Short comunication

Vascular Adaptations to Spaceflight: Results from the Vascular Series Experiments

Adaptaciones vasculares al vuelo espacial: resultados de experimentos de la Serie Vascular

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ABSTRACT

Long-duration spaceflight on the International Space Station (ISS) could be detrimental to astronaut health because of the prolonged period of physical unloading and other stressful factors including isolation and radiation in the microgravity environment. The Vascular Series of experiments was designed to investigate the effects of spaceflight on the arteries. We tested the hypothesis that removal of the normal head-to-foot gravitational force experienced everyday on Earth would cause increased stiffness of the carotid arteries as well as development of insulin resistance that could also impact vascular health. In Vascular, the first experiment of the series, results confirmed increased carotid artery stiffness and insulin resistance; but, the study also revealed a more generalized artery stiffness extending into the lower body. Hormonal and oxidative stress markers could have also influenced vascular health. The next experiments in the Vascular Series, Vascular Echo and Vascular Aging will advance investigations of vascular health employing the ECHO device that has remote robotic control of the ultrasound by experts on the ground to enhance image acquisition while on ISS, and to follow post-flight recovery processes. Vascular Aging will introduce oral glucose tolerance testing on ISS to further quantify the magnitude and the cause of insulin resistance and impaired glucose handling during spaceflight. Together, these studies will provide critical information about the extent of vascular changes during spaceflight and will determine whether all factors that contribute to increased arterial stiffness are reversible, or if there are long-term cardiovascular health consequences.

Keywords: human spaceflight; cardiovascular; ultrasound; arterial stiffness.

RESUMEN

Los vuelos espaciales prolongados de la Estación Espacial Internacional (EEI) podrían afectar la salud de los astronautas, debido al largo tiempo de descarga física y otros factores estresantes, entre ellos el aislamiento y la radiación en un entorno de microgravedad. La Serie Vascular de experimentos fue diseñada para investigar los efectos de los vuelos espaciales en las arterias. Evaluamos la hipótesis de que la eliminación de la fuerza gravitacional normal de cabeza a pies experimentada cada día en la Tierra provocaría un aumento de la rigidez de las arterias carótidas, así como la aparición de resistencia insulínica, lo que también podría afectar la salud vascular. En el primer experimento de la serie, denominado Vascular, los resultados confirmaron un incremento de la rigidez de las arterias carótidas y resistencia insulínica. Sin embargo, el estudio también reveló una rigidez arterial más generalizada, la que se extendía a la sección inferior del cuerpo. Por otra parte, es posible que los marcadores hormonales y de estrés oxidativo también hayan afectado la salud vascular. Los próximos experimentos de la Serie Vascular, denominados Eco Vascular y Envejecimiento Vascular, impulsarán las investigaciones sobre salud vascular mediante el uso del dispositivo ECHO, que posibilita el control remoto robótico del ultrasonido por expertos desde la tierra para perfeccionar la adquisición de imágenes durante los vuelos de la EEI, así como el seguimiento de los procesos de recuperación posteriores al vuelo. El experimento conocido como Envejecimiento Vascular incorporará pruebas de tolerancia a la glucosa durante los vuelos de la EEI para perfeccionar la cuantificación de la magnitud y la causa de la resistencia insulínica y el manejo de la glucosa alterada durante los vuelos espaciales. En conjunto, esos estudios proporcionarán información fundamental sobre el alcance de los cambios vasculares durante los vuelos espaciales, y determinarán si todos los factores que contribuyen al aumento de la rigidez arterial son reversibles o si existen consecuencias cardiovasculares a largo plazo.

Palabras clave: vuelo espacial tripulado; cardiovascular; ultrasonido; rigidez arterial.

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VASCULAR SYSTEM IN SPACEFLIGHT

Removal of the head-to-foot force of gravity during long-duration spaceflight results in extreme unloading on the cardiovascular and musculo-skeletal systems that could negatively impact astronaut health. To date, spaceflight-related cardiovascular research focused on changes in aerobic fitness and arterial blood pressure regulation in space and on return to Earth. While aerobic fitness is negatively affected by spaceflight, astronauts can recover fitness with sufficient inflight exercise.[(1,2)] Likewise, blood pressure is well regulated in space and is impaired to varying degrees on return to Earth.[(3,4,5)] Countermeasures can be applied to affect blood pressure regulation reducing effects of spaceflight, and post-flight interventions can greatly reduce risk of orthostatic hypotension.[(4)]

A new line of investigation, initiated with the Vascular Series of experiments, is exploring novel aspects of cardiovascular structure and function that could have health consequences beyond the duration of exposure to microgravity and elevated radiation during missions to the International Space Station (ISS). These experiments were based on hypothesized potential for spaceflight to negatively impact vascular health through changes in arterial blood pressure throughout the body with removal of the gravity-induced hydrostatic gradient,[(6)] the unloading with reduced physical demands of spaceflight on cardio-metabolic factors,[(7)] changes in oxidative stress and inflammatory responses, perhaps affected by space radiation[(8)] and changes in hormones that direct impact vascular tissues.[(9)]

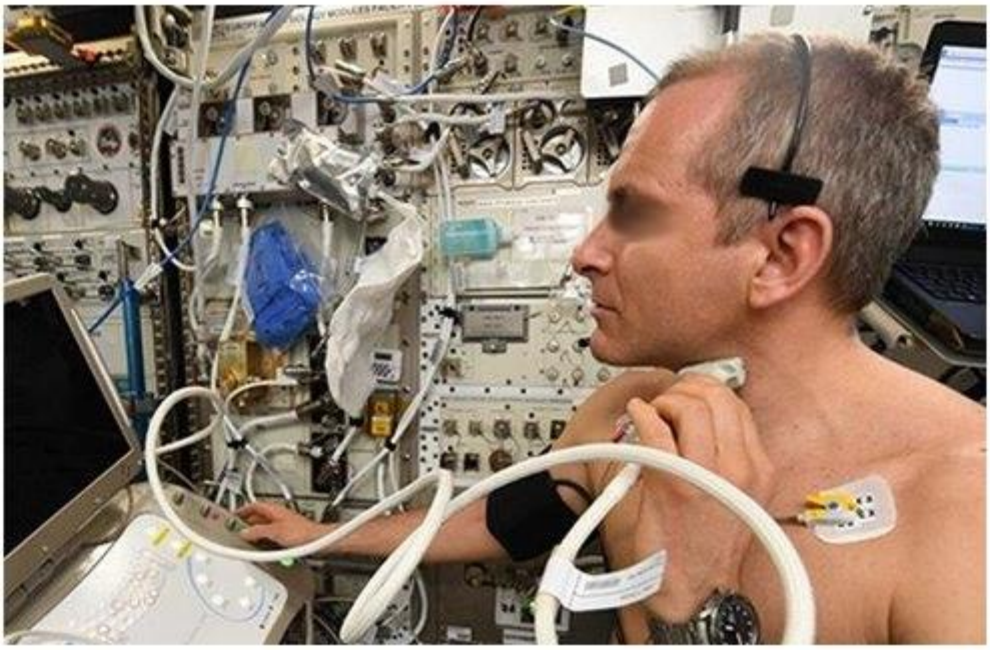
In the first experiment in the Vascular Series, called Vascular, results were obtained in support of the general hypothesis that arterial wall structure would change during spaceflight. Removal of the hydrostatic gradient on exposure to microgravity results in elevated arterial pressure above the heart, and reduced pressure below the heart compared to upright posture on Earth. The relative “hypertension” above the heart was anticipated to cause stiffer carotid arteries with increased intima-media thickness. This was observed in Vascular[(10)] and the Vessel Imaging study.[(11)] But, the reduction in arterial pressure below the heart did not cause less stiff arteries,[(10)] and the femoral artery intima-media layer increased.[11] Taken together, these results indicate that vascular changes with spaceflight cannot be explained solely on the basis of changes in arterial pressure.

The Vascular study also investigated cardio-metabolic health by measurement of the homeostasis model assessment of insulin resistance (HOMA-IR). In the 4 men and 4 women who participated in Vascular, fasting blood insulin concentration was elevated inflight in all astronauts ($P< 0.001$), fasting blood glucose had a between sex difference ($P= 0.037$), with increases in men but not women, and the HOMA-IR was increased in all astronauts ($P< 0.001$) (10). Even though development of insulin resistance during spaceflight had been speculated for many years, these were the first data to document this negative cardio-metabolic adaptation. Insulin resistance in the population on Earth is associated with prolonged periods of physical inactivity;[12] thus, it appears that the exercise performed by astronauts is sufficient to protect aerobic fitness, but not to prevent increases in HOMA-IR. We have documented that astronauts get only about 30-minutes per day of aerobic exercise plus periods of resistance exercise.[7,8,9,10] The long periods of complete unloading between these exercise bouts appears to be a contributing factor to changes in glucose handling.

Hormonal changes with spaceflight that might affect vascular health include increased activity in the renin-angiotensin-aldosterone system. Elevated plasma concentrations of renin ($P= 0.045$) and aldosterone ($P= 0.052$) during spaceflight, primarily in women, could underlie vascular wall growth (9). Reduced plasma superoxide dismutase in men with small elevation in women (interaction $P= 0.07$)[10] might reflect changing ability to handle reactive oxygen species that affect bioavailability of nitric oxide in vascular endothelial cells. Vascular wall repair mechanisms might be impaired as a consequence of reduced matrix metalloproteinase-2 in plasma of all astronauts ($P< 0.001$).[10]

From the Vascular study we concluded that astronauts' carotid arteries increased stiffness by the equivalent of aging approximately 20 years, that insulin resistance is increased during spaceflight, and that blood biomarkers changed in directions that could promote increased arterial stiffness. Because the Vascular study examined arterial stiffness only in the days immediately after return from 6-months in space, but not the recovery, the next experiment in the Series, Vascular Echo, was designed to follow the time course of vascular changes during spaceflight, and up to 12-months post-flight.

Vascular Echo is still collecting data on astronauts living approximately 6-months on ISS. The Vascular Echo study is able to make an important advance on vascular imaging by the incorporation of a robotically controlled ultrasound system (ECHO) that can be operated remotely from the ground. The ECHO device, developed and deployed on ISS by the French, European and Canadian Space Agencies (CNES, ESA, CSA), uses manually operated and robotically operated probes (Fig.). The robotic probes are positioned by the astronaut following guidance, but then controlled from the ground by experts who are able to obtain superior quality images. Novel data coming from the Vascular Echo study will provide arterial pulse wave velocity by measuring the timing from the R-wave of the electrocardiogram signal to the onset of the pulsed Doppler velocity waveform at the carotid artery, the superficial femoral artery, and the tibial artery. These data can provide the "gold standard" carotid-femoral pulse wave velocity as an index of central artery stiffness, and will permit explorations of peripheral artery stiffness indicators.



Canadian Space Agency astronaut David Saint-Jacques images the carotid artery and jugular vein in cross section with the ECHO device on ISS during the Vascular Echo study. Positioning of this probe is by remote guidance, other probes have motors for control from the ground by experts.

Fig. From CSA.

The third experiment of the Vascular Series, Vascular Aging, will extend the time course information on arterial properties using the ECHO device, and will be able to relate these to changes in insulin resistance measured by the oral glucose tolerance tests. The HOMA-IR results in the Vascular study reflect the balance between fasting blood glucose and insulin concentrations that are established by insulin-dependent hepatic glucose production and beta-cell response to glucose concentration. The oral glucose tolerance test will reflect the responsiveness of primarily skeletal muscle to absorb glucose from the blood after a standard load. Given the observations of impaired glucose uptake as physical inactivity affects the muscle glucose transport mechanisms, it is anticipated that prolonged elevation of blood glucose will be found as after a bed rest study.[13] Higher blood glucose could result in formation of advanced glycation end products including glycated albumin,[10] hemoglobin and proteins in vascular walls affecting arterial stiffness. Glucose homeostasis, body calcium metabolism and vascular health are intimately linked. Therefore, the Vascular Aging study will also measure blood biomarkers of bone formation, resorption, and calcium metabolism as potential indicators of risk for arterial calcification during spaceflight.[14]

Radiation exposure during a 6-month mission on ISS, approximately 72 millisieverts, is 10-fold greater than yearly exposure on Earth.[15] Space radiation is complex and is determined by multiple factors including distance from Earth. In low Earth orbit, the Van Allen Belts provide some shielding from deep space radiation, but also generate radiation through exposure to electrons and protons. Solar particle events generate high numbers of protons and are a risk for astronauts on ISS. Beyond low Earth orbit without the partial shielding of the Van Allen Belts, solar particle events and galactic cosmic radiation that includes high atomic number, high energy ions (e.g. iron, silicon, oxygen, carbon) represent a major threat to human health. A 180-day transit to Mars is expected to expose astronauts to 5-times the effective radiation exposure on ISS.[15] While cancer risk of radiation has been extensively reported, high radiation exposure could precipitate radiation-induced cardiovascular disease with high oxidative stress levels particularly in the vascular endothelium.[8] The Vascular Series of experiments has been collecting lymphocyte samples to assess the ability of telomere length to reflect cardiovascular risk of radiation exposure.

Long-term cardiovascular health of humans who go beyond low Earth orbit to the Moon or Mars should be a concern for space mission planners. The Vascular Series of experiments is gathering information on changes in vascular structure and function that could have health consequences for future space explorers. From studies on Earth, we know that arterial stiffness is an independent risk factor for major cardiovascular and cerebrovascular disease. Arterial stiffness is associated with changes in cognitive function even in young adults[16] and is a risk factor for cognitive impairment and Alzheimer's disease.[17] From the Vascular Series of experiments, we are learning about accelerated aging-like changes with spaceflight. These results should feedback to our societies to inspire healthier living on Earth.

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REFERENCE

1. Moore AD, Downs ME, Lee SMC, Feiveson AH, Knudsen P, Ploutz-Snyder L, et al. Peak exercise oxygen uptake during and following long-duration spaceflight. J Appl Physiol. 2014;117(3):231-8.
2. Moore AD, Lynn PA, Feiveson AH. The First 10 Years of Aerobic Exercise Responses to Long-Duration ISS Flights. Aerosp Med Hum Perf. 2015;86(12):A78-A86.
3. Meck JV, Reyes CJ, Perez S, Goldberger AL, Ziegler MG. Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts. Psychosomatic Medicine. 2001;63:865-73.
4. Lee SMC, Feiveson AH, Stein S, Stenger MB, Platts SH. Orthostatic Intolerance After ISS and Space Shuttle Missions. Aerosp Med Hum Perf. 2015;86(12):A54-A67.
5. Wood KN, Greaves DK, Hughson RL. Inflight leg cuff test does not identify the risk for orthostatic hypotension on return to Earth after long-duration spaceflight. NPJ Microgravity, In Press; 2019.
6. Hargens AR, Richardson S. Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. Respiratory Physiology & Neurobiology. 2009;(Supplement:S30-S3):169.
7. Fraser KS, Greaves DK, Shoemaker JK, Blaber AP, Hughson RL. Heart rate and daily physical activity with long-duration habitation of the International Space Station. Aviat Space Environ Med. 2012;83:577-84.
8. Hughson RL, Helm A, Durante M. Heart in space: effect of the extraterrestrial environment on the cardiovascular system. Nature Reviews in Cardiology. 2018;15:167-80.

9. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, Pathophysiology, and Therapy of Arterial Stiffness. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25(5):932-43.

10. Hughson RL, Robertson AD, Arbeille P, Shoemaker JK, Rush JWE, Fraser KS, et al. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. Am J Physiol Heart Circ Physiol. 2016;310(5):H628-H38.

11. Arbeille P, Provost R, Zuj K. Carotid and Femoral Artery Intima-Media Thickness During 6 Months of Spaceflight. Aerosp Med Hum Perf. 2016;87(5):449-53.

12. Healy GN, Matthews CE, Dunstan DW, Winkler EAH, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. European Heart Journal. 2011;32(5):590-7.

13. Heer M, Baecker N, Wnendt S, Fischer A, Biolo G, Frings-Meuthen P, et al. How Fast Is Recovery of Impaired Glucose Tolerance after 21-Day Bed Rest (NUC Study) in Healthy Adults? The Scientific World Journal. 2014. Disponible en: http://dx.doi.org/10.1155/2014/803083.

14. Linossier MT, Amirova LE, Thomas M, Normand M, Bareille M-P, Gauquelin-Koch G, et al. Effects of short-term dry immersion on bone remodeling markers, insulin and adipokines. PLoS ONE. 2017;12(8):e0182970.

15. Hassler DM, Zeitlin C, Wimmer-Schweingruber RF, Ehresmann B, Rafkin S, Eigenbrode JL, et al. Mars' Surface Radiation Environment Measured with the Mars Science Laboratory's Curiosity Rover. Science. 2014;343(6169):1244797.

16. Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, et al. Association of Aortic Stiffness With Cognition and Brain Aging in Young and Middle-Aged Adults: The Framingham Third Generation Cohort Study. Hypertension. 2016;67(3):513-9.

17. Iulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? Journal of Neurochemistry. 2018;144(5):527-48.

Conflict of interests

There is no conflict of interest in relation to the research presented.