Effect of acute exposure to hypergravity (Gₓ vs. Gᵧ) on dynamic cerebral autoregulation


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Serrador, J. M., S. J. Wood, P. A. Picot, F. Stein, M. S. Kassam, R. L. Bondar, A. H. Rupert, and T. T. Schlegel. Effect of acute exposure to hypergravity (Gₓ vs. Gᵧ) on dynamic cerebral autoregulation. J Appl Physiol 91: 1986–1994, 2001.—We examined the effects of 30 min of exposure to either +3Gₓ (front-to-back) or +3Gᵧ (head-to-foot) centrifugation on cerebrovascular responses to 80° head-up tilt (HUT) in 14 healthy individuals. Both before and after +3Gₓ or +3Gᵧ centrifugation, eye-level blood pressure (BPeye), end tidal PCO₂ (PETCO₂), mean cerebral flow velocity (CFV) in the middle cerebral artery (transcranial Doppler ultrasound), cerebral vascular resistance (CVR), and dynamic cerebral autoregulatory gain (GAIN) were measured with subjects in the supine position and during subsequent 80° HUT for 30 min. Mean BPeye decreased with HUT in both the Gₓ (n = 7) and Gᵧ (n = 7) groups (P < 0.001), with the decrease being greater after centrifugation only in the Gᵧ group (P < 0.05). PETCO₂ also decreased with HUT in both groups (P < 0.01), but the absolute level of decrease was unaffected by centrifugation. CFV decreased during HUT more significantly after centrifugation than before centrifugation in both groups (P < 0.02). However, these greater decreases were not associated with greater increases in CVR. In the supine position after centrifugation compared with before centrifugation, GAIN increased in both groups (P < 0.05, suggesting an autoregulatory deficit), with the change being correlated to an adaptation to reduced cerebral perfusion pressure during +Gₓ.

Cerebral autoregulation is the process by which cerebral blood flow (CBF) is maintained relatively constant over a wide range of cerebral perfusion pressure (CPP) (30). CPP is in turn defined as the arterial pressure at the level of the circle of Willis minus the opposing intracranial pressure. The range or set point of the curve representing cerebral autoregulation is variable and is influenced by prevailing perfusion pressure (Fig. 1). For example, chronic hypertension may shift the cerebral autoregulatory curve toward the high-pressure end (rightward shift), thereby predisposing affected individuals to hypoperfusion should lower pressures be experienced (30). In contrast, chronic local cerebral hypoperfusion (46) and some forms of chronic orthostatic hypotension (24) appear to shift the same curve leftward (22), potentially improving tolerance for reductions in CPP during orthostatic stress. Acute exposure to cardiovascular stresses such as head-up tilt...
(HUT) and lower body negative pressure (LBNP) may also result in a downward (4, 36) or rightward (48, 49) shift in the cerebral autoregulatory curve. However, the time course of such adjustments in humans is still poorly understood.

One goal of the present study was to determine whether cerebral hypotension experienced during up to 30 min of +3 Gz centrifugation (i.e., acceleration along the longitudinal or head-to-foot axis of the body) subsequently results in altered cerebrovascular control and orthostatic tolerance. Another goal was to determine whether +3 Gz centrifugation differs from +3 Gx centrifugation (i.e., acceleration along the naso-occipital or front-to-back axis of the body) with respect to its effect on cerebrovascular control and orthostatic tolerance. Because little change should be expected in CPP during a +3 Gx stimulus, we hypothesized that 30 min of +3 Gx exposure would lead to minimal changes in cerebrovascular responses during postcentrifugation (vs. precentrifugation) HUT. In contrast, we postulated that exposure to 30 min of +3 Gz would cause a leftward shift in the CBF autoregulatory curve because of the reductions in CPP produced by this stimulus, which would, in turn, lead to improved cerebrovascular control during postcentrifugation (vs. precentrifugation) HUT. Finally, based on evidence that the brain stem pathways involved in vestibular-autonomic reflexes in animals (43) also influence CBF (33) and cerebrovascular autoregulation (13), together with the recent finding that the cerebral autoregulatory curve may be shifted downward in motion-sick subjects after parabolic flight (36), we speculated that, if postcentrifugation changes in cerebrovascular control developed in the present study, they would relate to measurements of otolith-ocular reactivity in our individual subjects.

MATERIALS AND METHODS

Subjects. Fourteen healthy subjects (12 male and 2 female) participated in this study. The subjects averaged 26 yr in age (range = 22–38 yr), 73.8 ± 11.9 kg in weight, and 175 ± 5 cm in height. All subjects had a U.S. Naval or NASA physical examination and, on the basis of a normal examination as well as normal urine and blood test results, were determined by the examining physician to be free of neurological, cardio-

pulmonary, renal, or other systemic disease. In addition, each gave written, informed consent. Alcohol, heavy exercise, antimotion sickness, and all other medications were strictly prohibited for 24 h before testing. All protocols were approved by the Johnson Space Center Institutional Review Board and by the local Naval (Pensacola) and national (Public Health Services) bioethics committees.

Centrifugation. Subjects were assigned to experience up to 30 min of either +3 Gx (Gx group, n = 7) or +3 Gz (Gz group, n = 7) acceleration on the Coriolis Acceleration Platform located at the Naval Aerospace Medical Research Laboratory in Pensacola, Florida (19). During centrifugation, subjects were recumbent in a chair located at 6.25 m radius in an enclosed cabin. The chair was inclined 70.5° from vertical and fixed with the feet pointed either inward or outward so that the resultant of centrifugal and gravitational forces at maximum velocity (+3 G at 124°/s) were directed along either the naso-occipital x-axis or longitudinal z-axis, respectively. The centrifuge acceleration and deceleration rates were 0.16 G/s. A headrest stabilized the head in an erect position and permitted horizontal head movements during the adaptation periods.

Otolith-ocular responses were examined in all 14 subjects by measuring vertical nystagmus slow-phase velocities, as recently described by McGrath et al. (19), during an initial 5-min exposure to +3 Gz. For the purposes of this study, the level of otolith sensitivity was inferred from the magnitude of vertical slow-phase velocity (19). During this initial 5-min +3 Gz run, monocular (right) eye movements were recorded in darkness by using a helmet-mounted infrared video-oculography system (Cohu model 6412, San Diego, CA). This system consisted of a video camera that imaged the eyes from above by using dichroic mirrors and infrared light sources. During the recordings, subjects were asked to gaze straight ahead while fixating on a remembered center-calibration target −0.6 m in front of them. This target location was utilized to minimize effects of voluntary gaze strategies across subjects and to enhance our ability to compare differences in vertical nystagmus slow-phase velocity across subjects. To ensure that there was no relative motion between the cameras and the eye during +Gz stress, the camera was held firmly in place via an inflatable bladder and chin-strap system. After the completion of the initial 5-min +3 Gz run, the subject’s helmet and camera system were removed. Either immediately thereafter (Gz group) or 1–5 days later (Gx group), a 25-min +3 Gz run or 30-min +3 Gz run was then performed with the lights on after the same acceleration/ deceleration profile noted above. During +3 Gz centrifugation, no anti-G straining maneuvers were allowed, although all subjects wore a conventional five-bladder pneumatic anti-G suit pressurized at a linear schedule of 1.5 psi per G above −2 G, to prevent G-induced loss of consciousness (G-LOC). In the event that a subject experienced symptoms of incipient G-LOC (i.e., grey out, tunnel vision, etc.) despite G-suit prophylaxis, the centrifuge run was terminated early and postcentrifugation testing was commenced (see below).

During minutes 5–9 and 16–20 of the second portion of +3 Gz centrifugation (and during the equivalent portion of +3 Gx centrifugation), subjects carefully and continually performed yaw head movements starting at 15° to the left, then moving back to the center, then 15° to the right, then back to center, and so forth, in a repetitive fashion, holding each position for a total of 15 s. These head movements were designed to approximate those that might be performed by an astronaut or aviator during flight maneuvers. However, if at any time a subject began to experience stomach awareness, the head movements were stopped and gaze returned to the
center position. Predefined test-termination criteria for both +3-Gx and +3-Gz centrifugation also included severe nausea or actual vomiting.

Tilt testing. Supine and 80° HUT data were collected during identical pre- and postcentrifugation testing sessions. Both the centrifuge room and the adjacent precentrifugation/postcentrifugation testing facility were maintained at the same constant temperature and humidity during all sessions. The precentrifugation testing session occurred 1–5 days before centrifugation, and the postcentrifugation testing session occurred within 15 min after exiting the centrifuge. Differences in this time of subject transfer from the centrifuge and in the actual cardiovascular testing times were generally on the order of 5–10 min each. Two to three hours before both sessions, subjects consumed the same breakfast, which consisted of fruit, cereal grains, and optional low-fat milk.

For this investigation, the sequential activities of test subjects were as follows both before and immediately after centrifugation: 1) ambulation to the testing facility, located ~40 m from the centrifuge; 2) cardiovascular instrumentation (~10 min later); 3) 30–40 min of supine rest followed by 3–5 min of additional rest for pre-HUT supine recordings; and finally 4) HUT testing to 80° for a maximum of 30 min with the use of a motorized custom-tilt table (U.S. Navy, Pensacola, FL). The elapsed time of tilt to achieve 80° HUT was 9.4 ± 0.3 (SE) s.

In the precentrifugation/postcentrifugation testing facility before, during, and after HUT, mean cerebral flow velocity (CFV) in the middle cerebral artery (MCA) was measured via a 2-MHz pulsed flat transcranial Doppler probe (Transpect, Medasonics, Mountain View, CA) placed over the right temporal bone. The signal was range gated to a depth of 45–55 mm to ensure insonation of the M1 segment of the MCA. Once the signal was maximized, the probe was fixed in place for the duration of the test using a Velcro headband. In addition to minute-by-minute manual blood pressures obtained via standard sphygmomanometer for safety purposes, beat-by-beat blood pressure was obtained from a finger cuff (Finapres 2300, Ohmeda, Englewood, CO) fixed by an arm band at the level of the heart. To determine blood pressure at the level of the MCA (BPeye), the distance from the heart to the eyes was measured and the hydrostatic equivalent of blood pressure subtracted from the values obtained from the finger. End-tidal Pco2(PETCO2) and respiratory rate were also monitored via a nasal catheter (Puritan-Bennett, Wilmington, MA), whereas heart rate was determined by using a standard electrocardiogram. With the use of criteria previously established by NASA (34), orthostatic intolerance during HUT included any of the following: a sudden drop of systolic pressure >25 mmHg or of diastolic pressure >15 mmHg, an absolute manual systolic pressure <90 mmHg, a sudden and absolute drop in heart rate of >15 beats/min, an absolute heart rate <40 beats/min for subjects whose resting heart rate is >50 beats/min, severe lightheadedness, or severe nausea or actual vomiting.

Data analysis. The analog CFV, electrocardiogram, and blood pressure signals were sampled simultaneously at 10 kHz per channel by using an eight-channel digital tape recorder (TEAC RD-111T, Teac, Tokyo, Japan). Off-line data analysis was performed with customized data analysis software. The peak velocity envelope of the transcranial Doppler waveform was used to represent the instantaneous blood flow velocity in the MCA. Beat-by-beat signals were displayed during analysis, and any artifacts were removed. Regional cerebral vascular resistance (CVR) in the distribution of the MCA was estimated as CVR = BPeye/CFV.

The effects of centrifugation on orthostatic adjustments in cerebral hemodynamics were assessed by examining CFV, mean BPeye, PETCO2, and CVR responses. For this analysis, steady-state data of 1–3-min duration were selected both for the supine period and for the early (first 10 min) as well as the late (last 5 min) period of HUT. Visual inspection of all data segments ensured that none contained noise spikes or ectopic beats.

Dynamic autoregulation calculation. Cerebral autoregulation maintains CFV relatively constant by using changes in CVR to buffer changes in mean BPeye, that would otherwise cause large fluctuations in CBF. To assess dynamic cerebral autoregulatory responses both before and after centrifugation, the combined steady-state CFV and mean BPeye data from each of the supine, early, and late HUT periods were first obtained. In some cases, only 1–2 min of the supine data were usable. All steady-state data segments were then resampled at 5 Hz by using linear interpolation and low-pass filtered with a cutoff frequency of 1 Hz (8th-order zero-phase Butterworth) (28). For each data set, a transfer function gain (GAIN) between CFV and mean BPeye was then calculated using a standard fast Fourier transformation after the method of Panerai et al. (28). Calculations of GAIN correlate well with other measures of autoregulation (27, 47) and have been used in the past to differentiate patients with impaired vs. intact autoregulation (1, 27–29). Specifically, if dynamic autoregulation is functioning properly, changes in mean BPeye cause minimal changes in CFV, and thus GAIN is low. On the other hand, if dynamic autoregulation is impaired, changes in mean BPeye cause large changes in CFV, and thus GAIN is high. In addition to GAIN, we also calculated the coherence and phase delay between CFV and mean BPeye in the 0.02- to 0.5-Hz range (28).

Vestibular-cerebrovascular interactions. To examine a possible relationship between vestibular (otolith) gain and changes in cerebral autoregulation, vertical nystagmus slow-phase velocity values were compared with changes in autoregulatory parameters from pre- to postcentrifugation by using a Pearson-product moment correlation. Subjects with greater slow-phase velocity values are presumed to have greater otolithic sensitivity (19), and, as such, they were investigated for any potentially corresponding changes in cerebral autoregulation.

Statistics. The effect of HUT or group (Gx vs. Gz) on CFV, BPeye, PETCO2, CVR, GAIN, coherence, and phase delay was assessed by using a repeated-measures two-way ANOVA with a Newman-Keuls test for multiple comparisons. Data are presented as means ± SE with levels of P < 0.05 considered significant.

RESULTS

Of the 14 subjects who participated, 1 was unable to complete the 5-min +3-Gz run for vertical nystagmus slow-phase velocity and was excluded. One subject participated in both the +3-Gx and +3-Gz protocols several weeks apart. Therefore, of the 14 total long-duration centrifugation runs, half were in +3-Gx (Gx group, n = 7) and half were in +3-Gz (Gz group, n = 7). Because of pre-G-LOC symptoms, of the seven runs in +3-Gz, only one lasted for the entire 30 min. The average total duration of +3-Gz completed was 24.3 min (range = 10.9–30 min). On the other hand, all seven of the +3-Gx runs lasted for the entire 30 min. Although none of the subjects vomited within the centrifuge, two of the seven subjects in the Gx group and three of the seven subjects in the Gz group experienced
either transient headache or epigastric distress during centrifugation, with one of the subjects in the GZ group also experiencing severe but transient nausea during the final deceleration.

Tables 1–2 show the pre- and postcentrifugation values for mean BP<sub>eye</sub>, CFV, CVR, GAIN, heart rate, PET<sub>CO<sub>2</sub></sub>, and respiratory rate in the supine position immediately before HUT. None of these supine parameters changed from pre- to postcentrifugation with the exception of supine GAIN, which increased significantly after centrifugation in both groups (Table 1). Supine coherence also increased significantly after centrifugation, but only in the GZ group (Table 3).

Responses to HUT. Compared with supine, heart rate increased (Table 2; \( P < 0.001 \)) and mean BP<sub>eye</sub> decreased (Fig. 2; \( P < 0.001 \)) in both groups with HUT both before and after centrifugation. In addition, the decrease in mean BP<sub>eye</sub> with HUT was greater in the GZ group than in the GX group both before and after centrifugation (\( P < 0.01 \)). PET<sub>CO<sub>2</sub></sub> also decreased in all subjects during HUT both before and after centrifugation (Table 2; \( P < 0.01 \)), with no associated change in respiratory rate (Table 2).

In both groups before centrifugation, CFV decreased after the transition from supine to HUT. However, the decrease in CFV was significant (vs. supine) only in the GZ group during late HUT (Fig. 3; \( P < 0.02 \)). On the other hand, in both groups after centrifugation, CFV decreased significantly (vs. supine) during both early and late HUT (Fig. 3). Nonetheless, this change did not reduce the ability of any subject to complete HUT because no subject in either group developed intolerance to HUT as a result of centrifugation.

In the GX group, CVR did not change from supine to HUT either before or after centrifugation (Fig. 4). However, in the GZ group, CVR decreased (vs. supine) during early but not during late HUT both before and after centrifugation (Fig. 4; \( P < 0.05 \)), mirroring to some degree the simultaneous decreases in mean BP<sub>eye</sub> (Fig. 2).

Cerebral autoregulation and vestibular-cerebrovascular interactions. As noted above, after centrifugation, supine GAIN increased in both groups (Table 1) and supine coherence increased in the GX group (Table 3). Interestingly, however, the increase in supine GAIN was strongly correlated to vertical nystagmus slow-phase velocity in the GZ group (\( r = 0.76, P < 0.05 \), least squares linear regression) but not in the GZ group (\( r = 0.23, P = 0.60 \)). In addition, the significant increase in coherence in the GX group was strongly correlated to vertical nystagmus slow-phase velocity (\( r = 0.87, P < 0.01 \)).

Before centrifugation, GAIN was not influenced by HUT in either group (Fig. 5). In contrast, after centrifugation, GAIN decreased significantly during HUT in both groups (Fig. 5). With respect to the transfer function analyses (Table 3), HUT did not influence coherence before or after centrifugation in either group. However, in both groups, the phase delay between CFV and mean BP<sub>eye</sub> decreased during HUT (Fig. 4; \( P < 0.001 \)), mirroring to some degree the simultaneous decreases in mean BP<sub>eye</sub> (Fig. 2).

**Table 1. Values during supine baseline collections in pre- and postcentrifugation groups**

<table>
<thead>
<tr>
<th>Precentrifugation</th>
<th>Postcentrifugation</th>
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<tbody>
<tr>
<td>Mean BP&lt;sub&gt;eye&lt;/sub&gt;, mmHg</td>
<td>Gx Group</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>94 ±3</td>
<td>95 ±6</td>
</tr>
<tr>
<td>CFV, cm/s</td>
<td>51 ±3</td>
</tr>
<tr>
<td>CVR, mmHg</td>
<td>1.9 ±0.1</td>
</tr>
<tr>
<td>GAIN, (cm&lt;sup&gt;-1&lt;/sup&gt;s&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;/mmHg&lt;/sup&gt;</td>
<td>0.65 ±0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE. Gx, horizontal acceleration; Gz, longitudinal acceleration; BP<sub>eye</sub>, eye-level blood pressure; CFV, cerebral flow velocity; CVR, cerebral vascular resistance; GAIN, dynamic cerebral autoregulatory gain; pre, precentrifugation; post, postcentrifugation. *Significantly different from precentrifugation (\( P < 0.05 \)).

**Table 2. Cardiovascular and respiratory responses**

| | Precentrifugation | Postcentrifugation |
|-------------------|-------------------|
| Heart rate, beats/min | Gx | Gz |
| SUP Early Late | SUP Early Late |
| 62 ±2 | 74 ±4† | 78 ±6† | 58 ±1 | 77 ±2† | 75 ±3† |
| 39 ±2 | 35 ±2* | 34 ±2* | 41 ±2 | 33 ±3* | 36 ±2* |
| 15 ±2 | 14 ±1 | 14 ±1 | 15 ±1 | 14 ±1 | 15 ±1 |
| Heart rate, beats/min | Gx | Gz |
| SUP Early Late | SUP Early Late |
| 63 ±4 | 80 ±4† | 82 ±5† | 62 ±1 | 85 ±5† | 89 ±6† |
| 43 ±1 | 36 ±2* | 36 ±2* | 43 ±1 | 38 ±2* | 36 ±2* |
| 14 ±2 | 14 ±1 | 16 ±1 | 14 ±1 | 14 ±1 | 15 ±1 |

Values are means ± SE. SUP, supine period. Early data were taken during the first 10 min of head-up tilt (HUT), and late data were taken during the last 5 min of HUT. *Significantly different from SUP (\( P < 0.01 \)). †Significantly different from SUP (\( P < 0.001 \)).
+3-GX and +3-GZ centrifugation may have shifted the static cerebral autoregulation curve to the left (Fig. 6). This leftward shift, in turn, appeared to allow for a better maintenance of CBF in the face of hypotension immediately after centrifugation. Third, in our GX group, the increased GAIN after centrifugation was related to the extent of vestibular (otolith) reactivity as estimated from individual measurements of vertical nystagmus slow-phase velocity, suggesting that vestibular pathways might play a role in the regulation of CBF.

The finding that GAIN increased in the supine position postcentrifugation is unexpected, especially in our GX group. To our knowledge, no prior studies have reported a stimulus in humans that results in increased unstressed supine GAIN. Although this increased GAIN could potentially suggest that centrifugation shifted our subjects’ autoregulation curves rightward rather than leftward, our results are most consistent with a leftward shift because GAIN was restored (reduced) to precentrifugation levels during HUT, once CPP (BPeye) decreased below supine levels (Fig. 6). If the increase in supine GAIN had been truly driven by a rightward shift, with an associated initial set point position on the lower, not upper, nonautoregulated portion of the static curve, then GAIN should have remained high as BPeye was reduced during HUT. However, GAIN did not remain high during HUT, but rather decreased as BPeye decreased, suggesting an initial set point position on the upper, not lower, non-autoregulated portion of the static curve, and therefore an overall leftward shift. Moreover, supine PetCO2 values in the present study were unchanged in both groups after centrifugation when GAIN was simultaneously increased (Tables 1–2), suggesting that the increases in GAIN cannot be attributed to changes in PetCO2.

It has been previously demonstrated that infants with large changes in CFV during blood pressure variation (i.e., impaired autoregulation) also have larger GAIN values (28). Thus the increased supine GAIN in the present study after centrifugation potentially indicates that subjects developed impaired autoregulation within normal perfusion pressure ranges. Theoretically, this could be the result of overall impaired autoregulation (i.e., elimination of the cerebral autoregulation curve) or, as noted above, a shifting of the autoregulation curve so that normal perfusion pressure is no longer associated with the plateau (Fig. 1). However, if autoregulation was impaired across all CPP levels, then GAIN should have been increased both supine and during HUT. Because GAIN returned

### Table 3. Values from transfer function analysis between CFV and BPeye

<table>
<thead>
<tr>
<th></th>
<th>Precentrifugation</th>
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<tbody>
<tr>
<td></td>
<td>SUP</td>
<td>Early</td>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Gx Coherence</td>
<td>0.48 ± 0.04</td>
<td>0.66 ± 0.06</td>
<td>0.59 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Gx Phase, rad</td>
<td>0.17 ± 0.08</td>
<td>0.24 ± 0.04</td>
<td>0.25 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>Gz Coherence</td>
<td>0.54 ± 0.06</td>
<td>0.59 ± 0.06</td>
<td>0.55 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>Gz Phase, rad</td>
<td>0.07 ± 0.06</td>
<td>0.20 ± 0.04</td>
<td>0.32 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from SUP (P < 0.05). †Significantly different from precentrifugation (P < 0.05).
to precentrifugation levels during HUT, it suggests
that an autoregulatory plateau was present in the
upright position. Nonetheless, it should be noted that
GAIN values under these two conditions (supine and
HUT) do not provide us any precise information on the
inflection point of the autoregulatory curve.

In both groups after centrifugation, the increased
GAIN in the supine position followed by the normal-
ization of GAIN during HUT is reminiscent of a similar
combination of findings that has been reported, pre-
sumably as a beneficial adaptation, in patients with
chronic orthostatic hypotension (1, 35). On the other
hand, exposure of healthy subjects to 2 wk of head-
down bed rest (i.e., simulated microgravity) has been
reported to exacerbate an impairment of dynamic au-
toregulation that occurs in response to high levels of
LBNP (48, 49). Thus it appears that, whereas recent
exposure to simulated microgravity may impair dy-
namic cerebral autoregulation in the context of cardio-

vascular stress, recent exposure to hypergravity (GZ or
Gx) may have an opposite, protective effect. In the
present study, a leftward shift in the static autoregu-
lation curve after exposure to hypergravity is also
supported by the fact that, during postcentrifugation
HUT, CFV decreased to similar absolute levels as dur-
ing precentrifugation HUT despite relatively greater
falls in mean BPeye (Figs. 2–3). This improvement in
the static autoregulation curve was most remarkable
within the Gz group because their exacerbated de-
creases in mean BPeye with HUT after (compared with
before) centrifugation were statistically significant.
Therefore, especially in the Gz group, the overall find-
ings during post- vs. precentrifugation HUT suggest an
increment, not a decrement, in orthostatic tolerance.

Serrador et al. (36) recently examined changes in
dynamic cerebral autoregulation in human subjects
after parabolic flight, a stimulus that consists of alter-
nating exposures to both micro- and hypergravity. Per-
haps not surprisingly, there were no significant
changes in supine or upright GAIN from pre- to post-
parabolic flight within either an orthostatically toler-
ant subject group or an orthostatically intolerant sub-
ject group, suggesting that the effects of micro- and
hypergravity on dynamic autoregulation may have
generally offset one another under these circum-
stances. However, in the same study, the individuals
who became orthostatically intolerant after parabolic
flight had increases (as opposed to no change or de-
creases) in GAIN during the early portion of HUT both
pre- and postflight, suggesting that preflight measure-
ments of GAIN might be useful for predicting nascent
postflight deficits in orthostatic tolerance in related
environments such as spaceflight. CFV in the parabolic
flight study was also reduced during HUT when GAIN
was unchanged, potentially corroborating Bondar et al.’s
(4) suggestion that HUT causes a downward (rather
than leftward or rightward) shift in the static autoregu-
lation curve (Fig. 6).
As noted earlier, adaptation of the cerebral autoregulation curve to lower blood pressures occurs in both chronic local cerebral hyperperfusion (46) and orthostatic hypotension (1, 22, 24). However, the exact stimulus duration necessary to induce such shifts is unknown. Ossard et al. (26) demonstrated that, as exposure to a given level of +GZ progresses during centrifugation, CFV increases and then becomes maintained well above theoretical levels given the actual level of BPeye. This finding suggests that autoregulation may adapt rather acutely to the current range of CPP. Because our own subjects were exposed to relatively short durations (≤30 min) of +3 GZ or +3 GX, our findings are also consistent with the notion of acute adaptation. Nonetheless, both our GZ and GX groups had an increase in supine GAIN after centrifugation, whereas only the GZ group should have experienced a reduced perfusion pressure during centrifugation. This finding suggests that adaptation of the autoregulation curve in our study was not entirely dependent on reductions in CPP.

One potential explanation for the increased supine GAIN and presumptive leftward shift in the static cerebral autoregulatory curves of our subjects is a resetting of the sympathetic nervous system activity modulating cerebrovascular tone. For example, in primates, both unilateral superior cervical ganglionectomy and α-adrenergic blockade with intravenous phenoxybenzamine shift the autoregulation curve to the left (8, 15), thereby enhancing the maintenance of CBF in the face of hypotension but impairing the autoregulatory response to acute increases in pressure (15, 45). Such effects are nonetheless mainly reversed after chronic sympathectomy (8, 12). In turn, stimulation (rather than ablation) of the cerebral sympathetic nerve in primates acutely decreases CBF (14, 21) while shifting the autoregulation curve to the right (14, 18). Despite these observations, the question of whether the sympathetic nervous system plays a primary role in cerebral autoregulation is still under debate (30, 33).

In rhesus monkeys, for example, bilateral superior cervical ganglionectomy does not affect cerebral autoregulation, and attenuation (rather than complete disappearance) of cerebral vasodilation in sympathectomized animals during cerebellar fastigial nucleus stimulation suggests the existence of a second (presumably cholinergic) central or peripheral pathway (i.e., through ganglia) that also exerts an effect on the cerebrovascular bed (20).

In humans, the role that sympathetic pathways play in regulating CBF is even less clear. For example, stellate ganglion block increases CBF in humans as determined by single photon emission computed tomography (SPECT) (40) but not as determined by magnetic resonance imaging (MRI) (23). Moreover, the increase in CBF as determined by SPECT may have been partly due to increased skin blood flow because, in the MRI study, common carotid artery blood flow feeding extracerebral beds was increased whereas CBF remained unchanged. In another study involving direct stimulation of the stellate ganglion during surgery, CFV increased possibly because of a vasoconstriction at the MCA (41). However, patients in that study were anesthetized both with isoflurane, which is known to ablate autoregulation (38), and with nitrous oxide, which is a potent vasodilator when combined with isoflurane (37). Therefore, the increases in CFV during stellate ganglion stimulation were likely the result of increased mean arterial pressure augmenting CFV through vessels with impaired autoregulation. Direct intravenous infusions of norepinephrine into both anesthetized (39) and conscious (25) human patients also do not affect CBF or CVR. Thus it is not clear that inhibition or stimulation of the stellate ganglion affects CBF in humans.

The possibility that vestibular activation could modulate a leftward shift in the cerebral autoregulatory curve through an influence on central or peripheral neurogenic pathways must also be considered. In animals, neurons from the vestibular nuclei project directly to the nucleus tractus solitarii (44). Lesions of the nucleus tractus solitarii in turn globally impair cerebrovascular autoregulation independent of any specific effect on baroreceptor input (13). Vestibular pathways also influence neurons in the rostral ventral lateral medulla (43). The rostral ventral lateral medulla, in turn, originates not only descending sympathetic projections to intermediolateral cell column (i.e., to the preganglionic sympathetic neurons of the spinal cord) (43) but also sympathoexcitatory neurons that may serve as regulatory elements of the cerebral circulation (33). Finally, vestibular inputs also project significantly to cerebellar pathways whose fibers, upon stimulation, peripherally induce the so-called “fastigial pressor response” (43). Other than eliciting the intrinsic fastigial pressor response, stimulation of these pathways also elicits a neurogenic cerebral vasodilation that shifts the cerebral autoregulation curve upward rather than leftward or rightward (20). Moreover, this vasodilation is not entirely dependent on sympathetic pathways, but rather depends as well on a second neurogenic pathway that may be cholinergic in origin (20). Because the postcentrifugation changes in GAIN observed in our GX subjects were statistically related to vertical nystagmus slow-phase velocity, it seems possible that the leftward curve shift in this group could have been partly because of the effects of increased otolith activity induced by centrifugation. In support of this hypothesis, the aforementioned data of Serrador et al. (36) also suggest that, during parabolic flight-induced motion sickness, which requires an intact vestibular apparatus for induction, a downward shift occurs in the cerebral autoregulation curve even before the initiation of any postflight orthostatic stress.

It is interesting to note the difference in otolith stimulation between GZ and GX centrifugation. The linear acceleration stimulus to the otoliths during GZ centrifugation is primarily saccular as any change in the utricular neural activity with compressive forces will be negligible. In contrast, the shearing forces during GX centrifugation will stimulate both saccular and utricular otolith organs. Therefore, vestibular-medi-
ated effects after Gx centrifugation might be larger than after Gz centrifugation because Gx centrifugation stimulates both saccules and utricles, whereas Gz stimulates only the saccules. This interpretation is consistent with a previous study by Bles et al. (2), wherein greater vestibular effects after Gx centrifugation than after Gz centrifugation.

Alternative mechanisms by which a leftward shift in the autoregulation curve may have occurred are unclear. In spontaneously hypertensive rats, acute intravenous infusion of angiotensin-converting enzyme inhibitors results in a leftward shift of the cerebral autoregulation curve (31), which is thought to be mediated not via sympathetic nervous pathways but through reductions in circulating angiotensin II (31, 32). Although acute use of angiotensin-converting enzyme inhibitors in normotensive humans may also increase vasodilatory reserve (7), it does not consistently result in a leftward shift of the autoregulation curve (42). Direct infusion of angiotensin into the internal carotid arteries of awake humans also does not result in any change in CBF or CVR (25).

One potential explanation for decreases in CFV in general during HUT might be dilatation of the MCA at the point of insonation. However, recent measures of MCA diameter by MRI combined with transcranial Doppler assessment of CFV have demonstrated that MCA diameter at the M1 segment does not change despite large changes in CFV elicited by stimuli such as LBNP and changes in PetCO2 (35). Other work has examined the lower limit of cerebral autoregulation by using a combination of ganglionic blockade and LBNP to induce hypotension. These studies showed significant correlations between CBF (using 133Xe) and CFV (r2 = 0.60 and r2 = 0.73, respectively) (16, 17), further supporting the view that changes in cerebrovascular tone occur downstream from the segment used for transcranial Doppler measures. Thus it appears that changes in CFV proportionally reflect changes in CBF.

Other more obvious factors that can decrease CBF during HUT include inadequate perfusion pressure due to decreased BPeye and cerebral vasoconstriction due to decreases in PetCO2. With regard to the former, however, the ability of our Gz group to maintain upright CFV at similar levels after (compared with before) centrifugation in the face of significantly decreased BPeye suggests that some factor other than the fall in BPeye influenced CBF during postcentrifugation HUT. Moreover, it is highly unlikely that this unknown factor is related to changes in PetCO2, because decreases in PetCO2 during HUT in the Gz group (and in the Gx group) were unchanged as a result of centrifugation (Table 2). In our Gx group, the finding of increased supine GAIN after centrifugation also cannot be explained by exposure to reduced CPP (as it might be explained in the Gz group) or by reference to supine PetCO2 because, as noted earlier, supine PetCO2 was unchanged in both groups.

In conclusion, this study provides the first evidence that exposure to hypergravity (either +Gz or +Gx) influences cerebral autoregulation in humans. The particular finding that dynamic autoregulation was impaired in the supine position but restored in the upright position after BPeye was lowered specifically suggests that exposure to hypergravity results in a leftward shift of the static cerebral autoregulation curve. Although the mechanism for this proposed shift is unclear, it may involve adaptation to reduced CPP during +Gz exposure and/or possibly a vestibular-mediated effect on nervous pathways that modulate cerebrovascular tone. Because exposure to hypergravity appears to shift the cerebral autoregulation curve to the left, thereby improving orthostatic tolerance, an interesting question deserving of future study is whether exposure to the microgravity of spaceflight conversely shifts the cerebral autoregulation curve to the right, thereby impairing orthostatic tolerance in returning astronauts.

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