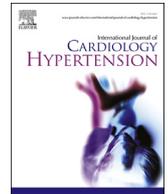




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Research Paper

An oscillometric approach in assessing early vascular ageing biomarkers following long-term space flights

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ABSTRACT

Purpose: The environmental conditions in space, particularly exposure to cosmic radiation, coupled with decreased mobility, altered glucose metabolism, and hemodynamic changes may promote cardiovascular disease. Therefore, we assessed early vascular aging markers and hemodynamics using a novel oscillometric blood pressure device.

Methodology: In eight cosmonauts (46.5 ± 5.3 yrs, 77.6 ± 8.2 kg, 176 ± 6.2 cm, 7 men/1 woman), we determined heart rate, peripheral blood pressure, central blood pressure, and pulse wave velocity in the supine position using an oscillometric brachial device coupled with transfer function analysis. We obtained measurements at baseline (65–90 days before flight) and four days (R+4) and eight days (R+8) after return from six months mission on-board the International Space Station.

Results: Compared to baseline, heart rate increased significantly on R+4 (58.6 ± 6.4 vs. 70.3 ± 5.2 bpm) but did not differ on R+8. Central systolic blood pressure increased from 112.5 ± 13.5 on baseline to 125.6 ± 18.5 on R+4 and 121.6 ± 9.5 mmHg, albeit showing no statistical significance compared to baseline (p = 0.243/0.295). Peripheral diastolic and systolic as well as central diastolic blood pressure measurements followed this trend. Pulse wave velocity increased non-significantly from baseline (6.7 ± 0.8 m/s) to R+4 (7.2 ± 0.8 m/s, p = 0.499) and stayed elevated on R+8 (7.1 ± 0.5 m/s, p = 0.614).

Conclusion: The important finding of our study is that six months in a near-earth orbit do not lead to clinically significant changes in early vascular ageing biomarkers. However, these findings cannot be extrapolated to the conditions encountered in deep space. Non-invasive testing of vascular biomarkers may have utility in detecting vascular risks during space travel at an early stage.

1. Introduction

The extreme environmental conditions in space, particularly exposure to cosmic radiation, coupled with decreased mobility, altered glucose metabolism, and hemodynamic changes may promote early vascular ageing and overt cardiovascular disease [11]. Compared to earth, radiation exposure increases 250-fold on board the International Space Station in near-earth orbit [5]. In vitro, radiation induces cardiovascular damage and atherosclerosis as final common path of DNA-damage, reactive oxygen species formation, cytokine release, and inflammation

[19]. Epidemiological studies in atomic bomb survivors in Hiroshima and Nagasaki [7,15], in Russian emergency workers following the Chernobyl accident [12], and in patients following radiation therapy showed increased cardiovascular disease prevalence [8]. These observations led to the recognition of radiation-induced cardiovascular disease. However, the small number of astronauts and cosmonauts and the limited follow-up make it difficult relating radiation exposure in space to premature vascular ageing and clinical cardiovascular events [9]. Increased larger artery intima media thickness has been reported during but not after space flight [1]. Another study showed shortened pulse wave transit

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times following space flights [2,11]. Since the future of manned space flight will include deep space missions, it is crucial to provide a cardiovascular health monitoring, which is easy-to-perform, non-invasive and observer-independent. Such medical devices providing central hemodynamics and vascular function measurements, are gaining more importance for cardiovascular risk stratification in the clinic [17]. Non-invasive central blood pressure measurements, estimating blood pressure in the ascending aorta, appear to have a particularly high prognostic value [13], which increases further in combination with pulse wave velocity and arterial stiffness analyses [4,14] in comparison to a risk stratification solely based on peripheral blood pressure. We hypothesized that if long-term space missions promoted early vascular ageing, pulse wave velocity and central blood pressure should, both, increase. Therefore, we assessed central hemodynamics including central blood pressure and pulse wave velocity before and after long-term spaceflight in cosmonauts using a new easy-to-perform and non-invasive method based on oscillometric, brachial cuff measurements [10,22]. The methodology has been validated against invasive catheter measurements and showed high reproducibility with low observer-dependency [10,23].

2. Methodology

In eight cosmonauts (46.5 ± 5.3 yrs, 77.6 ± 8.2 kg, 176 ± 6.2 cm, 7 men/1woman), we obtained automated brachial blood pressure and vascular measurements (Mobil-O-Graph® PWA, I.E.M GmbH, Stolberg, Germany). Preflight baseline data were obtained between 65 and 90 days before launch. Following 6 months onboard the International Space Station, post flight measurements were obtained four (R+4) and eight (R+8) days after return. Mean flight duration was 168 days. All measurements were obtained with cosmonauts in the supine position after at least 10 min of rest to attain steady-state conditions.

The measurement comprises two subsequent procedures. First, a regular oscillometric blood pressure measurement assessing heart rate and peripheral arterial systolic and diastolic blood pressure is obtained. Second, the cuff inflates to previously determined diastolic blood pressure and maintains the pressure for several seconds to continuously record pulse waves traveling underneath the cuff. Then, the device applies a generalized transfer function, pulse wave analysis, and wave separation analysis onto the averaged pulse waves for providing estimated aortic pulse wave velocity (PWV), central systolic and diastolic blood pressure as described elsewhere [10]. Central-to-peripheral systolic and pulse pressure amplification, two-dimensional measures which are not affected by absolute pressure levels, were also calculated and normalized for heart rate.

Statistical analysis was done using IBM SPSS Statistics 21 (IBM, Armonk, New York, USA). The three time points were compared using one-way ANOVA testing followed by the post-hoc Tamhane test. Level of significance was <0.05 . Values are given as mean \pm standard deviation. The protocol was approved by the ethics committee of the Institute of Biomedical Problems, Moscow, Russian Federation and the Human Research Multilateral Review Board of the National Aeronautics and Space Administration (NASA). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

3. Results

No cosmonaut showed signs or symptoms of cardiovascular disease during space travel or four and eight days after return to earth. Individual trends for heart rate, peripheral blood pressure, central blood pressure, pulse wave velocity, and central to peripheral amplification index before and after space travel are illustrated in Fig. 1 and their mean values are listed in Table 1.

At baseline, supine heart rate was 58.4 ± 6.5 bpm with a significant increase to 70.3 ± 5.2 bpm ($\Delta = 11.9$ bpm; $p < 0.001$) four days after return. The difference was attenuated eight days after return to earth. Peripheral arterial systolic and diastolic blood pressure followed a similar

trend with a numerical albeit statistically not significant increase on day four and a smaller increase on day eight after return. We observed similar trends for pulse wave velocity and central arterial systolic and diastolic blood pressure. Compared to baseline, the values were numerically albeit statistically not significant increased on day four and day eight after return with the highest level on day four. Central to peripheral systolic and pulse pressure amplification did not change significantly over all time points. Amplifications normalized to a heart rate of 75 bpm, decreased numerically on R+4 with a subsequent increase on R+8 without reaching baseline level. Systolic Amplification was significantly lower on R+4 compared to baseline.

However, individual responses varied and some cosmonauts exhibited modest pulse wave velocity increases that were sustained through day eight after return. The individual largest increase in central blood pressure four days after return was 38 mmHg for systolic and 13 mmHg for diastolic pressure, pulse wave increased at a maximum of 1.5 m/s. Eight days after return the individual highest increase for central blood pressure was 31 (systolic), respectively 18 (diastolic) mmHg and 1.1 m/s for pulse wave velocity.

4. Discussion

The important finding of our study is that six months in a near-earth orbit do not lead to clinically significant changes in early vascular ageing biomarkers. Indeed, all cosmonauts showed pulse wave velocities below 10 m/s, which is considered the threshold heralding excess cardiovascular risk [16]. The methodology applied in our study allows detecting differences in pulse wave velocity as low as 1 m/s with high validity and a 95%-confidence interval of -0.47 to 0.57 m/s for repeated measurements [10]. Moreover, all other measurements before and after spaceflight remained within the physiological range. Some, such as central blood pressure, tended to return to baseline values before spaceflight within a few days.

On earth, blood pressure and age are particularly strong predictors of pulse wave velocity [3]; 2010). In this and in previous studies, blood pressure and heart rate were increased in the days following return to earth [2,20]. Concomitant increases in heart rate and blood pressure are consistent with sympathetic nervous system activation. However, during prolonged space flight, blood pressure and heart rate tend to decrease. The response is likely explained by peripheral vasodilation [18]. The numerical increase in central blood pressure in our study following return to earth likely resulted from a transient pressor response rather than pathological vascular remodeling. The notion is supported by our measurements of systolic and pulse pressure amplification. The decrease in normalized amplification suggests an increase in the compliance of the arterial vasculature. The return of the values eight days after return to earth is also consistent with functional rather than structural vascular changes, like transient hypervolemia on return to earth. Worsened aortic compliance and stiffness measurements have been previously observed after 5–18 days in space [21]. Given the short exposure, it is unlikely that these changes were due to structural vascular remodeling. The more prolonged exposure to the extreme environmental conditions in space in our study is more informative in that regard. Others observed shortened pulse wave transit times in male astronauts measured at the fingertip [2, 11]. Carotid artery distensibility was also decreased, thus, confirming increased arterial stiffness [11].

Moreover, carotid artery ultrasound measurements on the International Space Station revealed increased intima-media thickness [1]. Increased intima media thickness is usually considered as a marker for preclinical cardiovascular disease. Strikingly, a similar change would require 20–30 years aging on earth. Yet, intima media thickness measurements after space flight were similar to measurements before space flight. We obtained similar results [1]. Transient intima media thickening in space may reflect reversible adaptation to the microgravity environment rather than pathological vascular remodeling.

The main limitation of our study is the small number of cosmonauts.

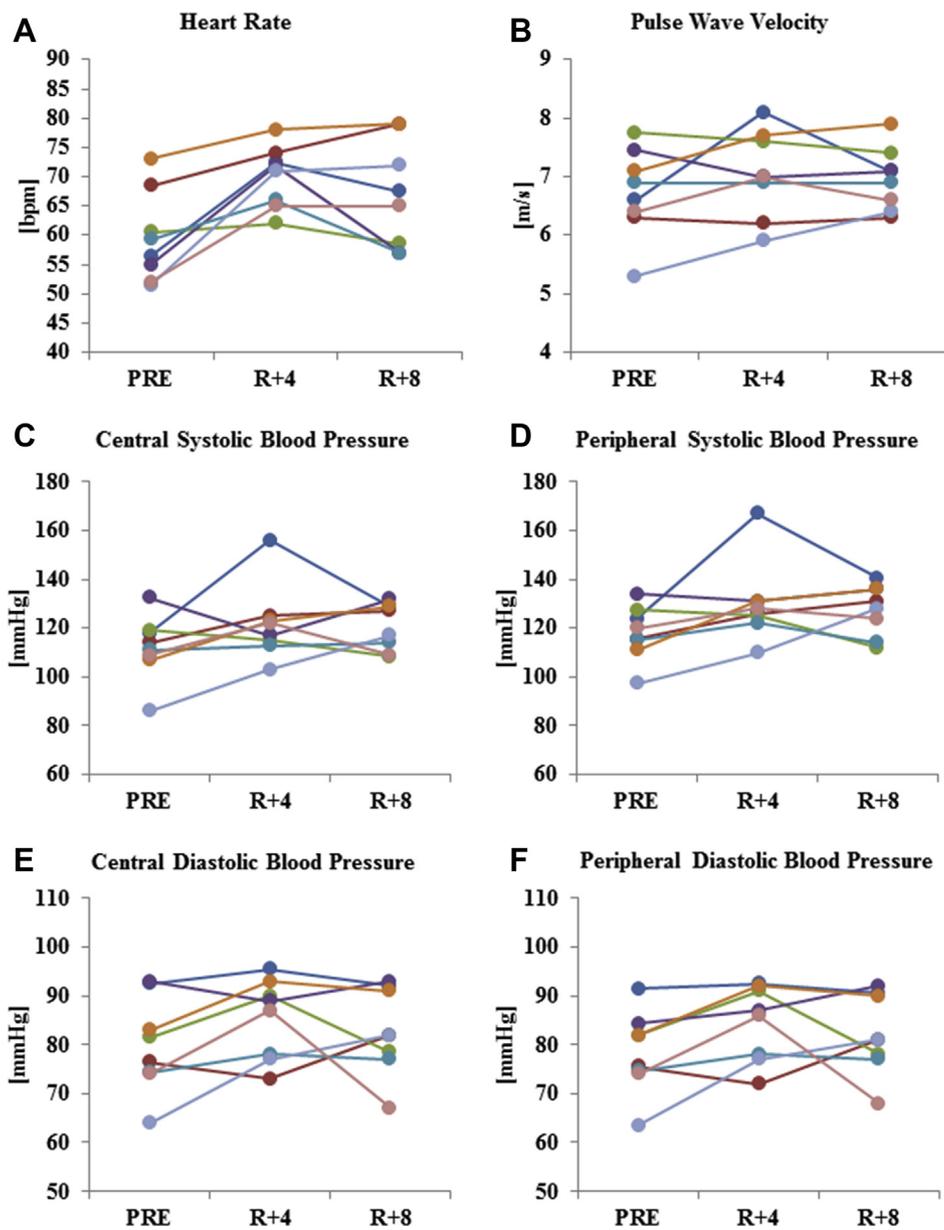


Fig. 1. Individual heart rate (A), pulse wave velocity (B), central systolic blood pressure (C), peripheral systolic blood pressure (D), central diastolic blood pressure (E), and peripheral diastolic blood pressure (F), all sorted by time point. PRE: 90 to 65 days before flight; R+4/R+8: post flight measurements four/eight days after return.

Table 1

Pooled subject values represented as mean ± standard deviation. The p-value to the right of R+4 and R+8 represent the level of significance ($p < 0.05$) with respect to PRE. HR: heart rate; PWV: pulse wave velocity; SBP_p/DBP_p: Peripheral systolic and diastolic blood pressure; SBP_c/DBP_c: Central systolic and diastolic blood pressure; Amplification systolic: absolute pressure independent amplification from central to peripheral for systolic measurements; Amplification pp: Amplification for pulse pressure from central to peripheral; HR75: Amplification normalized to a heart rate of 75 bpm; PRE: Baseline measurements 65–90 days before flight; R+4/R+8: postflight measurement four/eight days after return.

	PRE	R+4	p-value	R+8	p-value
HR [bpm]	58.6 ± 6.4 *	70.3 ± 5.2	<0.0001	66.1 ± 8.5	0.087
PWV [m/s]	6.7 ± 0.8	7.2 ± 0.8	0.499	7.0 ± 0.5	0.614
SBP _p [mmHg]	120.1 ± 13	134.1 ± 19.7	0.219	127.4 ± 11.5	0.376
DBP _p [mmHg]	78.9 ± 9.1	85.3 ± 7.8	0.213	82.6 ± 8.1	0.646
SBP _c [mmHg]	112.5 ± 13.5	125.6 ± 18.5	0.243	120.3 ± 9.8	0.295
DBP _c [mmHg]	79.7 ± 9.9	86.4 ± 8.4	0.246	83.3 ± 8.7	0.717
Amplification systolic	1.06 ± 0.04	1.07 ± 0.03	0.984	1.06 ± 0.04	0.989
Amplification systolic HR75	1.36 ± 0.18	1.15 ± 0.1	0.003	1.22 ± 0.14	0.103
Amplification pp	1.24 ± 0.15	1.27 ± 0.14	0.951	1.21 ± 0.13	0.918
Amplification pp HR 75	1.6 ± 0.34	1.37 ± 0.19	0.119	1.39 ± 0.17	0.145

Since we used a novel device prior and after space flight, data for a prospective power-calculation was not available. However, we performed a post-hoc power analysis based on our data. Given the observed standard deviation, 32 cosmonauts would have to be included to detect a 10 mmHg difference in central systolic blood pressure with $\alpha = 0.05$ (Dupont and Plummer 1990). The follow up was too short to detect delayed onset vascular disease. Indeed, radiation-induced cardiovascular disease may occur many years following radiation exposure. Nevertheless, the fact that we did not observe clinical relevant or significant changes is reassuring. Finally, all central hemodynamic parameters are calculated based on oscillometric brachial cuff measurements using unpublished algorithms [10,22]. The applied mathematical model is based on assumptions that may not be applicable after space travel. Aortic pulse wave velocity estimations include age, central systolic blood pressure and aortic characteristic impedance. Aortic characteristic impedance is estimated in this model, which could confound the analysis.

Despite these issues we suggest that six months in near earth orbit do not lead to medically relevant changes in early vascular ageing biomarkers immediately following return to earth. Studies conducted in cosmonauts staying in near earth orbit cannot be extrapolated to the conditions encountered in deep space. Indeed, the earth's magnetic field shields much of the cosmic radiation. For long-term missions in deep space and for individuals flying repeatedly, it may be prudent monitoring vascular health biomarkers regularly. A non-invasive and easy to perform test like the one applied in our study holds promise to meet these requirements. Our study may also have implications for cardiovascular medicine on earth. The rapid reversal of some of the so-called early vascular ageing biomarkers suggests that the methodologies have limitations in differentiating physiological vascular adaptation from true preclinical vascular disease.

Author contributions statement

FH & SM were equally in charge of data analysis and drafting the manuscript. EL, IF and RB conducted data acquisition. JJ and JT were project lead and reviewed the manuscript. The authors would like to state that I.E.M. GmbH had no influence on study design, data collection and analysis as well as manuscript drafting.

Conflict of interest

None.

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