Centrifuge-Simulated Suborbital Spaceflight in a Subject with Cardiac Malformation

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INTRODUCTION: Commercial spaceflight participants (SFPs) will introduce new medical challenges to the aerospace community, with unique medical conditions never before exposed to the space environment. This is a case report regarding the response of a subject with multiple cardiac malformations, including aortic insufficiency, pulmonary atresia, pulmonary valve replacement, ventricular septal defect (post-repair), and pulmonary artery stenosis (post-dilation), to centrifuge acceleration simulating suborbital flight.

CASE REPORT: A 23-yr-old man with a history of multiple congenital cardiac malformations 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 $+G_z$). Data collected included blood pressure, electrocardiogram, pulse oximetry, neurovestibular exams, and post-run questionnaires regarding motion sickness, disorientation, greyout, and other symptoms. Despite the subject's significant medical history, he tolerated the acceleration profiles well and demonstrated no significant abnormal physiological responses.

DISCUSSION: Potential risks to SFPs with aortic insufficiency, artificial heart valves, or valvular insufficiency include lower $+G_z$ tolerance, earlier symptom onset, and ineffective mitigation strategies such as anti-G straining maneuvers. There are no prior studies of prolonged accelerations approximating spaceflight in such individuals. This case demonstrates tolerance of acceleration profiles in an otherwise young and healthy individual with significant cardiac malformations, suggesting that such conditions may not necessarily preclude participation in commercial spaceflight.

KEYWORDS: Tetralogy of Fallot, cardiac malformation, acceleration, valvular insufficiency, valve replacement, G_z, G_x.

Blue RS, Blacher E, Castleberry TL, Vanderploeg JM. *Centrifuge-simulated suborbital spaceflight in a subject with cardiac malformation*. Aerosp Med Hum Perform. 2015; 86(11):999–1003.

Commercial spaceflight participants (SFPs) will introduce new medical challenges to the aerospace community, with unique medical conditions never before exposed to the spaceflight environment. Concern regarding the effect of acceleration forces on the cardiovascular system in subjects who are not anatomically or physiologically within the normal range, particularly SFPs with prior history of cardiac dysfunction or disease, has been expressed by aerospace medical professionals since the advent of the commercial spaceflight industry. Among the multitude of concerns was the potential for elevated preload and afterload, which could strain an already weak or abnormal heart or exacerbate valvular insufficiency with decreased cardiac output (CO) and cerebral perfusion. Such events could elevate the risk for G-induced loss of consciousness or induce earlier symptoms of decreased cerebral blood flow when compared to individuals without cardiac abnormality. As cardiac malformations, abnormalities, or the presence of significant disease has long been held as indisputable criteria for disqualification of individuals for flight-related (particularly high-acceleration) activities, data regarding the effects of acceleration upon known cardiac disease are limited.

Preliminary studies have demonstrated that individuals with a wide range of prior medical history have been able to tolerate exposure to the acceleration environments anticipated for short-duration, suborbital spaceflights.[2,3] Such studies postulated that the short duration of suborbital acceleration profiles

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This manuscript was received for review in April 2015. It was accepted for publication in August 2015.

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DOI: 10.3357/AMHP.4339.2015

limit the possibility of significant medical events or adverse effects of acceleration exposure. Efforts have been dedicated to demonstrating the tolerance of individuals with well-controlled medical disease to the G forces anticipated during suborbital flight, generally limited to less than or equal to +4 G_z and +6 G_x. Even so, concern remains regarding individuals with a multitude of medical concerns, particularly cardiovascular diseases, as though the amalgamation of numerous medical conditions might raise the risk of participation higher than singular, distinct, controlled conditions.

This is a case report regarding the response of a subject with multiple cardiac malformations, including aortic insufficiency (AI), pulmonary atresia, pulmonary valve replacement, ventricular septal defect (VSD) post-repair, right ventricular hypertrophy (RVH), and pulmonary artery stenosis (post-catheterization and dilation), to centrifuge acceleration simulating suborbital flight. This individual was exposed to centrifuge-simulated G-forces similar to those anticipated during the launch and reentry profiles of a short-duration, suborbital, commercial spaceflight to evaluate his tolerance to such acceleration. His participation was part of a larger trial that has been previously published.[2]

CASE REPORT

A 23-yr-old Caucasian man with a history of Tetralogy of Fallot volunteered for participation in the ongoing trial.[2] His past medical history was significant for multiple congenital cardiac malformations in association with the Tetralogy syndrome, including a membranous VSD, overriding aorta, pulmonary atresia, and RVH. He had undergone staged repair as an infant, including two unifocalizations of major aorto-pulmonary collaterals, followed by complete intracardiac repair at age 4, with placement of a pulmonary artery homograft with an outflow patch and VSD closure. He had a further history of multiple vascular stenoses in both lungs and had undergone catheterization and pulmonary artery balloon angioplasty at age 15 for his right middle- and lower-lobe pulmonary arteries. At the time of his catheterization, it was determined that he had nearly free pulmonary valve regurgitation, though right ventricular (RV) size was only mildly increased. At that time, he had a bovine pulmonary valve replacement without complication. He had undergone continuous electrocardiographic monitoring at age 15, with electrocardiograms (EKGs) demonstrating primarily normal sinus rhythm with right bundle branch block, with heart rate (HR) ranging from 74-145 bpm, with an average of 91 bpm, mild asymptomatic ectopy, and occasional premature atrial complexes and premature ventricular complexes (PVCs). An echocardiogram performed at age 16 demonstrated dilation of the RV with ejection fraction of 52%, with mild-to-moderate RVH, trivial tricuspid regurgitation, trace mitral regurgitation, and mild AI with a dilated aortic root.

At the time that he volunteered for the study, he had been monitored and deemed in stable condition for over 6 yr, with cardiologists continuing to monitor his mild/moderate RV dilation and mild AI. According to his personal physician and cardiologist, he had been moderately physically active for many years, regularly engaging in aerobic activity, including cycling and physical education activities without limitations. He could tolerate non-incline ambulation indefinitely and could manage multiple flights of stairs without increased work of breathing. The patient stated he occasionally noted himself winded after riding his bicycle up moderate inclines, but otherwise reported no abnormal symptoms to mild or moderate physical activity. EKG demonstrated only right bundle branch block with occasional PVCs, and no electrical evidence of RVH. He denied use of any medication.

Physical exam demonstrated a well-developed and well-nourished man, height 66" and weight 165 lb. His baseline HR was 71 bpm, baseline blood pressure (BP) 125/70 mmHg, and baseline oxygen saturation 98–100%. He had mild baseline jugular venous distension, but had no increase in distension with hepatojugular reflex. Cardiac auscultation demonstrated a 3/6 long blowing murmur loudest at the base and a low-pitched early diastolic murmur following the second heart sound. Extremities were warm and pink, and bilateral upper- and lower-extremity pulses were symmetric. He was observed to be capable of managing multiple flights of stairs without difficulty during his exam.

Based upon his stable cardiac condition and reasonable cardiovascular fitness, and with no objections from either his personal physician or cardiologist, the subject was approved for participation in the study. After informed consent, he underwent 7 centrifuge runs over 2 d as part of a larger trial of 86 individuals conducted at the National AeroSpace Training and Research (NASTAR) Center centrifuge and approved by the University of Texas Medical Branch Institutional Review Board.[2] 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/+G_z). Data collected included BP, EKGs, pulse oximetry, neurovestibular exams, and post-run questionnaires regarding motion sickness and other symptoms.

At the testing facility, resting BP and HR were recorded prior to initiating the centrifuge runs. The participants were taught basic anti-G straining (AGSM) and the "hook" (L-1 closed-glottis variant) maneuver and were advised to strain as needed by pressing on adjustable rigid pedals located on the gondola floor, but to use the hook maneuver only for greyout symptoms. Audiovisual simulation consisted of a projected monitor screen with cockpit-simulated images imitating real-time window views throughout the spaceflight profile, with matching flight-related sounds, such as rocket engine firing, designed to create an experience for the participants as close to an actual suborbital flight as possible.[2]

Despite the subject's significant medical history, he had no abnormal physiological responses to the centrifuge trials. The subject generally demonstrated a slightly higher than average HR response during peak accelerations of all profiles when compared to subjects in the cardiovascular cohort of the larger trial, though this finding was not statistically significant.[2] His post-spin HR

was significantly higher ($P < 0.01$) than age- and sex-matched control subjects in the larger trial (seven men ages 18-35, no medical disease). The subject demonstrated occasional single-episode PVCs during dynamic phases of all seven centrifuge runs (a common finding in study subjects regardless of medical history[2]). There were no other abnormal rhythms observed in this subject. Oxygen saturation was maintained at 98–100% by pulse oximetry before, after, and during all centrifuge trials.

The subject reported no subjective symptoms of palpitations or discomfort during any of the runs and his neurovestibular exams demonstrated only mild imbalance after later runs, not significantly different from expected imbalance following repetitive centrifuge exposure.[2] He also reported mildly increased work of breathing during high $+G_x$ exposures, which was reported by 72% of the subjects of the larger study.[2] He did note mild greyout during $+G_z$ onset of run 4 ($+G_z$ only run, with max $+3.5\ G_z$) and stated that he had forgotten to perform AGSM at the start of the acceleration profile. He further stated that all symptoms of greyout resolved with initiation of only gluteal muscle contraction, and that he had no need of the full AGSM and hook maneuver.

The subject's pre-spin and post-spin systolic and diastolic BP were not significantly different from the average BP of the subjects in the larger trial cardiac cohort.[2] His average HR immediately prior to centrifuge runs was 114 bpm, which is not significantly different from the averages of either the control group, matched for age, or the cohort average (**Table I**). His average HR immediately following centrifuge runs (≤ 1 min of cessation) was 125 bpm, which was found to be significantly higher than the control group's average of 85 ± 10 bpm ($t_7 = 2.36$, $P < 0.01$). However, subject HR values during the dynamic phases of peak accelerations during any trial were found to be of no significant difference to those of control subjects matched for age and sex (see **Table II**). When asked how he was feeling during times of tachycardia, he denied pain or discomfort, demonstrated no clinical symptoms of tachycardia or hemodynamic compromise, and stated only that he was very excited about the experience.

Table I. Mean Hemodynamic Responses Before and After Centrifugation for Our Subject Compared to the Average Response of Trial Subjects as Reported in the Larger Trial.[2]

PARAMETERS	SUBJECT MEAN	CONTROL MEAN	COHORT MEAN
BP			
Prespin Systolic (mmHg)	134	135 ± 9	141 ± 15
Prespin Diastolic (mmHg)	76	82 ± 9	87 ± 12
Postspin Systolic (mmHg)	138	137 ± 9	143 ± 19
Postspin Diastolic (mmHg)	98	81 ± 8	89 ± 13
HR			
Prespin HR (bpm)	114	90 ± 14	83 ± 19
Postspin HR (bpm)	125*	85 ± 10	84 ± 19

Control Means are subjects from the larger study's control group matched by age and sex to our case subject (men ages 18-35, no medical disease). Cohort Means are all subjects from the larger trial known to have heart disease, where $N = 15$.

BP: Blood pressure, HR: heart rate, bpm: beats per minute.

* Indicates statistically significant difference from control mean ($P < 0.05$). Note that no values are significantly different from cohort mean.

DISCUSSION

Potential risks to SFPs with AI or valvular dysfunction include lower $+G_z$ tolerance, earlier symptom onset from decreased cerebral perfusion, and ineffective mitigation strategies such as AGSM due to the inability of an insufficient aortic valve to withstand prolonged Valsalva. There are no known prior studies of prolonged accelerations approximating spaceflight in such individuals. This case demonstrates tolerance of acceleration profiles in an otherwise young and healthy individual with significant cardiac malformations, including valvular insufficiency and artificial (xenographic) valve replacement, and a prior history of pulmonary artery angioplasty.

Significant concerns were raised during consideration of this subject for inclusion in the trials. First, there was concern regarding the inclusion of a subject with known arterial stenosis, status-post revascularization procedures. The most significant concern following pulmonary artery angioplasty or other percutaneous interventions is the potential for restenosis, most commonly seen within 3-6 mo following intervention.[4] As this subject had been stable for years without evidence of restenosis, he was considered to be at very low risk for an adverse event secondary to unrecognized restenosis of pulmonary vasculature. Further, this subject was undertaking the role of passive participant, as would a commercial SFP. Thus, the potential for sudden incapacitation from hemodynamic compromise does not carry the same risks for an SFP as it would for a pilot of an aircraft.[2] Finally, previous studies have demonstrated unimpeded performance of individuals with revascularized coronary artery disease under similar acceleration exposure. It was felt that the risk for revascularized pulmonary vessels would not likely be greater than that of coronary vessels.[2,3]

The subject has a known history of AI, mild by echocardiogram. Even so, concerns were raised regarding whether or not aortic regurgitation secondary to acceleration forces or to AGSM-related alterations of preload/afterload might lead to decreased tolerance to acceleration forces, with increased risk of G-induced loss of consciousness or other symptoms of decreased cerebral perfusion. There was also concern expressed regarding whether or not exposure to acceleration may cause an adverse progression of his disease, with worsening aortic morphology and increased regurgitation. Valvular insufficiency and its impact on acceleration tolerance, as well as the impact of acceleration exposure on valvular morphology, have been well studied. One study demonstrated that prolonged and repetitive exposure to high G forces, specifically $> +9\ G_z$, over many years is associated with pulmonic insufficiency and tricuspid regurgitation, though no such association was demonstrated for aortic or mitral valves.[8] Another, larger study failed to detect any cardiac structural or functional abnormality (including right and left ventricular dimensions, wall thickness, aortic and atrial dimensions, and valvular inflow velocities) in active pilots regularly flying high-performance ($+7\ G_z$ for > 15 s) sorties when compared to pilots flying low-performance (low G) aircraft.[5] Other data have demonstrated that aviators exposed to sustained high G flying ($+5\ G_z$ for 60 s or longer for > 4 yr)

Table II. Mean Heart Rate Responses by Flight Phase for This Subject Compared to the Average Response of 7 Control Subjects from the Larger Trial Matched for Age and Sex (Men Ages 18-35, No Medical Disease).

SPIN PROFILE	EXPOSURE	SUBJECT HR	CONTROL MEAN HR
$+G_z$ Familiarization (+3.5 G_z)	Peak $+G_z$	108	140 ± 26
$+G_x$ Familiarization (+6.0 G_x)	Peak $+G_x$	144	100 ± 29
50% Integrated Spaceflight Simulation	Launch Peak ($+G_z$/$+G_x$)	100	132 ± 13
(Peak +2.0 G_z, +3.0 G_x)	Reentry Peak ($+G_x$)	104	102 ± 6
100% Integrated Spaceflight Simulation	Launch Peak ($+G_z$/$+G_x$)	125	139 ± 29
(Peak +3.5 G_z, +6.0 G_x)	Reentry Peak ($+G_x$)	117	108 ± 18
100% Integrated Spaceflight Simulation	Launch Peak ($+G_z$/$+G_x$)	121	136 ± 18
[Peak +3.5 G_z,+6.0 G_x, Combined +3.0 G_z/+4.5 G_x (resultant +6.0 G)]	Reentry peak ($+G_z$/$+G_x$)	116	125 ± 17

Average subject data is as reported in the larger trial.[2]
HR: Heart rate (presented in beats per minute).

show no evidence on repeated echocardiography of alterations to valvular morphology or integrity.[1,6] As this study sought to expose subjects to comparatively low $+G_z$ for relatively short periods of time (≤ 15 s), the risk of worsening the subject's condition by induced morphological changes was thought to be negligible.

Literature was not found to specifically address the potential for decreased CO (and, therefore, decreased $+G_z$-tolerance from poor cerebral perfusion) in individuals with aortic regurgitation, likely because such individuals are generally excluded from such studies. However, aircrew with mild AI are considered by the FAA to be fit for unrestricted flying activity without concern for increased susceptibility to adverse acceleration effects.[4] It was, therefore, felt that the moderate $+G_z$ exposure in this study would likely be well tolerated by the subject despite his mild AI.

The presence of a xenographic bioprosthetic valve was a further cause of concern. The FAA has granted Special Issuance of Class I medical certificates to pilots with aortic valve replacement, limiting such pilots to no more than +3 G_z acceleration loading;[7] however, cases involving pulmonary valve replacement are more difficult to identify. One concern for aortic bioprostheses is insufficiency under high $+G_z$ exposure, thought to be effectively mitigated by limitation to ≤ +3 G_z.[7] This risk would be lower for pulmonary valve replacement as transient G-induced pressure gradients are lower across the pulmonary valve than the aortic valve. Another concern regarding xenographic valve replacement was the risk for thromboembolism. This risk is highest within 6 mo of surgery and was, therefore, deemed to be low risk in this subject, 8 yr postsurgical replacement and without thromboembolic complications.[10]

There are few studies regarding cardiovascular function, particularly CO response, of even normal hearts under high $+G_x$ exposure, a cause for further concern in an individual with known cardiac morphology abnormalities. Prior studies have demonstrated no significant alteration to CO following sustained exposure for up to 10 min at +5 G_x in normal airmen.[11] As a result, we felt it unlikely that a subject with only mild AI and mild/moderate RV dilation would be significantly affected by $+G_x$ exposure. Indeed, the subject denied symptoms during any $+G_x$ centrifuge trials, demonstrating comparatively normal tolerance to the moderate $+G_x$ exposures.

Finally, significant concern was raised regarding the acceptance of a subject with a multitude of cardiac malformations. Despite relative comfort with one or two of this subject's conditions, the combination of all conditions raised concerns regarding cumulative risk. We were unable to identify prior studies of an individual with multiple cardiac malformations and abnormalities exposed to $+G_z$ and $+G_x$ accelerations as in this study and, as mentioned above, pilots who have been granted aeromedical certification following valve replacement are generally confined to low-acceleration flight profiles of ≤ +3 G_z, without the mixed $+G_z$/$+G_x$ experienced herein. However, it was felt that, given the information presented above, each of the subject's medical conditions was well controlled, and that he was at relatively low risk for adverse outcome during his participation. The graduated acceleration profiles used in this study allowed medical observers to monitor his performance and intervene, if necessary, prior to higher acceleration exposures. As each of his conditions represented an apparent low risk of adverse outcome, the subject was deemed likely to tolerate the moderate accelerations of a simulated commercial suborbital spaceflight.

This case represents a single individual's tolerance to moderate $+G_z$/$+G_x$ acceleration exposures, representative of those potentially experienced during a commercial, suborbital spaceflight. This individual's experience cannot be considered representative of all persons with similar disease or abnormal morphologies. In fact, the ability to draw conclusions from this one individual's performance is severely limited. First, the subject was anthropometrically predisposed to the likelihood of tolerance to $+G_z$ exposures seen here, as he is relatively short-statured (66"), with a resultant short hydrostatic column requiring less pressure to achieve adequate cerebral perfusion. His known AI was mild and stable, followed for a number of years with stable imaging, and is not representative of all individuals with known AI or valvular defect. His pulmonary valve replacement was similarly remote and stable to follow-up. Furthermore, pulmonary valves are not exposed to the increased pressure gradients seen across aortic valves during AGSM and, therefore, his tolerance cannot be considered representative of all valve replacements and relative performance. Similarly, his pulmonary stenosis had been well managed with pulmonary artery angioplasty, without evidence of restenosis. However, pulmonary stenosis should not be considered representative of,

for example, coronary stenosis or similar disease. Additionally, this study was not designed to evaluate his cardiovascular morphological responses or compensation to acceleration exposure. No invasive monitoring was performed, and no imaging before, during, or after acceleration exposure was required for his participation. As a result, we are unable to present cardiac chamber or valvular pressures or CO during centrifugation. Finally, this study could not evaluate cardiovascular response to microgravity. Microgravity exposure causes a substantial fluid shift and alterations of CO, which could be problematic for individuals with compromised diastolic function and should be evaluated with more detailed studies.[9]

The intent of the study was not to provide generalizations regarding the ability of individuals such as this to tolerate centrifuge acceleration. We sought only to demonstrate that individuals with concerning medical histories can be evaluated without automatic disqualification and may be deemed lower risk than initial evaluation might lead aerospace medical specialists to believe. This individual is young and, despite his medical history, relatively healthy with reasonable cardiovascular fitness. He was able to tolerate (and, in fact, enjoy) the centrifuge experience, as presented here, without evidence of any abnormal hemodynamic or physiological responses. Similar cases may present themselves as potential candidates for suborbital spaceflight. Evaluation and consideration of such individuals could help expand the realm of known medical conditions capable of tolerating acceleration exposure for the benefit of scientific knowledge and provide previously impossible opportunities for individuals with such disease. Further, demonstration of tolerance in this young and otherwise relatively healthy individual may offer a precedent for the evaluation of older individuals with other significant medical conditions. We believe that this work lays the foundation for further studies designed to evaluate individuals with reasonable cardiovascular compensation, despite concerning conditions, for the potential to tolerate suborbital spaceflight acceleration profiles. Such work may someday permit inclusion in the commercial arena of those previously believed to be too high-risk, perhaps allowing even those with significant medical conditions to pursue their own dreams of spaceflight.

ACKNOWLEDGMENTS

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