# Dose-Effect Relationship Between Mild Levels of Hypergravity and Autonomic Circulatory Regulation

Kaname Ueda; Yojiro Ogawa; Ryo Yanagida; Ken Aoki; Ken-ichi Iwasaki

**INTRODUCTION:** The dose-effect relationships between different levels of hypergravity ($>$ +1.0 $G_z$) and steady-state hemodynamic parameters have been reported in several studies. However, little has been reported on the dose-effect relationship between hypergravity levels and estimates of autonomic circulatory regulation, such as heart rate variability, arterial pressure variability, and spontaneous cardiac baroreflex sensitivity. We investigated dose-effect relationships between hypergravity levels from +1.0 $G_z$ to +2.0 $G_z$ ($\Delta$0.5 $G_z$) and autonomic circulatory regulation to test our hypothesis that autonomic circulatory regulation has a linear relationship with hypergravity levels.

**METHODS:** Using a short-arm human centrifuge, 10 healthy seated men were subjected to +1.0 $G_z$, +1.5 $G_z$, and +2.0 $G_z$ hypergravity. We evaluated steady-state hemodynamic parameters and autonomic circulatory regulation indices. Heart rate variability, arterial pressure variability, and spontaneous cardiac baroreflex sensitivity between arterial pressure and R-R interval variabilities were assessed by spectral analysis, sequence analysis, and transfer function analysis.

**RESULTS:** Steady-state heart rate, stroke volume, and sequence slope (indicating spontaneous cardiac baroreflex sensitivity in response to rapid changes in arterial pressure) showed linear correlations with increases in gravity (from +1.0 $G_z$ to +2.0 $G_z$). On the other hand, steady-state cardiac output, steady-state systolic arterial pressure, and low-frequency power of diastolic arterial pressure (indicating peripheral vasomotor sympathetic activity) remained unchanged with gravity increases.

**CONCLUSION:** Contrary to our hypothesis, the present study suggested that autonomic circulatory regulations show complex changes with hypergravity levels. Spontaneous cardiac baroreflex sensitivity reduces in a dose-dependent manner from +1.0 $G_z$ to +2.0 $G_z$, whereas peripheral vasomotor sympathetic activity seems to be maintained.

**KEYWORDS:** hypergravity, baroreflex, sequence method, transfer function analysis.

Ueda K, Ogawa Y, Yanagida R, Aoki K, Iwasaki K. *Dose-effect relationship between mild levels of hypergravity and autonomic circulatory regulation.* Aerosp Med Hum Perform. 2015; 86(6):535–540.

Airplane pilots and astronauts are often exposed to hypergravity environments. Some investigators have described the changes in steady-state hemodynamic parameters under hypergravity ($>$ +1.0 $G_z$). Reportedly, steady-state heart rate and steady-state stroke volume correlate linearly with a few levels of hypergravity achieved using a short-arm centrifuge.[14,16,22]

Little has been reported on the relationship between levels of hypergravity and estimates of autonomic circulatory regulation, such as heart rate variability, arterial blood pressure variability, and spontaneous cardiac baroreflex sensitivity. Although our previous report revealed that +1.5 $G_z$ hypergravity using a short-arm centrifuge reduced spontaneous cardiac baroreflex sensitivity and heart rate variability compared with +1.0 $G_z$,[23] it remains unclear whether levels of hypergravity above +1.5 $G_z$ induces further reduction of autonomic circulatory regulation. We investigated the dose-effect relationship between levels of hypergravity from +1.0 $G_z$ to +2.0 $G_z$ ($\Delta$0.5 $G_z$) and autonomic circulatory regulation indices to test our hypothesis that autonomic circulatory regulation has a linear relationship with levels of hypergravity.

From the Division of Anesthesiology, Department of Anesthesiology, and the Division of Hygiene, Department of Social Medicine, Nihon University School of Medicine, Tokyo, Japan.

This manuscript was received for review in September 2014. It was accepted for publication in March 2015.

Address correspondence to: Yojiro Ogawa, D.D.S., Ph.D., Assistant Professor, Division of Hygiene, Department of Social Medicine, Nihon University School of Medicine, Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan; ogawa.yojiro@nihon-u.ac.jp.



DOI: 10.3357/AMHP.4162.2015

## METHODS

### Subjects

The study procedure was approved in advance by the institutional review board of Nihon University School of Medicine (Itabashi-ku, Tokyo, Japan). Each subject provided written informed consent before participation. The procedures adhered to the tenets of the Declaration of Helsinki. All study subjects were screened by a physical examination, including electrocardiography (ECG) and intermittent blood pressure measurements. We investigated 10 healthy normotensive men with a mean age of 23.3 yr (range, 20–28 yr), a mean height of 170.6 cm (range, 159–185 cm), and a mean weight of 64.6 kg (range, 54–71.5 kg). These subjects were a subset of the group previously studied by us during an investigation on spontaneous arterial-cardiac baroreflex levels of hypergravity below +1.5 $G_z$.[23] All subjects fasted for 2 h before the experiments and refrained from heavy exercise and consuming caffeinated or alcoholic beverages for at least 24 h before the experiments. All subjects were familiarized with the measurement techniques and experimental conditions before the study.

### Equipment

Subjects were seated in the cabin of the centrifuge, in an environmentally controlled experimental room, at an ambient temperature of 23–25°C. ECG monitoring (Lifescope BSM-2101; Nihon Kohden, Tokyo, Japan) was applied. A nasal cannula with an infrared $CO_2$ sensor was applied for recording of capnography (OLG-2800; Nihon Kohden). Arterial pressure was continually measured on a beat-to-beat basis in the left radial artery at the heart level using tonometry, and calibrated before each data collection by intermittent blood pressure measured using the oscillometric method with a sphygmomanometer cuff placed over the right brachial artery (Jentow 7700; Colin, Aichi, Japan). Calibration was performed before data collection to avoid potential changes in the sensitivity of the tonometric sensor from movement of the subjects, the passage of time, and hypergravity. Each waveform of continuous arterial pressure, ECG, and capnography was recorded at a sampling rate of 1 kHz using commercial software (Notocord-hem 3.3; Notocord, Paris, France) throughout the experiment.

### Procedure

Centrifugation was performed on 2 d for data collection. All subjects underwent both the +1.0 $G_z$ to +1.5 $G_z$ experiment and +1.0 $G_z$ to +2.0 $G_z$ experiment. At least 7 d were allowed between the two experiments. The +1.0 $G_z$ data were collected twice and the average value of these measurements was recorded as +1.0 $G_z$ data. Details of the use of Nihon University's short-arm human centrifuge (Daiichi Medical, Tokyo, Japan) for this study were previously reported.[4,5] Briefly, the subject was seated in a chair located in the enclosed cabin at a radius of 1.7 m. The chair was in the center of the cabin, facing away from the center of rotation. The cabin was freely movable, with the top tipping toward the center during centrifugation. The resultant vector of gravitational force of the Earth and the force generated by the centrifuge was directed along the longitudinal z-axis (head-to-foot) of the subject's body. A headrest stabilized the subject's head. Centrifuge acceleration and deceleration rates were 0.5 $G \cdot min^{-1}$. We maintained centrifugation at 24.24 rpm (+1.5 $G_z$ at the heart level of the subject) or 30.17 rpm (+2.0 $G_z$ at the heart level of the subject) for 21 min. Baseline +1.0 $G_z$ data were collected for 6 min after 15 min of quiet rest in the centrifuge chair, following which the centrifugation was begun. Data collection at each level of hypergravity (+1.5 $G_z$, +2.0 $G_z$) was performed for 6 min from 15 min after exposure to +1.5 $G_z$ or +2.0 $G_z$ centrifugation (15–21 min of +1.5 $G_z$ or +2.0 $G_z$ hypergravity).

Stroke volume was calculated off-line from the arterial pressure waveform using a Modelflow program incorporated into Beatscope software (TNO-TPD; Biomedical Instrumentation, Amsterdam, Netherlands) in all subjects. The program is based on a three-element model that represents aortic characteristic impedance, arterial compliance, and systemic vascular resistance, describing the relationship between aortic flow and pressure, and computing stroke volume.[22] Steady-state stroke volume was obtained by averaging the 6-min data segment.

Beat-to-beat values of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and R-R interval (RRI) on the ECG were obtained using PC-based Notocord-hem 3.3 software (Notocord). Respiratory rate and partial pressure of end-tidal carbon dioxide ($ETco_2$) were measured from capnography. Steady-state SAP, DAP, heart rate, respiratory rate, and $ETco_2$ were obtained by averaging the 6-min data segment.

Using previously validated algorithms, spontaneous cardiac baroreflex sensitivity was determined from spontaneous changes in beat-to-beat SAP and RRI using sequence analysis[2,13] and transfer function analysis.[12,18,20] In sequence analysis, beat-to-beat time series of three or more consecutive beats with increasing or decreasing SAP and RRI were considered to be spontaneous cardiac baroreflex sequences if the following criteria were met: SAP change of $>$1 mmHg, RRI variation of $>$4 ms, and correlation coefficient for linear regression of an individual sequence of $>$0.80. All regression coefficients of these SAP-RRI sequences at each stage were averaged to calculate the slope, taken as the spontaneous cardiac baroreflex sensitivity at that stage.[2,13]

In spectral and transfer function analysis, the variability of beat-to-beat SAP and RRI were linearly interpolated and resampled at 2 Hz to create an equidistant time series for spectral and transfer function analysis. The time series of beat-to-beat SAP and RRI were first detrended with third-order polynomial fitting and then subdivided into 256-point segments with 50% overlap. This process resulted in five segments of data over the 6 min of data collection. Fast Fourier transforms were implemented with each Hanning-windowed data segment and then averaged to calculate the autospectra of SAP and RRI variability (**Fig. 1**). Low-frequency powers of SAP and RRI variability in the range of 0.05–0.15 Hz and high-frequency powers in the range of 0.15–0.50 Hz were calculated from the integrated autospectra.[8,12,20] Also, for estimation of peripheral vasomotor sympathetic activity, low-frequency powers of DAP variability in the range of 0.05–0.15 Hz were calculated from the integrated autospectra.[11,19] From the cross spectrum between SAP

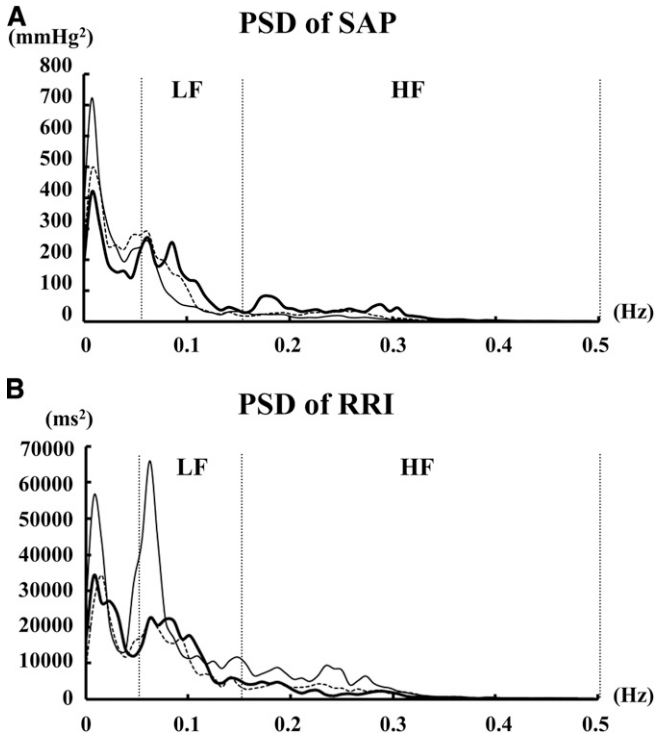


**Fig. 1.** Group averaged power spectral density (PSD) for 10 seated men undergoing 21 min each of +1.0, +1.5, and +2.0 $G_z$. A) PSD of systolic arterial pressure (SAP); B) PSD of R-R interval (RRI). +1.0 $G_z$, thin line; +1.5 $G_z$, dotted line; +2.0 $G_z$, bold line.

variability and R-R variability, transfer function gain, phase, and coherence (**Fig. 2**) were estimated as mean values in the frequency ranges of 0.05–0.15 and 0.15–0.35 Hz for low- and high-frequency powers, respectively.[17,18,23] Assumption of linearity and reliability of transfer function estimation was evaluated by coherence of >0.5. We used transfer function gain between SAP and RRI variability to reflect changes in beat-to-beat RRI in response to changes in beat-to-beat SAP mediated by spontaneous cardiac baroreflex sensitivity, whereas the time relationship between these two variables was reflected using the estimated phase. Data were analyzed using PC-based software (DADiSP; DSP Development, Newton, MA).

### Statistical Analysis

The variables were compared using one-way repeated-measures ANOVA (between +1.0 $G_z$, +1.5 $G_z$, and +2.0 $G_z$). When the normality test failed, a logarithmic transformation was performed before an ANOVA was calculated. To determine where significant differences occurred, the Student Newman-Keuls post hoc test was used for all pair-wise comparisons. A $P$-value of $< 0.05$ was considered statistically significant. Analyses were performed using PC-based software (SigmaStat; Systat Software, Inc., San Jose, CA). Data are presented as mean ± SD.

## RESULTS

The average values (± SD) of steady-state hemodynamics and respiratory conditions at each level of hypergravity are

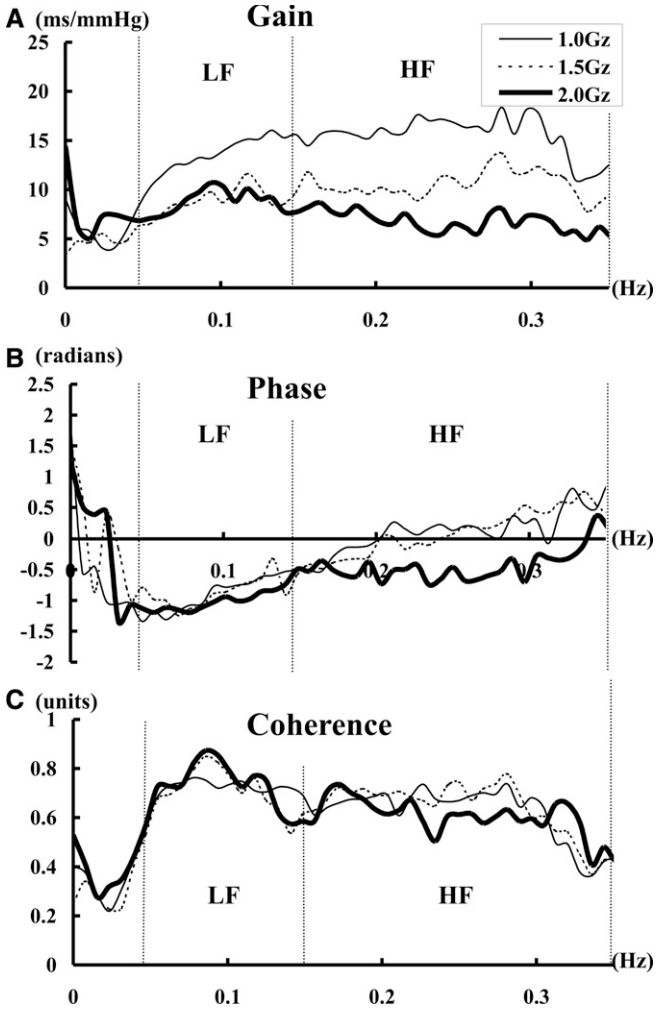


**Fig. 2.** Transfer function gain, phase, and coherence between systolic arterial pressure and R-R interval for 10 seated men undergoing 21 min each of +1.0, +1.5, and +2.0 $G_z$. A) Transfer function gain; B) phase; C) coherence. LF, low-frequency range; HF, high-frequency range; +1.0 $G_z$, thin line; +1.5 $G_z$, dotted line; +2.0 $G_z$, bold line.

presented in **Table I**. Steady-state heart rate linearly increased from +1.0 $G_z$ to +2.0 $G_z$ [$F(2,18) = 27.5$, $P < 0.001$], showing significant differences among the groups (+1.0 $G_z$ to +1.5 $G_z$: +8%, +1.5 $G_z$ to +2.0 $G_z$: +13%) (**Fig. 3**). Steady-state stroke volume linearly decreased from +1.0 $G_z$ to +2.0 $G_z$ [$F(2,18) = 14.5$, $P < 0.001$] and showed significant differences among the groups (+1.0 $G_z$ to +1.5 $G_z$: −11%, +1.5 $G_z$ to +2.0 $G_z$: −16%) (Fig. 3). Steady-state cardiac output and steady-state SAP did not change significantly under all conditions. Steady-state DAP did not change significantly from +1.0 $G_z$ to +1.5 $G_z$, but significantly increased from +1.5 $G_z$ to +2.0 $G_z$ (+20%) [$F(2,18) = 5.09$, $P = 0.018$]. Although respiratory rate did not change significantly from +1.0 $G_z$ to +2.0 $G_z$, $ETCO_2$ linearly decreased from +1.0 $G_z$ to +2.0 $G_z$ [$F(2,18) = 26.74$, $P < 0.001$], with significant intergroup differences (+1.0 $G_z$ to +1.5 $G_z$: −10%, +1.5 $G_z$ to +2.0 $G_z$: −9%).

The indices of heart rate variability and arterial blood pressure variability at each level of gravity tested are presented in **Table II**. While the low-frequency power of SAP variability

**Table I.** Steady-State Hemodynamics and Respiratory Conditions at the Different Levels of Gravity.

| | +1.0 $G_z$ | +1.5 $G_z$ | +2.0 $G_z$ |
|---|---|---|---|
| Heart rate (bpm) | 63.8 ± 5.9 | 68.7 ± 8.5* | 77.8 ± 10.0*† |
| Stroke volume (ml) | 81.1 ± 12.0 | 72.4 ± 14.6* | 61.0 ± 11.6*† |
| Cardiac output ($L \cdot min^{-1}$) | 5.14 ± 0.72 | 4.93 ± 0.98 | 4.69 ± 0.79 |
| Systolic arterial pressure (mmHg) | 115.5 ± 4.1 | 116.7 ± 11.3 | 117.6 ± 19.1 |
| Diastolic arterial pressure (mmHg) | 57.4 ± 3.7 | 57.8 ± 11.0 | 69.6 ± 11.6*† |
| Respiratory rate (breaths/min) | 14.0 ± 3.8 | 15.4 ± 1.9 | 16.3 ± 3.9 |
| $ET_{CO_2}$ (mmHg) | 40.0 ± 3.5 | 35.9 ± 2.9* | 32.6 ± 2.2*† |

Values are expressed as means ± SD. $ET_{CO_2}$, end-tidal carbon dioxide pressure.
* $P < 0.05$ versus +1.0 $G_z$, † $P < 0.05$ versus +1.5 $G_z$.

**Table II.** Indices of Heart Rate Variability and Arterial Blood Pressure Variability at the Different Levels of Gravity.

| | +1.0 $G_z$ | +1.5 $G_z$ | +2.0 $G_z$ |
|---|---|---|---|
| $LF_{SAP}$ ($mmHg^2$) | 11.1 ± 8.35 | 14.3 ± 10.7 | 17.8 ± 12.6 |
| $HF_{SAP}$ ($mmHg^2$) | 2.81 ± 1.64 | 4.34 ± 2.79 | 7.80 ± 8.24 |
| $LF_{DAP}$ ($mmHg^2$) | 9.25 ± 7.61 | 9.79 ± 8.50 | 8.28 ± 5.98 |
| $LF_{RR}$ ($ms^2$) | 2391 ± 2715 | 1316 ± 905 | 1640 ± 1843 |
| $HF_{RR}$ ($ms^2$) | 1043 ± 828 | 524 ± 520* | 457 ± 513* |

Values are expressed as means ± SD.
$LF_{SAP}$ and $HF_{SAP}$, power in low- and high-frequency range of systolic arterial pressure (SAP) variability, respectively; $LF_{DAP}$, power in low-frequency range of diastolic arterial pressure (DAP) variability; $LF_{RR}$ and $HF_{RR}$, power in low- and high-frequency of R-R interval (RRI) variability, respectively.
* $P < 0.05$ versus +1.0 $G_z$.

did not change significantly under all conditions, the high-frequency power of SAP variability tended to increase linearly from +1.0 $G_z$ to +2.0 $G_z$ [$F(2,18) = 3.37$, $P = 0.057$]. The low-frequency powers of DAP variability ($LF_{DAP}$) did not change significantly under all conditions. Further, the low-frequency power of RRI variability did not change significantly under all conditions. The high-frequency power of RRI variability ($HF_{RR}$) decreased significantly at +1.5 $G_z$ (−50%) and +2.0 $G_z$ (−66%) compared with +1.0 $G_z$ [$F(2,18) = 9.10$, $P = 0.002$], although the differences between the values at +1.5 $G_z$ and +2.0 $G_z$ were not significant (**Fig. 4**).

The indices of spontaneous cardiac baroreflex sensitivity at each level of gravity are presented in **Table III**. Sequence slope linearly decreased from +1.0 $G_z$ to +2.0 $G_z$ [$F(2,18) = 22.34$, $P < 0.001$], showing significant intergroup differences (+1.0 $G_z$ to +1.5 $G_z$: −34%, +1.5 $G_z$ to +2.0 $G_z$: −32%) (Fig. 3). Low-frequency transfer function gain (GainLF) decreased significantly at +1.5 $G_z$ (−32%) and +2.0 $G_z$ (−32%) compared with +1.0 $G_z$ [$F(2,18) = 7.00$, $P = 0.006$], although there was no significant difference between the levels at +1.5 $G_z$ and +2.0 $G_z$ (Fig. 4). High-frequency transfer function gain (GainHF) decreased significantly at +1.5 $G_z$ (−45%) and +2.0 $G_z$ (−57%) compared with +1.0 $G_z$ [$F(2,18) = 20.30$, $P < 0.001$]. Coherence function in the low- and high-frequency ranges was above 0.5 at all stages. Phase in these ranges did not change significantly, except for changes at high frequency between +1.0 $G_z$ and +2.0 $G_z$.

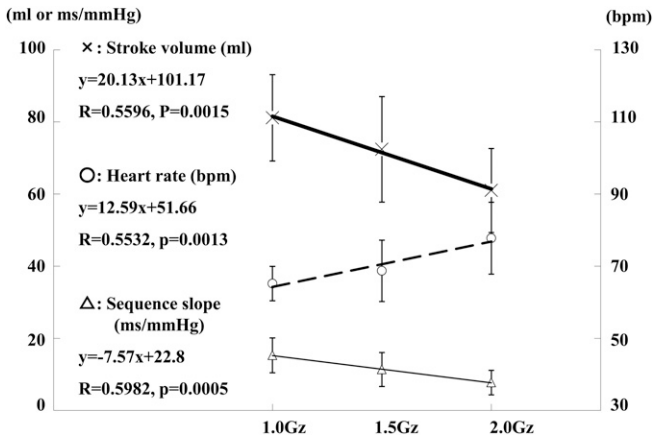


**Fig. 3.** Linear change of stroke volume (bold line), heart rate (dashed line), and sequence slope (thin line) for 10 seated men undergoing 21 min each of +1.0, +1.5, and +2.0 $G_z$. R, Pearson's correlation coefficient.

## DISCUSSION

The present study demonstrated linear hypergravity-induced changes in steady-state heart rate, stroke volume, and sequence slope (Fig. 3). GainLF and $HF_{RR}$ decreased at +1.5 $G_z$, remaining at the reduced levels at +2.0 $G_z$ (Fig. 4). On the other hand, steady-state SAP, steady-state cardiac output, and $LF_{DAP}$ remained unchanged with increases in gravity. Thus, each circulatory index showed different changes in response to increases in gravity.

The relationships between levels of hypergravity and steady-state parameters, such as blood pressure, heart rate, stroke volume, and cardiac output, have been previously described.[14,16,21] Previous studies showed a significant linear reduction in stroke volume during exposure to +1.0 $G_z$ to +3.0 $G_z$ hypergravity,[14,16] which are consistent with our results. During hypergravity, a shift in blood volume from the central compartment to the legs may cause reduction in central blood volume and a decrease in stroke volume.[1,17] The linear increase in steady-state heart rate with hypergravity from +1.0 $G_z$ to +2.0 $G_z$ in our study is also consistent with the results of previous experiments.[14,21] This increase in steady-state heart rate may compensate for the decreases in stroke volume caused by hypergravity, resulting in maintenance of steady-state cardiac output even when hypergravity is increased to +2.0 $G_z$. Also, $LF_{DAP}$ provides indirect evidence of sympathetic drive, which is closely related to low-frequency fluctuations in muscle sympathetic nerve activity.[11,19] Muscle sympathetic nerve activity plays important roles in the regulation of hemodynamic homeostasis against $+G_z$.[7] In the present study, $LF_{DAP}$ did not change significantly under any of the study conditions, implying persistence of peripheral vasomotor sympathetic activity during hypergravity. The increased steady-state heart rate and persistent peripheral vasomotor sympathetic activity would also likely lead to maintenance of steady-state SAP.

In our study, the indices of autonomic circulatory regulation showed complex changes with hypergravity from +1.0 $G_z$ to +2.0 $G_z$ (Δ0.5 $G_z$). Sequence slopes linearly decreased with increases in gravity from +1.0 $G_z$ to +2.0 $G_z$. Sequence analysis is based on the identification of three or more consecutive beats in which progressive increases/decreases in SAP are followed by progressive lengthening/shortening of RRI.[2,9,13] The sequence of three consecutive beats mainly reflects

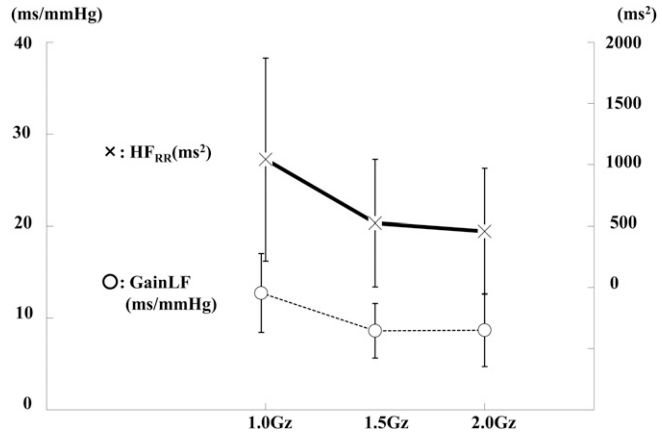


**Fig. 4.** High frequency spectral power (bold line) and low frequency gain between systolic blood pressure and RR interval (thin line) for 10 seated men undergoing 21 min each of +1.0, +1.5, and +2.0 $G_z$.

transmission from SAP oscillation to RRI oscillation via the parasympathetic pathway, because the parasympathetic nerve is associated with fast neurotransmission influences.[15] Moreover, the sequence slope correlates more with GainHF.[6,17] In the present study, sequence slope and GainHF seemed to change similarly, although GainHF was not significantly different at +1.5 $G_z$ and +2.0 $G_z$ (Fig. 2A). Therefore, we believe that spontaneous cardiac baroreflex sensitivity in response to rapid changes in arterial pressure could reduce in a dose-dependent manner from +1.0 $G_z$ to +2.0 $G_z$, as hypothesized.

On the other hand, GainLF and $HF_{RR}$ decreased at +1.5 $G_z$ and remained at the same level at +2.0 $G_z$. These results at 1.5 $G_z$ were consistent with those of our previous study.[23] In general, these indices indicate spontaneous cardiac baroreflex sensitivity in response to slow changes in arterial pressure and cardiac parasympathetic activity, respectively.[12,17,23] It is, therefore, possible that a few indices of autonomic circulatory regulation may reflect a regulatory mechanism that is saturated. However, the present study assessed only three levels of gravity (+1.0 $G_z$, +1.5 $G_z$, and +2.0 $G_z$); hence, further studies above +2.0 $G_z$ hypergravity are warranted, which could demonstrate that the relationship between these indices and levels of hypergravity show an S-shaped or U-shaped curve.

**TABLE III.** Indices of Spontaneous Cardiac Baroreflex Sensitivity at the Different Levels of Gravity.

| | +1.0 $G_z$ | +1.5 $G_z$ | +2.0 $G_z$ |
|---|---|---|---|
| Sequence slope (ms/mmHg) | 17.2 ± 6.3 | 11.3 ± 4.7* | 7.7 ± 3.4*# |
| GainLF (ms/mmHg) | 12.7 ± 4.3 | 8.6 ± 3.0* | 8.7 ± 4.0* |
| GainHF (ms/mmHg) | 16.1 ± 7.6 | 8.9 ± 4.4* | 6.9 ± 4.0* |
| CohLF (unit) | 0.71 ± 0.08 | 0.67 ± 0.10 | 0.72 ± 0.08 |
| CohHF (unit) | 0.63 ± 0.14 | 0.62 ± 0.14 | 0.62 ± 0.11 |
| PhaseLF (radians) | -0.92 ± 0.23 | -0.90 ± 0.20 | -1.01 ± 0.36 |
| PhaseHF (radians) | 0.14 ± 0.18 | 0.11 ± 0.34 | -0.39 ± 0.58 |

Values are expressed as means ± SD.
Sequence slope, regression coefficient between SAP and RRI by the sequence method; GainLF and GainHF, low- and high-frequency transfer function gain between SAP and RRI; CohLF and CohHF, low- and high-frequency coherence function between SAP and RRI; PhaseLF and PhaseHF, low- and high-Frequency phase between SAP and RRI.
* $P < 0.05$ versus +1.0 $G_z$, # $P < 0.05$ versus +1.5 $G_z$.

In this study, each circulatory index showed different changes in response to increases in gravity, although these changes (sequence slope, GainHF, GainLF, and $HF_{RR}$) at 1.5 $G_z$ were consistent with those observed in our previous study.[23] Also, hypergravity might increase peripheral blood volume, activating positive feedback reflexes from vascular sympathetic afferents, thereby inducing a reduction in baroreflex gain.[10] Moreover, cardiopulmonary receptor deactivation by central hypovolemia due to hypergravity not only stimulates vascular sympathetic efferents, but also possibly interacts with cardiac baroreflex sensitivity. In the present study, hypergravity from +1.0 $G_z$ to +2.0 $G_z$ led to a decrease in stroke volume, maintenance of peripheral vasomotor sympathetic activity, and reduction of cardiac baroreflex sensitivity due to interactions with cardiopulmonary baroreflexes.

The unchanged respiratory rate and linear decrease in $ETCO_2$ with hypergravity from +1.0 $G_z$ to +2.0 $G_z$ observed in this study are also consistent with the results of previous experiments.[3,5,16] The gravity-induced ventilation-perfusion mismatch, increased tidal volume, and increased functional residual capacity would contribute to hypocapnia in the sitting position with hypergravity.[3,5]

One of the major limitations of the present study is that we could not distinguish between the influence of rotation per se and the effect of hypergravity on hemodynamic and autonomic regulatory parameters. The centrifuge equipment used in the present study rotates a gondola-type cabin to generate artificial gravity. Although the rate of rotation was constant during data measurement of mild hypergravity and no subjects complained of any adverse symptoms such as dizziness and nausea, the possibility that vestibular stimulation may affect the autonomic nervous system and spontaneous cardiac baroreflex sensitivity through vestibulo-autonomic reflexes cannot be ruled out. Moreover, a few indices only showed tendencies of linear changes with levels of hypergravity. This could have been because of the small sample size in this study, which could lead to a type II error.

In conclusion, the present study investigated the dose-effect relationships between steady-state hemodynamics, autonomic circulatory regulation, and levels of hypergravity from +1.0 $G_z$ to +2.0 $G_z$ ($\Delta$0.5 $G_z$). Contrary to our hypothesis, circulation can be regulated intricately via the autonomic nervous system even under hypergravity (+1.0 $G_z$ to +2.0 $G_z$). While spontaneous cardiac baroreflex sensitivity probably reduces in a dose-dependent manner from +1.0 $G_z$ to +2.0 $G_z$, peripheral vasomotor sympathetic activity seems to be maintained at the same level.

## ACKNOWLEDGMENTS

This study was supported by The Uehara Memorial Foundation. We thank Drs. T. Suzuki and J. Kato for their important support during the project.

*Authors and affiliations:* Kaname Ueda, M.D., Department of Anesthesiology, Division of Anesthesiology, and Yojira Ogawa, D.D.S., Ph.D., Ryo Yanagida, M.D., Ken Aoki, Ph.D., and Ken-ichi Iwasaki, M.D., Ph.D., Department of Social Medicine, Division of Hygiene, Nihon University School of Medicine, Tokyo, Japan.

## REFERENCES


1. Bailliart O, Capderou A, Cholley BP, Kays C, Riviere D, et al. Changes in lower limb volume in humans during parabolic flight. J Appl Physiol (1985). 1998; 85(5):2100–2105.
2. Bertinieri G, Di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, et al. Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats. Am J Physiol. 1988; 254(2, Pt. 2):H377–H383.
3. Gisolf J, Wilders R, Immink RV, van Lieshout JJ, Karemaker JM. Tidal volume, cardiac output and functional residual capacity determine end-tidal $CO_2$ transient during standing up in humans. J Physiol. 2004; 554(Pt. 2):579–590.
4. Iwasaki K, Hirayanagi KI, Sasaki T, Kinoue T, Ito M, et al. Effects of repeated long duration +2 Gz load on man's cardiovascular function. Acta Astronaut. 1998; 42(1-8):175–183.
5. Iwasaki K, Ogawa Y, Aoki K, Yanagida R. Cerebral circulation during mild +Gz hypergravity by short-arm human centrifuge. J Appl Physiol (1985). 2012; 112(2):266–271.
6. Laude D, Elghozi JL, Girard A, Bellard E, Bouhadd M, et al. Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study). Am J Physiol Regul Integr Comp Physiol. 2004; 286(1):R226–R231.
7. Mano T. Autonomic neural functions in space. Curr Pharm Biotechnol. 2005; 6(4):319–324.
8. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation. 1994; 90(4):1826–1831.
9. Nagasaki G, Tanaka M, Nishikawa T. The recovery profile of baroreflex control of heart rate after isoflurane or sevoflurane anesthesia in humans. Anesth Analg. 2001; 93(5):1127–1131.
10. Pagani M, Pizzinelli P, Bergamaschi M, Malliani A. A positive feedback sympathetic pressor reflex during stretch of the thoracic aorta in conscious dogs. Circ Res. 1982; 50(1):125–132.
11. Pagani M, Montano N, Porta A, Malliani A, Abboud FM, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation. 1997; 95(6):1441–1448.
12. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension. 1995; 25(6):1276–1286.
13. Parlow J, Viale JP, Anna G, Hughson R, Quintin L. Spontaneous cardiac baroreflex in humans. Comparison with drug-induced responses. Hypertension. 1995; 25(5):1058–1068.
14. Pendergast DR, Olszowka A, Farhi LE. Cardiovascular and pulmonary responses to increased acceleration forces during rest and exercise. Aviat Space Environ Med. 2012; 83(5):488–495.
15. Persson PB, DiRienzo M, Castiglioni P, Cerutti C, Pagani M, et al. Time versus frequency domain techniques for assessing baroreflex sensitivity. J Hypertens. 2001; 19(10):1699–1705.
16. Rohdin M, Sundblad P, Linnarsson D. Effects of hypergravity on the distributions of lung ventilation and perfusion in sitting humans assessed with a simple two-step maneuver. J Appl Physiol (1985). 2004; 96(4): 1470–1477.
17. Saitoh T, Ogawa Y, Aoki K, Shibata S, Otsubo A, et al. Bell-shaped relationship between central blood volume and spontaneous baroreflex function. Auton Neurosci. 2008; 143(1-2):46–52.
18. Saul JP, Berger RD, Albrech P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol. 1991; 261(4, Pt. 2):H1231–H1245.
19. Sundlöf G, Wallin BG. The variability of muscle nerve sympathetic activity in resting recumbent man. J Physiol. 1977; 272(2):383–397.
20. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93(5):1043–1065.
21. Vettes B, Vieillefond H, Auffret R. Cardiovascular responses of man exposed to +Gz accelerations in a centrifuge. Aviat Space Environ Med. 1980; 51(4):375–378.
22. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol (1985). 1993; 74(5):2566–2573.
23. Yanagida R, Ogawa Y, Aoki K, Ueda K, Iwasaki K. Sustained mild hypergravity reduces spontaneous cardiac baroreflex sensitivity. Auton Neurosci. 2014; 185:123–128.