

Respiratory modulation of cardiovascular rhythms before and after short-duration human spaceflight

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Received 26 November 2006,
revision requested 15 January 2007,
final revision received 5 July 2007,
accepted 11 July 2007

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Abstract

Aim: Astronauts commonly return from space with altered short-term cardiovascular dynamics and blunted baroreflex sensitivity. Although many studies have addressed this issue, post-flight effects on the dynamic circulatory control remain incompletely understood. It is not clear how long the cardiovascular system needs to recover from spaceflight as most post-flight investigations only extended between a few days and 2 weeks.

Methods: In this study, we examined the effect of short-duration spaceflight (1–2 weeks) on respiratory-mediated cardiovascular rhythms in five cosmonauts. Two paced-breathing protocols at 6 and 12 breaths min^{-1} were performed in the standing and supine positions before spaceflight, and after 1 and 25 days upon return. Dynamic baroreflex function was evaluated by transfer function analysis between systolic pressure and the RR intervals.

Results: Post-flight orthostatic blood pressure control was preserved in all cosmonauts. In the standing position after spaceflight there was an increase in heart rate (HR) of approx. 20 beats min^{-1} or more. Averaged for all five cosmonauts, respiratory sinus dysrhythmia and transfer gain reduced to 40% the day after landing, and had returned to pre-flight levels after 25 days. Low-frequency gain decreased from 6.6 (3.4) [mean (SD)] pre-flight to 3.9 (1.6) post-flight and returned to 5.7 (1.3) ms mmHg^{-1} after 25 days upon return to Earth. Unlike alterations in the modulation of HR, blood pressure dynamics were not significantly different between pre- and post-flight sessions.

Conclusion: Our results indicate that short-duration spaceflight reduces respiratory modulation of HR and decreases cardiac baroreflex gain without affecting post-flight arterial blood pressure dynamics. Altered respiratory modulation of human autonomic rhythms does not persist until 25 days upon return to Earth.

Keywords arterial pressure, autonomic modulation, baroreflex, heart rate, microgravity, respiration, space medicine.

In astronauts returning from short-duration (1–2 weeks) spaceflight, various microgravity-induced cardiovascular adaptations are manifested by orthostatic tachycardia in all, and hypotension in up to two-thirds of the astronauts (Buckey *et al.* 1996). Cardiovascular adaptations include an excessive reduction in stroke volume upon standing (Levine *et al.* 2002), probably because of combined effects of hypovolaemia (Leach

et al. 1996), cardiac remodelling and compromised diastolic function (Perhonen *et al.* 2001). Further evidence is provided of post-flight-blunted vascular control mechanisms (Convertino & Cooke 2005), together with attenuated carotid baroreceptor cardiac reflexes following exposure to simulated and real microgravity (Convertino *et al.* 1990, Fritsch *et al.* 1992). The overall result of these adaptations is a reduction in

vasoconstrictor reserve, which has been identified as an important contributor of orthostatic intolerance after spaceflight (Buckey *et al.* 1996, Fu *et al.* 2004).

Although symptoms of orthostatic intolerance disappear rather quickly, the autonomic control system recovers more slowly after spaceflight. There is mounting evidence that blunted spontaneous cardiac baroreflex sensitivity (BRS) persists for at least 2 weeks after landing (Fritsch-Yelle *et al.* 1994, Cooke *et al.* 2000). Accordingly, respiratory sinus dysrhythmia (RSD), i.e. the respiration-synchronous cyclic component of variability in cardiac cycle-length, has not yet been fully recovered within this period (Migeotte *et al.* 2003). Post-flight investigations extending to time frames of more than 2 weeks are lacking; therefore, it is unclear how long alterations in dynamic heart rate (HR) control need to recover. Early ground-based experiments have suggested that 25 days of recovery should be sufficient to return to pre-flight conditions (Convertino *et al.* 1990).

In the autonomic intact state, mechanical effects of respiration on stroke volume are opposed by changes in HR (Triedman & Saul 1994), either caused by the baroreflex (de Boer *et al.* 1987, Keyl *et al.* 2000) or by central feed-forward effects of respiration on the vagal motor nucleus (Eckberg 2003). This mechanism is suggested to buffer variability in cardiac output (Casadei *et al.* 1992), which in turn appears to be the main source of respiration-synchronous fluctuations in arterial blood pressure (Toska & Eriksen 1993). There is a mounting evidence from cholinergic blockade experiments (Toska & Eriksen 1993) that a reduction in vagal-cardiac nerve traffic, and thus RSD, leads to enhanced respiratory arterial pressure fluctuations. Eliminating vagal cardiac influences by electrical cardiac pacing shows that the buffering role of RSD only accounts when mechanical effects of respiration are larger than those in supine humans (Taylor & Eckberg 1996). Whether reductions in RSD after spaceflight can be associated with augmented respiratory blood pressure dynamics upon standing in orthostatic tolerant astronauts has been argued (Cooke *et al.* 2000, Gisolf *et al.* 2005).

In the present study, we used a paced-breathing protocol to assess respiratory modulation of cardiovascular rhythms in five cosmonauts, before short-duration spaceflight (10 days), and after 1 and 25 days upon return to Earth. At the same time, we set out to determine the baroreflex response to standing, using transfer function BRS computations (Saul *et al.* 1991). With the above background we hypothesized that, if diminished RSD after spaceflight is related to a vagal-cardiac neural deficit, the post-flight circulatory response to standing should be associated with higher respiratory arterial pressure fluctuations compared with pre-flight.

Methods

Subjects

Five male cosmonauts who each took part in one of three different (10–11 days) European Space Agency (ESA) Soyuz missions (Odyssey, Cervantes, Delta) to the International Space Station (ISS) were enrolled in this study. At pre-flight data collection, average cosmonaut age was 40 (SD 3) years, height 180 (SD 4) cm and weight 76 (SD 10) kg. Because of time constraints, no routine physical exercise was performed onboard the ISS to counter post-flight orthostatic intolerance. Upon return, there was also no specific rehabilitation programme. Each subject was informed about the experimental procedures and signed an informed consent form. The experimental protocol was approved by the Ethics Committee of the local university and the ESA Medical Board. The study complies with the Declaration of Helsinki.

Experimental design

Subjects refrained from alcohol and caffeine for at least 9 h before the data collection. Pre-flight (between 30 and 45 days before launch), as well as early post-flight (R + 1; 1 day after landing) data collection was performed in the Medical Building of Gagarin Cosmonaut Training Center (Moscow, Russia) at ambient room temperature. Late post-flight (R + 25; between 25 and 28 days after landing) data collection was performed in a temperature-controlled laboratory (21–23 °C) in the University Hospital of Leuven, Belgium. Table 1 shows the days of data collection for pre- and post-flight measurements in the individual cosmonauts together with their weight at the time of measurement. Recording sessions took place in the morning before 1 PM. At the beginning of each session, subjects rested quietly in the supine position and breathed at a comfortable uncontrolled rate for about 15 min until haemodynamic equilibration. Subjects were then instructed to pace their breathing to an audio stimulus with visual feedback. A sequence of tones was generated by a laptop computer and target-breathing sequences were displayed graphically in real time on the screen (Beckers *et al.* 2004). The laptop computer was positioned on an adjustable stand so that the subject could view the screen comfortably throughout the entire protocol. Two breathing protocols were performed in succession in which respiratory sequences were evenly spaced in time at preset rates of 12 breaths min⁻¹ or 0.2 Hz [normal paced breathing (NPB)] and 6 breaths min⁻¹ or 0.1 Hz (slow paced breathing, SPB) to ensure blood pressure variations at these frequencies. Each breathing frequency was held for 3 min and interspaced by a 1-min

Table 1 Cosmonauts body weight on pre- and post-flight sessions

Cosmonaut	Pre-flight		Early post-flight		Late post-flight	
	Day	Weight (kg)	Day	Weight (kg)	Day	Weight (kg)
I	L - 30	88	R + 1	84	R + 25	89
II	L - 30	64	R + 1	58	R + 25	63
III	L - 45	68	R + 1	65	R + 28	68
IV	L - 45	81	R + 1	79	R + 25	80
V	L - 45	81	R + 1	78	R + 25	82

L - 30 and L - 45 represent 30 and 45 days before launch. R + 1, R + 25 and R + 28 represent 1, 25 and 28 days after landing.

rest period (spontaneous breathing). Subjects were then moved to the standing position and after a minimum of 10 min the breathing protocol was repeated. Although respiratory intervals were controlled, subjects were able to comfortably control depth of inspiration to preserve normal ventilation and to prevent hypocapnia (Cooke *et al.* 1998). Subjects were instructed by the authorities of the Russian human spaceflight programme to be seated for 3–5 min after supine recording and before standing up. The same procedures were reproduced at pre- and post-flight test sessions.

Instrumentation

The electrocardiogram (ECG) was recorded and beat-by-beat arterial pressure was estimated with a servo-controlled photoplethysmograph (Portapres; TNO, Amsterdam, the Netherlands) placed on the midphalanx of the right middle finger (Imholz *et al.* 1998). The latter was positioned at heart level and held in place using an arm sling to prevent hydrostatic pressure differences while standing. Finger-cuff pressures were calibrated against intermittent arm-cuff pressures (STBP-780; Colin, Komaki, Japan) and used to track arterial blood pressure changes. Respiratory rate was evaluated using an abdominal pressure sensor (MR10; Graseby Medical, Hertfordshire, UK). Finger blood pressure, ECG and respiration frequency were digitized at 1000 Hz using an external A/D converter (DATAQ Instruments, Akron, OH, USA) and stored on a laptop computer.

Data processing

A file containing the RR intervals (RRI) was created for each breathing frequency (3-min period). Mean arterial pressure (MAP) was calculated as the true integral of the arterial pressure wave divided by the corresponding beat interval duration. Pulse pressure (PP) was calculated as the difference between systolic arterial pressure (SAP) and diastolic arterial pressure (DAP). Two linear filters were applied to correct for data points outside a limit interval (Aubert *et al.* 1999). The resulting

beat-to-beat haemodynamic time series were interpolated using a cubic-spline approximation and were resampled at 2 Hz to construct equidistant time series. A sliding window of 128 s (256 samples) was applied with 16 s increments. This process resulted in four segments of data in each time series. The DC component was removed by subtracting the mean value, and a Hanning window was applied. A non-parametric 'run test' of means and mean square values was used to validate the stationarity of data within 5% of the confidence limits (Aubert *et al.* 1999). In the resulting time windows, power spectral density was averaged using Fast Fourier transform. The spectral resolution for all estimates equalled 0.0078 Hz. Respiratory powers were expressed as the area under the spectrum from 0.08 to 0.12 Hz (SPB) and from 0.18 to 0.22 Hz (NPB). During NPB (0.2 Hz), a second spontaneous rhythm occurring over an approximate 10-s cycle and resulting in a low-frequency band (0.04–0.15 Hz) was obtained as well. Power spectral units for RRI and arterial pressure fluctuations were squared amplitudes. The transfer function gain, phase and squared coherence between SAP and RRI were estimated by cross-spectral data derived with the same set of parameters used for power spectral analysis (Saul *et al.* 1991). All analysis software have been developed inhouse using LABVIEW 7.1 (National Instruments, Austin, TX, USA) for Windows.

Statistics

Statistical analysis was performed with spss version 8.0 for Windows (Scientific Packages for Social Sciences, Chicago, IL, USA). Data are given as mean \pm SE unless stated otherwise. Spectral data were logarithmically transformed before further statistical testing. Haemodynamic measurements, spectral and cross-spectral indices were averaged per body position and breathing frequency, and analysed across conditions using general linear model repeated-measures ANOVA with pre- and post-flight sessions, body posture and breathing frequency as test variables. Differences between pre- and

post-flight sessions were tested with Bonferroni correction for repeated measurements where appropriate. Pearson's correlation coefficient (r) was computed to evaluate the relationship between the mean RRI and RSD. P values < 0.05 were considered statistically significant.

Results

Subjects

Cosmonaut body weight at pre- and post-flight sessions is given in Table 1. Body weight at early post-flight sessions was significantly lower ($P = 0.042$) compared with pre-flight [73 (SD 11) kg vs. 76 (SD 10) kg] and returned to pre-flight body weight at late post-flight sessions [76 (SD 11) kg]. All five cosmonauts completed the entire pre- and post-flight protocols and were able to remain upright for the entire test duration. None suffered from problems of post-flight orthostatic intolerance.

Haemodynamic data

Figure 1 shows the pre- and post-flight recordings of HR and arterial blood pressure in one representative cosmonaut. The upper panels show the results from SPB (0.1 Hz), and the results from NPB (0.2 Hz) are presented in the lower panels. Blood pressure was variable but did not drop upon standing at both breathing frequencies. The corresponding averaged haemodynamic data from all five cosmonauts are given in Table 2. Comparing pre- to post-flight conditions shows that, in both the standing and supine postures,

HR differed significantly between sessions; *post hoc* analysis indicated an increased HR at early post-flight sessions compared with pre-flight (supine $P = 0.015$; standing $P = 0.010$). The post-flight changes in HR had returned to pre-flight levels after 25 days upon return. Supine and standing systolic, diastolic and MAP did not differ between pre- and post-flight conditions. Also, PP was not significantly different from pre-flight. On standing up, there was an increase in HR, DAP and MAP, whereas PP decreased significantly (all $P = 0.05$). The increase in HR upon standing was most pronounced at early post-flight sessions (Fig. 2).

Spectral analysis

All cosmonauts were able to track their respiratory rate with the visual targets closely ensuring blood pressure and RRI variations at frequencies of 0.1 and 0.2 Hz. SPB induced significantly larger RRI (Fig. 3) and MAP (Fig. 4) variations compared with NPB. On standing up, there was a tendency of less respiratory RRI variability (RSD) ($P = 0.137$), whereas respiration-synchronous MAP fluctuations significantly increased upon standing ($P = 0.001$). Comparing pre- to post-flight conditions, we found significant differences in RSD (Fig. 3, upper and middle panel), with the lowest values at early post-flight standing ($P = 0.001$) and supine ($P = 0.005$) conditions. Post-flight differences in RSD did not persist until 25 days after landing. Unlike post-flight changes in RSD, the magnitudes of paced-breathing-induced MAP fluctuations were not significantly different between pre- and post-flight sessions (Fig. 4, upper and middle panel).

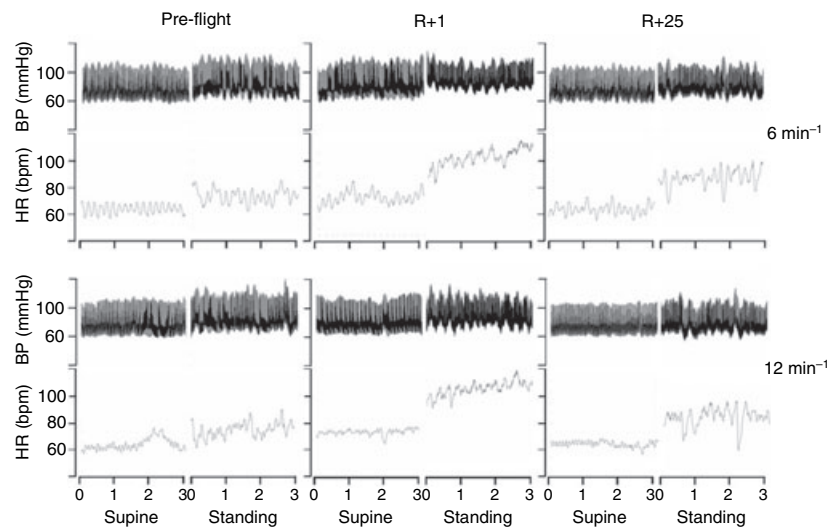


Figure 1 Supine and standing heart rate (HR) and arterial blood pressure (BP) recordings in a representative cosmonaut before flight (pre-flight), early post-flight (R + 1) and late post-flight (R + 25). Supine and standing recordings cover time periods of 3 min. Upper panels show results from slow paced breathing (6 breaths min^{-1}). Lower panels show results from normal paced breathing (12 breaths min^{-1}).

Table 2 Pre- and post-flight haemodynamic data in standing and supine cosmonauts

	6 breaths min ⁻¹ (0.1 Hz)			12 breaths min ⁻¹ (0.2 Hz)		
	Pre-flight	Early post-flight	Late post-flight	Pre-flight	Early post-flight	Late post-flight
Standing						
HR (beats min ⁻¹)	79 ± 12	99 ± 6	80 ± 6	81 ± 14	103 ± 9	85 ± 4
MAP (mmHg)	87 ± 7	93 ± 8	91 ± 5	87 ± 4	96 ± 4	84 ± 5
DAP (mmHg)	73 ± 6	78 ± 8	79 ± 4	73 ± 3	79 ± 5	82 ± 5
SAP (mmHg)	122 ± 10	128 ± 7	126 ± 7	126 ± 7	132 ± 3	127 ± 6
PP (mmHg)	49 ± 5	47 ± 2	47 ± 4	53 ± 5	47 ± 2	45 ± 4
Supine						
HR (beats min ⁻¹)	62 ± 4	70 ± 8	62 ± 5	59 ± 7	68 ± 9	60 ± 4
MAP (mmHg)	80 ± 3	88 ± 5	85 ± 5	81 ± 2	86 ± 5	83 ± 3
DAP (mmHg)	63 ± 2	70 ± 4	69 ± 4	63 ± 2	68 ± 5	67 ± 3
SAP (mmHg)	121 ± 3	126 ± 7	123 ± 7	122 ± 3	127 ± 4	121 ± 5
PP (mmHg)	59 ± 3	53 ± 5	54 ± 4	59 ± 2	58 ± 4	53 ± 3

Breathing was controlled at fixed frequencies of 6 (0.1 Hz) and 12 (0.2 Hz) breaths min⁻¹. Values are mean ± SE. HR, heart rate; MAP, mean arterial pressure; DAP, diastolic arterial pressure; SAP, systolic arterial pressure; PP, pulse pressure.

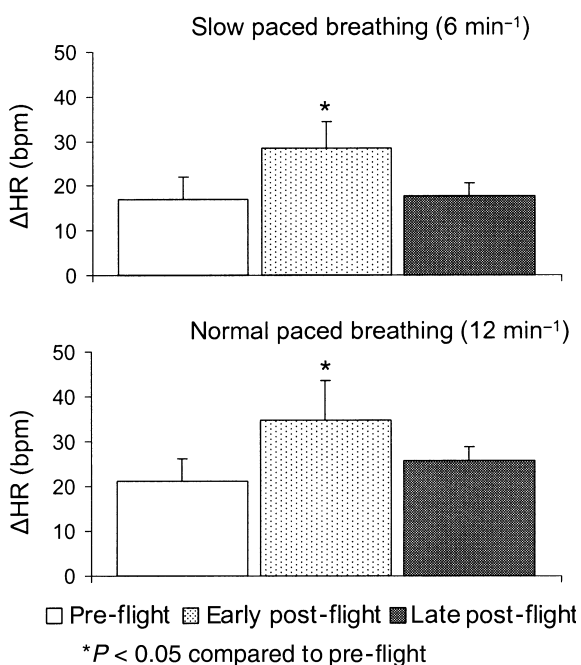


Figure 2 Average heart rate (Δ HR) response to standing before and after spaceflight. Data are presented of slow paced-breathing and normal paced-breathing protocols at pre-flight, early post-flight (R + 1) and late post-flight (R + 25) sessions.

Spectral estimates of spontaneous low-frequency rhythms are obtained during NPB (0.2 Hz) by integrating the area between 0.04 and 0.15 Hz (Figs 3 and 4, lower panel). Comparing pre- to post-flight conditions shows that, in the standing position, there was a significant reduction in spontaneous low-frequency RRI variability early post-flight (Fig. 3, lower panel).

Consequently, compared with supine, significant higher standing RRI oscillations at pre-flight disappeared early post-flight, and turned out to be higher again after 25 days upon return. Standing further resulted in significant higher spontaneous low-frequency MAP fluctuations compared with supine (Fig. 4, lower panel).

Transfer function analysis

Results of transfer function analysis are graphically presented in Figure 5. The supine and standing SAP-RRI coherence was generally high at the respiratory frequencies (shaded areas). Phase lags were consistently negative at SPB-induced oscillations, indicating that pressure variability leads interval variability. This is further denoted as the RRI-to-SAP time delay. The RRI-to-SAP time delay was close to zero at the NPB-frequencies in the supine position but tended to become negative upon standing ($P = 0.09$). Standing-up resulted in a significantly smaller SAP-RRI transfer function gain compared with supine at both slow and normal paced-breathing frequencies (Fig. 6, upper panel). Comparing pre- to post-flight conditions shows that, in the standing position, the gain and the phase lag of paced-breathing-induced SAP and RRI oscillations differed significantly between sessions; *post hoc* analysis indicated a lower transfer gain ($P = 0.009$) and larger RRI-to-SAP time delay ($P = 0.022$) at early post-flight sessions compared with pre-flight. The post-flight changes in transfer gain and phase lag had returned to pre-flight levels after 25 days upon return. There were no differences in the SAP-RRI coherence between pre- and post-flight conditions.

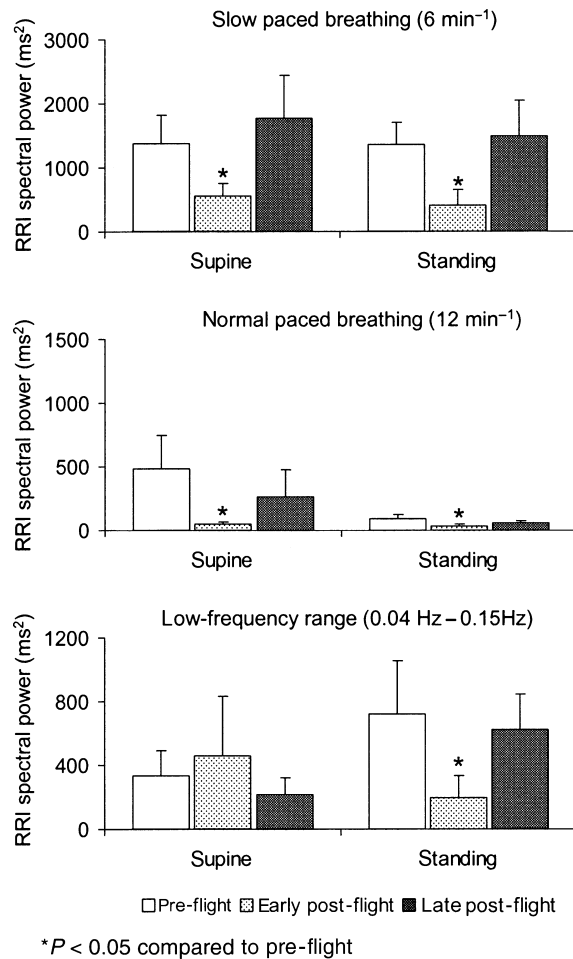


Figure 3 Average data of RR intervals (RRI) spectral powers in standing and supine cosmonauts before and after spaceflight. The respiratory RRI spectral powers are presented from slow paced breathing (upper panel) and normal paced breathing (middle panel), as well as powers from spontaneous low-frequency (0.04–0.15 Hz) RRI oscillations (lower panel) at pre-flight, early post-flight (R + 1) and late post-flight (R + 25) sessions.

The SAP–RRI coherence was generally high, and the phase lag was consistently negative (RRI-to-SAP time delay) in the low-frequency range (0.04–0.15 Hz) as indicated by the area between the shaded lines in the lower panel of Figure 5. Upon standing, there was a significant reduction in low-frequency transfer function gain compared with supine (Fig. 6, lower panel). At the same time, the RRI-to-SAP time delay was significantly larger in the standing position. Comparing pre- to post-flight conditions shows that, in the standing position, the low-frequency gain and the phase lag differed significantly between sessions; *post hoc* analysis indicated a lower transfer gain ($P = 0.019$) and larger RRI-to-SAP time delay ($P = 0.032$) at early post-flight sessions compared with pre-flight. Early post-flight changes in low-frequency transfer gain and phase lag

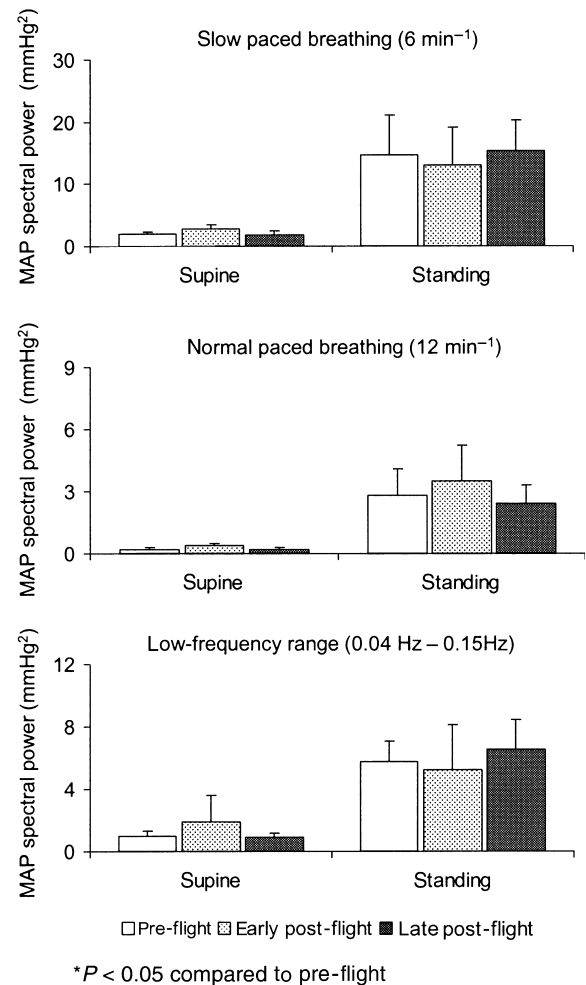


Figure 4 Average data of mean arterial pressure (MAP) spectral powers in standing and supine cosmonauts before and after spaceflight. The respiratory MAP spectral powers are presented from slow paced breathing (upper panel) and normal paced breathing (middle panel), as well as powers from spontaneous low-frequency (0.04–0.15 Hz) MAP oscillations (lower panel) at pre-flight, early post-flight (R + 1) and late post-flight (R + 25) sessions.

had returned to pre-flight levels after 25 days upon return. There were no differences in the SAP–RRI coherence between pre- and post-flight conditions.

Relationship between mean RRI and RSD

Figure 7 shows the relationship between mean RRI and spectral powers (logarithmically transformed) obtained from NPB-induced RRI oscillations (0.2 Hz) and SPB-induced RRI oscillations (0.1 Hz). There appears to be a linear relationship between mean RRI and spectral powers of NPB-induced RRI; however, this relationship does not account for SPB-induced RRI oscillations ($r = 0.47$; $P = \text{ns}$).

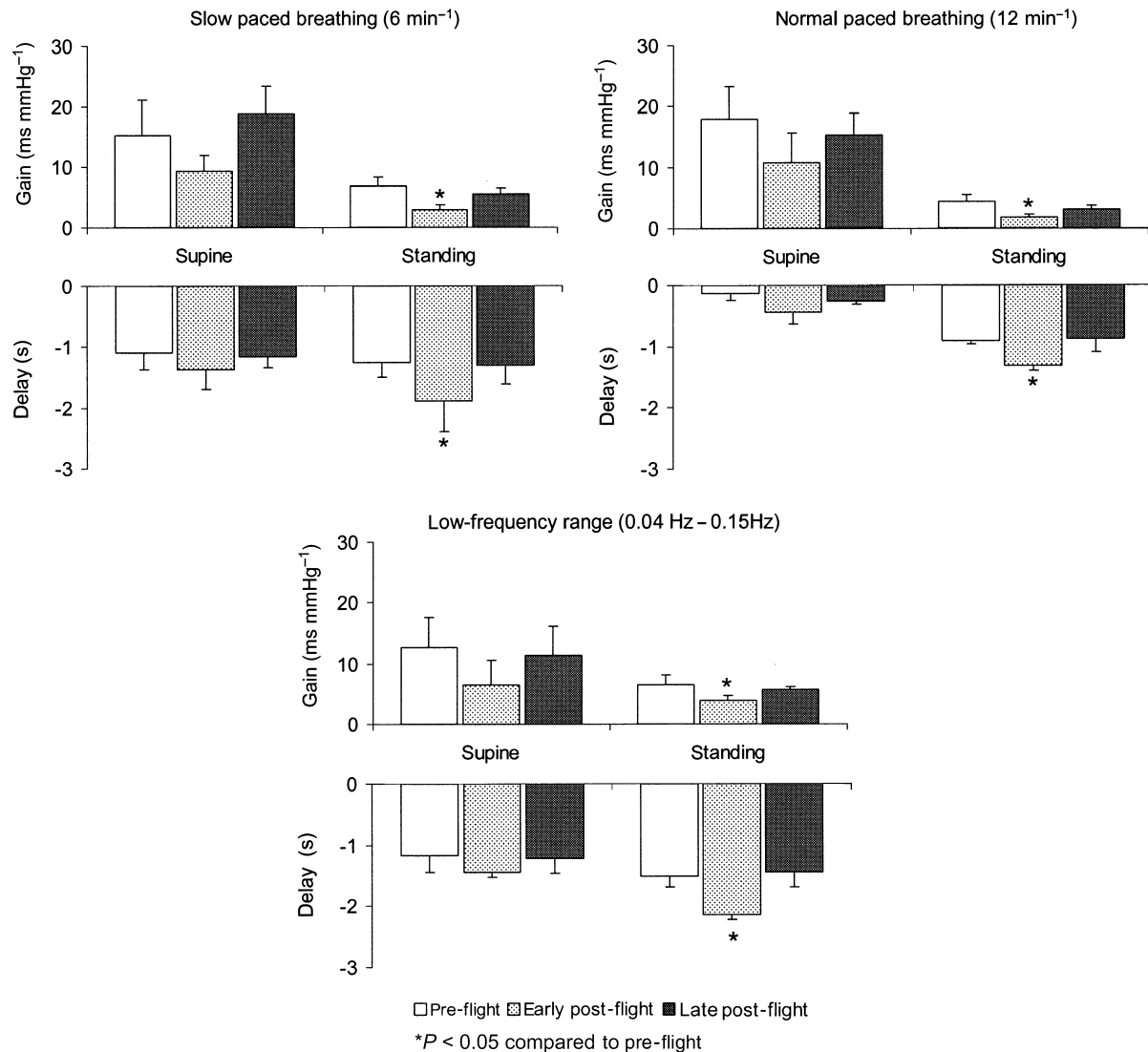


Figure 6 Average results of systolic arterial pressure (SAP)-RR intervals (RRI) transfer function gain and time delay in standing and supine cosmonauts before and after spaceflight. Results are obtained at respiratory frequencies from slow paced-breathing and normal paced-breathing protocols. In addition, the gain and delay are also presented from spontaneous low-frequency rhythms (0.04–0.15 Hz) during normal paced breathing. Results are presented from pre-flight, early post-flight (R + 1) and late post-flight (R + 25) sessions.

(Fritsch-Yelle *et al.* 1994, Cooke *et al.* 2000, Migeotte *et al.* 2003).

Sympathetic implications on vagal-cardiac assessments after spaceflight

Parallel impairments of RSD and spontaneous cardiac BRS after spaceflight may be causally related as both reflexes result primarily from vagal-cardiac adjustments (Kunze 1972). Our findings therefore support multiple previous reports of diminished vagal-cardiac outflow following short-duration spaceflight (Fritsch-Yelle *et al.* 1994, Cox *et al.* 2002, Levine *et al.* 2002, Migeotte

et al. 2003). However, the reliability of RSD as a quantitative index of vagal-cardiac nerve traffic has recently been argued (Parati *et al.* 2006, Taylor & Studinger 2006). Taylor & Studinger (2006) demonstrated that an increased sympathetic drive restricts RSD to lower levels at both rapid and lower breathing frequencies. Post-flight reductions in RSD and spontaneous cardiac BRS, therefore, may be partially ascribed to an increased sympathetic drive in orthostatic tolerant astronauts (Fritsch-Yelle *et al.* 1996, Cox *et al.* 2002, Levine *et al.* 2002). In the present study, an increased sympathetic effect on dynamic HR control is suggested from a larger RRI-to-SAP time delay early post-flight

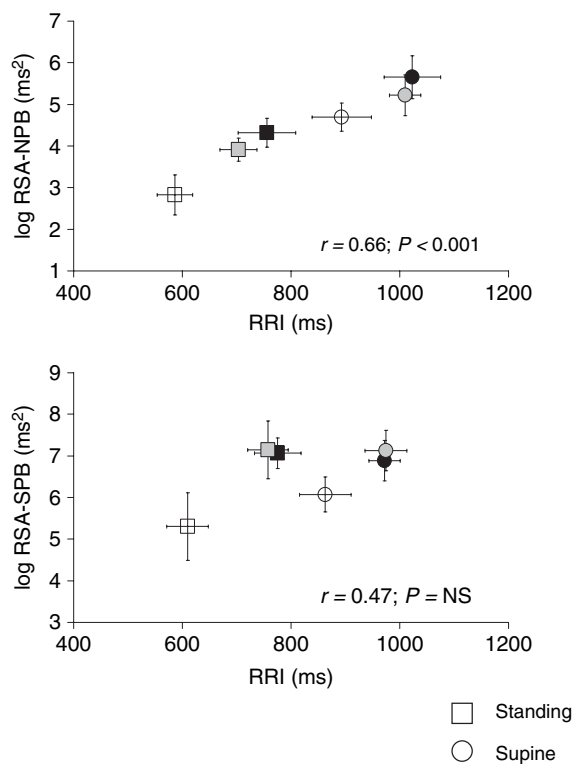


Figure 7 Relationship between mean RR intervals (RRI) and spectral powers (logarithmically transformed) obtained from normal paced-breathing-induced RRI oscillations (0.2 Hz) and slow paced-breathing-induced RRI oscillations (0.1 Hz). Data are presented as mean values and SE. Squared symbols, standing; circular symbols, supine; solid symbols, pre-flight; open symbols, early post-flight; shaded symbols, late post-flight.

(Fig. 6) (Gisolf *et al.* 2005). Indeed, an RRI-to-SAP delay of approx. 0 s can be expected for vagal HR control, whereas RRI-to-SAP time delays between 1 and 2 s are suggested to result from the combined effect of vagal and sympathetic baroreflex regulation of cardiac cycle length (de Boer *et al.* 1987).

Interestingly, the linear correlation between mean RRI and NPB-induced RRI oscillations disappears during SPB (Fig. 7). This frequency-dependent phenomenon is likely to be the result of sympathetic support to RSD during SPB (Cooke *et al.* 1998). Upon standing, a rise in HR can be explained by vagal-cardiac withdrawal as indicated by a reduction in RSD during NPB. Conversely, RSD was well maintained upon standing during SPB because of an increased sympathetic support to the more slowly respiratory RRI oscillations. In view of these findings, early post-flight reductions in RSD, both at SPB and NPB frequencies, support the concept that tachycardia after 10 days spaceflight can be related to vagal-cardiac withdrawal, rather than being the result of an increased sympathetic drive.

Hypovolaemia and circulatory control after short-duration spaceflight

Autonomic response changes after (simulated) microgravity are very consistent with those observed during acute interventions that favour central hypovolaemia, such as acute hypovolaemia with furosemide (Iwasaki *et al.* 2000), head-up tilting (Triedman *et al.* 1993) and lower-body negative pressure (Hughson *et al.* 1994). Studies using head-down bed rest (simulated microgravity) deconditioning showed that attenuated vagal-cardiac modulation (BRS) is mainly related to reduced plasma volumes (Iwasaki *et al.* 2000). This is supported by a later study demonstrating normalization of post-bed rest vagal-cardiac modulation with restoration of plasma volume (Iwasaki *et al.* 2004). Congruent results from three Neurolab-reports (Cox *et al.* 2002, Ertl *et al.* 2002, Levine *et al.* 2002) showed that lower plasma volumes importantly contribute to the augmented sympathetic drive in orthostatic tolerant astronauts after spaceflight. When considering our findings after spaceflight in light of these studies, early post-flight reductions in body weight (Table 1) may be partially explained by a reduction in plasma volume. Yet, other factors like diminished nutrition and space motion sickness may also have contributed to the post-flight reduction in body weight (Aubert *et al.* 2005).

Post-flight cardiovascular adaptations other than hypovolaemia

In addition to hypovolaemia, other cardiovascular adaptations have been reported after (simulated) microgravity including cardiac remodelling and/or compromised diastolic function (Perhonen *et al.* 2001). The consequence is a prominent fall in stroke volume during post-flight orthostasis. In orthostatic tolerant cosmonauts, the greater HR response to standing (Fig. 2) is likely to be related to steep falls in stroke volume on standing up early post-flight (Levine *et al.* 1997).

At this moment, the most likely explanation of orthostatic hypotension after spaceflight is a diminished vasoconstrictor reserve capacity (Buckey *et al.* 1996, Fritsch-Yelle *et al.* 1996, Waters *et al.* 2002). This mechanism explains the discrepancy in vascular function between orthostatic tolerant and intolerant astronauts (Convertino & Cooke 2005). The compromised ability to elevate vascular resistance in presyncopal astronauts has also been ascribed to systemic vascular remodelling (Delp *et al.* 2000) and/or low α_1 -adrenergic receptor sensitivity (Meck *et al.* 2004). Low-frequency systolic blood pressure spectral power is found to be decreased after bed rest, but increased after acute hypovolaemia (Iwasaki *et al.* 2000), suggestive of impaired vasomotor function following simulated

microgravity deconditioning. In the present study, post-flight arterial pressure did not decrease in orthostasis, and sympathetic vasomotor function was preserved at pre-flight levels. Therefore, as expected in orthostatic tolerant cosmonauts, we did not find evidence of a compromised ability to elevate vascular resistance.

Post-flight recovery after 25 days

In agreement with a previous ground-based experiment (Convertino *et al.* 1990), our data show that post-flight alterations in circulatory control do not persist until 25 days after return from short-duration spaceflight. This seems at odds with a preliminary study in three cosmonauts, reporting reduced high-frequency RRI spectral powers (0.15–0.4 Hz) up to 25 days after return to Earth (Beckers *et al.* 2003). A major contribution for this discrepancy, next to the limited number of subjects, may come from differing methodologies: fixed breathing rates were imposed in the present study instead of spontaneous breathing, which spreads out respiratory-mediated RRI powers over a broader frequency range (0.15–0.4 Hz). Under normal basal conditions, spontaneous breathing patterns of healthy subjects are rather variable (Tobin *et al.* 1988) and a substantial percentage of breaths may occur at frequencies below 0.15 Hz (Pinna *et al.* 2006). Hence, respiration should be controlled if RRI powers are to be interpretable (Brown *et al.* 1993). On the other hand, imposing fixed breathing frequencies could disturb the net effect of vagal-cardiac respiratory modulation under basal circumstances (Pagani *et al.* 1986). Therefore, interpretation of respiratory RRI oscillations from distinct breathing protocols must be found on knowledge and understanding of the respiratory patterns that shaped them (Pinna *et al.* 2006).

Limitations

Most limitations of this study are related to life science space research, which are generally associated with a low number of participants (especially in the post-Columbia accident era) and a wide range of parallel experiments. Although we have imposed standardization of experiments between the different missions, we cannot control differences in workload between these missions. Also, changes in sleep–wake cycles, personal exercise regimens, quantity and quality of sleep, fluid intake and nutrition before, during and after the flight could not be controlled. None of the cosmonauts developed orthostatic intolerance, which prohibited us from assessing failing adaptive mechanisms that may contribute to orthostatic presyncope after spaceflight. Alternatively, the analysis of autonomic response changes that assist in maintaining orthostatic stability is also limited.

Conclusion

Using a simple paced-breathing experiment, the present findings illustrate that, after short-duration spaceflight, reduced respiratory modulation (RSD) and baroreflex control (BRS) of HR does not persist until 25 days upon return to Earth. Despite early post-flight reductions in vagal-cardiac modulation, arterial blood pressure dynamics are well preserved in orthostatic tolerant cosmonauts rendering a fundamental neural deficit because of microgravity deconditioning unlikely. Post-flight autonomic adjustments made by orthostatic tolerant cosmonauts appear appropriate for their altered haemodynamic loading conditions.

Conflicts of interest

There are no conflicts of interest related to this article.

We thank cosmonauts from the ESA Odissea, Cervantes and Delta flights for their reliable and outstanding efforts both as researchers and as subjects in space. Special acknowledgement must also be made of the efforts of the European and Russian Space Agencies in supporting these missions. A special thanks to the persons at ESTEC, Noordwijk, the Netherlands and the Gagarin Cosmonaut Training Centre, Star City, Russia whose help before and after the spaceflights was invaluable. This work was funded by grant from ESA-PRODEX from the Belgian Federal Office of Scientific Affairs. Frank Beckers is a post-doctoral researcher of the Research Fund K.U.Leuven. Bart Verheyden and Kurt Couckuyt are supported by ESA-PRODEX grants from the Belgian Federal Office of Scientific Affairs. Jiexin Liu is supported by bilateral agreements of Belgium–China from the Belgian Federal Office of Scientific Affairs.

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