Tolerance of Centrifuge-Simulated Suborbital Spaceflight by Medical Condition

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Introduction: We examined responses of volunteers with known medical disease to G forces in a centrifuge to evaluate how potential commercial spaceflight participants (SFPs) might tolerate the forces of spaceflight despite significant medical history. ***Methods:*** Volunteers were recruited based upon suitability for each of five disease categories (hypertension, cardiovascular disease, diabetes, lung disease, back or neck problems) or a control group. Subjects underwent seven centrifuge runs over 2 d. Day 1 consisted of two $+G_z$ runs (peak = +3.5 G_z, Run 2) and two $+G_x$ runs (peak = +6.0 G_x, Run 4). Day 2 consisted of three runs approximating suborbital spaceflight profiles (combined $+G_x$ and $+G_z$, peak = +6.0 G_x/+4.0 G_z). Data collected included blood pressure, electrocardiogram, pulse oximetry, neurovestibular exams, and post-run questionnaires regarding motion sickness, disorientation, grayout, and other symptoms. ***Results:*** A total of 335 subjects registered for participation, of which 86 (63 men, 23 women, age 20-78 yr) participated in centrifuge trials. The most common causes for disqualification were weight and severe and uncontrolled medical or psychiatric disease. Five subjects voluntarily withdrew from the second day of testing: three for anxiety reasons, one for back strain, and one for time constraints. Maximum hemodynamic values recorded included HR of 192 bpm, systolic BP of 217 mmHg, and diastolic BP of 144 mmHg. Common subjective complaints included grayout (69%), nausea (20%), and chest discomfort (6%). Despite their medical history, no subject experienced significant adverse physiological responses to centrifuge profiles. ***Discussion:*** These results suggest that most individuals with well-controlled medical conditions can withstand acceleration forces of launch and re-entry profiles of current commercial spaceflight vehicles.

Keywords: G force, neurovestibular imbalance, hypergravity, hemodynamic, suborbital, commercial spaceflight.

INDIVIDUALS CONSIDERING participation in commercial suborbital spaceflight represent a wide range of medical conditions, ages, and degrees of preparation for flight. There is limited information about the tolerance of such individuals to the launch and re-entry acceleration profiles of commercial spaceflight vehicles, and it is unclear whether the hazardous endeavor of spaceflight poses an additional risk to individuals less healthy than career astronauts (1,4,14). While the passive role of the commercial spaceflight participant (SFP) does offer some protection in limiting the physiological stress of flight, certain high-risk medical conditions still raise significant concerns that spaceflight could put them at increased risk for an in-flight medical problem.

Of particular concern are conditions that have rarely been studied in high-acceleration environments, such as certain cardiovascular conditions and diabetes mellitus. Case reports have indicated the potential for incapacitating cardiac events related to high acceleration exposures, giving credibility to concerns regarding significant cardiovascular histories (2,8,18). Cardiac dysrhythmias are common in high-acceleration exposures, raising concerns about the potential for sudden incapacitating or even fatal events in individuals predisposed to electrical abnormalities (12,16,17). Diabetics have been traditionally disqualified from high-performance flight and spaceflight selections due to the potential for both in-flight incapacitating events, such as hypoglycemia, and for progressive end-organ disease. Other concerns include the potential for spinal injury due to sustained or repeated acceleration in the $+G_z$ (head-to-toe) direction, particularly in individuals already afflicted by prior back or neck injury (7,18). Individuals with pulmonary disease, such as asthma, raise concerns over the ability to tolerate acceleration atelectasis and airway closure seen under high G loading (2,13). Finally, some conditions are concerning due to the prevalence of such disease in the SFP population and the potential for worsening of the condition with sustained or repetitive acceleration exposure. Hypertension is such a condition, likely to be highly prevalent in the SFP population, with some studies suggesting worsening hypertension with repeat acceleration exposures or use of anti-G straining maneuvers (AGSM), raising concerns over the potential for injury related to severe elevations in blood pressure (6,11).

A pilot study published in 2012 presented data suggesting that most individuals with well-controlled medical conditions are capable of tolerating commercial

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spaceflight launch and re-entry acceleration profiles (5). However, evidence in this pilot study was limited to a small sample size that was not sufficient for statistical significance, representing only a few subjects with any given medical condition. To further analyze the risks posed by specific medical conditions, our study was conducted under the Federal Aviation Administration (FAA) Center of Excellence for Commercial Space Transportation to evaluate individuals with one or more of five medical conditions: hypertension, cardiac disease, diabetes, pulmonary disease, and a history of back or neck injury or disease. We examined the responses of volunteers with these conditions to G forces in a centrifuge to evaluate how potential commercial SFPs might tolerate the forces of spaceflight despite significant medical history.

METHODS

Subjects

A prospective cohort study, approved by the University of Texas Medical Branch Institutional Review Board, was designed to identify volunteers for participation in physiological training at the National Aerospace Training and Research (NASTAR) Center centrifuge. Volunteer registrants for the program were screened for inclusion in five cohorts of well-controlled diseases, including hypertension (HTN); cardiovascular disease (CV); diabetes (DM); lung disease, including respiratory compromise from chronic obstructive pulmonary disease (COPD), asthma, or similar obstructive or restrictive pulmonary processes (L); and back or neck injury or disease (BN) (**Table I**). Individuals with no known history of such diseases were further identified for inclusion in a control group.

Prior to taking part in centrifuge activity, participants were asked to complete a medical history questionnaire and undergo a physical exam by their personal physicians with results recorded on a form provided for this purpose. This process and the forms used were similar to the guidance and materials provided for FAA approved exams performed by Aviation Medical Examiners. All participants were required to provide a resting electrocardiogram (EKG).

TABLE I. INCLUSION AND EXCLUSION CRITERIA FOR SUBJECT COHORT SELECTION.

Disease Category	Inclusion Criteria	Exclusion Criteria
Hypertension	• Baseline systolic > 140, < 180 mmHg • Baseline diastolic > 90, < 105 mmHg • Well-controlled on any FDA-approved medication • Note: all alpha-blockade and peripheral dilator medications were stopped a minimum of 24 h prior to participation	• Baseline systolic > 180 mmHg • Baseline diastolic > 105 mmHg • Preflight systolic > 190 mmHg
Cardiovascular Disease	• Congenital malformations • Valvular disease • Dysrhythmias • Coronary artery disease • History of acute myocardial infarction • Percutaneous interventions, including stenting • Implanted continuous pacemakers • Coronary artery bypass grafting – none registered	• Automated implantable cardioverter-defibrillator • Cardiac transplant • EF < 50%
Diabetes	• Type I or Type II diabetes mellitus • Controlled with diet, oral medication, injectable medication, or insulin pump	• "Pre" diabetic with normal HbA1c (< 6.5%), no medications, no lifestyle change • HbA1c > 8.0%
Pulmonary Disease	• Asthma • Chronic obstructive pulmonary disease (COPD) • Chronic Restrictive Lung Disease • History of lung surgery	• Single, remote episodes of spontaneous or traumatic pneumothorax, completely resolved without evidence of bullae • Lung disease requiring continuous supplemental oxygen therapy
Spinal Injury/Disease	• Chronic back and neck disease, strain • Degenerative disc disease • Disc herniation • Impingement • Trauma (including fracture) • Surgical history (recovered) • Scoliosis • Sciatica	• Acute spinal injury • Acute postsurgical period (< 6 wk)

FDA: Federal Drug Administration, HbA1c: glycosylated hemoglobin, EF: cardiac ejection fraction.

All medical documentation was reviewed by a study investigator and aerospace medicine specialist. Participants could be approved directly, be requested to undergo further tests or provide more records, or be excluded altogether depending upon their medical status, history, and physical findings. The study medical monitors had final decision-making authority regarding any subject's participation. In general, participants with significant risk factors beyond age and sex were required to provide further information including lipid panels, chest radiography, spinal imaging, glycosylated hemoglobin (HbA1c) testing for subjects with diabetes, exercise stress testing, or pulmonary function testing. All participants signed informed consent and liability release forms before taking part in the centrifuge runs.

Procedures

Resting blood pressure (BP), heart rate (HR), and pulse oximetry (Po_2) were measured upon arrival at the testing facility. Subjects with significant cardiac histories underwent repeat EKGs for comparison to baseline. All subjects were advised to take all medication as per their usual schedule, with the exception of alpha-adrenergic antagonists and peripheral vasodilators, which were held a minimum of 24 h prior to participation. Prior to centrifuge runs, participants were taught basic AGSM and the "hook" (L-1 closed-glottis variant) maneuver. They were advised to strain during $+G_z$ exposure, but to use the hook maneuver only in the event of grayout or light-headedness. They were further advised against sudden head movements during centrifuge trials to avoid triggering Coriolis symptoms.

Approved participants underwent seven centrifuge runs over a 2-d time period, with the first four exposures completed on Day 1 and the final three exposures on Day 2. The initial exposure (Run 1) was a 2-min $+G_z$ centrifuge run with maximum peak of +2.15 G_z lasting 15 s. The second exposure (Run 2) was a 2-min $+G_z$ centrifuge run with maximum peak of +3.5 G_z lasting 15 s. The third exposure (Run 3) was a 2-min $+G_x$ (front-to-back) centrifuge run with a maximum peak of +3.0 G_x lasting 15 s. The fourth exposure (Run 4) was a 2-min $+G_x$ centrifuge run with a maximum peak of +6.0 G_x lasting 15 s. Subjects remained in the gondola during the break between Run 1 and Run 2 and during the break between Run 3 and Run 4.

The final three exposures were combined acceleration profiles using the $+G_z$ and $+G_x$ forces designed to simulate acceleration profiles anticipated for future suborbital spaceflights. The first two of these runs simulated a Virgin Galactic spaceflight profile as predicted by the acceleration exposures reported in tests flights performed by Scaled Composite's SpaceShipOne. The profile was executed at 50% intensity (Run 5) first, then it was repeated at full intensity (Run 6) after a short pause of less than or equal to 5 min. Subjects remained in the gondola during the break between Run 5 and Run 6. This profile simulates a flight where passengers would be seated upright during launch and supine during re-entry, and includes consecutive $+G_z$ and $+G_x$ components with maximums of +6.0 G_x and +3.8 G_z in Run 6. The final profile (Run 7) was designed to imitate anticipated acceleration profiles of a suborbital spaceflight with an occupant seated upright, resulting in combined and simultaneous $+G_x$ and $+G_z$ exposures during both launch and re-entry. This profile was performed at full intensity only, with maximum exposure limited to +4.5 G_x and +4.0 G_z and a resultant vector maximum of +6.0 G. Exposure to each phase of acceleration for all three of the final runs did not exceed 2 min and onset rates always remained less than 1.5 $G \cdot s^{-1}$ in the $+G_x$ direction and 0.5 $G \cdot s^{-1}$ in the $+G_z$ direction. The duration of time at the peaks of $+G_x$ and $+G_z$ was less than 5 s. The combined profiles are presented graphically in **Fig. 1**. Audiovisual simulation was provided during each trial by the multimedia system of the centrifuge gondola to enhance the realism of the experience. It should be noted that true suborbital flight profiles will include a short period of weightlessness between acceleration peaks

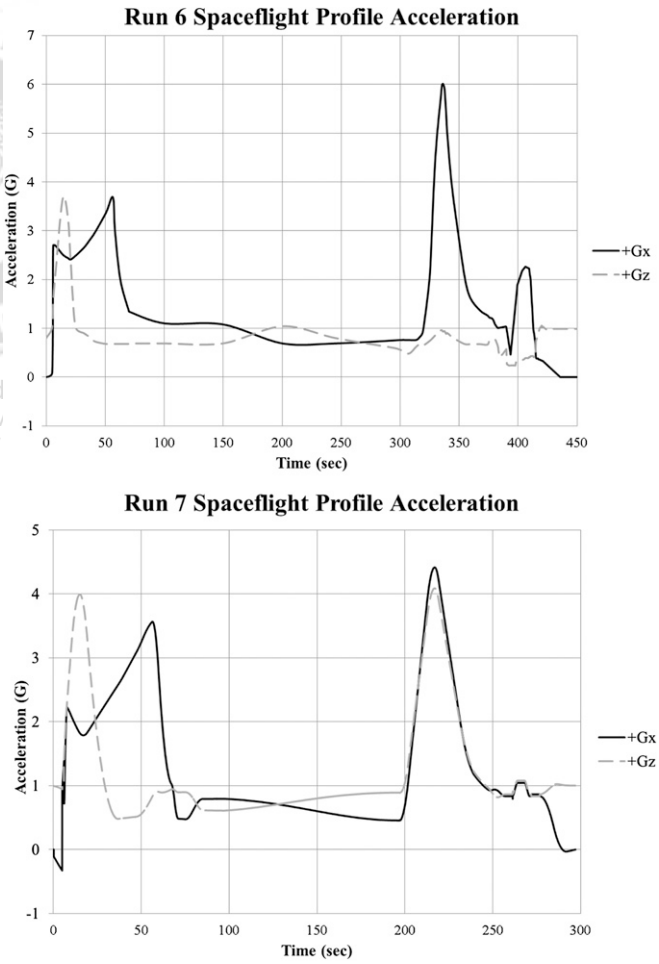

Fig. 1. Combined spaceflight profiles. Top: combined profile modeled after data from SpaceShipOne test flights, where passengers would be seated upright during launch and supine during re-entry. Bottom: combined profile demonstrating forces anticipated for a vehicle requiring upright, seated passengers during launch and re-entry. $+G_z$: head-to-toe acceleration, $+G_x$: chest-to-back acceleration.

that could adversely affect the physiological response, but cannot be simulated in a ground-based analogue.

Subjects were monitored at all times in the gondola by video, and both subjects and medical monitors were able to access two-way voice communication as needed. Hemodynamic data, including continuous EKG, were monitored and recorded in real time by the study medical monitors. HR, BP, and Po_2 were recorded at predetermined times before, during, and after each centrifuge run. Following each centrifuge trial, medical monitors administered a neurologic exam to each subject to assess neurovestibular function and proprioception based upon standard postflight neurovestibular physical exams administered to NASA astronauts after flight. Participants underwent post-run questionnaires regarding the occurrence of motion sickness, spatial disequilibrium, grayout, vertigo, or any other centrifuge-related symptoms experienced.

RESULTS

A total of 335 volunteers registered for the study. Of these, 179 completed the prescreening medical questionnaire and 124 submitted sufficient medical documentation to be considered for the study. There were 15 subjects who were disqualified due to weight [study maximum was 250 lb (114 kg) due to limitations of monitoring equipment fit] and 5 due to medical reasons (2 for uncontrolled psychiatric disorders, 3 for uncontrolled medical conditions including coronary artery disease, diabetes, and spinal disease following recent surgery). Due to scheduling conflicts, 18 subjects were unable to participate. The remaining 86 subjects (63 men, 23 women) participated in the centrifuge trials.

Of the 86 subjects who participated, average age was 46.7 ± 15.4 yr, median age 49 yr, range 20-78 yr. The control group was found to be significantly younger than the disease cohorts [control 40.4 ± 14.5 yr, disease 48.6 ± 15.2 yr, $t(84) = -2.37$, $P = 0.02$] and the CV and HTN cohorts were significantly older than the remainder of the subjects [HTN 56.0 ± 11 yr, non-HTN 41.7 ± 15.1 yr, $t(84) = -4.44$, $P < 0.01$; CV 57.3 ± 16.0 yr, non-CV 44.1 ± 14.2 yr, $t(84) = -3.19$, $P < 0.01$]. Average body mass index (BMI) for all subjects was 26.0 ± 4.4, range 18-40.7. There were 26 individuals who were required to provide further medical data than the minimally required information, including 10 required to provide documentation of recent fasting blood glucose trends and HbA1c, and 10 required to provide historical records of stress testing, echocardiogram, or other cardiac examinations. Of all participants required to provide additional testing or improved control of their medical problems, none were ultimately excluded from centrifuge exposure. Of the participants, 27 were included in the HTN category, another 15 in the CV cohort, 10 with DM, 14 with a history of lung disease, and 29 with a history of spinal injury or disease. There were 26 subjects (30.2%) who were included in more than one cohort. Also included in the study were 24 controls, with no significant history of any of the 5 disease groups. The study population included 3 current smokers, 21 former smokers, and individuals that self-reported their exercise tolerance ranging from none (5 subjects), minimal (15 subjects), moderate (31 subjects), and high (35 subjects). **Table II** lists disease histories reported by subjects included in the study.

There was no significant association with prescreening requirements and any hemodynamic alteration or subjective symptoms. Further, the performance of the 26 individuals who were required to provide more extensive screening was not significantly different than those who required only minimal screening. Five subjects did not complete all seven runs: three subjects withdrew due to anxiety reasons, one for back strain, and one did not complete the full training experience due to time constraints.

Maximum hemodynamic values recorded during the spins included HR as high as 192 bpm, systolic BP as high as 217 mmHg, and diastolic BP as high as 144 mmHg. However, it was noted that in-flight BP recordings seemed particularly labile and unreliable, likely due to the need for upper extremity muscle tension during AGSM and occasional use of inappropriately sized sphygmomanometer cuffs. Minimum Po_2 recorded was 90% and no clinical symptoms of hypoxia were noted at any time. There was no correlation between age and baseline HR or Po_2, or any HR or Po_2 recorded during the spins. Older subjects had significantly higher baseline and pre/post-spin mean arterial pressure (MAP) (baseline MAP: < 50 yr, 89.7 ± 12.6 mmHg; 50+ yr, 95.4 ± 11.2 mmHg; $t(84) = -2.21$, $P = 0.03$; pre-spin MAP: < 50 yr, 101.0 ± 9.5 mmHg; 50+ yr, 107.7 ± 8.7 mmHg; $t(84) = -3.37$, $P < 0.01$; post-spin MAP: < 50 yr, 102.4 ± 10.9 mmHg; 50+ yr, 111.3 ± 10.8 mmHg; $t(84) = -3.78$, $P < 0.01$). However, there was no significant linear correlation between MAP and age ($R^2 < 0.2$ for baseline, pre/post-spin MAP). There was no correlation between sex or BMI and any baseline or pre/post-spin BP, HR, or Po_2. Average hemodynamic values recorded at baseline and pre/post-spin are provided in **Fig. 2**.

TABLE II. MEDICAL CONDITIONS REPORTED BY SUBJECTS INCLUDED IN CENTRIFUGE TRIALS.

Medical Condition	Number of Subjects
Hypertension (controlled by ACE-I, BB, A-A, ARBs)	27
CAD (medically controlled, status post PCI, stenting)	5
Dysrhythmias (atrial fibrillation, tachycardia, heart block)	7
Pacemaker	2
Valvular disease (replacement, mitral valve prolapse, aortic valve regurgitation, pulmonic valve stenosis)	5
Congenital cardiac malformations	2
Diabetes mellitus (Type I, Type II)	10
Asthma	10
Nonasthmatic pulmonary disease [restrictive disease, lobectomy, pneumothorax (multiple)]	5
Cervical strain and chronic pain	5
Lumbar strain and chronic pain	18
Lumbar fractures, disc herniation	9

ACE-I: angiotensin-converting-enzyme inhibitor; BB: beta-adrenergic antagonist; A-A: alpha-adrenergic antagonist; ARB: angiotensin receptor blocker; CAD: coronary artery disease; PCI: percutaneous intervention.

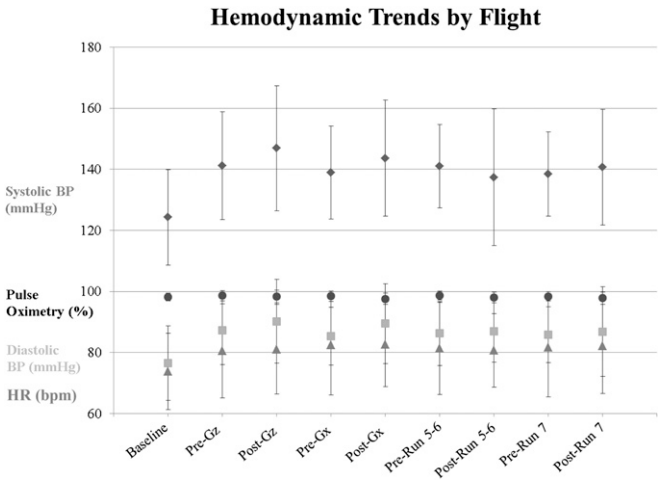

Fig. 2. Average hemodynamic trends during centrifuge runs. BP: blood pressure, HR: heart rate.

Nausea was a common complaint in each type of run (10–20% of subjects per trial), though usually not severe and generally resolved by the end of the run. One subject vomited following completion of Run 7, but was much improved after a short period of observation and had no further issues. Disequilibrium was a common complaint, described by subjects as a feeling of tumbling, spinning, or unsteadiness, and was often attributed to gondola reorientation at the end of each trial. There were a number of complaints of chest discomfort or pressure (2–6% of subjects per run), generally associated with higher $+G_x$ exposure. Similarly, mild to moderate dyspnea or increased work of breathing (WOB) was reported frequently during $+G_x$ exposure, as subjects complained of difficulty breathing against the mechanical load. Dyspnea was not associated with any change in Po_2. Chest discomfort and dyspnea symptoms resolved by the completion of the runs. There was no association between dyspnea, increased WOB, or chest discomfort with a current or past history of smoking. There were occasional complaints of headache and backache, generally attributed by subjects to the pressure of G exposure or to the use of AGSM. There was no significant difference between the cohorts in frequency of headache, chest discomfort or pressure, light-headedness or presyncope, palpitations, or nausea. There was no correlation between sex, age, or BMI with any subjective complaint. Subjective complaint frequencies by run are provided in **Table III**.

Grayout was common, with 69% of subjects experiencing some degree of grayout or tunnel vision at some point during the seven runs, with an inverse association between age and incidence of grayout (0-1 grayout events: 50.6 ± 14.2 yr; 2-4 grayout events: 41.7 ± 15.5 yr; $t(84) = 3.50$, $P < 0.01$). Generally, symptoms were rapidly corrected with the use of AGSM maneuvers. In some cases, particularly during later runs, participants would intentionally delay using the AGSM in order to experience grayout, artificially elevating these numbers. No participant experienced a G-induced loss of consciousness event. It was noted that participants occasionally confused mitigation techniques for $+G_z$ and $+G_x$ exposures, using AGSM unnecessarily for $+G_x$ runs and forgetting to employ the technique during $+G_z$ despite repeated reminders.

TABLE III. SUBJECTIVE SYMPTOM FREQUENCY BY CENTRIFUGE TRIAL.

Symptom	+Gz	+Gx	Run 5-6	Run 7
Disequilibrium	37.2%	47.7%	54.8%	28.1%
Nausea	17.4%	10.5%	11.9%	11.0%
Grayout	31.4%	2.3%	47.6%	52.4%
Symptoms despite attempted AGSM	1.2%	0.0%	8.1%	15.3%
Increased work of breathing	8.1%	72.1%	35.7%	28.1%
Palpitations	2.3%	4.7%	2.4%	3.7%
Presyncopal or light-headed	4.7%	2.3%	3.6%	2.4%
Chest pain or pressure	0.0%	2.3%	6.0%	4.9%
Headache	2.3%	4.7%	7.1%	6.1%
Backache	1.2%	4.7%	8.1%	4.7%

Symptoms were recorded after $+G_z$ exposure (Runs 1-2), $+G_x$ exposure (Runs 3-4), and integrated profiles (Runs 5-6 and Run 7).

There were infrequent reports of palpitations (2–5% of subjects per run), though abnormal cardiac rhythms were noted by medical monitors in 52% of subjects. Of the subjects, 45% had instances of premature atrial or ventricular contractions (PACs/PVCs), 16% demonstrated bigeminy or trigeminy, and 10% had episodes of sinus dysrhythmia during the trials. Prolonged, high (> 4) $+G_x$ exposures were the most provocative in inducing dysrhythmias. None of the dysrhythmic events caused any clinical symptoms aside from rare reports of palpitations and none required intervention by the medical monitors. All abnormal rhythms normalized by the end of G exposure. One subject, a 63-yr-old female control, had a single episode of a 7-beat run of ventricular tachycardia at the end of the final centrifuge run; the episode was asymptomatic and was followed by a return to normal sinus rhythm.

Neurovestibular examinations were performed at baseline and following exposures, with subjects generally demonstrating increasing neurovestibular imbalance with progressive Runs 1-6, then improved performance following Run 7 (see **Table IV**). There were no hemodynamic parameters, sex, age, or BMI significantly associated with post-run neurovestibular alterations.

Anxiety was a significant issue during the study, with 12 of the 86 subjects (14%) identified by monitors as demonstrating anxiety that impacted their enjoyment of

TABLE IV. PERCENT OF SUBJECTS WITH MILD TO MODERATE NEUROVESTIBULAR IMPAIRMENT COMPARED TO BASELINE FOLLOWING CENTRIFUGE RUNS.

	+Gz	+Gx	Run 5-6	Run 7
Mild impairment	25.6%	36.1%	40.0%	26.8%
Moderate impairment	3.5%	16.3%	23.5%	13.4%

Neurovestibular symptoms were recorded after $+G_z$ exposure (Runs 1-2), $+G_x$ exposure (Runs 3-4), and integrated profiles (Runs 5-6 and Run 7).

their experience. While the majority of these individuals were able to complete the centrifuge trials without significant issue, three subjects chose to withdraw prior to completion of all runs.

The HTN cohort demonstrated higher average baseline MAP compared to controls (baseline MAP: HTN 98.1 ± 10.0, control 88.3 ± 11.9; $t(49) = 2.77$, $P < 0.01$). However, there was no significant difference between HTN and non-HTN subject delta pressure changes from baseline to pre/post-run BP (see **Fig. 3**). HTN subjects demonstrated significantly lower HR compared to non-HTN subjects in all dynamic phases of spaceflight profiles involving $+G_z$ exposure (Run 5 launch: non-HTN 117.9 ± 28.8, HTN 97.7 ± 21.1, $t(84) = -3.24$, $P < 0.01$; Run 6 launch: non-HTN 126.4 ± 29.5, HTN 109.5 ± 21.7, $t(84) = -2.64$, $P < 0.01$; Run 7 launch: non-HTN 125.9 ± 26.4, HTN 104.1 ± 19.2, $t(84) = -3.74$, $P < 0.01$; Run 7 re-entry: non-HTN 121.1 ± 24.6, HTN 103.2 ± 24.4, $t(84) = -3.06$, $P < 0.01$). Despite these lower HR, symptoms of grayout were found to be more common in non-HTN subjects compared to the HTN cohort (number of reported grayout events: non-HTN: 1.5 ± 1.1; HTN 0.9 ± 1.0; $t(84) = 1.66$, $P = 0.05$). As mentioned above, grayout events were inversely correlated to age, likely indicative of the aforementioned correlation between age and BP. The HTN cohort did not demonstrate any difference compared to non-HTN subjects regarding incidence of headache, palpitations, chest discomfort, motion sickness or nausea, alterations in Po_2, or alterations in neurovestibular imbalance.

A subcohort of four subjects on beta-adrenergic antagonists (BB) was examined for evidence of hemodynamic compromise due to medication. Subjects on BB demonstrated significantly decreased HR in dynamic phases involving $+G_z$ compared to all other HTN cohort subjects (at $+3.5$ G_z: BB, 86.3 ± 16.7 bpm; non-BB, 114.7 ± 20.5 bpm; $t(24) = -2.61$, $P = 0.02$). This finding was not associated with any significant incidence of symptoms or subjective complaints during any of the centrifuge runs. There was no difference in pre/post-run delta BP or incidence of grayout in subjects on BB versus other HTN subjects. The CV cohort demonstrated no significant difference compared to non-CV subjects regarding BP delta from baseline values during any flight phase, HR changes during any spin, Po_2 before, during, or after any spin, motion sickness or nausea, grayout, neurovestibular imbalance, palpitations, or chest discomfort.

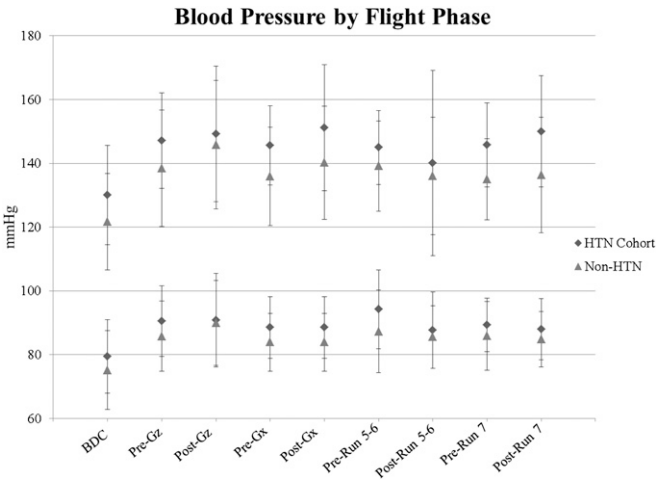

Fig. 3. Average systolic and diastolic blood pressure at baseline and pre/post spins.

Multiple methods of glycemic control (diet, oral, injectable, insulin pump) were used by subjects in the DM cohort; none was associated with any change in performance. Study subjects were not required to monitor blood glucose during the trials; those that voluntarily monitored their own glucose levels reported minimal alterations, with glucose ranging from 100-200 $mg \cdot dl^{-1}$ on the day of spins, similar to normal levels for those subjects. DM subjects demonstrated no significant difference compared to non-DM subjects with BP delta from baseline for any run, HR changes at any phase of any spin, Po_2 before, during, or after any spin, motion sickness or nausea, grayout, palpitations, or chest discomfort. DM subjects did show significantly increased neurovestibular imbalance compared to non-DM subjects (DM 3.6 ± 2.1, non-DM 2.2 ± 1.8, $t(84) = 2.21$, $P = 0.02$). One subject in the DM cohort demonstrated an episode of presumed hypoglycemia just following the $+G_z$ runs (Runs 1 and 2). A 66-yr-old male subject, taking metformin for control of his type II diabetes, became hypotensive (lowest BP 80/53 mmHg) following the $+G_z$ runs, with nausea, light-headedness, and diaphoresis. Of note, this subject also took an alpha-adrenergic antagonist (tamulosin) for benign prostatic hypertrophy that morning despite requests by the medical team that he hold this medication for the duration of the centrifuge trials. EKG at the time of symptom onset demonstrated no abnormality. At the time, it was unclear whether the alpha-adrenergic antagonist or hypoglycemia were causative of his symptoms; while blood glucose measurement was not available, food intake was sufficient to alleviate all symptoms, with BP returning to 130s systolic. The subject was able to return to the centrifuge and complete all remaining spins. The subject admitted to having taken his medications as normal that morning, but had skipped breakfast due to time constraints before arriving at the centrifuge facility.

The L cohort demonstrated no significant difference compared to the non-L subjects regarding BP delta from baseline for any run, HR changes during any phase of the spins, Po_2 before, during, or after any spin, motion sickness or nausea, grayout, neurovestibular imbalance, palpitations, or chest discomfort. The L cohort did subjectively report significantly increased WOB compared to control subjects (number of reported complaints of WOB: L 1.9 ± 1.2, control 1.0 ± 1.0, $t(36) = 2.38$, $P = 0.02$). Objectively, medical monitors noted significantly higher episodes of coughing during $+G_x$ exposure in L subjects compared to non-L subjects, though these events were often unnoticed by the subject themselves and were not associated with any decrease in Po_2 (number of coughing events: L 0.3 ± 0.6, non-L 0.1 ± 0.1, $t(84) = 3.53$, $P < 0.01$).

The BN cohort demonstrated no significant difference in BP delta from baseline for any run, HR changes during any phase of the spins, Po_2 before, during, or after any spin, motion sickness or nausea, neurovestibular imbalance, palpitations, or chest discomfort. BN subjects were significantly more likely to report back or neck discomfort during spins, most commonly during AGSM maneuvers (number of reported complaints: BN 0.4 ± 0.7 events, non-BN 0.08 ± 0.4 events, $t(84) = 2.33$, $P = 0.02$). All but two incidents of back or neck pain or discomfort resolved by the end of the centrifuge run; the remaining two resolved within 72 h of the centrifuge experience. One subject, a 49-yr-old man with no history of back or neck disease or injury, withdrew before completing all spins due to increasing back discomfort; he completed six of the seven runs before complaining of significant lumbar strain during an AGSM maneuver. His discomfort resolved 72 h after the spin with rest.

Subjects in the BN cohort were more likely to report grayout symptoms (BN 1.7 ± 1.2 events, non-BN 1.12 ± 1.0 events, $t(84) = 2.15$, $P = 0.03$). Additionally, subjects that did experience grayout in the BN cohort were more likely to continue having symptoms despite AGSM compared to the non-BN subjects (BN 0.4 ± 0.7 events, non-BN 0.14 ± 0.4 events, $t(84) = 2.34$, $P = 0.02$).

DISCUSSION

Despite a range of medical histories, the study participants successfully completed centrifuge trials with little difficulty. Prescreening requirements, such as the medical questionnaire, personal physician-administered exams, and EKGs, were felt to be effective in identifying subjects who would physically tolerate the centrifuge exposures. While some subjects were disqualified due to medical concerns raised by their personal physicians or identified during the medical questionnaire, no subject was disqualified based upon results of additional medical testing or historical records required by study investigators after the initial screening exam, nor did such requirements predict which individuals might have difficulty with G-force tolerance. No subject was disqualified from participation based upon the appearance of their EKG; even subjects with fairly significant electrical abnormalities were allowed to participate if they could demonstrate that the morphology had not changed from prior tracings and no adverse events occurred in any of these cases. The presence of abnormalities in continuous EKG tracings during centrifuge runs, including PACs/PVCs, bigeminy/trigeminy, and sinus dysrhythmia, did not result in any clinical adverse events. The rate of these occurrences was consistent with previously reported rates of ventricular ectopy during centrifuge acceleration exposures (12).

Despite the wide variation of age and medical history, there were no significant cardiac, cerebrovascular, or respiratory events during the study. It is worth noting that this subject population demonstrated a relatively high HR at the start of each run as compared with the more common military or centrifuge test participants (6,11,12). This is most likely secondary to excessive excitation of the subjects here, who lack a background of extreme environment physiological experience and training. While few adverse events occurred, such as instances of presumed hypoglycemia and hypotension, these were easily and effectively managed by medical monitors with complete resolution of symptoms shortly after intervention. There was no significant difference in any hemodynamic, subjective, or neurovestibular parameter associated with age or sex of the subject.

Subjective complaints of nausea, palpitations, headache, disequilibrium, and chest discomfort were common, but symptoms were not severe enough to cause distress to most participants. The majority of subjects reported resolution of any discomfort by the end of each centrifuge run. Further, most complaints appeared to be due to centrifuge-specific events (such as gondola reorientation) and not due to exposure to acceleration forces. This suggests that commercial SFP discomfort is likely to be less than that of centrifuge subjects, as the rotational movement of the gondola will be absent in a real spaceflight experience.

There were significant alterations noted in neurovestibular balance following centrifuge trials, with progressively worsened scores noted after each run. Interestingly, scores dramatically improved following the final run, suggesting either a learning effect or increased tolerance of centrifuge exposure following multiple runs. It is unclear whether the neurovestibular imbalance was due to the acceleration exposure or the rotational component of centrifuge training. A previous study had noted similar imbalance following centrifuge training, with concerns raised regarding prolonged and repetitive G exposure and precipitation of neurovestibular disturbances (5). While such disturbances could limit, for example, a commercial spaceflight pilot from performing multiple suborbital flights over a short period of time, the propensity for alterations as a result of acceleration exposure (as opposed to rotational exposure in a centrifuge) would be better evaluated by examining such pilots after actual spaceflight with only linear acceleration (10). Until such time as a pilot may be operating a spacecraft for multiple flights in a period of a few days, this is likely not a significant issue. Finally, it is unclear why DM subjects experienced increased alterations in their neurovestibular performance compared to other cohorts. There was no other significant association between age, sex, medical history, or any subjective or objective parameters and this finding. Further research may better elucidate why this may have occurred.

Finger-probe pulse oximetry was of limited utility, as multiple data points were lost due to dislodgement of the finger probe under G force or altered peripheral circulation due to G force or AGSM. Despite these issues, there were no recorded Po_2 values of less than 90%, regardless of G magnitude or direction. It is unlikely that Po_2 monitoring during commercial spaceflight will be of any greater utility.

Elevated BP appears to be protective regarding symptoms of grayout, as the HTN cohort experienced less

grayout than non-HTN subjects. In agreement with prior studies, age appears to be protective in providing higher grayout tolerance, likely due to comparatively elevated resting BP over that of younger subjects (5,9). BP monitoring before, after, and during the spins was of limited utility and often artificially elevated by AGSM maneuvers and cuff size, decreasing the reliability of the measurement. No subject was disqualified for any BP reading during the trials; subjects with severely elevated automated readings were administered manual sphygmomanometry and were found each time to have BP within acceptable ranges. Of note, subjects found BP cuffs and sphygmomanometry during centrifuge runs to be uncomfortable and distracting, as the automated device often pressurized the cuff to over 200 mmHg in an attempt to get a reading in a tensed extremity. Similarly, BP monitoring during commercial spaceflight may be of questionable utility and may instead be a distraction to SFPs with minimal benefit to justify its use.

The use of BB is potentially concerning for suborbital flight due to the potential of attenuated HR and BP response despite physiological stressors (19). During acceleration exposure, such attenuation could potentially cause an increased incidence of grayout due to an inability to compensate for decreased cerebral blood flow. The four subjects taking BB in this study performed well despite significantly decreased HR during all dynamic phases of the centrifuge trials. These results are similar to those in an earlier study, where seven subjects taking BB were found to have significantly decreased HR response to centrifuge exposure, but no increase in subjective complaints or symptoms during any run (5). These two studies suggest that, despite attenuated cardiovascular response, exposure to acceleration by centrifuge or by suborbital flight is likely no more harmful for subjects on BB than for other subjects. In contrast, subjects were advised to hold all alpha-adrenergic antagonists for a minimum of 24 h prior to the centrifuge trials. All but one subject complied with this request; as mentioned above, that subject experienced an incidence of hypotension likely related more to hypoglycemia than to the alpha-adrenergic antagonist. Even so, it would be recommended that similar medications be held prior to suborbital spaceflight to avoid unnecessary peripheral dilation or hypotension of unclear etiology during acceleration exposure.

While cardiovascular disease is often considered to be one of the most concerning issues regarding the safety of commercial spaceflight, subjects with cardiac history demonstrated no adverse events during any phase of this trial. While the CV cohort did contain a wide variety of histories and conditions, there are likely still many cardiovascular conditions that would raise concern in both a centrifuge and a commercial spaceflight setting.

The subjects in the DM cohort tolerated G-force exposure well, with only one adverse event related to hypoglycemia as discussed above. As there are currently no prior data regarding diabetic subjects in the setting of G tolerance of spaceflight profiles, this study suggests that individuals with well-controlled diabetes, employing any method of control (diet, oral medication, injectable medication, insulin pump), are likely able to tolerate similar commercial spaceflight profiles with minimal anticipated issues. It is important to note that the DM cohort specifically excluded severe cases of diabetes and sequelae; there were no subjects with severe neuropathy or end-organ disease included in the study.

The L cohort included multiple asthmatics and a number of individuals with restrictive disease processes. There were no subjects with a history of COPD as none registered to volunteer. L subjects were noted to have significantly increased subjective WOB and objective instances of coughing, particularly during $+G_x$ exposures. One possible explanation for such symptoms may be an increase in reactivity of airways with exposure to acceleration atelectasis, as would be expected under +6 G of force. Despite these symptoms, there were no adverse clinical events reported, no evidence of hypoxia, and no need for medical intervention such as use of rescue inhalers.

The BN cohort experienced increased back and neck discomfort compared to other subjects. Most subjects identified insufficient lumbar support as contributory to their symptoms, stating that the seat-back support was not adjusted for best comfort prior to spins in which they experienced discomfort. Similarly, adjustment of foot pedals was important to ensure proper use of the surfaces for AGSM engagement of the lower extremities. Subjects that had not properly used the foot pedals tended to experience more back discomfort during runs requiring use of AGSM. There were two cases of more significant lumbar strain due to improper AGSM straining techniques, with symptoms lasting as long as 72 h; in both circumstances, subjects placed their heels against the foot pedals, engaging their lower back muscles during AGSM as opposed to their lower extremities.

Interestingly, the BN cohort experienced increased incidents of grayout and increased grayout symptoms despite attempted use of AGSM techniques. This suggests that subjects with a history of back or neck injury are less effective at straining techniques, either due to a physical difficulty in performing the techniques or to decreased effort, perhaps out of concern for reinjury. Prior studies have demonstrated that neck muscle strengthening is associated with improved in-flight tolerance of $+G_z$ force, suggesting that the prior injuries in the BN cohort are potentially causative of their decreased $+G_z$ tolerance (3,15). This finding may be an area for further research, particularly regarding how best to train SFPs with a history of back or neck injury in performing AGSM safely and effectively.

Medical monitors identified anxiety as a significant concern, particularly in those subjects who indicated apprehension regarding the potential for an actual medical issue that they had experienced in the past. There were no elements of the medical history, subject demographics, or subject performance that indicated whether or not a subject would experience anxiety, and study investigators were unable to effectively predict which subjects would have the most difficulty with the trials. The issue

of anxiety is likely to be a significant concern in commercial space operations and should be investigated further.

One limitation of this study is that the microgravity period between acceleration peaks of launch and re-entry in actual suborbital flight cannot be simulated. This could adversely affect the physiological results similar to the "push-pull" effect experienced by high-performance military aircraft pilots, particularly during profiles with increased $+G_z$ exposure during re-entry. This acceleration-weightless-acceleration profile has never been investigated and only rarely experienced and, therefore, continues to represent an unknown that will be resolved only by actual suborbital flight experience.

Subjects representing a wide variety of medical history, disease processes, and physical condition were successful in tolerating G exposures simulating the acceleration forces of launch and re-entry of suborbital commercial spaceflight profiles. The relatively short duration of suborbital commercial flight limits the possibility of significant medical events during spaceflight, and the passive role of the SFP further protects them from substantial physiological strain that could lead to adverse events. The short duration of acceleration exposure during launch and re-entry phases was well tolerated by subjects despite, in some cases, even significant physiological limitations and medical history.

While careful prescreening and medical evaluation are important to ensure some level of physical fitness for any SFP, the results of this study suggest that physical requirements for SFPs are likely minimal and that most individuals with well-controlled medical conditions should be able to tolerate a commercial spaceflight experience. Further research and experience will better delineate which conditions continue to pose significant risk during spaceflight. This study further supports the belief that, despite significant chronic medical conditions, the dream of spaceflight is one that most people can achieve.

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