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Cardiovascular Autonomic Adaptation to Long-Term Confinement During a 105-Day Simulated Mars Mission

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Introduction: Long-term confinement and microgravity may entail alteration in the regulation of the cardiovascular system. A 105-d pilot study of a Mars mission simulation was conducted to test the cardiovascular response to slow-paced breathing and mental stress. ***Methods:*** Finger blood pressure and beat-to-beat heart rate were monitored in six male volunteers taking part in a 105-d Mars mission simulation. Data were collected before, during (Days 35-38, 70-72, and 100), and after confinement. Recordings were performed in the sitting position during 5-min spontaneous breathing, 3-min 12 cycle/min breathing, 3-min 6 cycle/min breathing, and 5-min mental task performance. ***Results:*** We found significant U-shaped changes across the confinement period in systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). In the first month of confinement, mental task performance significantly lowered SAP by 34.23 mmHg and MAP by 19.89 mmHg compared to spontaneous breathing, whereas these changes were reversed during other periods. Furthermore, no differences in arterial pressure and heart rate were found between spontaneous, 12 cycle/min, and 6 cycle/min breathing. ***Conclusions:*** Our findings are in line with and extend previous findings on the alteration of blood pressure regulation due to long-term confinement.

Keywords: confinement, blood pressure, autonomic nervous system, mental performance, slow paced breathing.

THE GROWING INTEREST in human exploration of the solar system, such as a mission to Mars, requires understanding the effect of confinement as well as microgravity and radiation on human physiology during long-duration space travel. On one hand, a number of adaptations within the cardiovascular system, also described as "cardiovascular deconditioning," and alterations in autonomic cardiovascular control induced by microgravity have been addressed (2,3). On the other hand, living and working in an isolated, confining, and hostile environment for prolonged periods of time can be very stressful (19). During a spaceflight to Mars, the crew will have to live in a small group, be isolated from family and friends, have limited communication with Earth, including a delay of up to 20 min in bidirectional communications, and have less privacy and personal space due to habitability constraints. Ground-based simulations in laboratories on Earth, such as confinement, have been undertaken to assess and understand the biomedical problems associated with long-term space missions (24). This allows disentangling the effects of confinement from the effects of microgravity, particularly helping us better understand the effect of long-term confinement on cardiovascular responses to different circumstances.

Human physiology and the cardiovascular system in particular may be affected by several external stressors during long-term confinement in an extreme environment (e.g., space missions, submarines, and Antarctic expeditions). Reduced circulating blood volume, reduced arterial diastolic blood pressure, reduced left ventricular mass, and decreases in ventricular stroke volume have been reported in numerous studies on the physiological effects of microgravity during spaceflight (2,29). Some studies using hermetically sealed environments (110 d and 240 d) (12) and prolonged bed rest (120-180 d) (17) observed decreases in hormonal patterns of blood volume regulation during long-term confinement, which might result from the elimination of mobility and action. However, very little is known about the influence of confinement on cardiovascular regulation.

In this study, we focused on the adaptation of blood pressure and heart rate before, during, and after long-term confinement, and we tested cardiovascular responses to different tasks (i.e., mental stress using a choice reaction time task and slow-paced breathing). We hypothesized that long-term confinement, separated

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from the effects of microgravity, would alter the cardiovascular adaptation in response to slow-paced breathing and mental stress.

METHODS

Subjects

Six healthy nonsmoking male volunteers (mean ± SD: height 181 ± 5 cm; weight 82 ± 12 kg; BMI 25 ± 3 kg · m^{-2}) were selected to participate in a 105-d mission to Mars simulation study organized by the European Space Agency (ESA) and the Institute for Biomedical Problems (IBMP) in Moscow, Russia. Participants were between 25 and 40 yr old (mean ± SD: 33 ± 6 yr). Two Europeans, a German engineer, and a French airline pilot were selected by the ESA. The four Russians crewmembers (selected by the IBMP medical expert committee) were two members of the team of cosmonauts, a medical doctor, and a sports physiologist.

They were sealed in the isolation facility at IBMP in Moscow from the 31st of March 2009 to the 14th of July 2009. As a pilot experiment to the Mars500 project, the study was planned to simulate a mission to Mars, including composition of the crew, activities, workload, and communication facilities. The participants were subjected to scientific experiments dealing with the psychological and physiological effect of confinement. The protocol of the study was approved 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, and all participants gave informed consent to participate in the study.

Procedure and Design

Data were collected during five periods: 8-10 d before the confinement (Pre), three times during confinement (D35: the 35th–38th day of confinement; D70: the 70th–72nd day of confinement; D100: the 100th day of confinement), and 8-10 d after the end of confinement (Post). Data were always collected at the same time of the day in the morning. Neither alcohol nor heavy exercises were allowed in the evening before data collection. A caffeine-free standard breakfast was permitted on the morning of data collection.

Recordings of beat-by-beat arterial pressure (The Portapres™, Finapres Medical Systems, Amsterdam, The Netherlands) were obtained with the participants in a sitting position, during 5 min of spontaneous breathing, 3 min of controlled breathing at 12 cycle/min, 3 min of controlled breathing at 6 cycle/min, and 5 min of a mental stress task. The breathing was controlled by visual instructions. The mental stress task was a serial choice reaction time task similar to procedures employed in previous studies (e.g., 27). In this task, two light bulbs, designated A and B, were positioned in front of participants. Each bulb corresponded to two buttons, designated 1 and 2, on a response pad. Stimulus onset (illumination of one of the two lights) was triggered by pressing button 1, and stimulus offset by pressing button 2 adjacent to the illuminated light. When a bulb was illuminated, using his dominant hand only, participants were instructed to extinguish the light by pressing its adjacent response button (button 2), and then pressing adjacent button 1 immediately following stimulus offset in order to trigger stimulus onset for the next trial. Lights were illuminated randomly and were counterbalanced. Participants were required to press the buttons as quickly and accurately as possible. The protocols were performed in the same order with 1-min intervals and were driven by software that guided the participants.

Measurements and Data Analysis

Noninvasive arterial blood pressure from the middle phalanx of the middle finger was measured continuously using a servo-controlled photoplethysmograph (Portapress TNO, Amsterdam, The Netherlands). The participants were instructed to put the hand comfortably on the table at heart level to prevent hydrostatic pressure differences. Data on finger blood pressure were collected with a sampling rate of 1000 Hz and stored on a laptop computer for off-line analysis.

A full beat-to-beat analysis was performed using Beatscope software with the purpose of deriving mean (MAP), diastolic (DAP), systolic (SAP) blood pressure, heart rate (HR), and the interbeat interval (IBI). SAP and DAP were derived from the arterial pressure waveform. MAP was the true integral of the arterial pressure wave over one beat divided by the corresponding beat interval. HR was computed as the inverse of the IBI and expressed as bpm.

Time series of IBIs were extracted to analyze heart rate variability (HRV). Time series of beat-to-beat SAP values were extracted to analyze blood pressure variability (BPV). The time series were processed with programs written in LabVIEW 7.1 (National Instruments, Austin, TX) for Windows (4). Using a cubic-spline approximation the resulting time series were interpolated and resampled at 2 Hz to construct equidistant time series (4). Data sets of 128 s (comprising 256 samples) were divided into 16-s increments, which resulted in four segments of data in each time series. The mean value was subtracted and a Hanning window was applied. A nonparametric "run test" of means and mean square values was used to validate the stationarity of data within 5% of the confidence limits (4). In the resulting time windows, power spectral density was estimated using Fast Fourier transform. The spectral resolution for all estimates equaled 0.0078 Hz. Respiratory powers were expressed as the area under the spectrum from 0.08 to 0.12 Hz (slow-paced breathing) and from 0.18 to 0.22 Hz (normal paced breathing). During normal paced breathing a second spontaneous rhythm occurring over an approximate 10-s cycle and resulting in a low frequency band (0.04–0.15 Hz) was obtained as well. Power was expressed as the area under the spectrum over the frequency range of interest [LF, low frequency (0.04–0.15 Hz); HF, high frequency (0.15–0.4 Hz); TP, total frequency (0.04–0.4 Hz) spectral power]. Normalized units of LF (LFnu) and HF (HFnu) were defined as the percent power in the LF and

HF band frequency, respectively [i.e., LFnu = LF/ (LF+HF) × 100; HFnu = HF/ (LF+HF) × 100]. In addition, the ratio of LF and HF powers (LF/HF) was calculated.

Statistical Analysis

A 5 × 4 repeated measures ANOVA was used to test the effects of confinement and task on the cardiovascular system. The independent variables were "confinement" (Pre, Day 35, Day 70, Day 100, and Post) and "task" (Baseline: 5-min spontaneous breathing, task B6: 3-min 12 cycle/min fixed breathing, task B12: 3-min 6 cycle/min fixed breathing, and task MTP: 5-min mental task performance) as within-subject factors. The dependent variables included hemodynamic measures, HRV, and BPV. When the interaction effect was significant, post hoc contrast analysis was performed with Tukey HSD. Statistical analysis was performed with Statistica 7.0. Reported *P*-values are Greenhouse-Geisser corrected and ϵ-values are reported. A *P*-value less than 0.05 was considered significant. All results are presented as mean ± SEM.

RESULTS

All participants completed the whole study. The mean values (± SEM) of the hemodynamic data of different tasks during the pre, in-, and post-confinement periods are presented respectively in **Table I**. A "U" shape was observed in SAP, DAP, and MAP during the confinement compared to the pre- and post- period (see the left column of **Fig. 1**). However, the main effect of confinement was not statistically significant. A contrast analysis was performed to further explore these data. The quadratic coefficients were specified as 2 for the variables of pre- and post- confinement, −1 for the variables of Day 35 and Day 100 during confinement, and −2 for the variables of Day 70 during confinement. The contrast was statistically significant for SAP [F (1,5) = 6.62, $P < 0.05$], DAP [F (1,5) = 12.39, $P = 0.02$], and MAP [F (1,5) = 11.35, $P = 0.02$].

Moreover, a significant interaction effect of confinement × task was observed in SAP and MAP [respectively, F (12, 60) = 5.22, $P = 0.01$, $\epsilon = 0.23$; F (12, 60) = 4.46, $P = 0.02$, $\epsilon = 0.26$]. The interaction was marginally significant in DAP [F (12, 60) = 3.22, $P = 0.051$, $\epsilon = 0.26$]. In the further analysis using Tukey HSD compared to baseline, SAP and MAP significantly increased during task MTP at pre-confinement, whereas they decreased on Day 35 of confinement (see the right column of Fig. 1).

Mean values for BPV and HRV parameters for baseline, B6, B12 and MTP conditions during the entire experimental period are presented in **Table II**. The main effect of task was significant in LFnu of BPV [F (3,15) = 10.64, $P < 0.01$, $\epsilon = 0.51$], IBI [F (3,15) = 12.11, $P < 0.01$, $\epsilon = 0.72$], LFnu of HRV [F (3,15) = 30.28, $P < 0.001$, $\epsilon = 0.55$], HFnu of HRV [F (3,15) = 13.62, $P < 0.01$, $\epsilon = 0.45$], and LF/HF ratio of HRV [F (3,15) = 6.94, $P = 0.04$, $\epsilon = 0.38$]. As Table II shows, compared to other tasks, task B6 increased LFnu of BPV, and LFnu and LF/HF of HRV significantly, while it decreased HFnu of HRV and IBI significantly.

DISCUSSION

The Mars105 project is a ground-based simulation of a Mars mission to collect data on the psychophysiological effects of being sealed in an enclosed environment for a long period. As a part of this project, the present study examined the effect of physical and mental stresses associated with long-term confinement without the influence

TABLE I. HEMODYNAMIC DATA OF DIFFERENT TASKS DURING PRE-, DURING, AND POST-CONFINEMENT.

		During Confinement			
	Pre-Confinement	**Day 35**	**Day 70**	**Day 100**	**Post-Confinement**
Baseline (spontaneous breathing)					
SAP (mmHg)	121.07 ± 4.08	125.00 ± 4.44	113.27 ± 5.90	108.87 ± 6.06	123.80 ± 11.56
DAP (mmHg)	72.72 ± 4.16	74.43 ± 3.23	65.14 ± 4.42	62.87 ± 4.87	76.11 ± 5.36
MAP (mmHg)	87.28 ± 3.93	90.02 ± 3.64	79.76 ± 4.90	77.22 ± 5.02	91.09 ± 6.83
HR (bpm)	65.93 ± 3.04	59.82 ± 1.12	59.41 ± 2.94	67.25 ± 2.70	64.15 ± 2.36
Fixed breathing (0.2 Hz)					
SAP (mmHg)	123.55 ± 4.47	118.69 ± 1.81	113.25 ± 5.26	109.35 ± 4.74	126.22 ± 9.22
DAP (mmHg)	72.10 ± 4.32	71.04 ± 2.89	64.48 ± 3.95	61.72 ± 4.85	75.57 ± 5.14
MAP (mmHg)	86.54 ± 4.55	85.16 ± 2.84	78.91 ± 4.38	75.94 ± 4.69	90.91 ± 6.35
HR (bpm)	72.74 ± 3.26	70.95 ± 4.35	63.44 ± 3.26	70.57 ± 2.50	67.40 ± 1.92
Fixed breathing (0.1 Hz)					
SAP (mmHg)	125.04 ± 2.85	107.49 ± 4.98	114.99 ± 4.60	108.30 ± 5.77	129.00 ± 11.27
DAP (mmHg)	75.63 ± 4.09	66.00 ± 4.91	66.52 ± 2.41	62.29 ± 5.60	76.77 ± 6.30
MAP (mmHg)	89.63 ± 3.84	79.09 ± 4.90	81.03 ± 2.83	76.34 ± 5.62	92.12 ± 7.63
HR (bpm)	66.31 ± 2.55	63.08 ± 1.75	60.78 ± 2.90	67.52 ± 3.02	63.48 ± 2.62
Mental task performance					
SAP (mmHg)	145.47 ± 5.60	90.77 ± 9.53	118.99 ± 7.19	110.23 ± 4.18	129.05 ± 13.63
DAP (mmHg)	83.36 ± 6.31	59.71 ± 5.81	71.03 ± 4.24	66.20 ± 2.74	77.52 ± 7.29
MAP (mmHg)	101.16 ± 5.15	70.13 ± 6.66	86.29 ± 4.94	80.30 ± 2.97	93.67 ± 8.78
HR (bpm)	68.50 ± 2.77	60.56 ± 2.42	60.11 ± 2.99	64.47 ± 2.43	61.78 ± 1.60

Data are presented as mean value ± SEM. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; HR = heart rate.

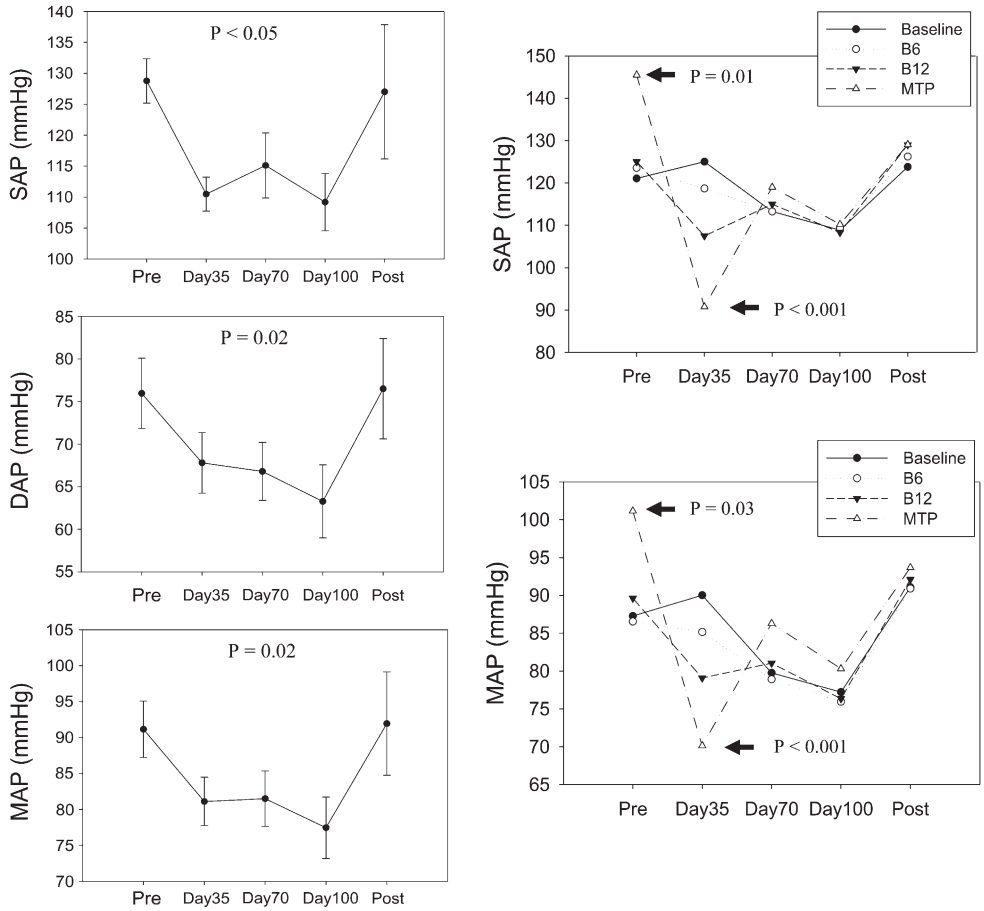

Fig. 1. The graphs in the left column display the effect of confinement on SAP, DAP, and MAP (vertical bars denote 0.95 confidence intervals). The graphs in the right column specifically display that the hemodynamic responses to mental stress were different on Day 35 of confinement than the other periods.

of microgravity on cardiovascular responses. Our primary findings are that blood pressure (SAP, DAP, and MAP) showed a U-shaped change with a decrease during confinement. Particularly, blood pressure decreased during the mental task performance in the first month of confinement. Moreover, we found that 105-d confinement did not influence the cardiovascular response to slow-paced breathing.

First, this study shows a U-shaped change across the confinement in blood pressure. Blood pressure significantly decreased during the confinement, whereas after the confinement it returned to a similar level as at pre-confinement. The increase in blood pressure during post-confinement was different from the "cardiovascular deconditioning" caused by microgravity, which usually remains till after the spaceflight (10,11). The reduction in blood pressure observed in the present study is likely caused by the decrease of psychological adaptations during the confinement via alterations in the balance of the autonomic nervous system (ANS). ANS is the neural interface relaying bottom-up and top-down information. The efferent premotor regions of ANS are not only modulated by the visceral sensations carried through vagal afferents, but also influenced by a set of upper brain regions, such as the amygdala, hippocampus, and prefrontal cortex (9,22). These regions are also associated with the regulation of emotional (e.g., depression, anxiety) and cognitive behaviors (e.g., decision making) and, therefore, linked to well-being and in the development of social behavior and coping strategy (14,26). A decrease in winterers' mood just after the middle of confinement, which was termed as "third-quarter phenomenon" was addressed not only in polar missions (6), but also in spaceflight simulations (21). In another study of the Mars105 project, similar U-shaped changes were observed in mood and brain cortical activity (25), which is in line with the previous findings of "third-quarter phenomenon" during the confinement (6,21). The decreases in cognitive-emotional responses may be translated into autonomic or endocrine outputs at the hypothalamus or brain stem, which then reduces the physiological responses to tasks.

Particularly, the cardiovascular response to the mental performance task presented a diverging pattern in the beginning of confinement from the other periods. Mental stress is routinely used in autonomic function testing and commonly provokes changes in cardiac function after increased sympathetic arousal (28). The increase in blood pressure in response to mental stress before confinement is in line with previous studies (5,8,13). The enhancement in arterial blood pressure during mental task performance is mostly elicited by peripheral

TABLE II. VALUE OF BPV AND HRV DATA DURING DIFFERENT TASKS.

	Baseline		B12		B6		MTP	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Blood pressure variability								
LFnu	39.29	5.97	27.73	5.53	64.57[a]	5.95	30.90	2.52
HFnu	0.56	0.19	1.27	0.30	0.18	0.22	0.77	0.13
LF/HF	8.12	1.83	2.89	0.87	31.82	10.13	6.42	1.01
Heart rate variability								
LFnu	42.96	5.80	26.18	2.04	72.28[b]	3.03	37.28	1.96
HFnu	17.59	3.23	30.42	4.61	9.73[c]	3.08	16.36	2.69
LF/HF	3.39	0.86	1.56	0.40	15.51[d]	4.87	3.60	0.92
IBI (ms)	962.46	23.44	939.68	29.65	875.30[e]	15.30	984.29	27.89

Data are presented as mean value and SEM. Baseline = spontaneous breathing; B12 = 12 cycle/min breathing; B6 = 6 cycle/min breathing; MTP = mental task performance; LF = low frequency power; HF = high frequency power; nu = normalized unit; IBI = the interbeat interval.
The further analysis using Tukey HSD shows significant differences between B6 and:
[a] B12 ($P < 0.001$);
[b] Baseline ($P < 0.001$) and B12 ($P < 0.001$);
[c] Baseline ($P < 0.01$), B12 ($P < 0.001$), and MTP ($P < 0.01$);
[d] B12 ($P < 0.01$);
[e] Baseline ($P < 0.01$), B12 ($P < 0.01$), and MTP ($P < 0.001$).

α-adrenergic vascular stimulation, mediated by central activation (5). However, the response of blood pressure to mental stress showed a reversed pattern in the beginning of confinement. Similarly, decrements in mental performance were observed during the first 3 wk of staying in space in a 438-d space mission (20). According to the decrease in perceived psychological and physiological states (25), this divergence might be due to changes of emotional state or a reduced perception of stress. The psychological states may affect the activities in the frontal cortex and limbic system at different cognitive-emotional levels or be translated into autonomic or endocrine outputs at the hypothalamus or brain stem, which, in turn, alters cardiovascular activities (18). On the other hand, the cardiovascular responses to mental stress were not changed by acute simulated microgravity (head-down tilt test) (13) nor by short-term exposure to microgravity (10-11 d space missions) (5). The significant changes observed in the present study might result from the longer duration of exposure to confinement (3 mo). Therefore, based on the findings of the pilot study, it would be necessary to correlate the cardiovascular responses to the levels of mood or affect in the next 520-d confinement study.

Secondly, the effect of slow-paced breathing on frequency domain of HRV in this study is compatible with previous studies (23). Respiratory frequency related cardiac interval oscillations, termed respiratory sinus arrhythmia (RSA), present fluctuations in consecutive R-R in a narrow band (0.15–0.30 Hz). With paced breathing at discrete frequencies (0.06–0.5 Hz), these fluctuations are transferred to the R-R interval (23). In this study, during slow-paced breathing, the frequency domain of HRV shifted from HF to LF, leading to the enhancement of the LF/HF ratio. In addition, the LF of BPV increased during slow breathing. The decrease in the vagal control and sympathetic tones could result in the enhancement of the R-R and blood pressure fluctuations at low frequencies (7), although the association between the LF of BPV and sympathetic activities was demonstrated by another study (1). Therefore, it is difficult to point out whether the specific spectral peaks could be related to the sympathetic or parasympathetic tones. In the Mars500 project, the duration of confinement was extended to 520 d in order to further verify the effect of long-term confinement on cardiovascular responses to different breathing tasks.

Before concluding, we acknowledge several limitations and confounding factors related to performing research on human functioning in highly specific situations, mimicking life in space. First, there is the very small number of subjects and the associated low power of several statistical tests. In addition, as a part of the Mars500 project, the participants are a highly selected and homogeneous population. The results of this study might not be compatible with other human science studies in a larger population of healthy subjects.

The second limitation of this study is that the subjective stress levels during mental task performance were not recorded. Since the induced cardiovascular response is not related to the subjective stress level (15,16), the changes we observed are likely to be due to the effect of confinement and task rather than the effect of stress level. The third limitation is the potential effect of a wide range of parallel experiments in the Mars100 project on the results of the present study. Numerous studies were conducted in this simulation of a Mars mission to examine the physiological and psychological aspect of spaceflight to Mars. Every day during confinement, each participant had to spend 8 h performing these studies. We acknowledge that there might be a potential influence of other studies on the cardiovascular responses in the present study.

This study is the first one to investigate the cardiovascular response to physical and mental stress during long-term space mission simulation. The hemodynamic changes and BPV and HRV in response to slow-paced breathing and mental task performance were examined in six participants before, during, and after confinement. We concluded that long-term confinement alters the regulation of blood pressure and this effect does not remain

after confinement. Particularly, the effect of confinement, which reduced the cardiovascular response to mental stress, predominated in the first month of confinement. Moreover, 105-d confinement does not affect BPV and HPV in response to slow paced breathing. In the next 520-d confinement study, the effect of confinement on cardiovascular adaptation should be correlated to the psychological state (e.g., the state of mood) in order to explore how their interactions lead to changes in ANS functioning and cardiovascular variability.

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No conflicts of interest are declared by the authors.

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Q1 : Is this correct? Is Finapres the manufacturer of the Portapres and is Amsterdam, The Netherlands, the correct location for them?