Circadian Rhythm of Autonomic Cardiovascular Control During Mars500 Simulated Mission to Mars

Daniel E. Vigo, Francis Tuerlinckx, Barbara Ogrinz,
Li Wan, Guido Simonelli, Evgeny Bersenev,
Omer Van den Bergh, and André E. Aubert

Vigo DE, Teurlinckx, Ogrinz B, Wan L, Simonelli G, Bersenev E, Van den Bergh O, Aubert AE. ***Circadian rhythm of autonomic cardiovascular control during Mars500 simulated mission to Mars*****. Aviat Space Environ Med 2013; 84:1–6.**

Introduction: The Mars500 project was conceived to gather knowledge about the psychological and physiological effects of living in an enclosed environment during the 520 d as would be required for a real mission to Mars. Our objective was to investigate the circadian profile of heart rate variability in the context of the Mars500 study. ***Methods:*** Before, during and after confinement, 24-h EKG records were obtained from the six crew members who participated in the mission. Autonomic activity was evaluated through time and frequency domain indexes of heart rate variability (HRV) analysis. Circadian rhythmicity was assessed both by averaging hourly HRV along wake and sleep scheduled periods and by fitting a 24-h harmonic to the hourly means. ***Results:*** During confinement, wake HRV showed (mean ± SE) a progressive increase in mean RR interval (from 778 ± 24 ms to 916 ± 42 ms), and in the amplitude (values are wavelet power coefficients) of very low (from 13.3 ± 0.3 to 14.1 ± 0.2) and high (from 7.8 ± 0.4 to 8.3 ± 0.3) frequency components. During sleep, the relative amplitude of the high frequency component of HRV decreased (from 11.8 ± 1.6 to 9.4 ± 1.8 normalized units). Overall, sleep-wake differences of HRV showed a progressive decrease of the relative amplitude of the high frequency component. Also, circadian HRV rhythms were dampened during confinement. ***Discussion:*** Data revealed diminished amplitude of the rest-activity pattern of autonomic nervous system parasympathetic function. Reduced daylight exposure and mood changes could account for this observation.

Keywords: space physiology, confinement, sleep, heart rate variability, wavelets.

IN PROLONGED SPACEFLIGHTS, the effect of long-term confinement on the autonomic regulation of the heart is difficult to separate from the effect of prolonged exposure to microgravity or other space-related stressors. In this regard, the Mars500 project was conceived to gather data, knowledge and experience about the psychological and physiological effects of living in an enclosed environment during the 520 d as would be required for a real mission to Mars. This allows us to study the effect of long term confinement without the influence of microgravity (25).

Although autonomic nervous system (ANS) activity may play a key role in adaptation during space missions (2), little is known about the specific impact of confinement on the circadian rhythm of ANS activity. The circadian rhythm is characterized by a sympathetic predominance during the wake periods that allows an active engagement with the external environment with increased utilization of energy, and a parasympathetic predominance during the night related with a disengagement from external environment for recovery (17).

A significant reduction of the adrenal hormonal levels of the pituitary-adrenal hormonal axis and reduced sympathetic activity during the day was reported during a 40-d stay in the Italian Antarctic Station of Terra Nova Bay (7). Similarly, in the context of the Mars500 pilot study (Mars105), we observed that a 105-d period of confinement was associated with an increase in parasympathetic activity during wakefulness. No significant differences were found in the length or phase of the sleep-wake periods (25).

Few physiological studies have been conducted with longer periods of confinement (> 105 d). In periods of up to 6 months in space, in-flight changes go toward homeostatic conditions similar to those found in the preflight supine position (23); being mean arterial blood pressure and heart rate lower than when compared with ground-based standing (22). A decrease in parasympathetic activity assessed during controlled respiration tests was reported during prolonged spaceflights (196 d) aboard the International Space Station (3). Regarding Earth-based experiments, during a 2-yr confinement period in the Biosphere 2 project, subjects showed a reduction in blood pressure. However, although this installation was materially closed, it was energetically open (sunlight and electric power), and subjects were under a calorically restricted low-fat diet (26). Still, none of these studies evaluated the circadian rhythm of autonomic activity.

Hence, we sought to investigate the circadian profile of heart rate variability during a 520-d confinement period in the context of the Mars500 study. Based on our

---

From the Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Universidad Católica Argentina and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina; Department of Psychology, University of Leuven, Leuven, Belgium; State Science Center of Russian Federation - Institute of Biomedical Problems of Russian Academia of Science, Moscow, Russia; and Laboratory of Experimental Cardiology and Interdisciplinary Centre for Space Studies, University of Leuven, Leuven, Belgium.

This manuscript was received for review in December 2012. It was accepted for publication in April 2013.

Address correspondence and reprint requests to: Dr. André E. Aubert, Laboratory of Experimental Cardiology and Interdisciplinary Centre for Space Studies, Katholieke Universiteit Leuven, Herestraat 49; B-3000 LEUVEN, Belgium; andre.aubert@med.kuleuven.be.

Reprint & Copyright © by the Aerospace Medical Association, Alexandria, VA.

DOI: 10.3357/ASEM.3612.2013

previous findings on Mars105 (25), we hypothesize that long term confinement is associated with an increase in parasympathetic activity during wake periods.

METHODS

Subjects

Six healthy nonsmoking male subjects (mean ± SD: age 34 ± 5 yr; height 176 ± 3 cm; weight 85 ± 9 kg; BMI 27 ± 3 $\text{kg} \cdot \text{m}^{-2}$) were selected to participate in the 520-d confinement study.

Design

The Mars 500 project (http://www.esa.int/Mars500), organized by the European Space Agency (ESA) and the Institute for Biomedical Problems (IBMP) in Moscow, was designed to simulate a mission to Mars in duration, composition of the crew, activities, full life support, and communication facilities with a Mission Control.

The study protocol was approved in advance by the Ethics Committee of the University Hospital Gasthuisberg of Leuven, Belgium, and the ESA Medical Board, which complied with all guidelines stated in the Declaration of Helsinki. Each subject provided written informed consent before participating.

The crew was selected from a pool of 9600 candidates. Criteria were the same as for the selection of astronauts (5). A preliminary group of eight candidates (6 months before the start of Mars500), was submitted to an astronaut training program with survival and team building activities included. After this process, the final group of six subjects was selected with a diverse cultural and scientific background: three Russians (a surgeon, a physician, and an engineer), one Chinese (an astronaut trainer), and two Europeans (both engineers).

Subjects were confined in the isolation facility at IBMP in Moscow from the 3th of June 2010 to the 4th of November 2011. The lay-out of the isolation facility comprised four hermetically sealed interconnected habitat modules resembling a spacecraft having the ability to communicate with Mission Control on a 24/7 basis. The total volume of the habitat modules was 550 m^3. Ambient temperature was maintained constant at 24°C, with a relative humidity of 35–45%, and artificial lighting conditions of 50 – 300 lux. Facilities included a medical module (two medical berths, medical and research equipment and a toilet), a habitable module (six compartments, a main control room and a toilet), a storage module (physical training facilities, food storage, a greenhouse and a bathroom), a Mars landing module simulator and a Martian surface simulator.

Subjects were involved in 105 different scientific protocols (74 projects from Russia, 15 from ESA, and 16 from other countries) that assessed physiological, psychological, biological, and technological aspects of confinement. All experiments were blindly selected by international reviewers. Besides measurements during confinement, also pre and post measurements were taken. The crew received specific preconfinement training to conduct all the experiments.

As in the International Space Station (ISS), their schedules were organized in order to maintain 8-h periods of work, leisure, and sleep. No night shifts were programmed. Duties were described in detail on an hourly and daily basis in "cyclograms" (time-charts), which were distributed every week. Workload was similar during the different phases of the missions.

The simulated timeline included the undocking from orbital assembly (15 Jun 2010), transfer to heliocentric orbit toward Mars (23 Jun 2010), shifting to spiral orbit toward Mars (24 Dec 2010), entering circular orbit around Mars (1 Feb 2011), undocking and landing on Mars (12 Feb 2011), egresses on simulated Martian Surface (14, 18 and 22 Feb 2011), ascent and docking (23, 24 Feb 2010), entering into spiral orbit away from Mars (2 Mar 2011), transfer to heliocentric orbit toward Earth (7 Apr 2011), and shifting to spiral orbit toward Earth (13 Oct 2011).

Procedure

We obtained 24-hour Holter signals at 10 time points: in 1 day in the period within the 2 months before confinement (Pre); each 2 months during the confinement period (T1-T8); and in 1 day during the 2nd week after confinement (Post). T1-T4 measurements correspond to the outbound journey, while T5-T8 measurements correspond to the inbound journey.

Electrocardiogram signal was recorded using a digital Holter device. Ventricular depolarizations (R waves) were detected through the device software. The time elapsed between R waves (RR intervals) was then computed. Heart rate variability (HRV) indexes were computed in 1-h segments. Premature and lost beats were identified by an automated filter and replaced by RR intervals resulting from linear interpolation. Segments with more than 20% of missing intervals were excluded from further analysis (11,18).

Time domain analysis was performed on heart rate by evaluating measures of variation over time. Among these, RRm (mean duration of RR intervals in milliseconds) quantifies the mean heart rate, SDNN (standard deviation of RR intervals in milliseconds) represents a coarse quantification of overall variability, and RMSSD (square root of the mean squared differences of successive normal RR) measures short-term heart rate variations (18).

Frequency domain measurements provide an evaluation of the power of the contributing frequencies underlying HRV. Its high-frequency (HF) component (0.15-0.4 Hz) is related to respiratory sinus arrhythmia and mediated by parasympathetic activity, whereas the low-frequency (LF) component (0.04-0.15 Hz) is related to baroreflex control and depends upon sympathetic and parasympathetic mechanisms. A very low frequency (VLF) component (0.003-0.04 Hz) of an uncertain origin is also found and has been attributed to thermoregulatory fluctuations in vasomotor tone as well as to humoral factors such as the renin-angiotensin system, with dependence on the presence of parasympathetic outflow (18,20).

To analyze the frequency components of HRV, the Discrete Wavelet Transform (DWT) was chosen rather than the traditional Fast Fourier Transform (FFT) because it is not affected by discontinuities or nonstationarities (4). Before applying the DWT, the linear trend and the mean value were subtracted from the signal. In addition, it was evenly sampled with a frequency of 2.4 Hz by means of a spline interpolation algorithm and zero padded to the next higher power of two (4). A nine-level wavelet decomposition was employed to analyze the signal, using a Daubechies 4 wavelet function. Using this decomposition, wavelet levels D2-D9 and A9 represent the total power (TP, 0–0.6 Hz), wavelet levels D6–D9 approximately correspond to the very low frequency band (VLF, 0.0023-0.0375 Hz), wavelet levels D4-D5 to the low frequency band (LF, 0.0375-0.15 Hz), and wavelet levels D2-D3 to the high frequency band (HF, 0.15-0.6 Hz). In DWT, the square of the standard deviation of wavelet coefficients at each level is concordant with the spectral power of that level (4). Reported values are expressed as the natural logarithm of TP, HF, LF and VLF; normalized units (nu) of LF [LF nu = 100XLF/(TP–VLF)] and HF [HF nu = 100XHF/(TP–VLF)]; and the ratio between LF and HF (18).

Circadian heart rate variability rhythms are driven by exogenous cycles of light and darkness, as well as endogenous circadian rhythmicity (21). To account for the exogenous rhythm, hourly HRV was averaged along wake and sleep periods. The sleep period was defined as the time between 23:00 and 07:00 h, according to the fixed schedule of the crew. HRV differences between sleep and wake averages were also calculated (13). To account for the endogenous circadian HRV rhythmicity, a 24-h harmonic was fitted by applying a partial Fourier analysis to the hourly means, and its significance was checked by an F-test. The Chronos-Fit software was used for this purpose (Zuther and Lemmer, Chronos-Fit, http://www.ma.uni-heidelberg.de/inst/phar/forschungLemmer.html, 2004). The following parameters were derived from this method: mesor (the average of the rhythm), amplitude (one half of the difference between the maximum and the minimum of the fitted function), acrophase (the lag from midnight to the time of the maximum value in the model), and proportion variance (the fraction of the total variance explained by the model).

Statistical Analysis

The differences with respect to the several HRV indices between different stages in the confinement were assessed by means of a repeated measures ANOVA test, followed by a Tukey HSD posthoc test. A Mauchly's sphericity test was conducted in order to test for the validity of a univariate approach for ANOVA analysis. When the sphericity assumption was not valid the Greenhouse-Geisser correction was applied, followed by a Bonferroni posthoc test.

RESULTS

A total of 56 (93%) Holter recordings were obtained, with 23.3 ± 0.3 valid 1-h bins. The four missing recordings corresponded to four different subjects in two different measurements days (T2 and T3). With exception of one recording at POST with only six valid segments, each recording had at least 19 (79%) valid bins. The failed recording was prematurely interrupted during the night; it was included for the rest activity analyses, since it can still provide useful information about sleep-wake differences of HRV (24), but excluded for the circadian analyses, due to the six recorded bins being consecutive and therefore a cosine curve could not be fitted.

Regarding the sleep-wake analysis of HRV, we averaged consecutive pairs of measurements within confinement (T1 and T2, T3 and T4; T5 and T6; T7 and T8). The new resulting measures were denoted as: T1-2, T3-4, T5-6, and T7-8, respectively. This averaging operation considerably reduced the noise, while the time trend was preserved. In addition, a possible issue of missing data was circumvented, since every pair of measurements days had at least one valid record, which was not the case for the original data. Moreover, it allowed the calculation of Mauchly's sphericity test, which could not be performed for the original data set because it was too unbalanced. To check the sensitivity of our results to the specific averaging, we collapsed the data in different ways and checked whether this gave rise to the same conclusions (e.g., PRE, T1 to T8, POST; PRE, confinement, POST; PRE, outbound journey, inbound journey, POST).

Table I shows the significance of HRV changes along the different measurement days. During wake periods, repeated measures ANOVA showed significant variations over time for mean RR, SDNN, RMSSD, ln TP, ln VLF, and ln HF (Table I). Posthoc analyses revealed that after the fourth month (T3-4, T5-6, T7-8) mean RR values were significantly higher than PRE and POST. Also, at T7-8 values were higher than T1-2, configuring a tendency of increasing mean RR over time (Fig. 1). SDNN, ln TP and ln VLF were higher than PRE at all measurement days along confinement (not shown). RMSSD was higher than PRE after the 4th month (T3-4, T5-6, T7-8)

TABLE I. F VALUES OF SLEEP – WAKE HRV CHANGES ALONG CONFINEMENT.

	Wake	Sleep	S-W
RRM (ms)	10.04 ‡	2.26	0.62 (GG)
SDNN (ms)	8.34 ‡	3.28 *	0.71 (GG)
RMSSD (ms)	5.44 †	1.32	0.25 (GG)
ln TP (wpc)	5.82 †	1.84	1.16
ln VLF (wpc)	8.46 (GG) *	2.62 (GG)	1.74
ln LF (wpc)	3.13 (GG)	3.14 (GG)	0.58
ln HF (wpc)	4.02 †	1.86 (GG)	0.58 (GG)
LF (nu)	0.74	2.72 *	3.56 *
HF (nu)	0.74	2.72 *	3.56 *
LF/HF	1.49 (GG)	1.89 (GG)	3.08 *

Shown are F values of univariate repeated ANOVA with 5,25 degrees of freedom, except for (GG) where degrees of freedom where corrected by the Greenhouse-Geisser method. RRm, mean of RR interval duration (ms); SDNN, standard deviation of RR intervals (ms); RMSSD, square root of the mean squared differences of successive normal RR (ms); TP, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

(not shown). Ln HF was higher than PRE after the 6th month (T5-6, T7-8) (**Fig. 1**).

During sleep periods, repeated measures ANOVA showed significant variations over time for SDNN, HFnu, and LFnu (Table I). Posthoc analyses revealed that SDNN at T5-6 was higher than PRE (not shown), and that HFnu was lower than PRE at T7-8 (Fig. 1), while LFnu was concomitantly higher than PRE at that stage (not shown).

Sleep – wake differences of HFnu, LFnu and LF/HF showed significant variations over time, as revealed by repeated measures ANOVA (Table I). Posthoc analyses revealed that HFnu sleep-wake differences were lower at T5-6 and T7-8 compared to PRE (Fig. 1), while LFnu sleep-wake differences were concomitantly reduced but in the opposite direction (this necessarily holds because HFnu = 100-LFnu) (not shown). Also, the sleep-wake difference of LF/HF was lower at T7-8 compared to PRE (not shown).

When analyzing different comparisons (PRE, T1 to T8, POST; PRE, confinement, POST; PRE, outbound journey, inbound journey, POST), we obtained similar results that lead to the same conclusions.

Regarding the circadian rhythm analysis of HRV, **Table II** depicts the number of measurements in which HRV variables showed significant circadian variations. We identified the variables that showed significant circadian variations in > 80% of the measured points, before, during and after confinement. Before confinement, most of HRV variables showed significant circadian variations, except ln LF and ln TP. During confinement, only RRM and RMSSD showed significant circadian variations. After confinement, apart from RRM and RMSSD, significant circadian variations were seen again in ln HF, HFnu, LFnu, and L/H. Therefore, except for RRM and RMSSD, it was not possible to calculate the circadian parameters that describe the 24-h rhythm of HRV at all stages, and no statistical comparisons were possible. Among RRM and RMSSD circadian parameters, only RRM mesor showed significant changes (F (1.92, 7.66) = 5.79, $P = 0.030$), being T3-4, T5-6, T7-8 > than PRE.

DISCUSSION

The main result of the present study is that during wake confinement, a progressive decrease in mean heart rate and a progressive increase in the amplitude of very low and high frequency components of HRV emerged. During sleep periods, the relative amplitude of the high frequency component of HRV decreased. Overall, sleep-wake differences of HRV showed a progressive decrease of the relative amplitude of the high frequency component of HRV. Also, during confinement most of HRV variables showed nonsignificant circadian rhythms.

Heart rate oscillations at all frequency levels (VLF, LF and HF) reflect parasympathetic influences (18,20), while LF fluctuations are also tightly coupled with synchronous oscillations of efferent sympathetic nervous activity (20). Thus, the increase during the day in VLF- and

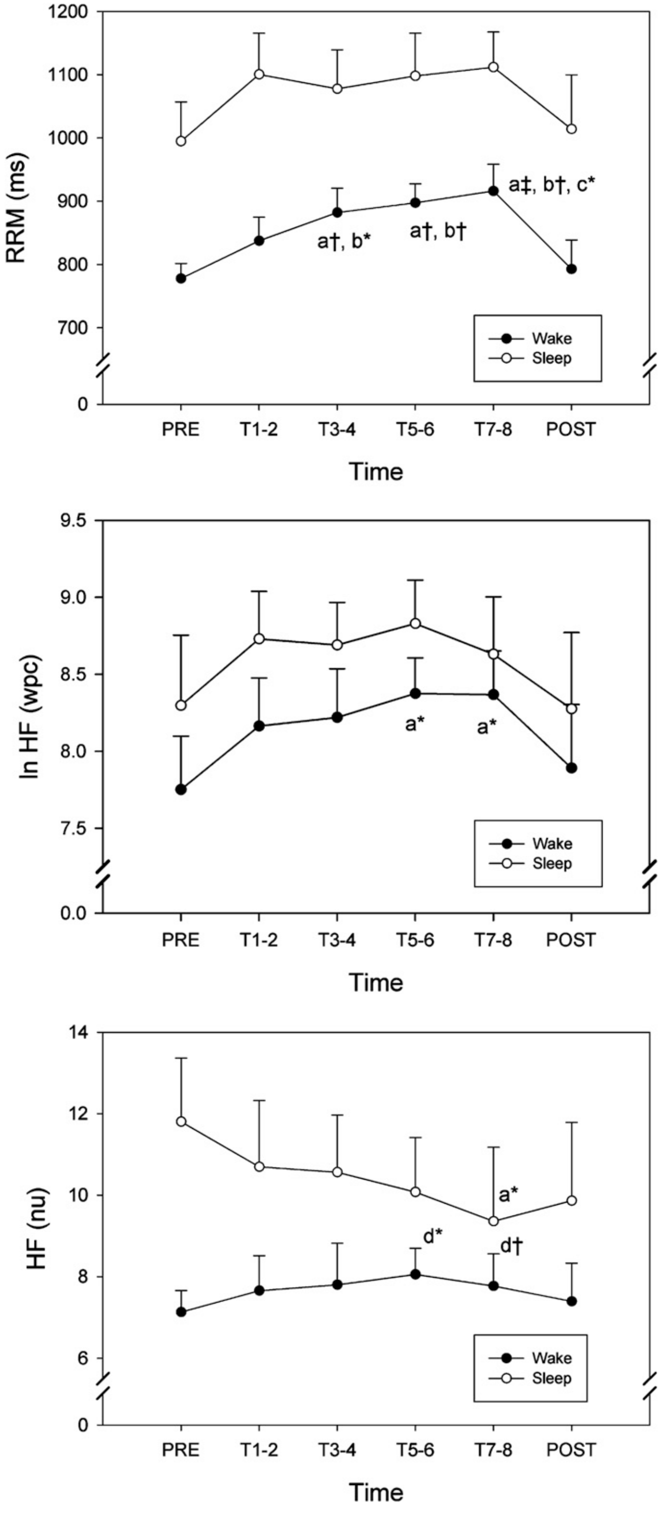

Fig. 1. RR interval duration and high frequency heart rate variability changes along confinement (mean + SEM). Data shown are means (SEM). Time points during confinement denote averaged bimesters as described in the text, resulting in six observations for each point. RRm, mean of RR interval duration (ms); HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units. a: significantly different from pre; b: significantly different from post; c: significantly different from T1-2; d: sleep-wake differences at T5-6 and T7-8 significantly different from sleep-wake differences at PRE. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

TABLE II. NUMBER OF MEASUREMENTS WITH SIGNIFICANT HRV CIRCADIAN VARIATIONS.

	PRE (N = 6)	CONFINEMENT (N = 44)	POST (N = 5)
RRM (ms)	6 (100%)	41 (93%)	5 (100%)
SDNN (ms)	5 (83%)	13 (30%)	2 (40%)
RMSSD (ms)	6 (100%)	38 (86%)	4 (80%)
ln TP (wpc)	3 (50%)	7 (16%)	0 (0%)
ln VLF (wpc)	5 (83%)	14 (32%)	2 (40%)
ln LF (wpc)	4 (67%)	26 (59%)	2 (40%)
ln HF (wpc)	6 (100%)	28 (64%)	5 (100%)
LF (nu)	5 (83%)	25 (57%)	4 (80%)
HF (nu)	5 (83%)	25 (57%)	4 (80%)
LF/HF	5 (83%)	23 (52%)	4 (80%)

Shown are frequencies (%) of the number of measurements in which HRV variables showed significant circadian variations. Confinement values are totals that include repeated measurements across the same subjects. RRm, mean of RR interval duration (ms); SDNN, standard deviation of RR intervals (ms); RMSSD, square root of the mean squared differences of successive normal RR (ms); TP, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units.

HF-HRV and the decrease of normalized HF-HRV during the night can be explained by an augmented parasympathetic activity during wake periods and a diminished parasympathetic activity during sleep periods, respectively. The observation that there was only a change for absolute HRV frequency indexes during wake, but during sleep only for the relative HRV frequency indexes, may be due to the fact that those indexes reflect different degrees of parasympathetic predominance, as seen when passing from standing to supine (higher values of frequency domain indexes) or when going from wake to NREM sleep (higher values of normalized HF%) (24).

As reported by other authors (21), we demonstrated significant circadian heart rate and HRV rhythms in basal conditions. These rhythms were mostly lost during confinement and only partially restored afterwards. This observation is consistent with lower sleep-wake HRV differences reported herein, but also points out that the endogenous rhythm may be altered by confinement. Although after a short laboratory confinement period of 13 d HRV still exhibits a significant circadian rhythm (21), no studies were found that reported changes of circadian HRV over longer periods.

These results are in line with our own observations during Mars105, where an increase in parasympathetic activity during wakefulness was reported, even though no differences were observed during sleep periods. Factors like prolonged exposure to artificial dim lighting conditions or changes in mood related to confinement stressors like boredom were proposed to explain the reported results (25). Preliminary observations of the complete simulation study also support our results. After 250 d of isolation core temperature rhythm seems to be diminished. This was attributed to end of time-restrictions on food intake for the crew (10). In addition, physical daily activity levels decreased significantly over the course of the study. The immediate reductions in physical activity after a demanding preisolation period explained only part of the results. The reductions were largely driven by more significant changes in the morning and evening (8). The sleep periods seemed also to be affected by confinement. Total sleep time and sleep efficiency were reduced, down to values of less than 450 min and 90%, respectively (14).

The disruption of the circadian rhythm of autonomic activity described in the present study adds to other circadian disruptions seen in space missions. As in Mars500, indoor lighting is of a much lower intensity, deficient in ultraviolet light and excessive in the light colors. After about 3 months in space, the influence of the endogenous circadian pacemaker on oral temperature and circadian rhythms related to subjective alertness are considerably weakened, probably resulting in disruptions in sleep. When subjects are in dim light conditions, such as in a spacecraft, the melatonin cycle loses its normal rhythm, with high levels in activity periods and low levels in rest periods (5).

Interestingly, the observed pattern of circadian autonomic activity is similar to other situations where the synchronization of the endogenous circadian pacemaker is disrupted by the absence of external cues, like continuous working under artificial dim lighting (12) or living in extreme latitudes (1). Also, the monotony during the inbound journey may affect mood state, and in turn contribute to explain the reported results. For example, depressed patients show a dampening of the amplitude of heart rate circadian rhythm and of the day-night heart rate difference, linked to a lesser increase of heart rate during the day and a reduced decrease at night (19). In these conditions, studies evaluating 24-h autonomic activity are scarce, and our results may help to understand the disease mechanisms responsible for the associated increased morbidity. On the other side, astronauts may benefit from interventions proven to be useful in these kinds of disorders, like the administration of light therapy or exogenous melatonin (15).

The monotony associated with the second half of the experiment as reported in qualitative interviews complement the aforementioned observations (16). It could be argued that monotony among crewmembers shows inadequate crew preparedness or motivation, as well as poor organization of the study. This was certainly not the case because, as detailed in Methods section, the crew underwent the same selection criteria and training as astronauts; the habitat was similar to a spacecraft, with full life support and a 24/7 full mission control; activities were tightly scheduled as on the ISS, with a similar workload across the different stages of the confinement period; and the mission was set-up with high fidelity to a real analog of spaceflight, including the simulation of a Mars descent. Moreover, the scientific structure of the study comprised 105 different experiments with pre- and postcontrol measurements, which were performed with a high degree of success, as reflected by preliminary reports on the results of Mars500 (8,10,14,16).

The present study is important because autonomic activity is related with cognitive performance. For example, higher levels of sympathetic activity were associated with better results in decision making tasks, suggesting that a higher basal activation of autonomic nervous system is beneficial for subsequent decision-making processes (6). In turn, due to the fact that autonomic activity plays a key role in adapting to a changing environment, crew members may benefit from training to regulate their autonomic and central nervous system responses.

The main limitation of this study is that conclusions are restricted due to the small numbers of subjects and the absence of a nonconfined control group. This is typical of this kind of research, where the opportunities for in-depth studies in life space sciences are sparse, and there are many confounding factors that are difficult to control (5). In addition, our results do not necessarily apply to females, who show a higher basal parasympathetic responsiveness that accounts for a differential cardiovascular response elicited by weightlessness (9). Therefore, results from Mars500 are restricted to a highly selected male population. Finally, it remains to be seen how these results would translate to real space missions, where the possibility of not getting back to Earth is a major stressor.

To conclude, data obtained during the 520-d isolation experiment revealed diminished amplitude of the circadian rhythm of the autonomic nervous system parasympathetic function. Several factors could account for this observation, including reduced daylight exposure related to the confinement situation. Further studies should address the association of these findings with changes in other physiological rhythms, and if they adversely affect cognitive performance during long-duration space missions.

ACKNOWLEDGMENTS

This work was supported by grants from the Belgian Federal Office of Scientific Affairs through an ESA-PRODEX. DEV is a Research Career Awardee from the Argentine Research Council (CONICET).

Authors and affiliations: Daniel E. Vigo, M.D., Ph.D., and Guido Simonelli, Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Universidad Católica Argentina and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina; Daniel E. Vigo, M.D., Ph.D., Francis Tuerlinckx, Ph.D., Barbara Ogrinz, M.A., Li Wan, M.D., Ph.D., and Omer Van den Bergh, Ph.D., Department of Psychology, University of Leuven, Leuven, Belgium; Evgeny Bersenev, Ph.D., State Science Center of Russian Federation - Institute of Biomedical Problems of Russian Academia of Science, Moscow, Russia; and André E. Aubert, M.D., Ph.D., Laboratory of Experimental Cardiology and Interdisciplinary Centre for Space Studies, University of Leuven, Leuven, Belgium.

REFERENCES

1. Arendt J. Biological rhythms during residence in polar regions. Chronobiol Int 2012; 29:379–94.
2. Aubert AE, Beckers F, Verheyden B. Cardiovascular function and basics of physiology in microgravity. Acta Cardiol 2005; 60:129–51.
3. Baevsky RM, Baranov VM, Funtova II, Diedrich A, Pashenko AV, et al. Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. J Appl Physiol 2007; 103:156–61.
4. Chan HL, Huang HH, Lin JL. Time-Frequency analysis of heart rate variability during transient segments. Ann Biomed Eng 2001; 29:983–96.
5. Clément G. Fundamentals of space medicine, 2 ed. New York: Springer Science+Business Media, LLC; 2011.
6. Drucaroff LJ, Kievit R, Guinjoan SM, Gerschcovich ER, Cerquetti D, et al. Higher autonomic activation predicts better performance in iowa gambling task. Cogn Behav Neurol 2011; 24:93–8.
7. Farrace S, Ferrara M, De AC, Trezza R, Cenni P, et al. Reduced sympathetic outflow and adrenal secretory activity during a 40-day stay in the Antarctic. Int J Psychophysiol 2003; 49:17–27.
8. Felsenberg D, Belavy DL, Daumer M, Fomina E, Gast U, et al. Progressive reductions in physical activity during isolation. Proceedings of the Mars500 International Symposium; 23-25 Apr 2012; Russian Academy of Sciences Moscow, Russia. Moscow: Institute of Biomedical Problems; 2012:84.
9. Grenon SM, Xiao X, Hurwitz S, Sheynberg N, Kim C, et al. Why is orthostatic tolerance lower in women than in men? Renal and cardiovascular responses to simulated microgravity and the role of midodrine. J Investig Med 2006; 54:180–90.
10. Gunga H, Werner A, Stahn A, Opatz O, Sattler F, et al. Core temperatures and circadian rhythms in humans during long-term isolation and confinement (MARS500). Proceedings of the Mars500 International Symposium; 23-25 Apr 2012; Russian Academy of Sciences Moscow, Russia. Moscow: Institute of Biomedical Problems; 2012:89–90.
11. Ho KK, Moody GB, Peng CK, Mietus JE, Larson MG, et al. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation 1997; 96:842–8.
12. Holmes AL, Burgess HJ, McCulloch K, Lamond N, Fletcher A, et al. Daytime cardiac autonomic activity during one week of continuous night shift. J Hum Ergol (Tokyo) 2001; 30:223–8.
13. Huikuri HV, Niemela MJ, Ojala S, Rantala A, Ikaheimo MJ, Airaksinen KE. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. Circulation 1994; 90:121–6.
14. Lv K, Wan YM, Qu LN, Wang HH, Chen HL, et al. Circadian rhythm patterns in isolation environments: results form a systematic biorhythm study during the simulated 520-day Mars spaceflight. Proceedings of the Mars500 International Symposium; 23-25 Apr 2012; Russian Academy of Sciences Moscow, Russia. Moscow: Institute of Biomedical Problems; 2012:92–3.
15. Pandi-Perumal SR, Trakht I, Spence DW, Srinivasan V, Dagan Y, Cardinali DP. The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. Nat Clin Pract Neurol 2008; 4:436–47.
16. Polackova I, Solcova I, Vinokhodova A. A story of a simulated flight to Mars. Proceedings of the Mars500 International Symposium; 23-25 Apr 2012; Russian Academy of Sciences Moscow, Russia. Moscow: Institute of Biomedical Problems; 2012:102.
17. Recordati G. A thermodynamic model of the sympathetic and parasympathetic nervous systems. Auton Neurosci 2003; 103:1–12.
18. Seely AJ, Macklem PT. Complex systems and the technology of variability analysis. Crit Care 2004; 8:R367–84.
19. Taillard J, Lemoine P, Boule P, Drogue M, Mouret J. Sleep and heart rate circadian rhythm in depression: the necessity to separate. Chronobiol Int 1993; 10:63–72.
20. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. Circulation 1998; 98:547–55.
21. Vandewalle G, Middleton B, Rajaratnam SM, Stone BM, Thorleifsdottir B, et al. Robust circadian rhythm in heart rate and its variability: influence of exogenous melatonin and photoperiod. J Sleep Res 2007; 16:148–55.
22. Verheyden B, Liu J, Beckers F, Aubert AE. Adaptation of heart rate and blood pressure to short and long duration space missions. Respir Physiol Neurobiol 2009;169(Suppl 1):S13–6.
23. 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 2010; 108:646–54.
24. Vigo DE, Dominguez J, Guinjoan SM, Scaramal M, Ruffa E, et al. Nonlinear analysis of heart rate variability within independent frequency components during the sleep-wake cycle. Auton Neurosci 2010; 154:84–8.
25. Vigo DE, Ogrinz B, Wan L, Bersenev E, Tuerlinckx F, et al. Sleep-wake differences in heart rate variability during a 105-day simulated mission to Mars. Aviat Space Environ Med 2012; 83:125–30.
26. Walford RL, Mock D, Verdery R, MacCallum T. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. J Gerontol A Biol Sci Med Sci 2002; 57:B211–24.

Author Query sheet–ASEM3612

There are no queries in this article.