Portal vein cross-sectional area and flow and orthostatic tolerance: a 90-day bed rest study.

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Arbeille, Philippe P., Stephane S. Besnard, Pascaleine P. Kerbeci, and Dania M. Mohty. Portal vein cross-sectional area and flow and orthostatic tolerance: a 90-day bed rest study. J Appl Physiol 99: 1853–1857, 2005; doi:10.1152/japplphysiol.00331.2005.—The objective of this study was to evaluate the changes in the portal vein cross-sectional area (PV CSA) and flow during a stand test associated with orthostatic intolerance. Eighteen subjects underwent a 90-day head-down tilt (HDT) bed rest at 6°: 9 controls (Con) and 9 with flywheel exercise countermeasures (CM). At post-HDT, nine subjects (5 CM, 4 Con) were tolerant, and nine were intolerant. The PV CSA was measured by echography. We found that at HDT day 85, the PV CSA at rest had increased less in the CM subjects than in the Con (+12% vs. +27% from pre-HDT supine; P < 0.05), whereas it increased similarly in tolerant and intolerant subjects (23 and 16%, respectively). Two days after the HDT, there was a decrease in the PV CSA supine compared with the pre-HDT PV CSA supine that was similar for all groups (Con: −11%, CM: −21%; tolerant: −10%, intolerant: −16%; P < 0.05). The PV CSA decreased significantly less from supine to standing in the Con than in the CM group (−2 vs. −10% compared with the pre-HDT stand test; P < 0.05). The PV CSA also decreased significantly from supine to standing compared with the pre-HDT stand test in the tolerant group but not in the intolerant group (−20 vs. +2%; P < 0.05). From these findings, we conclude the following. 1) Because the portal vein is the only output from the splanchnic vascular area, we suggest that the lower reduction in the PV CSA and flow associated with orthostatic intolerance was related to a lower splanchnic arterial vasoconstriction. 2) The flywheel exercise CM helped to reduce the distension of the splanchnic network at rest and to maintain partially the splanchnic vasoconstriction, but it did not reduce the orthostatic intolerance.

portal vein; echography; orthostatic tolerance

HEAD-DOWN TILT (HDT) bed rests of short duration (24 h/day for several days) have been found to induce cardiovascular deconditioning and orthostatic intolerance as measured by heart rate and blood pressure responses to orthostatic tests (8, 11, 12, 21, 23, 27, 29, 33, 35).

Hemodynamic measurements during orthostatic tests (lower body negative pressure, tilt and stand tests) have shown that in tolerant subjects (finishers) the stroke volume drops, the cerebral flow decreases slightly, and the lower limb flow drops because of a significantly increased vascular resistance in the lower limbs (2, 31). As a consequence, the cerebral-to-femoral flow ratio, which quantifies the distribution of blood flow in favor of the brain, increases significantly. In tolerant and intolerant subjects, the stroke volume is reduced by a similar factor, but the femoral flow is reduced to a lesser extent and the vascular resistance of the lower limbs vascular resistance increases significantly less in intolerant subjects than in tolerant subjects. The reduction of the lower limb flow in tolerant subjects may be considered to be part of the hemodynamic adaptation to the drop in stroke volume (1, 2, 31). Conversely, in nontolerant subjects, the lower limb flow does not decrease, which reduces the effectiveness of the hemodynamic adaptation. The second major hemodynamic change found in intolerant subjects is the greater distension of the lower limb vein in the stand test, which does not favor the venous return (2, 6, 9, 10, 18).

Such responses in the lower limbs have been observed and measured in a significant number of HDT subjects and cosmonauts, but limited data are available on the possible contribution of the splanchnic arterial and venous networks to the flow redistribution in response to the fluid shift induced by an orthostatic test. The portal vein flow, which is ~11/min, is the exclusive output from the splanchnic system, which means that the portal flow combines all the flows delivered to this network by the celiac trunk, mesenteric vessels, etc. The objectives of this study were 1) to quantify the changes induced in the portal flow volume at rest by HDT and 2) to quantify the portal vein cross-sectional area (PV CSA) changes associated with the fluid shift induced by a stand test in normal subjects before and after a 90-day long-term HDT bed rest with and without countermeasures.

METHODS

Subjects. Eighteen healthy young male subjects participated in a 90-day 6° HDT bed rest trial at the Medes Institut at Rangueil Hospital medical facility (Toulouse, France). At the start of the bed rest, the subjects were aged 33.1 ± 0.9 yr, with average height and weight of 1.75 ± 0.01 m and 71.1 ± 1.1 kg, respectively. All subjects passed the orthostatic tolerance test (10 min +80° head-up tilt test) during the selection process. They received a complete description of the experimental procedure before giving their written consent to the protocol approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Midi-Pyrénées (France). The protocol was in accordance with the Declaration of Helsinki. None of the subjects were taking cardiovascular medication at the time of the study and all subjects were nonsmokers. The subjects were randomly divided into two groups: nine controls and nine countermeasure (CM) subjects. The CM subjects performed a combined eccentric-concentric resistance exercise (flywheel exercise) every 3 days. At a later stage, after the bed rest the orthostatic intolerance was evaluated, the subjects were again divided into tolerant and intolerant subjects (9 in each group).

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HDT bed rest program. The experimental program consisted of a 15-day ambulatory control period followed by 90 days of bed rest at −6° HDT, followed by 15 days of post-bed rest recovery. During the bed rest period, the subjects remained in HDT continuously for all activities. The subjects were given a diet of 2,000 ± 300 kcal/day with a sodium input of 3 g/day. The water intake was limited to 3 l/day. Energy (~600 kcal extra) and water (~1 liter extra) supplements were offered to the CM subjects on the exercise days. The subjects were supervised and monitored 24 h/day. The lighting was on between 0700 and 2300 each day. All studies were conducted in a quiet room at a temperature of ~24°C.

CM exercise protocol. The CM took part in a resistance-exercise program, which consisted of series of intermittent, rhythmic, explosive efforts alternating between eccentric and concentric contractions on the flywheel exercise device. Two types of exercise can be performed on this device: squat and calf-press (32). The former exercises the knee and hip extensor muscle groups, and the latter exercises the ankle plantar flexors. The mean power during the concentric phase of the squat and calf-press activities was 555 and 380 W, respectively. The exercises were carried out in 29 sessions, 1 every 3 days, starting on day 5 of the bed rest. Progressive warm-ups were carried out before 4 sets of 7 maximum-effort concentric and eccentric cycles of squat, followed by 4 sets of 14 cycles of calf press. Two minutes of rest were allowed between the sets and 5 min between the exercises. The subjects pushed with maximum concentric force until almost full extension, paused for a moment just after the turning point, and then attempted to stop the momentum of the device (eccentric force). The total duration of maximum muscle action averaged 35 min over the whole HDT period.

Orthostatic tolerance test (1 day before HDT and the first day after). Orthostatic tolerance was assessed using a tilt test on the day when the subjects stood up for the first time after HDT. The subject remained at rest in a supine position for 10 min and then tilted at 80° for 10 min on a tilt table with a footplate. Heart rate and arm blood pressure were monitored beat by beat with, respectively, a Portapres system (TNO, Biomedical Instrumentation Research Unit, Amsterdam, The Netherlands) and with an oscilloscope (Dynamap, Critikon, Tampa, FL). The tilt tests were aborted either on the subject’s request in case of discomfort, or if 1) the systolic blood pressure had decreased by ~30 mmHg below the initial value or the heart rate had increased by 15 beats/min within 1 min or 2) there were presyncope symptoms such as nausea, pallor, sweating, dizziness, or visual disturbances.

Portal vein echographic examination (2 days before HDT, after 85 days of HDT, and 2 days after HDT). The 3.5-MHz sector scan probe (Challenge 2000, Esaote, Firenze, Italy) was held by a sonographer on the chest of the subject approximately at the intersection of the mammalian line and xiphoid line. The acoustic window passed through an interspace coast to ensure that there was no intestinal barrier. The main trunk of the portal vein was identified from the portal vein bifurcation, and the measurements were performed in its straight portion parallel to the main biliary duct or hepatic artery.

The portal vein was measured both by echography and Doppler with the subject in supine position before HDT and on the 85th day of HDT. The PV CSA was measured using both longitudinal (diameter) and transverse cross-sectional echographic views. The portal vein mean flow velocity was measured using Doppler ultrasound on the longitudinal view. The portal vein flow volume was then calculated by multiplying the cross-sectional area by the mean flow velocity (flow volume (in ml/min) = mean velocity (in cm/s) × cross-sectional area (in cm²) × 60 s; Fig. 1). The actual portal vein flow volumes measured in supine subjects before HDT and on the 85th day of HDT were compared.

Two days before and 2 days after the HDT, all the subjects were subjected to a short stand test (15 min supine followed by 4 min sitting with legs dangling, and 10 min standing). During the stand test, only the PV CSA was measured using echography (no Doppler) to minimize the manipulations of the operator on the subject (displacement and pressure of the echo probe, Doppler adjustment, etc.) and the duration of the data capture during the stand test of the test. Published results show that the portal vein flow volume changes proportionally to the PV CSA in both supine and standing positions (5). The changes in the PV CSA during the stand test in the Con, CM, tolerant, and intolerant subjects were compared. The same sonographer performed all the echographic measurements.

Statistical analysis. The values were expressed as means (SD), and differences were considered statistically significant if P < 0.05. Data were analyzed using nonparametric tests because of the number of subjects. The comparisons between the Con and CM subjects and between the tolerant and intolerant subjects were made using the Mann-Whitney test for unpaired variables. Two periods within the same group were compared using the Wilcoxon test for paired data.

RESULTS

All subjects completed the HDT period of 90 days. The day after the HDT, a tilt test identified nine subjects (5 Con and 4 CM) as tolerant and nine as intolerant. On the 85th day of HDT, the PV CSA had increased less in the CM subjects than in the Con (+12 vs. +27% greater than
pre-HDT; \( P < 0.05 \), and there was a similar increase in tolerant and intolerant subjects (23 vs. 16%; not significant). The portal vein flow volume increased similarly in all groups (from 27 to 33%; \( P < 0.05 \); Fig. 2, Table 1).

Two days after HDT, the PV CSA, in a supine position, had significantly decreased by a similar amount in all groups (Con: –11%, CM: –21%; tolerant –10%, intolerant –16% compared with pre-HDT, \( P < 0.05 \)).

The decrease in PV CSA from supine to standing position 2 days after HDT was significantly less in the Con than in the CM group (2% vs. –10% compared with pre-HDT stand test; \( P < 0.05 \)). PV CSA decreased from supine to standing significantly in the tolerant group but not in the intolerant group (–20% vs. +2% compared with pre-HDT stand test \( P < 0.05 \); Fig. 3, Table 2).

**DISCUSSION**

**HDT induced splanchnic blood volume stagnation (at HDT day 85; Fig. 2, Table 1)**. This study shows that the portal vein flow volume (in ml/min; Table 1) increases significantly after several weeks of HDT in a similar proportion in all subjects (Con, CM, tolerant, intolerant). Because the portal vein is the only output of the splanchnic network, this result shows that there is an increased splanchnic arterial blood flow associated with the reduction of the vascular resistance in the splanchnic network. The capacity of the splanchnic arterial network to generate a vasoactive response has already been demonstrated during exercise. A progressive splanchnic vasoconstriction during exercise was first reported using invasive studies of indocyanine green uptake, and Doppler ultrasound has confirmed progressive reductions in the blood cell velocity, cross-sectional area, and quantitative portal vein flow (24). After 85 days of HDT, the subject is hypovolemic [10% plasma volume reduction (7)], which also suggests that there is splanchnic vasodilatation.

Moreover, the significant increase in the PV CSA (about +12 to +33%) suggests that there is an increase in blood

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**Table 1. Portal vein flow volume**

<table>
<thead>
<tr>
<th>PV Flow</th>
<th>Supine pre-HDT</th>
<th>HDT day 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerant</td>
<td>1,199 (170)</td>
<td>1,595 (316)</td>
</tr>
<tr>
<td>Nontolerant</td>
<td>1,384 (286)</td>
<td>1,751 (339)</td>
</tr>
<tr>
<td>Control</td>
<td>1,365 (261)</td>
<td>1,753 (387)</td>
</tr>
<tr>
<td>CM</td>
<td>1,135 (51)</td>
<td>1,515 (184)</td>
</tr>
</tbody>
</table>

Values are means (SD) in cm²/min. Measurements were performed pre-head-down tilt (HDT) in the supine position and at HDT day 85 in tolerant, nontolerant, counter measure (CM) and control groups. PV, portal vein.

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**Table 2. Portal vein cross-sectional area in supine and standing position, at pre- and post-stand test**

<table>
<thead>
<tr>
<th>PV CSA</th>
<th>Supine Pre</th>
<th>Stand Pre</th>
<th>Supine Post</th>
<th>Stand Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerant</td>
<td>1.25 (0.3)</td>
<td>1.02 (0.2)</td>
<td>1.11 (0.2)</td>
<td>0.69 (0.11)</td>
</tr>
<tr>
<td>Nontolerant</td>
<td>1.34 (0.21)</td>
<td>0.93 (0.13)</td>
<td>1.17 (0.11)</td>
<td>0.85 (0.13)</td>
</tr>
<tr>
<td>Control</td>
<td>1.39 (0.2)</td>
<td>1.02 (0.18)</td>
<td>1.21 (0.18)</td>
<td>0.88 (0.2)</td>
</tr>
<tr>
<td>CM</td>
<td>1.22 (0.23)</td>
<td>0.91 (0.2)</td>
<td>1.08 (0.16)</td>
<td>0.69 (0.14)</td>
</tr>
</tbody>
</table>

Values are means (SD) in cm². PV-CSA, portal vein cross-sectional area; Pre, pre-stand test; Post, post-stand test.
volume inside the splanchnic network associated with a significant blood stagnation. This enlargement of the PV CSA, like the enlargement of main cephalic veins (3), may be related to the fluid shift toward the upper half part of the body induced by the head-down position. If it is assumed that all the vessels participating in the splanchnic network increase in the same proportion as the portal vein, it can be suggested that the splanchnic blood volume increases by ~30%. This hypothesis suggests that a significant amount of blood is trapped in the splanchnic network and will be redistributed rapidly in response to a fluid shift toward the legs, induced during orthostatic testing or exercise. Additionally, although the flywheel exercise CMs did not reduce the degree of hypovolemia in the CM group compared with the Con (7), it significantly reduced the increase in the PV CSA and flow volume after 85 days of HDT and thus the stagnation of the splanchnic blood.

Potential role of splanchnic blood volume in the cardiovascular response to orthostatic tests (PV CSA change during stand test: Fig. 3, Table 2). This study demonstrates that, during the stand test after HDT, the PV CSA reduces significantly in tolerant subjects, whereas it does not change or reduces less in nontolerant subjects. In a previous study, our laboratory found that, during the stand test, the PV CSA changed in proportion to the flow volume calculated from the PV CSA and the mean flow velocity (Ref. 5; Fig. 4). It can be considered that the lower reduction in PV CSA is associated with a lower reduction in portal vein flow from supine to standing and therefore in splanchnic flow because the portal vein is the only output from this network. For this reason, it seemed more reasonable to measure only the PV CSA during the stand test and not the velocity to reduce the operator’s manipulations on the subject in an upright position.

This suggests that there is a splanchnic vasomotor response triggered in response to the fluid shift toward the lower limbs induced by the orthostatic test. This active response of the splanchnic network could explain why some tolerant subjects do not need vasoconstriction in the legs to preserve brain irrigation.

Failure to achieve adequate arterial vasoconstriction has been pointed as an important mechanism to explain orthostatic intolerance after spaceflight (1, 2, 8, 11, 12, 35). Attenuated sympathetic nervous system activity has been observed in subjects with a propensity to orthostatic hypotension (21, 28, 29). On the other hand, previous short and long-term bed rest (4 days and 42 days) and spaceflight (15 days and 6 mo) studies reported a lack of lower limb arterial vasoconstriction during lower body negative pressure and stand tests (1, 2) and also during pharmacological tests on animal models (19, 22, 23, 27, 33).

Moreover, the ratio of the cerebral to lower limb flow, measured by Doppler ultrasound, increases significantly (40–60%) during stand test in tolerant subjects and cosmonauts (15, 31), whereas it increases significantly less in intolerant subjects. Conversely, in stand tests after HDT or spaceflight, lower limb vascular resistance of some tolerant subjects did not increase, whereas the cerebral-to-femoral flow ratio increased significantly and adequately (4). Thus the cardiac output redistribution is not necessarily linked to lower limb vasoconstriction, and it is suggested that other vascular networks (renal, splanchnic, etc.) may contribute to the flow redistribution to the brain. Rowell et al. (26) have shown that the splanchnic circulation is extremely important for the regulation of the blood pressure in humans.

Nevertheless, here are potential differences in how vascular beds (e.g., splanchnic, lower limb, or skin) respond to orthostatic stress. The splanchnic reservoir is highly compliant and, unlike muscle vascular networks, subject to reflex control of the total intraluminal volume (14, 25). Vascular capacitance may be reduced by constriction of the veins and by constriction of the precapillary resistance vessels to alter flow and passive distention (20). Thus, in response to acute hypovolemia, there is a reflex discharge of splanchnic blood into the rest of the circulation (34), which is mediated by reflexes arising from the unloading of the atrial volume receptors and a reduced arterial baroreceptor activation (13, 16, 17).

Orthostatic stress (lower body negative pressure) induces splanchnic vasoconstriction that is dependent on the activation of both the sympathetic nervous system and the renin angiotensin system (30). If this reflex is attenuated, through reduced baroreflex gain or through attenuated end organ vascular response, the splanchnic flow reduction in relation to vasoconstriction will be less efficient, and therefore the reduction of the splanchnic flow will be lower.

Until now, the two main peripheral hemodynamic factors contributing to the redistribution of the cardiac output toward the brain in tolerant subjects were thought to be the reduction of the femoral flow by ~50% (1, 31) and the absence of lower limb vein distension in upright position after HDT (2, 6, 9, 10, 18). This study has identified another hemodynamic factor: the reduction in the PV CSA in the upright position. It can be seen that the reduction in the PV CSA was greater in Con than in Con subjects, which suggests that exercise CM may help to
empty this splanchic compartment in response to the stand test by reducing splanchic blood stagnation. Unfortunately, this observation was not associated with a measurably higher orthostatic tolerance in the CM group.

In conclusion, this study confirms that the fluid shift induced by a stand test triggers a significant reduction of the PV CSA. This work was supported by the Centre National d’Etudes Spatiales and the European Space Agency 2002.

REFERENCES


