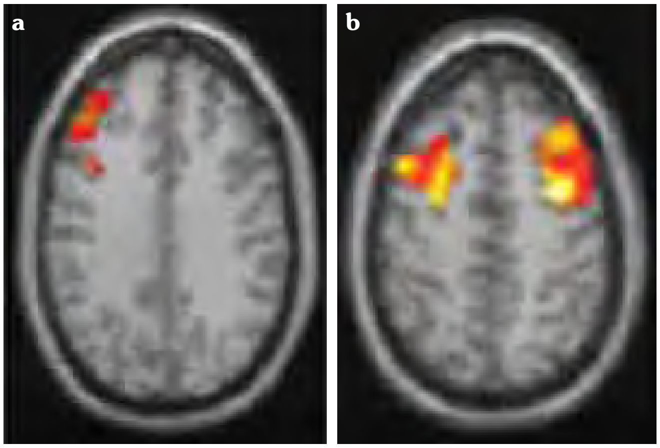

Figure 4. a, b. **(a) Functional MRI (fMRI) signal of the CE subjects at the middle frontal gyrus (MFG). (b) fMRI signal of the LE subjects at the MFG. The fMRI study is a potentially strong surrogate marker in evaluating the cognitive response and orientation state among the chronically-exposed hypobaric subjects, particularly in those who have associated altered inflammatory imaging markers. The subjects respond using a joystick and decide whether it took 2, 3, 4, or 5 moves to achieve a certain bead arrangement pattern on a platform consisting of three pillars. Figure A: Scale-based MRI of the CE and Figure B (LE) showing preprocessing data that were normalized to MNI atlas**

CE: Chronic exposure; LE: Low exposure

in the frontal cortex depleted steadily following travel to high altitudes (32). In the ISS, the onboard crews may experience a reduced oxygen pressure at 8.2 psia/32% O_2 during a long space flight (33).

Hypobaric Effect on Biogenetic Markers

There were evidences by studies that stated that high altitude causes cognitive brain malfunctions and increased plasma high-sensitivity C-reactive protein (hsCRP) levels (34). Biochemical parameters, such as hsCRP, homocysteine, and IL-6, were augmented during a dependent-altitude rise (35). As a result of brain–oxygen deprivation, the downregulation of brain-derived neurotrophic factor may ensue, leading to neuronal degeneration and memory impairment with adjoining elevation in the expression of DNMT1 and DNMT3b at the mRNA, as well as protein level (36, 37). A previous study reported that reduced levels of methyl transferase in the brain would shield the development of an ischemic injury (38–40).

Summary

Extreme environments are the potential attribute to the human physiological deconditioning. They have a detrimental effect on the human immune system that alters the normal physiological bodily process, leading to premature atherosclerosis, deregulation of insulin, cognitive function, and heart straining. Chronic exposure in extreme environments requires mitigative workout to avert the unexpected non-communicable disease via the cutting-edge molecular imaging diagnostic screening and intervention. Among the emerging roles of these imaging apparatuses are hybrid imaging modalities utilizing 18F-FDG PET–CT, 18F-FDG PET–MRI, functional MRI system, Doppler ultrasound systems, and applanation tomography for which early derangement at the cellular and genetic levels that underpin the activation of cytokines and the abnormal free radicals and immune regulation could be easily recognized through the molecular probe signaling. The contemporaneous approach via the enhancement of the fluorescence of organic molecules could signal the intramolecular modification that occurs in the hypoxic environment (41) For instance, the use of hypoxia-sensitive chemical functionalities, such as nitroaromatic, quinone, or azobenzene groups, has been used to develop hypoxia-sensitive ON/OFF FRET molecular probes. Other molecular probes for hypoxia, i.e., intracellular reduction of nitroaryl compounds, are inhibited by molecular oxygen that can be used to assess the level of intracellular oxygen present (42). The myocardial perfusion imaging with 82Rb PET would provide substantial information of the early changes of the myocardial perfusion of the myocardium in coronary artery disease (43). The 2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG) has been used as the gold standard for assessing myocardial glucose metabolism (44–46). Currently, SPECT myocardial perfusion imaging is considered a reliable and widely used tool in CVD, with the advantages of lower cost and compatibility with a wider variety of radiopharmaceuticals. Glucose metabolic remodeling is detectable in hypertensive patients before the development of left ventricular hypertrophy.

CONCLUSION

The molecular imaging markers utilizing the hybrid imaging modalities, i.e., MRI and ultrasound Doppler, would enable early changes to be measured on the human physiology deconditioning, leading to oxidative stress at the cellular level. The exceedingly uncommon environmental physiology that is documented in this review is deemed to underpin cellular deconditioning on the endothelium and the neuronal matrix if early prevention on the chronic course of the stated exposure is not being addressed adequately.

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