Internal Jugular Vein Volume During Head-Down Tilt and Carbon Dioxide Exposure in the SPACECOT Study

Karina Marshall-Goebel; Brian Stevens; Chethan Venkatasubba Rao; Jose I. Suarez; Eusebia Calvillo; Philippe Arbeille; Haleh Sangi-Haghpeykar; Dorit B. Donoviel; Edwin Mulder; Eric M. Bershad; the SPACECOT Investigators Group

BACKGROUND: Cerebral hemodynamics and venous outflow from the brain may be altered during exposure to microgravity or head-down tilt (HDT), an analog of microgravity, as well as by increased ambient CO_2 exposure as experienced on the International Space Station.

METHODS: Six healthy subjects underwent baseline tilt table testing at 0°, 6°, 12°, 18°, 24°, and 30° HDT. The right internal jugular (IJ) vein cross-sectional area (CSA) was measured at four intervals from the submandibular to the clavicular level and IJ volume was calculated. Further measurements of the IJ vein were made after ~26 h of 12° HDT bed rest with either ambient air or 0.5% CO_2 exposure, and plasma and blood volume were assessed after 4 h, 24 h, and 28.5 h HDT.

RESULTS: IJ vein CSA and volume increased with progressively steeper HDT angles during baseline tilt table testing, with more prominent filling of the IJ vein at levels closer to the clavicle. Exposure to 26 h of 12° HDT bed rest with or without increased CO_2, however, had little additional effect on the IJ vein. Further, bed rest resulted in a decrease in plasma volume and blood volume, although changes did not depend on atmospheric conditioning or correlate directly with changes in IJ vein CSA or volume.

DISCUSSION: The hydrostatic effects of HDT can be clearly determined through measurement of the IJ vein CSA and volume; however, IJ vein dimensions may not be a reliable indicator of systemic fluid status during bed rest.

KEYWORDS: analog, spaceflight, cerebral hemodynamics, cross sectional area, plasma volume.

Marshall-Goebel K, Stevens B, Rao CV, Suarez JI, Calvillo E, Arbeille P, Sangi-Haghpeykar H, Donoviel DB, Mulder E, Bershad EM, the SPACECOT Investigators Group. *Internal jugular vein volume during head-down tilt and carbon dioxide exposure in the SPACECOT Study*. Aerosp Med Hum Perform. 2018; 89(4):351–356.

The physiological effects of prolonged exposure to microgravity have been well studied for the past 50 yr of human spaceflight. More recently, with newer technologies and increased medical surveillance, it has been discovered that up to 50% of astronauts are developing neuro-ophthalmological changes during prolonged spaceflight on the International Space Station (ISS).[10] These structural and functional changes, seen on ophthalmological exam and orbital MRI, include optic disc edema, flattening of the posterior eye globe, choroidal folds, cotton-wool spots, increased optic nerve sheath diameter, hyperopic shifts up to 3 diopters, and increased intracranial pressure (ICP) postflight.[7,11] It is collectively referred to as the Spaceflight Associated Neuroocular Syndrome (formerly known as Visual Impairment and Intracranial Pressure Syndrome or Microgravity Ocular Syndrome).[12] The etiology of these changes is currently unknown, but may be related to cephalad fluid shifting in microgravity and increased ICP, potentially exacerbated by elevated carbon dioxide (CO_2) levels aboard the ISS.[8]

On Earth, head-down tilt (HDT) is commonly used as a ground-based analog of spaceflight to study the effects of cephalad fluid shifting and gravitational unloading in the head to foot axis (G_z).[15,23] Previous studies have demonstrated significant increases in the diameter and cross-sectional area (CSA) of the internal jugular (IJ) vein during HDT[13,18] as well as in spaceflight.[2] As the IJ veins are the primary route of cerebral

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From Massachusetts General Hospital/Harvard Medical School, Charlestown, MA; Baylor College of Medicine, Houston, TX; the University of Tours, Tours, France; and the Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany.

This manuscript was received for review in June 2017. It was accepted for publication in December 2017.

Address correspondence to: Eric Bershad, M.D., Baylor College of Medicine, Department of Neurology, 1 Baylor Plaza, NB–125, Houston, TX 77030; Bershad@bcm.edu.

DOI: https://doi.org/10.3357/AMHP.4934.2018

venous outflow in the supine and HDT positions,[5,22] increased IJ vein CSA during HDT may be a result of increased cerebral venous pressure due to hydrostatic effects on the venous blood column.[16] Therefore, assessment of the IJ vein CSA and/or volume may give an indirect indication of the intracranial venous status.

We measured IJ vein CSA and volume during various degrees of HDT ranging from 0° to 30° during baseline tilt table testing, and after 26 h exposure to 12° HDT with and without increased atmospheric CO_2. We hypothesized that IJ vein CSA and volume would increase with steeper degrees of HDT during tilt table testing and would be exacerbated by HDT bed rest with atmospheric CO_2 conditioning.

METHODS

The "SPACECOT Study" (Studying the Physiological and Anatomical Cerebral Effects of CO_2 during Head-Down Tilt) was an international collaborative study conducted at the German Aerospace Center (DLR) envihab facility in Cologne, Germany. The experimental protocol was approved in advanced by the Baylor College of Medicine IRB and the Ethics Committee of the Medical Council of North Rhine, Germany. Written informed consent was obtained prior to the study from all subjects. The details of the study design and implementation have been previously described.[14] Briefly, six healthy male subjects (mean ± SD: age: 41 ± 5 yr) participated in a randomized, double-blinded cross-over design study with two conditions: 29 h of 12° HDT with ambient air and 29 h of 12° HDT with 0.5% CO_2, with measurements of the IJ vein taken after 26 h HDT. Each of the two HDT campaigns was separated by 1 wk. Prior to each campaign, subjects underwent baseline data collection, including tilt-table testing. Further, the subjects' exposure to atmosphere was counterbalanced with respect to the order of exposure by campaign. Subjects A, B, and C had 12° HDT + 0.5% CO_2 in the first campaign, whereas subjects D, E, and F had 12° HDT + 0.5% CO_2 in the second campaign. The presented results represent a subset of measurements from a larger study.[6,20]

Procedure

Ultrasound imaging of the right IJ vein was performed by a single, experienced operator with a linear 7–10 MHz probe (Sonosite M-Turbo, Bothell, WA). Neck length was measured from the superior clavicular to the inferior mandibular region on the right side. The neck length was then divided into four equal intervals to mark the points for measurement for the CSA (**Fig. 1**). Two consecutive manual measurements of the IJ vein CSA were made at each interval, with the average used for statistical analysis. To obtain the IJ vein volume, each of the four CSAs were then summed and multiplied by the neck length. Subjects maintained a neutral straight-ahead head position throughout the testing procedure, and CSA images were captured at the end of expiration.

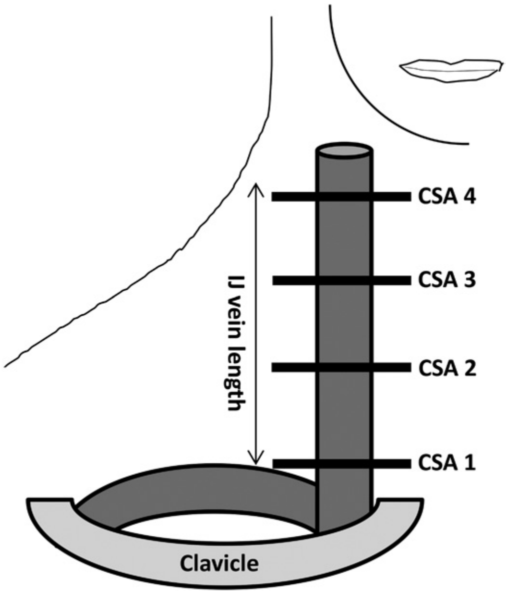

Fig. 1. Internal jugular vein cross-sectional area (CSA) was measured at four equally spaced locations along the vein length from the supraclavicular to the submandibular region. Internal jugular vein volume was calculated as the sum of the three interval volumes (i.e., CSA 1 to 2, CSA 2 to 3, and CSA 3 to 4).

During baseline tilt table testing, subjects were placed on an automated tilt table and rested for 5 min in the supine position to allow for hemodynamic stabilization. Then IJ vein CSA was measured at the four intervals during six different body positions: 0°, 6°, 12°, 18°, 24°, and 30° HDT in sequential order (i.e., 0° then 6°…30°). At least 3 min were given for hemodynamic stabilization after changing the body angle before measuring the IJ vein segments. The IJ vein was measured only in the 12° HDT position after 26 h of HDT bed rest during each campaign (12° HDT + 0.5% CO_2 and 12° HDT + ambient air).

Total hemoglobin, blood volume, and plasma volume were determined before HDT bed rest using the optimized carbon monoxide (CO) rebreathing technique.[17] In brief, after an initial resting period in the supine position for 20 min, a baseline 2.6-ml EDTA blood sample was obtained from an antecubital vein (S-Monovette, Sarstaedt AG & Co., Nümbrecht, Germany) and was immediately placed on ice for subsequent analyses. Basal CO concentration in the exhaled air was also determined (Pac 7000 CO Analyzer, Draeger, Germany). The subjects were then connected to a Krogh spirometer (Student Spirometer, ZAK, Germany) and began the rebreathing procedure: after a complete exhalation, subjects completely inhaled from a ~3-L bag containing pure oxygen. A bolus of 70 ml CO was simultaneously applied ($1.0\ \mathrm{ml} \cdot \mathrm{kg}^{-1}$ body mass for trained men, $0.8\ \mathrm{ml} \cdot \mathrm{kg}^{-1}$ body mass for untrained men with less than 2 h of physical activity per week). After an initial 10-s breath hold, subjects then breathed through the mouthpiece for 2 min of CO-rebreathing. Exhaled CO concentration was again assessed 2 min after termination of rebreathing and, 5 min after termination of rebreathing, a second 2.6-ml EDTA blood sample was obtained. Blood gas and blood count analyses were then immediately performed via routine clinical work (ABL 520, Radiometer, Brønshøj, Denmark, and ABX Pentra 60 Hematology Analyzer, Horiba ABX SAS, Montpellier Cedex, France).

Unlike long-duration bed rest studies where total hemoglobin is normally assessed at the end of the bed rest campaign, we anticipated that total hemoglobin content would remain unaltered in this short-duration HDT study. Conversely, we did expect some confounding effects of the CO-rebreathing on spirometry assessment. Hence, changes in plasma and blood volume were assessed based on blood count values of hematocrit and hemoglobin at the respective successive days while using a total hemoglobin content that was corrected for the successive blood draws. Blood parameter measurements were obtained during ambulatory baseline conditions the morning before HDT exposure and again after 4 h, 24 h, and 28.5 h of 12° HDT bed rest.

Statistical Analysis

For baseline tilt table testing, linear mixed effect (LME) models were created with HDT angle as a main effect and subject as a random effect. Post hoc analyses with difference of least square means (Tukey-Kramer, adjusted *P*-values) were then implemented for further comparison. For the bed rest portion of the study, LMEs were constructed with atmosphere (ambient vs. CO_2) and time (baseline vs. HDT) as main effects, allowing for an atmosphere-time interaction, and subject as a random effect. Further, correlation analyses with random intercepts were performed between IJ vein CSA 1–4 and volume with blood volume, plasma volume, age, body mass index, height, and weight. Data are presented as mean ± SD unless otherwise noted. Unadjusted *P*-values < 0.05 were considered significant. Statistical analysis was performed using SAS statistical software (version 9.4, Cary, NC).

RESULTS

During baseline tilt-table testing, a significant main effect of HDT angle was found for CSA interval 1 [$F(5,60) = 10.09$, $P < 0.001$], interval 2 [$F(5,60) = 8.47$, $P < 0.001$], interval 3 [$F(5,59) = 13.36$, $P < 0.001$], and interval 4 [$F(5,60) = 4.24$, $P = 0.002$] as well as for IJ vein volume [$F(5,60) = 26.33$, $P < 0.001$]. At interval 1, the supraclavicular region, IJ vein CSA was significantly increased from 0° baseline during 12° ($P = 0.006$), 18° ($P < 0.001$), 24° ($P < 0.001$), and 30° HDT ($P < 0.001$) with a trend toward increased CSA at 6° HDT ($P = 0.072$). At interval 2, IJ vein CSA significantly increased from 0° baseline to 6° ($P = 0.049$), 18° ($P < 0.001$), 24° ($P < 0.001$), and 30° HDT ($P < 0.001$) and trended toward an increase during 12° HDT ($P = 0.08$). At intervals 3 and 4, IJ vein CSA increased from 0° baseline during all HDT angles (**Fig. 2A**). In addition, IJ vein volume increased from 0° baseline during all HDT conditions ($P < 0.001$, **Fig. 2B**).

During the second part of the experiment, after HDT and atmospheric conditioning, IJ vein CSA at intervals 1–4 and volume were measured at 12° HDT after 26 h exposure to 12° HDT bed rest with either ambient air or 0.5% CO_2 (**Table I**). No significant main effects of time[$F(1,15) = 0.79$, $P = 0.39$] or atmosphere [$F(1,15) = 1.74$, $P = 0.2$] were found for CSA interval 1. At CSA interval 2, there was a significant atmosphere*time interaction [$F(1,15) = 6.88$, $P = 0.019$] and a significant main effect of time [$F(1,15) = 9.2$, $P = 0.008$], with a small increase in CSA from baseline to HDT in the presence of ambient air ($P = 0.0057$), but not with CO_2 ($P = 0.99$). At CSA interval 3, there was a significant main effect of time [$F(1,14) = 10.27$, $P = 0.006$], decreasing during 26-h HDT compared to baseline in the presence of increased CO_2 ($P = 0.019$) and a trend toward decreasing CSA with ambient air ($P = 0.086$). At CSA interval 4, there was a significant effect of time [$F(1,15) = 5.08$, $P = 0.04$], however, with no significant change in CSA during exposure to ambient air or 0.5% CO_2. IJ vein volume had a trend toward significance for the atmosphere*time interaction [$F(1,15) = 3.94$, $P = 0.066$], with a trend toward decreased volume from baseline to HDT during CO_2 exposure ($P = 0.06$). Furthermore, when comparing the IJ vein parameters during 26-h bed rest between atmospheric conditions, there was a significant difference in CSA only at interval 2 between the two atmospheric conditions ($P = 0.034$), but not for the calculated IJ volume ($P = 0.059$).

Further analysis of IJ vein CSA at levels 1–4 and volume revealed no significant correlation with plasma volume or blood volume measured after 28.5 h HDT, body mass index, age, or weight. However, height showed a negative association at CSA interval 2 ($F = 7.82$, $P = 0.01$), CSA interval 3 ($F = 4.92$, $P = 0.04$), and IJ volume ($F = 7.23$, $P = 0.015$).

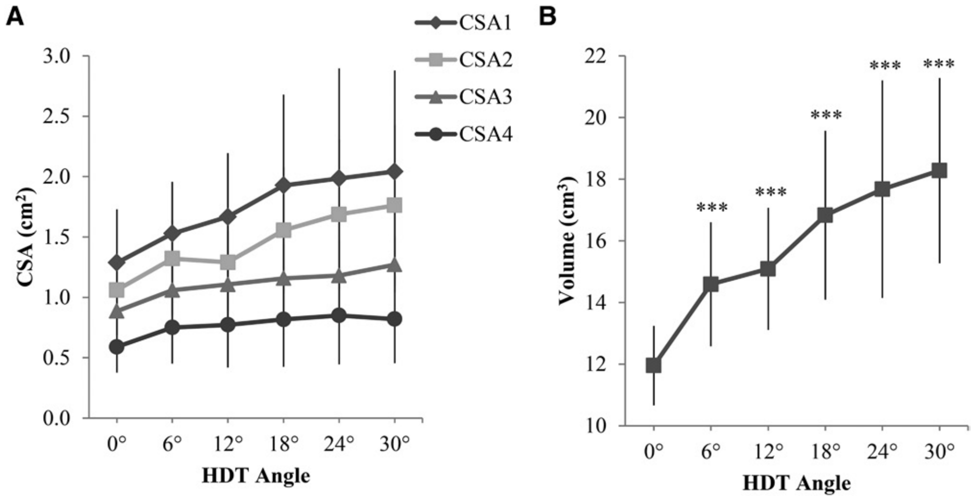

Fig. 2. A) Internal jugular vein cross-sectional area (CSA) at four equally spaced locations along the vein and B) internal jugular vein volume during various degrees of head-down tilt (HDT). Data presented as mean ± SD; change from 0° baseline designated by *** $P < 0.001$.

Table I. Internal Jugular (IJ) Vein Cross-Sectional Area (CSA) at Intervals 1, 2, 3, and 4 and IJ Vein Volume During 12° Head-Down Tilt (HDT) at Prebed Rest Baseline Conditions (Ambulatory, Ambient Air Exposure) and After 26 h of 12° HDT Bed Rest with Either Ambient Air or 0.5% CO_2 Atmosphere.

	12° HDT (BASELINE PREAMB)	26-h 12° HDT + AMB	12° HDT (BASELINE PRE-CO_2)	26-h 12° HDT + CO_2
CSA-1 (cm^2)	1.68 ± 0.55	1.93 ± 0.87	1.65 ± 0.46	1.63 ± 0.51
CSA-2 (cm^2)	1.23 ± 0.2	1.59 ± 0.4**	1.35 ± 0.28	1.38 ± 0.32
CSA-3 (cm^2)	1.11 ± 0.21	0.95 ± 0.35$^{\#}$	1.10 ± 0.21	0.87 ± 0.26*
CSA-4 (cm^2)	0.79 ± 0.37	0.65 ± 0.28	0.75 ± 0.30	0.60 ± 0.25
IJ volume (cm^3)	14.45 ± 1.81	15.18 ± 3.62	15.38 ± 2.26	13.84 ± 1.88$^{\#}$

Data presented as mean ± SD.
Amb = ambient air; change from prebed rest baseline designated by **$P < 0.01$, *$P < 0.05$, $^{\#}P$ 0.05–0.1.

There was a significant main effect of time on plasma volume [$F(3,38) = 6.67$, $P = 0.001$] and blood volume [$F(3,38) = 2.93$, $P = 0.046$], both decreasing from baseline during HDT, with more prominent changes in plasma volume (**Table II**). There was no main effect of atmosphere for plasma volume [$F(1,38) = 0.99$, $P = 0.3$] or blood volume [$F(1,38) = 1.75$, $P = 0.19$], nor a significant atmosphere-time interaction for either variable ($P > 0.9$).

DISCUSSION

Overall, we found IJ vein CSA and volume to increase with progressively steeper HDT angles from 0° up to 30° HDT during the baseline tilt table testing, with more prominent changes in the supraclavicular sections of the IJ vein. Additionally, the change in IJ vein CSA and volume did not increase in a linear manner, but began to reach a plateau toward the steeper HDT angles. Our study was not designed to assess the limits of IJ vein CSA, but this would be interesting to evaluate in future studies. For the purposes of the spaceflight environment we believe our HDT range covered the expected normal physiological range experienced by astronauts, except possibly during transient Valsalva maneuvers.

Exposure to 26 h of 12° HDT bed rest and atmospheric CO_2 during HDT bed rest had little additional effect on the IJ vein compared to 12° HDT during baseline tilt table testing. Blood and plasma volume both decreased with exposure to HDT bed rest; however, atmospheric conditioning during bed rest had no further effect and the changes did not correlate with changes in IJ vein CSA or volume. There was no significant difference in IJ vein volumes by atmosphere, consistent with the lack of effect of 0.5% CO_2 on the systemic measurements of plasma and blood volume. Additionally, given the expected decrease of plasma and blood volume with time in HDT, but an absence of decreasing IJ vein CSAs or volume, it is probable that IJ vein CSA or volume may not be a reliable indicator of systemic fluid status in this ground-based analog.

The IJ vein has been studied in a variety of ground-based spaceflight analogs, including HDT bed rest and dry immersion, as well as in microgravity. Previous studies have noted increased IJ vein diameter and CSA during HDT;[3,18] however, IJ vein CSA is rarely measured in multiple locations across the vessel. Increased IJ vein size during HDT is likely due to the great compliance of the venous system and the increased hydrostatic pressure gradient. Interestingly, measurements of the IJ vein closer to the supraclavicular level showed greater increases in CSA compared to the submandibular levels. This may be due to natural anatomical differences between these two parts of the IJ vein, as the vessel lumen increases when moving down the vessel from the skull.[21] In our study, we did not see any significant effects of atmosphere on the IJ vein volumes at the 12° HDT angle at 24 h, but several of the individual CSAs had differences by atmosphere: CSA 2 and 3 in the ambient atmosphere, and CSA 3 in the CO_2 atmosphere. Given that the overall IJ vein volumes did not significantly change due to atmosphere, it would be speculative to conclude that the differences for individual CSAs are physiological in nature. However, it raises an important issue for further studies that perhaps a continuous measurement of the entire length of the IJ vein rather than extrapolating the volume from several CSAs may improve the reliability of the measurement. In space, IJ vein volume has been found to increase 178% and 225% after 15 d and 4.5–5 mo on the ISS, respectively.[2] In addition, during 2-h exposure to dry immersion, an analog of microgravity, IJ vein volume has been found to increase 2 ml, signifying a cephalad fluid shift during neutral buoyancy.[1]

Decreased plasma volume during bed rest, a well described phenomenon,[4] did not correlate with changes in IJ vein CSA or volume. Notably, we observed a negative association between subject height and IJ vein CSA

Table II. Total hemoglobin (Hb), blood volume and plasma volume at baseline and after 4 h, 24 h and 28.5 h exposure to 12° HDT with either ambient air or 0.5% CO_2.

TIME	ATMOSPHERE	TOTAL HB (g)	BLOOD VOLUME (ml)	PLASMA VOLUME (ml)
Baseline	Amb	873 ± 184	6513 ± 1169	3975 ± 716
4 h HDT	Amb	870 ± 184	6344 ± 1214	3824 ± 730
24 h HDT	Amb	865 ± 184	6209 ± 1192	3676 ± 710*
28.5 h HDT	Amb	862 ± 184	6117 ± 1261$^{\#}$	3587 ± 765**
Baseline	Amb (pre-CO_2)	856 ± 101	6344 ± 716	3862 ± 495
4 h HDT	CO_2	843 ± 101	6281 ± 691	3826 ± 488
24 h HDT	CO_2	839 ± 101	6042 ± 644	3587 ± 407*
28.5 h HDT	CO_2	836 ± 101	5984 ± 715$^{\#}$	3530 ± 442*

Data presented as mean ± SD; change from respective baseline designated by **$P < 0.01$, *$P < 0.05$, $^{\#}P$ 0.05–0.1.
Amb = ambient air.

which was contrary to our expectations. We hypothesized that increased height would translate into increased hydrostatic pressure for a given HDT angle, and, thus, increased IJ CSA and volume. The negative association could be related to an increased length of the IJ vein in a taller individual and, thus, venous blood volume may be distributed over a longer length of the vein. Therefore, in each of the given measured sections, the CSA would be smaller for a taller individual. The other possibility is that the greater degree of hydrostatic pressure for taller subjects may have triggered more vasoconstriction on the arterial side, which then secondarily would decrease cerebral blood flow to a greater degree and thus decrease venous outflow and measured CSAs.

We acknowledge the following limitations in our study. First, the sample size is relatively small and only included men as this was primarily a pilot study. However, we implemented multiple repeated measurements for data collection. Second, we only measured the right IJ vein, therefore our results may have differed had we selected both IJ veins or the left IJ vein. It is known based on anatomical study of healthy individuals that the right IJ vein is either dominant or codominant in the majority of people;[9,19] thus, for practical purposes related to time constraints, we chose to measure the right side. Third, our method only measured the IJ vein CSAs and volume based on a column from the supraclavicular to the submandibular region. It is possible that a method taking into account the entire length of the IJ vein from the origin to the confluence may be more reliable; however, this would not be practical with ultrasound based methods.

HDT during baseline tilt table testing produced consistent increases in the IJ vein CSA and volume with steeper HDT. Of note, the changes for CSA 1 and 2 were more pronounced than those for CSA 4 (Fig. 2A). We believe this may be related to the intrinsic compliance and/or anatomical properties of the IJ vein given that the baseline CSA in supine position was larger for CSA 1 and 2 compared to CSA 3 and 4. Interestingly, we observed a trend of decreasing IJ volume with atmospheric CO_2 during short-duration HDT bed rest. The implications of this are uncertain and should be explored in a larger prospective study with simultaneous intracranial and systemic venous volume measurements. In the SPACECOT study, we obtained MRI-based cerebral blood flow measurements showing a significant main effect of decreasing cerebral blood flow (17–20%) from baseline with 26.5 h of 12° HDT, but this did not differ by atmosphere. Unfortunately, due to time limitations we did not obtain volumetric data on the dural venous sinus volumes.[6] Finally, the IJ vein CSAs and volume did not correlate with systemic measurements of plasma or blood volume, which may indicate that the determinants are related to local rather than systemic influences.

ACKNOWLEDGMENTS

We would like to acknowledge the supporting SPACECOT investigators group (in alphabetical order): Mathias Basner, Christine Becker, Jonathan Clark, Rahul Damani, Wolfgang Doering, Christian Dohmen, Petra Frings-Meuthen, Peter Gauger, Darius Gerlach, Olga Hand, Khader Hasan, Elfriede Huth, Bernd Johannes, Larry Kramer, Gabriele Kraus, Ulrich Limper, Uwe Mittag, Klaus Muller, Jad Nasrini, Ben Niederberger, Dirk Poddig, Matthias Putzke, Jörn Rittweger, Martina Sagner, Irmtrud Schrage-Knoll, Wolfram Sies, Claudia Stern, Henning Stetefeld, Gary Strangman, Annette von Waechter, Tobias Weber, and Martin Wittkowski. This study would not have been possible without the encouragement and support of Rupert Gerzer, Julie Do, and Jeff Sutton. This study was supported by the National Space Biomedical Research Institute (NSBRI) through NASA NCC 9-58, Baylor College of Medicine Center for Space Medicine and the German Aerospace Center (DLR) Institute of Aerospace Medicine.

Karian Marshall-Goebel and Brian Stevens contributed equally.

Authors and affiliations: Karina Marshall-Goebel, Ph.D., Massachusetts General Hospital/Harvard Medical School, Charlestown, MA; Brian Stevens, B.S., Chethan Venkatasubba Rao, M.D., Joe I. Suarez, M.D., Eusebia Calvillo, R.N.Haleh Sangi-Haghpeykar, Ph.D., Dorit B. Donoviel, Ph.D., and Eric M. Bershad, M.D., Baylor College of Medicine, Houston, TX; Philippe Arbeille, M.D., Ph.D., University of Tours, Tours, France; and Karina Marshall-Goebel, Ph.D., and Edwin Mulder, Ph.D., Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany.

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