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# Effect of Sustained Human Centrifugation on Autonomic Cardiovascular and Vestibular Function

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**ABSTRACT**

BACKGROUND: Repeated exposure to +Gz enhances human baroreflex responsiveness and improves tolerance to cardiovascular stress. However, both sustained exposure to +Gx and changes in otolith function resulting from the gravitational changes of space flight and parabolic flight may adversely affect autonomic cardiovascular function and orthostatic tolerance. HYPOTHESES: Baroreflex function and orthostatic tolerance are acutely improved by a single sustained (30 min) exposure to +3Gz but not +3Gx. Moreover, after 30 min of +3Gx, any changes that occur in autonomic cardiovascular function will relate commensurately to changes in otolith function. METHODS: Twenty-two healthy human subjects were first exposed to 5 min of +3Gz centrifugation and then subsequently up to a total of 30 min of either +3Gz (n = 15) or +3Gx (n = 7) centrifugation. Tests of autonomic cardiovascular function both before and after both types of centrifugation included: (a) power spectral determinations of beat-to-beat R-R intervals and arterial pressures; (b) carotid-cardiac baroreflex tests; (c) Valsalva tests; and (d) 30-min head-up tilt (HUT) tests. Otolith function was assessed during centrifugation by the linear vestibulo-ocular reflex and both before and after centrifugation by measurements of ocular counterrolling and dynamic posturography. RESULTS: All four +3Gz subjects who were intolerant to HUT before centrifugation became tolerant to HUT after centrifugation. The operational point of the carotid-cardiac baroreflex and the Valsalva-related baroreflex were also enhanced in the +3Gz group but not in the +3Gx group. No significant vestibular-autonomic relationships were detected, other than a significant vestibular-cerebrovascular interaction reported previously. CONCLUSIONS: A single, sustained exposure to +3Gz centrifugation acutely improves baroreflex function and orthostatic tolerance whereas a similar exposure to +3Gx centrifugation appears to have less effect.

**INDEX TERMS:** *orthostatic tolerance, otolith, autonomic, centrifugation, baroreflex*

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Recent evidence suggests that baroreflex responsiveness and orthostatic tolerance may be enhanced in military aviators and others who are briefly (but repetitively) exposed to gravitational forces along the heat-to-foot, or +Gz body axis (7, 8, 27, 28). However, it is not known whether such enhancements might also result from a singular, more sustained exposure to +Gz. In addition, the exact role that changes in signals from otolith organs might play in generating the observed improvements in baroreflex function in Gz--exposed individuals has not been previously investigated. A principal goal of the present study was therefore to investigate in detail the acute changes that develop, if any, in baroreflex function and orthostatic tolerance immediately after a single sustained (up to 30 min) exposure to +3Gz centrifugation, and to relate any such changes to concomitant changes in otolith function, if any.

In spite of the potential beneficial effects of +Gz training on baroreflex function, there is also evidence suggesting that novel inputs from the otolith organs may contribute not only to motion sickness and space adaptation syndrome (especially in the context of +Gx acceleration (3)), but also to autonomic cardiovascular disturbances such as early G-induced loss of consciousness (G-LOC) in military aviators (e.g., in the context of the "push-pull" effect) (6) and to actual orthostatic intolerance (OI) in both returning astronauts (42) and parabolic flyers (35). Thus, another goal of this study was to assess the role that changes in otolith function might play in generating autonomic cardiovascular deficits (as opposed to improvements) in centrifuged individuals.

Previous studies also suggest that exposure to sustained centrifugation can result in changes in otolith-mediated oculomotor responses (16) and postural control (4). Bles et al. (3) specifically reported that changes in otolith dependent measures were greater when the resultant gravitoinertial forces during 30 min of centrifugation were directed along the anterior-posterior (Gx) body axis rather than the heat-to-foot (Gz) body axis. The differential effects of Gz and Gx centrifugation on otolith function may be explained by the fact that the hair cells of the utricular maculae are predominantly oriented in the horizontal stereotaxic plane (9), making them less sensitive to the compressive forces during Gz centrifugation than the shearing forces during Gx centrifugation (12). A final

goal of our study was therefore to specifically determine the differential influence of +3Gz vs. +3Gx centrifugation on autonomic cardiovascular and orthostatic function.

We hypothesized that a single exposure to +3Gz centrifugation of up to 30 min would acutely improve baroreflex function and orthostatic tolerance, even in the absence of any concomitant changes in otolith function. Conversely, we hypothesized that exposure to +3Gx centrifugation, which induces a greater utricular shearing force than +Gz centrifugation but which does not induce an orthostatic challenge or the potential training enhancement (28) of +Gz centrifugation, might instead result in otolith-mediated decrements in autonomic cardiovascular control.

## MATERIALS AND METHODS

*Subjects.* Twenty-three healthy test subjects (21 men and 2 non-pregnant women, mean age 25 years, range 22-37 years) participated in the study, which was approved by the Johnson Space Center Institutional Review Board and by the local Naval (Pensacola) and national (Public Health Services) bioethics committees. Data were excluded for two subjects who did not complete the post-centrifuge measurements, including one male subject who aborted the +3Gx run with muscle cramps after 12 min and one male subject who aborted an initial +3Gz run after <2 min with lightheadedness. All subjects had passed a Naval physical examination or equivalent within the prior year, were normotensive nonsmokers with no history of cardiopulmonary, renal, vestibular, oculomotor or other systemic disease, and gave written, informed consent prior to participating in the study. Caffeine, alcohol, heavy exercise, anti-motion sickness medications and all other medications were strictly prohibited beginning 24 hr prior to any testing.

*+3Gz and +3Gx Centrifugation.* All measurements during both +Gz and +Gx centrifugation were obtained using the Naval Aerospace Medical Research Laboratory Coriolis Acceleration Platform in Pensacola, Florida. During the centrifugation subjects were recumbent in a chair located at 6.25 m radius in an enclosed cabin. The chair was inclined 70.5 deg from vertical and fixed with the feet pointed either inward or outward so that the resultant of centrifugal and gravitational force at maximum velocity (+3G at 124 deg/sec) was directed along either the anterior-posterior (Gx) axis or head-to-foot (Gz)

axis, respectively. The centrifuge profile consisted of a velocity trapezoid with acceleration at 6.5 deg/sec$^2$ (0.16 G/sec), rotation at constant velocity (3G) for up to 30 min, and deceleration at 6.5 deg/sec$^2$ to a stop. During both Gz and Gx centrifugation, a headrest was used to stabilize the head. During the +3Gz runs a conventional pneumatic anti-G suit was pressurized above approximately 2G, with subjects being instructed to avoid anti-G strain maneuvers during both Gz and Gx centrifugation. In the event that a subject experienced symptoms of incipient G-LOC (i.e., grey out, tunnel vision, etc.), the centrifuge run was terminated early and post-centrifugation testing was commenced.

*In-centrifugation protocol, including video-oculography recordings.* All subjects were first exposed to 5 min of +3Gz, during which vertical eye movements were recorded to obtain measures of the Gz-related linear vestibulo-ocular reflex (LVOR) (21). Of the 21 total subjects completing the post-centrifugation measurements, 15 (all males) then participated in an additional period of +3Gz (up to 25 min additional, see below) whereas 7 (5 males and 2 females) disembarked from the centrifuge and returned 24-48 hours later to complete a total of 30-min of +3Gx centrifugation instead. One subject performed both the +3Gz and +3Gx protocols.

During the initial 5-min +3Gz run, vertical eye movements were recorded in darkness using a helmet-mounted infrared video-oculography system. This system consisted of monochrome video cameras (Model 6412, Cohu Inc., San Diego, CA) that imaged the eyes from above using dichroic mirrors and infrared light sources. During these 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 LVOR slow phase velocity across subjects. Because of the discomfort generated by wearing the helmet-based video-oculography system in +3Gz for extended periods of time, the LVOR recordings in +3Gz were obtained only during the initial 5-min run. For subjects participating in the prolonged +3Gz runs, the centrifuge was decelerated and stopped for <5 min to remove the helmet and video-oculography equipment. After re-securing the subject, the centrifuge was re-accelerated at the same rate described above and up to 25 min of additional +3Gz

centrifugation was completed with the lights on. During min 5-9 and 16-20 of the second portion of +3Gz centrifugation (and during the equivalent portion of +3Gx centrifugation, which was also performed in its entirely with the lights on), subjects carefully 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. In the event that any subject began to subjectively experience motion sickness symptoms as a result of moving his/her head, the movements were terminated and the head returned to center-gaze for the duration of the run.

The vertical eye-movement data were recorded on videotape and analyzed offline using an eye tracking system implemented on a Macintosh PowerPC platform with an image frame grabber. The pupil-tracking algorithm utilizes a least squares fit on binary images based on a clipped circular disk model (41). This algorithm is used to derive the horizontal and vertical image coordinates of the pupil center, the pupil radius, and the degree to which the upper eyelid has occluded the pupil. Initial eye measurement calibrations were made by having subjects fixate a series of targets placed over a range of ± 10° horizontally and vertically on the wall at a distance of 0.6 m.

*Pre- and post-centrifugation protocol.* A specific sequence of autonomic and otolith function testing was conducted 4 ± 0.5 days (mean ± sem) before centrifugation, and then again immediately after the full +3Gz or +3Gx run in temperature- and humidity-controlled rooms located approximately 46 m from the centrifuge. The post-centrifugation test sequence, depicted in Figure 1, differed from the pre-centrifugation test sequence only in that it also contained an approximately 16 min period immediately before testing wherein subjects initially remained seated within the centrifuge for medical monitoring. After this monitoring, subjects donned a soft neck support to minimize head movements during assisted ambulation to the test area. The pre- and post-centrifugation testing protocols were otherwise equivalent and included: *1*) posture platform testing without head movements (10 min); *2*) cardiovascular instrumentation (detailed below); *3*) supine rest for 15 min; *4*) supine controlled frequency breathing at 0.25 Hz for 5 min, or until 256

consecutive heart beats and beat-to-beat BPs were recorded for subsequent spectral analyses; *5*) supine carotid-cardiac baroreflex testing (10 min); *6*) supine Valsalva maneuver testing (5 min); *7*) 3-5 min of additional supine rest; *8*) HUT testing (30 min or until presyncope, whichever occurred first); *9*) ocular-counterroll testing following a brief return to the supine position (15 min); and, finally, *10*) posture platform testing with head movements (15 min). The majority of these activities are described in greater detail below. The maximum differences in the time of subject transfer after centrifugation and the start time for autonomic testing was in the range of 20 min.

**[Figure 1 Here]**

*Assessment of postural control.* Dynamic posturography was conducted twice before and twice after centrifugation using a computerized platform (Equitest, Neurocom International, Clackamas, OR). This platform system consists of a motor-driven, dual footplate that was either fixed or rotated about the ankles to alter the normal ankle proprioceptive feedback by 'sway-referencing' the footplate relative to the subject's center of mass, typically in the anterior-posterior plane (30). During the initial session of each sequence, two of the standard Sensory Organization Tests (SOT) conditions (30) were utilized during which subjects were instructed to maintain upright stance for 20 sec. For SOT-1, the subjects' eyes were open with a fixed-support (normal visual, proprioception and vestibular input). For SOT-5, the subjects' eyes were closed with a sway-referenced support (absent vision, altered proprioception, normal vestibular input).

During the initial posture session, three consecutive trials of standard SOT-1 were conducted followed by three trials of standard SOT-5. This session was used to obtain an initial measure of the postural control following centrifugation, before and without any head movements that might promote readaptation (18) and confound the remaining tests. At the very end of the test sequence (Figure 1), three trials of the normal SOT-1 and SOT-5 conditions were repeated in a second posture session, followed by three trials of SOT-1 and six trials of SOT-5 with voluntary roll and pitch head tilts (22). During the head movement trials the head was maintained for 2 sec in each of the following positions:

upright, roll right, upright, roll left, upright, pitch forward, upright, pitch back, and upright. A head tracker system (Logitech 3D Head Tracker, Fremont, CA) was used to monitor the magnitude of head movement (approximately 30° in each direction) and provide feedback to ensure the subjects maintained consistency across trials. Finally, three trials of SOT-1 and six trials of SOT-5 were also performed using the same head movement sequence but with the subject standing on the footplate so that sway referencing was performed in the medial-lateral plane.

*Cardiovascular assessments.* Cardiovascular data were collected during identical pre- and post-centrifugation sessions in both the supine and 80-degree HUT positions. Two to three hours prior to both sessions, subjects consumed the same low-fat meal and non-caffeinated beverage.

Prior to cardiovascular testing, subjects were first instrumented with: *1*) electrocardiographic leads and electrodes (including an electrode for impedance measurements of abdominal-muscle respiratory excursions (Physio-Control, Redmond, WA); *2*) impedance cardiographic leads and electrodes (BoMed, Irvine, CA); and *3*) a finger photoplethysmographic device (Finapres 2300, Ohmeda, Englewood, CO) for beat-to-beat estimates of BP. For the purposes of a companion investigation (37), some subjects were also instrumented with transcranial Doppler (TCD) ultrasound for measurements of cerebral blood flow. The continuous cardiovascular signals from these devices were digitally recorded and integrated by using a special software program (20, 34) that automatically entrains beat-to-beat heart rate (HR), stroke volume (SV) and mean BP (MBP) to create a real-time pictorial representation for beat-to-beat cardiac output (CO = HR x SV) and total peripheral resistance (TPR = MBP/CO). Although the BoMed bioimpedance device may not give accurate information pertaining to absolute SV, it does provide accurate, reliable and reproducible estimations of changes in SV (26). Finally, manual recordings of systolic, diastolic and pulse blood pressure (SBP, DBP and PP respectively) were also obtained in all subjects on a minute-to-minute basis before, during and after tilt via a sphygmomanometer attached to the arm opposite the Finapres. During tilt, these manual recordings were increased to every 30 s upon the onset of new symptoms, TCD changes, or a marked decrease in BP.

*Derivation of power spectra.* Spectral powers were derived from the 5-min series of consecutive R-R intervals, SBPs and DBPs collected in the supine position during metronome-controlled breathing (5) at 0.25 Hz both pre- and post-centrifugation. Prior to the pre-centrifugation testing, subjects first chose a comfortable respiratory excursion (tidal volume) and practiced breathing to the metronome at that excursion. They were then asked to use this same excursion throughout all subsequent pre- and post-centrifugation tests involving controlled frequency breathing. During data collection itself, based upon our observation of end-tidal $CO_2$ levels and of abdominal and nasal respiratory movements and tracings, we also provided verbal feedback to the subjects as necessary to ensure that they were maintaining gross consistency in respiration.

For spectral analyses, the Welch algorithm for averaging periodograms (40) was used in accordance with the method of Rabiner *et al.* (33). Specifically, the continuous series of R-R intervals, SBPs or DBPs was fitted to a cubic spline function, interpolated at 8 Hz to obtain equidistant time intervals, and divided into seven equal overlapping segments. Segments were then de-trended, Hanning window filtered, fast-Fourier transformed, and averaged to produce the spectrum estimate. Spectral power was integrated over three defined frequency bandwidths: "low" frequencies between 0.05 and 0.15 Hz; "high" (or respiratory) frequencies between 0.20 and 0.30 Hz; and all frequencies (i.e., "total power") below 0.50 Hz (19). We also calculated a "sympathovagal index", defined as the ratio of the low frequency power of SBP to the high frequency power of R-R intervals (29, 35).

*Carotid-cardiac baroreflex responsiveness.* Both before and after centrifugation, supine carotid-cardiac baroreflex responsiveness was measured in subjects via pressure changes applied to a tightly sealing silastic neck chamber connected to a computer-controlled bellows (E-2000 Neck Baro Reflex System, Engineering Development Laboratories, Newport News, VA) (38). During held expiration, neck chamber pressure was raised to +40 mmHg and then reduced to -60 mmHg in consecutive R-wave-triggered steps of -20 mmHg. This sequence was then repeated seven times and the responses averaged for each test subject. R-R interval responses to carotid baroreceptor stimulation, defined as carotid distending pressure (SBP minus neck pressure), were reduced to the

maximum slope of the stimulus-response relation, the maximum range of R-R interval responses, and the operational point. The operational point [(R-R interval at 0 mmHg – minimum R-R interval) / R-R interval range x 100] is a measure of the buffering capacity of the carotid baroreflex to a hypotensive stimulus (13, 14).

*Valsalva measurements.* Valsalva maneuvers were completed at an expiratory pressure of 30 mmHg for 15 s as previously described (34). Prior to the strains, which were performed in triplicate, subjects first had at least 15 min of supine rest. Each strain was also preceded and followed by at least 1 min of controlled frequency breathing at 0.25 Hz. To produce the strains, subjects blew into a mouthpiece connected by short plastic tube to a calibrated pressure gauge while the electrocardiogram, impedance cardiogram, and arterial and expiratory pressures were continuously recorded.

Phasic changes in cardiovascular parameters during Valsalva maneuvers were calculated as follows: *1*) ΔPhase I was the change in the given parameter occurring between the maximal MAP value during phase I and the baseline MAP value prior to the maneuver; *2*) ΔPhase $II_e$ was the change in the given parameter occurring between the maximal MAP value during phase I and the minimal MAP value during phase $II_e$; *3*) ΔPhase $II_l$ was the change in the given parameter occurring between the minimal MAP value during phase $II_e$ and the maximal MAP value during phase $II_l$; *4*) ΔPhase III was the change in the given parameter occurring between the maximal MAP value during phase $II_l$ and the minimal MAP value during phase III; and *5*) ΔPhase IV was the change in the given parameter occurring between the minimal MAP value during phase III and the maximal MAP value during phase IV. For the decrease in MAP during phase $II_e$, estimates of baroreflex responsiveness (i.e., ΔR-R interval/ΔMAP) were also calculated (34).

*Head Upright Tilt (HUT) tests.* After supine autonomic testing both before and after centrifugation, subjects were secured and pitched acutely (9.4 +/- 0.3 s, mean +/- sem) into the 80-degree head-up position by using a custom-designed electronic tilt table. A padded arm extension secured to the table was used during tilt to maintain the Finapres finger cuff at the level of the heart. Once attained, 80-degree HUT was sustained for a total of 30 min or until orthostatic intolerance ensued. Orthostatic intolerance in this

study was defined on the basis of having to terminate HUT prior to 30 min for any of the following reasons: subject request at any time; sudden drop of systolic BP > 25 mmHg or of diastolic BP > 15 mmHg; sudden and sustained drop in HR of > 15 beats/min; absolute HR < 40 beats/min for subjects whose resting absolute HR is > 50 beats/min; absolute manual systolic BP < 80 mmHg; severe lightheadedness, severe nausea or actual vomiting.

For HUT-related analyses, we first obtained the value of each minute-to-minute cardiovascular parameter at the time of the manual BP measurements. Serial values for each parameter were then determined for individual subjects according to three epochs: epoch 1, the average of the two minute-to-minute values in the supine position immediately preceding HUT; epoch 2, the value obtained between min 4-5 of HUT (excluding any value obtained during or after the minute of orthostatic failure, if failure occurred during this minute); and, epoch 3, the average of two values from the last min of HUT. The averages from individual subjects were then used to derive corresponding epochal averages for groups of subjects (i.e., whole group, Gx group, Gz group).

*Ocular counterrolling and perception during roll-tilt.* Following the HUT tests in the subject's pitch (saggital) plane, the same two-axis motorized tilt table was configured to provide roll tilts from the upright position toward the subject's right or left shoulder. Subjects were restrained in a standing position by adjustable torso and foot restraints and straps across chest, feet and shoulders. The head position was stabilized in a natural upright position with adjustable clamps positioned over the forehead and sides of the head. Binocular eye movements were recorded in darkness using the near-infrared camera system described above. Communications with the subject were provided over a speaker that moved with the table to minimize auditory orientation cues. In addition to deriving horizontal and vertical eye position from the pupil center, torsional eye movements were calculated using the polar cross-correlation method (24). Pre- and post-test eye measurement calibrations were made by having subjects fixate a series of horizontal and vertical wall targets positioned ± 10°. Two low-power laser pointers were mounted to the chair and adjusted to project on the wall at 1.5 m distance at eye level either a single fixation point during ocular-counterrolling measurements or crosshair pattern during voluntary eye movements as described below.

Measurements were made in the upright, roll right (or left), upright, roll left (or right), and then upright orientations, with the order counterbalanced across subjects. Dynamic ocular counterrolling was measured while the subjects were tilted at 3°/s in darkness (10). At each tilt position, the subjects continued to stare straight ahead in darkness for 15 sec. 'Static' ocular counterrolling was then obtained while subjects fixated the single fixation point target for 10s. Subjects then performed a series of voluntary eye movements in darkness along perceived earth and head orientations as described previously (41). Finally, before being tilted into the next orientation, subjects made voluntary eye movements along horizontal and vertical head directions as guided by the laser crosshair target. The trajectories of the eye movements along the laser target axes, typically within ±1° of true head orientation, provided a measure of head fixation relative to the eye camera system.

*Statistics.* All results are reported as means ± SE. Because normality was often violated, we used the nonparametric Wilcoxon signed-rank test for within-group comparisons from pre- to post-centrifugation (15) and the Spearman rank correlation to examine relationships between variables (StatView 5.0, SAS Institute Inc., Cary, NC). Statistical significance was accepted at $P < 0.05$.

## RESULTS

*In-centrifugation symptoms.* Of the 15 subjects in the +3Gz group, only 4 were able to complete the entire 30 min of centrifugation. In spite of the G-suit prophylaxis, the remaining 11 subjects in the +3Gz group did not complete the runs due to pre-GLOC symptoms, including tunnel vision, grey out and lightheadedness. Pre-GLOC symptoms, when present, resolved shortly after deceleration of the centrifuge. None of the +3Gx subjects reported pre-GLOC symptoms. Eight of the 15 +3Gz subjects and 4 of the 7 +3Gx subjects reported mild motion sickness symptoms and subsequently limited head movements during centrifugation. These symptoms ranged from slight to mild nausea, headache, sweating and increased salivation. One subject in the +3Gz group vomited following deceleration. Motion sickness symptoms, if present, resolved while subjects

rested in the semi-supine position for an average of 16 min before ambulating to the initial posture test.

*Spectral power of supine R-R intervals and arterial pressures.* Pre- to post-centrifugation changes in supine R-R interval and arterial pressure spectral powers for the +3Gz and +3Gx groups are shown in Table I. In the +3Gz group, the low frequency power of SBP increased after centrifugation ($P<0.001$), as did the total power of SBP and the sympathovagal index ($P<0.05$). In the $+3G_x$ group, no significant changes were noted in any of the spectral parameters.

**[Table I Here]**

*Carotid-cardiac baroreflex responses.* Pre- to post-centrifugation changes in supine carotid-cardiac baroreflex responses for the +3Gz group are shown in Table II and Figure 2. Because of a mechanical problem that developed with the bellows device during one of the +3Gx testing weeks, carotid-cardiac baroreflex measurements could only be performed on three of the seven subjects in the +3Gx group. Therefore, statistical assessments were not performed for the +3Gx group and the limited carotid-cardiac baroreflex data for this group are not presented. For the +3Gz group, centrifugation had no effect on either the range or slope of the carotid-cardiac baroreflex. However, after centrifugation, the operational point of the carotid-cardiac baroreflex increased significantly in +3Gz group ($P<0.05$).

**[Table II, Figure 2 Here]**

*Valsalva responses.* Supine responses to Valsalva maneuvers before and after centrifugation in both the +3Gz and +3Gx groups are shown in Table III. In the +3Gz group, the rise in MAP during Valsalva phase I was significantly increased after centrifugation ($P<0.05$), as was the baroreflex sensitivity during Valsalva phase $II_e$ ($P < 0.01$). The temporal duration of the MAP rise during phase $II_l$ was also decreased in these same subjects ($P<0.05$). In the +3Gx group, there were no significant changes in any of the Valsalva-related parameters.

**[Table III Here]**

*Responses to HUT.* Before centrifugation, 11 of the 15 subjects in the +3$G_z$ group and all 7 subjects in the +3Gx group were able to tolerate 30 min of 80-degree HUT. The four subjects in the +3Gz group who were intolerant to HUT before centrifugation experienced typical vasovagal episodes (25) at that time. On the other hand, after centrifugation, all subjects in both groups were able to tolerate all 30 min of HUT. Based upon the published reproducibility of presyncopal or non-presyncopal outcomes in replicated HUT testing (2), these data indicate that general orthostatic tolerance was significantly improved in the +3Gz group as a result of centrifugation ($P= 0.013$, chi-squared approximation test). Table IV shows the HUT-related hemodynamic changes that occurred from pre- to post-centrifugation in both groups. In the supine position after compared to before centrifugation, there were no significant hemodynamic changes in the +3Gz group and only a decrease in PP in the +3Gx group ($P<0.05$). During min 4-5 of HUT after compared to before centrifugation, only PP was changed (decreased) in both groups ($P<0.05$). During the last min of HUT after compared to before centrifugation, DBP and MBP were increased in the +3Gz group only.

**[Table IV Here]**

*Vestibular measures.* Pre- and post-centrifugation responses to posturography and to ocular-counterrolling as well as baseline LVOR responses for both the +3Gz and +3Gx groups are shown in Table V. Although no significant changes were noted from pre- to post-centrifugation in the parameters germane to the initial posture trials (i.e., those trials without head-movements), there was a significant decrease in postural performance in the +3Gx group during the last set of posture trials in which the subjects made head movements while in the medial-lateral sway referenced orientation ($P<0.05$). During roll tilts, there was a significant increase in tilt perception in both groups as indicated by the saccade trajectories made along the perceived earth axes ($P<0.05$). There was also a trend for ocular counterrolling to be reduced following centrifugation as reported previously by Groen et al. (16). However, no other significant changes in the vestibular measures were

noted for either +3Gz or +3Gx groups. The range of LVOR responses recorded in the present study (0.7 - 14.4 deg/sec) was comparable to that reported earlier by McGrath et al. (21).

*Correlations between vestibular and autonomic measures.* To test the hypothesis that exposure to centrifugation would result in otolith-mediated decrements in autonomic cardiovascular function, we examined paired comparisons between changes in vestibular measures with individual changes in autonomic measures. This analysis was limited by the relatively small changes detected in the vestibular measures as noted above. Although not significant, there was a trend for subjects in the +3Gx group who showed larger decrements in ocular counterrolling to have greater change in pulse pressure during the early portion of HUT. Using the Spearman rank correlation, however, no statistically significant correlations were found.

## DISCUSSION

The major findings of this study were as follows. First, a single, sustained exposure to +3Gz centrifugation acutely improved baroreflex function and orthostatic tolerance, whereas a similar exposure to +3Gx centrifugation, although not diminishing orthostatic tolerance or baroreflex function, appeared to have less effect. Second, individual measurements of otolith function did not relate to changes in autonomic cardiovascular function following prolonged (up to 30 min) +3Gz or +3Gx centrifugation. However, the relatively small changes in the otolith-mediated dependent measures suggest that the vestibular adaptation following up to 30 min of +3G may have been insufficient or too short-lived to induce otolith-mediated decrements in autonomic cardiovascular function detectable by the measurements reported here.

The finding that baroreflex responsiveness increased after a single, sustained exposure to +3Gz supports previous studies showing a beneficial effect of +Gz training (i.e., short, repetitive exposures to +Gz) on baroreflex responsiveness (7, 8, 27, 28). However, in the present study, the pattern of improvement in baroreflex responsiveness was somewhat different from that described previously. For example, Convertino (7) has reported that the slope of the carotid-cardiac baroreflex is enhanced in +Gz-trained subjects, whereas this slope was not enhanced in our subjects singularly exposed to up to

30 min of +3Gz. Instead, only the operational point of the carotid-cardiac baroreflex was enhanced in our subjects, along with the baroreflex in Valsalva phase $II_e$. Since the Valsalva-related baroreflex is complex and probably involves arterial as well as cardiopulmonary baroreceptors (34, 39), it seems possible that an improvement in the responsiveness of one of the other baroreceptor populations (i.e., the aortic and/or cardiopulmonary baroreceptors) may have been responsible for the increased baroreflex responsiveness during Valsalva phase $II_e$. On the other hand, the increased operational point of the carotid-cardiac baroreflex (Figure 2) may have served to enhance the Valsalva-related baroreflex by keeping the R-R interval response on the steeper portion of the carotid distending pressure curve throughout the decrease in BP during Valsalva phase $II_e$.

Improvement of general orthostatic tolerance after +3Gz centrifugation was demonstrated by the fact that all 4 of the subjects in that group who could not complete 30 min of HUT before centrifugation were able to complete it after centrifugation. Moreover, in the $+3G_z$ group, end-upright DBP and MBP increased after compared to before centrifugation, potentially corroborating the improvement in tolerance. On the other hand, none of the subjects in the +3Gx group had a positive HUT test either before or after centrifugation. It therefore seems appropriate to conclude that up to 30 min of +3Gx centrifugation at least does not degrade orthostatic tolerance. Nonetheless, the fewer overall subjects in the +3Gx group, especially with respect to the carotid-cardiac baroreflex measurements, made changes in that group's baroreflex sensitivity and orthostatic tolerance more difficult to judge.

In our concurrent study involving transcranial Doppler measurements in these same subjects (37), we also observed changes in cerebral circulation after centrifugation (in both +3Gx and +3Gz groups, but especially in the latter group) that suggested an improvement in orthostatic performance at the cerebral level. Specifically, we found that in the supine position after centrifugation, dynamic autoregulation [the process by which cerebral blood flow (CBF) is maintained over a wide range of cerebral perfusion pressures (31)] was impaired, but that such regulation was restored in the upright position. Because the restoration of dynamic autoregulation occurred during a decrease in eye-level BP

during HUT and without greater increases in cerebral vascular resistance, we specifically concluded that exposures to hypergravity may improve orthostatic tolerance by causing a leftward shift of the static cerebral autoregulation curve, thus allowing for better maintenance of CBF in the face of any hypotension occurring in the upright position immediately following centrifugation (37). Similarly, the enhancement of the operational point of the carotid-cardiac baroreflex following +3Gz centrifugation in the present study may represent an increase in the buffering capacity of the carotid baroreflex to a hypotensive stimulus (14).

The increased baroreflex responsiveness and orthostatic tolerance of our +3Gz group contrasts with the decreased baroreflex responsiveness and orthostatic tolerance of returning astronauts (13, 14). Our +3Gz results therefore support the recent suggestion of Newman et al. (28) that the baroreflexes of humans exposed to a sustained hypergravity environment are capable of adapting to their changed conditions in much the same way as has been known to occur in long-duration space flight, except in the opposite direction. During long-duration space flight, therefore, the notion that artificial gravity might theoretically be used to beneficially adapt baroreflex function (or at least to counteract the deleterious effects of microgravity) and to improve incipient orthostatic tolerance appears to have scientific merit. One potential concern, however, involves Coriolis cross coupling and the accompanying nausea and peripheral vasodilitation (17) that might be experienced with artificial gravity during space flight, particularly during head movements. We ourselves have also recently demonstrated that in motion sick subjects after parabolic flight, orthostatic tolerance is often worsened even though carotid-cardiac baroreflex function is improved (35). This latter finding suggests that carotid-cardiac baroreflex responsiveness and orthostatic tolerance should not be equated, since central (especially neurovestibular) mechanisms that beneficially affect the former might deleteriously affect the latter, especially through simultaneous influences on cerebral vascular regulation (36). In addition, the institution of artificial gravity as a countermeasure for cardiovascular deconditioning during long-duration space flight might also be complicated by the fact that both rapid (1, 23) and repetitive (35, 36) transitions between micro- and hypergravity can

have deleterious effects on G-tolerance and orthostatic performance outside of the context of nausea and motion sickness.

There is evidence that the vestibular organs may provide "feed forward" signals that supplement feedback information provided by baroreceptors in maintaining orthostatic tolerance (11, 32). Nonetheless, we did not observe any significant correlations between autonomic cardiovascular and otolith measures (or the changes therein) following +3G centrifugation, other than the significant vestibular-cerebrovascular relationship that occurred in the same subjects involved in the present study, as previously reported (37). One potential reason may be that, as already noted, the changes in otolith function may have been too small following 30 min of centrifugation, and/or the time course of vestibular readaptation too short, for such relationships to be detected by the methods employed. Further study with longer duration centrifugation is warranted to examine the extent to which otolith-mediated changes might beneficially or adversely affect autonomic cardiovascular control.

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Table I. *Spectral power of R-R intervals and arterial pressures*

| | +3G*z* | | +3G*x* | |
|---|---|---|---|---|
| | Before | After | Before | After |
| *Spectral power of R-R intervals* | | | | |
| $LFP_{R-R}$ | 2.6 ± 0.8 | 4.3 ± 1.1 | 2.6 ± 0.8 | 3.4 ± 1.2 |
| $HFP_{R-R}$ | 8.0 ± 2.2 | 9.8 ± 2.9 | 4.6 ± 1.8 | 5.5 ± 1.2 |
| $TP_{R-R}$ | 15.4 ± 4.0 | 19.8 ± 4.9 | 11.7 ± 3.2 | 16.0 ± 3.5 |
| *Spectral power of systolic pressures* | | | | |
| $LFP_{SBP}$ | 7.5 ± 1.2 | 18.5 ± 3.0† | 6.8 ± 2.4 | 5.0 ± 1.5 |
| $HFP_{SBP}$ | 9.9 ± 2.4 | 6.9 ± 1.3 | 5.4 ± 0.9 | 4.1 ± 0.6 |
| $TP_{SBP}$ | 66.1 ± 10.7 | 125.6 ± 33.9* | 64.5 ± 20.3 | 72.1 ± 25.6 |
| *Spectral power of diastolic pressures* | | | | |
| $LFP_{DBP}$ | 4.3 ± 0.6 | 6.5 ± 1.1 | 4.3 ± 1.0 | 3.1 ± 0.9 |
| $HFP_{DBP}$ | 2.0 ± 0.6 | 2.3 ± 0.6 | 1.5 ± 0.9 | 1.6 ± 0.5 |
| $TP_{DBP}$ | 22.4 ± 4.7 | 27.9 ± 4.6 | 18.3 ± 4.8 | 18.3 ± 2.8 |
| *Sympathovagal index* | | | | |
| $LFP_{SBP}/HFP_{RR}$ | 2121 ± 572 | 5730 ± 1912* | 2537 ± 727 | 1202 ± 324 |

Gz, $n$=15; Gx, $n$=7; $n$, number of subjects. Values are means ± SE in units of $ms^2/Hz \times 10^3$ for spectral power of R-R intervals and $mmHg^2/Hz$ for spectral power of arterial pressures. LFP, low frequency power; HFP, high (or respiratory) frequency power; TP, total power; R-R, R-R intervals; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Assessments were made while supine. Within group changes (Wilcoxon sign-ranked test): *$P < 0.05$; †$P<0.01$.

Table II. *Carotid-cardiac baroreflex responses*

| | +3Gz | |
|---|---|---|
| | Before | After |
| *Pressure stimuli: +40 mmHg to –60 mmHg* | | |
| Range | 193 ± 24 | 172 ± 26 |
| Slope | 3.8 ± 0.5 | 3.6 ± 0.5 |
| Operational point | 17 ± 5 | 29 ± 7* |

Gz, $n$=15; $n$, number of subjects. Values are means ± SE in units of msec for Range, msec/mmHg for Slope, and % for Operational point. Assessments were made while supine. Within group changes (Wilcoxon sign-ranked test): *$P < 0.05$.

Table III. *Valsalva maneuver responses*

| | +3Gz | | +3Gx | |
|---|---|---|---|---|
| | Before | After | Before | After |
| *MAP responses* | | | | |
| ΔPhase I | 14 ± 1 | 17 ± 2* | 15 ± 1 | 17 ± 2 |
| ΔPhase $II_e$ | -14 ± 2 | -13 ± 2 | -13 ± 4 | -14 ± 3 |
| ΔPhase $II_l$ | 9 ± 2 | 5 ± 1 | 9 ± 2 | 5 ± 1 |
| ΔPhase III | -17 ± 2 | -18 ± 2 | -19 ± 2 | -21 ± 4 |
| ΔPhase IV | 17 ± 2 | 21 ± 3 | 17 ± 1 | 23 ± 5 |
| *Baroreflex responsiveness* | | | | |
| Phase $II_e$ | 10.24 ± 4.79 | 18.08 ± 4.40† | 15.29 ± 5.60 | 24.71 ± 5.64 |
| Phase IV | 18.48 ± 3.41 | 17.03 ± 3.35 | 13.87 ± 2.16 | 14.52 ± 2.85 |
| *Temporal duration of MAP responses* | | | | |
| Phase $II_e$ | 7.54 ± 0.56 | 7.03 ± 0.49 | 6.52 ± 0.39 | 7.19 ± 0.70 |
| Phase $II_l$ | 5.25 ± 0.57 | 4.63 ± 0.58* | 5.68 ± 0.55 | 4.38 ± 0.55 |

Gz, $n$=15; G$x$, $n$=7; $n$, number of subjects. Values are means ± SE in units of mmHg for MAP responses; msec/mmHg for baroreflex responsiveness (ΔR-R interval/ΔMAP); and sec for temporal duration. Assessments were made while supine. Within group changes (Wilcoxon sign-ranked test): *$P < 0.05$; †$P<0.01$.

Table IV. *Head Upright Tilt (HUT) responses*

| | +3Gz | | +3Gx | |
|---|---|---|---|---|
| | Before | After | Before | After |
| *Supine* | | | | |
| SBP (mmHg) | 122 ± 2 | 119 ± 3 | 121 ± 4 | 117 ± 4 |
| DBP (mmHg) | 74 ± 2 | 74 ± 3 | 76 ± 4 | 77 ± 2 |
| MBP (mmHg) | 90 ± 2 | 89 ± 3 | 91 ± 4 | 90 ± 3 |
| PP (mmHg) | 48 ± 3 | 45 ± 2 | 45 ± 2 | 40 ± 3* |
| HR (beats/min) | 59 ± 2 | 57 ± 2 | 61 ± 3 | 56 ± 2 |
| SV (ml) | 129 ± 5 | 124 ± 5 | 110 ± 11 | 114 ± 10 |
| CO (l/min) | 7.5 ± 0.4 | 7.1 ± 0.3 | 6.6 ± 0.8 | 6.3 ± 0.6 |
| TPR (mmHg/l/min) | 12.4 ± 0.6 | 13.0 ± 0.8 | 15.0 ± 2.0 | 15.1 ± 1.7 |
| *Early upright tilt (min 4-5)* | | | | |
| SBP (mmHg) | 119 ± 2 | 115 ± 3 | 116 ± 4 | 113 ± 4 |
| DBP (mmHg) | 77 ± 2 | 80 ± 2 | 77 ± 3 | 80 ± 4 |
| MBP (mmHg) | 91 ± 2 | 92 ± 2 | 90 ± 3 | 92 ± 4 |
| PP (mmHg) | 42 ± 2 | 35 ± 2* | 39 ± 2 | 31 ± 2* |
| HR (beats/min) | 79 ± 2 | 81 ± 3 | 76 ± 4 | 77 ± 2 |
| SV (ml) | 80 ± 5 | 76 ± 4 | 70 ± 7 | 66 ± 6 |
| CO (l/min) | 6.4 ± 0.5 | 6.1 ± 0.4 | 5.3 ± 0.5 | 5.1 ± 0.5 |
| TPR (mmHg/l/min) | 15.2 ± 1.1 | 15.9 ± 1.1 | 18.2 ± 2.2 | 19.5 ± 2.8 |
| *Last minute of upright tilt* | | | | |
| SBP (mmHg) | 112 ± 2 | 115 ± 3 | 118 ± 9 | 116 ± 6 |
| DBP (mmHg) | 76 ± 2 | 84 ± 2* | 85 ± 6 | 84 ± 4 |
| MBP (mmHg) | 88 ± 2 | 94 ± 2* | 96 ± 7 | 94 ± 5 |
| PP (mmHg) | 36 ± 2 | 31 ± 2 | 33 ± 4 | 32 ± 1 |
| HR (beats/min) | 82 ± 3 | 81 ± 3 | 77 ± 5 | 75 ± 4 |
| SV (ml) | 72 ± 4 | 71 ± 5 | 69 ± 8 | 65 ± 5 |
| CO (l/min) | 6.0 ± 0.4 | 5.8 ± 0.4 | 5.1 ± 0.3 | 4.8 ± 0.3 |
| TPR (mmHg/l/min) | 15.8 ± 1.2 | 17.6 ± 1.4 | 19.5 ± 1.9 | 20.3 ± 1.9 |

Gz, $n$=15; Gx, $n$=7; $n$, number of subjects. Values are means ± SE. SBP, DBP, MBP and PP: systolic, diastolic, mean and pulse blood pressures, respectively; HR, heart rate; SV, stroke volume; CO, cardiac output; and TPR, total peripheral resistance. Within group changes (Wilcoxon sign-ranked test): *$P < 0.05$.

Table V. *Vestibular (otolith) function responses*

| | +3G*z* | | +3G*x* | |
|---|---|---|---|---|
| | Before | After | Before | After |
| *Posturography no HMs* | | | | |
| SOT-1 | 96.5 ± 0.2 | 96.1 ± 0.5 | 97.2 ± 0.2 | 96.8 ± 0.2 |
| SOT-5 | 83.2 ± 1.2 | 84.1 ± 1.1 | 86.1 ± 0.9 | 87.2 ± 2.1 |
| *Posturography with HMs* | | | | |
| SOT-1 | 94.0 ± 0.4 | 93.7 ± 0.4 | 95.1 ± 0.3 | 93.7 ± 1.1 |
| SOT-5: AP sway | 74.7 ± 1.3 | 75.8 ± 1.4 | 78.2 ± 1.8 | 82.3 ± 1.9 |
| SOT-5: ML sway | 81.9 ± 1.4 | 83.9 ± 1.4 | 84.1 ± 1.2 | 75.9 ± 1.5* |
| *Roll Tilt* | | | | |
| OCR (deg) | 4.9 ± 0.3 | 4.1 ± 0.4 | 3.7 ± 0.4 | 3.5 ± 0.4 |
| PE saccades (deg) | 36.1 ± 1.4 | 39.3 ± 1.4* | 35.7 ± 2.2 | 38.4 ± 2.4* |
| PH saccades (deg) | 11.6 ± 1.4 | 12.0 ± 2.0 | 18.3 ± 3.5 | 20.9 ± 5.2 |
| LVOR (deg/sec) | 5.5 ± 1.0 | | 6.8 ± 1.6 | |

G*z*, $n$=15; G*x*, $n$=7; $n$, number of subjects. Values are means ± SE. Posturography values are 'EQ' scores, SOT, Sensory Organization Test, HM, head movements, AP, anterior-posterior, ML, medial-lateral, OCR, ocular counterroll, PE, perceived Earth orientation, PH, perceived head orientation, LVOR, linear vestibulo-ocular reflex. Within group changes (Wilcoxon sign-ranked test): *$P < 0.05$.

## FIGURE LEGENDS

**Figure 1.** The vestibular and autonomic test sequence performed both before and after centrifugation. The timeline represents the average elapsed times following the centrifugation (see text for details). HMs, head movements; CFB, controlled frequency breathing; OCR, ocular-counterroll test.

**Figure 2.** Average carotid-cardiac baroreflex response relations from 15 subjects before and after +3Gz centrifugation. Centrifugation had no effect on the range and slope of the carotid-cardiac baroreflex for decreasing pressure stimuli (+40 mmHg to –60 mmHg) applied to the anterior portion of the neck. However, after centrifugation, the operational point was increased significantly in the +3Gz group (17%±5% to 29%±7%; $P<0.05$). Measurements were made while subjects were supine.

FIG. 1

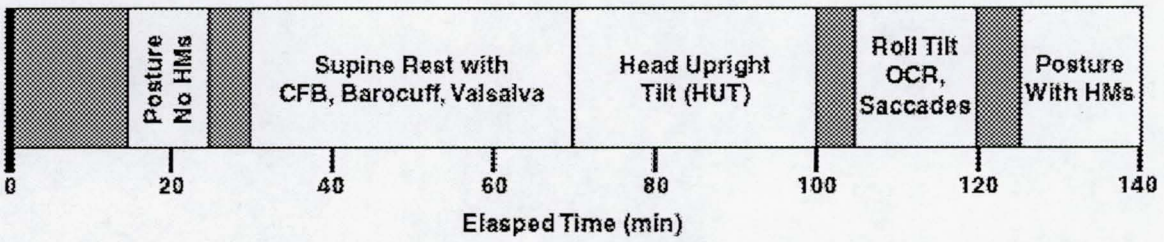
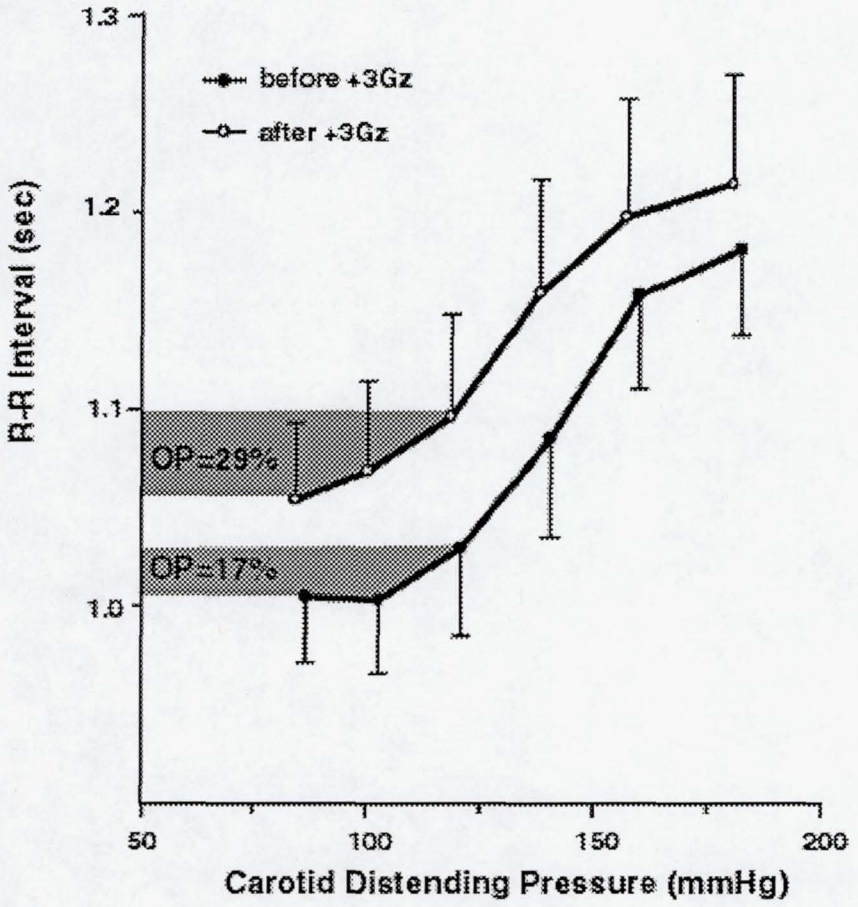



figure 1

FIG. 2


1.3
1.2
1.1
1.0
R-R Interval (sec)
before +3Gz
after +3Gz
OP=29%
OP=17%
50
100
150
200
Carotid Distending Pressure (mmHg)