Effects of an artificial gravity countermeasure on orthostatic tolerance, blood volumes and aerobic power after short-term bed rest (BR-AG1)

Dag Linnarsson,1 Richard L. Hughson,2 Katelyn S. Fraser,2 Gilles Clément,3 Lars L. Karlsson,1 Edwin Mulder,4 William H. Paloski,5,6 Jörn Rittweger,4,7 Floris L. Wuyts,8 and Jochen Zange4

1Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; 2Schlegel-University of Waterloo Research Institute for Aging, Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Ontario, Canada; 3International Space University, Illkirch-Graffenstaden, France; 4Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany; 5Neuroscience Research Laboratories, National Aeronautics and Space Administration/Johnson Space Center, Houston, Texas; 6Center for Neuromotor and Biomechanics Research, University of Houston, Houston, Texas; 7Institute for Biomedical Research into Human Movement and Health, Manchester Metropolitan University, Manchester, United Kingdom; and 8Department of Otolaryngology, Antwerp University Research Center for Equilibrium and Aerospace, Antwerp, Belgium

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Linnarsson D, Hughson RL, Fraser KS, Clément G, Karlsson LL, Mulder E, Paloski WH, Rittweger J, Wuyts FL, Zange J. Effects of an artificial gravity countermeasure on orthostatic tolerance, blood volumes and aerobic power after short-term bed rest (BR-AG1). J Appl Physiol 118: 29–35, 2015. First published October 23, 2014; doi:10.1152/japplphysiol.00061.2014.—Exposure to artificial gravity (AG) in a short-arm centrifuge has potential benefits for maintaining human performance during long-term space missions. Eleven subjects were investigated during three campaigns of 5 days head-down bed rest: 1) bed rest without countermeasures (control), 2) bed rest and 30 min of AG (AG1) daily, and 3) bed rest and 6 periods of 5 min AG (AG2) daily. During centrifugation, the supine subjects were exposed to AG in the head-to-feet direction with 1 G at the center of mass. Subjects participated in the three campaigns in random order. The cardiovascular effects of bed rest and countermeasures were determined from changes in tolerance to a head-up tilt test with superimposed lower body negative pressure (HUT), from changes in plasma volume (PV) and from changes in maximum aerobic power (VO2peak) during upright work on a cycle ergometer. Complete data sets were obtained in eight subjects. After bed rest, HUT tolerance times were 36, 64, and 78% of pre-bed rest baseline during control, AG1 and AG2, respectively, with a significant difference between AG2 and control. PV and VO2peak decreased to 85 and 95% of pre-bed rest baseline during control, AG1 and AG2, respectively, with a significant difference between AG2 and control. PV and VO2peak decreased to 85 and 95% of pre-bed rest baseline, respectively, with no differences between the treatments. It was concluded that the AG2 countermeasure should be further investigated during future long-term bed rest studies, especially as it was better tolerated than AG1. The superior effect of AG2 on orthostatic tolerance could not be related to concomitant changes in PV or aerobic power.

head-down tilt; short-arm centrifuge; intermittent; head-up tilt; lower body negative pressure

ASTRONAUTS OFTEN SHOW orthostatic intolerance and impaired exercise capacity when returning to normal gravity after space flight, and similar effects are found after periods of head-down tilt bed rest (HDBR) (2, 5, 10, 19, 24). The impairments of orthostatic tolerance (OT) and exercise capacity are multifactorial, including compromised cardiovascular reflexes and reductions in plasma and blood volumes (BV). Different types of countermeasures have been proposed (5, 10) to ensure sufficient capabilities for astronauts when (re)entering a gravitational field after shorter or longer times in weightlessness. Countermeasures include exercise and various forms of artificial gravity (AG). Daily exercise regimens have been used for decades during spaceflight; without them, cardiovascular deconditioning would likely have been even more severe, but additional countermeasures are highly desirable. AG could, at least theoretically, be applied to astronauts in space using a short-arm human centrifuge with a radius slightly longer than a human. A number of such centrifuge prototypes have been designed and tested on earth, with some of the tests made during HDBR studies (15, 25, 29). In addition to the expected benefits for cardiovascular function, AG could potentially also help to prevent muscle atrophy, bone demineralization, and impairment of neuromotor coordination, all of which are frequently observed after spaceflight, especially after long-duration flights (10).

However, the optimal AG protocol for all of these applications remains to be defined. The present study represents an effort to address the effects of AG on cardiovascular deconditioning. Signs of cardiovascular deconditioning can be observed after only a few days of HDBR; for example, Khan et al. (17) detected attenuated sympathetic nerve responses after 24 h of bed rest, whereas Johansen et al. (16) found a significant decrease of plasma volume (PV) after the same period. Several research groups have found impairments of OT and/or PV reductions after 4 days of bed rest (14, 26, 27, 29). It was hypothesized therefore that a 5-day HDBR period would be suitable to test a novel AG protocol with respect to its ability to serve as a countermeasure against cardiovascular deconditioning. Since AG in a short-arm centrifuge is associated with a large gravitational force (G) gradient along the body, a normal G level at the center of mass leads to ~2 G at the feet. This in turn gives rise to blood congestion and pain in many subjects (25). Therefore, the study protocol was designed to keep the daily AG sessions relatively short, while a variant of AG, with several very short centrifugations with rest in between, was also tested. It was hypothesized that this intermittent protocol would not only be better tolerated but also prove more efficient as a countermeasure. This theory was based on the suggestion by Vernikos et al. (26) that not only the duration...
but also the number of gravity stimuli periods may be an important factor.

MATERIALS AND METHODS

The present study reports a short-term bed rest trial made in preparation for more long-term events and was part of a series organized by the ESA. Experiments were performed at the Medes facility on the premises of the Rangeul University Hospital in Toulouse, France. Subjects were exposed to −6° HDBR. Several studies with widely differing objectives were performed in parallel; see, for example, Kos et al. (18), Feureecker et al. (9), Choukér et al. (3a), and Caiani et al. (3). These articles contain detailed descriptions of the overall experimental scenario, so only a brief description is given here. The bulk of this article focuses on the basic cardiovascular variables that make up part of the bed rest core data (BRCD). The BRCD will continue to be collected during future, longer bed rest studies to provide a comparison across studies of different durations. BRCD concerning musculoskeletal and neurovestibular functions were also collected during this study but will be presented elsewhere.

Twelve healthy men were selected to participate in a controlled crossover trial, which included three different, 5-day bed-rest campaigns in random order: 1) control with no other intervention (Con); 2) daily 30-min exposures to AG (AG1); and 3) daily exposures to six-repeated, 5-min AG periods with 3-min intervals (AG2).

Eleven subjects participated in all three campaigns. Data from one subject, who suffered from a medical problem unrelated to the study, was excluded from analysis. The age, body mass, and height of the remaining 11 subjects were 34 ± 6 (mean ± SD) years, 76.0 ± 6.0 kg, and 1.79 ± 0.07 m, respectively, at the start of the first campaign.

AG exposures were performed in the supine position in a short-arm human centrifuge. The speed of rotation and the positioning of the subjects were adjusted so that they were exposed to 1Ga. The center of mass of the body and subjects were adjusted so that they were exposed to 1Ga.

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Orthostatic tolerance. Before bed rest, subjects tolerated on average 30 min of HUT plus 8 min of superimposed LBNP down to −30 mmHg. Generally, the time until presyncope was shorter after HDBR; values post-HDBR were 59% of those before HDBR, and the corresponding values for Con, AG1, and AG2 were 36, 64 and 78%, respectively. As shown in Fig. 1 and Table 1, the pre-/postdifference was significantly less with the AG2 treatment than during Con ($P = 0.0043$), and there was a trend for a similar difference from Con with AG1 ($P = 0.0648$). There was no correlation between changes in OT and those of PV in any of the treatments.

A composite index of tolerance from the product of time and orthostatic stress could be computed similarly to that used by Iwase et al. (15), assuming that the HUT posture was equivalent to a LBNP of 40 mmHg. Such an index provided no more information than just the tolerance time in terms of differences between treatments.

Of the 63 completed OT sessions, the tests were interrupted by the medical supervisor because of a sudden drop in blood pressure on 19 occasions, due to tachycardia on one occasion and pallor on another. The most common reasons for the subject to interrupt the OT test were blurred vision (10 occasions) and nausea (10 occasions) often in combination with sweating. The distribution of signs and symptoms between conditions (pre-/post-Con and -AG) showed no consistent pattern.

Figures 2, 3, and 4 show time courses of heart rate and arterial blood pressure during the OT tests. Since test durations varied substantially between subjects and conditions, the figures show minute-by-minute values for the times until half of the subjects had finished the tests and group mean values for the final minute.

Heart rate time courses markedly differed between before and after bed rest; thus heart rate before bed rest stabilized at a plateau at around 80–90/min during the first 20–30 min, followed by a gradual increase as the graded LBNP was applied. In contrast, heart rate after bed rest increased to around 100–110/min during the first few minutes of upright posture, and most subjects finished the test before the onset of LBNP. Heart rate during the final minute tended to be lower after, rather than before, bed rest ($P = 0.064$) during Con, but there were no corresponding differences during the AG conditions.

Before bed rest, systolic arterial pressure showed an initial rise the first few minutes in an upright posture and then showed a plateau phase and finally fell gradually as LBNP was applied. After bed rest, there was no initial rise, and values tended to be some 5–10 mmHg lower than before bed rest and for a shorter duration. Diastolic arterial pressure showed a modest initial rise and then remained relatively stable for the rest of the test duration. For the final minute during Con, both systolic and diastolic arterial pressures were lower after bed rest than before ($P = 0.012$ and 0.004, respectively). No corresponding differences were observed during the AG conditions.

$Hb_{tot}$, BVs, and body mass. Data are shown in Table 1. Pre-/post-differences did not vary between interventions for any of the variables $Hb_{tot}$, $Hb$, $Hct$, BV, PV, RBCV, or body mass. $Hb$, $Hct$, BV, PV and body mass differed significantly between before and after HDBR, whereas $Hb_{tot}$ and RBCV did not. Overall there was a −15% change of PV at the end of the HDBR period compared with before, with concomitant relative changes of $Hb$, $Hct$, and BV amounting to +9%, +8%, and −11%, respectively. The change in body mass (−1.2 ± 0.5 kg) was about twice what could be accounted for by the loss of BV.

Aerobic power. Data are shown in Table 1. There were moderate changes of $V\dot{O}_{2peak}$ after HDBR compared with baseline, with no significant differences between interventions: For AG2 there was a −6% change ($P = 0.0057$), and there was a similar trend during AG1 (−4%). Peak HR was 5 to 6 beats/min higher after HDBR than before, with no differences between interventions. There were no correlations between the bed rest-induced $V\dot{O}_{2peak}$ changes and the corresponding changes of blood or PV.

![Fig. 1. Change of orthostatic tolerance (OT) time after a 5-day period of head down-tilt bed rest. Con, control; AG1, 30 min daily artificial gravity (AG); AG2, 6 periods of 5 min daily AG. Values are means ± SD.](http://jap.physiology.org/)

### Table 1. BVs, OT time, peak exercise performance, and body mass before and after a 5-day, head down-tilt bed-rest period

<table>
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<th>BVs, ml</th>
<th>OT, min</th>
<th>$V\dot{O}_{2peak}$, ml/min</th>
<th>$HR_{peak}$, beats/min</th>
<th>$V\dot{E}_{peak}$, l/min</th>
<th>Body Mass, kg</th>
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Values are means (SD). $Hb$: hemoglobin; $Hct$: hematocrit; $BV$: blood volume; $PV$: plasma volume; $RBCV$: erythrocyte volume; OT: orthostatic tolerance time; $V\dot{O}_{2peak}$, $HR_{peak}$, and $V\dot{E}_{peak}$: peak oxygen uptake, heart rate, and ventilation during a maximal exercise test; Con: control; AG1, 30 min daily artificial gravity (AG); AG2, 6 periods of 5 min daily AG; $n = 11$ if not indicated otherwise. *Prepost difference significantly different from Con; $^b$significantly different from Pre; $^{*n} = 10$; $^{*n} = 9$. 

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DISCUSSION

*Orthostatic tolerance. The major finding of the present study is that daily AG for 30 min partly prevents the impairment of OT that otherwise would result from a 5-day HDBR period. The notion that limited, repeated periods of AG can improve OT is not new. Evans et al. (8) showed that repeated AG exposures improved OT in ambulatory men. Neither is the concept of using AG or normal gravity as countermeasures against cardiovascular decondition during actual and simulated microgravity. Thus Vernikos et al. (26) showed that standing for 2 or 4 h in 15-min bouts partially (2 h) or completely (4 h) prevented post-HDBR decreases of OT. Furthermore, Stenger et al. (25) showed clear improvements of OT in a controlled study, including two groups of subjects who were exposed to 21 days of HDBR with or without 60 min of daily AG. Apart from the shorter duration of both the HDBR period and the 50% shorter daily AG exposure, there were other important differences between the present study and that of Stenger et al. In the latter, subjects were selected to withstand 75 min of AG, whereas in the present study, one of the participants could not tolerate the AG1 protocol. Furthermore, in the Stenger et al. study, the subjects were allowed to perform heel rises and shallow knee bends to counteract presyncope due to venous pooling during the AG sessions. Thus, they performed exercise that the authors characterized as “exercising to a small extent.” In contrast, in the present study subjects were permitted to flex their toes to relieve discomfort in the lower legs but not perform heel rises or knee bends.

Therefore, the novel aspects of the present study were that the AG exposure was as passive as could be tolerated and that one of the treatments was divided into 5-min AG-exposure periods with 3-min breaks in between. It is especially notable that the intermittent exposure design, comprising six of the 5-min AG exposures daily, preserved OT at a level of 78% of...
the pre-HDBR value, compared with 36% in the Con group. Corresponding values for Stenger et al. (25) were 79 and 54%. The difference in HDBR duration makes a direct comparison of the present data and those of Stenger et al. (25) difficult, but a conservative interpretation is that this intermittent exposure appears equivalent to 60 min of continuous AG in terms of preserving OT after bed rest, but is actually less stressful. This conclusion was subjectively reached by the subjects but is supported by their neuroendocrine responses. Choukèr et al. (3a) found that AG2 was associated with lower adrenocortical stress responses than AG1 in the same subjects.

The mechanism behind the improved OT after AG compared with control certainly cannot be an effect derived from a better maintained PV, as PV after HDBR was equally reduced in the AG conditions as in Con. Furthermore, there was no correlation between individual PV and OT changes within any of the conditions. Caiani et al. (3) studied resting cardiac function in the same subjects and found that bed rest had a marked, but transient, effect on both geometry and function of the heart. Left ventricular mass and volume decreased by 16 and 14%, respectively. Neither of the AG protocols could counteract these changes, which were considered to be caused by dehydration and hypovolemia. In summary, therefore, a cardiac mechanism seems unlikely as an explanation for the favorable effect of AG on OT.

In a further study on the same subjects, Chokèr et al. (3) studied neuroendocrine responses and found that urinary adrenalin was elevated during the AG conditions but not during Con. During day 5 of bed rest, that is the day before the OT test, this elevation was only found during AG2, the condition with the best preserved OT. This result is in line with that of Stenger et al. (23) who suggested that improved sympathetic responsiveness to orthostatic stress could be the factor behind the preservation of OT as a result of AG. These authors determined a range of markers of sympathetic activation during a similar bed rest study with and without an AG countermeasure. They found that AG improved OT and that this improvement was associated with increased tilt induced responses of plasma norepinephrine and increased low-frequency spectral power of the systolic pressure during the OT tests. At the same time they showed that there were bed rest-induced increases of plasma renin activity and angiotensin II in their control group, but there were no corresponding increases in the AG group. A possible interpretation is that there was a preexisting hyperadrenergic state before the post-bed rest OT tests in their control condition, reducing the vasoconstrictive reserve (3a, 4), but that this had been normalized in the AG condition.

An analysis of the time courses of heart rate and blood pressures during the OT tests provides some information, despite the fact that the test duration became very short for most of the subjects during Con, making comparisons with the AG conditions difficult. It appears, however, that the initial heart rate response after bed rest is similar between the three conditions. The initial tachycardic responses after bed rest resemble those of postural tachycardia syndrome [POTS, Mar and Raj (20)]. In POTS, the tachycardia exceeds 30/min and is inappropriate in the absence of postural systolic hypotension of more than 20 mmHg (20). This is also a fair description of the present post bed rest heart rate responses, where the initial hypotensive responses on the average were <20 mmHg and the initial tachycardic responses on the average exceeded 30/min. The most common causes of POTS are hypovolemic and hyperadrenergic states (20). Our subjects were indeed hypovolemic after bed rest, and to the same extent in both the Con and AG conditions. The limited neuroendocrine data of Choukèr et al. (3) do not support the notion of a preexisting, hyperadrenergic state before the OT tests after bed rest in the present subjects. Thus the urinary epinephrine excretion was not elevated during Con but rather in the AG conditions. In summary, therefore, the patterns of the heart rate and blood pressure responses during the OT tests do not suggest any specific mechanism behind the improved OT in the AG2 condition.

**BV, PV, and Hct.** In normal gravity, humans spend two thirds of their time in an upright posture, and the maintenance of an adequate central BV is essential for cardiac function. Reflexes originating from arterial and cardiopulmonary receptors control total body fluid volume and the blood distribution in the body (22). During actual and simulated microgravity, there is a headward fluid and blood distribution, and the above regulatory systems act to correct a too large central BV (11, 21). Although the exact mechanism behind the central hypovolemia differs between actual spaceflight and HDBR, there is
a rapid reduction of PV and an associated reduction of BV in both cases (6, 28).

Johansen et al. (16) studied PV during HDBR and showed that there was a 6% reduction by day 2 alone. The present overall reduction of 15% on day 5 is larger than that observed by Stenger et al. (25) on day 21 and by Johansen et al. (16) on day 42 (both –10%) but lower than that observed by Hiray-anagi et al. (12) after 3 days of HDBR (~19%). Furthermore, the present PV reduction is lower than that observed in six astronauts during their first day in flight [–17%, Alfrey et al. (1)]. In summary, the present PV data show HDBR induced decreases that are in the midrange of that found by others during similar conditions. In contrast to PV, there were no HDBR-induced changes in RBCV and Hbtot, and as a result there was a hemococoncentration as reflected by increases of Hb and Hct. This is likely to reflect a faster downregulation of PV than of RBC volume, since more prolonged exposures to HDBR or actual microgravity [Zwart et al. 2009 (30) and Alfrey et al. (1)] do not display the relatively large increase of Hct observed in the present study and in other studies reporting data from the first 2 to 5 days of HDBR (12, 16).

At first sight, one may expect AG to partly prevent a reduction of PV due to the daily periods of central hypovolemia, just as upright posture after HDBR or normal gravity upon return from space results in a restoration of PV (16). However, as shown by Stenger et al. (25) and the present data, this is not the case, at least not if the daily gravity stimulus is 1 h or less. In contrast, Vernikos et al. (26) showed that 2 h of standing per day partly and 4 h/day completely preserved PV after a 4-day bed rest. There are limited PV data from the first day or days of upright posture after more long-term periods of HDBR and spaceflight. Exercise stroke volume may be used as a surrogate variable for the restoration of cardiac preload, BV, and PV after HDBR (24) and spaceflight (19). Levine et al. (19) showed that exercise stroke volume had recovered to 1.2 days after 2 wk in space, and Spaak et al. (24) found a partial recovery of exercise stroke volume 3 days after the end of a 120-day-long HDBR period.

Interestingly, Convertino et al. (4) demonstrated that a bout of maximal exercise restored not only PV but also cardiovascular reflex responses and OT (7) after a 16-day HDBR period. Furthermore, Yajima et al. (29) and Iwase (15) demonstrated that when daily AG was performed at a similar level as in the present study and was combined with light leg exercise, then it prevented most of the PV loss that was found in a control group without AG during 4- and 14-day HDBR periods, respectively. Therefore, in conclusion, it appears that exercise is a more effective method of preserving PV during HDBR than AG without exercise.

**Aerobic power.** Levine et al. (19) showed that astronauts had a 22% reduction of preflight VO2peak on the first day of return after 9 to 14 days in space. The same subjects had an 11% reduction in PV, and on that basis, a more marked reduction of VO2peak would have been expected than the 5% observed across conditions in the present study. In the present experiments, VO2peak determination took place in the afternoon of R +0 and was preceded by an OT test approximately 5 h earlier. It is likely that the unknown, and probably variable, PV loss observed on the last day of HDBR had been restored during the period of upright posture and orthostatic stress that preceded the VO2peak tests on R +0. It is therefore not surprising that no correlation was found between end-HDBR changes of PV and post-HDBR changes of VO2peak in the present data. Since a bout of maximum exercise acts to restore OT after bed rest (4, 7), it seems impossible to perform both OT and VO2peak measurements on the first day after an HDBR period without the two tests interfering with each other.

**Conclusions.** Most of the impairment of OT induced by a short bed rest period could be prevented with daily exposure to AG for 30 min. An intermittent protocol with six periods of 5 min AG was better tolerated than a protocol without breaks, and was also more effective. The AG protocols had no effect on PV changes compared with control, so the favorable effect of AG on OT was presumably caused by mechanisms not requiring a maintained BV. Further studies of intermittent AG are recommended for more long-term bed rest studies and should be combined with exercise.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**
