

Nine months in space: effects on human autonomic cardiovascular regulation

WILLIAM H. COOKE,¹ JAMES E. AMES IV,² ALEXANDRA A. CROSSMAN,² JAMES F. COX,² TOM A. KUUSELA,³ KARI U. O. TAHVANAINEN,⁴ L. BOYCE MOON,⁵ JÜRGEN DRESCHER,⁶ FRIEDHELM J. BAISCH,⁶ TADAAKI MANO,⁷ BENJAMIN D. LEVINE,⁸ C. GUNNAR BLOMQVIST,⁵ AND DWAIN L. ECKBERG²

¹Center for Biomedical Engineering, Michigan Technological University, Houghton, Michigan 49931; ²Departments of Medicine, Physiology, and Mathematical Sciences, Medical College of Virginia at Virginia Commonwealth University, and Hunter Holmes McGuire Department of Veterans Affairs Medical Center, Richmond, Virginia 23249; ³Department of Applied Physics, University of Turku, Finland 20014; ⁴Department of Clinical Physiology, Kuopio University Hospital, Kuopio, Finland 33521; ⁵University of Texas Southwestern Medical Center, Dallas, Texas 75235; ⁶Deutsche Forschungsanstalt für Luft- und Raumfahrt, Institute of Aerospace Medicine, Köln, Germany 51147; ⁷Department of Autonomic Neuroscience, Research Institute of Environmental Medicine, Nagoya, Japan 504-8601; and ⁸Institute for Exercise and Environmental Medicine and Presbyterian Hospital, Dallas, Texas 75231

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Cooke, William H., James E. Ames IV, Alexandra A. Crossman, James F. Cox, Tom A. Kuusela, Kari U. O. Tahvanainen, L. Boyce Moon, Jürgen Drescher, Friedhelm J. Baisch, Tadaaki Mano, Benjamin D. Levine, C. Gunnar Blomqvist, and Dwain L. Eckberg. Nine months in space: effects on human autonomic cardiovascular regulation. *J Appl Physiol* 89: 1039–1045, 2000.—We studied three Russian cosmonauts to better understand how long-term exposure to microgravity affects autonomic cardiovascular control. We recorded the electrocardiogram, finger photoplethysmographic pressure, and respiratory flow before, during, and after two 9-mo missions to the Russian space station Mir. Measurements were made during four modes of breathing: 1) uncontrolled spontaneous breathing; 2) stepwise breathing at six different frequencies; 3) fixed-frequency breathing; and 4) random-frequency breathing. R wave-to-R wave (R-R) interval standard deviations decreased in all and respiratory frequency R-R interval spectral power decreased in two cosmonauts in space. Two weeks after the cosmonauts returned to Earth, R-R interval spectral power was decreased, and systolic pressure spectral power was increased in all. The transfer function between systolic pressures and R-R intervals was reduced in-flight, was reduced further the day after landing, and had not returned to preflight levels by 14 days after landing. Our results suggest that long-duration spaceflight reduces vagal-cardiac nerve traffic and decreases vagal baroreflex gain and that these changes may persist as long as 2 wk after return to Earth.

baroreflex; cardiac control; space station Mir

MICROGRAVITY PROVOKES AUTONOMIC changes that may contribute to orthostatic intolerance when astronauts

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Address for reprint requests and other correspondence: W. H. Cooke, Ctr. for Biomedical Engineering, Michigan Technological Univ., 1400 Townsend Dr., Houghton, Michigan 49931 (E-mail: whcooke@mtu.edu).

return to Earth (8). After space missions, astronauts' heart rates may increase inordinately with standing, their arterial pressures may decline, and they may even experience frank syncope. It is likely that several mechanisms contribute to these changes. Returning astronauts have blood volume reductions of 10–15% (5), impaired vagal baroreceptor-cardiac reflex responses (13, 16), and inadequate increases in total peripheral resistance during standing (4). Autonomic impairment has been documented after space missions lasting only 4–5 (13) and 8–14 days (16). Autonomic abnormalities persisted for 10 days after 4- to 5-day missions (13) but had disappeared 3 days after 8- to 14-day missions (16). It is not clear how long autonomic dysfunction persists after brief space missions. Differences in the rate of readaptation to Earth's gravitational field after missions of different durations suggest that changes of autonomic mechanisms may depend on the duration of exposure to microgravity.

As the focus of manned space exploration shifts from brief to prolonged missions in low earth orbits and to exploration of neighboring planets, understanding the effects of long-duration space travel on human physiology assumes great importance. We studied autonomic cardiovascular control mechanisms in three cosmonauts exposed to 9 mo of microgravity aboard the Russian space station Mir. On the basis of earlier research (13, 16), we expected that microgravity would reduce vagal-cardiac neural outflow and vagal baroreceptor-cardiac reflex responses. Therefore, in this project, we tested the hypothesis that the magnitude of

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autonomic changes and the time course of their recovery would be proportional to the duration of exposure to microgravity. Our data suggest that autonomic changes develop early but do not necessarily progress as the duration of exposure to microgravity increases. We found that the most dramatic changes occurred soon after landing and that some autonomic abnormalities persisted for 2 wk after return to Earth.

METHODS

Subjects. We studied three male Russian cosmonauts, ages 36, 45, and 47 yr, before, during, and after 9 mo aboard the Russian space station Mir, as part of NASA's Phase-1B American/Russian collaboration (Mir-23 and Mir-25 missions). We obtained measurements 14 days before launch; on *in-flight days 18, 120, 140, and 180*; and on *postflight days 1 and 14*. Our protocol was approved by the Johnson Space Center Human Research Policies and Procedures Committee (Houston, TX), The Institute for Biomedical Problems (Moscow, Russia), the Human Research Committees of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center, the Medical College of Virginia at Virginia Commonwealth University, and The University of Texas Southwestern Medical Center.

Measurements. We recorded the electrocardiogram and estimated beat-by-beat arterial pressure with finger photoplethysmography (Portapres, TNO, Amsterdam, The Netherlands). We measured end-tidal CO_2 at the mouth (GASMAP, Marquette, Milwaukee, WI) before and after each mission. Respiratory flow was measured by a Fleisch pneumotachograph (M956, Medikro Oy, Kuopio, Finland) that was part of an electronic module placed in an IBM ThinkPad (Model 750C, Armonk, NY). Nasal airflow was prevented with a nose clip, and cosmonauts breathed via a mouthpiece and a two-way respiratory valve (Hans Rudolph, Kansas City, MO). The electrocardiogram, arterial pressure, and end-tidal CO_2 were recorded directly to optical disk (Medex, Pancosmos, Munich, Germany). Respiratory flow was recorded on the laptop hard-drive and time-stamped to data stored on the Medex system through an RS232 data cable.

Protocol. Cosmonauts were supine during all pre- and postflight measurements. The laptop computer with the Medikro insert was positioned above and in front of the cosmonaut, at a distance of ~ 0.4 m, so that he could view the screen comfortably. Breathing protocols were performed in succession and were driven by software that guided the cosmonauts to perform the experiment on themselves in space. Once the controlled breathing protocol was initiated, cosmonauts were prompted by the computer to breathe spontaneously for 5 min. After this initial baseline period, the cosmonauts performed a 12-min stepwise breathing protocol, consisting of six different breathing frequencies of 2 min each (at 0.3, 0.25, 0.2, 0.15, 0.1, and 0.05 Hz), followed by fixed-rate breathing for 5 min (0.25 Hz) and random-rate breathing for 6 min (between 0.05 and 0.3 Hz). Our laboratory has recently shown that it is not necessary to calculate and control inspired volumes during identical controlled-frequency breathing protocols (6). In the present investigation, respiratory frequency, but not inspired volume, was strictly controlled.

Because we were able to study only three cosmonauts, we evaluated the reproducibility of our measurements on Earth by asking 10 subjects to perform controlled-frequency breathing (0.25 Hz) twice, separated by at least 4 wk (range 4–8 wk; W. H. Cooke, unpublished data). Repeated-measures ANOVA revealed no significant differences for R-R intervals ($P = 0.15$),

R-R interval standard deviations ($P = 0.22$), R-R interval spectral power at the respiratory frequency ($P = 0.45$), or baroreflex gain ($P = 0.11$; sequence method). Coefficients of variation calculated for these variables were 8, 12, 20, and 10%, respectively.

Data analysis. We analyzed all results with custom software written to accommodate the merged and synchronized data from the Medikro and Medex acquisition systems. We calculated power spectra as follows: the nonequidistant R-R interval (electrocardiogram; sampled at 500 Hz) and systolic pressure (Portapres; sampled at 200 Hz) time series were spline interpolated (linear), resampled at 5.0 Hz, and passed through a low-pass filter with a cut-off frequency of 0.5 Hz. Data sets comprising 60 s, sliding every 10 s, were trend eliminated (linear regression), windowed (Hanning method), and fast Fourier transformed. Power was expressed as the area under the spectrum over the frequency range of interest [low frequency (0.04–0.15 Hz); respiratory frequency (0.15–0.4 Hz); and total (0.04–0.4 Hz) spectral power (3)]. We calculated the squared coherence between systolic pressures and R-R intervals by dividing their cross-spectral densities by the product of the individual power spectral densities and calculated the transfer function by dividing the cross-spectra of the two signals by the power spectra of the input signal, systolic pressure (29).

Arterial baroreflex gain in the time domain was estimated from three or more beat sequences of increasing systolic pressures and R-R intervals during uncontrolled spontaneous breathing (15). We also required that systolic pressure increase by at least 0.5 mmHg per beat and that each protocol have a minimum of five satisfactory sequences. The mean slope of such sequences was taken as an index of vagal baroreceptor-cardiac reflex gain. We also estimated baroreflex gain in the frequency domain with the transfer function between systolic pressure and R-R interval cross-spectra in the low frequency range, 0.04–0.15 Hz, during random-frequency breathing (1, 2). The transfer function was considered valid only if the squared coherence was >0.50 (30).

RESULTS

This research was plagued by problems. Three days after the *flight day 18* session during the Mir-23 mission, an oxygen canister caught fire aboard the space station. Ensuing and other unrelated but serious complications prohibited *cosmonaut 1* from performing this experiment in space beyond *flight day 18*. During *flight day 140* of the Mir-25 mission, data were corrupted for *cosmonaut 2*. On about *flight day 190*, *cosmonaut 2* began taking the beta-blocker, atenolol, for undisclosed medical reasons. On the day after this mission ended, this cosmonaut also was prohibited from performing the experiment. Fourteen days after landing, however, *cosmonaut 2* was allowed to perform the experiment, and at that time he was taking no medications. Therefore, our data set comprises measurements from three cosmonauts studied 2 wk before launch and 2 wk after landing; two cosmonauts studied on *flight days 120 and 180* and 1 day after landing; one cosmonaut studied on *flight day 18*; and one cosmonaut studied on *flight day 140*.

Although the cosmonauts we studied were not medically trained, they were able to collect data on themselves and each other using the Medex/Medikro laptop-based data acquisition system. Figure 1 depicts data

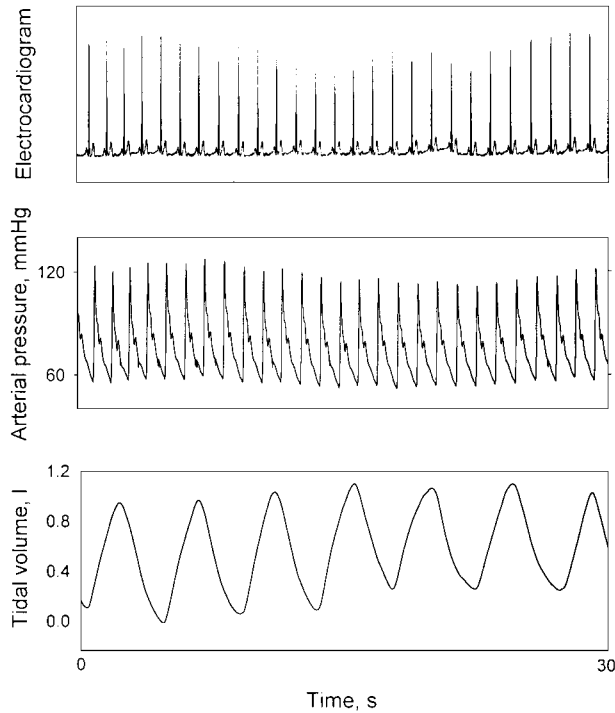


Fig. 1. A representative tracing of original in-flight data from one cosmonaut.

from one cosmonaut recorded during fixed-frequency breathing at 0.25 Hz. The cosmonauts were able to track their respiratory rates with the visual targets closely. Respiratory rates during each breathing protocol before, during, and after flight were similar.

Baseline measurements. We compared in-flight and postflight measurements with measurements made 14

days before launch. Although we report many of our observations, we comment only on those that seem to reflect trends. Table 1 lists measurements obtained during 5 min of uncontrolled spontaneous breathing. R-R intervals changed in-flight but with no consistent pattern. Arterial pressures also changed in-flight with no consistent pattern but were elevated in all cosmonauts in postflight recordings.

End-tidal CO₂ (not listed) was high during all breathing protocols ($6.3 \pm 1.7\%$; mean \pm SD) but was similar during pre- and postflight sessions. (Equipment malfunction prevented measurement of in-flight CO₂.)

Controlled-frequency breathing. Figure 2 depicts R-R interval and systolic pressure spectral powers during 0.25 Hz (15 breaths/min) breathing for one cosmonaut. In this cosmonaut, R-R interval spectral powers at low end-respiratory frequencies were substantially lower, and systolic pressure spectral power at the breathing frequency was moderately higher postflight than during the preflight recording session. R-R interval standard deviations during 0.25-Hz breathing were decreased in all cosmonauts in the majority of experimental sessions, as shown in Fig. 3.

Preflight inspired tidal volumes changed predictably as a function of breathing frequency. Inspired volumes (corrected for BTPS) during 0.3-, 0.25-, 0.2-, 0.15-, 0.1-, and 0.05-Hz-frequency breathing were 0.77 ± 0.04 , 0.94 ± 0.15 , 0.95 ± 0.8 , 1.13 ± 0.24 , 1.47 ± 0.32 , and 1.86 ± 0.6 liters (means \pm SD). Inspired volumes were similar in- and postflight (mean values were well within 1 SD).

Figure 4 shows average changes of R-R interval and systolic pressure spectral powers at all breathing frequencies for preflight measurements and mea-

Table 1. *Baseline measurements made during uncontrolled breathing*

Variable	Preflight	In-Flight				Postflight	
		Day 18	Day 120	Day 140	Day 180	Day 1	Day 14
RRI, ms							
<i>Cosmonaut 1</i>	1130	964(85)	NA	NA	NA	924(82)	979(87)
<i>Cosmonaut 2</i>	992	NA	1147(116)	NA	1307(132)	NA	882(89)
<i>Cosmonaut 3</i>	899	NA	835(93)	835(93)	915(102)	784(87)	849(94)
RRI SD, ms							
<i>Cosmonaut 1</i>	45	28(62)	NA	NA	NA	32(71)	51(113)
<i>Cosmonaut 2</i>	110	NA	54(49)	NA	63(57)	NA	67(61)
<i>Cosmonaut 3</i>	54	NA	38(70)	38(70)	47(87)	30(56)	42(78)
SAP, mmHg							
<i>Cosmonaut 1</i>	97	121(124)	NA	NA	NA	142(146)	120(124)
<i>Cosmonaut 2</i>	125	NA	115(92)	NA	108(86)	NA	152(122)
<i>Cosmonaut 3</i>	144	NA	123(85)	169(117)	131(91)	173(120)	143(99)
DAP, mmHg							
<i>Cosmonaut 1</i>	49	63(128)	NA	NA	NA	61(124)	59(120)
<i>Cosmonaut 2</i>	73	NA	59(81)	NA	57(78)	NA	91(125)
<i>Cosmonaut 3</i>	71	NA	53(75)	72(104)	44(62)	95(134)	83(117)
BRS, ms/mmHg							
<i>Cosmonaut 1</i>	20	10(50)	NA	NA	NA	7(34)	15(75)
<i>Cosmonaut 2</i>	46	NA	26(56)	NA	35(76)	NA	21(45)
<i>Cosmonaut 3</i>	10	NA	8(81)	7(67)	8(81)	5(50)	9(90)

Values are raw data; values in parentheses are percentages of preflight. NA, data not available; RRI, R-wave-to-R wave (R-R) interval; RRI SD, R-R interval standard deviation; SAP, systolic arterial pressure (from Portapres); DAP, diastolic arterial pressure (from Portapres); BRS, baroreflex slope (ascending sequence method).

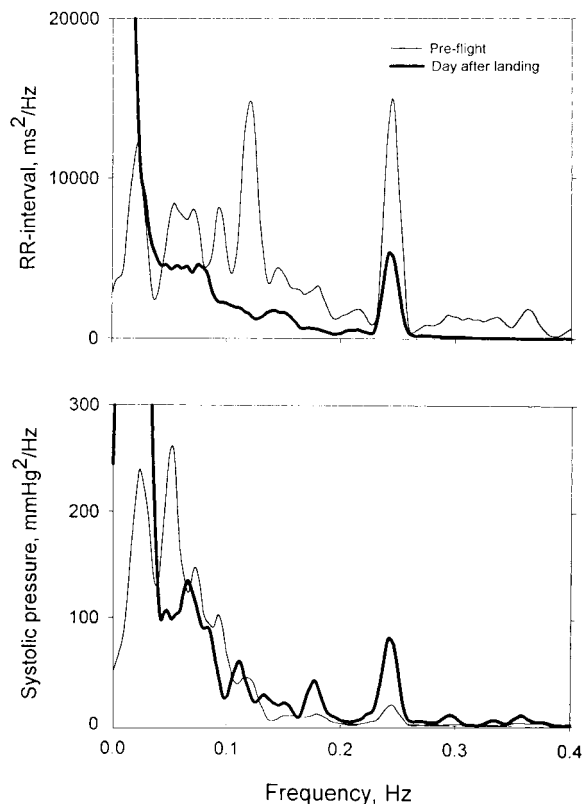


Fig. 2. R wave-to-R wave (R-R) interval and systolic pressure spectral power during fixed-frequency breathing (0.25 Hz; 5 min) in one cosmonaut 14 days before launch and 1 day after landing.

measurements made 14 days after landing for all three cosmonauts. Despite disparate changes in these measurements in-flight, systolic pressure spectral power was higher and R-R interval spectral power was lower in all cosmonauts at all breathing rates 14 days after landing than preflight.

Vagal baroreflex gain. We estimated vagal baroreceptor-cardiac reflex gain two ways. First, we analyzed three or more increasing systolic pressure and R-R interval sequences with linear regression during un-

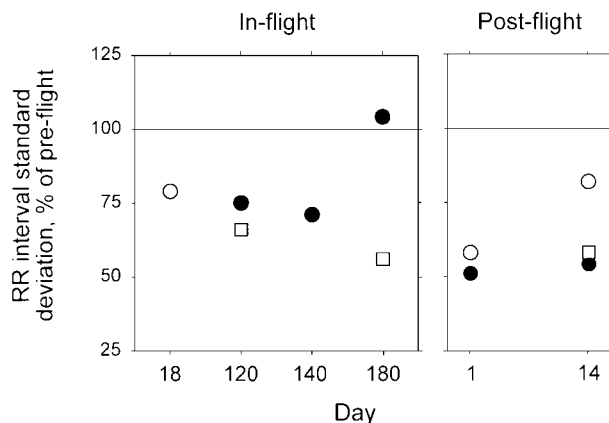


Fig. 3. R-R interval standard deviations during 0.25-Hz breathing for each session and cosmonaut. \circ , *Cosmonaut 1*; \square , *cosmonaut 2*; \bullet , *cosmonaut 3*.

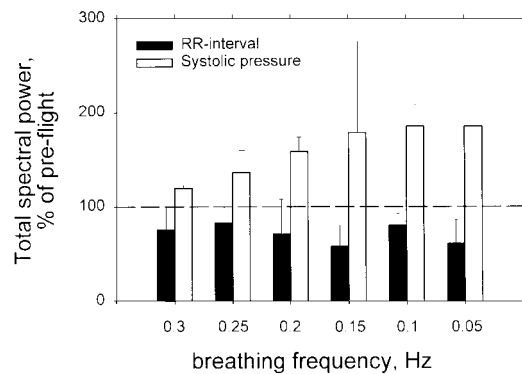


Fig. 4. Total (0.04–0.4 Hz) R-R interval and systolic pressure spectral power at each breathing frequency during the stepwise-frequency protocol 14 days after return to Earth. Values are means \pm SD; $n = 3$.

controlled breathing. The slopes of ascending baroreflex sequences were diminished during all in- and post-flight sessions compared with preflight measurements. Baroreflex slopes averaged 26.6 preflight and 15.0 ms/mmHg 14 days after landing (Table 1). Second, we estimated baroreflex gain at low frequencies from the transfer function between systolic pressure and R-R interval spectral powers when the squared coherence was greater than 0.50 (see METHODS). During 0.1-Hz breathing, the transfer function was less in-flight for two of the three cosmonauts and unchanged in one. One day after landing, the transfer function was 8.0 and 5.6 ms/mmHg (preflight values: 19.4 and 9.0), in *cosmonauts 1* and *3*. Fourteen days after landing, the transfer function averaged 6.8 ms/mmHg in all three cosmonauts (average preflight value: 18.1).

Figure 5 shows coherence and transfer functions between systolic pressures and R-R intervals in *cosmonaut 2* during random-frequency breathing. Coherence between ~ 0.04 and 0.15 Hz was comparable before, during, and after spaceflight. In this cosmonaut, at low frequencies, the transfer function was slightly decreased on *flight day 180* compared with the preflight value and was dramatically decreased on the day after landing. Similar transfer function reductions were recorded in *cosmonaut 1* on *flight day 18* and one day after landing, and in *cosmonaut 3* on *flight days 120* and *180*. Transfer functions for all cosmonauts for all sessions are depicted in Fig. 6. Fourteen days after landing, the transfer function was 9.7, 17.5, and 10, compared with preflight values of 19.4, 25.8, and 9.0 ms/mmHg for *cosmonauts 1, 2, and 3*.

DISCUSSION

We used a simple breathing algorithm to perturb autonomic cardiovascular function in three Russian cosmonauts before, during, and after 9-mo sojourns in the Russian space station Mir. Our observations on the effects of very-long-duration microgravity exposure are unique: we report what may be the first registrations of beat-by-beat arterial pressure from space and the first study in which controlled breathing was used as an

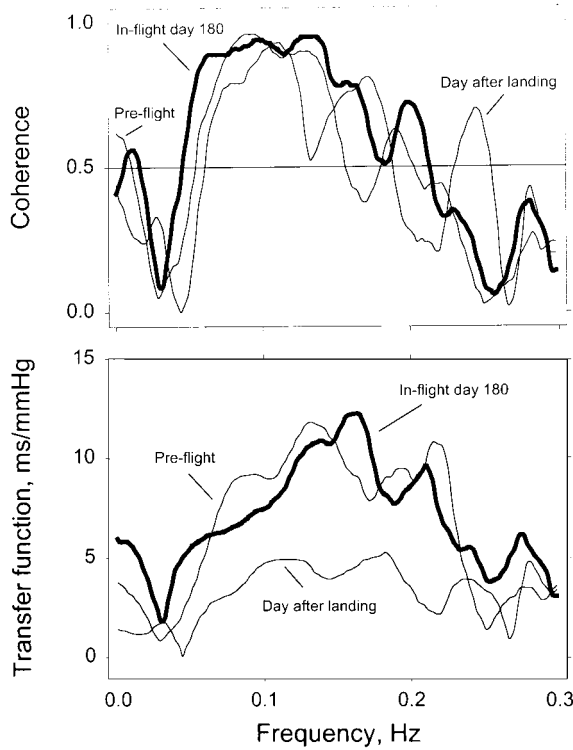


Fig. 5. Coherence (top) and transfer function magnitude (bottom) from one cosmonaut during random-frequency breathing.

intervention to study autonomic function in space. The principal conclusions from this work are that long-duration microgravity exposure diminishes human vagal cardiac efferent neural outflow and vagal baroreflex gain and that these changes persist for at least 2 wk after return to Earth.

R-R interval fluctuations. Microgravity decreased R-R interval standard deviations in all cosmonauts (Fig. 3) and decreased respiratory frequency R-R interval spectral power in two cosmonauts. These findings are consistent with results published earlier. Goldberger and co-workers (18) reported analyses of Holter recordings made in six Russian cosmonauts who were

in microgravity for 131, 175, and 179 days and documented reduced R-R interval standard deviations. Fritsch-Yelle et al. (17) also reported reduced R-R interval standard deviations derived from Holter recordings. Goldberger's group (18) also reported unchanged respiratory-frequency R-R interval spectral power. In Goldberger's study, however, breathing frequency was neither measured nor controlled. We report R-R interval spectral power at the measured breathing frequency and document reductions from preflight values.

Published evidence suggests that fluctuations of R-R intervals at all frequencies are mediated primarily by fluctuations of vagal-cardiac nerve activity. All R-R interval oscillations are nearly abolished by large-dose atropine (27, 28). Large-dose atropine does not alter the rate of denervated human sinoatrial nodes (10) and, therefore, appears to exert its effects by opposing ongoing vagal-cardiac nerve traffic. In healthy humans, R-R interval standard deviations (19) and respiratory peak-minus-valley R-R interval changes (22) correlate well with the R-R interval shortening that occurs when large-dose atropine is given after large-dose propranolol (the current "gold standard" for estimation of human vagal-cardiac traffic). In spontaneously breathing dogs (21), peak-minus-valley R-R interval changes correlate superbly with directly measured vagal-cardiac nerve traffic. These observations support our inference that the reductions of R-R interval standard deviation and respiratory sinus arrhythmia we documented in space signify reductions of vagal-cardiac nerve traffic. This conclusion is reinforced by observations made after the cosmonauts returned to Earth (Figs. 2 and 4 and Ref. 25). Our study does not indicate why vagal-cardiac nerve traffic is diminished in space. One obvious explanation is the well-documented reduction of blood volume (24) that occurs during even brief space missions.

In their study of Holter recordings made in space, Fritsch-Yelle and colleagues (17) made the observation that heart rates are lower in space than on Earth. However, Fritsch-Yelle et al. (17) compared Holter recordings during the hours astronauts were awake and active in space to corresponding preflight recordings when astronauts were awake, active, and upright on Earth. Results are likely to be different when resting supine measurements on Earth are compared with resting measurements in space. Our study and the ones cited above provide indirect evidence that vagal-cardiac nerve activity is reduced in space. Additionally, muscle sympathetic nerve activity and whole-body norepinephrine spillover are augmented in space (J. F. Cox and co-workers, unpublished data, and Ref. 11). Reduced vagal restraint and increased sympathetic stimulation should increase, not decrease, heart rates under resting conditions. Unfortunately, we did not observe consistent heart rate changes (expressed as R-R intervals) in the small number of cosmonauts we studied in space (see Table 1).

Vagal baroreflex responses. We also documented reduced vagal baroreflex gain, as reflected by three or more beat sequences of increasing systolic pressures

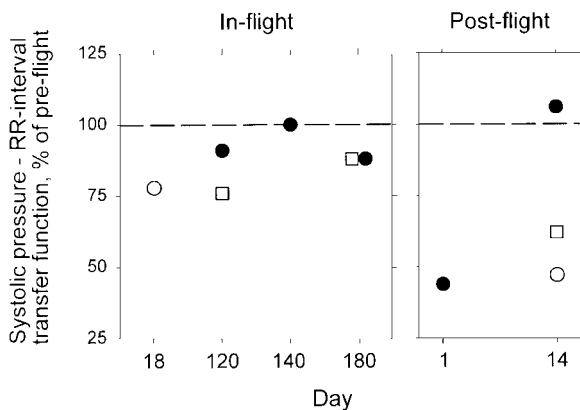


Fig. 6. Transfer function magnitude during random-frequency breathing from all cosmonauts during each experimental session. ○, Cosmonaut 1; □, cosmonaut 2; ●, cosmonaut 3.

and R-R intervals (15, 26) and systolic pressure-R-R interval transfer functions during random-frequency breathing (2). These findings are consistent with observations made during (Ref. 14, and J. F. Cox et al., unpublished data) and before and after short-duration space missions (13, 16, 25). Reduced vagal baroreflex gain and reduced vagal-cardiac nerve traffic may be causally related, because arterial baroreceptor activity is a strong determinant of vagal-cardiac neural outflow (9, 23). In unanesthetized cats, sinoaortic denervation greatly reduces R-R interval fluctuations at all frequencies (7).

In our study, reduced R-R interval fluctuations were associated with augmented systolic arterial pressure fluctuations at all breathing frequencies, before and after microgravity exposure (Figs. 2 and 4). These changes are internally consistent. Floras and colleagues (12) showed, in a multivariate regression analysis, that vagal baroreflex gain was the only independent determinant of arterial pressure variability in a group of hypertensive patients.

Limitations. The most important limitations are the small number of cosmonauts studied and the fact that different numbers of cosmonauts were studied at different times during the missions. We estimated arterial pressure changes with finger photoplethysmography; although photoplethysmograms do not track absolute arterial pressure changes exactly, the correlations are quite good (20). Also, we used respiratory sinus arrhythmia as an index of vagal-cardiac nerve traffic (21); this usage is accepted but is not perfect (22). (There is no published report of directly measured human vagal-cardiac nerve activity.)

In conclusion, we studied the effects of long-duration spaceflight on autonomic cardiovascular regulation of three Russian cosmonauts. Our results suggest that long-duration spaceflight decreases vagal cardiac neural outflow and vagal baroreflex gain and that these effects persist for at least 2 wk after return to Earth. Our results indicate that these changes occur early and persist; however, we cannot say whether they progress or stabilize as a function of the duration of exposure to microgravity. Our data highlight the ease with which astronauts who are not trained in physiology or medicine can perform sophisticated physiological experiments on themselves and each other and may provide insights for future research aboard the International Space Station.

We offer sincere gratitude to the Russian cosmonauts who volunteered to perform our experiment in space; without their voluntary participation, this research would not have been possible. For outstanding support of our science, we thank Elkin Romero, Charlie Williamson, John McBrine, John Charles, John Uri, and Scott Smith of Lockheed Martin and NASA, Houston, and the numerous Russian specialists and trainers from Star City and the Institute of Biomedical Problems, Moscow. We also thank the Russian and American personnel stationed at Star City for assisting us during our sojourns to Russia.

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