Elevated End-Tidal Pco₂ During Long-Duration Spaceflight

Richard L. Hughson; Nicholas J. Yee; Danielle K. Greaves

BACKGROUND: Elevated ambient Pco₂ in the International Space Station (ISS) has been cited as a potential contributor to the vision impairment intracranial pressure syndrome (VIIP), a significant health risk for astronauts during long-duration space missions. The elevation in ambient Pco₂ is rather modest and normal respiratory compensation could minimize the impact on arterial Pco₂.

METHODS: In nine male astronauts, breaths measured prior to a rebreathing maneuver were examined to assess inspired and end-tidal Pco₂ during upright seated preflight and in-flight conditions.

- **RESULTS:** Inspired Pco_2 increased from preflight baseline ($0.6 \pm 0.1 \text{ mmHg}$) to in flight ($3.8 \pm 0.4 \text{ mmHg}$). End-tidal Pco_2 also increased from preflight baseline ($36.0 \pm 3.2 \text{ mmHg}$) to in flight ($42.1 \pm 3.7 \text{ mmHg}$). The difference between end-tidal Pco_2 comparing in flight to preflight ($6.1 \pm 1.6 \text{ mmHg}$) was greater than the difference between inspired Pco_2 comparing preflight to in flight ($3.3 \pm 0.5 \text{ mmHg}$).
- **DISCUSSION:** The greater increase in end-tidal vs. inspired Pco_2 might reflect alveolar hypoventilation due to differences in ventilatory control with spaceflight. These data suggest that further studies should focus on arterial Pco_2 and acid-base balance to determine if CO_2 dilates cerebral and retinal vessels and might contribute to the incidence of VIIP in astronauts.

KEYWORDS: astronaut, respiratory control, arterial Pco₂, vision impairment intracranial pressure syndrome.

Hughson RL, Yee NJ, Greaves DK. Elevated end-tidal Pco2 during long-duration spaceflight. Aerosp Med Hum Perform. 2016; 87(10):894–897.

The chronic elevation of atmospheric CO₂ on the International Space Station (ISS) has been proposed as a potential contributor to vision impairment intracranial pressure syndrome (VIIP), a significant health risk for astronauts during long-duration spaceflight.⁴ VIIP is associated with several symptoms, including vision changes with hyperopic shifts, disc edema, posterior globe flattening, choroidal folds, cotton wool spots, and increased optic nerve sheath diameter.^{4,15}

The relatively small increase in PCO_2 of inspired air from about 0.3 mmHg on Earth to approximately 3-4 mmHg on $ISS^{7,8,16}$ might be expected to have minimal impact on arterial PCO_2 based on observations in ground-based studies^{3,5} and previous reports of end-tidal PCO_2 ($P_{ET}CO_2$) from short- and long-duration spaceflights^{10–12} or submarine simulations.² During short-duration space shuttle flights, $P_{ET}CO_2$ was not increased on the first Space Lab Life Sciences flight, but increased 4.5 mmHg on the second mission as inspired CO_2 was also elevated. The ambient PCO_2 during shuttle missions could be controlled below 0.1%; this differs from the current ISS environment. With longer duration flights on ISS, $P_{ET}co_2$ was reported to increase 2.3 mmHg,¹² but it was not known if this was a consequence of elevated inspired Pco_2 or altered ventilatory control.¹¹

Given the potential for CO_2 to contribute to VIIP through its actions as a dilator of cerebral and retinal vessels, it is appropriate to examine changes in $P_{ET}CO_2$ during long-duration spaceflight. In the current study, we had the opportunity to directly measure CO_2 for several breaths prior to a rebreathing maneuver to assess cardiac output during preflight seated baseline and on the ISS. We tested the hypothesis that $P_{ET}CO_2$ would be elevated during spaceflight.

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This manuscript was received for review in February 2016. It was accepted for publication in June 2016.

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METHODS

Nine male astronauts (ages 37–53 yr, height 168–185 cm, weight 70–92 kg) volunteered to participate in the study known by the operational name "BP Reg" between December 2012 and May 2015. Each astronaut gave informed consent to a proposal that was reviewed and approved by five autonomous Ethics Review Boards: the Office of Research Ethics at the University of Waterloo, the NASA Institutional Review Board, the NASA Human Research Medical Review Board, the Japanese Space Agency Medical Review Board (NASA MPA 7116301606HR; FWA 00,019,876). The experiments conformed to the guidelines of the Declaration of Helsinki.

Participants did not consume alcohol, blood pressure medications, over-the-counter cold medications, or allergy medications within 24 h prior to the test, they did not exercise prior to the testing session, and they did not eat or consume caffeine within 2 h of testing. Preflight testing occurred at Johnson Space Center approximately 2-3 mo prior to launch. Fractional concentrations of oxygen and CO₂ were recorded at the mouth by infrared photo-acoustic and magneto-acoustic multigas analyzers while breathing ambient air through a mouthpiece with nose clip attached (Pulmonary Function System, Danish Aerospace Company, Odense, Denmark, and European Space Agency, Paris, France). The analyzer was calibrated prior to each test with precision measured tanks using an automated sampling routine. Fractional concentrations were converted to partial pressures for inspired conditions using ambient barometric pressure, temperature, and water vapor recorded by the device and, for expired conditions, incorporating corrections for body temperature and pressure with saturated vapor pressure. Analyzed breaths were obtained from a period of normal breathing that occurred prior to three separate rebreathing maneuvers, separated by 5 min, to measure cardiac output. P_{ET}co₂ was determined from full breaths prior to the start of a rebreathing maneuver (Fig. 1). In-flight testing occurred between flight days 119-166. The same procedure was followed with the flight models of the same equipment for gas analysis.

Statistical analysis was completed with paired *t*-tests when comparing preflight to in flight for inspired and end-tidal PCO₂, and for differences in PCO₂ after testing for normality (SigmaPlot version 12.5). Significance was accepted at P < 0.05 and data are presented as mean \pm SD.

RESULTS

Inspired Pco₂ increased from preflight values (0.6 ± 0.1 mmHg) to in flight [3.8 ± 0.4 mmHg, t(8) = -21.391, P < 0.001, **Fig. 2**]. P_{ET}co₂ also increased from preflight (36.0 ± 3.2 mmHg) to in flight [42.1 ± 3.7 mmHg, t(8) = -11.352, P < 0.001, Fig. 2]. The difference between inspired Pco₂ when comparing preflight to in flight (3.3 ± 0.5 mmHg) was less than the difference between preflight to in flight P_{ET}co₂ [6.1 ± 1.6 mmHg, t(8) = -4.743, P = 0.001].



Fig. 1. Representative breaths showing Pco_2 throughout the respiratory cycle are shown for one astronaut preflight seated rest (dotted line) and in flight (solid line), with evident upward shift for in-flight conditions. The peak value at the end of each breath was taken as the end-tidal Pco_2 .

DISCUSSION

The 6 mmHg increase in $P_{ET}CO_2$ found in these astronauts during long-duration spaceflight on the ISS was greater than observed previously with short-duration flights¹⁰ or in the earlier missions to ISS.¹² The higher in-flight $P_{ET}CO_2$ might have resulted from long-term exposure to elevated inspired PCO_2 in flight. Increased $P_{ET}CO_2$ is consistent with an elevated arterial PCO_2 that might contribute to cerebral and retinal vascular dilation increasing blood flow and potentially affecting blood volume and fluid pressures in the head and eye, with consequences for VIIP.

The mechanisms responsible for VIIP are still under investigation. The NASA Summit Report on VIIP suggested that elevated intracranial pressure was the primary candidate, but that vision changes occurred in astronauts without presence



Fig. 2. Individual values for inspired and end-tidal Pco_2 are shown for preflight conditions (black circles, solid lines) and in flight (white circles, dashed lines). Offset symbols (squares) with error bars represent mean \pm SD. Statistical *P*-values are for comparisons between preflight and in flight.

of headache, which is classically present with elevated intracranial pressure on Earth. Recently, it has been suggested that intracranial pressure might not be elevated above supine values on Earth, but that lack of diurnal variations could be relevant.⁹ Since VIIP has not been found in all astronauts, there are probably other factors related to anatomical, physiological or genetic differences, or external factors such as diet and ambient Pco₂,^{4,7} or a pressure differential between intraocular and intracranial pressures.¹⁵

The elevation in ambient Pco₂ on ISS to about 3–4 mmHg is relatively small and normally not considered to be a burden to respiratory control where it is anticipated that increased inspired Pco₂ is met by an increase in alveolar ventilation to maintain arterial PCO₂ relatively constant. For example, a brief 15-min increase in inspired Pco₂ to 7–14 mmHg in carefully controlled laboratory studies resulted in less than 1 mmHg increase in arterial Pco₂.⁵ However, from longer duration studies with greater elevations of inspired Pco₂, a different pattern emerges. A sustained 4-d elevation in inspired CO₂ to 2.49%, approximately 18 mmHg, was combined with a reduction in inspired oxygen to 16.73% in a simulation of a disabled submarine,² causing $P_{ET}CO_2$ to increase from 42.2 to 45.7 mmHg. A 23-d exposure to 1.2% inspired PCO₂ caused reduced ventilatory response to CO_2 with a 19.6% increase in $P_{ET}CO_2$ on day 2^3 and a 35% increase in cerebral blood flow velocity,¹⁴ but these variables returned toward normal by the 22nd day.

Cerebral blood flow velocity measured during spaceflight has revealed only small, variable changes.^{1,6} Similar to the 23-d CO_2 exposure study,¹⁴ Arbeille et al.¹ found an almost 20% increase in cerebral blood flow velocity and a reduction in the cerebrovascular resistance index in the first 2–4 d of spaceflight. However, with prolonged spaceflight there might be a reduction in cerebrovascular reactivity to CO_2 .¹⁶ Further, it is necessary to consider that a chronic change in PcO_2 might result in an adaptation of acid-base with a reduction in arterial bicarbonate to normalize pH. In such a case, cerebral blood flow velocity would also normalize to maintain cerebral tissue pH.

The data of the current study are preliminary and were obtained as part of another investigation that examined rebreathing cardiac output. Thus, a critical assumption was that measurement of several breaths of inspired and expired gases represent the chronic steady-state for respiratory control on ISS. We did not measure respiratory exchange ratio as an index of steady state conditions and the small decrease in P_{ET}CO₂ shown in Fig. 1 over successive breaths might reflect the imposed pattern of the rebreathing maneuver for cardiac output. This could contribute to the range of P_{ET}CO₂ values observed in flight (from 35.6 to 45.7 mmHg) as well as to the change in $P_{ET}CO_2$ from preflight to in flight (up to 8.7 mmHg higher in flight). Changes in P_{ET}CO₂ are used as a surrogate for changes in arterial Pco2.13 Changes in ventilation to perfusion ratio in the lungs could affect P_{ET}CO₂ to arterial PCO₂, but Prisk¹¹ reported only small changes in this variable. Also, the current study used seated rest as the baseline with values that were almost identical to those measured by Prisk et al.¹² in the standing posture. In the latter study, P_{ET}CO₂ increased 3 mmHg from standing to

supine, but there was no difference between supine posture and measurements on ISS. Thus, part of the 6 mmHg increase in the current study might simply reflect the upright to supine difference in normal gravity.

We have shown a rise in $P_{ET}CO_2$ in nine male astronauts living on ISS that was greater than anticipated based on previous laboratory research^{3,5} and spaceflight.¹¹ The findings reflect a change in ventilatory sensitivity to CO_2 during spaceflight that are important because of potential links to VIIP and should be confirmed in future research because of potential consequences for cerebral and retinal blood flow, and for cerebral and whole body acid-base balance. Careful longer duration measurements of the profile of expired PCO_2 or transcutaneous PCO_2 measurements might provide the required data that will enable an investigation into relationships between the magnitude of change in $P_{ET}CO_2$ and presence of symptoms of VIIP.

ACKNOWLEDGMENTS

The authors are grateful to the astronauts who dedicated themselves to the success of the BP Reg study. We received excellent support from the Danish Aerospace Company, CADMOS, and NASA. The Canadian Space Agency provided extensive technical support and funded the project through contract 9F053-111259.

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REFERENCES

- Arbeille P, Fomina G, Roumy J, Alferova I, Tobal N, Herault S. Adaptation of the left heart, cerebral and femoral arteries, and jugular and femoral veins during short- and long-term head-down tilt and spaceflights. Eur J Appl Physiol. 2001; 86(2):157–168.
- Castellani JW, Francis JR, Stulz DA, DeLany JP, Hoyt RW, et al. Body fluid regulation in a simulated disabled submarine: effects of cold, reduced O₂, and elevated CO₂. Aviat Space Environ Med. 2005; 76(8):753–759.
- Elliott AR, Prisk GK, Schöllmann C, Hoffmann U. Joint NASA-ESA-DARA study - Part two: hypercapnic ventilatory response in humans before, during, and after 23 days of low level CO₂ exposure. Aviat Space Environ Med. 1998; 69(4):391–396.
- Fogarty JA, Otto C, Kerstman E, Oubre C, Wu J. The Visual Impairment Intracranial Pressure Summit Report. NASA / TP- 2011–216160. Hanover (MD): NASA Center for AeroSpace Information; 2011.
- Forster HV, Klein JP, Hamilton LH, Kampine JP. Regulation of PaCO₂ and ventilation in humans inspiring low levels of CO₂. J Appl Physiol. 1982; 52(2):287–294.
- Iwasaki Ki, Levine BD, Zhang R, Zuckerman JH, Pawelczyk JA, et al. Human cerebral autoregulation before, during and after spaceflight. J Physiol. 2007; 579(3):799–810.
- Law J, Van Baalen M, Foy M, Mason SS, Mendez C, et al. Relationship between carbon dioxide levels and reported headaches on the International Space Station. J Occup Environ Med. 2014; 56(5):477–483.
- Moore AD, Downs ME, Lee SMC, Feiveson AH, Knudsen P, Ploutz-Snyder L. Peak exercise oxygen uptake during and following longduration spaceflight. J Appl Physiol. 2014; 117(3):231–238.
- Petersen LG, Petersen JCG, Andresen M, Secher NH, Juhler M. Postural influence on intracranial and cerebral perfusion pressure in ambulatory neurosurgical patients. Am J Physiol Regul Integr Comp Physiol. 2016; 310(1):R100–R104.

- Prisk GK, Guy HJB, Elliott AR, Paiva M, West JB. Ventilatory inhomogeneity determined from multiple-breath washouts during sustained microgravity on Spacelab SLS-1. J Appl Physiol (1985). 1995; 78(2):597–607.
- Prisk GK. Microgravity and the respiratory system. Eur Respir J. 2014; 43(5):1459–1471.
- Prisk GK, Fine JM, Cooper TK, West JB. Vital capacity, respiratory muscle strength, and pulmonary gas exchange during long-duration exposure to microgravity. J Appl Physiol. 2006; 101(2):439–447.
- Serrador JM, Hughson RL, Kowalchuk JM, Bondar RL, Gelb AW. Cerebral blood flow during orthostasis: role of arterial CO₂. Am J Physiol Regul Integr Comp Physiol. 2006; 290(4):R1087–R1093.
- Sliwka U, Krasney JA, Simon SG, Schmidt P, Noth J. Effects of sustained low-level elevations of carbon dioxide on cerebral blood flow and autoregulation of the intracerebral arteries in humans. Aviat Space Environ Med. 1998; 69(3):299–306.
- Zhang LF, Hargens AR. Intraocular/intracranial pressure mismatch hypothesis for Visual Impairment Syndrome in space. Aviat Space Environ Med. 2014; 85(1):78–80.
- Zuj KA, Arbeille P, Shoemaker JK, Blaber AP, Greaves DK, et al. Impaired cerebrovascular autoregulation and reduced CO₂ reactivity after long duration spaceflight. Am J Physiol Heart Circ Physiol. 2012; 302(12):H2592–H2598.