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Operational point of neural cardiovascular regulation in humans up to 6 months in space

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Verheyden B, Liu J, Beckers F, Aubert AE. Operational point of neural cardiovascular regulation in humans up to 6 months in space. *J Appl Physiol* 108: 646–654, 2010. First published January 14, 2010; doi:10.1152/japplphysiol.00883.2009.—Entering weightlessness affects central circulation in humans by enhancing venous return and cardiac output. We tested whether the operational point of neural cardiovascular regulation in space sets accordingly to adopt a level close to that found in the ground-based horizontal position. Heart rate (HR), finger blood and brachial blood pressure (BP), and respiratory frequency were collected in 11 astronauts from nine space missions. Recordings were made in supine and standing positions at least 10 days before launch and during spaceflight (*days 5–19*, *45–67*, *77–116*, *146–180*). Cross-correlation analyses of HR and systolic BP were used to measure three complementary aspects of cardiac baroreflex modulation: *1*) baroreflex sensitivity, *2*) number of effective baroreflex estimates, and *3*) baroreflex time delay. A fixed breathing protocol was performed to measure respiratory sinus arrhythmia and low-frequency power of systolic BP variability. We found that HR and mean arterial pressure did not differ from preflight supine values for up to 6 mo in space. Respiration frequency tended to decrease during prolonged spaceflight. Concerning neural markers of cardiovascular regulation, we observed in-flight adaptations toward homeostatic conditions similar to those found in the ground-based supine position. Surprisingly, this was not the case for baroreflex time delay distribution, which had somewhat longer latencies in space. Except for this finding, our results confirm that the operational point of neural cardiovascular regulation in space sets to a level close to that of an Earth-based supine position. This adaptation level suggests that circulation is chronically relaxed for at least 6 mo in space.

microgravity; spaceflight; cardiovascular physiology; autonomic nervous system; baroreflex

DURING NORMAL EARTHBOUND activities, the gravitational field is an important determinant of cardiovascular function. In humans in the upright position, a gravity-induced decrease in venous return, and thus in cardiac output, is detected by thoracic baroreceptors, which initiate a pressor response that prevents arterial blood pressure from falling. The absence of gravitational stimuli during spaceflight induces a number of adaptive changes within the cardiovascular system that might affect crew health and safety, especially upon return to Earth (2, 36). Most imperative, cardiovascular modifications occurring in microgravity consist of altered blood volume distribution (26, 48), impaired myocardial properties (13, 24, 32), and/or end-organ (i.e., vascular) remodeling (11, 39, 49). In addition, the baroreflex in space is chronically unchallenged due to removal of intravascular hydrostatic pressure gradients. The interplay between baroreflex and hemodynamic and body fluid alterations is likely to affect neural mechanisms involved in dynamic cardiovascular regulation. The way in which this occurs in astronauts in space is still poorly understood.

Life science experiments in space are loaded with many technical and logistical challenges. Consequently, sample sizes have been small and results lack consistency. Even primary measurements like in-flight heart rate (HR) and blood pressure have not provided univocal results (4, 12, 17, 18, 31); however, prevalent findings have suggested lower values in space than in ground-based upright posture (43). Nowadays, there remains a lack of normative data to document the level of cardiovascular regulation in space with respect to standing and supine reference values on Earth. Therefore, the operational point of circulatory control under sustained microgravity conditions is an as yet unresolved issue.

A direct assessment of cardiac baroreflex modulation in space has been performed in only a few spaceflight studies, and these have pointed to a physiological adaptation to weightlessness rather than baroreflex deconditioning for up to at least 1 wk into spaceflight (9, 12, 21). Data on the action of other neural mechanisms involved in cardiovascular regulation seem to confirm this hypothesis of a normal physiological adaptation to microgravity in space (6, 7, 14, 28). However, published data on the long-term spaceflight adaptations for several months are rare (4, 8). This is of particular interest for future long-duration space missions, especially to Mars.

In the present study, we tested the hypothesis that exposure to microgravity will shift the operational point of neural circulatory control toward the preflight supine level for extended flight durations of up to 6 mo in space. Our purpose was to investigate three complementary aspects of cardiac baroreflex function, i.e., *1*) a qualitative index (baroreflex sensitivity; BRS), *2*) a quantitative index (number of effective baroreflex estimates), and *3*) a temporal index (time delay), as a function of spaceflight duration across different short- and long-duration space missions. We further sought to explore possible in-flight adaptations of other neural markers of circulatory control quantified by power spectral analysis of HR and blood pressure variability. Functional operational points obtained in both the standing and supine positions before spaceflight were used as a reference for in-flight measurements.

METHODS

Subjects. We studied 11 male astronauts who each took part in one of nine different space missions aboard the International Space Station (ISS). At the time of preflight data collection, mean age of the subjects was 44 (SD 5) years, height 179 (SD 4) cm, and weight 76 (SD 12) kg. Five astronauts participated in three European Space Agency (ESA)-Soyuz missions with short flight durations of 10–11 days. Six

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astronauts took part in 6 long-duration Increment missions of up to 6 mo aboard the ISS. More flight details for individual crew members are given in Table 1.

Because of time constraints, no routine physical exercise was performed during the ESA-Soyuz missions. In contrast, the Russian system of countermeasures was implemented from the second week in space during the Increment missions (25). Exercise training was performed over a 4-day training regimen, including 3 exercise days followed by 1 day of rest. Each exercise day included time for training for up to 2 h. The training program consisted of dynamic exercise on a treadmill and/or on a bicycle ergometer and isometric exercise using special loading devices. Lower body negative pressure sessions were performed on a regular basis over the last 2 mo aboard the ISS. Because of variable conditions of life and work on the station, the number of training sessions performed, their volume, and their intensity were individually adapted to the daily schedule of the crew. No data are available on the performance of countermaneuvers and exercise training protocols in space.

The Ethics Committee of the local university and the ESA Medical Board approved the experimental protocol, which complied with all guidelines stated in the Declaration of Helsinki. All astronauts signed an informed consent form on the experimental procedures.

Experimental protocol. Preflight data recording was conducted in a quiet, environmentally controlled room with ambient temperature of 21–23°C, at the Medical Building of the Gagarin Cosmonaut Training Center (Moscow, Russia). Baseline data recording took place at least 10 days before launch and was performed twice in six astronauts (Table 1). During spaceflight, data were collected at regular time intervals, i.e., between 5 and 19 days after launch (IF1), between 45 and 67 days after launch (IF2), between 77 and 116 days after launch (IF3), and between 146 and 180 days after launch (IF4). A 24-h daily schedule with alternating sleep-wake and work cycles was kept during the flight. All recording sessions took place in the morning before 1:00 PM. The astronauts were instructed to refrain from alcohol and caffeine beverages for at least 9 h before data collection.

Preflight data collection started with a 5-min period for instrumentation, calibration, and hemodynamic equilibration in the recumbent position. This was followed by a 10-min data recording period during which subjects rested quietly and maintained a regular breathing pattern. Subjects were then instructed to pace their breathing to an audio stimulus with visual feedback at a preset rate of 12 breaths/min (0.2 Hz) for 5 min. Subjects were then moved to a standing position for a stand test that was terminated after 10 min and followed by the paced breathing protocol. In-flight data recording was performed in floating conditions with the feet of the astronauts under a belt to keep position in the ISS.

Instrumentation preflight. During preflight data recording sessions, ECG (Medtronic 9690, Minneapolis, MN) was recorded together with beat-to-beat finger arterial pressure (Portapres Model-2, FMS, Amsterdam, The Netherlands). A servo-controlled photoplethysmograph was placed on the middle finger of the right hand, which was held at heart level during the stand test using an arm sling (22). Brachial blood pressures were measured three times in each body position by means of an automated device (STBP-780, Colin, Komaki, Japan) at the left arm. Respiratory movements were detected by an abdominal pressure sensor, connected to the MR10 respiration monitor (Graseby Medical, Hertfordshire, UK). Finger arterial pressure, ECG, and respiratory movements were digitized at 1,000 Hz using an external analog-to-digital converter (DATAQ Instruments, Akron, OH) and stored on a laptop.

Instrumentation in-flight. Astronauts were carefully trained to perform the in-flight measurements by themselves. They were guided through the experiment by dedicated software, which allowed standardization of each test procedure (5). A log-file was automatically created; this file contained reference values of brachial blood pressure measurements obtained in space. Beat-to-beat finger blood pressure was recorded together with the ECG and respiration movements using an integrated spaceflight-certified device (Cardioscience, TNO-BMI, Amsterdam, The Netherlands). Data were sampled at 100 Hz per channel and stored on a flash memory for off-line analysis.

Time domain analysis. Consecutive R-R intervals (RRI) obtained from the 10-min baseline ECG recordings were averaged to calculate mean HR. Because inadequate finger-cuff positioning by the astronauts in space may affect the precision of in-flight blood pressure measurements (43), we used arm-cuff blood pressure readings to obtain reliable absolute values. Three consecutive brachial blood pressure readings were averaged to calculate systolic (SAP) and diastolic arterial pressure. Mean arterial pressure (MAP) was calculated by adding one-third of the pulse pressure to diastolic arterial pressure.

Baroreflex analysis. Cardiac baroreflex function was quantified by cross-correlation analysis of spontaneous oscillations in SAP and the RRI, without making use of an external stimulus (47). Beat-to-beat finger SAP and RRI time series were fitted with cubic spline functions and resampled at 1-s intervals over the 10-min baseline recordings. Correlation and regression slopes were computed between 10-s series of SAP and RRI samples for time delays in RRI of 0–5 s. The combination with that time delay giving highest cross-correlation was selected, if significant at $P < 0.01$. The regression slope was recorded as one baroreflex estimate, together with time delay. Subsequently, the process was repeated for SAP and RRI samples 1 s later (46). This technique makes it possible to assess three complementary aspects of cardiac baroreflex function: *1*) a qualitative index (BRS); *2*) a quan-

Table 1. *Baseline information and time schedule of pre- and in-flight experiments*

Astronaut	Age, years	BMI, kg/m^2	Preflight, BDC	IF1	IF2	IF3	IF4
1	41	20	L-45; L-10	8	NA	NA	NA
2	40	24	L-45; L-10	8	NA	NA	NA
3	40	27	L-45; L-10	8	NA	NA	NA
4	40	21	L-60; L-10	5	NA	NA	NA
5	45	26	L-193; L-30	5	NA	NA	NA
6	45	25	L-30	19	55	77	152
7	40	24	L-30	5	67	116	168
8	52	22	L-30			99	165
9	52	18	L-30	7	48	83	180
10	47	23	L-395; L-30	17	58	84	148
11	41	29	L-30		45	86	146
Mean (SD)	44 (5)	24 (3)	37 (10)	9 (5)	55 (9)	92 (14)	160 (13)

Time points where no experiments were conducted because of the short duration of the flight are indicated (NA, not applicable). Blanks indicate instances where data were lost due to technical problems. Time is expressed in days before launch (L) for preflight experiments and in days from launch for in-flight (IF) experiments. IF1, between 5 and 19 days after launch; IF2, between 45 and 67 days after launch; IF3, between 77 and 116 days after launch; IF4, between 146 and 180 days after launch. Body mass index (BMI) = weight (kg)/length^2 (m^2) BDC, baseline data collection.

titative index (number of effective baroreflex estimates), and *3*) a temporal index (time delay).

Spectral analysis. Spectral analysis was carried out on the central 3-min window of each RRI and SAP time series obtained during paced breathing, using methods previously described (42). Briefly, equidistant time series were constructed by a cubic-spline interpolation. Data were resampled every 0.5 s. A sliding window of 128 s (256 samples) was applied with 16-s increments. This process resulted in four segments of data for each recording. The DC component was removed by subtracting the mean value, and a Hanning-window was applied. A nonparametric run test of means and mean square values was used to validate the stationarity of data within 5% of confidence limits (3). In the resulting time windows, power spectral density was calculated using fast Fourier transform. The spectral resolution for all estimates equaled 0.0078 Hz. Respiratory-mediated RRI fluctuations were expressed as the area under the spectrum from 0.18 to 0.22 Hz and used as a marker of respiratory sinus arrhythmia (RSA). Low-frequency oscillations of SAP variability were calculated within 0.04- to 0.15-Hz limits as a marker of sympathetic vasomotor function. Power spectral units were squared amplitudes. All of the analysis software for power spectral analysis were developed in-house using LabVIEW 7.1 (National Instruments, Austin, TX) for Windows.

Statistical analysis. Statistical analysis was performed with SPSS version 13.0 for Windows (Scientific Packages for Social Sciences, Chicago, IL). Data are given as means ± SD unless stated otherwise. Spectral data were logarithmically transformed to approximate normal distributions. Reproducibility of measurements was determined by calculating retest reliability across two preflight measurements in six astronauts. This was followed by a two-sided paired *t*-test to detect possible systematic changes across preflight sessions. Absolute reliability was evaluated by computing a typical error (SEM), expressed as a coefficient of variation (20). Limits of random variation were quantified by the range of values within which 95% of the ratios between the second and the first measurement are expected to lie due to pure random variation (33). Relative reliability was assessed by the intraclass correlation coefficient (ICC). The ICC and SEM were derived from one-way random effects ANOVA.

Data obtained from both preflight sessions were pooled for statistical comparison with in-flight data in six astronauts. Preflight standing and supine data were used to assess functional operational curves by means of linear regression analysis with 95% confidence intervals. In-flight data points were scattered along the regression line to evaluate the adaptation to weightlessness in space. Graphical analysis was followed by hypothesis testing (univariate ANOVA) to compare in-flight data to preflight standing and supine reference values with multiple contrast analysis at 0.05 significance level. Possible differences in time delay (optimal delay) between conditions were tested using the χ^2-test after normalization of data. P values <0.05 were considered statistically significant.

RESULTS

The results in Table 1 show individual flight details for the 11 crew members. The astronauts' age and body-mass index during preflight data recording sessions were homogeneously distributed among subjects, with mean values of 44 (SD 5) yr and 24 (SD 3) kg/m, respectively. In-flight data collection points were launch + 9 (SD 5) days ($n = 9$) for IF1, launch + 55 (SD 9) days ($n = 5$) for IF2, launch + 92 (SD 14) days ($n = 6$) for IF3, and launch + 160 (SD 13) days ($n = 6$) for IF4. Preflight data recording sessions were completed by all astronauts. The data sets obtained in space were of good quality, except for three instances where data were lost due to technical problems. All astronauts were able to track their respiratory rate closely with the visual targets, ensuring respiratory-mediated RRI and SAP variations at the imposed breathing frequency of 0.2 Hz (Fig. 1).

Repeatability of measurements. Test-retest reliability of measurements is reported in Table 2. No systematic change was observed across preflight baseline sessions for any of the parameters (P = not significant for paired t-test). The typical error and 95% limits of random variation indicate substantial to good repeatability for both primary and secondary measurements (20). As expected, absolute reliability was highest for primary measurements (HR, blood pressure, and respiration rate; all <10%), whereas intra-individual stability of measurements was less for most derived (spectral and baroreflex) indexes. The ICC of all measurements ranged between 0.62 and 0.96, meaning that most of the measurement variability can be ascribed to the physiological characteristic being measured (33).

Hemodynamic data. None of the astronauts showed signs or symptoms of orthostatic intolerance during the preflight 10-min stand test. Figure 2 shows HR (*top*) and MAP (*middle*) as individual values for preflight standing and supine conditions and for in-flight measurements. As expected in the upright position before flight, HR (63 ± 7 vs. 77 ± 10 beats/min; $P < 0.001$) and MAP (87 ± 9 vs. 95 ± 8 mmHg; $P = 0.02$) results were significantly higher than in supine. Individual transitions from Earth's gravity to weightlessness are shown for the first in-flight measurement (Fig. 2). Compared with the standing position on Earth, there was a reduction in HR and MAP during the first weeks of spaceflight in all astronauts. In-flight values of HR and MAP were then maintained near the preflight supine level for the remaining flight duration of up to 6 mo. Figure 2, *bottom*, shows the evolution of the spontaneous breathing frequency, derived from the respiratory movements during baseline recording sessions, across the different pre- and in-flight sessions. No differences in breathing frequency were observed between the standing and supine positions before spaceflight and during the first weeks in space. This was followed by a tendency of slightly lower breathing frequencies during extended flight durations of up to 6 mo aboard the ISS ($P = 0.063$).

Operational point of cardiovascular neural regulation. Figure 3 shows RSA (respiratory modulation of RRI) and cardiac BRS (regression slopes between SAP and RRI) as a function of mean RRI, collected in the standing and supine positions before spaceflight and during in-flight data recording sessions. RSA was derived from RRI times series obtained during 3 min of fixed-frequency breathing (0.2 Hz; 12 breaths/min), whereas BRS was calculated during spontaneous respiration over the 10-min baseline recordings. Preflight individual scores are shown together with their mean values, showing a functional reduction in mean RRI upon standing that was significantly related to a decrease in RSA ($r = 0.55$; $P = 0.004$) and a lower cardiac BRS ($r = 0.74$; $P < 0.001$). In-flight measurements of RSA and cardiac BRS fitted well within the 95% prediction limits of these preflight relationships, with mean values close to those expected for the supine position on Earth. No evolution was observed over consecutive in-flight measurements of RSA (see also respiratory component in Fig. 1, *top*) and cardiac BRS. Each in-flight data point differed significantly from the preflight standing level ($P < 0.016$ for RSA and $P < 0.03$ for cardiac BRS).

Figure 4 shows the number of cardiac baroreflex estimates as a function of baroreceptor input, i.e., the low-frequency com-

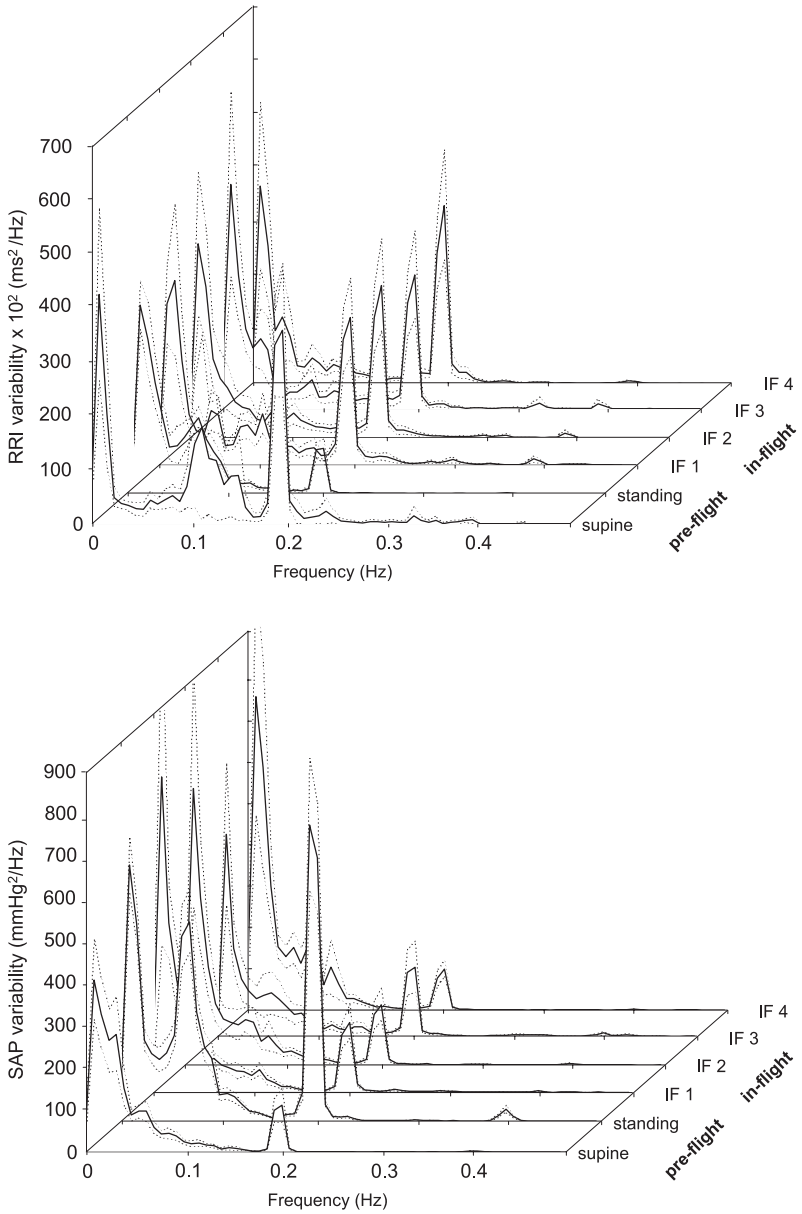

Fig. 1. Power spectral density charts of heart rate variability (*top*) and blood pressure variability (*bottom*) across different preflight and in-flight data recording sessions during fixed-frequency breathing (0.2 Hz; 12 breaths/min). Solid line: mean spectrogram of all astronauts; dashed line: 95% confidence intervals. SAP, systolic arterial pressure; RRI, R-R interval.

ponent of SAP variability (~10-s cycle intervals) during preflight and in-flight data recording sessions. As expected before flight, there was a rise in SAP low-frequency power on standing up, which resulted in more baroreflex estimates than in the supine position ($r = 0.65$; $P = 0.001$). The in-flight data points fitted well within the 95% prediction limits of the preflight stimulus-response relationship of cardiac BRS, with values close to those expected for the supine position on Earth. No evolution was observed over consecutive in-flight measurements, and each in-flight data point differed significantly from the preflight standing level (all $P < 0.02$).

Figure 5 shows the distribution of baroreflex time delays determined from the strongest cross-correlation between SAP and RRI in the standing and supine positions before spaceflight and during in-flight data recording sessions. In the supine position before spaceflight, ~50% of cardiac baroreflex estimates had a time delay of 0 s. The upright posture resulted in a shift in this distribution toward more time delay of 1 s and less time delay of 0 s ($P < 0.001$). During spaceflight, the time delay distributions adapted to a level in between the preflight supine and standing distributions, showing equal amounts of 0-s and 1-s time delays. This was maintained for up to 6 mo in space.

DISCUSSION

This is the first study to evaluate the level of neural cardiovascular regulation in up to 6 mo in space as a function of ground-based standing and supine reference values. Our data demonstrate that qualitative and quantitative components of cardiac baroreflex modulation in space adapt to a level close to that of the ground-based recumbent position. This was also true for in-flight measurements of respiratory vagal-cardiac modulation and dynamic sympathetic vasomotor function. Conse-

Table 2. *Statistical results on the retest reliability of measurements taken in 6 astronauts during 2 baseline sessions*

	Paired *t*-Test	SE	95% Limits of Random Variation	ICC
Hemodynamic analysis				
HR, beats/min	0.36	6%	0.97–1.10	0.80
SAP, mmHg	0.43	6%	0.90–1.06	0.66
MAP, mmHg	0.32	4%	0.92–1.04	0.88
DAP, mmHg	0.48	6%	0.92–1.07	0.87
Baroreflex analysis				
Slope, ms/mmHg	0.12	9%	0.87–1.03	0.83
Number, slopes/min	0.24	19%	0.76–1.08	0.96
Optimal time delay, s	0.48	21%	0.90–1.35	0.62
Frequency-domain analysis				
Respiration, breaths/min	0.91	10%	0.89–1.12	0.63
lnRSA, ms^2	0.60	14%	0.84–1.14	0.63
lnSAP low-frequency power, $mmHg^2$	0.13	27%	0.57–1.33	0.68

HR, heart rate; SAP, MAP, and DAP, systolic, mean, and diastolic arterial pressure, respectively; RSA, respiratory sinus arrhythmia. SE, standard error of measurements expressed as a coefficient of variation (%); 95% limits of random variation, 95% confidence intervals of the ratio between 2 measurements (X2/X1); ICC, intra-class correlation coefficient.

quently, in-flight HR and MAP did not differ from their preflight supine values, supporting the hypothesis that weightlessness relaxes the circulation in humans for extended flight durations of several months. Of note, the time delay distributions of cardiac baroreflex modulation in space showed more time delays of 1 s than expected for the supine position on Earth. Whether this increased baroreflex time delay in space may constitute a state of unstable HR regulation (19), leading to symptoms of postspaceflight orthostatic intolerance, remains to be established.

A major strength of this study is the explicit effort in obtaining uniform data across different spaceflight missions by applying standardized experimental procedures using a computer-guided protocol (5). This strategy was used to improve the reliability of measurements of neural circulatory control, for which the intra-individual variance has been reported to depend chiefly on the stability of experimental conditions (36a). A test-retest analysis of reliability across two preflight measurements in six astronauts revealed low levels of random variation, indicating satisfactory repeatability (20). Moreover, only small portions of the measurement variability across astronauts were due to random variation (ICC $>$ 0.6). This means that subsequent measurements mostly reflect true values in the physiological characteristics being measured (33).

Another novel aspect of this study concerns the use of the dynamic relationships between qualitative components of vagal-cardiac modulation and the mean RRI as a reference to assess the in-flight level of adaptation to microgravity (Fig. 3). This type of analysis is warranted, since mean RRI has been identified as a major determinant of overall HR variability (38). Likewise, the effectiveness of cardiac baroreflex modulation in driving the sinoatrial node in space was investigated as a function of its dynamic input-output relationship (Fig. 4). The probe input to the baroreceptors was considered the dynamic 10-s component of SAP variability, since baroreflex regression slopes were all computed between 10-s series of SAP and RRI samples. The number of effective baroreflex estimates was used as the quantitative output of cardiac baroreflex function. Results of this analysis illustrate that the operational point of neural cardiovascular regulation in space adapts to a level close to what can be expected for the supine position on Earth (15). In particular, our data confirm that vagal-inhibitory effects occurring early in microgravity (41) prevail during prolonged space missions (4), supporting the hypothesis that the cardiovascular system is chronically relaxed in space (31).

Relaxation of the cardiovascular system in space is most likely due to the removal of hydrostatic pressure gradients, causing increased stretch of the carotid sinuses together with thoracic fluid centralization. In addition, expansion of the lungs and the rib cage in weightlessness creates negative pressures around the heart and the central vessels (44), which increase venous return and thus cardiac output (31). On the basis of our in-flight blood pressure results (Fig. 2), we can speculate that the increased cardiac output previously observed in space (31) might stimulate cardiovascular depressor reflexes, possibly mediated by the release of natriuretic and vasodilator peptides (29). In this view, the adaptation of autonomic circulatory control to spaceflight seems to reflect neuroplasticity, triggered by changes of autonomic sensory inputs to the central nervous system (16), rather than some kind of autonomic nervous system deconditioning (28). This seems at odds with an earlier report by Cox et al. (9) of impaired vagal-cardiac baroreflex responses to blood pressure changes provoked by Valsalva maneuvers in space. In their study, however, a chronically increased steady-state sympathetic outflow to the muscle vascular bed was also observed (14), which might have been an alternative mechanism responsible for the degradation of vagal-cardiac baroreflex responses (37). In addition, there is mounting evidence that blunted adrenergic control over peripheral blood vessels might contribute more to the mechanism of postspaceflight orthostatic hypotension than impaired baroreflex control of HR (27).

The present concept of cardiovascular relaxation with sustained microgravity exposure seems to be in contrast to the previously reported high levels of sympathetic nervous activity during spaceflight (7, 14). A possible explanation for this inconsistency could be that the increased sympathetic drive in space is aimed at preventing arterial blood pressure from falling too much. In this view, the activation of sympathetic outflow is secondary to a decreased blood pressure, causing chronic baroreceptor unloading. Note, however, that enhanced sympathetic outflow usually impedes vagal-cardiac modulation (37), which definitely was not the case in our study (Fig. 3). Moreover, we found that the low-frequency oscillations in

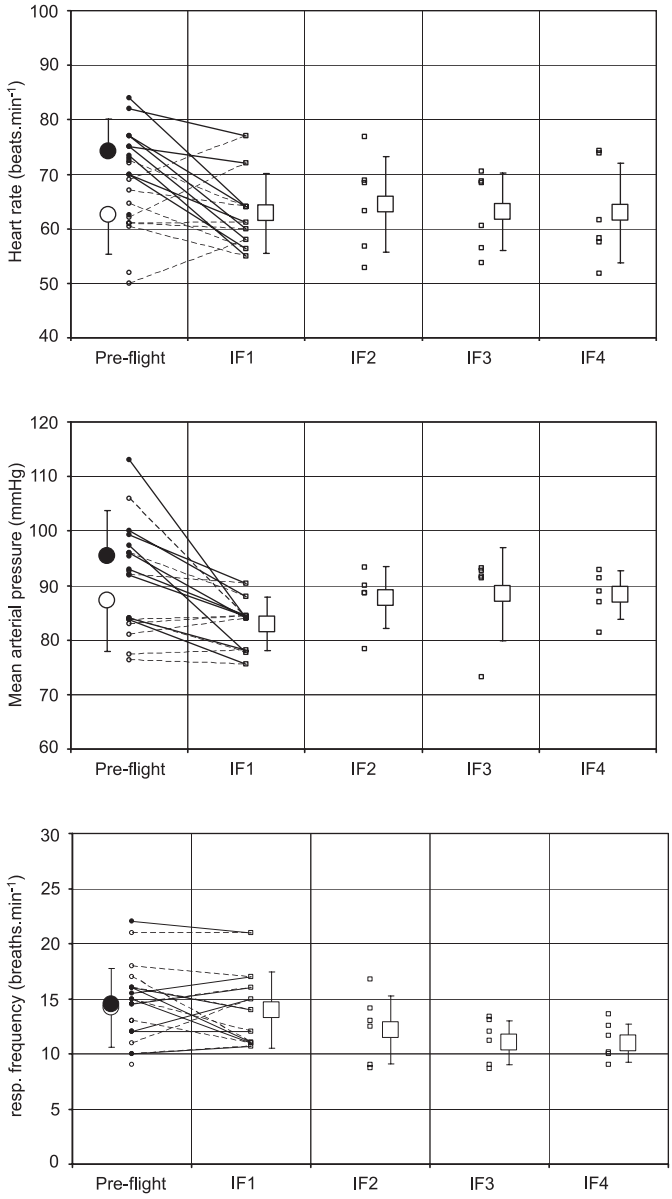

Fig. 2. Patterns of heart rate (*top*), mean arterial pressure (*middle*), and respiration frequency (*bottom*) across preflight and in-flight data recording sessions. Individual transitions from Earth gravity to weightlessness are shown for the first in-flight measurement. ●, Standing position; ○, supine position; □, in-flight data.

SAP, which mirror those in sympathetic nervous activity (34), were not at all increased in space (Fig. 4). Whether the specificity of cardiovascular oscillations in reflecting sympathetic outflow in space is limited should be investigated in the future. It is possible that changes in the vascular wall properties during spaceflight (49) may affect resonance in the baroreflex loop, causing dampening of sympathetically mediated SAP oscillations (40).

Concerning the operational point of neural cardiovascular regulation, it is noteworthy that the in-flight level of adaptation that we observed is fairly similar to how cardiac output, systemic vascular resistance, and renal responses to saline and water loadings adapt to spaceflight (30, 31). These consistent findings illustrate that expansion of the thoracic cavity in

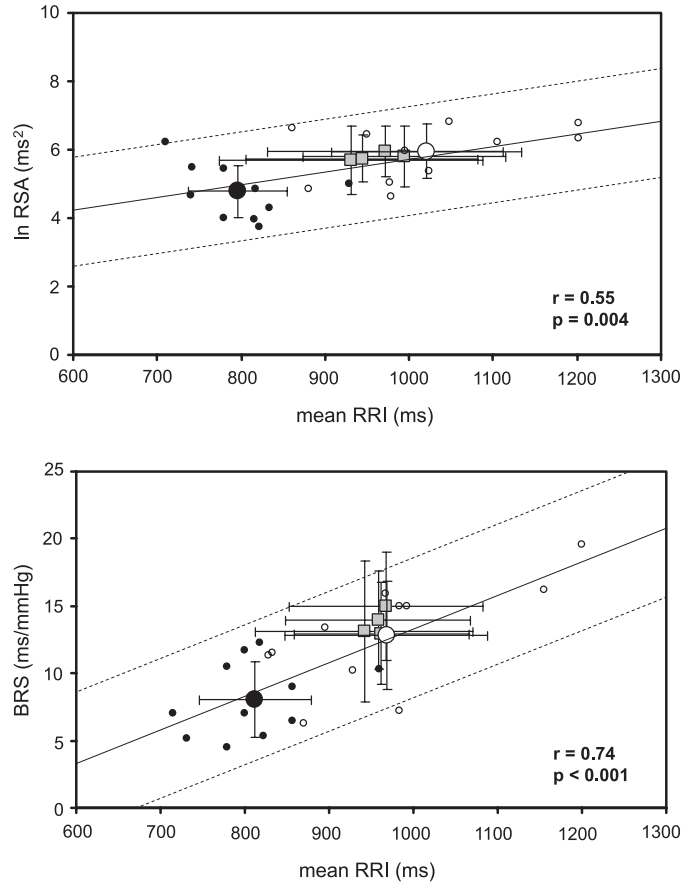

Fig. 3. Respiratory sinus arrhythmia (RSA; *top*) and cardiac baroreflex sensitivity (BRS; *bottom*) as a function of mean RRI. Preflight standing (●) and supine (○) scores are used to assess functional operational curves by means of linear regression with 95% confidence intervals. In-flight data points (squares) are scattered along the regression line to evaluate the adaptation to microgravity.

weightlessness plays an important role as to how the central circulation adapts to microgravity. Otherwise, fluid volume acclimation to microgravity, which results in a reduction in plasma volume (45), appears to exert a less important effect on

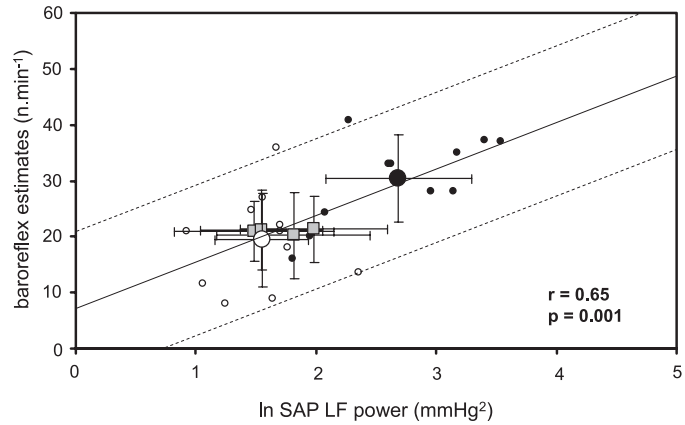

Fig. 4. Number of cardiac baroreflex estimates as a function of the low-frequency (LF) component of SAP variability (~10-s cycle intervals). Preflight standing (●) and supine (○) scores are used to assess functional operational curves by means of linear regression with 95% confidence intervals. In-flight data points (squares) are scattered along the regression line to evaluate the adaptation to microgravity.

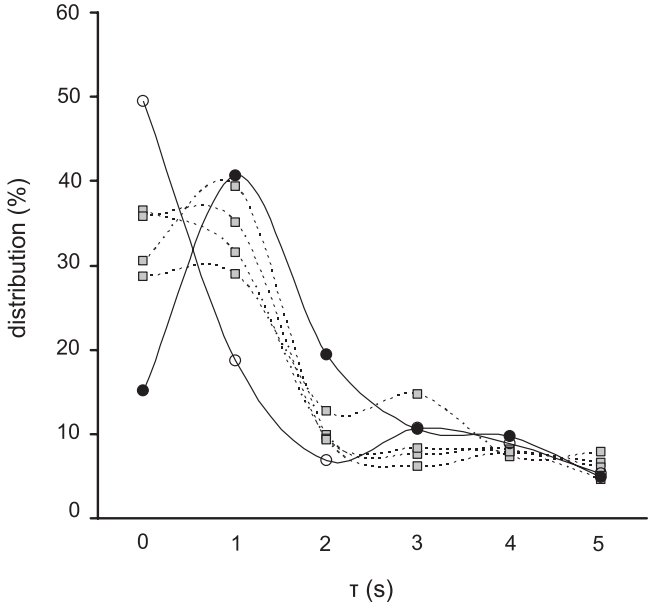

Fig. 5. Distributions of baroreflex time delays (τ) determined from the strongest cross-correlation between SAP and RRI in the standing (●) and supine (○) positions before spaceflight and during in-flight (squares) data recording sessions.

integrative circulatory control during prolonged space missions. Whether the operational point of circulatory control in space differs from that in the upright seated posture on Earth is undecided; however, it seems unlikely to be based on prior studies using this position as a reference for the cardiovascular homeostatic condition (12, 31).

Considering the observed vagal dominance of in-flight HR control, our finding of a shift toward longer baroreflex latencies in space, compared with the preflight supine time delay distributions, is surprising. Normally, a 0-s time delay is expected for baroreflex responses acting through the "fast" vagal cardiac pathways, with increasing time delay values resulting from the combined effect of vagal and sympathetic adjustments to cardiac cycle length (10). A longer baroreflex time delay that is associated with larger postural stress supports the suggestion that a decreased BRS in the upright position results from vagal cardiac withdrawal and/or increased sympathetic activity (23, 46). With this information as a background, our finding of a shift in the optimal time delay distribution toward higher values is not supported by a decreased vagal-cardiac (baroreflex) modulation (Fig. 3) but seems in line with prior data of enhanced sympathetic nervous activity during prolonged exposure to microgravity (7, 14). Whether the cardiac baroreflex latency might represent a more sensitive index of sympathetic HR modulation than the slope and qualitative component of this relationship warrants further investigation. As an opposing view, prolonged baroreflex latencies in space might result from an increased time delay in processing afferent baroreceptor information within the central nervous system. Whether this may contribute to an unstable state of HR regulation (19), leading to reduced orthostatic tolerance in astronauts after spaceflight, is uncertain. In our study, none of the astronauts had symptoms or signs of impending syncope during a 10-min stand test and 45-min 60° head-up tilt test the first days after landing.

A reduction in respiration frequency during prolonged microgravity exposure has been reported previously (4) but is still difficult to interpret. An overall reduction in the total metabolic rate might provide an answer here (35); however, more studies will be needed, focusing on the cardiorespiratory coupling instead of examining these systems separately to provide definitive answers.

Limitations. One of the most prevalent limitations of life science experiments carried out in space concerns the small sample sizes (~4–6 subjects in most previous investigations). In our study, we included 11 subjects who were taking part in nine different space missions, with 6 subjects participating in long-duration spaceflights. Another limitation inherent to spaceflight examinations is the wide range of parallel experiments that might yield flight-specific confounding influences on the study outcome. In an attempt to control for most of these side effects, we have imposed strict standardization of experimental conditions using a computer-guided protocol across different space missions. However, we could not control for differences in workload between these missions. Also, changes in sleep-wake cycles, personal exercise regimens, physical countermeasures, quantity and quality of sleep, and fluid intake and nutrition before and during the flight could not be controlled. Our finding that none of the astronauts had symptoms or signs of impending orthostatic syncope the first days after landing strongly supports the involvement of effective countermeasures in the adaptation process to prolonged space flight missions. The individual performance on countermeasures should therefore be revealed to scientists in the future to improve the scientific outcome of these studies. We obtained our earliest in-flight measurement after 5 days in space when all acute symptoms had already abated; therefore, we limit the analysis and conclusions to the chronic adaptations to microgravity. Finally, it was beyond the scope of this study to assess possible failing adaptive mechanisms during spaceflight that might explain the occurrence of postspaceflight orthostatic intolerance.

In conclusion, exposure to prolonged microgravity in space induces a shift in the neural mechanism of circulatory control toward the ground-based supine operational point, except for the distribution of optimal time delays of cardiac baroreflex modulation, which showed a shift toward longer latencies in space.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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