Countermeasures to Space-flight-induced Orthostatic Hypotension

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Introduction

Astronauts generally adapt well to the space flight environment, but this may bring about physiologic changes that can negatively impact their health and performance on entry into Earth gravity or the partial-gravity environments of the moon and Mars. The structure and function of the human cardiovascular system are particularly affected by space flight, which may lead to an astronaut's inability to appropriately regulate blood pressure and cerebral perfusion, resulting in a clinical condition called orthostatic intolerance. Orthostatic intolerance, in its more benign form, can be manifested as an elevated heart rate and/or decreased blood pressure when seated or standing; but, in more extreme cases, it may result in lightheadedness (presyncope) and fainting (syncope). Presyncopal symptoms or syncope during a 10-minute stand or an 80-deg head-up tilt affects approximately 30% of astronauts after short-duration missions (4–18 days), and approximately 80% of astronauts after long-duration missions (≥30 days). Orthostatic intolerance after space flight could impair an astronaut's ability to perform routine tasks, and is a significant concern for emergency egress scenarios. During future visits to the lunar surface and human flights to Mars, astronauts will be working in environments without ground support teams, so the occurrence of severe orthostatic intolerance could be disastrous. It is paramount that countermeasures to orthostatic intolerance be developed to protect astronaut health and mission success.

Midodrine

Pharmacological countermeasures to orthostatic intolerance are attractive because they require little storage space and few resources during long-duration missions. We recently studied midodrine, an α_1-adrenergic agonist used to treat clinical cases of orthostatic hypotension. For the initial testing, we administered midodrine to shuttle crew members within 2 hours following space shuttle landings, and determined its side effects 1 hour later under controlled conditions in the baseline data collection clinic. Astronauts who were previously not prone to presyncope on landing day experienced no negative side effects; and in the one astronaut who had a history of presyncope, the midodrine protected against orthostatic hypotension. The next study built on the success of this initial study by testing the efficacy of midodrine under operational conditions. Astronaut subjects ingested midodrine prior to the shuttle deorbit burn to protect against hypotension on landing. They then participated in a tilt test within 30 minutes of shuttle wheelstop on the crew transport vehicle. The five control astronaut subjects who did not ingest the midodrine participated in the same tilt test in the crew transport vehicle.

Unfortunately, one side effect of midodrine is that it may cause ventricular arrhythmias (i.e., torsades de pointes) in subjects who have a prolonged QT_c interval. While this is not an issue following short-duration space flight, we found that in long-duration space flight midodrine may cause a prolonged QT_c interval in some individuals. Because of this limitation and the potential for untoward interactions with other pharmaceutical agents, our laboratory is pursuing the development of non-pharmaceutical countermeasures.

Hypovolemia model of space-flight-induced orthostatic intolerance

Our laboratory developed a model of space-flight-induced orthostatic intolerance in normal ambulatory subjects. Using furosemide, an FDA [Food and Drug Administration]-approved diuretic, followed by a very-low-sodium diet, we create a condition of hypovolemia in which the plasma volume is reduced in subjects to a level similar to that experienced by astronauts during space flight. Consequently, test subjects experience symptoms that mimic those experienced by astronauts on landing day. The hemodynamic responses of six veteran astronauts to 80-deg head-up tilt during hypovolemia reproduced their responses to tilt testing on landing day after a previous space shuttle mission. This verified the model.

NASA and Russian antigravity suits

Using this model, we initiated a series of studies to examine the efficacy of mechanical compression garments applied to the lower body to prevent peripheral venous pooling and protect against orthostatic hypotension. In the first study, we compared the level of protection afforded by NASA's current antigravity suit (AGS) (figure 1), worn under the U.S. advanced crew escape suit (ACES) by crews returning on the space shuttle, to the Russian Kentavr

re-entry garment (figure 2), worn under the Russian Sokol suit by crews returning on the Soyuz capsule.

The AGS has five interconnected inflatable air bladders covering the abdomen, thighs, and calves. It can be inflated to pressures ranging from 0.5 psi (25.9 mmHg) to 2.5 psi (129.3 mmHg), but typically is inflated to 1.5 psi (77.7 mmHg) during shuttle re-entry and landing. The Kentavr is composed of shorts that extend from the waist to the knee and a pair of gaiters, made of an elastic fabric, that covers the calves. Each component of the Kentavr has lacings to allow an individualized fit. The nominal pressure provided by the Kentavr is 0.6 ± 0.1 psi (30 ± 5 mmHg).

We tested 35 subjects for orthostatic intolerance under hypovolemic conditions while wearing either the Kentavr (n=10), the AGS (n=9), or no countermeasure (n=16). All 19 subjects wearing either the Kentavr or the AGS were able to complete a 15-minute, 80-deg head-up tilt test. Only 44% (seven of 16) of the control subjects completed this tilt test. Both the Kentavr and the AGS provided protection against orthostatic intolerance under hypovolemic conditions, suggesting that the compression of the AGS applied in this study (~78 mmHg) might be in excess of that required (Kentavr = ~30 mmHg) to mitigate orthostatic hypotension.

Fig. 1. *NASA's AGS currently worn with the advanced crew escape suit post-bedrest.*

Fig. 2. *Russia's Kentavr suit worn by cosmonauts under the Sokol suit during re-entry and landing.*

JOBST® compression garments

In the second compression garments study, we compared clinically available JOBST® custom thigh-high compression garments (figure 3) to the AGS. JOBST® compression garments are custom-fit to each subject based on pre-test measurements of leg circumference to create a graduated pressure gradient spanning the length of the leg. The JOBST® compression pressure is highest at the ankle (~55 mmHg) and lowest at the thigh (~6 mmHg), with an average of 25 mmHg over the length of the garment. In this study, the AGS was inflated to

Fig. 3. *JOBST® thigh-high compression garments.*

0.5 psi (~25 mmHg), based on observations from our previous study and reports by astronauts that 1.5 psi is uncomfortable, especially on the abdomen, following the mandated fluid-loading regimen prior to re-entry. Initial results from this ongoing ground study suggest that both this style of JOBST® compression garment and the AGS at this level of inflation are protective, but perhaps not to the same degree as higher-pressure garments.

These JOBST® custom, thigh-high compression garments were recently tested on five astronauts on the landing day of a space shuttle mission. During re-entry and landing, these astronauts wore the standard AGS. After removing their ACES and AGS following shuttle egress, they donned JOBST® compression garments. All of the astronauts participated in a 10-minute, 80-deg head-up tilt at the baseline data collection facility within 4 hours of landing. We completed a comparison of the hemodynamic responses to tilt in these five astronauts to nine other astronauts who also participated in a tilt test without compression garments following space shuttle flights of a similar duration. During tilt, there were no incidences of orthostatic intolerance in astronauts wearing JOBST® compression garments. In contrast, three of the nine subjects in the control group experienced presyncope during tilt and were unable to complete the tilt test. Astronauts who wore the JOBST® thigh-high compression garments had higher systolic blood pressure, stroke volume, and cardiac output throughout tilt than those who did not wear the compression garments. Continued ground-based testing and future testing with more astronaut crews will be required to confirm the efficacy of these JOBST® thigh-high compression garments.

Conclusions

We will continue to investigate the most efficacious method to protect returning space crews against orthostatic intolerance. Although pharmacological interventions show promise, concerns with the unintended side effects of these medications may limit their use. Our results demonstrate that, in a ground-based model of space-flight-induced orthostatic hypotension, compression garments are effective, but the nominal application of compression of the NASA garment may be greater than is necessary. Current and future studies will focus on the required level and location of compression required to protect astronauts from orthostatic intolerance. For example, to determine whether additional compression of the splanchnic vasculature would be beneficial, we recently initiated testing with breast-high, custom JOBST® compression garments with an average compression of 25 mmHg over the length of the leg and of 12 mmHg over the gut. Additionally, we will later study knee-high garments that cover only the calves, the site of greatest fluid accumulation during standing, but will provide greater levels of compression (35 mmHg average over the length of the garment). These tests will be conducted using subjects who have induced hypovolemia. If those results are promising, further tests will be conducted on astronauts after space flight. The overall objective of this work is to determine the specifications of the compression garment that performs most effectively against orthostatic intolerance while still being comfortable for the astronaut.

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