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ORIGINAL RESEARCH

Impact of Daily Lower-Body Negative Pressure or Cycling Followed by Venous Constrictive Thigh Cuffs on Bedrest-Induced Orthostatic Intolerance

Jan-Niklas Hönemann, MD; Fabian Hoffmann, MD; Laura de Boni, MD; Peter Gauger, MSc; Edwin Mulder, PhD; Stefan Möstl, PhD; Karsten Heusser, MD; Marie-Therese Schmitz, MSc; Marcel Halbach, MD; Steven S. Laurie, PhD; Stuart M. C. Lee, PhD; Brandon R. Macias, PhD; Jens Jordan, MD; Jens Tank, MD

BACKGROUND: Orthostatic intolerance occurs following immobilization in patients on Earth and in astronauts after spaceflight. Head-down tilt bedrest is a terrestrial model for weightlessness and induces orthostatic intolerance. We hypothesized that lower-body negative pressure (LBNP) or cycling followed by wearing venous constrictive thigh cuffs mitigates orthostatic intolerance after head-down tilt bedrest.

METHODS AND RESULTS: We enrolled 47 healthy individuals (20 women, 35±9 years) to a 30-day strict head-down tilt bedrest study. During bedrest, they were assigned to 6 hours of 25 mm Hg LBNP (n=12) per day and 1 hour of supine cycling followed by 6 hours of venous constriction through thigh cuffs 6 days per week (n=12), 6 hours of daily upright sitting (positive control, n=11), or no countermeasure (negative control, n=12). We measured orthostatic tolerance as the time to presyncope during 80° head-up tilt testing with incremental LBNP before and immediately after bedrest. We determined plasma volume with carbon monoxide rebreathing before and at the end of bedrest. After bedrest, orthostatic tolerance decreased 540±457 seconds in the control group, 539±68 seconds in the cycling group, 217±379 seconds in the LBNP group, and 289±89 seconds in the seated group ($P<0.0001$ time point, $P=0.009$ for group differences). Supine and upright heart rate increased in all groups following bedrest. Plasma volume was only maintained in the cycling group but decreased in all others (interaction countermeasure×time point $P<0.0001$).

CONCLUSIONS: Six hours of moderate LBNP training was as effective as sitting in attenuating orthostatic intolerance after 30 days of head-down tilt bedrest. Daily cycling exercise followed by 6 hours of wearing venous constrictive thigh cuffs, while maintaining plasma volume, did not improve orthostatic tolerance.

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Orthostatic intolerance commonly occurs in individuals with autonomic nervous system disorders or structural heart disease and following deconditioning through bedrest or weightlessness in space.[1–3] While orthostatic intolerance in current astronauts following spaceflight appears to be milder compared with the early days of spaceflight,[4] the condition could be life-threatening following emergency landings on Earth or another celestial body. Orthostatic intolerance following spaceflight has been attributed to

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Correspondence to: Jens Tank, MD, Institute of Aerospace Medicine, Linder Hoehe; 51147 Cologne, Germany. Email: jens.tank@dlr.de

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CLINICAL PERSPECTIVE

What Is New?

- Moderate lower-body negative pressure over 6 hours per day is as effective as upright sitting in attenuating orthostatic intolerance after 30 days of head-down tilt bedrest.
- Exercise followed by wearing venous constrictive thigh cuffs maintained plasma volume but not orthostatic tolerance.

What Are the Clinical Implications?

- Maintenance of orthostatic tolerance during bedrest deconditioning requires specific preventive measures that providing an orthostatic stimulus to the cardiovascular system.

Nonstandard Abbreviations and Acronyms

HDTBR	head-down tilt bedrest
LBNP	lower-body negative pressure
SANS-CM	Spaceflight-Associated Neuro-Ocular Syndrome Countermeasure

weightlessness-induced cardiovascular deconditioning, reduced blood volume, and altered neurohumoral cardiovascular control.[5] Because weightlessness is the root cause of these changes, countermeasures producing cardiovascular changes akin to standing on Earth and physical exercise have been suggested as potential countermeasures.[6] Yet, studies on lower-body negative pressure (LBNP) and exercise as potential orthostatic intolerance countermeasures yielded varying outcomes.[7,8] While physical activity is crucial in maintaining fitness during spaceflight, orthostatic tolerance may not be addressed.[9,10] Physical exercise over 2 to 3 hours per day and LBNP of 0.5 to 1 hours every second or third day toward the end of spaceflight are currently implemented countermeasure strategies.[11,12]

We reasoned that countermeasures like LBNP applied for a sufficiently long period of time to mitigate neuro-ocular changes and physical exercise combined with interventions producing caudal fluid shifts could also maintain orthostatic tolerance.[13,14] We tested this hypothesis as part of the SANS-CM (Spaceflight-Associated Neuro-Ocular Syndrome Countermeasure) study. The SANS-CM study compared daily LBNP for 6 hours and supine bicycle ergometry, followed by 6 hours of venous thigh constriction against a negative and a positive control group. The primary goal of the study was prevention of spaceflight-associated neuro-ocular syndrome, which challenges brain and ocular health in astronauts. In our substudy, we determined whether daily LBNP or cycling followed by wearing venous constrictive thigh cuffs (cycling) attenuates reductions in orthostatic tolerance following bedrest. We computed orthostatic tolerance as the time to presyncope during tilt-table testing followed by incremental LBNP.[15] These results were compared with a control group without countermeasure and participants who remained upright seated for 6 hours per day. Furthermore, we determined whether the magnitude of plasma volume loss during bedrest was related to changes in orthostatic tolerance. This approach allowed us to test the idea of a possible multipurpose countermeasure against cardiovascular deconditioning and spaceflight-associated neuro-ocular syndrome.

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METHODS

Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. The SANS-CM study was conducted at the German Aerospace Center envihab research facility in close collaboration and supported by the National Aeronautics and Space Administration. All participants were recruited following detailed psychological and medical screening. General information on recruitment, randomization, and standardization of bedrest studies have been published previously.[16,17] Briefly, men and women who were physically and psychologically healthy, aged between 24 and 55 years, with a body mass index between 19 and 30 kg/m^2, and were nonsmokers were potentially eligible. Key exclusion criteria comprised requirements for prescription medications except hormonal contraception in women; health conditions that would preclude participation, such as history of cardiovascular disorders including syncope, musculoskeletal, neurological, metabolic, or endocrine disturbances; or increased thrombosis risk among others. Woman had to have a 26- to 32-day menstrual cycle. All participants provided written informed consent before study entry. The study was approved by the North Rhine Medical Association Ethics Committee and prospectively registered on the German Clinical Trials Register (DRKS00027643 and DRKS00030848).[18]

Study Design and Protocol

The study comprised a 14-day ambulatory baseline period, 30-day 6° strict head-down tilt bedrest (HDTBR), and a 14-day recovery period. Throughout the study, participants were on a highly standardized diet tailored to individual resting metabolic rates with the goal to maintain body weight. Daily fluid intake from food and beverages was set at 50 mL/kg body weight per day at baseline and during bedrest. Daily sodium consumption was 2264 ± 108 mg/d. Participants were awakened at 6:30 AM, and lights were turned off at 10:30 PM.

During the bedrest period, participants were assigned to either daily 2×3 hours of lower body negative pressure with 25 mm Hg (n=12), 60 minutes cycling on a supine bike, followed by wearing venous constrictive thigh cuffs for 6 hours 6 days per week, 6 hours upright seated (n=11; positive control), or no countermeasure (n=12; negative control).

Power calculation for sample size justification was based on the primary end point of the SANS-CM study, namely, total retinal thickness derived from optical coherence tomography images. For 12 participants per group, which corresponds to the maximum bed occupancy of the facility, a simulation based on previous HDTBR data[19] calculated a power of 80% to detect a 15-micron difference in the expected increase of total retinal thickness among the groups. A graphical overview of the study protocol is provided in Figure 1.

Orthostatic Tolerance Testing

We conducted orthostatic tolerance testing 5 days before the bedrest phase and immediately following 30 days bedrest in the morning hours. At baseline, participants walked to the tilt table; at the end of bedrest, they were taken on a 6° head-down tilt stretcher to the tilt table. Then, participants were instrumented with a 3-lead ECG, finger blood pressure (Finometer midi, Finapres Medical Systems, Netherlands), and oscillometric brachial blood pressure every 2 minutes. A lower-body negative pressure chamber was placed at

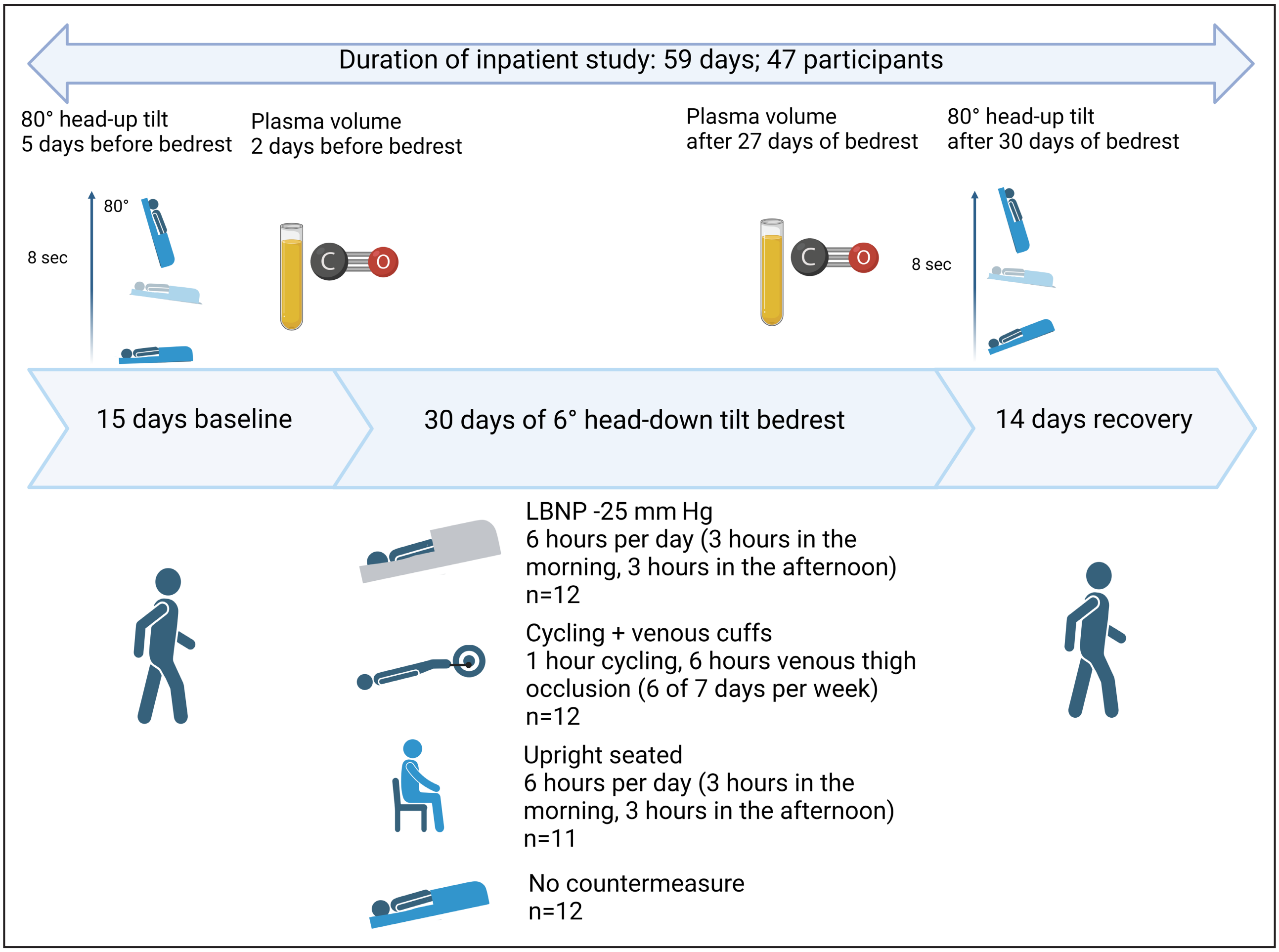

Figure 1. Overview of interventions in the SANS-CM (Spaceflight-Associated Neuro-Ocular Syndrome Countermeasure) study, which enrolled 47 healthy participants to 30 days of bedrest.

Subjects were assigned to 2×3 hours of daily lower-body negative pressure (−25 mm Hg) per day (n=12) and 1 hour of cycling with 45% of maximal VO_2, followed by wearing venous constrictive thigh cuffs for 6 hours 6 days per week (n=12). These strategies were compared with a positive control, who remained in an upright seated body position for 2×3 hours per day (n=11; positive control) and a negative control group without countermeasure (n=12). Orthostatic tolerance was computed as time to presyncope in 80° head-up tilt-table testing with incremental lower-body negative pressure following 15 minutes of upright standing (International Standard Measure protocol). Tilt-table testing was conducted in the morning hours following an overnight fast 5 days before and immediately after bedrest. Plasma volume was measured 2 days before and at day 28 of bedrest. Control indicates no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs on 6 days per week; LBNP, lower-body negative pressure for 6 hours per day, and seated, upright seated body position for 6 hours per day.

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the level of the iliac crest. Following instrumentation, participants remained in the supine position for 10 minutes. We obtained baseline measurements in the last 5 minutes of this period. Then, we conducted a head-up tilt to 80°. After 15 minutes of head-up tilt, we added incremental lower-body negative pressure of −10 mm Hg every 3 minutes.[20] We terminated orthostatic tolerance testing when participants wished to abort the test or when presyncope occurred. We defined presyncope as sudden onset of pallor, blurred vision, lightheadedness, sweating, and nausea, accompanied by a >40% heart rate reduction or >40% systolic blood pressure reduction compared with the first 5 minutes of asymptomatic standing as described before.[21] We defined orthostatic tolerance as the time from head-up tilt onset to presyncope. We determined heart rate and systolic and diastolic blood pressure in the supine position, during 15 minutes of 80° head-up tilt, and with stepwise increase of lower-body negative pressure every 3 minutes until presyncope occurred. Figure 2 illustrates typical heart rate and blood pressure tracings during the combined head-up tilt and LBNP test until presyncope.

Plasma Volume

We measured plasma volume by carbon monoxide rebreathing at baseline and at day 28 of bedrest as described before.[22] Briefly, a baseline 2.6-mL EDTA blood sample was taken via peripheral venous catheter, and the percentage of carboxyhemoglobin was estimated with a hemoximeter (ABL 90, Radiometer, Denmark). Afterwards, subjects breathed oxygen-rich gas for 1 minute for elimination of nitrogen from airways. Next, all participants received a bolus (1.0 mL/kg for men and 0.75 mL/kg for women) of 99.997% chemically pure carbon monoxide and rebreathed this gas mixture for 9 minutes. Subsequently, we collected another 2.6-mL peripheral venous blood sample, and the percentage of carboxyhemoglobin was estimated again. We measured plasma volume, blood volume, and total hemoglobin mass by using the dilution principle on the basis of the number of absorbed carbon monoxide molecules and the changes in fraction of carboxyhemoglobin in the collected blood samples (Detalo Performance, Detalo Health, Denmark).[23]

Statistical Analysis

We report results as mean±SD and performed all statistical analyses with Prism version 10.0.2 (GraphPad Software, La Jolla, CA). Based on the repeated measures design, we used a linear mixed-effects model with Šídák's multiple comparisons test to analyze changes in orthostatic tolerance, hemodynamics, and plasma volume between all groups before and after bedrest. The time point (bedrest effect), the countermeasure (group effect), and the interaction between time point and countermeasure were the fixed effects. Study participants were considered as random effects. Post hoc testing for estimation of adjusted *P* values was conducted only if a significant group difference or interaction was shown in primary testing and comprised a difference of means before and after bedrest in each group. Therefore, the number of post hoc comparisons was limited to 4. We tested for Gaussian distribution with the Shapiro–Wilk test. To detect correlation between changes in plasma volume and orthostatic tolerance, we conducted the nonparametric Spearman correlation coefficient analyses (r=0.10–0.29, weak correlation; r=0.30–0.49, moderate correlation; $r \geq 0.5$, strong correlation). $P<0.05$ indicated statistical significance. We present *P* values of the primary statistical analysis (group, time point, interaction) and results of post hoc testing using adjusted *P* values.

RESULTS

Intervention Groups

Out of 7418 returned initial screening questionnaires, 78 candidates were invited for detailed assessment including a multistep medical and psychologic testing; 48 participants and 4 reserve candidates were selected.[18] Of 48 selected participants, 47 completed the study (20 women, 27 men; age, 35±9 years, body mass index [BMI], 23.7±2.6 kg/m^2). One participant had to be excluded due to noncompliance with the study protocol. All participants were randomly assigned to intervention groups. Twelve subjects were assigned to the LBNP group (6 women, 6 men; age: 36 ± 9 years; BMI, 24.1 ± 2.6 kg/m^2), 11 to the seated group (5 women, 6 men; age, 36 ± 9 years; BMI, 24 ± 2.7 kg/m^2), 12 to the cycling group (4 women, 8 men; age, 34 ± 8 years; BMI, 23.2 ± 2.3 kg/m^2), and 12 to the control group (5 women, 7 men; age, 35 ± 8 years; BMI, 23.1 ± 2.3 kg/m^2). For 1 participant in the seated group, incremental LBNP during tilt-table testing was not recommended for medical reasons and the subject was therefore excluded from the statistical analysis. There was no significant difference in demographics between the groups.

Orthostatic Tolerance

Figure 3 shows Kaplan–Meier plots illustrating the time to presyncope during tilt-table testing in the seated, LBNP, cycling, and control groups. Before bedrest, the time to presyncope was 1312±273 seconds in the seated, 1134±390 seconds in the LBNP group, 1276±333 seconds in the cycling group, and 953±477 seconds in the control group. Following 30 days of bedrest, the time to presyncope decreased by 289±281 seconds in the seated group, by 217±379 seconds in the LBNP group, by 539±235 seconds in the cycling group, and by 540±457 seconds in the control group

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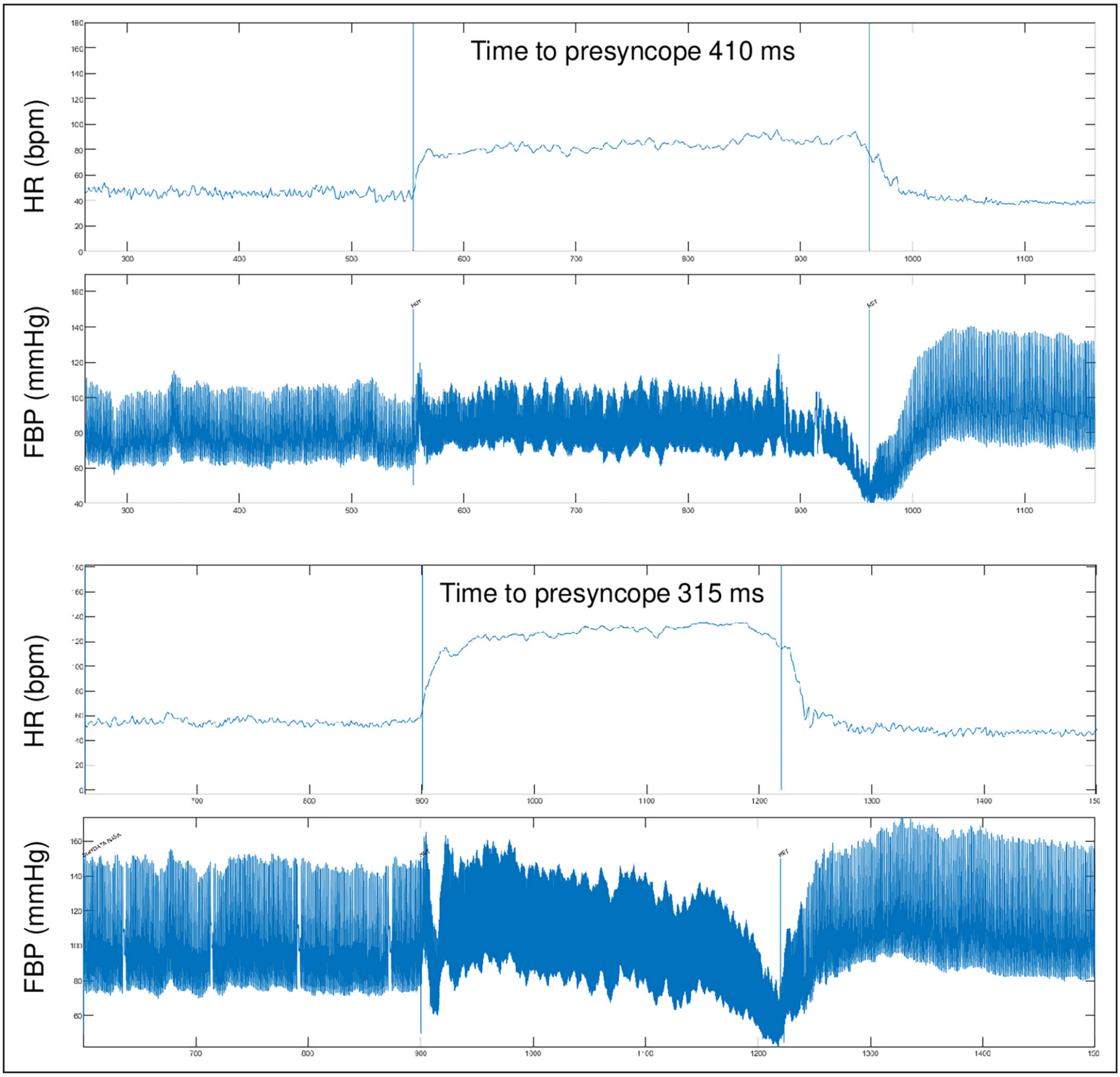

Figure 2. Continuous FBP and HR before (upper row) and after bedrest (lower row) in a representative participant during combined head-up tilt testing and LBNP.

Time to presyncope decreased following bedrest. The participant also showed markedly increased HR while supine and during orthostatic testing following bedrest. bpm indicates beats per minute; FBP, finger blood pressure; HR, heart rate; and LBNP, lower-body negative pressure.

(time point, *P*<0.0001; groups, *P*=0.0090; interaction, *P*=0.0595). Post hoc tests revealed that the reduction in orthostatic tolerance with bedrest was attenuated in the seated and the LBNP groups but not in the cycling and control groups (Figure 3).

Blood Pressure and Heart Rate

The Table provides an overview on hemodynamic parameters before and after bedrest in the supine position and while standing (first 5 minutes after tilting to 80°). At baseline before bedrest, supine hemodynamic parameters did not differ between groups, except a lower diastolic blood pressure in the cycling group (adjusted *P*=0.063). Figures 4 and 5 illustrate individual supine and standing heart rate and blood pressure measurements before and after bedrest together with the primary *P* values of the linear mixed-effects analysis (time and group effects, interaction) and the adjusted *P* values from post hoc comparisons.

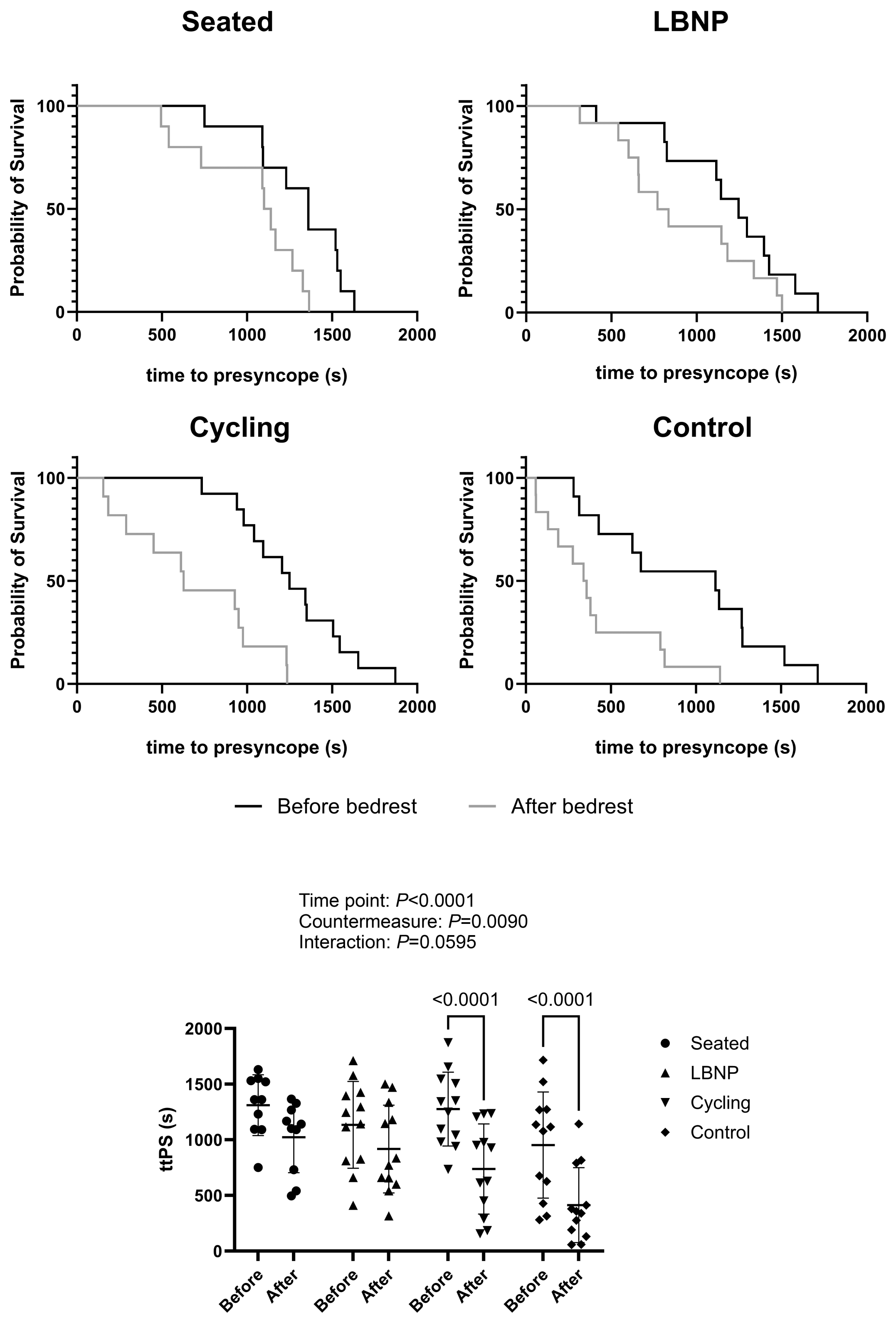

Figure 3. Kaplan–Meier survival analyses on time to presyncope, which was computed to compare orthostatic tolerance, before and after in each group.

The lower panel shows individual data on orthostatic tolerance before and after bedrest for each intervention group (*P* values for linear mixed-effects analysis). Control indicates no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs on 6 days per week; LBNP, lower-body negative pressure for 6 hours per day; seated, upright seated body position for 6 hours per day; and time to presyncope (ttPS),.

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Table. **Mean±SD Values of Hemodynamic Parameters in Each Group**

Parameter	Group	Before bedrest	After bedrest
Systolic blood pressure, supine, mm Hg	LBNP	130±8	133±6
	Seated	128±8	131±7
	Cycling	123±10	129±14
	Control	127±7	131±11
Systolic blood pressure, standing, mm Hg	LBNP	129±12	138±10
	Seated	129±6	132±9
	Cycling	130±16	133±19
	Control	123±12	129±15
Diastolic blood pressure, supine, mm Hg	LBNP	85±11	79±6
	Seated	87±9	80±7
	Cycling	73±7	75±9
	Control	76±5	84±8
Diastolic blood pressure, standing, mm Hg	LBNP	90±11	88±8
	Seated	90±7	85±8
	Cycling	79±8	84±13
	Control	80±8	87±11
Heart rate, supine, bpm	LBNP	67±9	74±9
	Seated	66±10	71±12
	Cycling	67±7	72±10
	Control	73±9	89±12
Heart rate, standing, bpm	LBNP	89±10	112±13
	Seated	86±12	109±13
	Cycling	92±14	115±12
	Control	104±17	128±18

Mean±SD values of each group on central hemodynamic parameters. LBNP indicates lower-body negative pressure.

Supine and upright systolic blood pressure values were slightly higher after bedrest in all groups. No interaction or group effects were detected. In contrast, supine and upright diastolic blood pressure increased in the control group but not in the intervention groups. The significant interaction indicates that all interventions attenuated bedrest effects on supine diastolic blood pressure and to a lesser extent also on upright diastolic blood pressure.

Supine and upright heart rate increased after bedrest. Despite significant bedrest and group effects, an interaction was detected only in the supine position. The interventions did not completely prevent bedrest-induced orthostatic tachycardia. However, the control group showed the numerically largest increase in heart rate, both in the supine position and while standing.

Plasma Volume

Before bedrest, plasma volume was 3157±610 mL in the LBNP group, 3045±309 mL in the cycling group, 3270±519 mL in the seated group, and 2851±459 mL in the control group. There was no evidence for statistical group differences at baseline. At the end of bedrest, plasma volume was decreased by 603±407 mL in the LBNP group, by 593±212 mL in the seated group, and 286±153 mL in the control group, but was maintained in the cycling group (time point, $P<0.0001$; groups, $P=0.6439$; interaction, $P=0.0001$; Figure 6). Plasma volume changes revealed an inverse correlation with reductions in orthostatic tolerance (Figure 7).

DISCUSSION

The important finding of our study is that daily moderate LBNP training for 6 hours attenuated reductions in orthostatic tolerance following 30 days of HDTBR comparable with the effect of sitting upright for 6 hours per day. In contrast, daily 60-minute cycling followed by wearing venous constrictive thigh cuffs while maintaining plasma volume did not preserve orthostatic tolerance. However, none of the interventions completely abolished worsening of orthostatic tolerance with bedrest deconditioning. Although our primary goal was to inform future space missions, the study may have implications for individuals experiencing orthostatic intolerance on Earth.[24]

HDTBR is an established terrestrial model to mimic cardiovascular adaptions to spaceflight including orthostatic intolerance.[25] The model also provides valuable information regarding the role of deconditioning in the pathogenesis of orthostatic intolerance on Earth. In these standardized studies, countermeasures against cardiovascular deconditioning and orthostatic intolerance can be evaluated in a highly controlled fashion.[26] Indeed, meticulous standardization of the bedrest protocol, incorporating controlled sodium, fluid, and energy intake allowed us to assess changes in orthostatic tolerance in the absence of these confounding variables. Another strength of our study is the methodology to assess orthostatic tolerance using combined head-up tilt testing and LBNP. Previous studies showed the reproducibility of the approach and yielded effective treatments for orthostatic intolerance.[27–29]

In our study, contrasting actions of LBNP and physical exercise followed by wearing venous constrictive thigh cuffs on orthostatic tolerance and plasma volume are thought provoking and may have clinical relevance. Bedrest led to reductions in orthostatic tolerance, increased supine and upright heart rate, and decreased plasma volume, which are hallmarks of cardiovascular deconditioning.[30,31] Preservation of heart rate while supine in the cycling and seated groups provides evidence that these interventions may have partly maintained cardiovascular autonomic control following bedrest. The response is consistent with known effects of exercise training on cardiac vagal tone, which lowers resting heart rate and increases cardiac stroke volume.[32]

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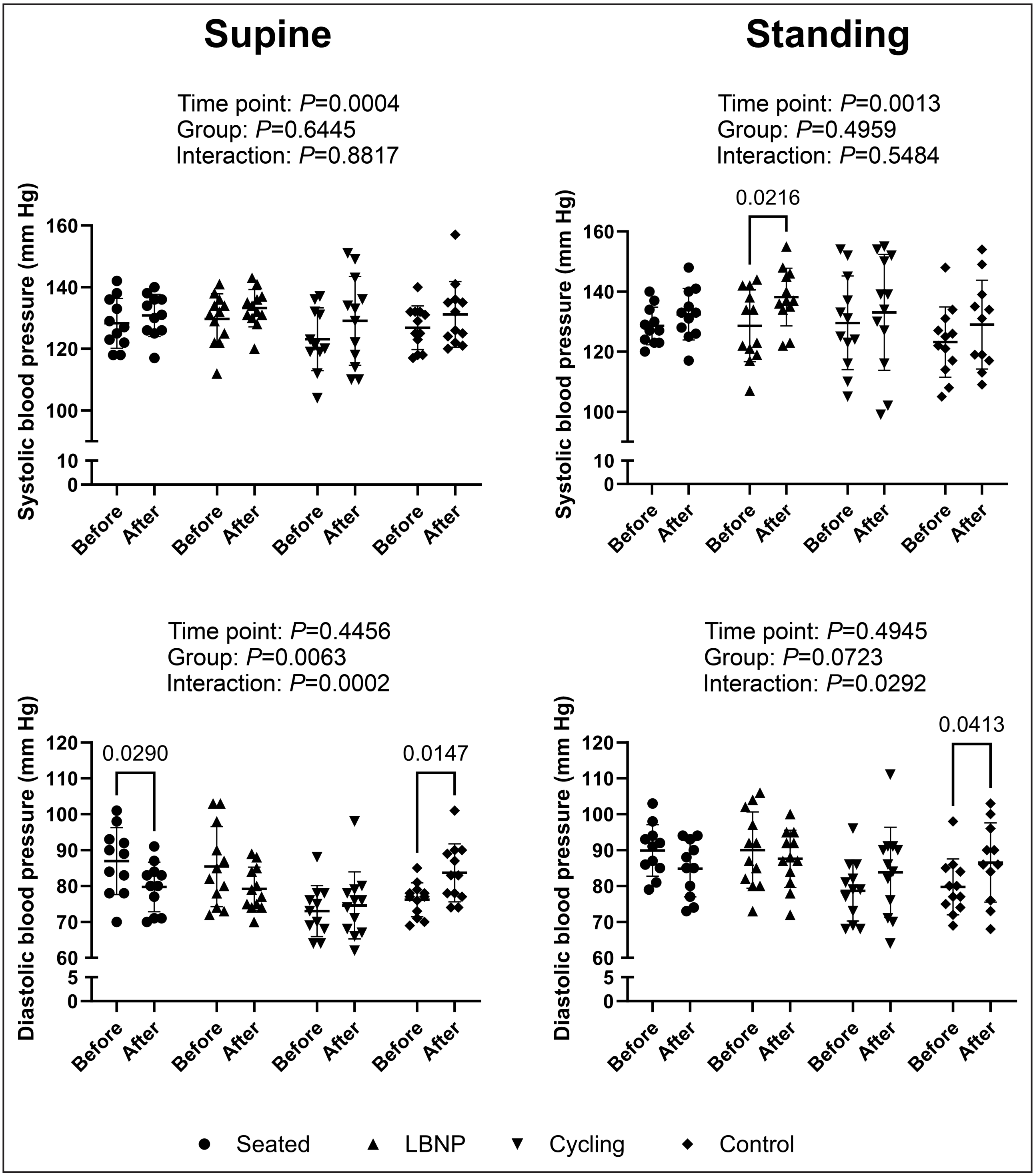

Figure 4. Individual values including mean±SD of systolic and diastolic blood pressure before and after bedrest in supine and standing position including adjusted *P* values.

Upper-arm blood pressure was measured every 2 minutes, resulting in up to 3 measurements at baseline and in the first 5 minutes of standing after an initial hemodynamic stabilization of ≈1 minute. Control indicates no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs 6 days per week; LBNP, lower-body negative pressure for 6 hours per day; and seated, upright seated body position for 6 hours per day.

In fact, 3 to 4 hours of exercise per week suffice to significantly adapt cardiovascular autonomic control.[33] Cycling followed by wearing venous constrictive thigh cuffs was also more effective in maintaining plasma volume compared with daily LBNP or upright sitting. Increases in plasma volume with endurance training

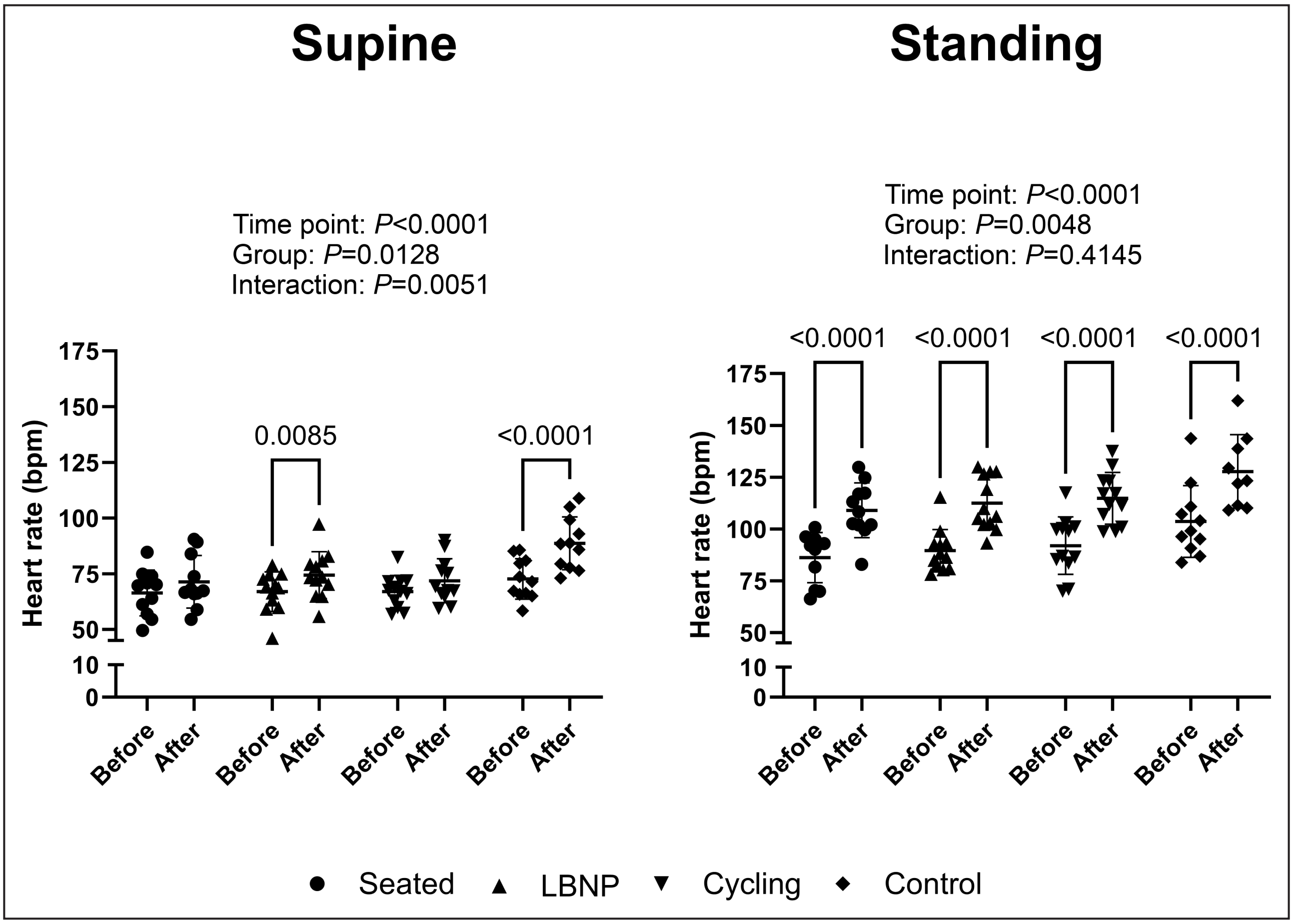

Figure 5. Individual values including mean±SD of heart rate before and after bedrest in supine and standing position as well as adjusted *P* values.

Data were obtained of continuous heart rate recordings via ECG. Data collection of 5 minutes was strived, but respecting hemodynamic instability while standing following bedrest, a minimum of 60 seconds of stable signals were included in the analysis. bpm indicates beats per minute; control, no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs 6 days per week; LBNP, lower-body negative pressure for 6 hours per day; and seated, upright seated body position for 6 hours per day.

have been previously observed[34] and plasma volume is considered a crucial parameter for cardiorespiratory fitness.[35]

Given the importance of cardiovascular autonomic control, plasma volume, and cardiopulmonary fitness in coping with hemodynamic challenges, one might expect the greatest orthostatic intolerance improvement in the exercise and venous constrictive thigh cuffs group. Yet the intervention was ineffective in maintaining orthostatic tolerance. In contrast, LBNP attenuated reductions of orthostatic tolerance despite reductions in plasma volume. Similarly, improvements in orthostatic tolerance with daily short-arm centrifugation during bedrest were not related to changes in plasma volume. Yet acute volume loading and increased sodium ingestion are useful when managing individuals with orthostatic intolerance.[36,37] The discrepancy may suggest that the effect of a change in plasma volume on orthostatic tolerance is confounded by the mechanism eliciting this change. For example, sodium loading and endurance exercise have effects on cardiovascular control independently from plasma volume.[38–40] This interaction could also explain why endurance exercise, while improving plasma volume, may lower orthostatic tolerance.[41] Moreover, plasma volume, autonomic control, and cardiopulmonary fitness alone may not be sufficient to explain variability in deconditioning-induced orthostatic tolerance. For example, we did not assess cardiac structure and function, which could affect orthostatic tolerance.[9] Previous studies suggested that changes in fluid balance may also occur in the heart and affect cardiac muscle mass.[42]

Fluid redistribution during sitting or LBNP may possibly elicit a specific training effect, perhaps on capacitance vessels in the splanchnic circulation or in the legs, which is not produced by exercise followed by wearing venous constrictive thigh cuffs. A similar effect may occur during short-arm centrifugation, which

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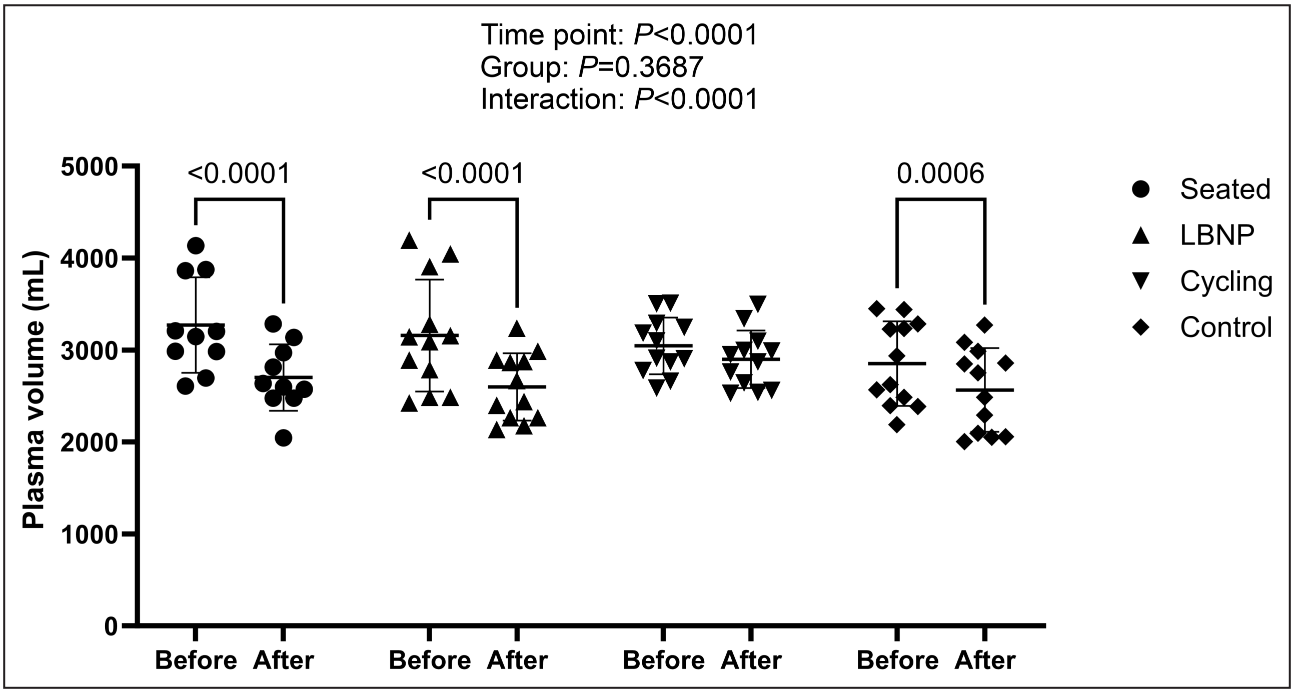

Figure 6. Individual values including mean±SD and adjusted *P*-values of plasma volume, which was measured by CO-rebreathing before and at the end of bedrest.

We observed a reduction of plasma volume following immobilization in all participants, except in the cycling group. Control indicates no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs 6 days per week; LBNP, lower-body negative pressure for 6 hours per day; seated, upright seated body position for 6 hours per day.

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is another potential countermeasure for spaceflight.[43] Indeed, daily artificial gravity training on a short-arm centrifuge attenuated orthostatic intolerance following 60 days of HDTBR.[21] Recent studies also highlighted the potential of a spatial reduction of the cerebral fluid shift by artificial gravity.[44,45]

The major limitation of our study is the relatively small sample size, which is explained by the complexity and costs of bedrest studies, particularly a study with 4 intervention groups. The response to countermeasures could be affected by sex or age, which cannot be discerned in our study. Furthermore, HDTBR may not fully reproduce all cardiovascular responses encountered during real space missions.

Despite these issues, our study supports the use of LBNP during space missions to maintain orthostatic tolerance when landing on Earth or another celestial body. Yet there is still room for improvement, as none of the interventions completely maintained orthostatic tolerance. Furthermore, our results suggest that maintenance of plasma volume during prolonged bedrest is not sufficient to preserve orthostatic tolerance.

Our study encourages further research on combining countermeasures such as centrifugation and targeted exercise, which could improve efficacy and also prove useful for other health challenges such as musculoskeletal deconditioning and spaceflight-associated neuro-ocular syndrome.[46] For example, countermeasures helping to maintain plasma volume may have to be combined with interventions attenuating blood pooling in critical regions involved in hemodynamic regulation, such as the splanchnic tract or the legs. Indeed, an exercise regimen that improved plasma volume and strengthened muscles in areas prone to venous pooling was beneficial in patients with syncope.[47] Equally important is how these countermeasures are best implemented during future space missions. Countermeasures may have to be individualized depending on differences in physiological states between astronauts and intraindividual changes over time. Obviously, relevant, reliable, and easy-to-obtain physiological readouts, perhaps through wearable devices, would be required. Moreover, specific risk mitigations may have to be prioritized depending on the stage of a mission. For example, countermeasures improving orthostatic tolerance may be more important shortly before landing. An important message for people on Earth is that a very sedentary lifestyle, which was modeled by sitting for 6 hours per day in our study, will worsen orthostatic tolerance. However, in bedridden individuals who cannot be fully mobilized, sitting can help to at least partly maintain orthostatic tolerance. Finally, our study suggests that to develop better preventive measures against orthostatic intolerance for people in space and on Earth, deeper mechanistic understanding is required.

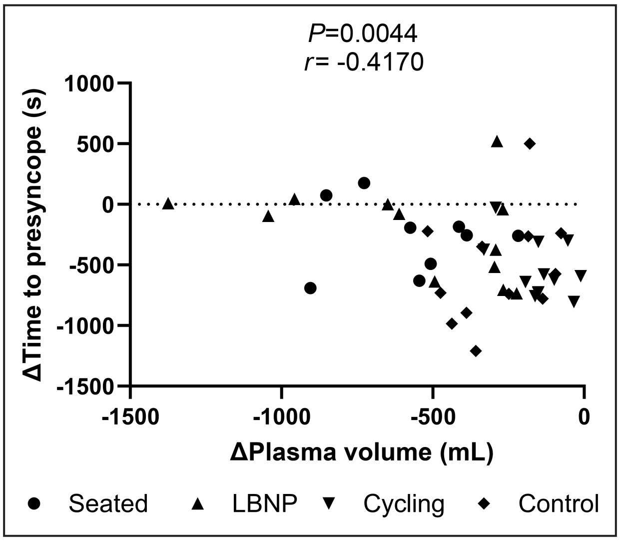

Figure 7. Correlation of changes in plasma volume following bedrest (*x* axis) with differences in time to presyncope (*y* axis) before and after bedrest in a pooled correlation analysis.
Both values were compared by a Spearman regression as changes in plasma volume did not meet criteria for normal distribution in Shapiro–Wilk test (*W*=0.8848, *P*=0.0003). In contrast to previous assumptions, maintenance of plasma volume during bedrest did not lead to preserved orthostatic tolerance. Control indicates no countermeasure; cycling, 1 hour of cycling followed by 6 hours of wearing venous constrictive thigh cuffs 6 days per week; LBNP, lower-body negative pressure for 6 hours per day; and seated, upright seated body position for 6 hours per day.

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Affiliations

Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany (J-N.H., L.d.B., P.G., E.M., S.M., K.H., J.J., J.T.); Faculty of Medicine and University Hospital Cologne, Clinic III for Internal Medicine, University of Cologne, Cologne, Germany (J-N.H., F.H., M.H.); Institute of Medical Biometry, Informatics and Epidemiology (IMBIE), University Hospital Bonn, Bonn, Germany (M-T.S.); KBR, Houston, TX (S.S.L., S.M.L.); NASA Johnson Space Center, Houston, TX (B.R.M.); and Medical Faculty, University of Cologne, Cologne, Germany (J.J.).

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Disclosures

Dr Jordan served as advisor for Theravance, received research support from Boehringer-Ingelheim and Novo-Nordisk, served as lecturer for Menarini Diagnostics and Berlin-Chemie, and is cofounder of Eternygen GmbH. The remaining authors have no disclosures to report.

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