Chapter 5. Orthostatic blood pressure control before and after space flight, determined by time-domain baroreflex method

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Orthostatic tachycardia and hypotention after space flight are related to volume depletion and excessive venous pooling. In the following study we investigate whether the postflight orthostatic response can be mimicked preflight, by using venous occlusion thigh cuffs to 'trap' venous blood in the lower limbs. We report preflight baseline, preflight venous occlusion and postflight hemodynamics, as well as time- and frequency domain baroreflex sensitivities.

Introduction

Astronauts returning from spaceflight suffer from varying degrees of orthostatic intolerance [25; 26], and they commonly present with orthostatic tachycardia and hypotension. The cardiovascular adaptations to microgravity leading to post-flight reduced orthostatic tolerance have been studied extensively. The carotid baroreceptor cardiac reflex response (BRS), as established using the neck cuff method to provoke neck pressure changes, is found to be decreased postflight [46]. Furthermore standing systemic vascular resistance is reported to be greater in those who could complete a stand test compared to those who could not [25; 47]. This does not appear to be due to an impaired sympathoadrenal system by exposure to microgravity, as found by examining the cardiovascular response to plasma catecholamines in human volunteers before and after space flight [130]. Results of muscle sympathetic nerve activity recordings during post-spaceflight stand tests also suggest an intact and appropriate sympathetic response [84]. Rather than malfunction of the sympathetic response, decreased orthostatic function after spaceflight (or bed-rest deconditioning) has been attributed to excessive reductions in stroke volume [25; 84; 130] possibly due to hypovolemia [98] and increased pooling of blood during standing [24]. We therefore set out to determine the blood pressure, heart rate and baroreflex response to standing, before and after space flight, using time- and frequency domain BRS computation. We conducted a preflight stand test with and without venous thigh cuffs to induce venous 'trapping' of blood in the lower limbs [4; 87]. We hypothesized that if the tachycardia and hypotension after space flight are indeed related central hypovolemia and excessive pooling of blood during orthostatic stress, reductions in central blood volume could mimic post-space flight response to standing.

Methods

Subjects

We studied 5 male cosmonauts who each took part in one of 3 different (10-11 day) Soyuz missions. At preflight data collection, average cosmonaut age was 40 (SD 3) years, 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 (21-23ºC) in the Academic Medical Center in Amsterdam, 3-5 months before launch. Subjects refrained from alcohol and caffeine for at least 5 hours prior to 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 [51]. Pneumatic cuffs (D.E. Hokanson Inc., Issaquah, Washington, U.S.A.) 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 N.C., U.S.A.) 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 carbon dioxide partial pressure (PCO_2) within a normal range as viewed on an in-house developed feedback leds-bar. A practice head-up tilt (HUT) to 70º and back to supine was carried out and paced breathing was practiced.

*Preflight*The baseline protocol started after at least 15 minutes 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, followed by 6/min and finally 15/min. Each breathing frequency was held for a duration of one minute plus two extra breaths and followed by a minute 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 70º; after 5 minutes HUT they were tilted back to supine. After a short break (3-5 min), venous return from the legs was impeded by inflating thigh cuffs to 40 mmHg; cuff pressure was maintained at this level while subjects were supine. Subjects rested for 4 minutes before repeating the paced breathing protocol. They were then tilted to 70º HUT within one second [51] and simultaneously thigh cuff pressure was increased to 100 mmHg, to compensate for the hydrostatic pressure increase during tilt. After 5 minutes in the HUT position they were tilted back to supine; simultaneously thigh cuffs were deflated completely.

Postflight Within 3 days of landing, a post-spaceflight protocol was conduced in the Gagarin Cosmonaut Training Center in Russia. Subjects refrained from alcoholic or caffeinated beverages starting at least 5 hours prior to 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 minutes followed by paced breathing at 10, 6 and 15 /min as described previously); however, the supine measurements were followed by 5 minutes active standing rather than passive HUT; furthermore in 3 of the 5 sessions the subject was seated for 3-5 minutes following supine recording and prior to standing up. PCO_2 was not monitored but the cosmonauts were carefully instructed to avoid hyperventilation and the experimenter visually checked respiratory excursions during paced breathing.

Immediately postflight One of the cosmonauts performed a 10-minute stand test in the medical tent at the landing site, within hours after landing. The crew surgeon conducted non-invasive finger blood pressure measurements using Portapres M2.

Measurements and Data Processing

Arterial blood pressure was continuously measured by a servo-controlled photophletysmograph (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 [69], 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 using a capnometer (Hewlett Packard).

Finger blood pressure was digitised at 100 Hz. Mean arterial blood pressure (MBP) was the true integral of the arterial pressure wave over 1 beat divided by the corresponding beat interval. Heart rate (HR) was computed as the inverse of the inter-beat 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 minutes prior to tilt/standing.

For frequency analysis, beat-to-beat systolic blood pressure (SBP) and IBI time series were detrended and Hanning Windowed. Power spectral density and cross-spectra of SBP and IBI were computed using discrete Fourier Transform [38]. 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/standing recording, 4 minutes were analysed (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 to 0.5 Hz, respectively.

For time-domain analysis of spontaneous baroreflex sensitivity (XBRS) we used the cross-correlation method PRVXBRS [129]. 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 to 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 a XBRS estimate if the correlation was significant at P=0.01. In figures 5.1 and 5.3, 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 mid-position, thus indicating joint events [129].

Statistical Analysis

Data are given as mean (SD) unless stated otherwise. Hemodynamic measurements, spectral indices and XBRS results were averaged per body position and per paced breathing frequency where appropriate and analysed across conditions as well as across frequency regions, using 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 using paired T-Test. Differences in Tau (optimal delay, output of PRVXBRS) between conditions were tested using the Chi Square 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

All 5 cosmonauts completed the entire pre- and postflight protocols and were able to remain upright for the duration of the tests.

Hemodynamic data

The landing site blood pressure recording is shown Figure 5.1; blood pressure is maintained while standing, with an elevated heart rate and a reduced, variable pulse pressure. Figure 5.2 shows the preflight and postflight hemodynamics for all cosmonauts. Heart rate in the upright posture was increased postflight compared to preflight (P=0.07); baseline preflight heart rate was 79 bpm; inflated thigh cuffs, 75 bpm, did not approach the postflight upright value of 88 bpm. Supine and upright systolic, diastolic and mean arterial pressure did not differ between pre- and postflight conditions.

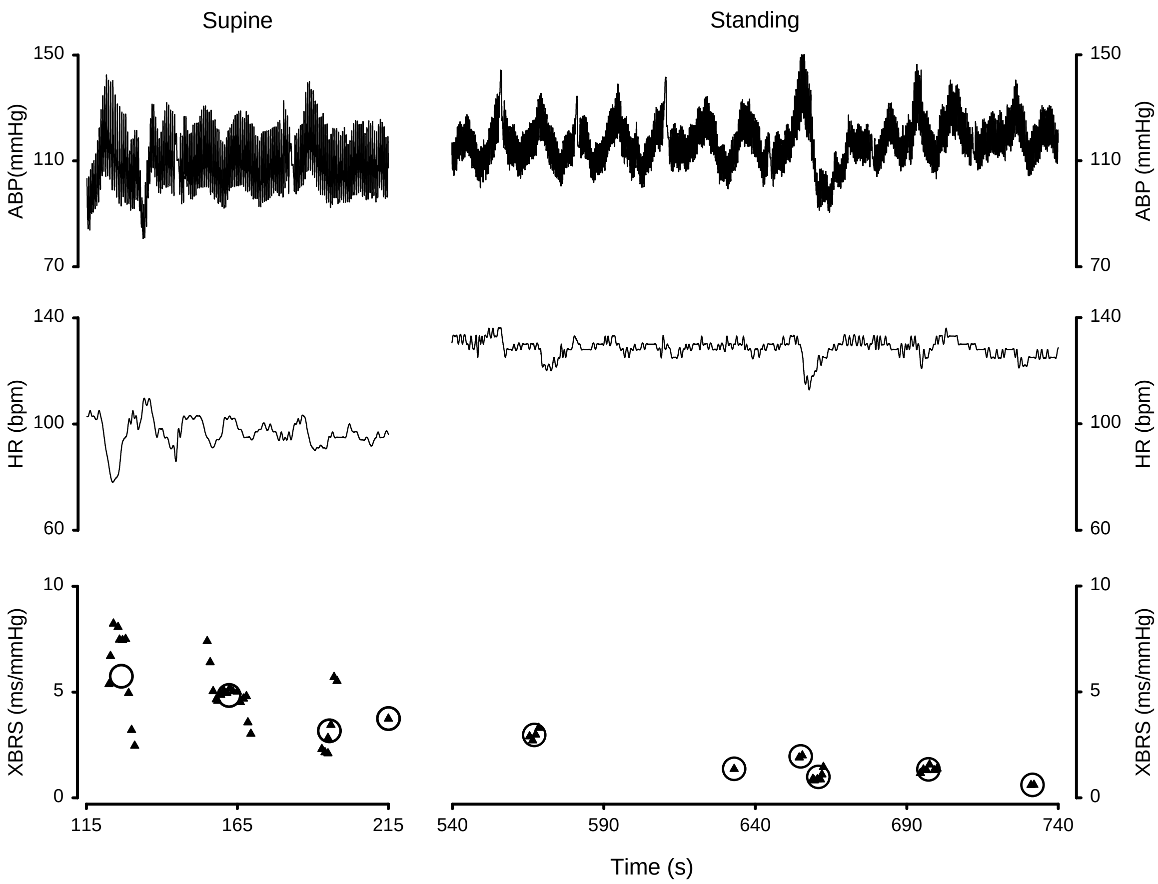


Figure 5.1
Post-spaceflight 10-minute stand test within hours after landing
ABP, arterial blood pressure; HR, heart rate; XBRS, time domain baroreflex sensitivity. Triangles are XBRS estimates; open circles are cluster averages of XBRS runs.

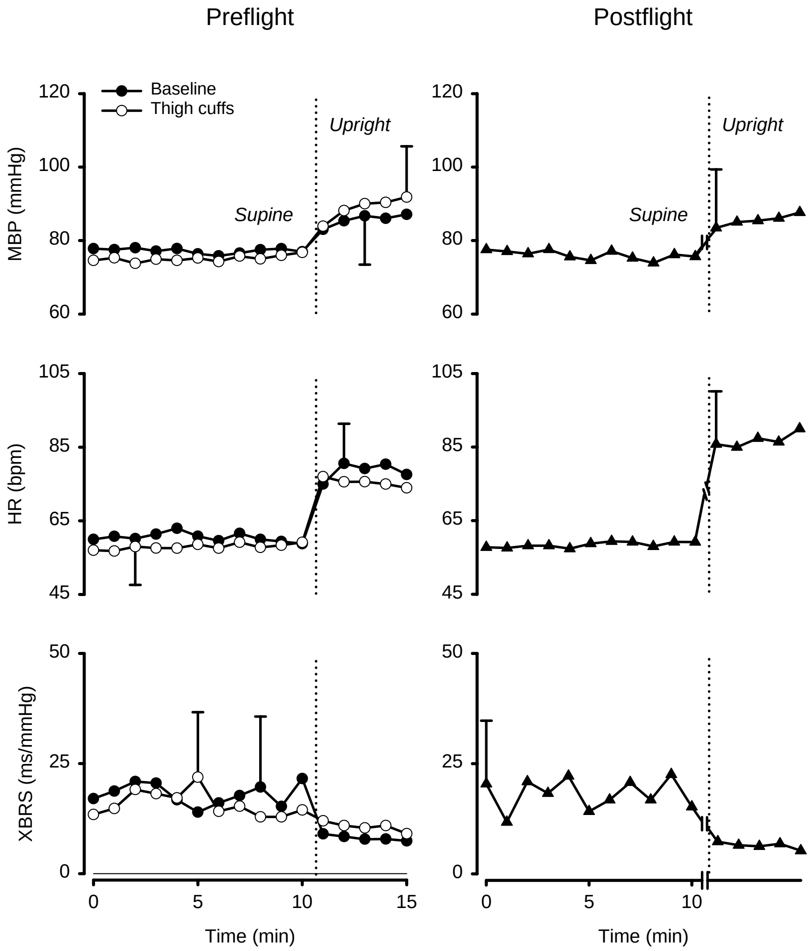


Figure 5.2
Mean blood pressure, heart rate, and time-domain baroreflex in the supine and upright posture during baseline recording, venous occlusion and postflight
Symbols represent the averages per minute; error bars represent the maximal SD The break in the axis indicated where 3 of the 5 cosmonauts sat for 3-5 minutes before standing up. MBP, mean blood pressure; HR, heart rate; XBRS, time domain baroreflex

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. 5.4). 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 5.1. 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 Figure 5.5; LF variability was greater than and HF variability. This was true for preflight baseline, venous occlusion and for postflight sessions. In the low frequency range, where cross-spectral coherence between SBP and IBI was high (Table 5.2), the transfer gain differed between sessions, with the greatest gain during venous occlusion and the lowest gain post-flight. 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 of IBI to SBP differed between conditions; phase lag was smallest during venous occlusion and greatest post-flight. The LF decrease in phase lag during standing, preflight baseline vs postflight, was not significant (P=0.10).

Table 5.1
Cross-spectral gain, phase and coherence of paced breathing-induced variations in systolic blood pressure and interbeat interval in the supine postion.

	Paced breathing								
	6/min (~ 0.1 Hz)			10/min (~ 0.17 Hz)			15/min (~ 0.25 Hz)		
	BL	TC	PF	BL	TC	PF	BL	TC	PF
Transfer function (ms/mmHg)	21 (19)	17 (9)* *P=0.09	14 (9)	24 (13)	17 (7)* *P=0.09	18 (10)	16 (9)	12 (5)* *P=0.09	16 (6)
Phase (degrees)	-39 (20)* *P=0.04	-20 (28)	-21 (66)	-24 (26)* *P=0.04	-18 (16)	-29 (20)	-4 (14)* *P=0.04	-8 (29)	-19 (14)
Coherence	0.83 (0.04)	0.83 (0.04)	0.74 (0.29)	0.82 (0.11)	0.75 (0.14)	0.86 (0.10)	0.88 (0.05)	0.80 (0.10)	0.89 (0.04)

Table 5.2
Cross-spectral gain, phase and coherence of spontaneous systolic blood pressure and interbeat interval variations in the upright postion.

	Spontaneous IBI and SBP variations					
	LF (0.06-0.15 Hz)			HF (0.15-0.50 Hz)		
	BL	TC	PF	BL	TC	PF
Transfer function (ms/mmHg)	8.1 (4.0) §P=0.07	9.4 (4.3) §P=0.07	6.8 (3.4) §P=0.07	6.7 (2.3)	9.8 (3.5)	4.9 (1.2)
Phase (degrees)	-53 (13) *P=0.04	-47 (11) *P=0.04	-68 (16) *P=0.04	-7 (21) §P=0.07;*P=0.04	0 (29) §P=0.07; *P=0.04	-24 (22) §P=0.07;*P=0.04
Coherence	0.85 (0.10) *P=0.04	0.80 (0.12) *P=0.04	0.84 (0.03) *P=0.04	0.37 (0.03) *P=0.04	0.43 (0.09) *P=0.04	0.44 (0.07) *P=0.04

Values are mean (SD). LF, low frequency; HF, high frequency; BL, preflight baseline; TC, preflight venous occlusion thigh cuffs; PF, postflight. *Differences between LF and HF, within a session: preflight, venous occlusion or postflight (Wilcoxon Signed Rank Test). §Differences between sessions at BL, TC and PF (two-way ANOVA on ranks), tested per frequency range

Time domain (PRVXBRS)
Baroreflex sensitivity evaluated in the time domain decreased from supine to upright in all three conditions (Fig. 5.2); from 17(10) ms/mmHg supine to 8(3) ms/mmHg standing at baseline preflight (P=0.085); from 15(7) to 10(5) ms/mmHg with thigh cuffs (P=0.058) and from 17(6) to 6(3) ms/mmHg after space flight (P=0.006). There were no significant differences in XBRS between preflight baseline, venous occlusion and post-flight conditions. The distributions of Tau (the 0-5 sec optimal delay of IBI to SBP) are shown in Figure 5.6. Compared to supine, the upright position resulted in a shift in the distribution toward higher values of Tau. After space flight, Tau distribution shifted toward higher Tau values compared to preflight baseline (P<0.001).

Time vs frequency domain
Comparing the average LF transfer gains (frequency domain BRS), to the average XBRS results (time domain BRS) of 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) (Figure 5.7).

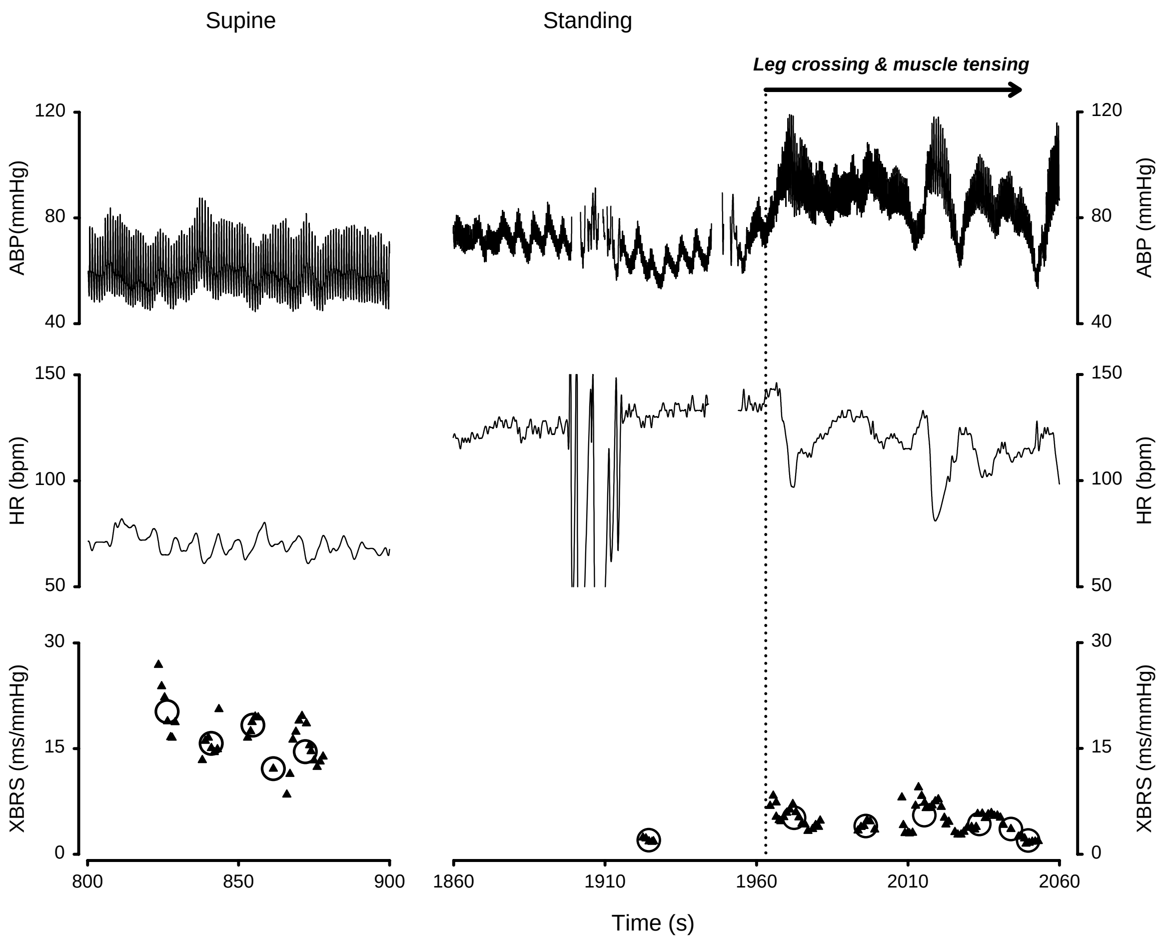


Figure 5.3
Ten minute stand test 5 days after space flight
At the end of a 10-minute stand test, a cosmonaut crossed his legs and tensed his muscles while standing. ABP, arterial blood pressure; HR, heart rate; XBRS, time domain baroreflex sensitivity. Triangles are XBRS estimates; open circles are cluster averages of XBRS runs.

Additional stand test with leg crossing

The end of an additional 10 minute stand test of one cosmonaut 5 days after landing is shown in Figure 5.3; 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, while brachial pressure (Omron automatic digital blood pressure monitor HEM-705CP) was 120/68 mmHg and HR was 63 bpm. Immediately after standing up the brachial blood pressure was 105/75, HR was 106 bpm. At the end of the 10-minute stand test, pulse pressure was reduced (Fig 5.3), 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.

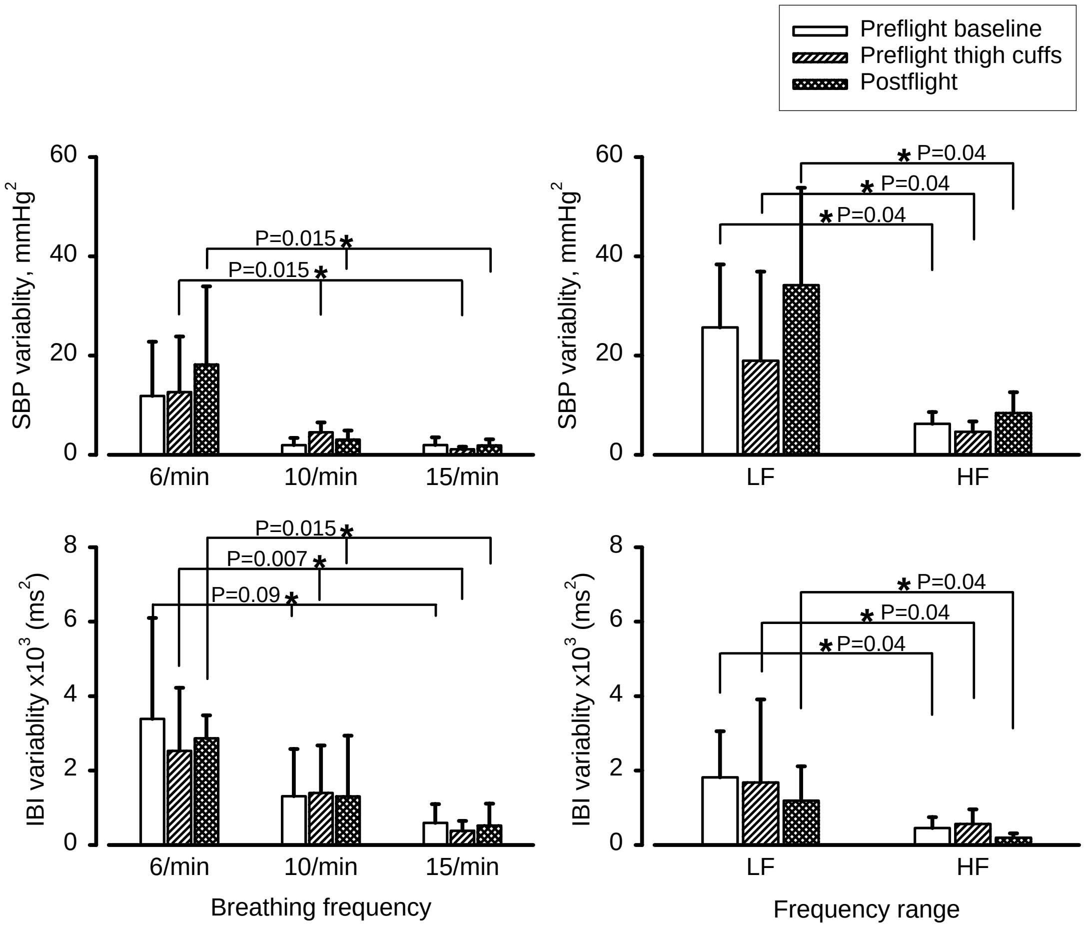
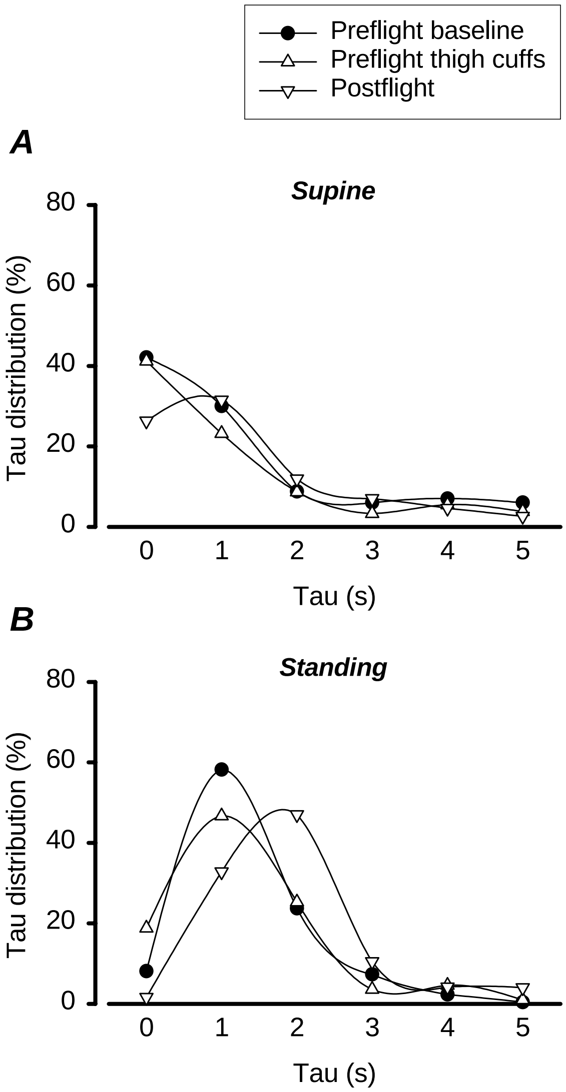


Figure 5.4 (*Left*)
Frequency analysis results of paced breathing in the supine position, before and after spaceflight

Figure 5.5 (*Right*)
Frequency analysis results of spontaneous blood pressure and beat interval variability in the upright position, before and after space flight
Systolic blood pressure (SBP) and inter-beat interval (IBI) variability are computed per breathing frequency.(Fig. 5.4, left) or between set frequency ranges (Fig. 5.5, right). P-values of differences between breathing frequencies are given when below 0.10. There are no significant differences across the conditions: baseline, thigh cuffs and postflight. N=5. LF = low frequency; HF = high frequency



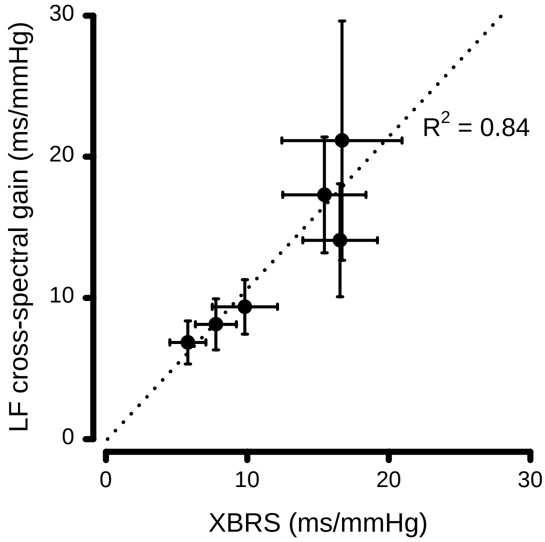


Figure 5.6
Preflight and post-spaceflight distributions of Tau
Time-domain baroreflex program PRVXBRS computes the correlation between beat-to-beat SBP and IBI, resampled at 1 Hz, in a sliding 10 s window. Delays of 0-5 s between SBP and IBI are computed; the delay (Tau) with the greatest positive correlation is selected when significant at the P=0.01 level. A: supine; and B: upright position.

Figure 5.7
Correlation between time and frequency domain 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. BRS, baroreflex sensitivity; LF, low frequency. Error bars represent S.E.

Discussion

The findings of the current investigation are first that reduced baroreflex sensitivity and increased IBI to SBP lag during standing, as demonstrated with 'traditional' frequency domain analysis and time domain computation of the IBI to SBP lag, suggest an increased sympathetic influence on HR after space flight. Second, the postflight increase in HR, decrease in BRS and greater IBI to SBP lag while standing were not approximated preflight with venous occlusion cuffs; we therefore have to reject our hypothesis that the postflight cardiovascular response to standing can be mimicked using pre-flight thigh cuffs to trap venous blood in the legs and impede venous return. Also of interest, leg crossing and muscle tensing while standing, performed by one cosmonaut, lead to a rapid increase in pulse pressure. Leg crossing and muscle tensing are known to result in an increase in cardiac output [123], and are therefore a useful counter-manoeuvre to abort [79] and prevent vasovagal episodes in otherwise healthy patients who are prone to syncope. This might be a useful manoeuvre to combat the onset of vasovagal syncope in post-flight cosmonauts as well. Moreover, the success of this manoeuvre underlines the dominant role of decreased venous return in postflight orthostatic problems.

In post-flight cosmonauts we found alterations in cardiovascular control in the upright position: namely, standing HR was increased compared to preflight and LF transfer function gain decreased. A right-ward shift in Tau distribution indicated a greater lag of IBI response to SBP variations in the standing position, after space flight. Altogether these results suggest an increase in sympathetic influence on heart rate in the upright position, after space flight. This confirms previous reports of increased sympathetic tonus and/or vagal withdrawal after bed-rest [98] and space flight [35; 36; 45; 46; 84], using a variety of techniques to assess sympathetic and/or vagal tone. Hypovolemia induced by diuretics, in the absence of cardiovascular deconditioning associated with space flight and bed rest, also results in vagal withdrawal and decreased transfer function gain [70]. Recently, restoration of plasma volume has been reported to normalize bed-rest induced reductions in vagally mediated arterial-cardiac baroreflex function [92] (ahead of print). Interestingly, the aortic baroreflex control of HR is greater in the hypovolemic state [34].

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 [87]. 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 stroke volume, indicating a reduction in the circulating blood volume compared with precuff values [4]. It remains to be investigated whether 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 to diuretics-induced fluid depletion.

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 post-flight measurements were conducted as part of routine medical procedures, in some cases the cosmonaut was instructed to sit for 3-5 minutes before standing; therefore we could not gauge the direct transition from supine to standing. Orthostatic stress was induced preflight using a tilt table, postflight by active standing. Finally, sympathetic tone was assessed indirectly in this study from HR and blood pressure measurements, analysed in the frequency and time-domain, 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 space flight; 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 post-spaceflight sessions suggest increased sympathetic tone during standing. Thigh cuffs, applied to reduce venous return in preflight cosmonauts, did not predict post-spaceflight cardiovascular response to standing. Leg crossing and muscle tensing performed by one post-flight cosmonaut while standing, rapidly restored a reduced pulse pressure. This could prove a useful counter manoeuvre to combat orthostatic intolerance after space flight.

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