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EFFECT OF ACUTE EXPOSURE TO HYPERGRAVITY (G$_X$ VS. G$_Z$) ON DYNAMIC CEREBRAL AUTOREGULATION

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Running Title: Hypergravity Exposure & Dynamic Cerebral Autoregulation

Abstract

We examined the effects of 30 min of exposure to either $+3G_X$ or $+3G_Z$ centrifugation on cerebrovascular responses to 80° head-up tilt (HUT) in 14 healthy individuals. Both before and after $+3G_X$ or $+3G_Z$ centrifugation, eye-level blood pressure (BP_{eye}), end tidal CO_2 ($P_{ET}CO_2$), 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 BP_{eye} decreased with HUT in both the G_X (n= 7) and G_Z (n=7) groups (P<0.001), with the decrease being greater after centrifugation only in the G_Z group (P<0.05). $P_{ET}CO_2$ 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 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 compared to before centrifugation, GAIN increased in both groups (P<0.05, suggesting an autoregulatory deficit), with the change being correlated to a measure of otolith function (the linear vestibulo-ocular reflex) in the G_X group (R=0.76, P<0.05) but not in the G_Z group (R=0.24, P=0.60). However, GAIN was subsequently restored to pre-centrifugation levels during post-centrifugation HUT (i.e., as BP_{eye} decreased), suggesting that both types of centrifugation resulted in a leftward shift of the cerebral autoregulation curve. We speculate that this leftward shift may have been due to vestibular activation (especially during $+G_X$) or potentially to an adaptation to reduced cerebral perfusion pressure during $+G_Z$.

INTRODUCTION

Orthostatic intolerance is common after space flight (5, 8). However, the pathophysiology of this problem is complex and varies among affected individuals (5). Although peripheral vascular resistance responses are often compromised with standing in returning astronauts (5, 8), it is clear that other mechanisms also contribute to diminished orthostatic performance after space flight (2, 5). In some crewmembers, for example, postflight orthostatic intolerance develops without concurrent hypotension, suggesting that control of the cerebral circulation may be altered in a relatively isolated fashion (5). This notion is supported by the fact that paradoxical vasoconstriction of the cerebral circulation is known to precede not only vasovagal presyncope in both the clinical (9, 10) and research (4) settings, but also the orthostatic intolerance that occurs after parabolic flights (33, 35).

Cerebral autoregulation is the process by which cerebral blood flow (CBF) is maintained over a wide range of cerebral perfusion pressures (CPP) (29). The range or set point of the curve representing cerebral autoregulation is variable and is influenced by prevailing CPP (Fig. 1). For example, chronic hypertension may shift the cerebral autoregulatory curve towards the high-pressure end (rightward shift) thereby predisposing affected individuals to hypoperfusion should low CPP be experienced. In contrast, chronic local cerebral hypoperfusion (45) and some forms of chronic orthostatic hypotension (23) appear to shift the same curve leftward (21), potentially improving tolerance for reductions in CPP during orthostatic stress. Although previous work suggests that shifts in the cerebral autoregulatory curve can also occur acutely during cardiovascular stresses such as lower body negative pressure (LBNP) (47, 48) and head-up tilt (HUT) (3), the time course of such adjustments in humans is nonetheless still poorly understood.

One goal of the present study was to determine whether cerebral hypotension experienced during up to 30 min of $+3G_z$ centrifugation subsequently results in altered cerebrovascular control and orthostatic tolerance. Another goal was to determine if $+3G_z$ centrifugation differs from $+3G_x$ centrifugation with respect to its effect on cerebrovascular control and orthostatic tolerance. Because the acceleration experienced during $+3G_x$ is along the nasooccipital axis of the body, little change should be expected in CPP during this stimulus. We therefore hypothesized that 30 min of $+3G_x$ exposure would lead to minimal change in cerebrovascular responses during post-centrifugation (vs. pre-centrifugation) HUT. In contrast, we postulated

that exposure to 30 minutes of $+3G_z$ (i.e., acceleration along the longitudinal, or head-to-foot axis of the body) would cause a leftward shift in the CBF autoregulatory curve due to the reductions in CPP produced by this stimulus, in turn leading to improved cerebrovascular control during post-centrifugation (vs. pre-centrifugation) HUT. Finally, based on evidence that the brainstem pathways involved in vestibular-autonomic reflexes in animals (42) also influence CBF (32) and cerebral autoregulation (12), along with the recent finding that the cerebral autoregulatory curve may be shifted downward in motion sick subjects after parabolic flight (35), we speculated that if post-centrifugation changes in cerebrovascular control developed in the present study, that they would relate to measurements of otolith-ocular reactivity in our individual subjects.

Materials and Methods

Subjects. Fourteen healthy subjects (twelve male and two female) participated in this study. The subjects averaged 26 yrs in age (range = 22-38), 73.8 ± 11.9 kg in weight and 175 ± 5 cm in height. All subjects passed a US Naval or NASA physical examination and on the basis of the examination, urine and blood tests were determined by the examining physician to be free of neurological, cardiopulmonary, renal or other systemic disease. In addition, each gave written, informed consent. Alcohol, heavy exercise, anti-motion sickness and all other medications were strictly prohibited for the 24 hours prior to 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 $+3G_x$ (G_x group, n=7) or $+3G_z$ (G_z group, n=7) acceleration on the Coriolis Acceleration Platform located at the Naval Aerospace Medical Research Laboratory in Pensacola, Florida (18). A chair in a cabin located 20.5 ft from the center of the centrifuge was utilized for testing. For $+3G_x$ centrifugation, subjects sat head erect in the chair with a headrest used to position and stabilize the head. For $+3G_z$ centrifugation, subjects were recumbent in a chair with head towards the center of the centrifuge. The centrifuge profile consisted of a constant angular acceleration for 19s to a constant velocity of 122 deg/s. This created a constant $+3G_x$ or $+3G_z$ force depending on subject position. To end exposure, a constant deceleration lasting 19s was used.

Otolith-ocular responses were examined in all 14 subjects by measuring vertical nystagmus slow-phase velocities, as recently described by McGrath, et al. (18), during an initial 5-min exposure to $+3G_z$. For the purposes of this study, the level of otolith sensitivity was inferred from the magnitude of vertical slow-phase velocity (18). During this initial 5-min $+3G_z$ run, monocular (right) eye movements were recorded in darkness 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 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 approximately 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 $+G_z$ stress, the helmet was held firmly in place via an inflatable bladder and chin-strap system. After the completion of the initial 5-min $+3G_z$ run, the subject's helmet and camera system were removed. Either immediately thereafter (G_z group) or 1-5 days later (G_x group), a 25-min $+3G_z$ run or 30-min $+3G_x$ run was then performed with the lights on following the same acceleration/deceleration profile noted above. During $+3G_z$ centrifugation, no anti-G straining maneuvers were allowed, although all subjects wore a standard naval antigravity suit to prevent G-induced loss of consciousness (G-LOC). These suits inflated automatically when the force exceeded $+2G_z$. In the event that a subject experienced symptoms of incipient G-LOC (i.e., grey out, tunnel vision, etc.) in spite of G-suit prophylaxis, the centrifuge run was terminated early and post-centrifugation testing was commenced (see below). During min 5-9 and 16-20 of the second portion of $+3G_z$ centrifugation (and during the equivalent portion of $+3G_x$ centrifugation), subjects carefully and continually performed yaw head movements initially 15 deg to the left, then back to the center, then 15 deg to the right, then back to center, etc., 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. Pre-defined test-termination criteria for both $+3G_x$ and $+3G_z$ centrifugation also included severe nausea or actual vomiting.

Tilt Testing. Supine (SUP) and 80° HUT data were collected during identical pre- and post-centrifugation testing sessions. Both the centrifuge room and the adjacent pre-/post-centrifugation testing facility were maintained at the same constant temperature and humidity during all sessions. The pre-centrifugation testing session occurred 1-5 days before centrifugation and the post-centrifugation testing session within 15 min after exit from the centrifuge. Two to three hours prior to both sessions, subjects consumed the same breakfast consisting 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 ~ 150 ft from the centrifuge; 2) cardiovascular instrumentation approximately 10 min later; 3) 30-40 min of SUP rest followed by 3-5 min of additional rest for pre-HUT SUP recordings; and, finally 4) HUT testing to 80° for a maximum of 30 min using a motorized custom tilt table (United States Navy, Pensacola, FL). Variance in the time of subject transfer from the centrifuge and in the actual cardiovascular testing times were generally on the order of 5-10 min each.

In the pre-/post-centrifugation 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 (TCD) probe (Transpect, Medasonics, Mountain View, CA) placed over the right temporal bone. The signal was range gated to a depth of 45 to 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. Beat-by-beat blood pressure (BP) was obtained from a finger cuff (Finapres 2300, Ohmeda, Englewood, CO) fixed by an arm board at the level of the heart. To determine BP at the level of the MCA (BP_{eye}), the distance from the heart level to the eyes was measured and the hydrostatic equivalent of BP subtracted from the values obtained from the finger. End-tidal CO_2 ($P_{ET}CO_2$) and respiratory rate (RR) were also monitored via a nasal catheter (Puritan-Bennett, Wilmington, MA) while heart rate (HR) was determined using a standard electrocardiogram. Criteria for orthostatic intolerance during HUT included any of the following: a sudden drop of systolic BP > 25 mmHg or of diastolic BP > 15 mmHg; an absolute systolic BP < 70 mmHg; a sudden and sustained drop in HR of > 15 bpm; an absolute HR < 40 for subjects whose resting absolute HR is > 50; severe lightheadedness; severe nausea or actual vomiting.

Data Analysis. The analog CFV, ECG and BP_{eye} signals were sampled simultaneously at 10 kHz per channel using an 8-channel digital tape recorder (TEAC RD-111T, Teac Inc., Tokyo, Japan). Off-line data analysis was performed with customized data analysis software. The peak velocity envelope of the TCD waveform was used to represent the instantaneous blood flow velocity in the MCA. Beat-by-beat signals were displayed during analysis and any artifacts removed. Regional cerebral vascular resistance (CVR) in the distribution of the MCA was estimated as $CVR= BP_{eye} /CFV$.

The effects of centrifugation on orthostatic adjustments in cerebral hemodynamics were assessed by examining CFV, mean BP_{eye}, $P_{ET}CO_2$ and CVR responses. For this analysis steady state data of 1-3 min duration were selected both for the SUP period and for the early (ELY, first 10 min) as well as the late (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 BP_{eye} 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 BP_{eye} data from each of the SUP, ELY and LATE HUT periods were first obtained. In some cases only 1-2 min of the SUP data were usable. All steady state data segments were then resampled at 5 Hz using linear interpolation and low pass filtered with a cutoff frequency of 1 Hz (8th order zero-phase Butterworth) (27). For each data set, a transfer function gain (GAIN) between CFV and mean BP_{eye} was then calculated using a standard fast Fourier transformation after the method of Panerai et al. (27). Calculations of GAIN correlate well with other measures of autoregulation (26, 46), and have been used in the past to differentiate patients with impaired vs. intact autoregulation (1, 26-28). Specifically, if dynamic autoregulation is functioning properly, changes in mean BP_{eye} cause minimal changes in CFV, and thus GAIN is low. On the other hand, if dynamic autoregulation is impaired, changes in mean BP_{eye} cause large changes in CFV and thus GAIN is high. In addition to GAIN, we also calculated the coherence (COH) and phase delay (PHASE) between CFV and mean BP_{eye} in the 0.02-0.5 Hz range (27).

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 to changes in autoregulatory parameters from pre- to post centrifugation using a linear least squares method. Subjects with greater slow-phase velocity values are presumed to have greater otolithic sensitivity (18) and as such they were investigated for any potentially corresponding changes in cerebral autoregulation.

Statistics. The effect of HUT or Group (G_X vs. G_Z) on CFV, BP_{eye}, $P_{ET}CO_2$, CVR, GAIN, COH and PHASE was assessed using a repeated-measures two-way ANOVA, respectively, with a Student-Newman-Keuls test for multiple comparisons. Data are presented as mean±SEM with levels of P<0.05 considered significant.

RESULTS

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

Tables 1-2 show the pre- and post-centrifugation values for mean BP_{eye}, CFV, CVR, GAIN, HR, $P_{ET}CO_2$, and RR in the SUP position immediately prior to HUT. None of these SUP parameters changed from pre- to post-centrifugation with exception of SUP GAIN, which increased significantly after centrifugation in both groups (Table 1). SUP COH also increased significantly after centrifugation, but only in the G_X group (Table 3).

Responses to HUT. Compared to SUP, HR increased (Table 2, P<0.001) and mean BP_{eye} decreased (Fig. 2, P<0.001) in both groups with HUT both before and after centrifugation. In addition, the decrease in mean BP_{eye} with HUT was greater both before and after centrifugation in the G_Z group than in the G_X group (P<0.01). $P_{ET}CO_2$ also decreased in all subjects during HUT

both before and after centrifugation (Table 2, P<0.01), with no associated change in RR (Table 2).

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

In the G_X group, CVR did not change from SUP to HUT either before or after centrifugation (Fig. 4). However, in the G_Z group, CVR decreased (vs. SUP) during ELY 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_{eye} (Fig. 2).

Cerebral Autoregulation and Vestibular-Cerebrovascular Interactions: As noted above, after centrifugation, SUP GAIN increased in both groups (Table 1) and SUP COH increased in the G_X group (Table 3). Interestingly, however, the increase in SUP GAIN was strongly correlated to vertical nystagmus slow-phase velocity in the G_X group (R=0.76, P<0.05, least squares linear regression) but not in the G_Z group (R=0.24, P=0.60). In addition, the significant increase in COH in the G_X 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 COH before or after centrifugation in either group. However, in both groups, the PHASE between CFV and mean BP_{eye} tended to increase during HUT, but with upright values becoming significantly greater than SUP values only in the G_Z group during LATE HUT (P<0.05).

DISCUSSION

The major findings of this study were as follows. First, short-term (10-30 min) exposure to either $+3G_X$ or $+3G_Z$ impaired dynamic cerebral autoregulation (i.e., increased GAIN) in the SUP position. Second, this increased SUP GAIN occurred without any simultaneous change in

SUP CFV and resolved during a decrease in BP_{eye} with HUT, suggesting that both $+3G_X$ and $+3G_Z$ 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 G_X 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 SUP position post-centrifugation is unexpected, especially in our G_X group. To our knowledge, no prior studies have reported a stimulus in humans that results in increased unstressed SUP GAIN. Although this increased GAIN could potentially suggest that centrifugation shifted our subjects' autoregulation curves rightward rather than leftward (Fig. 1), our results are most consistent with a leftward shift since GAIN was restored (reduced) to pre-centrifugation levels during HUT, once BP_{eye} decreased below SUP levels (Fig. 6). If there had been a rightward shift, GAIN should have remained high as BP_{eye} was reduced. Moreover, SUP $P_{ET}CO_2$ 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 $P_{ET}CO_2$.

In both groups after centrifugation, the increased GAIN in the SUP position followed by the normalization of GAIN during HUT is reminiscent of a similar combination of findings that has been reported, presumably as a beneficial adaptation, in patients with chronic orthostatic hypotension (1, 34). On the other hand, exposure of healthy subjects to 2 weeks of head-down bed rest (i.e., simulated microgravity) has been reported to exacerbate an impairment of dynamic autoregulation that occurs in response to high levels of LBNP (47, 48). Thus it appears that whereas recent exposure to simulated microgravity may impair dynamic cerebral autoregulation in the context of cardiovascular stress, recent exposure to hypergravity (G_Z or G_x) may have an opposite, protective effect. In the present study, a leftward shift in the static autoregulation curve after exposure to hypergravity is also supported by the fact that during post-centrifugation HUT, CFV decreased to similar absolute levels as during pre-centrifugation HUT in spite of relatively greater falls in mean BP_{eye} (Figs. 2-3). This improvement in the static autoregulation curve was especially remarkable within the G_Z group since their exacerbated decreases in mean BP_{eye} with

HUT after (compared to before) centrifugation were statistically significant. Especially in the G_z group therefore, the overall findings during post- vs. pre-centrifugation HUT suggest an increment, not a decrement, in orthostatic tolerance.

Serrador et al. (35) have recently examined changes in dynamic cerebral autoregulation in human subjects after parabolic flight, a stimulus that consists of alternating exposures to both micro- and hypergravity. Perhaps not surprisingly, there were no significant changes in SUP or upright GAIN from pre- to post-parabolic flight within either an orthostatically tolerant subject group or an orthostatically intolerant subject group, suggesting that the effects of micro- and hypergravity on dynamic autoregulation may have generally offset one another under these circumstances. However, in the same study, the individuals who became orthostatically intolerant after parabolic flight had increases (as opposed to no change or decreases) in GAIN during the early portion of HUT both pre- and postflight, suggesting that preflight measurements of GAIN might be useful for predicting nascent postflight deficits in orthostatic tolerance in related environments such as space flight.

As noted earlier, adaptation of the cerebral autoregulation curve to lower BPs occurs in both chronic local cerebral hypoperfusion (45) and orthostatic hypotension (1, 21, 23). However, the exact stimulus duration necessary to induce such shifts is unknown. Ossard and colleagues (25) have demonstrated that as exposure to a given level of $+G_z$ progresses during centrifugation, CFV increases and then becomes maintained well above theoretical levels given the actual level of BP_{eye}. This finding suggests that autoregulation may adapt rather acutely to the current CPP range. Because our own subjects were exposed to relatively short durations (≤ 30 min) of $+3G_z$ or $+3G_x$, our findings are also consistent with the notion of acute adaptation. Nonetheless, both our G_z and G_x groups had an increase in SUP GAIN after centrifugation, whereas only the G_z group should have experienced a reduced CPP 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 SUP 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 alpha adrenergic blockade with intravenous

phenoxybenzamine enhance the maintenance of CBF in the face of hypotension, shifting the autoregulation curve acutely to the left (7, 14) and impairing the autoregulatory response to acute increases in BP (14, 44). However, these effects are mainly reversed after chronic sympathectomy (7, 11). Moreover, stimulation of the cervical sympathetic nerve in primates acutely decreases CBF (13, 20) while shifting the autoregulation curve to the right (13, 17). Nonetheless, the question of whether the sympathetic nervous system plays a primary role in cerebral autoregulation is still under debate (29, 32). 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) intrinsic or extrinsic nervous pathway also exerting an effect on the cerebrovascular bed (19).

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) (39) but not as determined by magnetic resonance imaging (MRI) (22). 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 while CBF remained unchanged. In another study involving direct stimulation of the stellate ganglion during surgery, CFV increased possibly due to a vasoconstriction at the MCA (40). However, patients in that study were anaesthetized both with isoflurane, which is known to ablate autoregulation (37), and with nitrous oxide, which is a potent vasodilator when combined with isoflurane (36). Therefore, the increases in CFV during stellate ganglion stimulation were likely the result of increased mean BP augmenting CFV through vessels with impaired autoregulation. Direct intravenous infusions of norepinephrine into both anaesthetized (38) and conscious (24) 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 influence an extrinsic or intrinsic neurogenic pathway and modulate a leftward shift in the cerebral autoregulatory curve must also be considered. In animals, neurons from the vestibular nuclei project directly to the nucleus

tractus solitarii (NTS) (43). Lesions of the NTS in turn globally impair cerebrovascular autoregulation, independent of any specific effect on baroreceptor input (12). Vestibular pathways also influence neurons in the rostral ventral lateral medulla (RVLM) (42). The RVLM in turn originates not only descending sympathetic projections to intermediolateral cell column (i.e., to the preganglionic sympathetic neurons of the spinal cord) (42), but also sympathoexcitatory neurons that may serve as regulatory elements of the cerebral circulation (32). Finally, vestibular inputs also project significantly to cerebellar pathways whose fibers, upon stimulation, induce the so-called "fastigial pressor response" (FPR) peripherally (42). Besides eliciting the intrinsic FPR, stimulation of these pathways also elicits a neurogenic cerebral vasodilation that shifts the cerebral autoregulation curve upward rather than leftward or rightward (19). Moreover, this vasodilation is not entirely dependent upon sympathetic pathways, but rather depends as well on a second neurogenic pathway that may be cholinergic in origin (19). Since the post-centrifugation changes in GAIN observed in our G_x subjects were statistically related to vertical nystagmus slow-phase velocity, it seems possible that the leftward curve shift in this group could have been due in part to the effects of increased otolith activity induced by centrifugation. In support of this hypothesis, the aforementioned data of Serrador et al. (35) 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.

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 (ACE) inhibitors results in a leftward shift of the cerebral autoregulation curve (30), thought to be mediated not via sympathetic nervous pathways, but through reductions in circulating angiotensin II (30, 31). Although acute use of ACE inhibitors in normotensive humans may also increase vasodilatory reserve (6), it does not consistently result in a leftward shift of the autoregulation curve (41). Direct infusion of angiotensin into the internal carotid arteries of awake humans also does not result in any change in CBF or CVR (24).

One potential explanation for decreases in CFV in general during HUT might be dilation of the MCA at the point of insonation. However, recent measures of MCA diameter by MRI combined with TCD 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 $P_{ET}CO_2$ (34). Other work has examined the lower limit of cerebral autoregulation using a combination of ganglionic blockade and LBNP to induce hypotension. These studies showed significant correlations between CBF (using ^{133}Xe) and CFV, $r^2=0.60$ (15) and $r^2=0.73$ (16), further supporting the view that changes in cerebrovascular tone occur downstream from the segment used for TCD 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 CPP due to decreased BP_{eye} and cerebral vasoconstriction due to decreases in $P_{ET}CO_2$. With regard to the former, however, the ability of our G_Z group to maintain upright CFV at similar levels after (compared to before) centrifugation in the face of significantly decreased BP_{eye} suggests that some factor other than the fall in BP_{eye} influenced CBF during post-centrifugation HUT. Moreover, it is highly unlikely that this unknown factor related to changes in $P_{ET}CO_2$ since decreases in $P_{ET}CO_2$ during HUT in the G_Z group (and in the G_X group) were unchanged as a result of centrifugation (Table 2). In our G_x group, the finding of increased SUP GAIN after centrifugation also cannot be explained by exposure to reduced CPP (i.e., as it might be explained in the G_Z group) or by reference to SUP $P_{ET}CO_2$ because, as noted earlier, SUP $P_{ET}CO_2$ was unchanged in both groups.

Conclusions

This study provides the first evidence that exposure to hypergravity (either $+G_Z$ or $+G_X$) influences cerebral autoregulation in humans. The particular finding that dynamic autoregulation was impaired in the SUP position but restored in the upright position after BP 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 $+G_Z$ exposure and/or possibly a vestibular-mediated effect on nervous pathways that modulate cerebrovascular tone. Since 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 space

flight conversely shifts the cerebral autoregulation curve to the right, thereby impairing orthostatic tolerance in returning astronauts.

Acknowledgments

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Figure Legends

Figure 1 - Theoretical shifts in cerebral autoregulation curve during chronic exposure to hypotension (gray line) or hypertension (dotted line).

Figure 2 - Changes in mean blood pressure at eye level (BP_{eye}) for the G_X and G_Z groups, respectively, both prior to (PRE, open circles) and after (POST, filled circles) centrifugation in the supine (SUP) and early (ELY) and late (LATE) upright (HUT) positions. Values are means ± SEM. *, significantly different from SUP (P<0.001). α, significantly different than PRE value (P<0.05).

Figure 3 – Changes in CFV for the G_X and G_Z groups, respectively, before (PRE, open circles) and after (POST, filled circles) centrifugation in the supine (SUP) and early (ELY) and late (LATE) upright (HUT) positions. Values are means ± SEM. *, significantly different from SUP (P<0.05).

Figure 4 – Changes in CVR for the G_X and G_Z, groups, respectively, before (PRE, open circles) and after (POST, filled circles) centrifugation in the supine (SUP) and early (ELY) and late (LATE) upright (HUT) positions. Values are means ± SEM. *, significantly different from SUP (P<0.05).

Figure 5 – Assessment of dynamic autoregulatory gain (GAIN) in the G_X and G_Z groups, respectively, before (PRE, open circles) and after (POST, filled circles) centrifugation in the supine (SUP) and early (ELY) and late (LATE) upright (HUT) positions. Increased GAIN indicates autoregulation is impaired. Values are means ± SEM. *, significantly different from SUP (P<0.05). α, significantly different than PRE value (P<0.05).

Figure 6 – Theoretical shift in the cerebral autoregulation curve due to short-term exposure to either +3G_X or +3G_Z centrifugation, and to head-up tilt (HUT, see Bondar et al. (3)). The arrows indicate the direction of the theoretical shifts.

Tables

Table 1 – Values during Supine Baseline Collections in Both Groups Pre and Postflight

	G_X Group		G_Z Group	
	Pre	**Post**	**Pre**	**Post**
Mean BP_{eye} (mmHg)	94 ± 3	95 ± 6	86 ± 3	81 ± 3
CFV (cm/s)	51 ± 3	56 ± 6	50 ± 6	53 ± 5
CVR (mmHg/cm·s⁻¹)	1.9 ± 0.1	1.8 ± 0.2	1.9 ± 0.2	1.7 ± 0.3
GAIN ((cm·s⁻¹)²/mmHg²)	0.65 ± 0.07	0.83 ± 0.7*	0.71 ± 0.14	1.04 ± 0.11*

Values are Mean ± standard error. *, significantly different from pre-centrifugation ($P<0.05$)

Table 2 – Cardiovascular & Respiratory Responses

		Pre-Centrifugation			Post-Centrifugation		
		SUP	**EARLY**	**LATE**	**SUP**	**EARLY**	**LATE**
G_X	**HR** (beats/min)	62 ± 2	74 ± 4 †	78 ± 6 †	58 ± 1	77 ± 2 †	75 ± 3 †
	$P_{ET}CO_2$ (mmHg)	39 ± 2	35 ± 2 *	34 ± 3 *	41 ± 2	33 ± 3 *	36 ± 2 *
	RR (breaths/min)	15 ± 2	14 ± 1	14 ± 1	15 ± 1	14 ± 1	15 ± 1
G_Z	**HR** (beats/min)	63 ± 4	80 ± 4 †	82 ± 5 †	62 ± 1	85 ± 5 †	89 ± 6 †
	$P_{ET}CO_2$ (mmHg)	43 ± 1	36 ± 3 *	36 ± 3 *	43 ± 1	38 ± 2 *	36 ± 2 *
	RR (breaths/min)	14 ± 2	14 ± 1	16 ± 1	14 ± 1	14 ± 1	15 ± 1

Values are Mean ± standard error. *, significantly different from SUP ($P<0.01$). †, significantly different from SUP ($P<0.001$)

Table 3 – Values from Transfer Function analysis between CFV and BP_{eye}

		Pre-Centrifugation			Post-Centrifugation		
		SUP	EARLY	LATE	SUP	EARLY	LATE
G_x	Coherence	0.48 ± 0.04	0.66 ± 0.06	0.59 ± 0.08	0.65 ± 0.05†	0.67 ± 0.05	0.70 ± 0.04
	Phase (rad)	0.17 ± 0.08	0.24 ± 0.04	0.25 ± 0.06	0.17 ± 0.06	0.25 ± 0.02	0.28 ± 0.04
G_z	Coherence	0.54 ± 0.06	0.59 ± 0.06	0.55 ± 0.07	0.60 ± 0.04	0.61 ± 0.04	0.60 ± 0.03
	Phase (rad)	0.07 ± 0.06	0.20 ± 0.04	0.32 ± 0.10 *	0.07 ± 0.08	0.24 ± 0.05	0.35 ± 0.05 *

Values are Mean ± standard error. *, significantly different from SUP ($P<0.05$). †, significantly different from Pre-Centrifugation ($P<0.05$)

Figures

Fig 1.

Cerebral Blood Flow
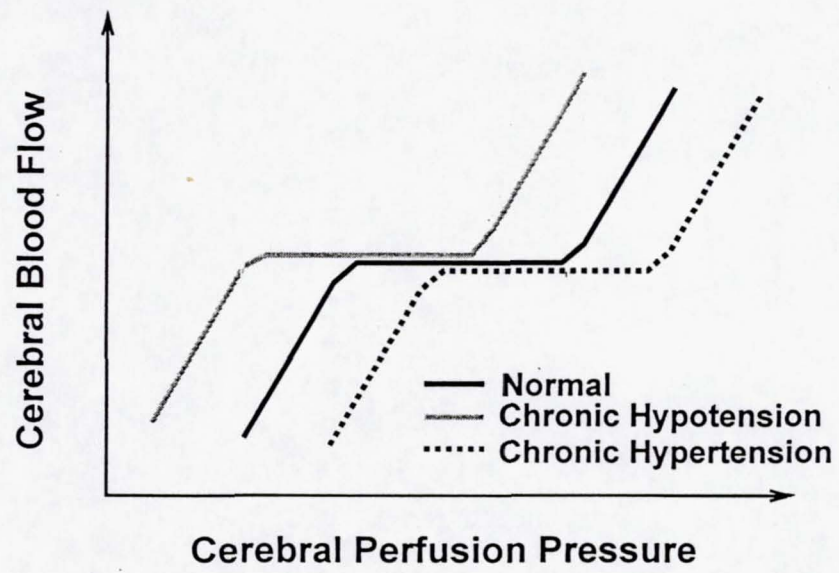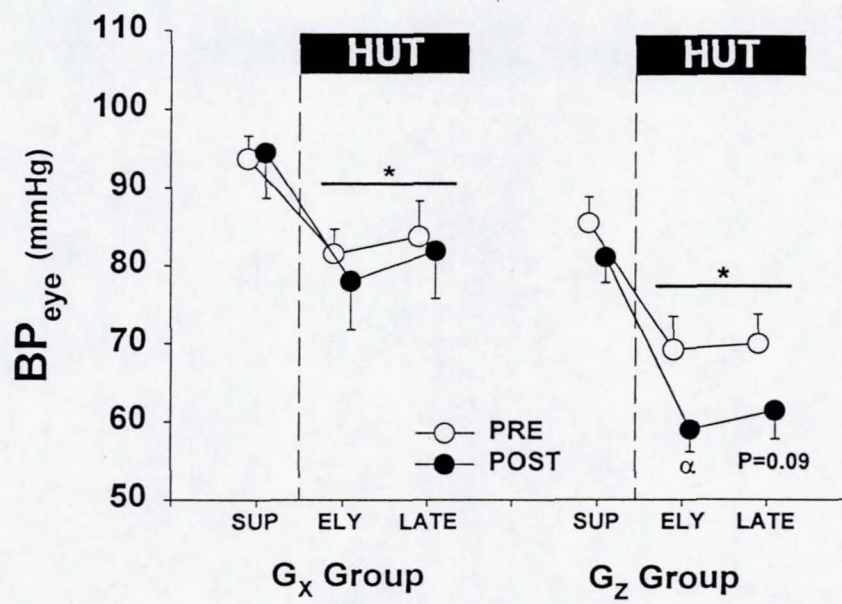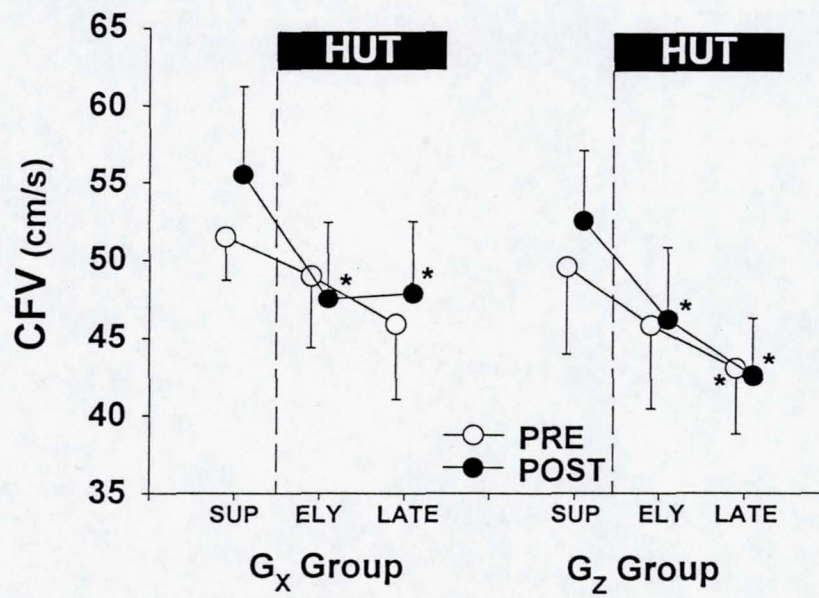
Normal
Chronic Hypotension
Chronic Hypertension

Cerebral Perfusion Pressure

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig.6