Respiratory Sinus Arrhythmia on the ESA-Short-Arm Human Centrifuge

A Comparison of Hypergravity Versus Microgravity Influences on Cardiorespiratory Interactions

BY PIERRE-FRANÇOIS MIGEOTTE, NATHALIE PATTYN, ROBBY VANSPAUWEN, XAVIER NEYT, MARC ACHEROY, PAUL VAN DE HEYNING, AND FLORIS L. WUYTS

In this article, we investigated the hypothesis that the effects of hypergravity on respiratory sinus arrhythmia (RSA) can mimic the effects observed after spaceflight cardiovascular deconditioning. Artificial gravity along the head-to-feet axis on a short-arm centrifuge induces gravity gradients. This physiological condition of significantly higher g at the feet than at the heart level is specific and likely induces blood sequestration in the lower limbs. After spaceflight, astronauts are in a condition of cardiovascular deconditioning, where blood pooling in the lower part of the body and autonomic adaptation are factors contributing to orthostatic intolerance and changes in heart-rate variability (HRV). ECG and respiration were recorded during imposed and controlled breathing (ICB) protocols, which were repeated at different levels of artificial gravity as well as during supine and standing control conditions, and the changes were analyzed.

RSA, usually the high-frequency (HF) (0.15 Hz $<$ HF $<$ 0.4 Hz [10]) component of HRV, is a cardiorespiratory interaction mediated by the vagus nerve. RSA has thus been considered a marker of the parasympathetic modulation of heart rate [1]. However, in the light of recent studies [2], [3], care has to be taken to infer changes in tonic level activity from changes in the phasic parasympathetic modulation, especially when the respiration is not controlled. Previous studies reported decrease in RSA or HF component of HRV after spaceflight [4]–[6]. Whether these changes can be interpreted as resulting from autonomic adaption following exposure to microgravity or only resulting from a decreased blood volemia is still a matter of debate. It is hypothesized that the hypergravity on the European Space Agency (ESA) short-arm human centrifuge (SAHC) can generate blood shift from the thoracic region to the lower part of the body (pooling in the splanchnic region [11], [12] or the legs) that mimic the postspaceflight autonomic response. This hypothesis will be subscribed in this study by the analysis of RSA during ICB experiments, similar to those performed during previous short-duration spaceflights [6], [7]. The slope of RSA amplitude with the duration of the breath cycle (T_{resp}) has been shown to characterize the gain of RSA [7], which reflects the capacity of the autonomic nervous system (ANS) to respond to challenges. Results from SAHC experiments are compared with the results from ICB experiments performed before, during, and after a short-duration (11 days) space mission [7].

Digital Object Identifier 10.1109/MEMB.2009.934618

Methods

The ESA SAHC is a short-arm centrifuge (outer radius = 2.82 m) that can generate up to 6 g at the feet of the subject and contains two bed nacelles and two chairs that are radially oriented. The bed nacelles can be rotated from $-20°$ (head down) to $+50°$ to generate different gravity gradients along the head-to-foot direction (Gz). The positions of the horizontally oriented beds were chosen so that, when lying supine, the heart was typically situated at 1.05 m from the center of rotation. Rotations were set at approximately 24, 29, and 32 r/min to obtain heart levels at 0.7, 1, and 1.2 Gz, respectively. This yielded values of approximately 0.47, 0.66, and 0.80 Gz at the head and 1.5, 2.2, and 2.6 Gz at the feet. Per Gz level, test time lasted approximately 20 min. Load conditions of 0.7 and 1 Gz were imposed without general stop of the centrifuge. Between 1 and 1.2 Gz however, a pause of 10 min was applied to unload the lower limbs. The fixed order of the g-load conditions was chosen to ensure optimal tolerance from the subjects.

During this study, the SAHC was located at the premises of the Antwerp University Research Centre for Equilibrium and Aerospace (AUREA) in the Antwerp University Hospital. Ethical approval was obtained by the Institutional Review Board, and informed consent was signed by the subjects. Six healthy male subjects were enrolled in this study (age: 22–45 years; weight: 60–84 kg; height: 170–184 cm). Subjects were tested in the afternoon at least 2 h after the last meal and were asked to refrain from caffeinated beverage in the hours prior to the experiment. Electrocardiogram (lead II ECG), blood pressure, and respiration were continuously recorded during the experiments. ECG and respiratory movements were digitally recorded at 1 kHz and 200 Hz, respectively, with the LifeShirt System, while finger blood pressure was acquired at 1 kHz through the analog output from a Portapres device, with a finger cuff placed on the middle finger of the left hand fixed at the heart level. A series of three ICB protocols were repeated five times during the three different g-load conditions. Imposed breathing was set at 6, 9, and 15 breaths/min for at least nine breaths. The imposed breathing protocol were

0739-5175/09/$26.00©2009IEEE

The effects of hypergravity on respiratory sinus arrhythmia can mimic the effects observed after spaceflight cardiovascular deconditioning.

set so that inspiration and expiration periods were equal (i.e., both accounting for 50% of the total breath cycle). In between a series of three imposed breathing protocols, a 1-min break was inserted, during which subjects were allowed to perform exercise with the lower limbs. Controlled breathing was achieved by the display of a moving vertical bar on a flat screen situated in front of the subject in a dark environment canopy, which was placed over the upper part of the body to ensure that the subjects had no visual cue of any moving reference. Prior to the rotation of the SAHC, control measurements were obtained in standing and supine position.

Similar ICB experiments were performed before, during, and after the 11 days' Odissea mission to the international space station (ISS) on three male subjects. Recordings were performed on days 1, 2, 4, 9, 15, 19, and 25 after landing and inflight on days 5 and 8 after the launch. However, only the early postflight (days 1 and 2) results are discussed in the present article, while the other results are reported elsewhere [7]. Similar recordings were performed with imposed breathings set at 6, 7.5, 9, 12, and 15 breaths/min for 180 s in both standing and supine positions.

The parasympathetic response of the ANS to the orthostatic challenge induced by the different g loads was assessed through the analysis of short-term HRV by means of a time-domain algorithm, the polar representation of the RSA [8]. Briefly, this method is based on the modelization of RR-interval (RRI) oscillation in the breathing cycle and allows the determination of the amplitude and phase of RSA on short recordings (three breaths). It consists of a conversion of the time axis of heart beats occurring at t_k^{rr} into their phase in the breath cycle. We define, $\theta_{k,i}$, the phase of the heart beat k in the breath cycle i, with onsets of inspiration at t_i^{in} and expiration at t_i^{ex}, as $\theta_{k,i}^{\mathrm{in}}$ or $\theta_{k,i}^{\mathrm{ex}}$, depending or whether the heart beat occurs in the inspiration ($t_i^{\mathrm{in}} < t_k^{\mathrm{rr}} < t_i^{\mathrm{ex}}$) or expiration ($t_i^{\mathrm{ex}} < t_k^{\mathrm{rr}}$) period:

$$\begin{aligned} \theta_{k,i}^{\mathrm{in}} &= 0.5(t_k^{\mathrm{rr}} - t_i^{\mathrm{in}})/\Delta_i^{\mathrm{in}}, \\ \theta_{k,i}^{\mathrm{ex}} &= 0.5 + 0.5(t_k^{\mathrm{rr}} - t_i^{\mathrm{ex}})/\Delta_i^{\mathrm{ex}}, \end{aligned} \tag{1}$$

where $\Delta_i^{\mathrm{in}} = t_i^{\mathrm{ex}} - t_i^{\mathrm{in}}$ and $\Delta_i^{\mathrm{ex}} = t_{i+1}^{\mathrm{in}} - t_i^{\mathrm{ex}}$, respectively, are the duration of the inspiration and expiration periods for the respiration cycle i. The total breathing period ($\mathrm{T_{resp}}$) is $\mathrm{T_{resp}} = \Delta_i^{\mathrm{in}} + \Delta_i^{\mathrm{ex}}\tilde{v}$ and the inspiration starts at $\theta = 0\%$. The 0.5 value in (1) are set according to the imposed breathing protocol, where inspiration period was set to 50% of the total breathing period and thus was equal to the expiration period. Therefore, the beginning of expiration is set to 50%, and $\theta = 100\%$ corresponds to the end of expiration (i.e., the beginning of a new respiratory cycle). With such a change of coordinate, RRI from different respirations can be superimposed (Figure 1). Consequently, a large RSA then appears as a consistent oscillation in the breath cycle and can be modeled by a cosine curve:

$$\mathrm{RRI}_{k,i} = R + \rho_c \cos[(\theta_{k,i} - \theta_c)2\pi/100], \tag{2}$$

where R, ρ_c, and θ_c are the estimated parameters: R is the mean RRI, and ρ_c and θ_c, respectively, are the amplitude and phase of the cosine, respectively. θ_c is denoted as the phase shift and ρ_c as amplitude (Figure 1).

The use of a cosine curve in the model corresponds to the analysis of the respiratory peak in the traditional Fourier spectral analysis. As the end of the cycle is physiologically equivalent to the beginning of a new cycle, we take advantage of a polar coordinate representation, where the radial coordinate ρ is the RRI and the angular coordinate θ is the phase in breath cycle. In this representation, the RSA is modeled by a circle with radius R and center c with coordinates (ρ_c, θ_c), in which a large RSA appears as a large offset of the center of the fitted circle, whereas absence or very small RSA provides a centered circle on the origin (for details, see [8]). This alleviates the issue of the fitting of a cosine with small amplitude and its consequent unreliable estimation of the phase.

A regression analysis of RSA amplitude and phase as a function of the imposed breathing period ($\mathrm{T_{resp}}$) was applied to assess the gain of RSA amplitude at the different g loads for the chosen heart–feet g gradient. Statistical significance of the differences between regression parameters were analyzed with the classical method of sum of squares for the comparison of two regressions [9]. Individual values of regression parameters, slopes (gain) and intercepts, are reported with their 95% confidence interval (CI) [2 SD].

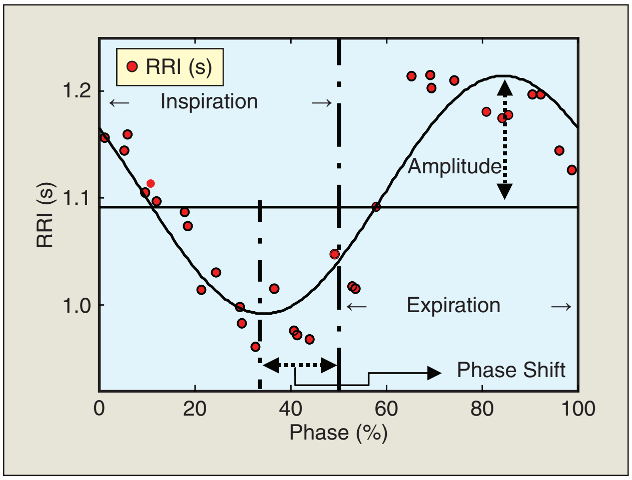


Fig. 1. Model of respiratory sinus arrhythmia. The red circles represent the RRI versus phase in the breath cycle and the solid curve is the cosine-fitted curve, as discussed in (2).

RSA mediated by the vagus nerve has been considered a marker of the parasympathetic modulation of heart rate.

Results

Baseline measurements from the SAHC experiments are presented in Figure 2. The effects of different gravity conditions are presented in Figure 3 for RRI and Figure 4 for RSA. As expected, RRI decreases with the increase in Gz. In addition, the slopes (RRI increasing with T_{resp}) are significantly different from zero and positive, showing (Figure 3) that RRIs were significantly larger ($P < 0.05$) for slow-breathing ($T_{resp} = 10$ s) than for fast-breathing ($T_{resp} = 4$ s) protocols.

The mean values (±SD) of HR and blood pressure at different g loads and for the first (Rep 1) and fifth (Rep 5) repetitions are presented in Table 1. This shows that, while HR significantly increased with g load ($P < 0.05$), blood pressure values were stable over different protocols.

Figure 4 presents the regression analysis of RSA amplitude with T_{resp} for the different g-load conditions. The slope for the high Gz condition (5.34 ± 1.4 ms/s) is the lowest and presents only a significant difference ($P < 0.05$) compared to supine (12.2 ± 1.5 ms/s). The influence of the repetition of protocols during the higher Gz condition and, thus, the analysis of the influence of the duration of exposure to one particular

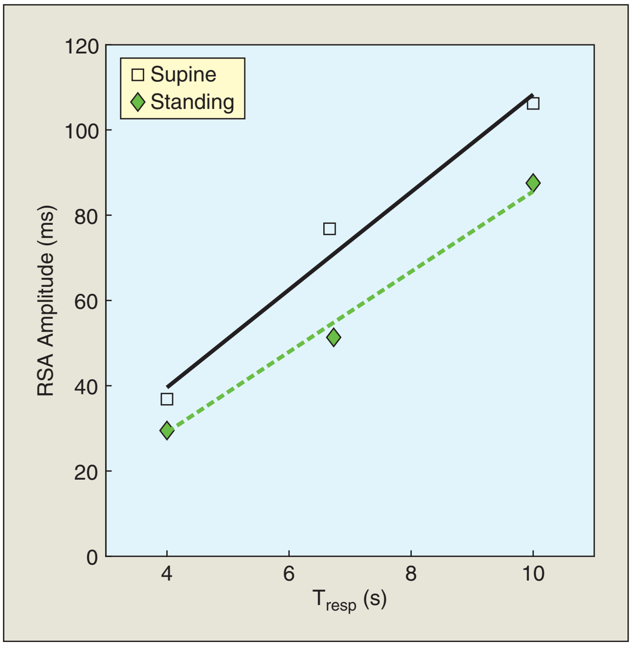


Fig. 2. Regression analysis of RSA amplitude versus imposed breathing period (T_{resp}) for SAHC baseline supine and standing data. Supine data at rest (open square) are larger than the standing (green diamond) values at all T_{resp}.

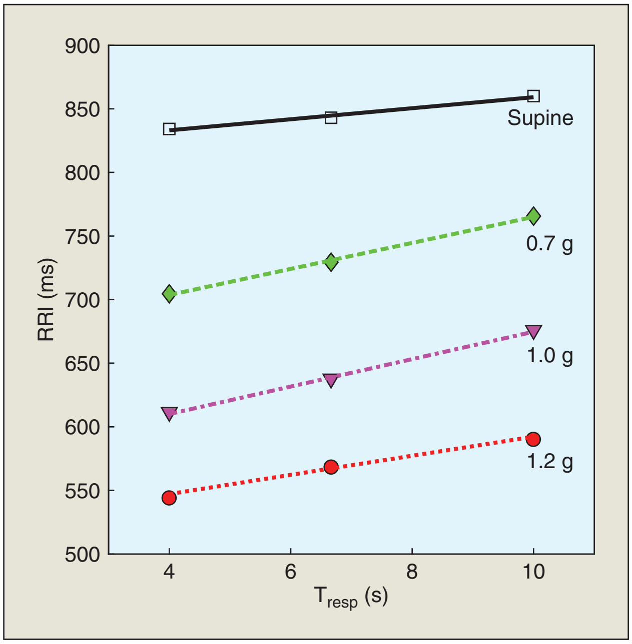


Fig. 3. RRI (ms) versus imposed breathing period (T_{resp}) for the different g-load conditions on the SAHC. Measurements at rest supine (open square) are larger at all T_{resp} than do RRI in all artificial g-load conditions: 0.7 g (green diamond), 1 g (purple inverted triangle), 1.2 g (red circle). For all g-load conditions, RRI at the longer T_{resp} is significantly larger than that at the shortest T_{resp} ($P < 0.05$).

Table 1. Average values (±SD) of HR, diastolic, and systolic blood pressure for the different g-load conditions on the SAHC during the first (Rep 1) and fifth (Rep 5) conditions.

	Rep 1			Rep 5		
g load (g)	0.7	1	1.2	0.7	1	1.2
HR (breaths/min)	78.2 ± 2.1	87.9 ± 2.1	96.4 ± 2.1	86.5 ± 3.5	104.7 ± 4.1	118.1 ± 3.5
Diastolic (mmHg)	82.5 ± 3.7	93.9 ± 3.7	89.5 ± 3.7	89.6 ± 2.6	94.3 ± 3.1	98.7 ± 2.6
Systolic (mmHg)	132.8 ± 3.0	138.7 ± 3.0	134.9 ± 3.0	136.0 ± 3.7	133.7 ± 4.4	139.1 ± 3.7

orthostatic stress is presented in Figure 5. Individual values of RSA tend to decrease with the duration of exposure to hyper g, and the slope also shows a tendency to decrease. The lowest slope (4.8 ± 1.4 ms/s) is reached for the last repetition during the higher g-load condition ($P < 0.05$ compared to supine).

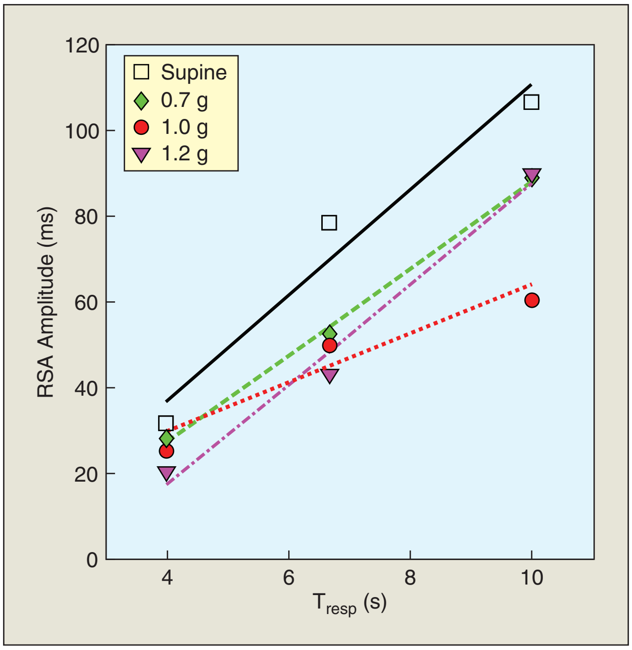


Fig. 4. Regression analysis for the different g-load conditions on the SAHC. Symbols used are as in Figure 3.

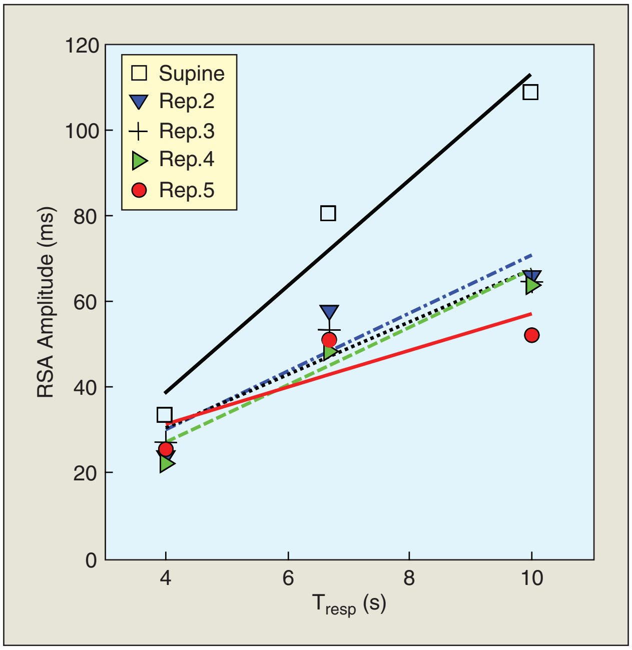


Fig. 5. Regression analysis of RSA versus T_{resp} for the last four repetitions of the high-g load (1.2 g) condition: (blue inverted triangle) Rep 2, (plus symbol) Rep 3, (green slanted triangle) Rep 4, (red circle), and Rep 5. All repetitions at the higher g load are lower than supine baseline data (open square). The lowest slope is seen for the last repetition of the higher g-load condition.

The results from the regression analysis of RSA performed on the recordings of the Odissea spaceflight mission are presented in Figures 6 and 7 for supine and standing data, respectively. Early postflight RSA amplitude is significantly decreased ($P < 0.05$) at all T_{resp}, and the slope of the

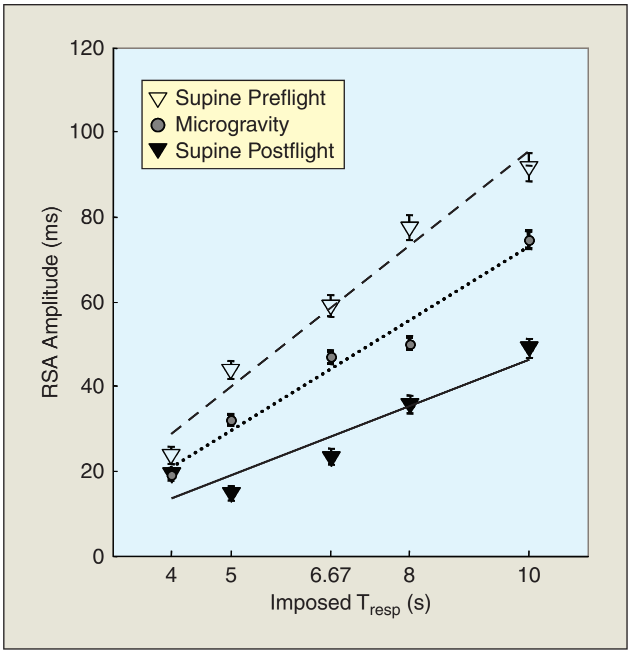


Fig. 6. Regression analysis of RSA amplitude versus imposed breathing period (T_{resp}) for supine data from the short-duration spaceflight. Supine preflight values (open inverted triangle) are larger than inflight (filled circle) and postflight data (filled inverted triangle).

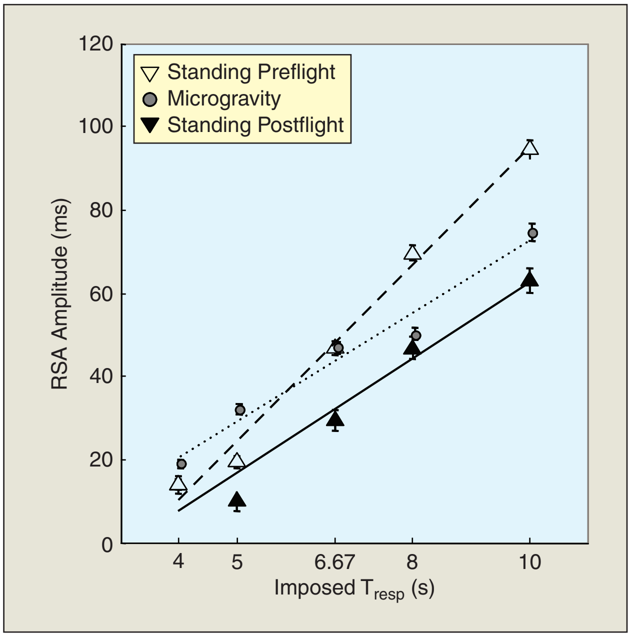


Fig. 7. Regression analysis of RSA amplitude versus imposed breathing period (T_{resp}) for standing data from the short-duration spaceflight. Preflight standing (open triangle) and inflight (filled circle) values of RSA are larger than postflight data (filled triangle) at all imposed T_{resp}.

Artificial gravity along the head-to-feet axis on a short-arm centrifuge induces gravity gradients.

regression of RSA amplitude with T_{resp} is decreased ($P < 0.05$) compared with preflight. Preflight for the supine data (Figure 6): the slope of the regression (millisecond of RRI per second of T_{resp}) was 10.8 $\pm$ 1.2 ms/s and a significant decrease ($P < 0.05$) of the slope was observed early postflight (5.5 $\pm$ 1.4 ms/s), while for inflight (8.8 $\pm$ 1.3 ms/s), this decrease was less pronounced ($0.05 < P < 0.1$). Although significant ($P < 0.05$), this change was less important for standing data (see Figure 7): 14.0 $\pm$ 1.2 ms/s preflight versus 9.3 $\pm$ 1.8 ms/s postflight.

Discussion

Confirming our hypothesis that artificial gravity can induce changes in the gain of RSA similar to those observed after spaceflight, RSA amplitude at all T_{resp} and gain of RSA were both decreased in the higher g-load conditions, and the lowest values were seen for the last repetitions at higher Gz.

Supine RSA values were larger than the standing ones, and RSA increased with T_{resp} in both the experimental setups, i.e., results from artificial gravity and spaceflight. This is in agreement with the previous literature on RSA. Since the gain of RSA represents the capability of the ANS to respond to various stimuli, the higher the slope the larger the range. As such, the gain of RSA is a measure that differs from the static response at a particular T_{resp}. Notice also the influence of the g gradient. Even at a moderate 0.7 g at the heart level, RRI (Figure 3) and RSA (Figure 4) were largely decreased compared with the baseline supine values.

In addition, the increase of RRI with T_{resp} (Figure 3) suggests that slow breathing potentiates the parasympathetic effect of RSA on HR, possibly through resonance with the low-frequency component (0.1 Hz) of HRV. Exposure to hyper g resulted in decreased values of RRI and RSA together with a decreased gain of RSA. The lowest gain of RSA was seen during the last repetition at the highest g load, thus showing a cumulative time effect with a short time constant.

The spaceflight experiment showed similar results: amplitude of RSA decreased at each T_{resp}, and the gain of RSA decreased. This similarity in autonomic responses in both experimental setup suggests a common interpretation: the exposure to the postflight orthostatic stress together with the well-documented postflight hypovolemia [13] and the likely pooling of blood in the lower part of the body achieved on the SAHC induced a decreased gain of RSA and decreased RSA amplitude. Taken together, this suggests a parasympathetic withdrawal and an ANS working with a reduced capacity to respond to challenge, possibly through the mechanical sequestration of a portion of circulating blood. Therefore, this shows that artificial gravity and gravity gradients can cause similar changes in HRV as the one seen in astronauts after a short-duration spaceflight. Blood pooling in the lower part of the body, mimicked by centrifugation of healthy subjects, could thus be one factor explaining the HRV response observed after spaceflight. Our experimental design does not allow to differentiate between legs and splanchnic blood pooling. However, despite the fact that recent publications [11], [12], demonstrated that, in the case of head-up tilt, blood pooling in the splanchnic region is larger than in the lower limbs, the hyper-g conditions with a gravity gradient like it is in the SAHC study is not comparable to a simple head-up-tilt.

Postflight, we can speculate that, due to the possibly decreased vascular stiffness, and a more than normal blood pooling in the lower part of the body, a situation is generated where the heart is exposed to the terrestrial 1 G, but in the lower limbs, a pooling is present similar to what is seen during a higher g-load at the legs. The net result would be the same: an increased distensibility experienced by the vascular bed in the lower legs while the heart is at 1 g.

Conclusions

Our results on the SAHC show that the g-load induced blood pooling lead to increased HR and decreased RSA amplitude at all T_{resp}. The response of the ANS to the orthostatic challenge was evidenced by a parasympathetic withdrawal or sympathetic activation (increased HR and decreased RSA amplitude) and decreased gain of RSA (decreased slope of RSA amplitude with T_{resp}). The Gz gradient was an important factor of orthostatic challenge: even at moderate 0.7 Gz at the heart, HR was significantly increased compared to supine, and at 1.2 Gz, this difference was even much more accentuated.

Lastly, this study provides some evidences that mechanical blood pooling in the lower part of the body (legs or splanchnic region) achieved by centrifugation has a major influence on HRV and, more particularly, on RSA, and this can partially reproduce the observed changes in the gain of RSA observed after a short-duration spaceflight.

Acknowledgments

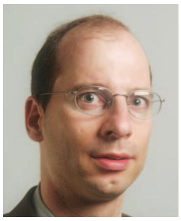
This research was supported by the Belgian Federal Science Policy via the PRODEX (Programme de Développement d'EXpériences scientifiques) program. We thank the astronauts and the volunteers of the SAHC study. We acknowledge ESA for the support and the opportunity of performing experiment on the SAHC during its commissioning phase in the AUREA.

Pierre-François Migeotte received his M.Sc. degree in physics and Ph.D. degree in sciences from the Université Libre de Bruxelles, Belgium, in 1996 and 2003, respectively. His doctoral work focused on HRV and adaptation of human

physiology to microgravity. He is currently a researcher at Royal Military Academy (RMA) of Belgium. His research interests include the adaptation of cardiovascular and autonomic nervous system to microgravity, artificial gravity, and other extreme environments.

Nathalie Pattyn received her master's degree in clinical psychology from the Vrije Universiteit Brussel and Ph.D. degrees from both the Vrije Universiteit Brussel and the RMA. She is currently an assistant professor at both the Vrije Universiteit Brussel and the RMA. Her research interests include focuses on the function of the autonomic nervous system in an integrative physiology framework and on field research on real-life performance monitoring.

Robby Vanspauwen received his Ph.D. degree in medical sciences in September 2009. The topic of his doctoral studies was in the area of the human vestibular system and more specific the design and development of a vestibular test and its integration in clinical and experimental environments.



Xavier Neyt received his master's degree in engineering from the Free University of Brussels (ULB) in 1994, a postgraduate degree in Signal Processing from the University of Liege (ULg) in 2004, and a Ph.D. degree in applied science from the RMA and ULg in 2008. In 1995, he received the Frerichs Award from the ULB and the special IBM grant from the Belgian National Fund for Scientific Research (NFWO). Since 2008, he has been leading the Scatterometer Engineering Support Laboratory for the European Space Agency (ESA) at the RMA. He is also applying signal processing methods to biomedical signals. He is currently an associate professor at the Communication, Information, Systems and Sensors Department of the RMA, Belgium.

Marc Acheroy received his engineering degree in mechanics from the RMA in 1971 and the engineering degree in control automation and Ph.D. degree in applied sciences from the Université Libre de Bruxelles, Brussels, in 1981 and 1983, respectively. He is currently a professor in signal processing and automatic control with the Polytechnic Faculty, the head of the Communication, Information, Signal and Sensor Department, and the head of the Signal and Image Centre, RMA. He has a solid expertise in image restoration and compression, in pattern recognition, data fusion, and mine action technologies. He is leading several projects, among which are Defence, European Commission, ESA, and Belgian Scientific Policy.

Paul Van de Heyning is the chair of the University Department of Otorhinolaryngology and Head and Neck Surgery, Antwerp University Hospital, and Dean of the Faculty of Medicine, University of Antwerp. He is also on the Board of The Politzer Society.

Floris L. Wuyts received his Ph.D. degree in physics in 1990 at the University of Antwerp. In 1994, he joined the Ear Nose Throat Department at the University Hospital of Antwerp where he became head of the Vestibular Function Laboratory. He was responsible for the development of new techniques for vestibular function assessment in patients with dizziness problems. This led to grants by National Aeronautics and Space Administration and ESA to investigate space motion sickness. His laboratory is renamed as AUREA (Antwerp University Research Center for Equilibrium and Aerospace) where researchers from different disciplines are working around equilibrium and space. He became a professor at the faculty of Sciences of the University of Antwerp in 2002 and teaches several courses such as medical physics and biostatistics, not only at the UA but also at the University College of London in the United Kingdom.

Address for Correspondence: Pierre-François Migeotte, Signal and Image Centre, Electrical Engineering Department, Royal Military Academy, 30 Avenue de la Renaissance, B-1000 Brussels, Belgium. E-mail: pierre-francois.migeotte@elec.rma.ac.be.

References

[1] P. G. Katona and F. Jih, "Respiratory sinus arrhythmia: Noninvasive measure of parasympathetic cardiac control," *J. Appl. Physiol.*, vol. 39, no. 5, pp. 801–805, 1975.
[2] D. L. Eckberg, "Sympathovagal balance: A critical appraisal," *Circulation*, vol. 96, no. 9, pp. 3224–3232, 1997.
[3] E. Pyetan and S. Akselrod, "Do the high-frequency indexes of HRV provide a faithful assessment of cardiac vagal tone? A critical theoretical evaluation," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 6, pp. 777–783, 2003.
[4] J. M. Fritsch-Yelle, J. B. Charles, M. M. Jones, L. A. Beightol, and D. L. Eckberg, "Spaceflight alters autonomic regulation of arterial pressure in humans," *J. Appl. Physiol.*, vol. 77, no. 4, pp. 1776–1783, 1994.
[5] J. M. Fritsch-Yelle, J. B. Charles, M. M. Jones, and M. L. Wood, "Microgravity decreases heart rate and arterial pressure in humans," *J. Appl. Physiol.*, vol. 80, no. 3, pp. 910–914, 1996.
[6] P. F. Migeotte, G. K. Prisk, and M. Paiva, "Microgravity alters respiratory sinus arrhythmia and short-term heart rate variability in humans," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 284, pp. 1995–2006, 2003.
[7] P.-F. Migeotte, R. C. Sá, G. K. Prisk, and M. Paiva, "Respiratory sinus arrhythmia: A marker of decreased parasympathetic modulation after spaceflight," *J. Gravit. Physiol.*, vol. 12, no. 1, pp. 73–74, 2005.
[8] P. F. Migeotte and Y. Verbandt, "A novel algorithm for the heart rate variability analysis of short-term recordings: Polar representation of respiratory sinus arrhythmia," *Comput. Biomed. Res.*, vol. 32, no. 1, pp. 56–66, 1999.
[9] P. Armitage and G. Berry, *Statistical Methods in Medical Research*, 3rd ed. Oxford, U.K.: Blackwell, 1994.
[10] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use," *Circulation*, vol. 93, no. 5, pp. 1043–1065, 1996.
[11] I. Taneja, C. Moran, M. S. Medow, J. L. Glover, L. D. Montgomery, and J. M. Stewart, "Differential effects of lower body negative pressure and upright tilt on splanchnic blood volume," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 292, no. 3, pp. H1420–H1426, Mar. 2007.
[12] J. Gisolf, R. V. Immink, J. J. van Lieshout, W. J. Stok, and J. M. Karemaker, "Orthostatic blood pressure control before and after spaceflight, determined by time-domain baroreflex method," *J. Appl. Physiol.*, vol. 98, no. 5, pp. 1682–1690, May 2005.
[13] A. Diedrich, S. Y. Paranjape, and D. Robertson, "Plasma and blood volume in space," *Amer. J. Med. Sci.*, vol. 334, no. 1, pp. 80–85, July 2007.