Short-term variability of blood pressure: effects of lower-body negative pressure and long-duration bed rest

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Am J Physiol Regul Integr Comp Physiol 303: R77–R85, 2012. First published May 2, 2012; doi:10.1152/ajpregu.00050.2012.—Mild lower-body negative pressure (LBNP) has been utilized to selectively unload cardiopulmonary baroreceptors, but there is evidence that arterial baroreceptors can be transiently unloaded after the onset of mild LBNP. In this paper, a black box mathematical model for the prediction of diastolic blood pressure (DBP) variability from multiple inputs (systolic blood pressure, R-R interval duration, and central venous pressure) was applied to interpret the dynamics of blood pressure maintenance under the challenge of LBNP and in long-duration, head-down bed rest (HDBR). Hemodynamic recordings from seven participants in the WISE (Women’s International Space Simulation for Exploration) Study collected during an experiment of incremental LBNP (−10 mmHg, −20 mmHg, −30 mmHg) were analyzed before and on day 50 of a 60-day-long HDBR campaign. Autoregressive spectral analysis focused on low-frequency (LF, ~0.1 Hz) oscillations of DBP, which are related to fluctuations in vascular resistance due to sympathetic and baroreflex regulation of vasomotor tone. The arterial baroreflex-related component explained 49 ± 13% of LF variability of DBP in spontaneous conditions, and 89 ± 9% (P < 0.05) on day 50 of HDBR, while the cardiopulmonary baroreflex component explained 17 ± 9% and 12 ± 4%, respectively. The arterial baroreflex-related variability was significantly increased in bed rest also for LBNP equal to −20 and −30 mmHg. The proposed technique provided a model interpretation of the proportional effect of arterial baroreflex vs. cardiopulmonary baroreflex-mediated components of blood pressure control and showed that arterial baroreflex was the main player in the mediation of DBP variability. Data during bed rest suggested that cardiopulmonary baroreflex-related effects are blunted and that blood pressure maintenance in the presence of an orthostatic stimulus relies mostly on arterial control.

arterial blood pressure; variability; baroreflex; lower body negative pressure; bed rest

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MILD OR NONHYPOTENSIVE LOWER body negative pressure (LBNP; −20 mmHg < LBNP < 0 mmHg) has been used to selectively unload cardiopulmonary baroreceptors (25, 44, 46, 50). However, straightforward observations of the time course of mean arterial pressure (MAP) following rapid onset of mild LBNP (17, 18) evidenced a transient decrease followed by a recovery of pre-LBNP onset values, suggesting that arterial baroreceptors are affected by mild LBNP as well. More detailed analyses of such transient decreases of MAP in LBNP (13) showed that also systolic blood pressure (SBP) and diastolic blood pressure (DBP) fall and are restored within ~15 heart beats, confirming a direct involvement of arterial baroreflex, consistently with previous reports (23, 35, 45). However, to our knowledge, the quantification of the relative dynamic contribution of arterial and cardiopulmonary baroreflex has not been addressed yet. Fu et al. (13) concluded that arterial baroreflex is engaged and unloaded by mild LBNP, but they could not determine the proportional influence of cardiopulmonary vs. arterial baroreflex on the restoration of blood pressure during low levels of LBNP. Work by Jacobsen et al. (23) showed that arterial baroreceptors can actually have greater importance than low-pressure baroreceptors in mediating vasoconstriction in response to mild LBNP, but they did not provide quantitative indices of their relative weight.

In this paper, hemodynamic measurements collected during a mild LBNP experiment, repeated before and on day 50 of a long-duration, head-down bed rest (HDBR) study, were analyzed by a black box, multi-input–single-output model for the prediction of short-term, beat-by-beat DBP fluctuations from variability signals of SBP, central venous pressure (CVP), and R-R interval. DBP variability was assumed to reflect vasomotor tone control of arterial blood pressure (ABP) of neural and nonneural origin. The components of its control, related to arterial baroreflex, cardiopulmonary baroreflex, and R-R to ABP feed-forward effects, were disentangled by the proposed data analysis approach. The relative dynamic contribution of these components was then investigated in the frequency domain by spectral analysis, before and during HDBR.

Black box model-based analysis of cardiovascular (CV) recordings has been extensively used to extract information on neural regulation of circulation (1, 2, 4–7 29–34, 40, 48), and it enables one to attain greater insight into the complexity of CV variability (CVV) with respect to straightforward observations of a short and rapid transient change of ABP (13, 17, 18). Approaches based on the analysis of multiple cardiorespiratory signals (5) have shown the importance of including CVP in the analysis of changes in circulation control when LBNP is applied, and specifically on the possible presence of the Bainbridge reflex in humans (5).

Hence, the goals of this modeling work are 1) to quantify the relative contribution of arterial and cardiopulmonary baroreflex-related components of blood pressure control during mild LBNP; and 2) to investigate its alterations due to long-duration HDBR.
Regarding the second goal, the response of neural mechanisms responsible for the maintenance of ABP under the pseudo-orthostatic stimulus represented by LBNP is affected by cardiovascular deconditioning (CVD) induced by prolonged exposure to actual or simulated microgravity. In such conditions, a reset of baroreflex systems may occur, and differences in the adaptation of arterial and cardiopulmonary baroreflex may be observed. Therefore, the application of our model to HDBR data was aimed at investigating the changes in the proportional contribution of the two baroreflex branches to vasomotor tone variability under mild LBNP. In particular, cardiopulmonary baroreflex could be expected to be less efficient, possibly as an effect of hypovolemia, and it was hypothesized to be less sensitive to further reductions in venous return due to the onset of LBNP on day 50.

These objectives were addressed through the presentation and discussion of indices computed by the black box data analysis model, with particular emphasis on the influence of low-frequency oscillations of components of DBP variability.

MATERIALS AND METHODS

Experimental protocol. The data analyzed in this study are a subset of data collected during the Women’s International Space Simulation for Exploration (WISE-2005) study described in detail elsewhere (3, 10, 15, 19, 42). The subset consisted of seven healthy women (age 33 ± 1 yr, height 165 ± 4 cm, weight 59 ± 3 kg) selected from the original 24 subjects based on (1) not being assigned to the exercise countermeasure group, and (2) data quality. The model applied (described below) required exceedingly high-quality signals with no unfilterable artifacts or noise and more than 2 min of recordings in each level of suction. The research was conducted at the Institute for Space Physiology and Medicine Clinical Research Facility in Toulouse, France. All procedures received prior ethics clearance from University of Waterloo, Canada, and the French Committee for Health; they were conducted in accordance with the Helsinki convention. All participants gave prior informed consent.

The Continuous Lower-Body Negative Pressure Experiment was a subset of the battery of cardiophysiology tests completed during a 60-day-long, 6° head-down bed rest (HDBR). Subjects were placed in a custom-made LBNP chamber and sealed at the iliac crest with a neoprene “skirt”. They were then outfitted with a 3-lead ECG (Colin, St. Antonio, TX, USA), respiration belt (PowerLab), finger blood pressure cuff (reconstructed to brachial and height-corrected, Finometer, FMS, Amsterdam, The Netherlands) and a 2.5-cm, 22-gauge catheter was inserted in the right antecubital vein. The catheter was connected to a pressure transducer held at the level of the heart to estimate CVP, as previously described (11), according to the dependent right arm technique (14). Signals were collected at 1,000 Hz on a PowerLab Data Acquisition System running Chart software (PowerLab, Sydney, Australia).

The subjects were then taken through progressively stronger levels of lower body suction (0, −10, −20, −30 mmHg, at least 2 min per level, transition time between each level was <5 s). The experiment was completed once before entry into bed rest and then repeated again on day 50 of HDBR. Epochs were labeled BLPRE (baseline, pre-HDBR), 10PRE (LBNP = −10 mmHg, pre-HDBR), 20PRE (LBNP = −20 mmHg, pre-HDBR), 30PRE (LBNP = −30 mmHg, pre-HDBR), BLBR (baseline, day 50 of HDBR), 10BR (LBNP = −10 mmHg, day 50 of HDBR), 20BR (LBNP = −20 mmHg, day 50 of HDBR), 30BR (LBNP = −30 mmHg, day 50 of HDBR).

Signal preprocessing. R-R series were derived by identification of QRS complexes and of R peaks on ECG waveforms. DBP and SBP values between consecutive R peaks were extracted from ABP waveforms, and the correspondent beat-by-beat series were derived. DBP (i) was considered as the onset of the current beat on the ABP waveform following R (i); thus, SBP (i) follows DBP (i), while R-R (i-1) designates the difference between R (i), that is the occurrence of the R peak in the current beat, and R (i-1), that is the occurrence of the R peak in the previous beat.

Beat-by-beat series of CVP were obtained as the series of the mean values of continuously recorded CVP over each cardiac cycle, i.e.,
between two consecutive R peaks. Figure 1 shows an example of beat-by-beat series from one subject during the LBNP experiment.

Two-minute-long stationary segments were selected for each LBNP phase. Zero-mean normalized beat-by-beat variability series \( v(i) \) were derived for each hemodynamic variable from the corresponding beat-by-beat series \( x(i) \) by subtracting the mean value \( \mu \) calculated over the selected segment, and dividing by \( \mu \):

\[
v(i) = \frac{x(i) - \mu}{\mu}
\]

Beat-by-beat variability series were resampled in the time domain at 1 Hz by means of zero-order hold techniques, to obtain evenly spaced time series.

Model-based system identification of DBP variability. A model for the prediction and spectral decomposition of beat-by-beat variability of ABP previously proposed by our group (2) was improved to include the relationship between CVP and DBP to model the control of arterial blood pressure by cardiopulmonary baroreflex:

\[
DBP(i) = \sum_{j=1}^{n} \sum_{i=1}^{n} h_{a}(j) \cdot SBP(i - j) + \sum_{i=1}^{n} h_{b}(j) \cdot CVP(i - j) + h_{c} \cdot R-R(i - 1) + u_{a}(i)
\]

(2)

The model order \( n \) was determined by Akaike’s Information Criterion, and it was typically in the range between 8 and 12. Model parameters were determined by least-squares minimization procedure. The features of the model were presented in detail elsewhere (2). The black-box input-output relationships between CV variables in Eq. 2 are assumed to be representative of different effects on the beat-by-beat variability of DBP:

- **SBP → DBP** (DBP\_shp) represents the black box model of vasomotor tone control related to arterial baroreflex-mediated regulation of DBP and sympathetic tone control;

- **CVP → DBP** (DBP\_cvp) represents the black box model of vasomotor tone control related to cardiopulmonary baroreflex control of DBP (28, 30); beat-by-beat oscillations in our venous measure were considered representative of central venous pressure oscillations, since CVP was estimated from a peripheral measurement by applying the dependent right arm technique (14) (this procedure conclusively demonstrated that amplitude of changes in a peripheral venous pressure measurement are the same as in a central venous pressure measurement); and

- **R-R → DBP** (DBP\_rr) models the effect of diastolic runoff and accounts for the feed forward effect of R-R interval variability on ABP (4) and for the buffering of slow fluctuations of blood pressure driven by total peripheral resistance (TPR) due to cardiac output (33).

The residual error (DBP\_noise) may account for sources of variability that are not measured, such as autoregulation-mediated control of peripheral resistance, besides noise and model errors (2).

This black box modeling approach is aimed at emphasizing the effect of baroreflex control of vasomotor tone on blood pressure oscillations. Although in the study by Aletti et al. (2), DBP was predicted by SBP and R-R only, the availability of CVP measurements enabled us to refine the model, by inclusion of the CVP to DBP relationship, accounting for cardiopulmonary baroreflex control of vasomotor tone. This enhanced the accuracy of the model in the interpretation of our experiment, in conditions that strongly affected circulating volumes (long-duration bed rest) and venous return (LBNP).

Prior works proposed a system identification of baroreflex-mediated control of CVV by focusing on beat-by-beat fluctuations of MAP (3, 30). Our choice to analyze DBP and its variability, in a previous work (2) and in this paper as well, is based on the relationship between the diastolic decay and TPR (27, 31), and on the observation that DBP spectral power is mostly concentrated in the low-frequency (LF, ~0.1 Hz) band, i.e., the band of vasomotor and resistance fluctuations. Therefore, DBP was assumed to be specifically sensitive to vasomotor tone, and modulations in the LF band were assumed to reflect baroreflex-mediated regulation of vascular resistance, whereas auto-regulation phenomena may be confined to slower oscillations, typical of the very low-frequency band (VLF; \( f < 0.04 \) Hz), as shown by Stauss et al. (43). The choice of SBP as the input to the arterial baroreflex-related component of the model was consistent with typical approaches to the assessment of cardiac baroreflex, which use SBP as the input, since it is known to convey both the phasic and tonic dynamic features to which baroreceptors are sensitive, and heart rate or R-R as the output. For these reasons, the input-output relationship between SBP and DBP was hypothesized to describe arterial baroreflex-mediated control.

Frequency domain indices. Autoregressive (AR) spectra were computed for each variability series obtained from measurements and from model prediction, before and during bed rest. Spectral indices computed from spectra included power distribution in the low-frequency band (LF; 0.04 Hz \( \leq f < 0.15 \) Hz), total power (TOT) obtained as the sum of power in the LF band and power in the high-frequency or respiratory band (HF; 0.15 Hz \( < f < 0.4 \) Hz), LF/HF ratio, and relative power in the LF band, obtained as LF/TOT.

To assess the proportional contribution of the arterial baroreflex-related component vs. the cardiopulmonary baroreflex-related component to the variability of DBP, the following ratios were computed: LF power of DBP\_shp over LF power DBP (LF DBP\_shp/LF DBP) to quantify the amount of DBP variability explained by SBP, LF power of DBP\_cvp over LF power DBP (LF DBP\_cvp/LF DBP) to quantify the amount of DBP variability explained by CVP.

Statistical analysis. A two-way repeated-measures ANOVA test was performed, with LBNP epochs being the repeated factor and PRE and HDBR conditions the second factor. One-way repeated-measures ANOVA was applied to spectral indices obtained both in PRE and HDBR. Post hoc comparisons were performed by Fisher’s least significant difference test to verify significant differences between a specific level of LBNP and BL. Paired two-sample Student’s t-test was used to compare PRE and HDBR for each LBNP epoch (e.g., BLPRE vs. BLBR), to verify the effects of CVD on the response to LBNP. Significance to reject the null hypothesis that variations between the mean values of spectral indices before and during bed rest were not significant was set at \( P < 0.05 \).

RESULTS

Time domain parameters. Both before (PRE) and during HDBR (Table 1), CVP significantly decreased from baseline, progressively with increasing intensities of LBNP. Heart rate (HR) significantly increased and pulse pressure (PP) significantly decreased from BL in HDBR for LBNP \( \leq -20 \) mmHg. Reduction of SBP from BL was significant at \(-30 \) mmHg before bed rest. Only PP and R-R changed significantly during bed rest, resulting in lower values in each of the four experimental epochs with respect to their values before bed rest.

Frequency domain parameters. Figure 2 shows both the results of identification of the components of DBP variability (left), and of computation of the relevant spectra (right), before and on day 50 of HDBR (bottom). Because of normalization, signals are unitless, spectral densities are in \([\text{Hz}^{-1}]\), and power of spectral components is unitless. DBP\_mod is the prediction of DBP from the model, i.e., the sum of DBP\_shp, DBP\_cvp, and DBP\_rr.

Table 2 reports LF, LF%, and total power for the main hemodynamic variables. These are the most meaningful indices, since the LF band is related to sympathetic control of...
vascular tone, which causes blood pressure to fluctuate (1, 2, 39), and DBP power is concentrated in the LF band.

Regarding the indices of heart rate variability, which are traditionally interpreted as representative of the impact of sympathovagal balance on heart rate, both total R-R power and its LF% tended to decrease at the onset of LBNP in PRE and to increase again for larger levels of LBNP. A significant increase in LF% was found on day 50 of HDBR, with increasing levels of LBNP, possibly as a reflection of the reduced variability of heart rate and respiration, which can also reduce the power of R-R in the respiratory band.

DBP power did not change significantly in BL during bed rest, while its LF% was reduced from 10 in PRE to 10 in HDBR (~2%), $P < 0.05$. LF% power of SBP increased from PRE in HDBR at BL-BR ($P = 0.056$), 20BR ($P = 0.076$), and 30BR ($P = 0.016$). SBP total power was significantly higher at BL during bed rest with respect to PRE. A significant increase in total power of SBP was reported at 10 mmHg with respect to baseline in PRE, while this was not the case in HDBR. CVP absolute power did not show any significant variations. R-R LF/HF ratio was higher during bed rest, with respect to PRE (Table 2); further, post hoc comparisons showed a significant increase of LF/HF of R-R both during bed rest and PRE passing from BL to 30 mmHg LBNP.

Figure 3 and Table 3 report results of spectral decomposition of DBP and the relative contribution of its model components in the LF band. The contribution of SBP variability to the prediction of DBP variability ($DBP_{sbp}$) was largely predominant in all experimental conditions both before and during bed rest. LF of $DBP_{sbp}$ rose during bed rest from PRE at 20 mmHg (from 0.27 ± 0.14 $10^{-3}$ in PRE to 0.94 ± 0.79 $10^{-3}$ in HDBR, $P = 0.070$) and at 30 mmHg (from 0.27 ± 0.18 $10^{-3}$ in PRE to 0.81 ± 0.58 $10^{-3}$ in HDBR, $P = 0.081$). Total power of $DBP_{sbp}$ was larger in BL (from 0.53 ± 0.48 $10^{-3}$ in PRE to 1.19 ± 0.71 $10^{-3}$ in HDBR, $P = 0.048$) and at 30 mmHg (from 0.35 ± 0.22 $10^{-3}$ in PRE to 1.05 ± 0.65 in HDBR, $P = 0.057$).

Interestingly, two-way ANOVA comparison of LF and total power of $DBP_{sbp}$ reported a $P$ value of <0.01 for the condition factor (PRE and HDBR). CVP contributed little to the identification of DBP and to its power decomposition. No significant change was found in the main spectral indices computed for the $DBP_{mv}$ component of the model. Still, R-R appeared to have more influence on DBP variability than CVP.

The trend shown by $DBP_{sbp}$ in response to increasing LBNP intensity pointed to an increasing influence of this component in the identification of DBP variability during bed rest (Table 3), while the role of CVP in predicting DBP appeared further limited. The contribution of R-R variability was not affected by HDBR.

**DISCUSSION**

This paper sought to address the problem of disentangling and quantifying the proportional impact of arterial baroreflex-related and cardiopulmonary baroreflex-related control of DBP in response to mild LBNP and to assess its alterations during long-duration bed rest.

The novel contribution of this work is represented by the application of a black box model for the derivation of components of dynamic baroreflex control of ABP from noninvasively and minimally invasively collected CV signals. Only continuous measures were used, without including estimated quantities, such as TPR indirectly calculated from flow and pressure measurements. In this way, complex input-output dynamic relationships between CV variables can be disentangled, and quantitative indices related to autonomic control of circulation—specifically, vasomotor tone control—can be obtained from measurements that are routinely accessible in humans. Thus, a model-based analysis of blood pressure variability under the considered experimental challenges emerges as a valuable approach to monitor altered responses of control systems.

Our results have indicated that arterial baroreflex-mediated control was the main determinant of DBP variability in nonhypotensive LBNP, and its predominant role in responding to this stimulus was maintained in long-duration simulated microgravity. The additional input of CVP to our previous model of arterial control (2) evidenced a limited role of cardiopulmonary baroreflex in mediating vasomotor tone control in response to mild LBNP. Its further reduction in long-duration bed rest was consistent with observed cardiovascular deconditioning-induced adaptations to bed rest. These observations entail that baroreflex responsiveness was blunted, but not totally impaired, in healthy subjects dealing with conditions that may potentially lead to orthostatic intolerance. Consistent with our hypothesis on the effects of HDBR, arterial baroreflex-mediated control of vascular resistance during HDBR was even more important than in PRE, given the reduced contribution of cardiopulmonary baroreflex, but our data did not indicate any enhancement in arterial baroreflex. Our results were referred to the variation induced by mild LBNP from a basal condition of spontaneous oscillations at rest.
Arterial vs. cardiopulmonary baroreflex control during mild LBNP. The first goal of this paper was to quantify the contribution of arterial and cardiopulmonary baroreflex-mediated effects to the maintenance of blood pressure following rapid onset of mild LBNP through a data-driven approach.

Hisdal et al. (17, 18) reported similar transitory adjustments of ABP to nonhypotensive LBNP after this was imposed either by a fast onset (~0.3 s) or a slower one (~15 s). They concluded that, when the onset of mild LBNP is in the range between 0.3 s and 15 s, such as in the case of our protocol (~5 s), ABP maintenance has to display similar responses and to involve the same control mechanisms.

Simple inspection of the transient decrease of ABP following the rapid onset of mild LBNP (13, 17, 18) revealed that MAP (17, 18), DBP, and SBP (13), did, indeed, drop shortly after the onset of LBNP, and quickly recovered to pre-LBNP values. Our data, like data from other authors (50), did not show the same transient response. However, its presence can
variability before and during bed rest in each of the four experimental epochs of the continuous LBNP protocol.

Table 2. Main frequency domain indices of hemodynamic variability before and during bed rest in each of the four experimental epochs of the continuous LBNP protocol.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LF % DBP</strong>†</td>
<td>PRE</td>
<td>97 ± 2</td>
<td>98 ± 1</td>
<td>97 ± 2</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>96 ± 3</td>
<td>96 ± 1**</td>
<td>97 ± 2</td>
</tr>
<tr>
<td><strong>LF % SBP</strong>†</td>
<td>PRE</td>
<td>91 ± 4</td>
<td>95 ± 4</td>
<td>89 ± 10</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>96 ± 4</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
</tr>
<tr>
<td><strong>LF % CVP</strong>†</td>
<td>PRE</td>
<td>61 ± 19</td>
<td>77 ± 23</td>
<td>56 ± 22</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>38 ± 28</td>
<td>35 ± 29**</td>
<td>45 ± 34</td>
</tr>
<tr>
<td><strong>LF % RR</strong>‡</td>
<td>PRE</td>
<td>68 ± 18</td>
<td>61 ± 19</td>
<td>72 ± 15</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>79 ± 9</td>
<td>83 ± 9**</td>
<td>89 ± 6**§</td>
</tr>
<tr>
<td><strong>LF DBP, 10⁻³</strong></td>
<td>PRE</td>
<td>0.8 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>0.8 ± 0.4</td>
<td>0.8 ± 0.3</td>
<td>1.4 ± 0.9</td>
</tr>
<tr>
<td><strong>LF SBP, 10⁻³</strong></td>
<td>PRE</td>
<td>0.2 ± 0.1***</td>
<td>0.6 ± 0.3§</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>0.8 ± 0.5</td>
<td>0.7 ± 0.3</td>
<td>1.2 ± 1.2</td>
</tr>
<tr>
<td><strong>LF CVP, 10⁻⁷</strong></td>
<td>PRE</td>
<td>1.0 ± 0.8</td>
<td>3.1 ± 2.8</td>
<td>5.7 ± 6.5</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.4</td>
<td>4.3 ± 7.8</td>
</tr>
<tr>
<td><strong>LF RR, 10⁻³</strong></td>
<td>PRE</td>
<td>1.0 ± 0.6</td>
<td>0.8 ± 0.7</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>0.9 ± 0.6</td>
<td>0.8 ± 0.4</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td><strong>LF/HF RR</strong>†</td>
<td>PRE</td>
<td>3.0 ± 1.9</td>
<td>2.3 ± 2.1</td>
<td>2.4 ± 3.6</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>4.7 ± 2.5</td>
<td>6.5 ± 3.5**</td>
<td>10.0 ± 5.1**</td>
</tr>
<tr>
<td><strong>TOT, 10⁻³ DBP</strong></td>
<td>PRE</td>
<td>1.1 ± 0.7</td>
<td>1.7 ± 0.8</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>1.3 ± 0.7</td>
<td>1.2 ± 0.4</td>
<td>2.3 ± 1.9</td>
</tr>
<tr>
<td><strong>TOT, 10⁻³ SBP</strong></td>
<td>PRE</td>
<td>0.3 ± 0.2</td>
<td>1.0 ± 0.5§</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>1.4 ± 0.8**</td>
<td>1.2 ± 0.6</td>
<td>2.1 ± 2.0</td>
</tr>
<tr>
<td><strong>TOT, 10⁻³ CVP</strong></td>
<td>PRE</td>
<td>2.2 ± 2.0</td>
<td>6.4 ± 5.6</td>
<td>13.2 ± 13.1</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>3.5 ± 2.6</td>
<td>4.8 ± 5.0</td>
<td>10.9 ± 15</td>
</tr>
<tr>
<td><strong>TOT, 10⁻³ RR</strong></td>
<td>PRE</td>
<td>2.0 ± 1.2</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>1.6 ± 1.0</td>
<td>1.4 ± 0.6</td>
<td>1.7 ± 0.4</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. *Two-way ANOVA columns (effect of LBNP) and rows (effect of bed rest) factor, P < 0.05. †Two-way ANOVA condition factor, P < 0.05. ‡One-way ANOVA, P < 0.001. §One-way ANOVA, P < 0.05. $Significant post hoc comparisons between each LBNP level and BL (PRE and HDBBR). Paired t-test between the same LBNP phase, PRE vs. HDBBR: ‡P < 0.05; §§P < 0.01.

Fig. 3. Low-frequency (LF) power of components of DBP variability during the LBNP protocol. Mean values for seven subjects are shown; bars represent SD.

Our focus was placed on the variability of DBP. Application of mild LBNP, consistently with (13, 17, 18), did not affect the mean values of DBP, MAP, and SBP, as no significant variation was obtained from BLPRE to 10PRE (Table 1). Conversely, LF% power of DBP increased (Table 2), possibly as the result of an enhanced sympathetic stimulation of vasomotor tone to compensate for reductions in venous return. The arterial baroreflex-related component contributed to about half of overall variability of DBP in baseline (Table 3, LF DBPabp / LF DBP %), and cardiopulmonary baroreflex to about 20% (Table 3, LF DBPcwp / LF DBP %). During LBNP = -10 mmHg, the amount of DBP power predicted by DBPabp and by DBPcwp tended to increase and to decrease, respectively. Higher LBNP intensities induced a decrease in the role of the arterial baroreflex component, although it remained largely predominant in mediating LF oscillations of DBP, since it predicted about 5 times as much power of DBP predicted by the cardiopulmonary baroreflex component, for levels of LBNP equal to -10 and -20 mmHg (Table 3).

The relatively limited contribution of CVP to DBP variability through the cardiopulmonary baroreflex branch when LBNP was applied was consistent with data reported by Jacobsen et al. (23), who provided evidence of a larger contribution of sinoaortic receptors to reflex control skeletal muscle vasomotor tone under orthostatic stress, with respect to venous distention.

Table 3. Ratio between LF absolute power of each predicted component and LF absolute power of DBP.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LF DBPabp / LF DBP, %</strong></td>
<td>PRE</td>
<td>49 ± 13</td>
<td>53 ± 9</td>
<td>40 ± 8</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>89 ± 9**</td>
<td>58 ± 4</td>
<td>68 ± 11§</td>
</tr>
<tr>
<td><strong>LF DBPcwp / LF DBP, %</strong></td>
<td>PRE</td>
<td>17 ± 9</td>
<td>8 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>12 ± 4</td>
<td>50 ± 44</td>
<td>2 ± 1</td>
</tr>
<tr>
<td><strong>LF DBPcwp / LF DBP, %</strong></td>
<td>PRE</td>
<td>14 ± 4</td>
<td>12 ± 4</td>
<td>21 ± 4</td>
</tr>
<tr>
<td><strong>HDBBR</strong></td>
<td>PRE</td>
<td>17 ± 4</td>
<td>21 ± 7</td>
<td>16 ± 5</td>
</tr>
</tbody>
</table>

Values are expressed as % values means ± SD. *Two-way ANOVA condition factor, P value < 0.001. #One-way ANOVA, P = 0.066. Paired t-test same LBNP phase, PRE vs. HDBBR: **P < 0.05, ***P < 0.01, and §P value = 0.056.
tricular mechanoreceptors and other low-pressure baroreceptors.

The variability of DBP that was explained by neither SBP nor CVP was due to the feed-forward effect of R-R variability on ABP variability, which was relatively unaffected by LBNP. The residual error of the prediction was found in a previous study to convey important information on low-frequency oscillations of DBP (2). In this work, this was not as evident, mainly because of the capability of SBP to predict DBP well and because the length of data did not allow us to obtain sufficient frequency resolution to analyze these oscillations.

Baroreflex responsiveness during LBNP in bed rest. Once the first goal of the paper was attained, the second goal was to assess how prolonged weightlessness affected blood pressure control through our investigation of DBP variability under LBNP.

Tachycardia and lower values of PP (Table 1) suggested volemia reduction as it is commonly observed in HDBR (15, 22). Although no significant variations were found in the mean values of ABP indices when the same epochs of the protocol from PRE and HDBR were compared (Table 1), this should not exclude the possibility that CVD occurred, as mean values are not representative of dynamic adaptations of control systems.

On day 50 of HDBR, vasoconstrictive responses to LBNP were still present, as indicated by the unchanged mean value of DBP and of LF% power of DBP compared with the same levels of LBNP before bed rest (Table 2). These results could indicate that mechanisms responsible for ABP maintenance in the presence of the pseudo-orthostatic stimulus represented by LBNP were still responsive in HDBR. This could be due to the well-documented increase or maintenance in sympathetic activity during HDBR (24, 36, 41).

SBP fluctuated with larger variability in baseline during bed rest than before, and this could be related to the reset of baroreflex, which may occur during long-duration exposure to simulated or actual microgravity and to the aforementioned sympathetic overactivity.

The arterial baroreflex-related component of DBP variability had a much larger effect on DBP control during bed rest than in PRE (Table 3). The cardiopulmonary baroreflex-related component was unchanged at rest in HDBR, but it was significantly lower at LBNP = −30 mmHg. These two indices suggested that the role of cardiopulmonary baroreflex-mediated regulation of vasomotor tone was further reduced in HDBR. Thus, the maintenance of ABP may rely only on the residual responsiveness displayed by the arterial baroreflex, which was almost three times as large at 30BR as at 30PRE (Table 3). These observations confirmed our initial hypothesis, which we formulated taking into account the potential impact of hypovolemia in HDBR when LBNP was applied.

Our interpretation of these results is that cardiopulmonary baroreflex-mediated control was not so sensitive to mild LBNP on day 50 of HDBR as it was before bed rest. An augmented power of beat-by-beat fluctuations around the mean value of a variable entails larger variance of the variable itself in the time domain. Hence, this would, in turn, implicate a less tight maintenance of the set-point values of blood pressure.

Limitations. There are limitations to this study that should not be overlooked. Our protocol included LBNP stimulation at −30 mmHg, which can be a model of moderate hemorrhage (8), while mild LBNP is usually lower than this value of intensity. However, no stronger stimulus was applied in our protocol. Therefore, our results could be considered representative of responses to mild LBNP, but also informative on the transition between a nonhypotensive and a potentially hypertensive stimulus. For this reason, another limitation of the current data is that a full comprehension of the baroreflex failure, which occurs when CVD induces orthostatic intolerance, would be possible only if one were to analyze the response to LBNP levels up to the tolerance threshold, within the same mathematical framework.

Perspectives and Significance

The model-based approach presented in this work addressed for the first time the quantification of the proportional role of arterial vs. cardiopulmonary baroreflex on the maintenance of vascular tone in response to the rapid onset of mild LBNP. Further, this quantitative analysis was applied to compare the variations from spontaneous oscillations due to LBNP and the same variations under the adaptations occurring in long-duration HDBR, therefore, contributing to the elucidation of longstanding problems of 1) unloading of arterial and cardiopulmonary baroreceptors in the presence of mild LBNP and 2) alterations and potential blunting of baroreflex responsiveness because of exposure to long-duration weightlessness.

The larger influence of arterial baroreflex on blood pressure maintenance during long-duration HDBR, even in the absence of evidence pointing to its enhancement, and the simultaneous reduction of the role of cardiopulmonary baroreflex can contribute toward the interpretation of the occurrence of syncope in individuals who have completed HDBR (20), or in astronauts upon return to earth. In addition, these conclusions could also be of importance in interpreting the pathology of subjects who are prone to syncope and orthostatic intolerance. The application of the proposed mathematical technique to protocols, including higher levels of LBNP stimulation in both healthy and pathological subjects, would enable further integration of the results presented in this paper.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES


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