Roman M. Baevsky, Victor M. Baranov, Irina I. Funtova, André Diedrich, Andrey V. Pashenko, Anja G. Chernikova, Jürgen Drescher, Jens Jordan and Jens Tank

J Appl Physiol 103:156-161, 2007. First published Apr 19, 2007; doi:10.1152/japplphysiol.00137.2007

You might find this additional information useful...

This article cites 43 articles, 26 of which you can access free at:
http://jap.physiology.org/cgi/content/full/103/1/156#BIBL

This article has been cited by 3 other HighWire hosted articles:

Human vagal baroreflex mechanisms in space
D. L. Eckberg, J. R. Halliwill, L. A. Beightol, T. E. Brown, J. A. Taylor and R. Goble
J. Physiol., April 1, 2010; 588 (7): 1129-1138.
[Abstract] [Full Text] [PDF]

Operational point of neural cardiovascular regulation in humans up to 6 months in space
B. Verheyden, J. Liu, F. Beckers and A. E. Aubert
J Appl Physiol, March 1, 2010; 108 (3): 646-654.
[Abstract] [Full Text] [PDF]

Cardiovascular changes of conscious rats after simulated microgravity with and without daily -Gx gravitation
L.-F. Zhang, J.-H. Cheng, X. Liu, S. Wang, Y. Liu, H.-B. Lu and J. Ma
J Appl Physiol, October 1, 2008; 105 (4): 1134-1145.
[Abstract] [Full Text] [PDF]

Updated information and services including high-resolution figures, can be found at:
http://jap.physiology.org/cgi/content/full/103/1/156

Additional material and information about ***Journal of Applied Physiology*** can be found at:
http://www.the-aps.org/publications/jappl

This information is current as of April 26, 2010 .

Journal of Applied Physiology publishes original papers that deal with diverse areas of research in applied physiology, especially those papers emphasizing adaptive and integrative mechanisms. It is published 12 times a year (monthly) by the American Physiological Society, 9650 Rockville Pike, Bethesda MD 20814-3991. Copyright © 2005 by the American Physiological Society. ISSN: 8750-7587, ESSN: 1522-1601. Visit our website at http://www.the-aps.org/.

Downloaded from jap.physiology.org on April 26, 2010

J Appl Physiol 103: 156–161, 2007.
First published April 19, 2007; doi:10.1152/japplphysiol.00137.2007.

Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station

Roman M. Baevsky,[1] Victor M. Baranov,[1] Irina I. Funtova,[1] André Diedrich,[3] Andrey V. Pashenko,[1] Anja G. Chernikova,[1] Jürgen Drescher,[4] Jens Jordan,[2] and Jens Tank[2]

[1]*Institute of Biomedical Problems, Moscow, Russia;* [2]*Medical Faculty of the Charité, Franz Volhard Clinic, Helios Clinic, Berlin, Germany;* [3]*Department of Medicine, Division of Clinical Pharmacology, Autonomic Dysfunction Center, Vanderbilt University School of Medicine, Nashville, Tennessee; and* [4]*German Aerospace Center, Cologne, Germany*

Submitted 1 February 2007; accepted in final form 9 April 2007

Baevsky RM, Baranov VM, Funtova II, Diedrich A, Pashenko AV, Chernikova AG, Drescher J, Jordan J, Tank J. Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. *J Appl Physiol* 103: 156–161, 2007. First published April 19, 2007; doi:10.1152/japplphysiol.00137.2007.—Impaired autonomic control represents a cardiovascular risk factor during long-term spaceflight. Little has been reported on blood pressure (BP), heart rate (HR), and heart rate variability (HRV) during and after prolonged spaceflight. We tested the hypothesis that cardiovascular control remains stable during prolonged spaceflight. Electrocardiography, photoplethysmography, and respiratory frequency (RF) were assessed in eight male cosmonauts (age 41–50 yr, body-mass index of 22–28 kg/m^2) during long-term missions (flight lengths of 162–196 days). Recordings were made 60 and 30 days before the flight, every 4 wk during flight, and on *days 3* and *6* postflight during spontaneous and controlled respiration. Orthostatic testing was performed pre- and postflight. RF and BP decreased during spaceflight ($P < 0.05$). Mean HR and HRV in the low- and high-frequency bands did not change during spaceflight. However, the individual responses were different and correlated with preflight values. Pulse-wave transit time decreased during spaceflight ($P < 0.05$). HRV reached during controlled respiration (6 breaths/min) decreased in six and increased in one cosmonaut during flight. The most pronounced changes in HR, BP, and HRV occurred after landing. The decreases in BP and RF combined with stable HR and HRV during flight suggest functional adaptation rather than pathological changes. Pulse-wave transit time shortening in our study is surprising and may reflect cardiac output redistribution in space. The decrease in HRV during controlled respiration (6 breaths/min) indicates reduced parasympathetic reserve, which may contribute to postflight disturbances.

autonomic nervous system; microgravity; spaceflight; heart rate variability; cardiovascular physiology

THE LACK OF GRAVITATIONAL stress during prolonged spaceflights is associated with adaptation in cardiovascular structure and neurohumoral control circuits (22, 36, 41, 42). These alterations could increase cardiac arrhythmias and diminish the ability of the cardiovascular system to cope with gravitational stress after returning to Earth (36, 41). Together with loss of bone and skeletal muscle mass, cardiovascular maladaptation could conceivably limit the duration of space travel. Moreover, the effects of long-term spaceflight on blood pressure (BP) as a subsequent risk factor are unknown. However, a recent analysis challenges the concept that spaceflights are "unhealthy" for the cardiovascular system (30). Experimental evidence suggesting increased risk for cardiac disease during prolonged spaceflights is lacking (8). The current concepts regarding cardiovascular adaptation in space may be biased by the large number of short-term studies (42). Published data on long-term flights, which could have relevance on the recently touted plans to visit Mars, are rare. Even data on simple measurements such as heart rate (HR), BP, respiratory frequency (RF), or heart rate variability (HRV) are conflicting (10, 17, 18, 29, 30, 40). Furthermore, cardiovascular deconditioning was not a major scientific health issue during the long-term missions aboard the Russian MIR (25). Early results from animal experiments on Russian space satellites II–V and from the first cosmonauts Gagarin and Titov provide no long-term insight into cardiovascular regulation (32). In addition, results from the International Space Station (ISS) reported earlier that were based on 24-h recordings are confounded with physical countermeasure routines or the work schedule (18, 19). We tested the hypothesis that cardiovascular control remains stable during prolonged spaceflight aboard the ISS.

METHODS

Subjects. We studied eight male cosmonauts during space missions aboard the ISS (age 41–50 yr, height 1.74–1.82 m, weight 70–90 kg). The duration of the missions varied between 162 and 196 days. A 24-h daily schedule with alternating sleep-wake and work cycles was maintained during the flight. The daily routine included time for exercise for up to 2 h. Three exercise days were followed by 1 day without exercise. All cosmonauts had extravehicular activities during the flight. The Committee for Research Policies and Procedures of the Institute for Biomedical Problems (Moscow, Russia) approved the protocol, which followed all guidelines stated in the Helsinki accords.

Protocol. Cosmonauts were carefully trained to perform the in-flight measurements by themselves. Measurements were obtained 60 and 30 days before the flight, approximately monthly during flight, and on *days 3* and *6* after return to Earth. Subjects rested for at least 30 min before measurements were started. Periods of 10 min of spontaneous respiration and 3 min of controlled respiration following a timer at 12 and 6 breaths/min were recorded. Orthostatic testing (10 min supine, 10 min upright) was performed during pre- and postflight measurements. Cosmonauts were in a semi-supine position during controlled respiration to follow the instructions on the laptop screen. Ambient conditions on the ground were comparable to the conditions aboard the ISS. Measurements were performed at least 2 h after the last food or fluid intake and preceded physical exercise or work tasks.

Address for reprint requests and other correspondence: J. Tank, Franz-Volhard Clinical Research Center, Haus 129, Wiltbergstr. 50, 13125 Berlin, Germany (e-mail: jens.tank@charite.de).

Data acquisition and analysis. The hardware-software diagnostic complex “Pulse” (Fig. 1) was used during pre-, in-, and postflight experiments. ECG, photoplethysmography, and respiration were recorded at 1-kHz sample rate (Fig. 1); results were saved on memory cards for off-line analysis on Earth. HR, RF, and HRV in the time and frequency domain were analyzed. Brachial BP was measured by use of the onboard oscillometric device (TensoPlus). The pulse-wave transit time (PWTT) was determined as time interval between the R peak in the ECG and the onset of the photo pulse wave at the finger tip. The software “Orbit” was used, which consists of the data-acquisition system, display of the biosignals, and the instructions guiding the cosmonaut throughout the tests.

Spectral analysis. HRV was determined by spectral analysis (1, 39). Briefly, beat-to-beat series were interpolated and resampled at 4 Hz. The power spectra density was estimated by the Welsh method with zero padding, linear trend elimination, and a 50% overlapped Hanning window. Low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–0.4 Hz), and the LF-to-HF ratio (LF/HF) were calculated. HF power reflects mainly parasympathetic HR control. LF power reflects both sympathetic and parasympathetic HR control. The LF/HF has been suggested by some investigators to reflect sympathovagal balance of HR control (1, 13, 31).

Statistics. Data are expressed as means ± SE. One-way ANOVA for repeated measures was used to test for differences. The posttest was computed only if the overall P was <0.05. We relied on the Bonferroni post hoc test. Differences between preflight and in-flight values after 5 mo in space were compared by the nonparametric Wilcoxon matched-pairs test. Linear regression analysis was used if indicated. A value for $P < 0.05$ was considered significant.

RESULTS

All data sets obtained in space were of good quality, with <2% artifacts in the records. Preflight (−60 and −30 days) recordings of one cosmonaut could not be analyzed completely because of artifacts in the ECG signal. Thus the Pulse device, combined with Orbit software, was suitable for self-guided experiments in space. BP and RF decreased during spaceflight. Comparisons between individual preflight values and values obtained after 5 mo in space showed significant differences (Fig. 2; $P < 0.05$). RF decreased to values close to 6 breaths/min (i.e., 0.1 Hz) in some cosmonauts. Mean HR did not change during spaceflight. The individual changes in HR after 5 mo in space were correlated with preflight supine values ($r^2 = 0.572$, $P < 0.05$). Figure 3 shows the mean values of HR, RF, and BP before, during, and after spaceflight.

PWTT, which is thought to be negatively correlated with arterial BP, was shorter in space and decreased further after spaceflight (Fig. 4). Return to Earth rapidly reversed the changes for BP, HR, and RF but not for PWTT. Indeed, BP, HR, and RF after return to Earth exceeded the baseline values before spaceflight. Power spectral densities in the LF and the HF band and the LF/HF did not change significantly during spaceflight (Fig. 5). The large interindividual differences are in accordance with the results from other studies. After the cosmonauts had landed, HF power of HRV was shown to be

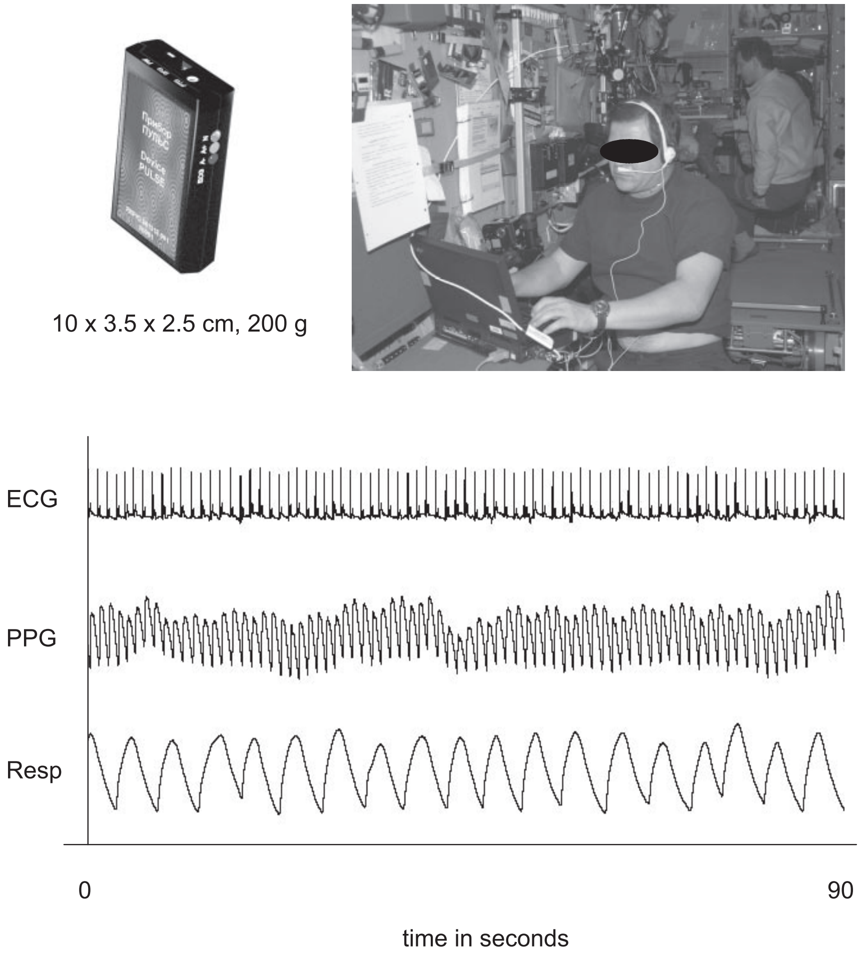


Fig. 1. The “Pulse” device (*top left*), 1 cosmonaut during the experiment aboard the International Space Station (*top right*), and a representative tracing of data recorded during controlled respiration (12 breaths/min) (*bottom*). PPG, photoplethysmogram; Resp, respiration.

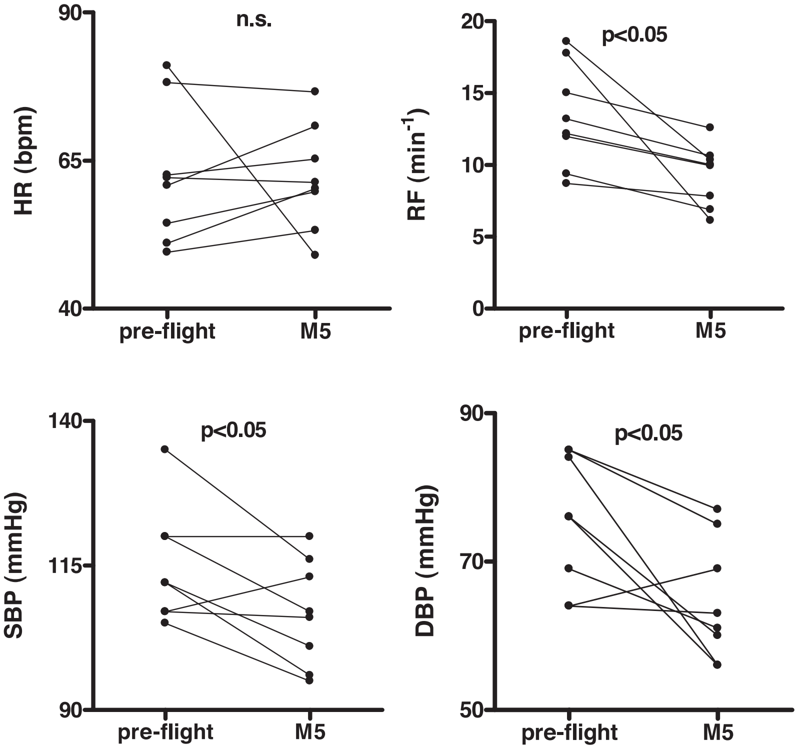


Fig. 2. Individual values of heart rate (HR; *top left*), respiratory frequency (RF; *top right*), systolic blood pressure (SBP; *bottom left*), and diastolic blood pressure (DBP; *bottom right*) before flight (preflight) compared with individual values after 5 mo in space (M5); $n = 8$ subjects. $P < 0.05$ (Wilcoxon matched pairs test).

decreased compared with preflight values. However, our study does not have the statistical power to identify a subtle change in HRV. LF power, HF power, and the LF/HF differed dramatically between controlled respiration at a frequency of 12 breaths/min and spontaneous breathing. The RF of ~6 breaths/min in some cosmonauts explains the high LF-power values during spontaneous respiration and the tendency of an increased LF/HF. HRV was not decreased in space in our study.

Controlled respiration in the LF range (6 breaths/min) profoundly increases HRV power to an individual maximum (23) in normal subjects by concentrating and augmenting the HRV power in the LF band. Therefore, the HRV power, calculated as mean value in the LF range during controlled respiration at 6 breaths/min, reflects individual parasympathetic capacity. Despite large interindividual differences, LF power of HRV attained during controlled respiration at 6 breaths/min decreased during flight in six cosmonauts and increased in one cosmonaut (Fig. 6). Total power of HRV during spontaneous respiration did not decrease during flight (preflight: 1,918 ± 728 ms^2, after 5 mo in space: 1,847 ± 473 ms^2, not significant) and remained lower than HRV power attained during controlled respiration at 6 breaths/min.

The mean HR change with standing was 12 ± 1 beats/min on preflight *day 60*, 14 ± 2 beats/min on preflight *day 30*, 21 ± 2 beats/min on postflight *day 3*, and 21 ± 2 beats/min on postflight *day 6* (not significant between days). Only one cosmonaut (*cosmonaut 1*) exhibited a greater HR increase than 30 beats/min (31 beats/min), which is the diagnostic cut-off value for diagnosing postural orthostatic tachycardia (2). He declined to undergo orthostatic testing on postflight *day 6*. He showed the highest HF power of HRV during controlled breathing (12 breaths/min) in-flight, the most pronounced increase in BP postflight, and high-preflight HR.

DISCUSSION

We studied eight Russian cosmonauts before, during, and after a long-term space mission aboard the ISS. The main findings of our study were that BP and RF decreased in space, whereas mean HR and HRV did not change. However, the maximum respiratory sinus arrhythmia reached during controlled respiration at RF of 6 breaths/min decreased in six of seven cosmonauts during flight and did not reach preflight values after return to Earth. Sustained orthostatic intolerance after return to Earth was uncommon. Previous studies were conducted during short-term spaceflights (18, 21, 29), relied on 24-h Holter monitoring (18, 19), did not control for RF (18, 19, 21), or were limited by the small sample size (10, 38).

Differences between earlier studies and our study may be explained by different mechanisms involved in acute and chronic adaptation to spaceflight (21, 22, 38, 42). Initially, microgravity causes acute fluid shifts toward the upper parts of the body. Many cosmonauts describe flu-like symptoms, including headache, swelling of the head (“puffy faces”), and nasal congestion (20). Remarkably, central venous pressure decreases (5). The acute phase is accompanied by motion sickness (24) and increased sympathetic activity (7, 14, 17). Chronically, plasma volume and red cell mass decrease with normalization in interstitial volumes (5, 6, 9, 12, 17, 26, 28). Left ventricular mass decreases 12% over 10 days in space (33). We obtained our first measurements after 1 mo in space when all acute symptoms had already abated. Our results are giving insight in chronic cardiovascular and respiratory adaptation to microgravity.

We observed a depressor response in space while HR remained stable. In contrast, after 120 and 180 days in space, Cooke et al. (10) observed HR reduction in one of two

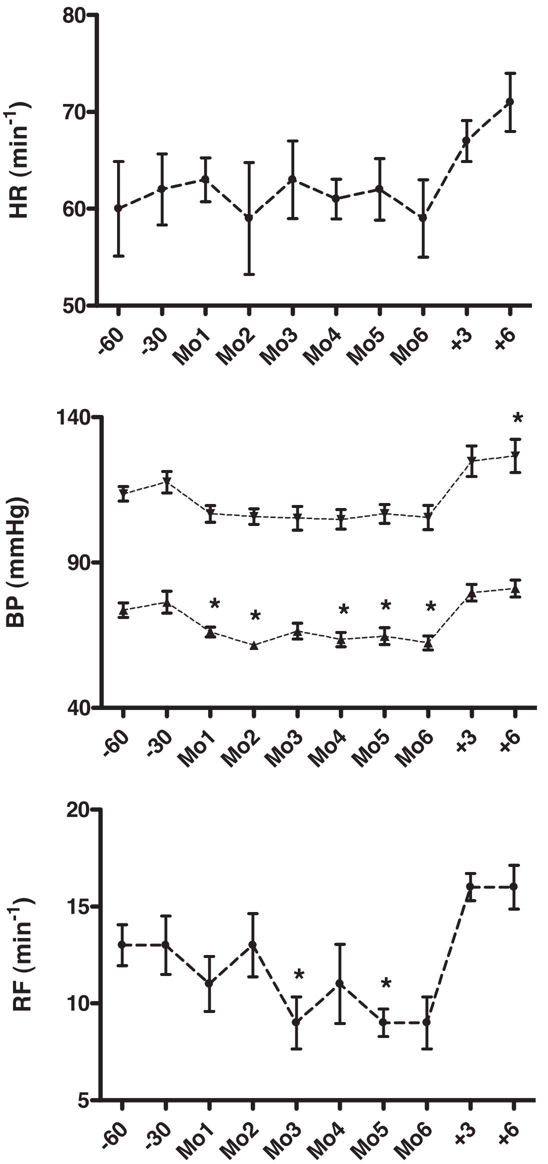


Fig. 3. Mean values ± SE of HR (*top*), SBP (▼) and DBP (▲) (*middle*), and RF (*bottom*) 60 and 30 days before the flight (−60, −30), during flight (monthly measurements, M01–M06), and 3 and 6 days after landing (+3, +6). The preflight and postflight values are supine measurements. bpm, Beats/min. *$P < 0.05$ (one-way ANOVA for repeated measures compared with preflight values).

cosmonauts. Diastolic BP decreased in both cosmonauts reported in that study. In another long-term observation, HR and diastolic BP decreased (18). Polysomnography testing showed HR reduction both while subjects were awake and during all sleep stages (21). Mean HR obtained over periods of up to 24 h did not vary over the course of a long-term mission (19). HR was found to be reduced by 9 beats/min compared with preflight standing values but above supine preflight values during prolonged spaceflights (35). Thus most studies suggest that long-term exposure to microgravity decreases BP. HR responses in space appear to depend on preflight values (21) and differ interindividually.

The depressor response may result from vasodilatation in space because cardiac output tends to increase (30) and cardiac contractility remains stable (3). Therefore, PWTT shortening in our study is surprising. The observation suggests increased rather than decreased peripheral vascular tone. Furthermore, an earlier study showed increased calf vascular resistance during short-term spaceflight (40). One possible explanation for the discrepancy is cardiac output redistribution in space. Differential resistance vessel remodeling may be involved (43).

RF reduction has not been previously shown in space. Lung volumes were found to be reduced during short-term spaceflight (16). Tidal volume, pulmonary ventilation, and metabolic rate were found to be reduced compared with preflight standing measures (35). Vital capacity and respiratory muscle strength are maintained during long-term spaceflight (34). It is possible that RF reduction is not compensated for by increased tidal volume, which could be a physiological response to reduced metabolic demand (21, 34, 37).

One important implication of our study is that HRV data in space cannot be interpreted in the absence of RF measurements or controlled respiration experiments. The difference in HRV between controlled and spontaneous breathing increased dramatically in space and was mainly related to the reduced RF in space. The trend of increased LF/HF in space during spontaneous breathing was reversed during controlled breathing at 12 breaths/min. With short-term exposure to simulated or real microgravity, HRV (10, 18, 19) and baroreflex sensitivity (10, 15) decreased in several studies. In others, HRV was similar to preflight values (21, 29). HRV reduction in some studies may be secondary to acute physiological and psychological stress exerted during early phases of spaceflight. Our study suggests that resting autonomic HR control remains relatively stable with chronic microgravity. Numerically, mean resting HRV even increased in space, which may be explained by increased parasympathetic or decreased sympathetic HR control at least

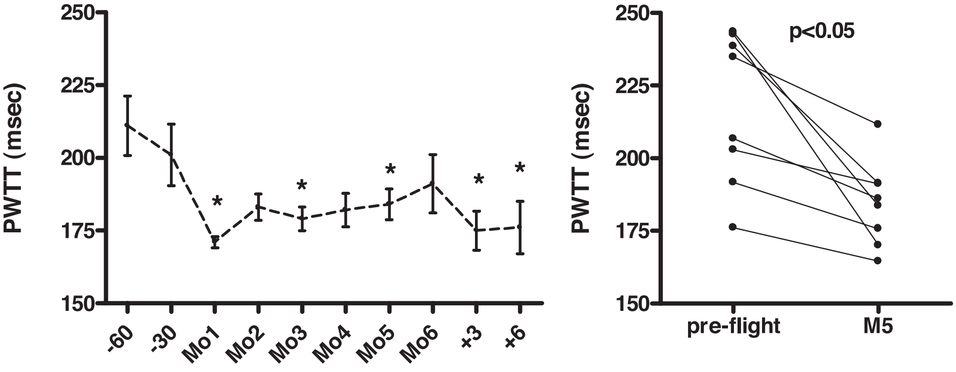


Fig. 4. *Left*: mean values ± SE of pulse-wave transit time (PWTT; in ms) 60 and 30 days before the flight, during flight (monthly measurements), and 3 and 6 days after landing. *$P < 0.05$ (one-way ANOVA for repeated measures compared with preflight values). *Right*: individual values of PWTT before flight compared with individual values after 5 mo in space (M5); $n = 8$ subjects. $P < 0.05$ (Wilcoxon matched pairs test).

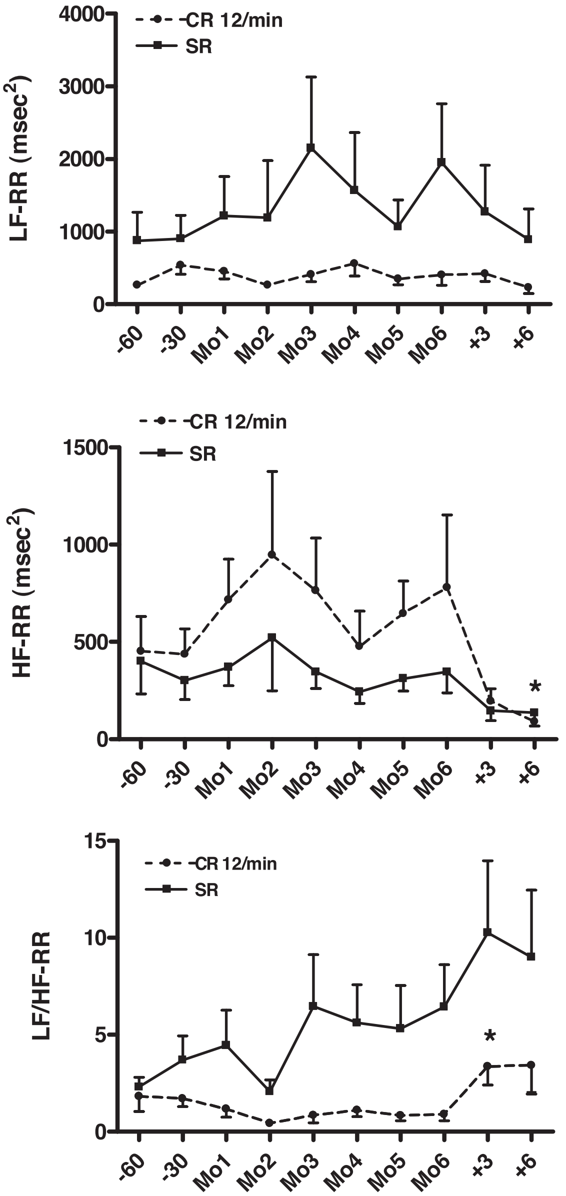


Fig. 5. Mean values ± SE of absolute HR variability data in the low-frequency (LF-RR) and high-frequency (HF-RR) bands and the LF/HF ratio (LF/HF-RR) during controlled respiration (CR 12 breaths/min) compared with spontaneous respiration (SR) at 60 and 30 days before the flight, during flight (monthly measurements), and 3 and 6 days after landing. *$P < 0.05$ (one-way ANOVA for repeated measures compared with preflight values).

in some cosmonauts. However, interindividual differences were large and depended on preflight HR control. Respiratory sinus arrhythmia is primarily mediated through the parasympathetic nervous system. HRV reduction during controlled respiration at RF of 6 breaths/min may indicate reduced parasympathetic capacity or reserve (27). Attenuated functional reserve during spaceflight exceeding an individual threshold may perhaps predispose to complications after return to Earth (4).

One of eight cosmonauts experienced orthostatic intolerance 3 days after flight. Sympathetic baroreflex regulation, α_1-adrenoreceptor responsiveness, and tyramine-evoked norepinephrine release appear to be altered in astronauts prone to experiencing orthostatic symptoms after return to Earth (28). Whether reduced parasympathetic reserve is involved in postflight orthostatic intolerance deserves further study.

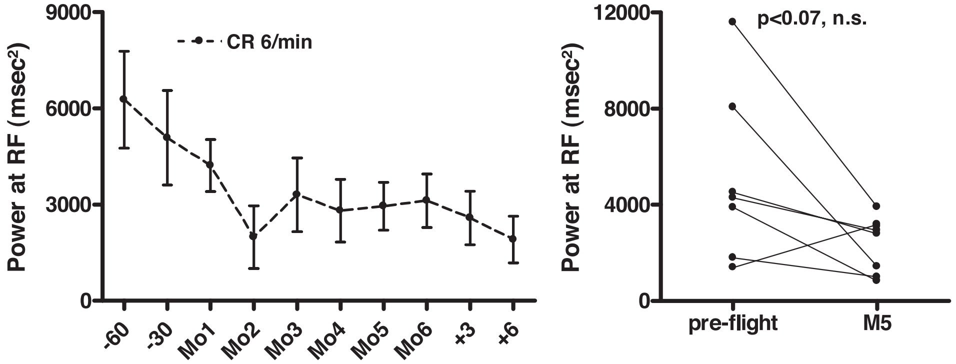
Measurements on the ISS are difficult. The cosmonauts have a busy schedule and reside in cramped quarters. Therefore, our study has limitations. The controlled breathing tests on Earth were not obtained in a perfectly supine position, which may have influenced our results. We did not control tidal volume during spaceflight. However, it has been shown that it is not necessary to control inspired volumes during identical controlled-frequency breathing protocols (11). We have not been able to obtain longer-term follow-up in our subjects. We also cannot comment on long-term cardiovascular risk engendered by prolonged spaceflight on the basis of these data.

Perspectives. Trained cosmonauts are able to perform simple autonomic cardiovascular tests during spaceflight. These tests may have utility in guiding personal training and work time schedules. The observed decreases in RF and BP may support the provocative hypothesis that flying in space is healthy for the human cardiovascular system (30). Moreover, our results indicate that the cardiovascular training program aboard the ISS was sufficient to prevent substantial cardiovascular symptoms after return to Earth. Elucidation of mechanisms responsible for the remodeling of the central nervous system circuits involved in respiratory and cardiovascular control may help to define new treatments for the prevention of in-flight and postflight disturbances.

GRANTS

This work was supported by grants from the Bundesministerium fuer Bildung und Forschung and the German Aerospace Center.

Fig. 6. *Left*: mean values ± SE of absolute HR variability power in the RF range (power at RF) during controlled respiration at 6 breaths/min (CR 6/min) 60 and 30 days before the flight, during flight (monthly measurements), and 3 and 6 days after landing. *Right*: individual values of HR variability power in the RF range during controlled respiration at 6 breaths/min before flight compared with individual values after 5 mo in space (M5); $n = 7$ subjects. $P < 0.05$ (Wilcoxon matched pairs test). ns, Not significant.



REFERENCES

1. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 17: 354–81, 1996.
2. **Ali YS, Daamen N, Jacob G, Jordan J, Shannon JR, Biaggioni I, Robertson D.** Orthostatic intolerance: a disorder of young women. *Obstet Gynecol Surv* 55: 251–259, 2000.
3. **Atkov OY, Bednenko VS, Fomina GA.** Ultrasound techniques in space medicine. *Aviat Space Environ Med* 58: A69–A73, 1987.
4. **Baevsky RM.** [Analysis of variability of cardiac rhythm in space medicine.] *Fiziol Cheloveka* 28: 70–82, 2002.
5. **Buckey JC Jr, Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Yancy CW Jr, Meyer DM, Blomqvist CG.** Central venous pressure in space. *J Appl Physiol* 81: 19–25, 1996.
6. **Buckey JC Jr, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, Blomqvist CG.** Orthostatic intolerance after spaceflight. *J Appl Physiol* 81: 7–18, 1996.
7. **Christensen NJ, Heer M, Ivanova K, Norsk P.** Sympathetic nervous activity decreases during head-down bed rest but not during microgravity. *J Appl Physiol* 99: 1552–1557, 2005.
8. **Convertino VA, Cooke WH.** Evaluation of cardiovascular risks of spaceflight does not support the NASA bioastronautics critical path roadmap. *Aviat Space Environ Med* 76: 869–876, 2005.
9. **Convertino VA, Ludwig DA, Elliott JJ, Wade CE.** Is there resetting of central venous pressure in microgravity? *J Gravit Physiol* 8: 51–52, 2001.
10. **Cooke WH, Ames JE, IV, Crossman AA, Cox JF, Kuusela TA, Tahvanainen KU, Moon LB, Drescher J, Baisch FJ, Mano T, Levine BD, Blomqvist CG, Eckberg DL.** Nine months in space: effects on human autonomic cardiovascular regulation. *J Appl Physiol* 89: 1039–1045, 2000.
11. **Cooke WH, Cox JF, Diedrich AM, Taylor JA, Beightol LA, Ames JE, Hoag JB, Seidel H, Eckberg DL.** Controlled breathing protocols probe human autonomic cardiovascular rhythms. *Am J Physiol Heart Circ Physiol* 274: H709–H718, 1998.
12. **Cox JF, Tahvanainen KU, Kuusela TA, Levine BD, Cooke WH, Mano T, Iwase S, Saito M, Sugiyama Y, Ertl AC, Biaggioni I, Diedrich A, Robertson RM, Zuckerman JH, Lane LD, Ray CA, White RJ, Pawelczyk JA, Buckey JC Jr, Baisch FJ, Blomqvist CG, Robertson D, Eckberg DL.** Influence of microgravity on astronauts' sympathetic and vagal responses to Valsalva's manoeuvre. *J Physiol* 538: 309–320, 2002.
13. **Eckberg DL.** Sympathovagal balance: a critical appraisal. *Circulation* 96: 3224–3232, 1997.
14. **Eckberg DL.** Bursting into space: alterations of sympathetic control by space travel. *Acta Physiol Scand* 177: 299–311, 2003.
15. **Eckberg DL, Fritsch JM.** Human autonomic responses to actual and simulated weightlessness. *J Clin Pharmacol* 31: 951–955, 1991.
16. **Elliott AR, Prisk GK, Guy HJ, West JB.** Lung volumes during sustained microgravity on Spacelab SLS-1. *J Appl Physiol* 77: 2005–2014, 1994.
17. **Ertl AC, Diedrich A, Biaggioni I, Levine BD, Robertson RM, Cox JF, Zuckerman JH, Pawelczyk JA, Ray CA, Buckey JC Jr, Lane LD, Shiavi R, Gaffney FA, Costa F, Holt C, Blomqvist CG, Eckberg DL, Baisch FJ, Robertson D.** Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space. *J Physiol* 538: 321–329, 2002.
18. **Fritsch-Yelle JM, Charles JB, Jones MM, Wood ML.** Microgravity decreases heart rate and arterial pressure in humans. *J Appl Physiol* 80: 910–914, 1996.
19. **Goldberger AL, Bungo MW, Baevsky RM, Bennett BS, Rigney DR, Mietus JE, Nikulina GA, Charles JB.** Heart rate dynamics during long-term space flight: report on Mir cosmonauts. *Am Heart J* 128: 202–204, 1994.
20. **Greenleaf JE.** Physiology of fluid and electrolyte responses during inactivity: water immersion and bed rest. *Med Sci Sports Exerc* 16: 20–25, 1984.
21. **Gundel A, Drescher J, Spatenko YA, Polyakov VV.** Heart period and heart period variability during sleep on the MIR space station. *J Sleep Res* 8: 37–43, 1999.
22. **Hargens AR, Watenpaugh DE.** Cardiovascular adaptation to spaceflight. *Med Sci Sports Exerc* 28: 977–982, 1996.
23. **Hirsch JA, Bishop B.** Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *Am J Physiol Heart Circ Physiol* 241: H620–H629, 1981.
24. **Jennings RT.** Managing space motion sickness. *J Vestib Res* 8: 67–70, 1998.
25. **Kozlovskaya IB, Grigoriev AI.** Russian system of countermeasures on board of the International Space Station (ISS): the first results. *Acta Astronaut* 55: 233–237, 2004.
26. **Levine BD, Pawelczyk JA, Ertl AC, Cox JF, Zuckerman JH, Diedrich A, Biaggioni I, Ray CA, Smith ML, Iwase S, Saito M, Sugiyama Y, Mano T, Zhang R, Iwasaki K, Lane LD, Buckey JC Jr, Cooke WH, Baisch FJ, Eckberg DL, Blomqvist CG.** Human muscle sympathetic neural and haemodynamic responses to tilt following spaceflight. *J Physiol* 538: 331–340, 2002.
27. **Malliani A, Pagani M, Lombardi F, Cerutti S.** Cardiovascular neural regulation explored in the frequency domain. *Circulation* 84: 482–492, 1991.
28. **Meck JV, Waters WW, Ziegler MG, deBlock HF, Mills PJ, Robertson D, Huang PL.** Mechanisms of postspaceflight orthostatic hypotension: low α_1-adrenergic receptor responses before flight and central autonomic dysregulation postflight. *Am J Physiol Heart Circ Physiol* 286: H1486–H1495, 2004.
29. **Migeotte PF, Prisk GK, Paiva M.** Microgravity alters respiratory sinus arrhythmia and short-term heart rate variability in humans. *Am J Physiol Heart Circ Physiol* 284: H1995–H2006, 2003.
30. **Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, Gabrielsen A, Christensen NJ.** Vasorelaxation in space. *Hypertension* 47: 69–73, 2006.
31. **Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E.** Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 59: 178–193, 1986.
32. **Parin VV, Gazenko OG.** Soviet experiments aimed at investigating the influence of space flight factors on the physiology of animals and man. *Life Sci Space Res* 1: 113–127, 1963.
33. **Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, Peshock RM, Weatherall PT, Levine BD.** Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol* 91: 645–653, 2001.
34. **Prisk GK, Fine JM, Cooper TK, West JB.** Vital capacity, respiratory muscle strength, and pulmonary gas exchange during long-duration exposure to microgravity. *J Appl Physiol* 101: 439–447, 2006.
35. **Prisk GK, Guy HJ, Elliott AR, Deutschman RA, III, West JB.** Pulmonary diffusing capacity, capillary blood volume, and cardiac output during sustained microgravity. *J Appl Physiol* 75: 15–26, 1993.
36. **Sides MB, Vernikos J, Convertino VA, Stepanek J, Tripp LD, Draeger J, Hargens AR, Kourtidou-Papadeli C, Pavy-LeTraon A, Russomano T, Wong JY, Buccello RR, Lee PH, Nangalia V, Saary MJ.** The Bellagio Report. Cardiovascular risks of spaceflight: implications for the future of space travel. *Aviat Space Environ Med* 76: 877–895, 2005.
37. **Smirk FH.** Casual, basal and supplemental blood pressures in 519 first-degree relatives of substantial hypertensive patients and in 350 population controls. *Clin Sci Mol Med Suppl* 3: 13s–17s, 1976.
38. **Spaak J, Sundblad P, Linnarsson D.** Impaired pressor response after spaceflight and bed rest: evidence for cardiovascular dysfunction. *Eur J Appl Physiol* 85: 49–55, 2001.
39. **Tank J, Diedrich A, Szczech E, Luft FC, Jordan J.** α_2 Adrenergic transmission and human baroreflex regulation. *Hypertension* 43: 1035–1041, 2004.
40. **Watenpaugh DE, Buckey JC, Lane LD, Gaffney FA, Levine BD, Moore WE, Wright SJ, Blomqvist CG.** Effects of spaceflight on human calf hemodynamics. *J Appl Physiol* 90: 1552–1558, 2001.
41. **White RJ, Averner M.** Humans in space. *Nature* 409: 1115–1118, 2001.
42. **Zhang LF.** Vascular adaptation to microgravity: what have we learned? *J Appl Physiol* 91: 2415–2430, 2001.
43. **Zhang LF.** Vascular adaptation to microgravity. *J Appl Physiol* 97: 1584–1585, 2004.