# Tolerance of Centrifuge-Simulated Commercial Spaceflight in a Subject with Hemophilia A

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**INTRODUCTION:** With increasing engagement of commercial spaceflight participants in spaceflight activities, the evaluation of individuals with medical conditions not previously characterized in the spaceflight environment is of particular interest. Factors such as acceleration forces experienced during launch, reentry, and landing of spacecraft could pose an altered risk profile in some individuals due to known disease. Bleeding diatheses present a unique concern in the spaceflight environment given hypergravity exposure and, particularly, the potential for injury resulting from transient or impact acceleration.

**CASE REPORT:** A 26-yr-old Caucasian man with severe hemophilia A and no detectable endogenous Factor VIII (FVIII) volunteered for participation in hypergravity exposures simulating spaceflight. His treatment regimen included 50 IU · $kg^{-1}$ FVIII-Fc fusion protein intravenous administration every 96 h, with supplemental FVIII administration as needed for injury or bleeding. The subject experienced two profiles at the National Aerospace Training and Research Center (NASTAR), with maximum exposure +4.0 $G_z$, +4.5 $G_x$, 6.1 G resultant, and maximum onset rate <0.5 $G_z \cdot s^{-1}$ and +1 $G_x \cdot s^{-1}$. The subject reported no abnormal events during the profiles other than brief mild vertigo. No petechial hemorrhage, ecchymosis, or other bleeding was noted during or after profiles. Supplemental FVIII was not required before, during, or after exposure.

**DISCUSSION:** Inherited bleeding disorders present several potential concerns that must be evaluated prior to spaceflight participation. Cautious review and management of medical history, adherence and barriers to treatment, duration of spaceflight and longitudinal management concerns, and a thorough and detailed risk/benefit assessment may provide a future pathway for inclusion of individuals with hematological disorders in commercial spaceflight.

**KEYWORDS:** hemophilia A, bleeding diathesis, Factor VIII, human centrifuge, hypergravity, commercial spaceflight, acceleration, hematology.

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With increasing engagement of commercial spaceflight participants (SFPs) in spaceflight activities, the evaluation of individuals with medical conditions not previously characterized in the spaceflight environment is of particular interest. In addition to the physiological changes that occur in spaceflight, factors such as acceleration forces experienced during launch, reentry, and landing of spacecraft could potentially affect preexisting medical conditions or pose an altered risk profile in some individuals due to known disease. Bleeding diatheses present a unique concern in the spaceflight environment given hypergravity exposure and, particularly, the potential for injury resulting from transient or impact acceleration. Given that hematological abnormalities are generally disqualifying for military service and career astronaut fitness-for-duty standards,[10,25] there are little to no published data on the clinical response of individuals with known bleeding disorders in a high-acceleration environment.

Known hematologic complications of hypergravity exposures, especially from sustained exposure to greater than +6 $G_z$ acceleration, include cutaneous petechiae attributable to capillary rupture in dependent and unsupported areas of the body, sometimes termed "G-measles".[16] This condition is generally

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self-limited and associated with mild discomfort. In addition, less frequently reported hematologic or vascular sequelae of hypergravity (generally $+G_z$) or associated anti-G straining maneuvers (AGSM) and protective garments include hematomas,[5,20] phlebitis,[30] and one case report of large vessel dissection.[3] Data regarding sustained exposures in alternative vectors ($\pm G_y$, $+G_x$) are more limited, though prior studies have evaluated layperson tolerance of up to +4 $G_z$ and +6 $G_x$ sustained acceleration, with no evidence of known hematological or vascular sequelae associated with these profiles.[7–9] Recurrent Valsalva in various environments is correlated to ocular sequelae, including subconjunctival hemorrhage, preretinal macular hemorrhage, superchoroidal hemorrhage, vitreous hemorrhage, and Valsalva retinopathy.[13,32] In addition, any transient hypergravity exposure from off-nominal, impact, or traumatic environments (such as hard landings or crashes) would pose a substantial risk to unmitigated hematological disorders and bleeding diatheses.

The most common inherited bleeding disorders are von Willebrand disease, which affects roughly 1% of the general population, and hemophilia A, or Factor VIII (FVIII) deficiency, with an incidence of approximately 1:5000 male births.[15,18,29] Bleeding disorders (including hemophilia A) exist on a clinical spectrum, with symptoms and sequelae dependent upon the levels of FVIII. Severe hemophilia A is generally defined as FVIII levels below 1%, and it is associated with an increased risk of life-threatening and spontaneous bleeding.[27,28] However, with the advent of recombinant FVIII products, affected individuals are often treated prophylactically to prevent bleeding episodes[24,27] or mitigate hematological consequences resulting from trauma.[28] In a case where FVIII levels are maintained, via prophylaxis, above the threshold required for hemostasis, the risk of serious bleeding is significantly decreased.[27] Lifespan and functional capacity expectations for an individual with well-controlled hemophilia are similar to those of other individuals in the general population.[15,24]

There are recent data to suggest that individuals with a variety of systemic diseases and conditions, if well-controlled, can tolerate the acceleration forces associated with short-duration commercial spaceflight launch and return profiles.[8,9,31] Here we report a case of a young male subject with severe hemophilia A on exogenous FVIII factor replacement and his response to variable and sustained $+G_x$ and $+G_z$ acceleration forces during centrifuge-simulated spaceflight.

## CASE REPORT

A 26-yr-old Caucasian man with severe hemophilia A and no detectable endogenous FVIII volunteered for participation in hypergravity exposures simulating suborbital spaceflight. The subject was diagnosed at 15 mo of age and has been treated throughout his life with prophylactic recombinant FVIII therapy. At the time of the study, his treatment regimen included 50 IU · $kg^{-1}$ FVIII-Fc fusion protein intravenous administration every 96 h, with supplemental FVIII administration as needed for any injury or bleeding episodes. His condition was being actively managed by a hematologist at a major academic medical center and he provided documented history of stable condition for several years, no frequent bleeding episodes or hospitalizations since reaching adulthood, no hemarthrosis or baseline disability, no recent use of supplemental FVIII outside of his normal dosing schedule (for at least several months), and full preservation of basic musculoskeletal function and activities of daily life. Prior to participation, he provided documentation of current physical and medical status, with no other significant medical history or physical limitations reported aside from a generalized caution from his hematologist to avoid high-risk contact sports. A pharmacokinetic (PK) study had been performed on his current treatment regimen, demonstrating that his regimen provided >100% factor availability on the first day of his 4-d cycle, >20% on the second, >5% on the third, and >1% on the fourth, as well as that any emergent FVIII administration would promptly raise FVIII levels to >100% (within 1 h of administration). Given the novelty of his medical condition in a hypergravity environment, his medical history, current status, and effectiveness of treatment regimen were closely reviewed prior to participation by a panel of board-certified Aerospace Medicine physicians with additional certifications in Internal Medicine, Critical Care Medicine, and Emergency Medicine.

The subject participated in two centrifuge profiles in a single day at the National Aerospace Training and Research Center (NASTAR) centrifuge (at Environmental Tectonics Corporation, Southampton, PA). The first profile approximated a suborbital spaceflight in a winged vehicle where the occupant was seated semi-upright for both launch and reentry, resulting in $+G_z$ and $+G_x$ sequential exposures on ascent and combined simultaneous $+G_x$ and $+G_z$ exposures during descent (maximum exposure +4.0 $G_z$, +4.5 $G_x$, 6.1 G resultant). Each phase of acceleration was <2 min and G-onset rates were <0.5 G · $s^{-1}$ in the $+G_z$ direction and <1.5 G · $s^{-1}$ in the $+G_x$ direction. The duration of time at peak $+G_x$ and $+G_z$ was <5 s. The second profile simulated a capsule launch in which an abort procedure occurred with activation of a launch escape system (LES). The profile provided a rapid $+G_x$ acceleration (maximum +3.3 $G_x$, onset rate +1 G · $s^{-1}$) during the LES simulation, followed by descent acceleration of maximum +1.9 $G_x$ (onset rate <0.5 G · $s^{-1}$). Subsequent profile acceleration exposures representing drogue and main parachute deployment were followed by a simulated water landing and sinusoidal waveforms representing capsule motion on water. Finally, the profile included brief transient $-G_z$ acceleration (maximum −0.74 $G_z$ with sustained $-G_z$ exposure time <1 s) during simulated drogue deployment and landing, similar to expected acceleration profiles of an actual LES abort. Between transient $-G_z$ accelerations, the gondola occupant's head is at rest at between 0° and −15° head-down positioning due to seatback angle. The centrifuge profiles included audiovisual capabilities to add to the fidelity of the simulation. The participant was continuously monitored with real-time audio and video communication.

The subject participated in centrifugation on the second day of his normal 96 h treatment regimen (approximately 24 h after the most recent FVIII dosage). Prior to the initiation of centrifuge runs, the subject's vital signs, including resting blood pressure (BP) and heart rate (HR), were recorded. The subject was taught AGSM and the "hook" (L-1 closed-glottis variant) maneuver, plus indications for use. He was advised to use lower extremity muscular strain during any $+G_z$ exposure and to initiate the hook maneuver, but to reduce or eliminate Valsalva effort in the absence of symptoms (visual changes or light-headedness). He was also cautioned against sudden head movements during centrifuge trials, in order to avoid triggering Coriolis symptoms. Supplemental FVIII was available for use if needed and the subject was monitored during both centrifuge profiles by two board-certified aerospace and emergency medicine physicians.

Data was collected post-centrifugation in the form of questionnaires about symptoms and monitoring of physical condition in the following days. The subject reported no abnormal events during the simulated flights other than brief mild vertigo, which resolved prior to the completion of each run, and a transient inversion sensation associated with the slight head-down angle and cyclical onset/offset of hypergravity during the descent portion of the second profile. No petechial hemorrhage, ecchymosis, joint discomfort, effusion, or other bleeding was noted during or after acceleration exposures. He reported use of lower extremity strain throughout all $+G_z$ exposures, but noted no visual symptoms at any time; following the initial $+G_z$ exposure in the first profile, he did not further employ the hook/Valsalva portion of AGSM.

The subject was able to ambulate normally immediately upon exiting the centrifuge and had no immediate adverse effects from the experience, nor any apparent neurovestibular imbalance. Following the centrifuge runs, the subject continued his normal FVIII treatment regimen with no changes. There was no indication for use of supplemental dosing of FVIII at any time during or after the centrifuge experience. The subject continued to self-monitor for several days and noticed no delayed symptoms.

## DISCUSSION

As far as the authors are aware, this represents the first reported case of an individual with an inherited bleeding disorder undergoing acceleration forces approximating those of spaceflight launch and landing. In the setting of chronic, well-controlled, and stable disease on an effective treatment regimen, this individual tolerated the hypergravity exposures well and without any adverse effects or bleeding. Additionally, there was no need for alteration of his baseline treatment regimen or administration of supplemental FVIII products outside of his standard prescribed management due to any concern or injury from the hypergravity exposures. In this case, aeromedical risk was considered acceptable after review by trained and experienced aerospace medicine physicians. The subject's prior PK studies demonstrated that his expected FVIII activity on the second day of his treatment regimen was ≥20%, a level which is associated with minimal risk of bleeding outside of major trauma.[6] Practitioner familiarity with centrifuge profiles and relative risk of traumatic injury during centrifugation helped to limit risks and ensured appropriate informed consent prior to participation.

In consideration of the generalizability of this experience, it is important to highlight both the clinical spectrum of inherited bleeding disorders and the large variability in treatment regimens and outcomes. In this case, the individual, while having severe disease by definition, has been treated prophylactically with regular FVIII infusions since diagnosis early in life and, subsequently, achieved a preservation of normal quality of life and functional status. This is in stark contrast to individuals with severe inherited bleeding disorders and no access to care, poor adherence to treatment regimens, or treatment in an "on-demand" regimen, in which factor products are administered only after bleeding or symptoms have occurred. When treated sporadically, insufficiently, or not at all, severe hemophilia is profoundly detrimental to health and associated with high risk of spontaneous bleeding, including life-threatening events such as gastrointestinal or intracranial hemorrhage.[15,27] For reference, prior to the introduction of clotting factor concentrates in the 1970s, life expectancy for severe hemophilia was generally 10–20 yr, due to the high likelihood of severe spontaneous hemorrhagic episodes and complications from such events.[19] Since the late 1990s, substantial advances have been made in the management of inherited bleeding disorders, including recombinant (nonhuman plasma-derived) products and novel therapeutics extending half-life and providing alternate routes of administration.[4,15]

From the perspective of commercial SFPs, inherited bleeding disorders present several potential concerns that must be evaluated prior to participation. Because of the clinical variability of hematological disorders, it will be essential to first assess the baseline management of the condition prior to discussing possible risks from the spaceflight environment. As a corollary to spaceflight considerations, aeromedical certification for piloting activities in an individual with a history of hemophilia or similar bleeding diatheses is variable and dependent upon the certification body. While the International Civil Aviation Organization (ICAO) considers severe hemophilia A to be incompatible with flight duties,[17] the Federal Aviation Administration (FAA) requires case-by-case evaluation due to the aforementioned heterogeneity of hematological conditions.[14] FAA Special Issuance of Medical Certification in the case of hemophilia requires a review of current clinical documentation and a detailed status report of the condition, followed by a review by hematology subject matter experts in consultation with the FAA medical review panel.[14]

One published case report in 2013 described an individual with severe hemophilia A, who only received "on-demand" FVIII administration, seeking First Class medical certification.[33] In this case, a hematology consultant recommended Special Issuance only if prophylactic factor administration

could be required prior to flight. As the FAA does not generally provide directed treatment requirements, the case ultimately resulted in denial based on frequency of bleeding episodes, joint injury from recurrent hemarthrosis, the patient's current on-demand treatment regimen, and an unenforceable need for treatment adherence to ensure safe piloting duties.[33] This case highlights another concern to be weighed when considering approval of an individual with hemophilia A for spaceflight activities. Insufficient management of the disease burden throughout life may have manifestations other than the risk of acute bleeding episode: recurrent hemarthrosis or similar non-life-threatening events may result in mobility or functional restrictions that could manifest as limitations in a high-risk environment. For example, while SFPs may not be responsible for nominal operational activities, in the case of an in-flight emergency, all vehicle occupants may be required to engage in critical operational actions or rapid evacuation. A thorough evaluation of functional capacity is warranted to rule out any critical limitation from prior disease sequelae that may ultimately pose a risk in a spaceflight environment. Medical comorbidities additionally predisposing to vascular injury (e.g. connective tissue disorders, Ehlers-Danlos, Marfan) may further compound bleeding risk if present concomitantly with a bleeding disorder.[22] Other considerations may be necessary if the individual in question has a more operationally critical role during the spaceflight (for example, pilot vs. participant).

One method by which individual treatment of bleeding disorders is optimized in clinical practice, and which may have useful implications for aeromedical certification, is through PK studies; indeed, risk analysis in this case was partly based upon the subject's PK studies and known FVIII activity on his current treatment regimen. Various factor concentrate products and individual variability will result in differing response to any given treatment regimen. PK studies can help individualize care by demonstrating effectiveness of treatment over time, most commonly through standard clotting factor assays such as FVIII activity levels. Thus, prophylactic treatment can be targeted to achieve factor levels sufficient for clotting for all or the majority of the time between scheduled doses.[15,17] Often, an FVIII activity level greater than 1% is sufficient to reduce bleeding (i.e., conversion from severe to moderate hemophilia) as part of a prophylactic treatment regimen. Treatment remains an individualized process, and a higher target of 5–15% or greater may provide further benefit in certain individuals. Regardless, it is not necessary to have 100% FVIII activity to prevent bleeding episodes.[32]

In some cases, FVIII administration can result in the development of neutralizing antibodies, or inhibitors, rendering factor replacement therapy unsuccessful.[2,11,15] In most cases, such inhibitor development occurs in childhood or adolescence;[12] thus, as commercial spaceflight participation presumably would require an age of majority to allow for acceptance of informed consent, failure of replacement factor would most likely have been previously recognized. Further, development of inhibitors would not be expected to be subtle or rapid enough to result in a sudden factor resistance in adulthood with unexpected clinical manifestations at the time of a brief spaceflight experience.

For individuals with well-controlled disease and no functional limitations, there is a possibility that spaceflight experience may be tolerated with minimal or no impact related to the bleeding disorder. Further considerations in the spaceflight environment include the logistical and practical considerations of managing the condition (for example, during remote or isolated periods around the launch, such as any prelaunch quarantine or a remotely located launch facility), as well as the treatment needs during spaceflight. A short-duration suborbital flight, for example, would be far easier for disease management than a longer orbital flight, where treatment regimens would potentially require pharmaceutical administration while in orbit. In such circumstances, the benefits of prophylactic and maintenance therapy must be weighed against the constraints of infusion frequency, storage and management of pharmaceuticals (for example, need for refrigeration), and challenges of on-orbit administration, particularly as many products may require administration every 48–96 h.[1,2] The majority of treatment products for hemophilia require intravenous administration,[2] which presents unique challenges of its own in a microgravity environment.[21,26] However, other bleeding disorders, like von Willebrand disease, can sometimes be treated adjunctively with therapies like intranasal desmopressin (DDAVP), and newer treatments for hemophilia include those with subcutaneous injections.[4,23] Such treatment options may further enable consideration for including individuals with hematological disease in more varied flight environments.

Commercial spaceflight provides a unique pathway for individuals with previously disqualifying conditions to potentially engage in spaceflight activities. This report suggests that a young, otherwise healthy individual with a severe bleeding disorder that is well-managed and stable can physiologically tolerate acceleration forces similar to those that would be experienced by a commercial SFP in a short-duration spaceflight. There are important and substantial limitations to the generalizability of this information, and many factors contribute to the risk of injury or bleeding beyond those simulated in this study. However, from the perspective of widening the spaceflight experience to those individuals affected by chronic and severe medical conditions, it is important to continually broaden research endeavors and better characterize these risks, thus providing a framework for aeromedical evaluation. Ultimately, the decision to include an individual with bleeding diatheses, including hemophilia, in commercial spaceflight activities will be determined by a risk assessment and acceptance of such risk by both the potential SFP and the industry provider, through guidance from trained and experienced aeromedical practitioners. Cautious review and management of medical history, adherence and barriers to treatment, duration of spaceflight and longitudinal management concerns, and a thorough and detailed risk/benefit assessment may provide a future pathway for the inclusion of individuals with hematological disorders in commercial spaceflight.

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