Orthostatic blood pressure control before and after spaceflight, determined by time-domain baroreflex method

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Gisolf, J., R. V. Immink, J. J. van Lieshout, W. J. Stok, and J. M. Karemaker. Orthostatic blood pressure control before and after spaceflight, determined by time-domain baroreflex method. J Appl Physiol 98: 1682–1690, 2005. First published January 13, 2005; doi:10.1152/japplphysiol.01219.2004.—Reduction in plasma volume is a major contributor to orthostatic tachycardia and hypotension after spaceflight. We set out to determine time- and frequency-domain baroreflex (BRS) function during preflight baseline and venous occlusion and postflight orthostatic stress, testing the hypothesis that a reduction in central blood volume could mimic the postflight orthostatic response. In five cosmonauts, we measured finger arterial pulse pressures and an increase in heart rate of 30 beats/min or more during standing after spaceflight. Overall, there were indications of increased sympathetic response to standing, even though we can expect (partial) restoration of plasma volume to have taken place. Preflight venous occlusion did not mimic the postflight orthostatic response.

METHODS

Subjects

We studied five male cosmonauts who each took part in one of three different (10–11 day) Soyuz missions. At preflight data collection, average cosmonaut age was 40 (SD 3) yr, height 180 (SD 4) cm, and weight 76 (SD 10) kg. Each subject was informed of the experimental procedures and signed an informed consent form. The experimental protocol was approved by the Medical Ethics Committee of the Academic Medical Center, Univ. of Amsterdam (MEC00/069), the ESA Medical Board, and the JSC Institutional Review Board.

Experimental Design and Protocol

Preflight measurements were conducted in a temperature-controlled laboratory (21–23°C) in the Academic Medical Center in Amsterdam, 3–5 mo before launch. Subjects refrained from alcohol and caffeine for at least 5 h before data collection. After answering some preliminary questions regarding caffeine habits (none of the subjects habitually drank more than 3 units of caffeinated beverages per day), subjects were instrumented on a motorized, computer-controlled tilt table in the supine position (8). Pneumatic cuffs (D. E. Hokanson, Issaquah, WA) were applied to the upper thighs, kept in place with Velcro, and connected to an air compressor (Stratos model 65 pressure regulator, Fairchild, Winston-Salem, NC) to ensure smooth and rapid inflation. Subjects were instructed to pace their breathing to an audio stimulus. They learned to prevent hypocapnia by varying the depth of breathing and keeping their end-tidal PCO2 within normal limits.

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a normal range as viewed on an in-house developed feedback device. A practice head-up tilt (HUT) to 70° and back to supine was carried out, and paced breathing was practiced.

Preflight. The baseline protocol started after at least 15 min of rest in the supine position. Cuffs were kept deflated throughout the baseline session. To induce variations in blood pressure at several frequencies, in the supine position the breathing was paced first at 10 min⁻¹, followed by 6 min⁻¹, and finally 15 min⁻¹. Each breathing frequency was held for a duration of 1 min plus two extra breaths and followed by a 1-min rest (spontaneous breathing). The complete capnogram was displayed on an oscilloscope and visually checked by the experimenters; paced breathing was repeated if necessary. Subjects were then rapidly tilted to 70°; after 5-min HUT, they were tilted back to supine. After a short break (3–5 min), inflating thigh cuffs to 40 mmHg impeded venous return from the legs; cuff pressure was maintained at this level while subjects were supine. Subjects rested for 4 min before repeating the paced breathing protocol. They were then tilted to 70° HUT within 1 s (8), and simultaneously thigh cuff pressure was increased to 100 mmHg, to compensate for the hydrostatic pressure increase during tilt. After 5 min in the HUT position, they were tilted back to supine; simultaneously, thigh cuffs were deflated completely.

Postflight. Within 3 days of landing, a postspaceflight protocol was conducted in the Gagarin Cosmonaut Training Center in Russia. Subjects refrained from alcoholic or caffeinated beverages starting at least 5 h before measurements. The sessions took place at an ambient room temperature; a bed was used instead of a tilt table. The protocol was largely similar to preflight baseline (a supine rest period of at least 10 min followed by paced breathing at 10, 6, and 15 min⁻¹ as described previously); however, the supine measurements were followed by 5 min of active standing rather than passive HUT; furthermore, in three of the five sessions, the subject was seated for 3–5 min after supine recording and before standing up. PCO₂ was not monitored, but the cosmonauts were carefully instructed to avoid hyperventilation and the experimenter visually checked respiratory excursions during paced breathing.

Measurements and Data Processing

Arterial blood pressure was continuously measured by a servo-controlled photoplethysmograph (preflight: Finapres, model 5; postflight: Portapres, model 2; Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation, TNO-BMI, Amsterdam, The Netherlands) placed on the midphalanx of the middle finger of the right hand (9), which was positioned at heart level and held in place using an arm sling. The finger cuff pressure was used to track arterial blood pressure. Preflight, expiratory carbon dioxide was sampled continuously and measured by using a capnometer (Hewlett-Packard). The electrocardiogram was measured continuously for monitoring purposes only (Hewlett-Packard 78345A). To estimate changes in segmental blood volume in the lower limbs during orthostasis with deflated and inflated thigh cuffs, calf impedance was measured. Impedance plethysmography (AI-601G, Nihon-Kohden) was used, with the electrodes taped circumferentially around the leg, above the ankle and just below the knee.

Finger blood pressure and electrical impedance were digitized at 100 Hz. Mean arterial blood pressure was the true integral of the arterial pressure wave over 1 beat divided by the corresponding beat interval. HR was computed as the inverse of the interbeat interval (IBI) and expressed in beats per minute. For preflight baseline, preflight thigh cuffs and postflight sessions, minute averages of hemodynamic variables were calculated, starting 10 min before tilt or standing. Lower limb electrical impedance was averaged for 5 min HUT with first deflated, and then inflated thigh cuffs.

For frequency analysis, beat-to-beat systolic blood pressure (SBP) and IBI time series were detrended and Hamming windowed. Power spectral density and cross-spectra of SBP and IBI were computed using discrete Fourier transform (4). Spectra of paced breathing recordings were computed per breathing frequency; spectral density and cross-spectral gain, phase, and coherence were computed at the appropriate (respiratory) frequency band. Of the HUT and standing recording, 4 min were analyzed (omitting data from the first minute in the upright position). Spontaneous spectra were computed in the low-frequency (LF) and high-frequency (HF) band, ranging from 0.06–0.15 and 0.15–0.5 Hz, respectively.

For time-domain analysis of spontaneous baroreflex sensitivity (xBRS) we used the cross-correlation method PRVXBRS (21). The SBP and IBI time series were spline interpolated and resampled at 1 Hz. In 10-s windows, the correlation and regression slopes between SBP and IBI were computed. Delays of 0–5 s increments in IBI were computed, and the delay with the highest positive coefficient of correlation was selected; the optimal delay (Tau) was stored. The slope between SBP and IBI was recorded as an xBRS estimate if the correlation was significant at P = 0.01. In Figs. 1 and 2, individual xBRS estimates are shown as well as clusters; clusters of estimates not more than 1.5 s apart were averaged and timed at the cluster midpoint, thus indicating joint events (21).

Statistical Analysis

Data are given as means (SD) unless stated otherwise. Hemodynamic measurements, spectral indexes and xBRS results were averaged per body position and per paced breathing frequency where appropriate and analyzed across conditions via the Friedman test (equivalent to a two-way ANOVA on ranks) or Wilcoxon signed rank test where appropriate. Differences between preflight baseline and postflight conditions were tested by paired t-test. Differences in Tau (optimal delay, output of PRVXBRS) between conditions were tested using the χ² test. Agreement between time- and frequency-domain BRS was calculated as a linear regression correlation coefficient. P values below 0.10 are given; P values greater than 0.10 are indicated as not significant (NS).

RESULTS

Cosmonaut body weight 10 days before launch and on measurement days is given in Table 1. Lower limb electrical impedance was obtained preflight in four of the five cosmonauts (technical failure prevented measurement in cosmonaut D); differences in electrical impedance indicated a larger calf blood volume during HUT with inflated than with deflated thigh cuffs (Table 1) (16). All five cosmonauts completed the entire pre- and postflight protocols and were able to remain upright for the duration of the tests.

Hemodynamic Data

Postflight blood pressure recordings of all five cosmonauts are shown Fig. 1. Generally, blood pressure was variable but did not decrease while standing: xBRS decreased on standing up. In cosmonauts A and B, HR increased by ~30 beats/min or more, standing, and pulse pressure reduced drastically. Figure 3 shows the averaged preflight and postflight hemodynamics. HR in the upright posture was increased postflight compared with preflight (P = 0.07); baseline preflight HR was 79 beats/min; inflated thigh cuffs, 75 beats/min, did not approach the postflight upright value of 88 beats/min. Supine and upright systolic, diastolic, and mean arterial pressure did not differ between pre- and postflight conditions.

Frequency Domain

Supine: paced breathing. Paced breathing, to ensure blood pressure variations at several frequencies, induced greatest
SBP and IBI variation at the lowest breathing frequency (Fig. 4). There were no differences in paced-breathing-induced SBP and IBI variation between pre- and postflight sessions. The results of cross-spectral analysis of breathing-induced blood pressure oscillations are given in Table 2. There were no differences in transfer gain, phase, and coherence between preflight baseline, venous occlusion cuffs, and postflight sessions (two-way ANOVA on ranks).

Upright: spontaneous variability. Results of spectral analysis of SBP and IBI spontaneous variability are shown in Fig. 5; LF variability was greater than HF variability. This was true for preflight baseline and venous occlusion and for postflight sessions. In the LF range, where cross-spectral coherence between SBP and IBI was high (Table 3), the transfer gain differed between sessions, with the greatest gain during venous occlusion and the lowest gain postflight. Comparing baseline
preflight to postflight transfer gain at LF, the gain was decreased postflight ($P = 0.033$ with paired $t$-test). In the HF range, phase lag but not transfer function gain of IBI to SBP differed between conditions; phase lag was smallest during venous occlusion and greatest postflight. The LF decrease in phase lag during standing, preflight baseline vs. postflight, was not significant ($P = 0.10$).

**Time Domain (PRVXBRS)**

Baroreflex sensitivity evaluated in the time domain decreased from supine to upright in all three conditions (Fig. 3):

<table>
<thead>
<tr>
<th>Cosmonaut</th>
<th>Stand-Test Day</th>
<th>Calf Imp, $\Omega$</th>
<th>Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>R + 2</td>
<td>70.56</td>
<td>81</td>
</tr>
<tr>
<td>B</td>
<td>R + 1</td>
<td>60.50</td>
<td>62</td>
</tr>
<tr>
<td>C</td>
<td>R + 3</td>
<td>48.44</td>
<td>68</td>
</tr>
<tr>
<td>D</td>
<td>R + 2</td>
<td>77.62</td>
<td>88.5</td>
</tr>
<tr>
<td>E</td>
<td>R + 2</td>
<td>76.25</td>
<td>85.5</td>
</tr>
</tbody>
</table>

**Table 1. Cosmonaut preflight lower limb electrical impedance during head-up tilt with deflated and inflated thigh cuffs; body-weight preflight (10 days prior to launch) and postflight on the measurement day**

from 17 (SD 10) ms/mmHg supine to 8 (SD 3) ms/mmHg standing at baseline preflight ($P = 0.085$), from 15 (SD 7) to 10 (SD 5) ms/mmHg with thigh cuffs ($P = 0.058$), and from 17 (SD 6) to 6 (SD 3) ms/mmHg after spaceflight ($P = 0.006$). There were no significant differences in xBRS between preflight baseline, venous occlusion, and postflight conditions. The distributions of Tau (the 0- to 5-s optimal delay of IBI to SBP) are shown in Fig. 6. Compared with supine, the upright position resulted in a shift in the distribution toward higher values of Tau. After spaceflight, Tau distribution shifted toward higher Tau values compared with preflight baseline ($P < 0.001$).

**Time vs. Frequency Domain**

When comparing the average xBRS results (time-domain BRS) to LF transfer gains (frequency-domain BRS) in supine and upright position during preflight baseline, preflight thigh cuffs, and postflight, there is a good correlation between these methods (correlation coefficient $R^2 = 0.84$) (Fig. 7).

**Additional Stand Test With Leg Crossing**

The end of an additional 10-min stand test of one subject (cosmonaut A) 5 days after landing is shown in Fig. 2; at the end of the stand test he crossed his legs and tensed leg muscles while still standing. Finger blood pressure was low in supine position, whereas brachial pressure (Omron automatic digital
blood pressure monitor HEM-705CP) was 120/68 mmHg and HR was 63 beats/min. Immediately after standing up, the brachial blood pressure was 105/75, HR was 106 beats/min. At the end of the 10-min stand test, pulse pressure was reduced (Fig. 2), but prodromal symptoms were not reported. While still standing, the cosmonaut crossed his legs and tensed his leg muscles; this was followed by a rapid recovery of pulse pressure and a decrease in HR.

**DISCUSSION**

The findings of the present investigation are that, after spaceflight, HR was higher in standing position compared with preflight; the IBI-to-SBP lag, computed with time-domain baroreflex cross-correlation method, was increased. An IBI-to-SBP lag of ~0 s can be expected for vagal control of HR. This apparent delay of 0 s is due to the data representation: SBP and duration of the ongoing beat share the same spot on the time axis. Consequently, cross-spectral analysis also shows a phase difference of 0° (4). A cross-spectral phase lag of approximately ~70° at the 0.1-Hz band corresponds with an IBI-to-SBP lag of ~2 s in the time domain; this lag is due to the combined effect of vagal and sympathetic baroreflex regulation of cardiac cycle length (4). The increase in IBI-to-SBP lag postflight observed in this study therefore suggests an increased sympathetic influence on HR. HF spectral results of supine and standing blood pressure and IBI did not give further indication of increased vagal withdrawal after spaceflight: HF IBI spectral power and HF transfer gain were not significantly lower than preflight. We recognize that measurements were conducted between 1 and 3 days postflight (rather than immediately after landing) and also that n = 5 might not be sufficient for demonstrating statistical difference in spectral parameters, which show considerable time and subject variation. There was a wide interindividual range in response to standing after spaceflight, with two of five cosmonauts showing a highly variable blood pressure, small pulse pressures, and a postural tachycardia in the first 5 min of standing. The postflight hemodynamic response to standing was not approximated preflight with venous occlusion cuffs; we therefore have to reject our hypothesis that the postflight cardiovascular response to standing can be mimicked by using preflight thigh cuffs to trap venous blood in the legs and impede venous return.
Present Results Compared With Bed Rest and Acute Hypovolemia Data

Cardiovascular changes after bed rest (simulated microgravity) include a reduction in plasma volume, an increase in HR, and a decrease in SV with reduced orthostatic tolerance (11, 14). Concomitant changes in cardiac baroreflex control include a decrease in HF IBI spectral power and HF transfer function gain, indicating vagal withdrawal (11). In the same subjects, acute hypovolemia alone, induced by furosemide administration to produce a reduction of plasma volume similar to that after bed rest, resulted in a similar cardiovascular state and similar cardiac baroreflex control of HR, i.e., a decrease in HF IBI spectral power and transfer function gain. Vagal withdrawal after simulated microgravity therefore seems related to a reduction in plasma volume; this was supported by a further study demonstrating recovery of post-bed-rest HF spectral changes with restoration of plasma volume (10). When considering the present findings in postflight cosmonauts in light of these studies, it is surprising that we found no significant reduction in HF IBI power or transfer function gain, supine or standing, compared with preflight: this was seen after bed rest and after acute hypovolemia, apparent even in a small subject number (also 5) (11). Vagal withdrawal may well have been present immediately postflight; we may have missed this phenomenon by taking measurements only 1 to 3 days after landing. We can expect some restoration of plasma volume (and vagal withdrawal) to have taken place between landing and...
and measurement days, even though cosmonauts’ body weights were still reduced compared with preflight.

**Postflight Cardiovascular Adaptation Other Than Hypovolemia**

Whereas a decrease in HF IBI spectral power as a reflection of vagal withdrawal seems to result from plasma volume reduction, (simulated) microgravity leads to various additional cardiovascular adaptations. LF SBP spectral power is found to be decreased after bed rest but increased after acute hypovolemia (11), suggestive of impaired vasomotor function after bed rest. A study in hindlimb unloaded rats indicated that structural and functional remodeling of the arterial microvasculature occurs in skeletal muscles of these rats, apparently as a result of reductions in transmural pressure and wall shear stress (5). The authors remark that if in microgravity altered fluid pressure gradients and unloading of postural muscles leads to similar changes in mechanical forces acting on resistance arteries in humans, systemic vascular remodeling may underlie the compromised ability to elevate peripheral vascular resistance that underlies orthostatic hypotension after spaceflight (5). In the present study, however, arterial pressure did not decrease in orthostasis; we therefore did not find evidence of inability to sufficiently increase arterial vascular resistance. Nonneuronal mechanisms contributing to a steep decrease in SV on standing up after bed rest include cardiac atrophy (14, 18). Relative physical inactivity and plasma volume reduction during bed rest are thought to reduce cardiac loading conditions and be responsible for cardiac atrophy; the consequence is a prominent fall in SV during orthostasis (14). These observations were later confirmed for simulated microgravity and tentatively confirmed for actual microgravity; the authors concluded that bed rest deconditioning leads to changes in cardiac morphology (remodeling of the

<table>
<thead>
<tr>
<th>Transfer function, ms/mmHg</th>
<th>BL</th>
<th>TC</th>
<th>PF</th>
</tr>
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<tbody>
<tr>
<td>8.1 (4.0)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>*P = 0.07</td>
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<td></td>
<td></td>
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<tr>
<td>Phase, degrees</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>53 (13)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>*P = 0.07</td>
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<tr>
<td>0.85 (0.10)</td>
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<tr>
<td>Coherence</td>
<td></td>
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<tr>
<td>0.85 (0.10)</td>
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Values are means (SD). LF, low frequency; HF, high frequency. *Differences between sessions at BL, TC, and PF (2-way ANOVA on ranks), tested per frequency range.

**Table 3. Cross-spectral gain, phase, and coherence of spontaneous systolic blood pressure and interbeat interval variations in the upright position**

<table>
<thead>
<tr>
<th>Spontaneous IBI and SBP Variations</th>
<th>LF (0.06–0.15 Hz)</th>
<th>HF (0.15–0.50 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer function, ms/mmHg</td>
<td>BL</td>
<td>TC</td>
</tr>
<tr>
<td>8.1 (4.0)</td>
<td></td>
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<tr>
<td>Phase, degrees</td>
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<td>53 (13)</td>
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<td>0.85 (0.10)</td>
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Fig. 6. Preflight and postspaceflight distributions of delay (Tau). The time-domain baroreflex program PRVXBR computes the correlation between beat-to-beat SBP and IBI, resampled at 1 Hz, in a sliding 10-s window. Delays of 0–5 s between SBP and IBI are computed; the Tau with the greatest positive correlation is selected when significant at the *P = 0.01* level. A: supine. B: upright position.

Fig. 7. Correlation between time- and frequency-domain baroreflex sensitivity (BRS). Linear regression and correlation between average LF (0.06–0.15 Hz) transfer gains (frequency-domain BRS) and average xBRS results (time-domain BRS) of supine (breathing at 0.1 Hz) and upright position during preflight baseline, preflight thigh cuffs, and postflight. Error bars represent SE.
heart) first by changes in volume and secondarily via changes in muscle mass (18). In the present study, the high HR and small pulse pressure while standing, observed in two of five postflight cosmonauts, are likely to be related to steep falls in SV on standing up. The abnormal orthostatic response in Fig. 1, showing tachycardia and reduced pulse pressure during standing, also points to cardiovascular changes other than hypovolemia; plasma volume is likely to be (at least partially) restored 5 days postflight.

**Venous Occlusion Cuffs**

Venoconstrictive thigh cuffs have several applications, including venous occlusion plethysmography to quantify calf compliance and blood flow, and use in microgravity to effectively prevent fluid redistribution (15). Application of 30-mmHg thigh “bracelets” during a head-down tilt bed rest study resulted in immediate blood volume reduction in aorta, cerebral and femoral arteries, and a reduction in SV, indicating a reduction in the circulating blood volume compared with precuff values (1). It remains to be investigated whether in the present study venous occlusion of the legs did not mimic the typical postflight response to standing because the magnitude of circulating blood volume reduction was insufficient or because the mechanism of venous trapping of blood in the lower legs leads to a different cardiovascular response compared with diuretics-induced fluid depletion. Furthermore, postflight orthostatic fluid shifts are not related to plasma volume alone; plasma volume is reduced postflight, but extravascular (interstitial) fluid volume also plays an important role as a reservoir for maintenance of plasma volume and a determinant of interstitial fluid pressure, which positively influences orthostatic tolerance by resisting capillary filtration, compressing veins, and assisting the skeletal muscle pump (20). As an alternative explanation of why thigh cuffs did not mimic the postflight orthostatic response, we consider that although restoration of extravascular fluid volume may have taken place on measurement days in the present study, the application of thigh cuffs may have the reverse effect on extravascular fluid in the lower extremities (an increase) compared with spaceflight (a decrease), leading to opposite effects on orthostatic tolerance.

**Leg Crossing and Muscle Tensing**

In the present study, leg crossing and muscle tensing while standing, performed by one cosmonaut, led to a rapid increase in pulse pressure. Leg crossing and muscle tensing are known to result in an increase in cardiac output (19) and are therefore a useful countermaneuver to abort (12) and prevent vasovagal episodes in otherwise healthy patients who are prone to syncope. This might be a useful maneuver to combat the onset of vasovagal syncope in postflight cosmonauts as well.

**Limitations**

The multitude of limitations of the present study are partly related to space research, which can generally be associated with a low number of participants and a wide range of parallel experiments in a huge technical, medical, and logistic enterprise. The limited number of participating cosmonauts presented a difficulty in demonstrating statistical differences between conditions. Because postflight measurements were conducted as part of routine medical procedures, in some cases the cosmonaut was instructed to sit for 3–5 min before standing; therefore, we could not gauge the direct transition from supine to standing. Orthostatic stress was induced preflight by using a tilt table, postflight by active standing. Finally, sympathetic tone was assessed indirectly in this study from HR and blood pressure measurements, analyzed in the frequency and time domains, rather than more direct methods such as muscle sympathetic nerve activity recordings.

In conclusion, the present study demonstrates that time-domain BRS computation provides a high time-resolution indication of baroreflex response to standing after spaceflight; distribution of Tau is a novel way of expressing IBI-to-SBP lag as an indication of sympathetic tone similar to the phase lag in frequency analysis. Time and frequency analysis of postspaceflight sessions suggest increased sympathetic tone during standing but give no further indication of vagal withdrawal on measurement days, possibly owing to volume restoration after landing. Abnormal orthostatic responses in two of the five cosmonauts suggest cardiovascular adaptations other than hypovolemia. Thigh cuffs, applied to reduce venous return in preflight cosmonauts, did not predict postspaceflight cardiovascular response to standing. Leg crossing and muscle tensing performed by one postflight cosmonaut while standing rapidly restored a reduced pulse pressure.

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**GRANTS**

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**REFERENCES**


