Acute and chronic head-down tail suspension diminishes cerebral perfusion in rats

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Although inadequate cerebral tissue perfusion is often the antecedent of microgravity-induced orthostatic intolerance (44), research into the problem has focused primarily on peripheral and systemic adaptations that disrupt control of mean arterial pressure (6, 16, 42). However, reports exist indicating some individuals who are orthostatically intolerant maintain a normal mean arterial pressure (6, 44). These observations have led researchers to propose that cerebral vascular autoregulation may be altered by bed rest and exposure to microgravity (4, 19, 30, 44).

To investigate how microgravity or the head-down position may affect cerebral vessels, Geary et al. (18) used head-down tail suspension (HDT) with the rat as a model. They showed that cerebral arteries have an enhanced myogenic vasoconstrictor response following a 20-day period of HDT. Smooth muscle cell hypertrophy and a corresponding increase in medial cross-sectional area of the cerebral arteries appear to be an underlying factor for the enhanced myogenic responsiveness (45–47). In addition, an increase in cerebral artery diameter has been reported in rats following prolonged HDT (46, 47). The stimulus for this change in vascular morphology was suggested to be a chronic increase in cerebral perfusion (46, 47), because prolonged elevations in blood flow induce an arterial remodeling that enlarges intraluminal cross-sectional area (5, 14, 27).

In support of the hypothesis that HDT induces an increase in cerebral perfusion, several investigations have reported that short-duration head-down tilt in humans increases cerebral blood flow velocity (15, 24, 25). Therefore, the purpose of the present study was to determine the effects of HDT on cerebral blood flow and blood flow distribution. From the observations that cerebral blood flow velocity increases during short-term head-down tilt in humans (15, 24, 25) and the type of vascular remodeling reported in cerebral arteries of HDT rats (46, 47), we hypothesized that HDT would increase cerebral blood flow during acute (10 min) and chronic (7 and 28 days) HDT. In addition, cerebral vascular resistance was calculated to determine whether chronic elevations in resistance might be the stimulus for the hypertrophy of cerebral vascular smooth muscle cells (45).

Materials and Methods

Animals. All procedures performed in this study were approved by the Texas A&M University Institutional Animal Care and Use Committee and conform to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (DHEW Publication No. (NIH) 85-23, Revised...
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Six- to eight-month-old male Sprague-Dawley rats were obtained (Harlan) and housed in an environmentally controlled room maintained at 23 ± 2°C. The animals were given food (commercial rat chow) and water ad libitum. The animals were randomly assigned to either cage control (n = 8), 7-days HDT (n = 11), or 28-days HDT (n = 9) groups. The hindlimbs of the HDT animals were elevated to an approximate spinal angle of 40–45° from horizontal, as previously described (45). Briefly, the animals were injected with pentobarbital sodium (Nembutal, 30 mg/kg ip; Abbott) to induce anesthesia. While anesthetized, the animal’s tail was washed and dried, and a length of breathable nonelastic adhesive tape (Curity Porous tape, Kendall) with a hook attached to the end was placed on the proximal two-thirds of the tail, which allowed the end of the tail to remain unattached. The ends of the adhesive tape were further bonded to the tail with an additional adhesive (Goop) and allowed to dry for 20 min before suspension. While anesthetized, the animal’s tail was performed, checking for discoloration or tissue damage from the suspension apparatus. The hook attached to the adhesive tape was connected by a small chain to a swivel apparatus fixed at the top of the cage. Adjustments to the length of the chain were made as necessary to prevent the rat hindlimbs from touching any supportive surfaces while the forelimbs maintained contact with the cage floor. This allowed the animal free range of movement about the cage. Control animals were maintained in a normal cage environment, whereas 7- and 28-day HDT rats were kept in the head-down position for 7 and 28 days, respectively.

Surgical procedures. One day before the end of the animal’s treatment period, control and HDT rats were anesthetized with pentobarbital sodium (Nembutal, 30 mg/kg ip). The HDT rats were anesthetized while remaining in the head-down position. A catheter [Silastic, inner diameter (ID) 0.6 mm, outer diameter (OD) 1.0 mm; Dow Corning] filled with heparinized saline (200 U/ml) and connected to a pressure transducer and chart recorder was advanced into the left ventricle of the heart via the right carotid artery as previously described (9, 10). This catheter was subsequently used for the infusion of radiolabeled microspheres. A second polyurethane catheter (Micro-renathane, ID 0.36 mm, OD 0.84 mm; Braintree Scientific), used for the withdrawal of a reference blood sample and measurement of arterial blood pressure, was implanted in the caudal artery of the tail and filled with heparinized saline as previously described (8). Both catheters were externalized and secured on the dorsal cervical region.

Experimental protocol. After the animal recovered from the catheter implantation surgery for 24 h, all catheters and instrumentation were connected while the animals remained in their respective conditions. The conscious rats were allowed to stabilize for 15–20 min from the instrumentation connection before the microsphere infusion procedure was performed. Pulsatile intraventricular pressures (and, hence, heart rates) were monitored during this period, which was sufficient for the heart rate to stabilize. Blood flow in the control group was first measured while the animals were in a normal standing position. The hindlimbs of control rats were then elevated via tail suspension similar to that of the chronic HDT rats. After 10 min of acute HDT, a second microsphere infusion was made to measure blood flow in this position. We have previously demonstrated that two sequential microsphere infusions under the same condition results in similar cerebral blood flows (9, 39). Therefore, differences in cerebral flows between control standing and 10 min of HDT are not due to an ordering effect of the microsphere infusions. In the 7- and 28-day HDT rats, blood flow was measured with the animals in the head-down position. When the microsphere infusion and reference withdrawal sampling were completed, euthanasia solution (0.22 ml/kg, Euthanasia-5 Solution; Henry Schein) was infused through the carotid catheter to anesthetize the animals before euthanasia by exsanguination. The eyes, skull, soleus muscle, and spinal cord (cervical through lumbar portion) were removed from the carcass. The brain and pituitary were removed from the skull, detaching cranial nerves, and the brain was dissected into regions of the olfactory bulbs, left and right cerebrum, thalamic region, midbrain, cerebellum, pons, and medulla. The samples were weighed and placed in counting vials for blood flow determination.

Blood flow determination. Radiolabeled (46Sc, 85Sr, or 113Sn) microspheres (New England Nuclear) with a 15.5 ± 0.2-μm diameter were used for blood flow measurements as previously described (10, 12, 29). Microspheres were suspended by infusion by 10 min of sonication followed by 1 min of agitation on a vortex mixer. Approximately 0.5 million spheres were infused into the rats over a 15- to 20-s period followed by a warm 1.0-ml saline flush. It has been previously shown that the infusion of this number of microspheres induces no detectable hemodynamic disturbances (9, 39). After dissection, tissue samples were weighed and counted in a gamma counter (Packard Cobra II Auto-Gamma) and flows computed (PCGERDA version 2.9 software) from counts per minute and tissue wet weights. Total brain flow was calculated by summing the flows to tissues encompassed by the blood brain barrier. Thus flow to the eye, pituitary, and spinal cord were excluded from calculations of total brain blood flow and vascular resistance.

Arterial pressure, heart rate, and vascular resistance determination. Mean arterial pressure was electronically averaged from beat-to-beat pressure measurements from the caval catheter for periods of 2 min. Heart rate was estimated from pulsatile left intraventricular pressure tracings over 2 min. Pressure recordings made with the pressure transducer (BP100, ADInstruments) at the level of the animal’s head were recorded using the MacLab system and MacLab Chart software (ADInstruments) immediately before and after each microsphere infusion and averaged, because simultaneous pressure recordings and blood withdrawal were not possible. Ocular, regional cerebral, and spinal cord vascular resistances (mmHg/ml-1·min-1·100 g) were calculated by dividing mean arterial pressure (mmHg) by the tissue blood flow rate (ml/min·100 g). Total brain vascular resistance (mmHg· ml-1·min-1) was calculated by dividing arterial pressure (mmHg) by total brain blood flow (ml/min).

Statistical analysis. For each variable (body and tissue mass, arterial pressure, heart rate, tissue blood flow, vascular resistance, and soleus muscle-to-body mass ratio) a one-way analysis of variance was used to compare means across conditions. Duncan’s multiple-range test was used as a post hoc test to determine the significance of differences among means. For all analyses, the 0.05 level was used to indicate statistical significance.

RESULTS

HDT efficacy. Whereas body mass was not different among groups, soleus muscle mass of 7- and 28-day HDT rats was 13% and 35% lower than that in control rats, respectively (Table 1). Similarly, HDT resulted in a 12% and 33% reduction in the soleus muscle-to-body mass ratio in 7- and 28-day HDT rats, respectively.
**Table 1. Cardiovascular and mass characteristics of rats**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 8)</th>
<th>10 min (n = 8)</th>
<th>7 day (n = 11)</th>
<th>28 day (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure, mmHg</td>
<td>128 ± 4</td>
<td>139 ± 3†</td>
<td>132 ± 2†</td>
<td>127 ± 3†</td>
</tr>
<tr>
<td>Heart rate, beats/</td>
<td>449 ± 9</td>
<td>436 ± 9</td>
<td>449 ± 5</td>
<td>438 ± 15</td>
</tr>
<tr>
<td>min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soleus muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mass, mg</td>
<td>230 ± 12</td>
<td>200 ± 6*</td>
<td>149 ± 11‡</td>
<td></td>
</tr>
<tr>
<td>Body mass, g</td>
<td>440 ± 14</td>
<td>437 ± 11</td>
<td>424 ± 15</td>
<td></td>
</tr>
<tr>
<td>Soleus-to-body mass</td>
<td>0.52 ± 0.02</td>
<td>0.46 ± 0.01‡</td>
<td>0.35 ± 0.02†</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rats. HDT, head-down tail suspension. *Mean different from standing control (P < 0.05). †Mean different from 10-min HDT (P < 0.05). ‡Mean different from 7-day HDT (P < 0.05).

(Table 1). Soleus muscle atrophy, which is characteristic of reduced hindlimb skeletal muscle weight-bearing activity, confirms the efficacy of the HDT treatment.

**Heart rate and arterial pressure.** Heart rate was not different among conditions (Table 1). Mean arterial pressure after 10 min of HDT was higher than that of the other conditions (Table 1).

**Blood flow and vascular resistance.** Relative to that in the control standing condition, total brain blood flow was 48, 24, and 27% lower with 10-min and 7- and 28-day HDT, respectively (Fig. 1). Flow to the spinal cord was not altered by acute or chronic HDT (Table 2). Blood flow to the olfactory bulbs, left and right cerebrum, thalamic region, midbrain, and eye were reduced with 10 min of HDT and remained lower than that during control standing through 28 days of HDT. However, flow to some of these tissues (olfactory bulbs, thalamic region, and midbrain) during prolonged HDT was higher than that at 10 min of HDT. Perfusion of the cerebellum, pons, medulla, and pituitary were reduced with 10 min of HDT but returned to control levels by 7 days of HDT.

Total brain vascular resistance at 10-min and 7- and 28-day HDT was 116, 45, and 38% greater than that during control standing, respectively (Fig. 1). Vascular resistance in the spinal cord was not different among conditions (Table 3). Vascular resistance in the olfactory bulbs, left and right cerebrum, thalamic region, midbrain, cerebellum, pons, medulla, eye, and pituitary was acutely elevated with 10 min of HDT, and resistance remained elevated above that of control in most of these regions of the brain with 7 and 28 days of HDT.

**DISCUSSION**

Previous work has demonstrated that HDT in rats induces cephalic fluid shifts (21, 32, 45). In humans, cephalic fluid shifts induced by head-down bed rest and

**Table 2. Regional blood flows**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control (n = 8)</th>
<th>10 min (n = 8)</th>
<th>7 day (n = 11)</th>
<th>28 day (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory bulbs</td>
<td>125 ± 8</td>
<td>62 ± 9*</td>
<td>94 ± 5†</td>
<td>79 ± 7*</td>
</tr>
<tr>
<td>Left cerebrum</td>
<td>126 ± 7</td>
<td>65 ± 9</td>
<td>90 ± 8*</td>
<td>84 ± 5*</td>
</tr>
<tr>
<td>Right cerebrum</td>
<td>124 ± 9</td>
<td>66 ± 6</td>
<td>93 ± 10*</td>
<td>77 ± 5*</td>
</tr>
<tr>
<td>Thalamic region</td>
<td>74 ± 6</td>
<td>35 ± 4</td>
<td>55 ± 7†</td>
<td>50 ± 4*</td>
</tr>
<tr>
<td>Midbrain</td>
<td>89 ± 7</td>
<td>42 ± 4*</td>
<td>67 ± 7†</td>
<td>64 ± 8†</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>103 ± 9</td>
<td>50 ± 5*</td>
<td>81 ± 9†</td>
<td>78 ± 7†</td>
</tr>
<tr>
<td>Pons</td>
<td>72 ± 7</td>
<td>32 ± 4*</td>
<td>50 ± 8</td>
<td>47 ± 4*</td>
</tr>
<tr>
<td>Medulla</td>
<td>61 ± 5</td>
<td>33 ± 3*</td>
<td>53 ± 8</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>Eye</td>
<td>70 ± 8</td>
<td>44 ± 7*</td>
<td>41 ± 5*</td>
<td>51 ± 4*</td>
</tr>
<tr>
<td>Pituitary</td>
<td>88 ± 8</td>
<td>25 ± 13*</td>
<td>56 ± 13</td>
<td>90 ± 21†</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>39 ± 5</td>
<td>29 ± 5</td>
<td>28 ± 4</td>
<td>36 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE (in ml·min⁻¹·100 g⁻¹); n, number of rats. *Mean different from standing control (P < 0.05). †Mean different from 10-min HDT (P < 0.05).

**Table 3. Regional vascular resistances**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control (n = 8)</th>
<th>10 min (n = 8)</th>
<th>7 day (n = 11)</th>
<th>28 day (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory bulbs</td>
<td>1.1 ± 0.1</td>
<td>2.5 ± 0.3*</td>
<td>1.4 ± 0.1‡</td>
<td>1.7 ± 0.1‡</td>
</tr>
<tr>
<td>Left cerebrum</td>
<td>1.1 ± 0.1</td>
<td>2.4 ± 0.3*</td>
<td>1.6 ± 0.2‡</td>
<td>1.6 ± 0.1‡</td>
</tr>
<tr>
<td>Right cerebrum</td>
<td>1.1 ± 0.1</td>
<td>2.2 ± 0.2*</td>
<td>1.6 ± 0.2*</td>
<td>1.7 ± 0.1*</td>
</tr>
<tr>
<td>Thalamic region</td>
<td>1.5 ± 0.1</td>
<td>4.3 ± 0.5*</td>
<td>2.8 ± 0.4*</td>
<td>2.6 ± 0.2*</td>
</tr>
<tr>
<td>Midbrain</td>
<td>1.5 ± 0.1</td>
<td>3.5 ± 0.4*</td>
<td>2.3 ± 0.3*</td>
<td>2.3 ± 0.3*‡</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.3 ± 0.1</td>
<td>2.9 ± 0.3*</td>
<td>1.9 ± 0.3*</td>
<td>1.7 ± 0.1†‡</td>
</tr>
<tr>
<td>Pons</td>
<td>1.9 ± 0.2</td>
<td>4.8 ± 0.7*</td>
<td>3.4 ± 0.5‡</td>
<td>2.7 ± 0.2*‡</td>
</tr>
<tr>
<td>Medulla</td>
<td>2.2 ± 0.2</td>
<td>4.5 ± 0.5*</td>
<td>3.0 ± 0.4‡</td>
<td>3.1 ± 0.4‡</td>
</tr>
<tr>
<td>Eye</td>
<td>2.0 ± 0.3</td>
<td>4.0 ± 0.8*</td>
<td>3.8 ± 0.6*</td>
<td>2.6 ± 0.2‡</td>
</tr>
<tr>
<td>Pituitary</td>
<td>1.6 ± 0.2</td>
<td>7.6 ± 3.9*</td>
<td>2.8 ± 0.4‡</td>
<td>2.1 ± 0.5†‡</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>3.7 ± 0.4</td>
<td>5.8 ± 1.0</td>
<td>5.1 ± 0.5</td>
<td>4.1 ± 0.6‡</td>
</tr>
</tbody>
</table>

Values are means ± SE (in mmHg·ml⁻¹·100 g⁻¹·s⁻¹); n, number of rats. *Mean different from standing control (P < 0.05). †Mean different from 10-min HDT (P < 0.05).
microgravity have been associated with increases in cerebral blood flow velocity (24, 25, 44). These observations in humans served as the basis for the hypothesis that cerebral blood flow would increase during HDT in conscious rats. Contrary to our hypothesis, the results demonstrate that cerebral blood flow decreases and vascular resistance increases in rats exposed to 10 min of HDT (Fig. 1). Although the magnitude of this decrease in cerebral perfusion is attenuated over 7 and 28 days of HDT, total cerebral flow remains lower than that during control standing, and correspondingly, cerebral vascular resistance remains higher.

According to Poiseuille’s law, one determinate of blood flow is the pressure gradient between the arterial and venous portions of the circulation. With HDT, the hydrostatic shift of fluid toward the head increases both arterial pressure by ~10 mmHg (present study, 7, 33) and venous pressure by 3–5 mmHg (31, 41). Thus the pressure gradient across the cerebral circuit is preserved with HDT and therefore an altered perfusion pressure cannot account for the decrease in cerebral blood flow. Several other factors, however, could underlie the decrease in cerebral perfusion during HDT. These include 1) vascular compression attributable to a hydrostatic shift in cerebrospinal fluid (CSF) cephalically and a corresponding increase in CSF pressure, and 2) a myogenic vasoconstriction of cerebral resistance arteries in response to increased arterial pressure. Because the contribution of these factors to the decrease in cerebral perfusion may vary as a function of the duration of the HDT, each will be considered for the three HDT conditions.

Like that which occurs in the arterial and venous portions of the circulation, the head-down position induces a reversal of the CSF pressure gradient, resulting in an increase in CSF pressure of 3–4 mmHg within the cranium during the first 60 min of HDT (32). Although this increase in extravascular pressure may compress cerebral vessels within the skull and contribute to the acute decrease in cerebral blood flow (Fig. 2), the magnitude of the increase in CSF pressure appears insufficient to greatly influence cerebral blood flow or vascular resistance. A more likely determinant of the elevation in cerebral vascular resistance with acute HDT is a myogenic autoregulatory vasoconstriction in response to an increase in arterial transmural pressure. Such a response is likely in extracranial resistance arteries where extravascular pressure is not greatly elevated with acute HDT and in intracranial resistance arteries if the elevation in arterial pressure exceeds the elevation in CSF pressure. The observation that the largest increase in cerebral vascular resis-
tance occurs simultaneously with the greatest elevation in arterial pressure is consistent with the potent autoregulatory capacity of the cerebral resistance vasculature (11, 23). This suggests myogenic vasoconstriction is the predominant factor in the elevation of cerebral vascular resistance with acute HDT. However, it is also possible that the stress associated with the onset of HDT could contribute to the magnitude of increase in cerebral vascular resistance.

Although total brain blood flow following 7 days of HDT is significantly greater than that during 10 min of HDT, it is still lower than during control standing. This lower flow does not appear to be related to vascular compression, because CSF pressure returns to baseline after 60–90 min of HDT (32). Therefore, the mechanism likely responsible for the higher cerebral vascular resistance with 7 days of HDT is a continued myogenic vasoconstriction in response to an elevated arterial transmural pressure. With the 7-day duration of HDT, arterial pressure is 4 mmHg higher than that during control standing. Although this higher absolute pressure is not significant, other studies have demonstrated that arterial pressure during 7–14 days of HDT is significantly greater than during control standing (7, 33). Thus the stimulus for myogenic vasoconstriction in the cerebral circulation is present for up to several weeks.

Unlike that with 10 min and 7 days of HDT, the persistent elevation in cerebral vascular resistance with 28 days of HDT does not appear to be related to elevations in CSF pressure or arterial transmural pressure, because CSF pressure (32) and production (17) are not elevated with prolonged HDT and arterial pressure has returned to control levels (present study, 7). Therefore, an additional factor that could underlie the decrease in cerebral perfusion and increase in vascular resistance with prolonged HDT is an enhanced vasoconstrictor responsiveness of cerebral resistance arteries. In support of this possibility, Geary and colleagues (18) reported that isolated middle cerebral arteries from 20-day HDT rats have an increased myogenic vasoconstrictor responsiveness. More recently, studies of isolated basilar artery rings from 28-day HDT rats showed greater vasoconstrictor responsiveness to KCl, arginine vasopressin, and 5-hydroxytryptamine (48). This increased intrinsic vasoconstrictor responsiveness has been suggested to be the result of an increased cerebral artery transmural pressure and the corresponding elevation in cerebral vascular resistance (Fig. 2). Over time, the chronic contraction of the smooth muscle leads to smooth muscle hypertrophy, which normalizes the circumferential stress within the wall of the cerebral arteries caused by the elevated transmural pressure (45). A similar sequence, as proposed by Folkow (13), has been experimentally demonstrated in cerebral arteries from hypertensive rats (5, 22, 23, 35, 36). In these hypertensive animals, smooth muscle cell hypertrophy/hyperplasia increases the intrinsic myogenic and vasoconstrictor responsiveness of the cerebral arteries (14, 26, 27).

Evidence for cerebral artery smooth muscle hypertrophy in HDT rats has been provided by several laboratories (45–47). Preliminary evidence for cerebral vascular hypertrophy/hyperplasia with HDT was first provided in several review-type reports (46, 47). Zhang et al. (46, 47) reported that HDT increased the medial cross-sectional area and lumen diameter of basilar arteries with no change in medial wall thickness. The authors speculated that the stimulus for the increased diameter was a chronic increase in perfusion. Subsequently, Wilkerson et al. (45) likewise noted in a research report that the medial cross-sectional area of the basilar artery was increased with HDT but that lumen diameter was reduced. Thus an important distinction between the above-mentioned reports (45–47) is that the increase in medial cross-sectional area reported by Wilkerson et al. (45) resulted from an increase in medial wall thickness, which, along with the smaller vessel diameter, is indicative of a circumferential stress-induced vascular remodeling in response to an increased transmural pressure (14, 27, 45). In contrast, the increase in medial cross-sectional area reported by Zhang et al. (46, 47) was the result of an increase in lumen diameter, which infers a shear stress-induced remodeling in response to an increased blood flow (5, 14, 27).

Results from the present study demonstrate that the stimulus for the cerebral arterial remodeling with HDT cannot be the result of a chronic increase in blood flow but rather is likely due to an increase in the arterial wall circumferential stress (45) and the prolonged increase in cerebral vascular resistance. The reason for the discrepancy between the reports of Wilkerson et al. (45) and Zhang et al. (46, 47) are unknown but may be related to the methods employed to determine vascular morphology. For example, Wilkerson et al. (45) isolated, maximally dilated, and fixed basilar arterial segments while intraluminal pressure was precisely controlled, a critical variable for accurate determination of diameter and wall thickness. Unfortunately, few methodological details are given in the reports of Zhang and co-workers (46, 47). The whole animal was apparently perfusion fixed, but no details are given concerning the contractile state of the vasculature, whether pressure and perfusate flow were controlled during fixation, or how the vessels were isolated and measured.

As illustrated in Fig. 2, one functional consequence of remodeling the cerebral resistance artery structure appears to be alterations in vascular responsiveness. As mentioned above, chronic HDT results in enhanced agonist-induced (48) and myogenic (18) vasoconstrictor responsiveness. Myogenic responsiveness is an important component of cerebral autoregulatory control (11, 23) that preserves blood flow despite variations in arterial pressure. An increase in the intrinsic myogenic responsiveness of cerebral arteries could produce a downward shift in the cerebral autoregulation curve so that for any given arterial pressure cerebral blood flow would be lower. Such appears to be the case with chronic HDT. Despite the fact that arterial pressure is similar between control and 28-day HDT rats, cerebral
blood flow is lower and vascular resistance is higher. This apparent shift in the autoregulatory curve with HDT does not appear to be unique to the rat. For example, Zhang et al. (50) investigated the effects of head-down bed rest on cerebral hemodynamics in humans using lower body negative pressure to perturb arterial pressure. They reported that middle cerebral artery blood flow velocity for a given mean arterial pressure was lower postbed rest, which is indicative of a downward shift in the cerebral autoregulation curve.

One of the purposes of this study was to investigate whether HDT affects the regional distribution of blood flow within the brain. In human subjects, both head-up and head-down tilt appear to alter regional flow distribution (37, 40, 43), and sudden changes in intracranial pressure (38) or intra-arterial pressure (3) also produce heterogeneous changes in flow within the brain. Results from the present study demonstrate that reductions in blood flow with HDT occur fairly uniformly throughout the brain. However, this does not rule out the possibility that the perfusion rate could have been maintained in more discreet regions within the areas sampled.

The reported decreases in cerebral blood flow during HDT in the present study appear at odds with previous reports showing cerebral blood flow velocity either remains unchanged or increases during head-down tilt in humans (1, 15, 20, 24). The reason(s) for the discrepancy is unknown (1, 15, 20). One possible explanation is that the control mechanisms that regulate cerebral perfusion during postural manipulations differ in rats and humans. An alternative explanation is that cerebral blood flow and blood flow velocity are not necessarily equivalent (1, 30, 49). According to the equation utilized to determine flow from transcranial Doppler ultrasound velocity measurements, flow (ml/min) = velocity (cm/min) × area (cm²) (30). Therefore, changes in velocity are proportional to changes in flow only if the diameter of the vessel being measured remains constant during tilt. If similar changes in cerebral artery morphology and vasomotor properties occur in humans subjected to prolonged head-down tilt as has been shown in rats (18, 45, 48), then it is possible that cerebral artery diameter does not remain constant during postural manipulations, making an actual decrease in blood flow through a constricted vessel appear as an increase in blood flow velocity.

In conclusion, the findings of the present study demonstrate that cerebral blood flow in the rat decreases, and correspondingly, cerebral vascular resistance increases in response to acute and chronic HDT. These findings are consistent with the hypothesis that acute HDT produces increases in extravascular pressure within the cranium and increases in transmural pressure in resistance arteries leading to the brain, which, in turn, causes vascular compression and an autoregulatory vasoconstriction, respectively (Fig. 2). Furthermore, the chronic elevation in both cerebral arterial circumferential wall stress and vascular resistance with HDT induce a remodeling of the cerebral arterial vasculature so that the intrinsic vasoconstrictor responsiveness of these vessels is greater. Such an alteration is purported to cause a downward shift in cerebral autoregulatory control of blood flow.

Perspectives. One of the prevailing questions among scientists interested in the effects of headward fluid shifts produced by microgravity is whether alterations in cerebral blood flow autoregulation occur postspaceflight. For example, it was suggested that several astronauts who were unable to complete a 10-min postflight stand test despite having a normal mean arterial pressure may have had an impaired ability to autoregulate cerebral perfusion (6). An orthostatic stress, such as that produced by a stand test or lower body negative pressure shifts the operating point toward the left on the cerebral autoregulation curve. Therefore, a downward shift in the autoregulatory curve, such as that noted in 28-day HDT rats, and a leftward shift in the operating point during standing would theoretically bring individuals closer to the threshold where cerebral blood flow is inadequate to maintain consciousness (4, 19, 30). If alterations in cerebral resistance artery structure and function occur in humans during prolonged bed rest or microgravity, similar to those reported to occur in HDT rats (18, 45, 48), then this could induce a downward shift in the cerebral blood flow–arterial pressure relationship, and, correspondingly, be a primary or contributing factor to the orthostatic intolerance experienced by these subjects (6, 50).

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