

Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration

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Iwasaki, Ken-ichi, Rong Zhang, Merja A. Perhonen, Julie H. Zuckerman, and Benjamin D. Levine. Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration. *Am J Physiol Regul Integr Comp Physiol* 287: R1256–R1262, 2004. First published July 8, 2004; doi:10.1152/ajpregu.00613.2002.—Adaptation to spaceflight or head-down-tilt bed rest leads to hypovolemia and an apparent abnormality of baroreflex regulation of cardiac period. In a previous study, we demonstrated that both chronic (2 wk) head-down-tilt bed rest and acute induced hypovolemia led to similar impairments in spontaneous baroreflex control of cardiac period, suggesting that a reduction in plasma volume may be responsible for this abnormality after bed rest. Therefore we hypothesized that this reduced “baroreflex function” could be restored by intravenous volume infusion equivalent to the reduction in plasma volume after bed rest. Six healthy subjects underwent 2 wk of -6° head-down bed rest. Beat-by-beat arterial blood pressure and ECG were recorded during 6 min of spontaneous respiration and fixed-rate breathing (0.2 Hz), and transfer function analysis between systolic blood pressure and R-R interval was performed. Plasma volume was measured with Evans blue dye, and cardiac filling pressures were directly measured (Swan-Ganz catheter). After bed rest, studies were repeated before and after plasma volume restoration, with which both plasma volume and left ventricular end-diastolic pressure were restored to pre-bed rest levels by intravenous dextran₄₀ infusion (288 ± 31 ml). Transfer function gain in the high-frequency range, used as an index of vagally mediated arterial-cardiac baroreflex function, decreased significantly (13.4 ± 3.1 to 8.1 ± 2.9 ms/mmHg, $P < 0.05$) after bed rest. However, reduced transfer function gain was normalized to the pre-bed rest level (12.2 ± 3.6 ms/mmHg) after precise plasma volume restoration. This result confirms that reductions in plasma volume, rather than a unique autonomic nervous system adaptation to bed rest, are largely responsible for the observed changes in spontaneous arterial-cardiac baroreflex function after bed rest.

spectral analysis; hypovolemia; microgravity; dextran infusion

SPACEFLIGHT or simulated microgravity (head-down-tilt bed rest) leads to a reduction in plasma volume (2, 3, 6, 9, 14, 17) and apparent changes in baroreflex function (6–10, 12–17, 24, 29). Despite extensive study of cardiovascular reflex control after spaceflight or bed rest, it is unclear whether the observed changes in baroreflex function after bed rest are due to hypovolemia alone or represent a unique adaptation of the autonomic nervous system to bed rest deconditioning. In a previous study (17), we demonstrated in the same subjects that both

chronic (2 wk) head-down-tilt bed rest and acute hypovolemia matched for loss of plasma volume led to similar reductions in transfer function gain between blood pressure and R-R interval. This similarity of the response under both conditions in the same subjects suggested, but did not prove, that a reduction in plasma volume may be largely responsible for the abnormality of baroreflex regulation of cardiac period after bed rest. In the present study, we hypothesized that this reduced spontaneous baroreflex sensitivity after bed rest could be normalized to the pre-bed rest level by precise plasma volume restoration with intravenous volume infusion. To test this hypothesis directly, we quantified dynamic baroreflex sensitivity by using transfer function analysis between spontaneous changes in arterial pressure and R-R interval before and after 2 wk of head-down-tilt bed rest and after precise plasma volume restoration by dextran infusion, which normalized both plasma volume and cardiac filling pressures.

METHODS

Subjects. Five healthy men and one woman with a mean age of 38 (SD 8) yr (range: 28–49 yr), height of 181 (SD 4) cm, and body weight of 80 (SD 15) kg were studied. No subject smoked, used recreational drugs, or had significant chronic medical problems. No subject was an endurance-trained athlete, and subjects were excluded if they exercised for >30 min/day, more than three times per week, with either dynamic or static exercise. Subjects were screened with a careful history and physical examination including ECG and echocardiogram. All subjects signed an informed consent approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

Experimental protocol. All experiments were performed in the supine position, in the morning, at least 2 h after a light breakfast and more than 12 h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory with an ambient temperature of 25°C . A 6-F balloon-tipped, flow-directed pulmonary arterial catheter (Edwards Swan-Ganz, Baxter) was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. With the balloon inflated, the catheter was advanced into the pulmonary capillary wedge position, which was confirmed fluoroscopically and by the presence of characteristic pressure waveforms. Right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) were referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero reading set at 5 cm below the sternal angle in the supine position. The pressure waveform was amplified (Hewlett-Packard 78534A and Astromed ASC909) and displayed on a strip-chart recorder

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(Astromed MT 95000) with 0.5-mmHg resolution. The mean PCWP was determined at end expiration.

An analog ECG was obtained from a CM₅ lead, and beat-by-beat arterial blood pressure was obtained at the finger by photoplethysmography using the Penaz principle (Finapres, Ohmeda). Intermittent blood pressure was measured in the arm by electrophygmomanometry (Suntech) with a microphone placed over the brachial artery and the detection of Korotkoff sounds gated to the ECG. Cardiac output was measured with a modification of the foreign gas rebreathing method using acetylene as the soluble and helium as the insoluble gas (25, 33). Resting stroke volume was then calculated from heart rate measured via ECG at the same time.

After establishment of quiet, resting, hemodynamic steady state (usually ~30 min of repeated measurements until sequential cardiac output measurements within 500 ml), arterial blood pressure and ECG were recorded during 6 min of spontaneous respiration. After spontaneous respiration, the subjects were asked to control their respiratory frequency at a fixed rate of 12/min (0.20 Hz) by following a controlled breath graph on a laptop computer mounted above the subject's face. After a 2-min adjustment period of breathing control, 6 min of data were recorded again. The data from the fixed-breathing protocol were used to concentrate the spectral input around the respiratory rate for the spectral analysis and to verify the results of transfer function analysis during the spontaneous breathing protocol. After this data collection period, plasma volume was measured using the Evans blue dye technique (11).

Head-down-tilt bed rest (simulated microgravity). After the initial baseline experiments (pre-bed rest experiments), the subjects were placed at complete bed rest with -6° head-down tilt. Subjects were allowed to elevate up on one elbow for meals but otherwise were restricted to the head-down position at all times. Subjects were given a standard diet 3 days before each testing session both before and after bed rest, consisting of fixed calorie and sodium contents (2,500 kcal, 3.5 g). Fluids were allowed ad libitum, but all fluid intake and urine output were carefully recorded. The same experiments (post-bed rest experiments) were repeated after 2 wk of head-down-tilt bed rest.

Volume restoration. After post-bed rest experiments, both plasma volume and left ventricular end-diastolic pressure were restored to pre-bed rest levels by dextran₄₀ infusion as follows. First, the exact amount of plasma lost during bed rest was quantified by Evans blue dye. This volume was infused rapidly (~1,000 ml/h) and then allowed to equilibrate for 30 min. If PCWP was still below baseline pre-bed rest values, additional dextran was infused in 100- to 250-ml increments until baseline PCWP was achieved. Hemodynamic measurements (cardiac output, stroke volume, heart rate, blood pressure) were initiated 30 min after completion of the last dextran infusion and repeated until stable as described above, which generally required an additional 30 min. Data collection periods for spontaneous and controlled breathing were then repeated, ~1 h after completion of dextran infusion.

Spectral and transfer function analysis. The analog ECG and arterial pressure were analyzed as previously reported (17). High-frequency power of R-R interval and SBP in the range of 0.15–0.25 Hz and low-frequency power in the range of 0.05–0.15 Hz were calculated from the integration of the autospectra during the fixed breathing protocol. These values were also divided by the total spectral power to minimize the effect of the changes in total power on the values of low- and high-frequency components. This approach derives normalized spectral indexes. This data-acquisition and processing strategy conforms to recommendations of international consensus panels for the assessment of cardiovascular variability (30).

The transfer function gain, phase, and coherence (the squared coherence function) between SBP and R-R interval (or heart rate) were estimated using the cross-spectral method (9, 17, 22, 27, 28) (Fig. 1). Transfer function gain, phase, and coherence between SBP variability and R-R interval (or heart rate) variability were estimated as mean values in the high-frequency range (0.15–0.35 Hz for the data

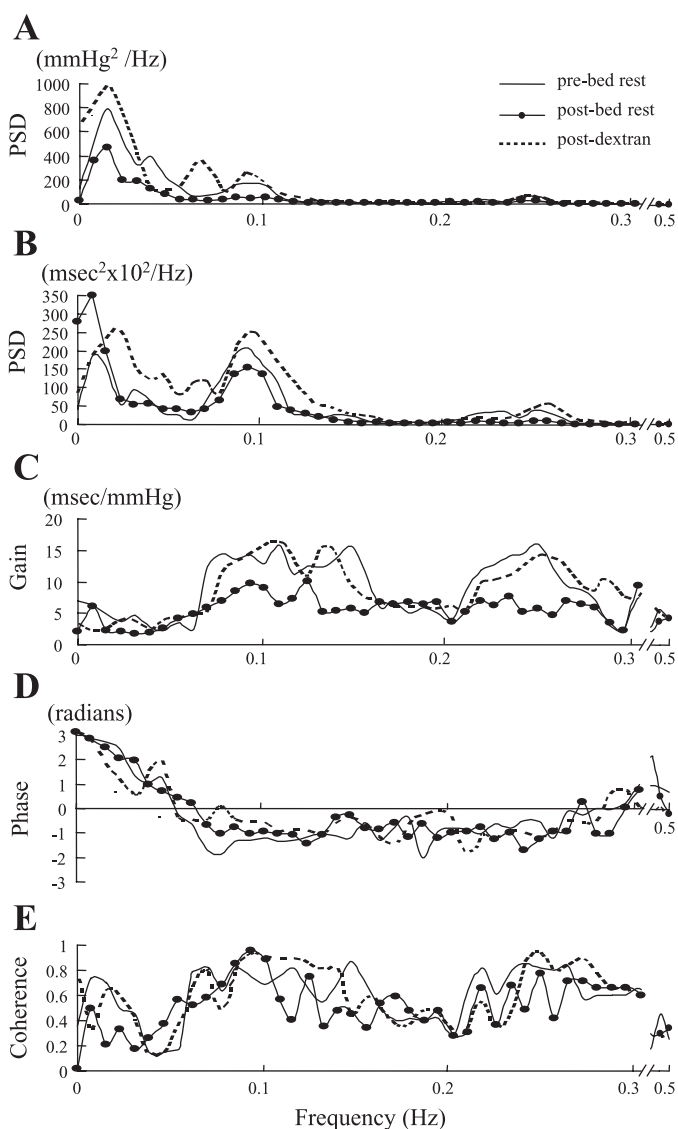


Fig. 1. Representative frequency-domain analysis of changes in R-R interval and systolic blood pressure in a subject before head-down-tilt bed rest, after head-down-tilt bed rest, and after dextran infusion. *A*: power spectral density (PSD) of systolic blood pressure. *B*: power spectral density of R-R interval. *C*: transfer-function gain between systolic blood pressure and R-R interval. *D*: phase relationship between systolic blood pressure and R-R interval. *E*: coherence function.

from the spontaneous breathing protocol; 0.15–0.25 Hz for the data from the fixed breathing protocol) and in the low-frequency range (0.05–0.15 Hz). These frequency ranges were chosen because of the high coherence function. The transfer function gain between rhythmic changes in the SBP and R-R interval was used to reflect baroreflex function, while the estimated phase was used to reflect the temporal relationship between these two variables (9, 28). The assumption of linearity and reliability of the transfer function estimation was evaluated by the coherence, which ranges between 0 and 1.

In addition, the calculated gain for heart rate (in $\text{beats} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$) was multiplied by the resting stroke volume to determine the effective change in systemic flow (i.e., cardiac output) induced by baroreflex-mediated changes in heart rate, or the “effective gain” of the baroreflex regulation of heart rate (18).

The range of baroreflex stimuli and baroreflex response. The global range of the baroreflex stimulus was estimated by the range in SBP

variation and the SD of SBP variation. The global range of baroreflex response was estimated by the range in R-R interval and SD of R-R interval variation.

Statistical analysis. Variables were compared using one-way repeated-measures ANOVA with time (pre-bed rest, post-bed rest, and post-dextran), in conjunction with the Dunnett post hoc test for comparisons with pre-bed rest values. A *P* value of <0.05 was considered statistically significant. The analysis was performed using a PC-based software (ABstat, Anderson Bell). Data are presented as means \pm SE.

RESULTS

Plasma volume and dextran infusion. Plasma volume significantly decreased after bed rest ($3,190 \pm 120$ to $2,920 \pm 90$ ml, *P* < 0.05). Associated with this change, PCWP and RAP significantly decreased after bed rest (*P* < 0.05) (Table 1); 288 ± 31 ml of dextran₄₀ were used to restore both plasma volume and cardiac filling pressures to pre-bed rest levels (Table 1).

Hemodynamic variables. Hemodynamic data after head-down bed rest and dextran infusion are listed in Table 1. Heart rate significantly increased after bed rest. However, it returned to near pre-bed rest levels after dextran infusion. Neither SBP nor diastolic blood pressure changed significantly. Stroke volume and cardiac output significantly decreased after bed rest. However, they returned to near or above pre-bed rest levels after dextran infusion.

Spectral analysis. Spectral power data are listed in Table 2. The high-frequency power of R-R interval variability and the normalized high-frequency power tended to decrease after bed rest, consistent with vagal withdrawal (*P* = 0.10, *P* = 0.08, respectively). However, the low-frequency power of R-R interval variability did not change. Associated with these changes, the ratio of low- to high-frequency power significantly increased after bed rest (*P* < 0.05). It returned to the pre-bed rest level after dextran infusion. Neither low-frequency power of SBP variability nor high-frequency power of SBP variability changed significantly.

Transfer function analysis of baroreflex function. High-frequency transfer function gain expressed as R-R interval, used as an index of vagally mediated arterial-cardiac baroreflex function, significantly decreased after bed rest (*P* < 0.05). However, this reduced transfer function gain was normalized to the pre-bed rest level after plasma volume restoration (Fig. 2) (Table 3). In contrast, as noted previously (17), transfer function gain expressed as heart rate did not decrease signifi-

Table 1. Hemodynamics after head-down bed rest and after dextran infusion

	Pre-Bed Rest	Post-Bed Rest	Post-Dextran
PCWP, mmHg	10.1 \pm 0.7	7.9 \pm 0.5*	10.9 \pm 0.7
RAP, mmHg	7.1 \pm 0.8	5.0 \pm 0.4*	7.2 \pm 0.6
Heart rate, beats/min	64 \pm 2	69 \pm 3*	67 \pm 3
SBP, mmHg	117 \pm 3	117 \pm 2	122 \pm 4
DBP, mmHg	70 \pm 3	72 \pm 3	72 \pm 2
Stroke volume, ml	113 \pm 8	95 \pm 6*	118 \pm 6
Cardiac output, l/min	7.38 \pm 0.29	6.52 \pm 0.43*	8.22 \pm 0.28*

Values are means \pm SE. PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP and DBP, systolic and diastolic blood pressure measured by automated cuff. **P* < 0.05 compared with the levels before bed rest (pre-bed rest).

Table 2. Changes in cardiovascular variability after bed rest and dextran infusion during fixed breathing protocol

	Pre-Bed Rest	Post-Bed Rest	Post-Dextran
Fixed breathing protocol (0.2 Hz)			
LFR-R, ms ²	472 \pm 170	417 \pm 150	622 \pm 186
HFR-R, ms ²	411 \pm 109	129 \pm 21	445 \pm 132
		(<i>P</i> = 0.1)	
LF/HFR-R	1.0 \pm 0.26	2.4 \pm 0.17*	2.0 \pm 0.9
LFBP, mmHg ²	6.0 \pm 0.9	3.7 \pm 0.8	5.1 \pm 0.9
HFBP, mmHg ²	3.1 \pm 0.5	5.3 \pm 1.2	3.8 \pm 1.4
NormLFRR	0.21 \pm 0.05	0.26 \pm 0.06	0.20 \pm 0.05
NormHFRR	0.18 \pm 0.08	0.11 \pm 0.07	0.16 \pm 0.11
		(<i>P</i> = 0.08)	

Values are means \pm SE. LFR-R, power in low frequency of R-R variability; HFR-R, power in high frequency of R-R variability; LF/HFR-R, the ratio of low- to high-frequency power of R-R interval variability; LFBP, power in low frequency of blood pressure variability; HFBP, power in high frequency of blood pressure variability; NormLFRR, normalized power in low frequency of R-R variability; NormHFRR, normalized power in high frequency of R-R variability; **P* < 0.05 compared with the levels before bed rest (pre-bed rest).

cantly after bed rest during the fixed breathing protocol (*P* = 0.2) (Table 3). However, when the gain in terms of heart rate was multiplied by the resting stroke volume to determine the effective change in systemic flow induced by baroreflex-mediated changes in heart rate, there was virtually the same change in "effective gain" compared with that observed with R-R interval (*P* < 0.05) (Table 3).

Low-frequency transfer function gain did not change significantly (Table 3), although the gain expressed as R-R interval tended to decrease after bed rest during the spontaneous breathing protocol (*P* = 0.12) (Fig. 2). It was also normalized to the pre-bed rest level after plasma volume restoration (Fig. 2).

Estimation of coherence function was >0.5 in both high- and low-frequency range under all conditions: 0.57 ± 0.04 in the high-frequency range and 0.54 ± 0.03 in the low-frequency range during the spontaneous breathing protocol; 0.67 ± 0.04 in the high-frequency range and 0.55 ± 0.04 in the low-frequency range during the fixed breathing protocol. A negative phase between the SBP and the R-R interval and a positive phase between the SBP and the heart rate were observed in all cases, and these phases did not change.

The range of baroreflex stimuli and baroreflex response. The range in SBP variation and the SD of SBP variation as the global range of baroreflex stimuli during spontaneous breathing increased after bed rest and then returned to pre-bed rest levels after dextran infusion. Conversely, the range in R-R interval and SD of R-R interval variation as the global range of baroreflex response decreased after bed rest and then returned to pre-bed rest levels after dextran infusion (Table 4).

DISCUSSION

These results extend and confirm our previous report that showed significant reductions in the transfer function gain between blood pressure and R-R interval, or blood pressure and heart rate \times stroke volume after head-down-tilt bed rest or induced hypovolemia (17). The fact that these reduced transfer function baroreflex gains were normalized to the pre-bed rest levels by plasma volume restoration demonstrates convincingly that reductions in plasma volume, rather than a unique

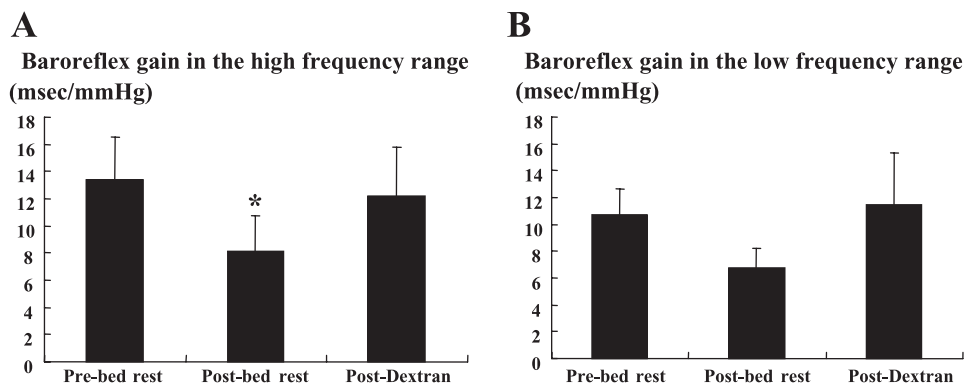


Fig. 2. Mean changes in baroreflex gain in the high- (A) and low-frequency range (B) after bed rest (post-bed rest) and after dextran infusion (post-dextran) when transfer function gain was expressed in the traditional units of ms/mmHg. **P* < 0.05 compared with the levels before bed rest (pre-bed rest).

autonomic nervous system adaptation to bed rest, are largely responsible for the observed changes in dynamic arterial-cardiac baroreflex control around the operating point after bed rest.

Baroreflex control and plasma volume. There is much literature regarding the effect of spaceflight or microgravity simulation on reflex control of the circulation. The carotid-cardiac baroreflex (6, 8, 10, 12, 13) and the spontaneous arterial-cardiac baroreflex function estimated by either transfer function (7, 9, 16, 17) or by sequence analysis (14, 16, 24, 29) may be impaired after spaceflight or bed rest and is associated with a reduction in plasma volume (2, 3, 6, 9, 14, 17). Decreases in spontaneous arterial-cardiac baroreflex indexes after spaceflight or microgravity simulation are consistent with most

reports that measured these indexes during acute interventions such as head-up tilt (24, 34) or lower body negative pressure (9, 14, 15, 24). Thus it seems that a common feature of central hypovolemia is a reduction in spontaneous arterial-cardiac baroreflex function estimated by transfer function analysis and/or sequence techniques.

A reasonable interpretation of these data is that the reduction in spontaneous arterial-cardiac baroreflex function is due to a reduction in plasma volume and/or central hypovolemia. However, one previous report using a neck chamber technique showed that the time course of changes in blood volume and the carotid-cardiac baroreflex were not parallel during bed rest (6). These investigators argued that the reduction in blood volume therefore may not be the sole cause of carotid-cardiac baroreflex abnormalities after bed rest. In fact, the carotid-cardiac baroreflex as assessed by a neck chamber technique may not be altered at all by hypovolemia (31). Moreover, one additional report showed that arterial-cardiac baroreflex function estimated by infusion of phenylephrine also did not decrease after bed rest (8), and there are similar reports that global-cardiac baroreflex function estimated by steady-state phenylephrine infusion (5) or the Valsalva maneuver (21) did not decrease after hypovolemia.

There are several possible explanations for this discrepancy between the present results examining the spontaneous arterial-cardiac baroreflex and other studies using a neck collar or phenylephrine infusion (5, 6, 8, 21, 31). First of all, these different methods evaluate different components of baroreflex function (17). For example, methods employing steady-state infusions of vasoactive drugs such as phenylephrine evaluate the static performance of the baroreflex, while the transfer

Table 3. Changes in baroreflex gain after head down bed rest and after dextran infusion

	Pre-Bed Rest	Post-Bed Rest	Post-Dextran
Spontaneous breathing protocol			
GainLF-RR, ms/mmHg	10.7±2.0	6.7±1.5	11.5±3.9
GainHF-RR, ms/mmHg	13.4±3.1	8.1±2.9*	12.2±3.6
GainLF-HR, beats·min ⁻¹ ·mmHg ⁻¹	-0.72±0.11	-0.51±0.10	-0.82±0.22
GainHF-HR, beats·min ⁻¹ ·mmHg ⁻¹	-0.89±0.15	-0.53±0.15*	-0.74±0.18
Effective Gain, ml·min⁻¹·mmHg⁻¹			
Effective GainLF	-83±17	-49±11	-98±27
Effective GainHF	-100±23	-48±17*	-87±29
Fixed breathing protocol (0.2 Hz)			
GainLF-RR, ms/mmHg	10.2±1.6	7.1±2.2	10.4±3.7
GainHF-RR, ms/mmHg	14.2±4.2	8.9±4.1*	13.8±4.1
GainLF-HR, beats·min ⁻¹ ·mmHg ⁻¹	-0.66±0.06	-0.54±0.11	-0.74±0.20
GainHF-HR, beats·min ⁻¹ ·mmHg ⁻¹	-0.70±0.12	-0.51±0.11	-0.70±0.21
Effective gain, ml·min⁻¹·mmHg⁻¹			
Effective GainLF	-77±13	-50±10	-87±25
Effective GainHF	-80±16	-43±9*	-82±26

Values are means ± SE. GainLF-RR, low-frequency transfer function gain; GainHF-RR, high-frequency transfer function gain; GainLF-HR, low-frequency transfer function gain for heart rate (beats·min⁻¹·mmHg⁻¹) multiplied by the resting stroke volume; Effective GainHF, high-frequency transfer function gain for heart rate (beats·min⁻¹·mmHg⁻¹) multiplied by the resting stroke volume; **P* < 0.05 compared with the levels before bed rest (pre-bed rest).

Table 4. Baroreflex stimuli and baroreflex response during spontaneous breathing protocol

	Pre-Bed Rest	Post-Bed Rest	Post-Dextran
Baroreflex stimuli			
Range of SBP variations, mmHg	22±2	29±1	27±3
SDSBP, mmHg	4.0±0.4	5.6±0.2*	5.0±0.5
Baroreflex response			
Range of R-R interval variations, ms	268±44	206±31	267±45
SDR-R, ms	45.8±5.9	38.3±6.1*	54.3±8.8

Values are means ± SE. SDSBP, standard deviation of SBP variations; SDR-R, standard deviation of R-R interval variations; **P* < 0.05 compared with the levels before bed rest (pre-bed rest).

function gain reflects dynamic properties of baroreflex function (1, 28). Probably more importantly, transfer function and sequence analysis estimate baroreflex gain during spontaneous beat-to-beat oscillations of blood pressure within a relatively narrow range of baroreflex input pressures, centered around the "operating point" of the stimulus-response curve. In contrast, the steady-state phenylephrine infusion technique evaluates only the baroreflex response to baroreflex loading (hypertension), not unloading (hypotension). In addition, the neck chamber technique gives estimations of baroreflex gain over greater ranges of pressure than that achieved during spontaneous respiration, even though the 20- to 30-mmHg range of blood pressure variations reported during spontaneous respiration in Table 4 is comparable to the 10–15 mmHg of hypertension induced by steady-state phenylephrine infusion in some studies (8).

These differences in the methods of assessing the baroreflex may reconcile these apparently contradictory results. For example, central hypovolemia reduces stroke volume and pulse pressure, and these reductions increase heart rate via baroreflex-mediated sympathetic activation and vagal withdrawal. Combined, these alterations in neural input appear to reposition the operating point on the static stimulus-response curve of the baroreflex, closer to the threshold of baroreflex activation (12). As a consequence of this shift, further decreases in arterial pressure are met with a smaller degree of baroreflex unloading than when the operating point is positioned closer to its maximal gain. However, when hypertension is induced by phenylephrine, the baroreflex is fully capable of being stimulated normally and may respond with normal (carotid) or even enhanced (aortic) increases in vagal outflow. Similarly, if the operating point has moved closer to threshold, there will be little additional baroreflex unloading during neck pressure, which is the initial part of the neck collar protocol used by previous investigators (6, 10). However, during the potent neck suction that follows, the baroreflex may still be stimulated normally, resulting in no change in maximal gain calculated by this technique. Thus, even if the static curve of the baroreflex does not change at all, spontaneous baroreflex function, which is heavily influenced by the slope of baroreflex curve around its operating point, may still change.

This difference in interpretation of how the baroreflex changes with bed rest and/or hypovolemia depending on the technique used to assess baroreflex function may have important physiological significance as well. For example, because bed rest induces orthostatic hypotension, rather than hypertension, how the baroreflex functions during decreases in arterial pressure associated with hypovolemia would seem to be more clinically relevant than how it responds to induced hypertension. If the reserve of the baroreflex to augment heart rate in response to upright posture is diminished, theoretically at least, blood pressure control could be compromised even if the response to hypertension remained intact. It is important to note, however, that in this and virtually all bed rest and spaceflight studies (2–4, 9, 12, 13, 19, 24, 29), the apparent abnormalities of baroreflex control of heart rate are not sufficient to impair the heart rate response to the upright posture and do not likely play a major role in the etiology of orthostatic hypotension under these conditions.

A few other methodological considerations should be addressed. First, as noted above, transfer function analysis of

spontaneous variations between blood pressure and R-R interval has been employed by many investigators for the evaluation of dynamic properties of baroreflex function around the operating point (1, 22, 26–28). Under normal conditions, this transfer function gain correlates significantly with other measures of cardiac-baroreflex function, including vasoactive drug methods and sequence analysis (15, 22, 26, 27). Therefore, we and others have considered that this technique is a useful and convenient tool for the assessment of dynamic cardiac-baroreflex function emphasizing the frequency dependence of R-R interval and blood pressure control. However, there are arguments over its limitations and/or interpretation as discussed previously (17). For example, the coherence function needs to be >0.5 to guarantee a fundamental assumption of linearity between changes in arterial pressure and cardiac period (27, 28). In the present study, the coherence function was sufficiently high in both frequency ranges, confirming the validity of using this technique for the assessment of gain and phase. Furthermore, the phase between the SBP and the R-R interval was always negative in all cases, minimizing the concern with the feed-forward effects of heart rate on SBP (1, 17).

The other problem with estimating the arterial-cardiac baroreflex function is whether to express the sensitivity by heart rate units (beats/min) or R-R interval (ms). However, regardless of whether transfer function gain was expressed as heart rate units (multiplied by stroke volume) or R-R interval, we observed decreases in baroreflex control, and these results are exactly the same as those we have reported previously (17). Therefore, the premise of this study is that the technique of transfer function analysis between blood pressure and R-R interval is a reliable tool for the assessment of spontaneous arterial-cardiac baroreflex function around the operating point after bed rest and/or hypovolemia.

Perspectives

In a previous study (17), we sought to determine whether the reduction in spontaneous arterial-cardiac baroreflex function could be due to a reduction in plasma volume. To address this question, the effect of head-down-tilt bed rest (chronic hypovolemia plus "deconditioning") was compared with acute hypovolemia without bed rest deconditioning in the same subjects. We found that transfer function gain in the high-frequency range decreased similarly after both head-down-tilt bed rest and acute hypovolemia. Therefore, we concluded that reduced arterial-cardiac baroreflex function in this frequency range after head-down-tilt bed rest was likely due primarily to a reduction in plasma volume associated with head-down-tilt bed rest. However, the evidence was not dispositive and was dependent on inference rather than correction of the changes in dynamic baroreflex control with normalization of plasma volume.

The present results, showing that precise plasma volume restoration with dextran could normalize decreased spontaneous arterial-cardiac baroreflex function, provide new direct evidence in support of this hypothesis. The results from the previous study and present study together, using completely different populations, provide very strong evidence that plasma volume reduction and consequent central hypovolemia is the key variable for the apparent abnormality of spontaneous arterial-cardiac baroreflex function after bed rest.

However, the exact mechanisms underlying orthostatic intolerance after microgravity exposure are certainly multifactorial. One important issue to consider is that along with plasma volume reductions, spaceflight and bed rest reduce interstitial fluid volume that was not restored with the present study design. Interstitial fluid volume contributes to tissue pressure and vascular transmural pressures, providing the reservoir for postural transcapillary fluid shifts (35). It is possible that reduced interstitial fluid volume therefore may contribute to other physiological manifestations of chronic microgravity exposure.

Despite the clearly reduced spontaneous baroreflex gain after bed rest in this study, there are a number of lines of evidence that suggest that this adjustment in the operating point of the baroreflex is not likely to be primarily responsible for orthostatic hypotension, although there may be indirect effects that contribute in part to this multifactorial syndrome. First, as noted above, the heart rate response to upright posture appears to be preserved, possibly by augmented sympathetic activity after vagal withdrawal has been complete. This requirement for increased sympathetic activity to increase heart rate may, however, contribute to stimulation of cardiac afferents in a small, relatively empty heart, and may facilitate the elaboration of a fainting reflex (32). Second, although plasma volume restoration with dextran normalized the decreased baseline spontaneous baroreflex function after bed rest, previous studies have failed to normalize orthostatic tolerance after bed rest by saline infusion (3, 4), although it could be argued that the magnitude of plasma volume restoration was not as precise or sustained as was accomplished in this study. Nevertheless, one preliminary report from these same subjects showed that post-bed rest orthostatic intolerance was minimally affected even by infusion of dextran adjusted to plasma volume and cardiac filling pressure (23). We speculate that factors related to cardiovascular remodeling during bed rest, other than reduced arterial-cardiac baroreflex function by reduced plasma volume, may be primarily responsible for the orthostatic hypotension after spaceflight or bed rest (19, 20).

In conclusion, the present study confirmed that chronic head-down-tilt bed rest leads to reductions in the vagally mediated spontaneous arterial-cardiac baroreflex function and the ability of the baroreflex to modify systemic flow (heart rate \times stroke volume; effective gain). However, those abnormalities in baroreflex control were completely normalized by plasma volume restoration. Hence, the present results provide confirmatory evidence that reductions in plasma volume may be largely responsible for the reduced spontaneous arterial-cardiac baroreflex function after bed rest.

GRANTS

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