Altered hormonal regulation and blood flow distribution with cardiovascular deconditioning after short-duration head down bed rest


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Fischer D, Arbeille P, Shoemaker JK, O’Leary DD, Hughson RL. Altered hormonal regulation and blood flow distribution with cardiovascular deconditioning after short-duration head down bed rest. J Appl Physiol 103: 2018–2025, 2007. First published September 13, 2007; doi:10.1152/japplphysiol.00121.2007.—This study tested the hypothesis that cardiovascular and hormonal responses to lower body negative pressure (LBNP) would be altered by 4-h head down bed rest (HDBR) in 11 healthy young men. In post-HDBR testing, three subjects failed to finish the protocol due to presyncopal symptoms, heart rate was increased during LBNP compared with pre-HDBR, mean arterial blood pressure was elevated at 0, −10, and −20 mmHg and reduced at −40 mmHg, central venous pressure (CVP) and cardiac stroke volume were reduced at all levels of LBNP. Plasma concentrations of renin, angiotensin II, and aldosterone were significantly lower after HDBR. Renin and angiotensin II increased in response to LBNP only post-HDBR. There was no effect of HDBR or LBNP on norepinephrine while epinephrine tended to increase at −40 mmHg post-HDBR (P = 0.07). Total blood volume was not significantly reduced. Splanchnic blood flow taken from ultrasound measurement of the portal vein was higher at each level of LBNP post-compared with pre-HDBR. The gain of the cardiopulmonary baroreflex relating changes in total peripheral resistance to CVP was increased after HDBR, but splanchnic vascular resistance was actually reduced. These results are consistent with our hypothesis and suggest that cardiovascular instability following only 4-h HDBR might be related to altered hormonal and/or neural control of regional vascular resistance. Impaired ability to distribute blood away from the splanchnic region was associated with reduced stroke volume, elevated heart rate, and the inability to protect mean arterial pressure.

splanchnic blood flow; lower body negative pressure; orthostatic tolerance; angiotensin II; epinephrine

IMPAIRMENT OF ORTHOSTATIC tolerance is well documented after spaceflight and head-down bed rest (HDBR). Up to 64% of astronauts are unable to complete a 5- or 10-min stand test after short-duration Space Shuttle flights (3, 15) and the incidence of orthostatic intolerance increases with longer flights (33). Similar reductions in tolerance to upright posture or lower body negative pressure (LBNP) occur after HDBR (21, 24). Interestingly, orthostatic tolerance is impaired after HDBR as short as 2 to 4 h (6, 32).

The mechanisms responsible for orthostatic intolerance are complex and probably vary between short- and long-duration HDBR. Considerable effort has been devoted to investigation of the roles of reduced blood volume, decreased cardiac muscle mass, increased compliance in dependent leg veins, and ineffective arterial vasoconstriction mediated by the sympathetic nervous system or circulating hormonal control (2, 3, 10, 13, 15, 22, 40, 43, 48, 49). Rapid alterations also occur in hormonal regulation of the arterial blood pressure and blood volume during HDBR (18–20, 23, 36). Recently, it has been shown that alterations in blood flow distribution between the splanchnic and peripheral circulations with elevated splanchnic flow might contribute to orthostatic intolerance after 90-days HDBR (1) as well as in some patients with postural tachycardia syndrome (45).

In this study, we investigated mechanisms that might contribute to cardiovascular deconditioning during the short-term 4-h model of HDBR. We hypothesized that circulating levels of vasoconstrictor hormones would be reduced while epinephrine would be increased after short-duration HDBR and that these changes in vasoconstrictor hormones would be associated with elevated splanchnic blood flow compared with the pre-HDBR condition during the challenge of LBNP.

METHODS

Subjects. Eleven healthy men (age 23 yr, SD 3) participated in this study. The study received ethics approval from the Office of Research Ethics at the University of Waterloo and each subject provided written consent on an approved form. Subjects were nonsmokers who were free from any cardiovascular or metabolic disease and had not taken any medication for 3 mo prior to the study. Subjects were instructed to abstain from caffeine, alcohol, and heavy exercise for 24 h prior to the study.

Experimental design. Subjects reported to the laboratory in the morning after a light, low-fat breakfast including 250 ml juice. The study commenced at ~8:30 AM, 90 min after breakfast. A catheter was inserted in the antecubital vein of the right arm on arriving in the laboratory and 30 min of seated rest was provided to normalize for postural blood volume shifts before the pre-HDBR baseline. The subjects assumed a supine position inside an LBNP chamber for the random and constant LBNP protocols as described below. Blood was drawn again at the maximum applied stress (~40 mmHg) in the constant LBNP protocol. On completing the LBNP protocols and immediately prior to 4-h 6° HDBR, total blood volume was measured in the supine posture by carbon monoxide rebreathing (4). Subjects ate a low-fat lunch of turkey breast sandwich and consumed 250 ml of water during the first hour of HDBR. Subjects also drank 125 ml of water at hours 2 and 3 of HDBR. Following 4 h of HDBR, subjects were retested with the same series of experiments in the same order.

Random LBNP. Random levels of LBNP were applied to the body during an 11.5-min protocol (see Fig. 1) that used three levels of LBNP (~10, −20, −30 mmHg). This protocol allowed for studies of
Blood pressure, HR, and CVP were measured as previously described during the random LBNP protocol. The portal vein was imaged and velocity determined using a 3.75-MHz ultrasound probe. Depth was adjusted on an individual basis, typically between 8 and 12 cm. Visualization of the bifurcation ensured that the portal vein was in the same plane throughout imaging to determine diameter and velocity as described below.

**Blood processing and analysis.** A 3-ml sample of whole blood for determination of catecholamines was mixed with 75 μl of EGTA-glutathione anticoagulant and was centrifuged at 4°C for 15 min. The 5-ml sample of whole blood for determination of angiotensin II and endothelin-1 was mixed with 125 μl of EDTA anticoagulant and centrifuged at 4°C for 15 min. The 2-ml sample of whole blood for determination of aldosterone was left to stand for 10 min in room air to clot and then rimmed and centrifuged for 10 min.

Catecholamines were extracted from the plasma by adding acid-washed alumina and mixing by inversion. The pellet was washed with distilled water and the catecholamines were released into 0.1 M perchloric acid and separated by centrifugation. The concentrations of epinephrine and norepinephrine were determined by HPLC with electrochemical detection (2465 Electrochemical Detector, Waters, Milford, CT) and quantified by determining the area under the peak. Working and internal standards were used to correct the measurements.

Endothelin-1 was determined in duplicate by a TiterZyme enzyme immunoassay assay (Assay Designs, Ann Arbor, MI). A microplate reader (SPECTRAmax PLUS 384, Sunnyvale, CA) was used to read each well and a four-parameter logistic curve-fitting program calculated the concentration of endothelin-1. Active renin was measured in duplicate on serum samples with the Active Renin IRMA (2-site immunoradiometric assay; Diagnostic Systems Laboratories, Webster, TX). Samples were rapidly frozen after centrifugation at room temperature then rapidly thawed to avoid the temperature range 2–8°C. Renin was isolated by sandwiching between anti-human renin antibodies labeled with 125I and a coated bead and then read by gamma counter (Beckman Gamma 5500, Irvine, CA). Plasma angiotensin II was measured in duplicate by an enzyme immunoassay (Bertin Group). The wells were read by a microplate reader between 405 and 414 nm. A linear curve-fitting program was used to quantify the concentrations of angiotensin II. Plasma aldosterone was measured in duplicate using a Coat-A-Count125I radioimmunoassay (Diagnostic Products, Los Angeles, CA) and read by gamma counter (Beckman Gamma 5500).

**Data analysis.** Instantaneous aortic blood velocity, BP, ECG, and CVP were transferred to data-acquisition hardware (Powerlab 16 channel SP unit, ADInstruments, Colorado Springs, CO) and collected at 200 Hz. Beat-to-beat data were obtained as the mean arterial pressure (MAP), CVP, and aortic blood velocity between each R-R interval. Cardiac output (Q) was calculated from the product of HR and beat-by-beat stroke volume determined from aortic blood velocity and cross sectional area. TPR was calculated from (MAP – CVP)/Q.

Portal vein diameter was measured leading edge to trailing edge of the lumen proximal to the bifurcation. Care was taken to ensure that clear images of the near and far wall of the portal vein were used for measurements. Mean portal blood flow velocity and diameter of the portal vein were obtained from three separate frozen screen images at each level of LBNP and averaged to give a mean velocity and a mean diameter that were used to estimate splanchic blood flow. Blood cell velocity was measured proximal to the bifurcation and determined from the Doppler shift equation with correction of the angle of insonation if necessary based on a visual inspection of the incident beam and the long axis of the portal vein. An index of splanchic vascular resistance (SVRi) was calculated from (MAP – CVP)/SBF. Measurements were taken during the last minute of each LBNP level during the constant LBNP protocol.

**Cardiopulmonary baroreflex.** An index of cardiopulmonary baroreflex function was determined by applying autoregressive moving average cardiovascular responses to changes in central venous blood volume with a focus on cardiopulmonary baroreflex control of arterial blood pressure. Cardiac output was calculated from the instantaneous blood velocity in the ascending aorta measured with a 2-MHz pulsed wave Doppler ultrasound probe (model 500 M, Multigon Industries) and cross-sectional area of the aortic root (model SSH-140A, Toshiba, Tochigi-Ken, Japan). The depth of the pulsed wave signal was adjusted on an individual basis, typically between 8 and 12 cm. Blood pressure (BP) was measured on the left middle finger (Finometer, Finapres Medical Systems, Amsterdam, Netherlands). Heart rate (HR) was measured from a three-lead electrocardiograph, and central venous pressure (CVP) was estimated using the dependent right arm technique (17), with the CVP pressure transducer (TranStar, Medex, Carlsbad, CA) set at the height of the right heart using a laser level with the position marked on the skin for replication purposes during post-HDBR testing.

**Constant LBNP.** The constant LBNP protocol consisted of 2-min stages of increasing LBNP of 0, −10, −20, −30, and −40 mmHg.
average (ARMA) analysis to data from the random LBNP protocol. The model considered the effects of two simultaneous inputs, CVP and MAP, on the output response of TPR for calculation of baroreflex gain (25, 35). ARMA modeling parameters were determined by a parameter reduction algorithm (35, 37). Error analysis based on three criteria was used to choose the best model and eliminate inappropriate solutions from the algorithm (25, 37): 1) minimal residuals (difference between measured response and modeled response), 2) residuals that had a Gaussian distribution and did not correlate with the inputs, and 3) appearance of reasonable responses. The theoretical step responses were calculated to determine the response of cardiopulmonary gain to a sustained 1-cmH₂O decrease in CVP and the time to 95% response was determined.

Statistical analysis. A two-way repeated measures analysis of variance (SAS Institute, Cary, NC) was used to compare main effects of condition (pre- and post-HDBR) and level of LBNP for HR, MAP, CVP, and SBF. When interaction effects between condition (pre- or post-HDBR) and LBNP were observed, planned comparisons of pre-vs. post-HDBR were made at each level of LBNP by the least squares difference post hoc test. Plasma hormone concentrations were analyzed with one-way repeated measures analysis of variance to achieve planned comparisons to determine whether resting baseline was changed from pre- to post-HDBR and whether concentrations changed from baseline with application of −40 mmHg LBNP. Absolute P values are reported. Relationships between variables were analyzed by linear regression. Data are presented as the mean and standard deviation (SD).

RESULTS

Random LBNP protocol. The time series data for the random LBNP protocol are shown for a single subject in Fig. 1. Cardiovascular variables were calculated over the final 10 s of each LBNP stage. SV measured by Doppler ultrasound was not different from pre- to post-HDBR at 0 mmHg [pre: 92 ml (SD 18) vs. post: 89 ml (SD 18)] but was significantly reduced post-HDBR at −10 mmHg [89 ml (SD 16) vs. 82 ml (SD 21)], −20 mmHg [85 ml (SD 19) vs. 76 ml (SD 23)] and −30 mmHg [83 ml (SD 19) vs. 69 ml (SD 20); interaction effect HDBR·LBNP, P < 0.02]. A linear regression calculated for all individual pairs of CVP and SV data revealed no change from pre- to post-HDBR (pre: SV = 4.63 CVP + 51.6, vs. post: SV = 4.60 CVP + 52.6). The Q was reduced slightly at the higher levels of LBNP post-HDBR, but this difference was not significant. A linear regression for the relationship between TPR and CVP revealed a greater slope following HDBR (pre: TPR = −0.57 CVP + 21.9, vs. post: TPR = −1.01 CVP + 25.1; P < 0.002; Fig. 2).

Cardiopulmonary baroreflex gain was estimated with the ARMA model from the random LBNP protocol time series using CVP and MAP as inputs and TPR as the output. The calculated step gain for CVP → TPR was significantly elevated from pre- to post-HDBR [Fig. 3, P < 0.05, pre: 0.76 TPRunit/cmH₂O (SD 0.45) vs. post: 1.35 TPRunit/cmH₂O (SD 0.73)] but the time to 95% of the calculated step was unchanged following HDBR [pre: 27.2 s (SD 12.0) vs. post: 22.2 s (SD 11.0)]. The calculated step gain for the MAP → TPR response was not different from pre- to post-HDBR [pre: 0.22 TPRunit/mmHg (SD 0.25) vs. post: 0.19 TPRunit/mmHg (SD 0.15)].

Constant LBNP protocol. Three subjects were unable to complete the entire 2-min stage of LBNP at −40 mmHg in the post-HDBR testing because of signs of presyncope. During the constant LBNP phase of the testing, HR was significantly elevated post- compared with pre-HDBR (main effect of HDBR, P < 0.0001; interaction effect HDBR·LBNP, P < 0.01; Fig. 4). MAP was significantly different post-HDBR (interaction effect of HDBR·LBNP, P < 0.01; Fig. 4), where baseline (P < 0.01), −10 mmHg (P < 0.05), and −20 mmHg LBNP (P < 0.02) means were significantly elevated post-HDBR and MAP was unchanged at −30 mmHg LBNP (P = 0.43) and was significantly reduced at −40 mmHg LBNP (P < 0.02). CVP was significantly reduced following HDBR (main effect of condition, P < 0.001; Fig. 4).

Splanchnic blood flow. Splanchnic blood flow was unchanged in baseline following 4-h HDBR, but was significantly elevated post-HDBR at all levels of LBNP (interaction effect of HDBR·LBNP, P < 0.05; Fig. 5), with significant increases in red blood cell velocity through the portal vein (main effect of HDBR, P < 0.01) and in portal vein diameter (main effect of HDBR, P < 0.0001). Post-HDBR, there was a reduced slope in the relationship between splanchnic vascular resistance index (SVRi) and CVP (pre: SVRi = −6.32 CVP + 99.8 vs. post: SVRi = −2.91 CVP + 69.1, P < 0.001; Fig. 2).

Blood measurements. Norepinephrine levels (Fig. 6) were not different at baseline or at −40 mmHg LBNP after HDBR. Baseline epinephrine levels were also unchanged at rest and the elevation in epinephrine at −40 mmHg LBNP after HDBR was not significant (P = 0.07; Fig. 6B). Endothelin-1 levels were significantly elevated at −40 mmHg LBNP in both pre- and post-HDBR (P < 0.003; Fig. 6C). Plasma renin was reduced after HDBR at baseline (P < 0.001; Fig. 6D) and was significantly elevated from baseline to −40 mmHg LBNP only for the post-HDBR tests (P < 0.02). Likewise, angiotensin II levels were depressed following HDBR at baseline (P < 0.002) and increased from baseline to −40 mmHg LBNP (P < 0.04; Fig. 6E). Aldosterone was depressed after HDBR at baseline (P < 0.004; Fig. 6F) and was not affected by LBNP in either pre- or post-HDBR tests.

Total blood volume. Total blood volume [pre: 5,775 ml (SD 916) vs. post: 5,830 ml (SD 1,005); P = 0.65], red blood cell volume [pre: 2,300 ml (SD 390) vs. post: 2,389 ml (SD 415);
DISCUSSION

The current study provides new insight into mechanisms that contribute to rapid cardiovascular deconditioning after only 4-h of HDBR. We observed important differences in regional distribution of blood flow during the LBNP test after HDBR. Portal vein blood flow was elevated due to an attenuated vasoconstrictor response that was associated with lower plasma levels of renin and angiotensin II. In contrast with the attenuated vasoconstriction in the splanchnic circulation, total peripheral resistance increased more after HDBR, reflecting the increased gain of the cardiopulmonary baroreflex. Underlying the cardiovascular responses after HDBR was a reduction in CVP that caused decreased stroke volume and increased heart rate to maintain cardiac output. That 4-h HDBR caused impaired orthostatic tolerance was evident from the failure of 3 of 11 subjects to finish the relatively mild stress of 2-min stages up to −40 mmHg LBNP. Overall these data reveal rapid changes in mechanisms responsible for the control of blood flow distribution and the neural-hormonal protection of mean arterial blood pressure that increased the likelihood of syncope with an orthostatic challenge.

Central cardiovascular and cardiopulmonary baroreflex responses. The reduction in CVP is the primary mechanism underlying the decrease in stroke volume and the requirement for the elevated heart rate in acute cardiovascular deconditioning after HDBR as revealed by the response of the subject in Fig. 1. Furthermore, with this particular subject it is apparent in the post-HDBR testing that a marked increase in TPR was necessary to attempt to maintain mean arterial pressure. This subject was one of three who was unable to complete 2-min at −40 mmHg during the constant LBNP phase of the study. The initial response on going to supine or head down postures is an increase in CVP relative to the upright position but CVP does not remain elevated (16). The increase in CVP is a function of the shift of fluids into the thorax along with a transient increase in blood volume that has returned close to baseline values in 4 h (18, 23). It is anticipated that blood volume would be reduced below baseline with longer duration bed rest or space-flight (14, 16, 19, 21). The reduction in CVP with time during 4-h HDBR might be due to increased central vein compliance (5). The present study and recent observations from 90-day HDBR (1) also suggest that changes in blood flow distribution might affect venous return and thus CVP, which in turn could affect stroke volume requiring an increase in heart rate and possibly vasoconstriction.

We employed a modeling approach to investigate the gain of the cardiopulmonary baroreflex from the relationship between CVP and TPR during a test that intermittently applied mild levels of LBNP for either 30 s or 1 min. There were two primary reasons that we employed the random LBNP protocol. The first was very practical in that application of LBNP at these low levels for very brief periods of time did not induce symptoms of presyncope, as observed with progressive 2-min stages to −40 mmHg in our constant LBNP protocol. Success-
fully completing the protocol can have great advantages for investigation of cardiopulmonary baroreflex in populations that might be susceptible to fainting, such as astronauts returning from long-duration spaceflight. The second reason for employing the random LBNP protocol was that the beat-by-beat data were modeled to obtain the characteristic response of the integrated baroreflex function. Recognizing that the TPR response is a consequence of simultaneous input from the arterial and cardiopulmonary baroreflex responses in addition to circulating hormonal and local myogenic components (25), we employed an autoregressive moving average (ARMA) analysis (25, 35) to solve for two simultaneous inputs (CVP and MAP) and one output (TPR). The solution then partitioned the TPR response into components due to CVP, MAP, and unrelated factors (residual noise). The significant increase in the gain of the CVP → TPR component of the baroreflex response after 4-h HDBR reflected the requirement for increased vasoconstriction to maintain arterial blood pressure in the face of reduced cardiac stroke volume and is consistent with results from Convertino and colleagues (8) who examined forearm vascular resistance. A similar conclusion could be reached by comparing the slopes of the relationship between TPR and CVP from the values taken from the average of the final 10 s of each stage of LBNP during the same test (Fig. 2). The gain from the ARMA analysis and the slope of the linear regression provided the same qualitative information but there were quantitative differences that could reflect the ability of the ARMA model to partition changes in TPR to CVP in isolation. In the current study, we did not detect any difference in the time course of the cardiopulmonary baroreflex after HDBR, but this factor should not be ignored as we have shown with a similar modeling approach that important changes can occur such as in the slower cerebrovascular autoregulatory response with elevated arterial CO₂ (11).

The ARMA model also gives an index of the vascular component of the arterial baroreflex (MAP → TPR). In the current study, the ARMA model indicated that for any change in MAP there was a directionally similar change in TPR, an observation consistent with a myogenic response (25, 30) and not reflex neural modulation of vascular tone. This contrasts with evidence for increased sympathetic nerve activity during activation of the arterial baroreceptors by neck suction (38), with upright posture (43) as well as with acute reductions in MAP such as following premature ventricular contractions where a discharge of sympathetic vasoconstrictor nerves is observed (50). Thus it appears that a feedforward control of TPR achieved by modulation of the cardiopulmonary baroreflex in the supine posture with moderate LBNP is sufficient to establish the sympathetic neural regulation of vasoconstriction (47) and that the arterial baroreflex, which does provide tonic regulation of heart rate (24) and probably contributed to the increase in HR after HDBR, is a reserve to protect arterial pressure in the face of acute or sustained deviations from the set point.

Blood flow distribution and hormonal effects. The classic study of Johnson and colleagues (27) revealed greater sympathetic vasoconstrictor activity in peripheral (muscle) than splanchnic vascular beds during activation of the cardiopulmo-
nary baroreflex. Our study is the first to show that regional blood flow distribution can rapidly be altered by a short period of HDBR. We observed after only 4-h HDBR that there were greater increases in TPR as CVP was reduced during LBNP while there were actually smaller increases in splanchnic vascular resistance during LBNP (Fig. 2). Increases in sympathetic nerve activity during LBNP might account for the greater vasoconstriction, but many studies have reported no change or even a reduction in sympathetic nerve activity both at rest and during an orthostatic stress after HDBR or spaceflight (28, 31, 39, 42, 43). An elevation in myogenic tone is a possible contributor to increased TPR (30). The mechanism responsible for the regional differences with less vasoconstriction in the splanchic region after HDBR is not clear; however, the possible role of angiotensin II should be considered. The importance of angiotensin II for orthostatic tolerance has been well identified by Greenleaf and colleagues (22). It is possible that beneficial effects of angiotensin II might be directly related to the magnitude of splanchnic vasoconstriction during LBNP. Stadeager et al. (44) studied splanchnic blood flow responses in subjects in whom the renin-angiotensin system was activated by diuretic-induced moderate salt depletion. Under these conditions, splanchnic vascular resistance increased during LBNP and blood flow was reduced. However, when they reduced production of angiotensin II by the angiotensin converting enzyme inhibitor enalapril, splanchnic vascular resistance was lower at rest and did not increase during LBNP although TPR increased. These findings from Stadeager et al. suggest that the lower concentration of angiotensin II that we found after 4-h HDBR might directly influence splanchnic vascular resistance and also interact with normal sympathetic activation to modify regional blood flow distribution. With longer duration HDBR, the renin-angiotensin system is activated (19) and the response to infused angiotensin II is reduced (9).

Fig. 6. Blood hormone levels measured in the supine resting baseline condition and at ~40 mmHg LBNP in both the pre-HDBR (gray bars) and post-HDBR (black bars). Values are mean ± SD, significant differences indicated by: *baseline pre- vs. post-HDBR, P < 0.05; † ~40 mmHg LBNP vs. corresponding baseline, P < 0.05.
The reduction in angiotensin II concentration in the current study was a direct consequence of the translocation of fluids to the upper body during the period of HDBR. Consistent with other studies we observed reductions in plasma renin, angiotensin II, and aldosterone after 4-h HDBR (18, 23). We did not see a significant change in the resting baseline plasma concentrations of norepinephrine, epinephrine, or endothelin-1 after 4-h HDBR. In previous research, plasma norepinephrine has been reduced in the first hour of HDBR in some (18, 23) but not all studies (20), whereas plasma epinephrine tends to be more variable and is often unaffected early in HDBR (20, 23).

The LBNP challenge in the current study to investigate hormone responses was rather mild, consisting of 2-min stages at −10, −20, −30, and −40 mmHg. Thus it is not surprising that we were unable to detect changes in plasma norepinephrine during LBNP in either the pre- or post-HDBR tests compared with application of greater stimuli with stand tests (48, 51) or more prolonged LBNP (22). Although the LBNP stimulus was mild, there was a small increase in plasma epinephrine in the post-HDBR tests (P = 0.07), which might have contributed to vasodilation at −40 mmHg LBNP as proposed previously (13, 48, 49). Endothelin-1 was increased by LBNP in both the pre- and post-HDBR conditions although the magnitude of increase was small. This observation is consistent with previous findings of increased endothelin-1 during head-up tilt (29) but endothelin was not increased in astronauts during tilt (34) or by LBNP (22).

The plasma renin, angiotensin II, or aldosterone concentrations were not affected by LBNP during the pre-HDBR tests. This again reflected the relatively mild nature of the LBNP stress, as these hormones are typically elevated by standing or greater levels of LBNP (22, 51). However, in the post-HDBR tests LBNP caused a significant increase in renin and angiotensin II, indicating that these low levels of LBNP were now more stressful. After 4-h HDBR, the stimulation of the renin-angiotensin-aldosterone system might be important for the regulation of arterial blood pressure.

Limitations. The possibility of a circadian influence on the hormonal and vascular responses cannot be completely excluded in the current study. Variations in fasting portal vein flow have been identified in patients with liver cirrhosis (41), but during the hours when the current study was conducted the fluctuations were relatively minor. In addition, portal vein flow is elevated after a meal but it returns to baseline within ~3 h (41). In the current study, baseline portal vein flow at 0 mmHg was not different pre- vs. post-HDBR (Fig. 5), suggesting there was no residual effect of the sandwich consumed during the first hour of HDBR. A sub-group of five subjects was investigated for portal vein flow after 4-h HDBR compared with after 4-h seated rest with all other conditions the same. In contrast to the 196 ± 93 ml/min increase in flow from baseline to −40 mmHg LBNP after 4-h HDBR, there was a slight 29 ± 23 ml/min reduction in flow after 4-h sitting. While these data suggest that the alterations in splanchnic flow were a consequence of the 4-h HDBR, it is important to acknowledge that a complete control group was not included in the current study and we therefore cannot exclude the possibility that other factors, including time of day, might have affected splanchnic blood flow. Plasma concentrations of hormones in the renin-angiotensin-aldosterone system vary throughout the day (26); however, we previously showed that HDBR has an independent effect on plasma renin activity compared with a seated control condition and that concentrations returned to baseline after a meal within 3 h (23).

Conclusions and perspectives. Cardiovascular deconditioning following only 4-h HDBR was recognized in the current study by the elevated heart rate response to mild levels of LBNP, the drop in mean arterial blood pressure, and the inability of three subjects to complete the 2-min stage at −40 mmHg LBNP. Our modeling approach to integrative cardiovascular control revealed the role of the cardiopulmonary baroreflex to increase vasoconstriction in response to the reduction in central venous pressure. The failure to reduce splanchnic blood flow to the same extent as in pre-HDBR and its association with lower angiotensin II levels after short-duration HDBR could have practical implications. First with regard to investigations of bed rest and spaceflight, the data add to the recent results of Arbeille and colleagues (1) and show the importance of the splanchnic circulation as a contributing factor to orthostatic intolerance even in the presence of increased vascular resistance in other regions of the body and an increased gain of the cardiopulmonary baroreflex. Second, these results might be relevant to individuals who nap or are confined to bed with injury or illness during the daytime. Elderly women who napped during the day were at increased risk of falling and suffering hip fracture, but the time of day of the fall was not available (46). Patients convalescing from cardiovascular disease or other illnesses should receive frequent exposure to an orthostatic stress to prevent syncope during their return to upright ambulation (7). Future research should examine the potential for alterations in regional blood flow contributing to orthostatic hypotension after spaceflight, HDBR, daytime naps, and patients restricted to bed.

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DISCLOSURES

There are no conflicts to be disclosed concerning this research.

REFERENCES

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