

Hemodynamic and Neuroendocrinological Responses to Artificial Gravity

Stefan Schneider^{1,2,3}, Vanja Sebastian Zander^{1,2}, Tobias Vogt^{1,2}, Vera Abeln^{1,2}, Heiko K. Strüder¹, Amrei Jacubowski¹, Heather Carnahan⁴, and Petra Wollseiffen¹

¹*Institute of Movement and Neurosciences, German Sport University Cologne, Germany;* ²*Centre for Health and Integrative Physiology in Space, German Sport University Cologne, Germany;* ³*Faculty of Science, Health, Education and Engineering, University of Sunshine Coast, Maroochydore, Queensland, Australia;* ⁴*Offshore Safety and Survival Centre, Marine Institute, Memorial University of Newfoundland, Canada*

ABSTRACT

The aim of this study was to determine the hemodynamic and neuroendocrinological responses to different levels and protocols of artificial gravity, especially in comparison to what is expected during a moderate bout of exercise. Ten male participants were exposed to artificial gravity using two different protocols: the first was a centrifugation protocol that consisted of a constant phase of 2 Gz for 30 minutes, and the second consisted of an intermittent phase of 2 Gz for two minutes, separated by resting periods for three minutes in successive order. Near infrared spectroscopy (oxyhemoglobin and deoxyhemoglobin) at the prefrontal cortex, *Musculus biceps brachii*, and *Musculus gastrocnemius*, as well as heart rate and blood pressure were recorded before, during, and after exposure to artificial gravity. In order to determine effects of artificial gravity on neuroendocrinological parameters (brain-derived

neurotrophic factor, vascular endothelial growth factor, and insulin-like growth factor 1), blood samples were taken before and after centrifugation. During the application of artificial gravity the concentration of oxyhemoglobin decreased significantly and the concentration of deoxyhemoglobin increased significantly in the prefrontal cortex and the *Musculus biceps brachii* muscle. Participants exposed to the continuous artificial gravity profile experienced peripheral pooling of blood. No changes were observed for brain-derived neurotrophic factor, vascular endothelial growth factor, or insulin-like growth factor 1. Intermittent application of artificial gravity may represent a better-tolerated presentation for participants as hemodynamic values normalize during resting periods. During both protocols, heart rate and arterial blood pressure remained far below what is experienced during moderate physical activity.

Key words: Exercise Countermeasure; NIRS (Near Infrared Spectroscopy); Hemodynamics; Neuroendocrinology; Artificial Gravity; Spaceflight

Correspondence to: Prof. Dr. Stefan Schneider
Institute of Movement and Neurosciences
German Sport University
Am Sportpark Müngersdorf 6
D-50933 Cologne, Germany
Telephone: +49 (0) 221 4982 7520
Fax: +49 (0) 221 4973 454
E-Mail: schneider@dshs-koeln.de

INTRODUCTION

Astronauts experience arterial blood pressure (ABP) variations, decrements in bone density, cardiovascular degradation, and neurocognitive deconditioning during long-term space missions (Schneider, 2016). In order to prevent these physiological changes, efficient countermeasures applicable during human spaceflight are needed (Clement et al., 2015; Richter et al., 2017; Tanaka et al., 2017; Linnarsson et al., 2015; Waki et al., 2005). Various countermeasures have been investigated

during space missions in recent years. Lower body negative pressure devices, exercises with bungee cords, modified bicycles, self-propelled centrifuge devices, and fixed treadmills have been assessed and used to counteract negative physiological responses (Clement and Bukley, 2007). However, all countermeasures mentioned require a significant amount of crew time and still appear to be inefficient in counteracting the degradation of physiological structures. The application of artificial gravity (AG) generated by, for example, a short arm human centrifuge (SAHC) is under intense scientific investigation (Chouker et al., 2013; Clement and Pavy-Le Traon, 2004; Dern et al., 2014; Evans et al., 2015; Goswami et al., 2015; Linnarsson et al., 2015; Zhang et al., 2017). Centrifugation in a sitting or supine position generates a centrifugal force, which simulates the gravity-induced physiological effects, similar to standing. In addition to the implementation of SAHC in microgravity environments, these devices could be installed on planetary destinations, such as Mars or the Moon, where gravity is only a fraction of Earth's gravity. Additionally, the application of AG generated by a SAHC is also thought to be beneficial in the fields of competitive sports (Barr et al., 2015), rehabilitation, and therapy for immobilized persons (Pavy-Le Traon et al., 2007). Besides possible positive effects on the musculoskeletal system, there are also possible beneficial effects of AG on the cardiovascular system (Migeotte et al., 2009), which are considered to be as effective as exercise to counteract physiological deconditioning during spaceflight (Clement and Bukley, 2007).

The primary aim of this study was to determine the effects of various AG protocols on the cardiovascular system in order to determine (1) if AG at a tolerable level stimulates an increase in ABP and heart rate (HR), similar to what would be expected during a moderate bout of exercise, and (2) if different protocols, intermittent AG vs. continuous AG, might have a different impact on the above mentioned parameters.

The activation of the cardiovascular system has a modulating effect on the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1) (Knaepen et al., 2010; Rojas Vega et al., 2010; Schiffer et al., 2009), which all play key roles in the signaling pathways of neurogenesis (BDNF),

synaptogenesis (BDNF, IGF-1), and angiogenesis (IGF-1, VEGF) (Lista and Sorrentino, 2010). The second aim of this study was to determine the effect of AG on the release of these proteins. Based on the assumption of cardiovascular system activation, we hypothesized that BDNF, VEGF, and IGF-1 would increase after exposure to AG.

The third aim of this study was to further investigate blood volume redistribution following different levels of AG (Schneider et al., 2013). It was hypothesized that AG generated by a SAHC would decrease cerebral oxygenation, increase cerebral deoxygenation, and increase peripheral intravascular pooling, which can be assessed using near infrared spectroscopy (NIRS). Although alterations in hemodynamics have been assessed in previous studies, the relationship between the gradient in the centrifugal force generated by a SAHC, and oxygenation of various tissues, such as the brain, during continuous and intermittent application of AG has been under-investigated.

MATERIALS AND METHODS

Participants and Procedures

Ten healthy males (29.57 ± 6.61 years, 183.21 ± 5.11 cm, 82.14 ± 7.24 kg) participated in this study. Participants had a varied experience with AG and hypergravity. All participants underwent a preliminary medical screening performed by medical personnel at the Institute of Aerospace Medicine/German Aerospace Centre (DLR), Cologne, Germany, and all gave their written consent to participate in the study. None of the participants reported taking any medication during the study. Before the centrifugation at the SAHC, the participants were informed about the experimental protocol and the risks of centrifugation (nausea, syncope, tachycardia, dizziness, etc.). All experimental procedures were performed according to national legislation and the Declaration of Helsinki; methods were performed in accordance with relevant regulations and guidelines and were approved by the Medical Council – North Rhine (Ärztammer Nordrhein, Düsseldorf, Germany).

Experimental protocol procedure

The study was conducted at the Institute of Aerospace Medicine at the German Aerospace Centre in Cologne, Germany, which granted access to the SAHC, which is owned and operated by the European Space Agency (ESA).

On experimental days, participants arrived two hours before centrifugation. Two different AG protocols were performed with a time lag of at least 48 hours between each. Participants were exposed to AG in a supine position and exposure to the two protocols was randomized. To avoid influencing hemodynamic parameters, participants were instructed not to flex their leg muscles during AG. The Gz-load was measured at foot level. The “continuous” AG protocol is illustrated in Figure 1A; it commenced with a phase of 1 Gz, 2 Gz, and 3 Gz for 120 s each (incremental phase 1), followed by a continuous phase of 2 Gz for 30 min, and ended with a phase of 1 Gz, 2 Gz, and 3 Gz for 120 s each (incremental phase 2; Figure 1A). For detailed analysis, the phase of continuous Gz-load was divided into six time segments. In contrast, the intermittent protocol is illustrated in Figure 1B, and included a phase of intermittent Gz-load of 2 Gz and approximately 0.0279 Gz (baseline rotation of 5 rounds per minute (RPM)) for 180 s. The intermittent sequence was performed five times, and started and ended with a phase of 1 Gz, 2 Gz, and 3 Gz for 120 s each (Figure 1B). If participants showed abnormal vital signs and/or syncope, a physician would determine whether to terminate the protocol. This was based upon cardiovascular parameters, such as cardiac arrhythmias, including increased HR > 80% of maximal HR (220-age) for more than 10 s, decreased HR < 50% of initial HR, or continuous decrease of HR or ABP for more than 15 s below initial values. Additionally, audio and video surveillance, as well as a “panic button,” were available for the participant’s safety during the experiment. Baseline measurement was performed during baseline rotation at 5 RPM before incremental phase 1 with the participant in a supine position, eyes closed and no one except the participant in the centrifuge room.

Hemodynamic Parameters

Electrocardiogram electrodes and a blood pressure (BP) cuff dedicated to the portable medical surveillance system (Intelivue XDS, Philips, Amsterdam, Netherlands), as well as a continuous BP device (Finometer, Portapress/TVO, Amsterdam, Netherlands), were used to monitor and record cardiovascular parameters and the vital signs of the participant. BP was continuously assessed at the participant’s index finger and calculations were performed to obtain a value valid at heart level. Changes in oxyhemoglobin (O₂Hb) and

deoxyhemoglobin (HHb) in the underlying tissue were recorded using a four-channel NIRS system (Oxymon MKIII, Artinis, Amsterdam, Netherlands) at the prefrontal cortex (PFC), the *Musculus biceps brachii*, and the *Musculus gastrocnemius* at a sampling frequency of 50 Hz. The distance between the optodes and the receiver was 3.5 cm, and this allowed a depth of penetration of approximately 2.5 cm. The wavelengths used were 858 nm and 764 nm. The NIRS optodes were fixed at the measurement points in order to avoid artifacts during the application of AG. Onset of the Gz load was assessed by an accelerometer and a trigger signal in the NIRS recording allowed for temporal alignment of the signals. O₂Hb and HHb averages for left PFC, *Musculus biceps brachii*, and *Musculus gastrocnemius*, as well as ABP and HR for each Gz level were calculated and exported for later statistical analysis.

Blood Collection

BDNF, VEGF, and IGF-1 were measured from blood samples taken through a permanent venous catheter, which was inserted into each participant’s left arm by a physician two hours prior to acceleration and was kept open by a 0.9% saline dilution. Immediately before the centrifugation started, and after the end of the centrifugation, 10 ml of EDTA blood was drawn in pre-chilled vacutainers®. Blood samples were centrifuged at 5000 RPM for 10 min after collection in a cooled centrifuge. The plasma was divided into fractions, first stored at -20°C for 8 h, and later frozen at -80°C until final analysis.

In order to quantify the serum prolactin and cortisol concentrations, an in vitro test using quantitative sandwich enzyme immunoassays (Elisa, R&D Systems, USA) was conducted. Monoclonal antibodies specific for human BDNF, IGF-1, and VEGF were pre-coated onto a microplate. The standards and samples were pipetted into the wells and BDNF, IGF-1, or VEGF present in the sample were bound by the immobilized antibodies. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human BDNF, IGF-1, or VEGF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and the color developed in proportion to the amount of proteins bound in the initial step. When the color development stopped, the intensity of the color was measured.

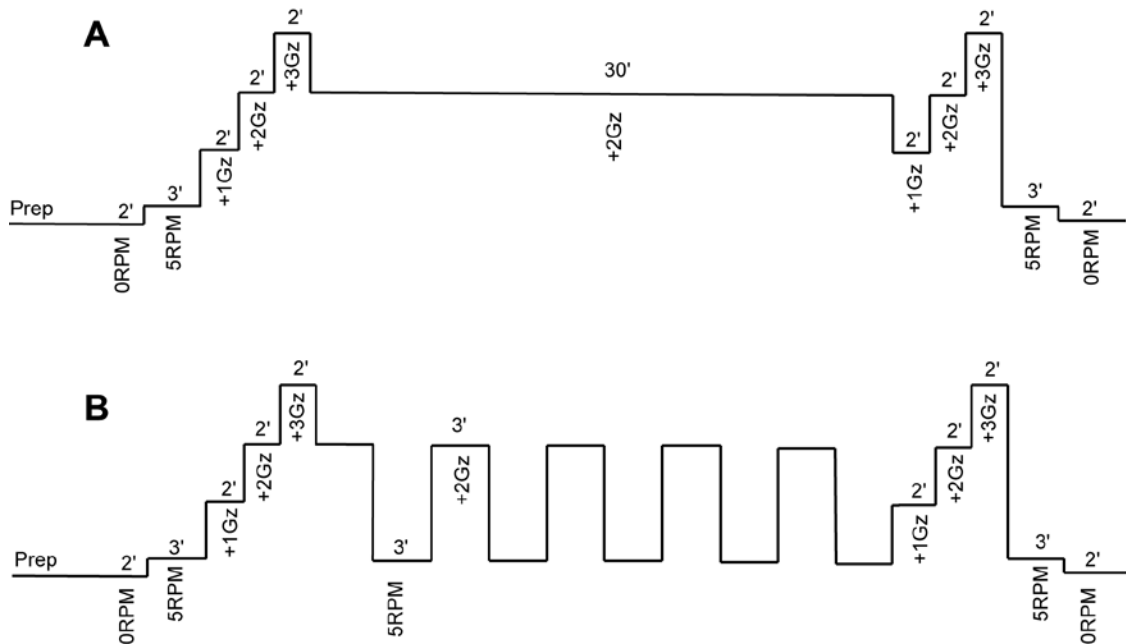


Figure 1. Experimental protocol of continuous (A) or intermittent (B) application of artificial gravity (AG). Panel (A) displays the results generated by a short arm centrifuge, illustrating periods of baseline measurement and all Gz accelerations (at 5 RPM, 1 Gz, 2 Gz, and 3 Gz), including the duration of each Gz acceleration (1', 2', and 30'). Panel B displays the results generated by a short arm centrifuge, illustrating periods of baseline measurement and all Gz accelerations (at 5 RPM, 1 Gz, 2 Gz, and 3 Gz), including the duration of each Gz acceleration (1', 2', 3', and 30'). ' indicates minutes.

Statistical Analysis

Before further analysis, all data were tested for normal distribution using a one sample Kolmogorov-Smirnov test. For O₂Hb and HHb, an ANOVA test with the inter-individual factor PROTOCOL (continuous, intermittent) and the intra-individual factor TIME (course of different Gz levels and baseline, see Figure 1) was calculated for the three measurement points at the PFC, the *Musculus biceps brachii*, and the *Musculus gastrocnemius*. Least Significant Difference post-hoc tests were used in order to differentiate between the different Gz levels during the AG profiles. A second ANOVA with the inter-individual factor PROTOCOL (continuous, intermittent) and the intra-individual factor TIME (pre, post) was calculated for HR, ABP, BDNF, VEGF, and IGF-1. Significance for all statistical testing was set at $p < .05$. Statistical analysis was performed using Statistica 7 (StatSoft, Tulsa, OK). Values in the text are designated as mean \pm confidence intervals (95%).

RESULTS

Hemodynamic Response

Continuous profile

O₂Hb and HHb in the prefrontal cortex, the *Musculus biceps brachii*, and the *Musculus*

gastrocnemius were significantly affected by the changes in gravity level. Within the prefrontal cortex O₂Hb decreased ($F_{(13, 117)}=26.36$, $p<.001$), whereas HHb increased ($F_{(13, 117)}=11.12$, $p<.001$) with increasing gravity levels. Similar effects were obtained for the *Musculus biceps brachii* (O₂Hb $F_{(13, 117)}=16.49$, $p<.001$; HHb $F_{(13, 117)}=11.18$, $p<.001$). At the *Musculus gastrocnemius*, an increase of both O₂Hb ($F_{(13, 117)}=1.90$, $p<.05$) and HHb ($F_{(13, 117)}=4.96$, $p<.001$) was observed.

Whereas HR increased with increasing gravity levels ($F_{(13, 130)}=20.34$, $p<.001$), ABP only increased during the initial 2G and 3G phases ($F_{(13, 130)}=1.89$, $p<.05$). Post-hoc analyses showing significant changes to baseline conditions are displayed in Figure 2 (left).

Intermittent profile

O₂Hb and HHb values at the PFC, *Musculus biceps brachii*, and *Musculus gastrocnemius* all showed significant changes, mimicking the acceleration profile. PFC oxygenation again decreased with gravity levels (O₂Hb $F_{(17, 170)}=18.12$, $p<.001$), whereas HHb increased with increasing gravity levels ($F_{(17, 170)}=5.30$, $p<.001$). Similar findings were obtained for O₂Hb ($F_{(17, 170)}=9.50$, $p<.001$) and HHb ($F_{(17, 170)}=5.69$, $p<.001$) at the *Musculus biceps brachii*. At the *Musculus gastrocnemius*,

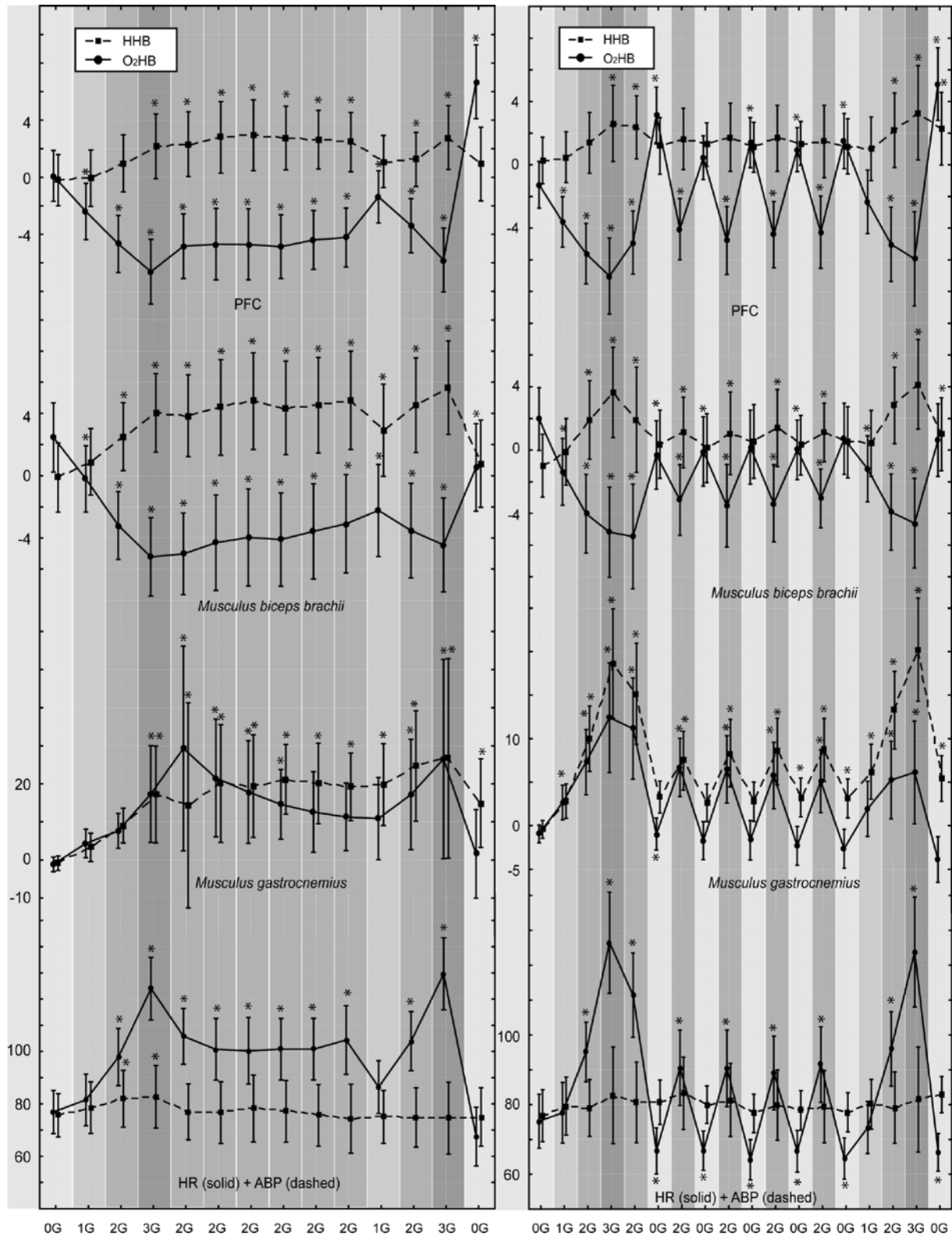


Figure 2. Analysis of oxygenated blood (O₂Hb) and deoxygenated blood (HHb) in response to either continuous or intermittent artificial gravity (AG) application. Means and confidence intervals (95%) for O₂Hb and HHb concentrations in the prefrontal cortex (PFC) are shown in the graphs on the top row, for the *Musculus biceps brachii* in the graphs in the second row, for the *Musculus gastrocnemius* in the graphs on the third row, and for heart rate (HR) and blood pressure (BP) in the graphs on the bottom row. The graphs on the left are the results from the continuous protocol, while the graphs on the right are the results from the intermittent protocol. Asterisks (*) mark differences ($p < .05$) from baseline (0 G, 5 RPM) values.

O₂Hb ($F_{(17, 170)}=19.02$, $p<.001$), as well as HHb ($F_{(17, 170)}=22.79$, $p<.001$) increased with increasing gravity levels. Analysis of HR also showed significant changes, mimicking the acceleration profile ($F_{(17, 170)}=75.60$ $p<.001$). There were no significant changes in ABP ($F_{(17, 187)}=.52$ $p=.94$). Post-hoc analysis showing significant changes to baseline conditions are

displayed in Figure 2 (right).

Neuroendocrinological Response

We did not observe any changes in BDNF ($F_{(1, 10)}=2.13$, $p=.17$), IGF-1 ($F_{(1, 9)}=.00$, $p=.98$), or VEGF ($F_{(1, 10)}=.18$, $p=.68$) values from pre to post centrifugation in either protocol. These results are presented in Table 1.

Table 1. Brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1(IGF-1), and vascular endothelial growth factor (VEGF) values pre and post interventions.

	AG constant [pg/ml]		AG intermittent [pg/ml]	
	Pre	Post	Pre	Post
BDNF n=11	12212,66±8716,77	10028,43±10637,02	9912,01±10748,13	12195,94±11949,15
IGF-1 n=10	139,31±68,64	144,48±74,03	137,99±60,75	143,53±69,55
VEGF n=10	174,77±146,25	159,61±169,65	186,29±166,47	180,22±181,45

Data is presented as mean ± standard deviation.

DISCUSSION

One aim of this study was to describe the hemodynamic and tissue oxygenation responses to continuous and intermittent periods of AG compared to what would be expected during a moderate bout of exercise. This study was conducted in a SAHC, with the aim of investigating the use of AG as a potential countermeasure to physiological deconditioning during long-duration human spaceflight. The results suggest that both the continuous and the intermittent AG protocols induced an increase in *Musculus gastrocnemius* O₂Hb and HHb, most likely representing an increased pooling of blood in the lower limbs. Considering a simple shift of blood away from the head and upper body during centrifugation, one might assume there would be a decrement in both O₂Hb and HHb concentrations. Instead, as we have proposed previously (Schneider et al., 2013), there was a reduction in arterial flow to the brain and *Musculus biceps brachii* muscle during the continuous application of 2 Gz and 3 Gz, evidenced by the reduction in O₂Hb in these regions. The reduction in flow to the upper body can be explained by a reduced pressure gradient for flow towards the upper body (against the AG) (Schneider et al., 2013), and as a result,

less oxygenated blood reaches the brain and the biceps. There were no apparent ill effects of this response; participants did not demonstrate any signs of syncope and BP remained relatively constant. The rise in HHb at the PFC and biceps during the constant AG protocol is consistent with a decreased tissue oxygenation index observed during hypergravity (Kurihara et al., 2007; Schneider et al., 2013) and during head-up tilt (Kurihara et al., 2003). This may represent a relative increase in oxygen extraction from the circulation to compensate for the lower arterial flow to the upper body. It is also plausible that oxygen demand, and therefore extraction, is higher during hypergravity due to increased physical demands, as reflected by the observed increase in HR.

During the intermittent protocol, there were rapid and large increases in O₂Hb at the PFC and the biceps during the periods of reduced centrifugal forces in the head-to-toe axis. Consistent with the earlier interpretation, this likely reflects a transient restoration of the pressure gradient towards the upper body, and an increase in blood flow to the head and arms. In some cases, this increase in O₂Hb exceeded baseline values, particularly at the PFC, which may represent a reactive hyperaemia response to the periods of AG. These transient increases in

O₂Hb (and flow) might also be mediated by central hemodynamic changes, whereby an abrupt increase in venous return to the right atria with a reduction in gravity (0 G) contributes to an increase in stroke volume and driving pressure for blood flow. The observed reduction in HR during the periods of 0 G to levels below baseline might partly be a compensatory response to maintain cardiac output. Interestingly, these periods of normal gravity and restored upper-body blood flow during the intermittent protocol were associated with a slight ($p < .05$) attenuation of rise in HHb, particularly at the *Musculus biceps brachii* ($p < .05$), compared with the continuous protocol. This may again reflect a reduced metabolic demand and oxygen use, and/or a reduced local oxygen extraction during periods when arterial flow is restored. Another major reason for hemodynamic changes after the reduction of centrifugal force and the gradient of the centrifugal force might be an increment of flow-through carotid arteries and a decrement of deoxygenized blood in the brain, caused by blood being pulled from the brain by gravitational forces.

We recently suggested (Schneider *et al.*, 2013) that a reduction in gravity allows more oxygenated blood with each pulse wave to be directed to the low-resistance vessels of the head. This leads to a significant increment in O₂Hb concentration. In contrast to that, the HHb concentration decreases only slightly, since no additional gravitational forces are pulling blood out of the brain, and the oxygen consumption of the brain remains stable throughout the application of AG (Schneider *et al.*, 2013).

The absence of a significant change in BP during the application of AG was somewhat unexpected given the typical alterations in autonomic activity with changes in gravitational force (Linnarsson *et al.*, 2015; Migeotte *et al.*, 2009). The stable BP might be an adaptation, such that there is a sequestration of blood in capacitance veins in the lower peripheral extremities, demonstrated using computer-based simulations by Summers and colleagues (Summers *et al.*, 2010). Alternatively, a gradual venous pooling in the peripheral extremities might cause a reflex myogenic constriction, including the blood vessels in the index finger, which could have an impact on the continuous assessment of BP.

Although AG at a tolerable level (< 2 Gz) is related to an increase in HR, this increase is far below what is experienced during moderate

exercise. At this level of AG, no changes in ABP were detected. The positive effect of exercise on cardiovascular health is based on the physiological stress caused by exercise. Our data suggests that moderate doses of AG at or below 2 Gz are not sufficient to create a relevant physiological stressor for cardiovascular training. The same is true for the release of neurotrophic factors, which are not affected by either of the AG protocols (Table 1). Several studies on the effects of exercise on the release of neurotrophic factors showed that only high intensity exercise is related to an increase in neurotrophic factors (Rojas Vega *et al.*, 2006). As shown by Schiffer *et al.* (2011) using lactate infusion, the driving factor for a release of neurotrophic factors seems to be lactate, which in young healthy persons, is released only at exercise intensities that induce a HR of 180-age (Hollmann *et al.*, 2012; McArdle *et al.*, 2015).

With respect to the data in the present study, much higher values of AG=3 Gz (Figure 2) seem necessary to increase HR to a level similar to moderate physical activity, which is around 180-age. Nevertheless, this level is barely tolerated by the individual, at least not for a long duration. In order to promote vascular adaptations that offset the negative effects of spaceflight, an intermittent protocol with Gz=3 Gz would be a better choice compared to a constant protocol; intermittent AG might lead to increases in blood flow and shear stress, which would in turn promote maintenance or improvement of vascular function (e.g., endothelial function), or even vascular adaptations such as an increase in vessel size.

It should be acknowledged that the study is missing measures of central hemodynamics and blood flow. NIRS has the advantage of being applicable in extreme situations, but interpretation of findings needs to be validated by, for example, a Doppler Ultrasound. This would also clarify possible interference of scalp and/or skull perfusion and blood flow at the PFC. A recent study by Ogawa *et al.* (2016) showed a decrease in cerebral blood flow velocity when exposed to artificial gravity, similar to the O₂Hb values in the PFC described in the present study.

ACKNOWLEDGEMENTS

We would like to express our gratitude to all individuals who participated in this study. We would also like to acknowledge the SAHC staff of the German Aerospace Centre, Cologne, as well as Sebastian Dern, Amrei

Jacobowski, and Petra Wollseiffen for their help with data collection.

CONFLICT OF INTEREST

This study was funded by a research grant from the German Aerospace Centre (DLR, Grant 50WB1161). The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

VSZ, TV, AJ, and VA carried out the studies and participated in the analysis. SS and CDA drafted and finalized the manuscript, and HC edited the manuscript. HKS conceived of the study, and participated in its design and coordination, and helped to draft the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

REFERENCES

- Barr MJ, Gabbett TJ, Newton RU, Sheppard JM (2015) Effect of 8 days of a hypergravity condition on the sprinting speed and lower-body power of elite rugby players. *Journal of Strength and Conditioning Research* **29**: 722-729
- Chouker A, Feuerecker B, Matzel S, Kaufmann I, Strewe C, Hoerl M, Schelling G, Feuerecker M (2013) Psychoneuroendocrine alterations during 5 days of head-down tilt bed rest and artificial gravity interventions. *European Journal of Applied Physiology* **113**: 2057-2065
- Clement G, Buckley A (2007) *Artificial Gravity*, Berlin: Springer
- Clement G, Pavy-Le Traon A (2004) Centrifugation as a countermeasure during actual and simulated microgravity: a review. *European Journal of Applied Physiology* **92**: 235-248
- Clement GR, Buckley AP, Paloski WH (2015) Artificial gravity as a countermeasure for mitigating physiological deconditioning during long-duration space missions. *Frontiers in Systems Neuroscience* **9**: 92
- Dern S, Vogt T, Abeln V, Struder HK, Schneider S (2014) Psychophysiological responses of artificial gravity exposure to humans. *European Journal of Applied Physiology* **114**: 2061-2071
- Evans JM, Ribeiro LC, Moore FB, Wang S, Zhang Q, Kostas V, Ferguson CR, Serrador J, Falvo M, Stenger MB, Goswami N, Rask JC, Smith JD, Knapp CF (2015) Hypovolemic men and women regulate blood pressure differently following exposure to artificial gravity. *European Journal of Applied Physiology* **115**: 2631-2640
- Goswami N, Evans J, Schneider S, von der Wiesche M, Mulder E, Rossler A, Hinghofer-Szalkay H, Blaber AP (2015) Effects of individualized centrifugation training on orthostatic tolerance in men and women. *PloS One* **10**: e0125780
- Hollmann W, Knigge K, Knicker A, Strüder HK (2012) Methods for measurement of physical fitness and recommendations in studies on humans. In *Functional Neuroimaging in Exercise and Sport Sciences*, Boecker H, Hillman CH, Scheef L, HS (eds), pp 79-107. New York, Heidelberg, Dordrecht, London: Springer Science+Business Media
- Knaepen K, Goekint M, Heyman EM, Meeusen R (2010) Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Medicine* **40**: 765-801
- Kurihara K, Kikukawa A, Kobayashi A (2003) Cerebral oxygenation monitor during head-up and -down tilt using near-infrared spatially resolved spectroscopy. *Clinical Physiology and Functional Imaging* **23**: 177-181
- Kurihara K, Kikukawa A, Kobayashi A, Nakadate T (2007) Frontal cortical oxygenation changes during gravity-induced loss of consciousness in humans: a near-infrared spatially resolved spectroscopic study. *Journal of Applied Physiology* (1985) **103**: 1326-1331
- Linnarsson D, Hughson RL, Fraser KS, Clement G, Karlsson LL, Mulder E, Paloski WH, Rittweger J, Wuyts FL, Zange J (2015) Effects of an artificial gravity countermeasure on orthostatic tolerance, blood volumes and aerobic power after short-term bed rest (BR-AG1). *Journal of Applied Physiology* (1985) **118**: 29-35
- Lista I, Sorrentino G (2010) Biological mechanisms of physical activity in preventing cognitive decline. *Cellular and Molecular Neurobiology* **30**: 493-503
- McArdle WD, Katch FI, Katch VL (2015) *Exercise Physiology*, Baltimore: Wolters Kluwer Health
- Migeotte PF, Pattyn N, Vanspauwen R, Neyt X, Achero M, Van de Heyning P, Wuyts

- FL (2009) Respiratory sinus arrhythmia on the ESA-short-arm human centrifuge. *IEEE Engineering in Medicine and Biology Magazine* **28**: 86-91
- Ogawa Y, Yanagida R, Ueda K, Aoki K, Iwasaki K (2016) The relationship between widespread changes in gravity and cerebral blood flow. *Environmental Health and Preventative Medicine* **21**: 186-192
- Pavy-Le Traon A, Heer M, Narici MV, Rittweger J, Vernikos J (2007) From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006). *European Journal of Applied Physiology* **101**: 143-194
- Richter C, Braunstein B, Winnard A, Nasser M, Weber T (2017) Human biomechanical and cardiopulmonary responses to partial gravity - a systematic review. *Frontiers in Physiology* **8**: 583
- Rojas Vega S, Knicker A, Hollmann W, Bloch W, Struder HK (2010) Effect of resistance exercise on serum levels of growth factors in humans. *Hormone and Metabolic Research* **42**: 982-986
- Rojas Vega S, Struder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W (2006) Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Research* **1121**: 59-65
- Schiffer T, Schulte S, Hollmann W, Bloch W, Struder HK (2009) Effects of strength and endurance training on brain-derived neurotrophic factor and insulin-like growth factor 1 in humans. *Hormone and Metabolic Research* **41**: 250-254
- Schiffer T, Schulte S, Sperlich B, Achtzehn S, Fricke H, Struder HK (2011) Lactate infusion at rest increases BDNF blood concentration in humans. *Neuroscience Letters* **488**: 234-237
- Schneider S (ed) (2016) *Exercise in Space - A Holistic Approach for the Benefit of Human Health on Earth*, Switzerland: Springer
- Schneider S, Abeln V, Askew CD, Vogt T, Hoffmann U, Denise P, Struder HK (2013) Changes in cerebral oxygenation during parabolic flight. *European Journal of Applied Physiology* **113**: 1617-1623
- Summers RL, Platts S, Myers JG, Coleman TG (2010) Theoretical analysis of the mechanisms of a gender differentiation in the propensity for orthostatic intolerance after spaceflight. *Theoretical Biology and Medical Modelling* **7**: 8
- Tanaka K, Nishimura N, Kawai Y (2017) Adaptation to microgravity, deconditioning, and countermeasures. *Journal of Physiological Sciences* **67**: 271-281
- Waki H, Katahira K, Yamasaki M, Nagayama T, Katsuda S, Wago H, Okouchi T, H OI, Miyake M, Miyamoto Y, Shimizu T (2005) Effects of spaceflight on postnatal development of arterial baroreceptor reflex in rats. *Acta Physiologica Scandinavica* **184**: 17-26
- Zhang Q, Evans JM, Stenger MB, Moore FB, Knapp CF (2017) Autonomic cardiovascular responses to orthostatic stress after a short artificial gravity exposure. *Aerospace Medicine and Human Performance* **88**: 827-833