Risk of Nominal Acute and Chronic Ambient Carbon Dioxide Exposure in Crewed Vehicles Leading to In-Mission Health Effects or Performance Decrements (CO_2 Risk)
(Revision D.1)

Human System Risk Board (HSRB)

HSRB CR SA-07566
Approved: 2/13/2025

Risk Custodian Team

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Risk Record

- This package:
  - Provides operational evidence since 2021 and new evidence reported in the scientific literature
  - Provides new concerns
    - Orion's Laser Air Monitor is not validated
    - Orion's CO_2 and Humidity Control beds are degrading
    - Physiological impacts of Exploration Atmospheres altered pressure/O_2 with elevated ambient CO_2
  - Provides update to the Lunar Orbital Short Ops design reference mission (DRM) risk posture

This information was previously reviewed/dispositioned at:

Meeting	Date	Outcome/Direction
SMOCB & BRESCB	10/28/24	Approved
MOG	11/5/24	Informational
HSRB	11/7/24	Approved

Contents

1. Risk Title and Statement

- **Risk Title:** Risk of Nominal Acute and Chronic Ambient Carbon Dioxide Exposure in Crewed Vehicles Leading to In-Mission Health Effects or Performance Decrements

- **Risk Statement:** Given that average cabin CO_2 levels in spacecraft are maintained above ambient terrestrial levels with routine occurrence of short-term spikes and that the correlation between the cabin average and actual crew exposures remains unknown, there is a possibility that short-term and long-term CO_2 exposures will adversely impact crew health and performance.

2. Risk History

Item	Date	Outcome/Status
HSRB Risk Presentation	02/13/2025	Decisional – CR SA-07566 HSRB DAGtionary Updates and DAG Corrections; CR approved with modifications. Rev D.1
HSRB Risk	12/16/2024	Risk of Nominal Acute and Chronic Ambient Carbon Dioxide Exposure in Crewed Vehicles. Unanimous concurs among reviewers, approved out-of-board. (Rev. D)
HSRB Risk Presentation	11/07/2024	Informational – request CR Kickoff to update Risk (Rev. D)
HSRB Risk Presentation	5/11/2022	Decisional – CR SA-05096 HSRB Directed Acyclic Graphs Errata Changes; CR Approved out of board (Rev C.1)
HSRB Risk Presentation	9/9/2021	Decisional – CR Approved with Mods; Risk of Nominal Acute and Chronic Ambient Carbon Dioxide Exposure in Crewed Vehicles (Rev. C)
Risk Evaluated via CR	6/25/2021	CR SA-04044 Evaluation period ended 7/15/2021
HSRB Risk Presentation	6/17/2021	Informational – CR Kickoff to update Risk (Rev. C)
HSRB Risk Presentation	11/1/2018	Decisional – CR Approved with Mods
Risk Evaluated via CR	9/11/2018	Decisional – To update risk (Rev. B)
ECLSS SMT Presentation	3/8/2018	Informational – CO2 Scrubbing Technology to meet proposed standard
HMTA Recommendation	2/8/2018	Informational – Board agrees to add the 2mmHg for a CO2 Standard value to the NASA-STD-3001, Vol. 2, Rev B CR
HSRB Risk Presentation	5/18/2017	Informational – Risk scheduled "yearly" updates to include new evidence
Risk Evaluated via CR	8/19/2013	Decisional – Approved with Mods (Rev. A)
HSRB Risk Presentation	7/31/2013	Informational – Incorporate: 1. Chronic Exposure data 2. Results from Crew Symptoms and CO2 on ISS Analysis to package and submit CR for evaluation
Risk Evaluated via CR	9/3/2010	Decisional – Approved with Mods (Baseline)
HSRB Risk Presentation	8/25/2010	Informational – Content reviewed by the HSRB. Approval for release via out-of-board CR

3. Executive Summary

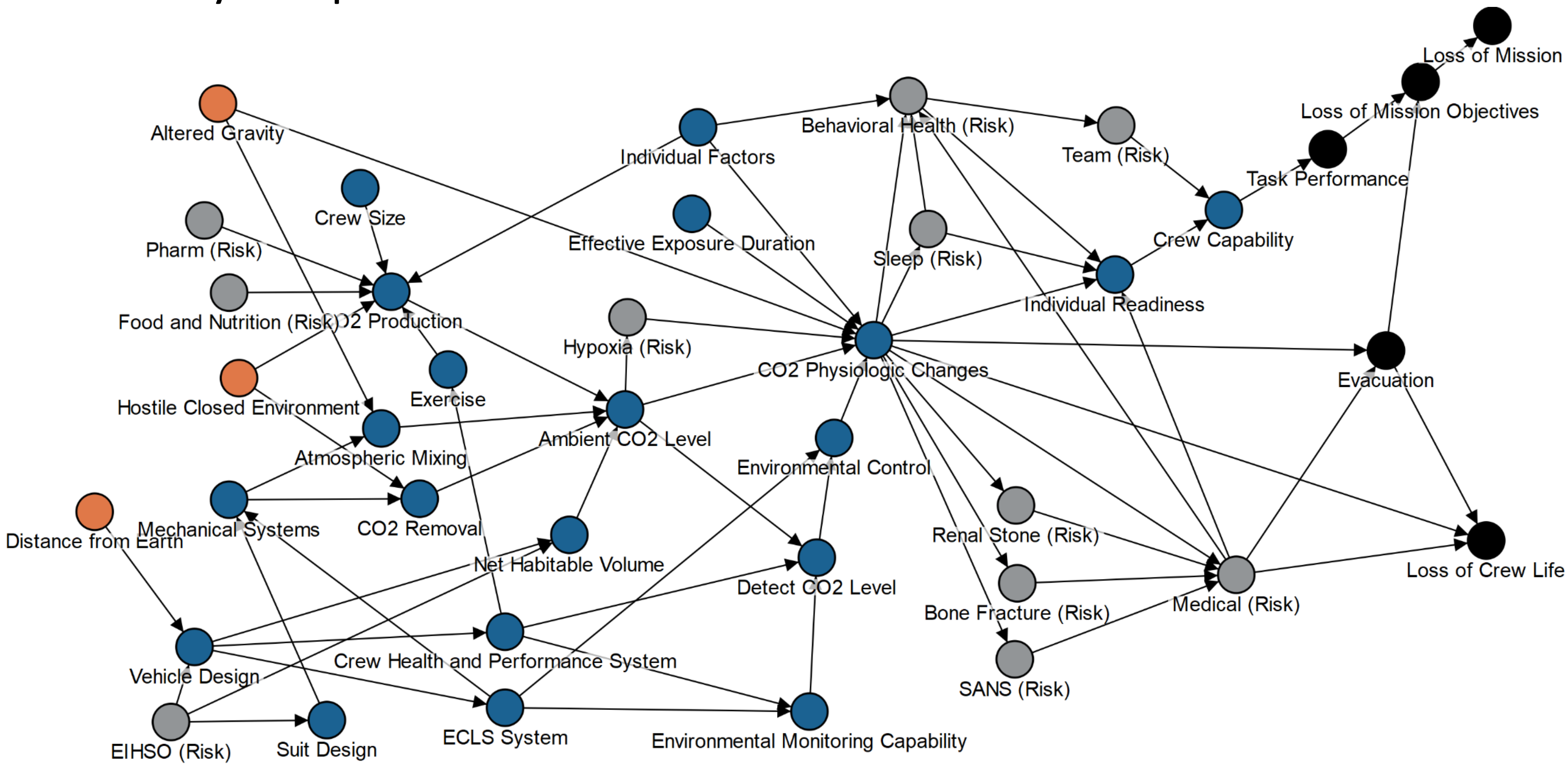
- The current NASA standard for CO_2 (NASA Standard 3001, Volume 2, Rev. D) limits the average one-hour CO_2 partial pressure in the habitable volume to no more than 3 millimeters of mercury (mmHg). The use of 1-hr average level is intended reduces the number and magnitude of spikes that would occur with averages reported each minute. However, programmatic constraints result in less conservative requirements and operational rules.

- Data continue to indicate that this standard is adequate because reported symptoms of toxicity, e.g., headache, are limited to some (sensitive) crewmembers and the effects are reversible.

- A possibility exists that spikes and swings in CO_2 levels and the nominal elevated background levels of CO_2 in the spacecraft (relative to indoor and outdoor terrestrial levels) could adversely impact crew health and performance and should be systematically evaluated. For example, crewmembers could be exposed to higher levels of CO_2 if environmental control and life support (ECLS) system fails during a technical demonstration, and when they work in front of the microgravity sciences glovebox for several hours or in Crew quarters/crew alternate sleep accommodation.

- Because evidence is lacking on the correlation between average CO_2 levels in the cabin and crew inhalational exposures, this should be systematically evaluated.

4. Directed Acyclic Graph – DAG



Directed Acyclic Graph – DAG (Narrative)

- The CO_2 concentration in the closed spacecraft environment is a balance between production (primarily, output from the crewmembers) and removal by the ECLS System.

- When the balance of production and removal is impacted by limited vehicle capability (limited ECLS system mass/power, for example) or production increases (when crewmembers exercise, for example), the CO_2 concentration will increase and may result in several different physiological changes.

- Monitoring CO_2 levels in a vehicle is essential to track anomalies and possible outcomes. However, averaging at the cabin level is currently relied upon almost exclusively. Local or area CO_2 monitoring can be effectively achieved using both a carbon dioxide monitor and personal CO_2 monitors. However, periodic individual monitoring (inspired CO_2, for example) is not currently available nor is a standardized method for assessing individual CO_2 exposure.

- CO_2 levels that are elevated significantly and/or chronically may lead to adverse mission outcomes, including loss of mission objectives or loss of mission (evacuation). Unexpectedly high acute levels may lead to loss of crew life, but the likelihood of this event is very low.

5. Likelihood and Consequence (LxC) Quick look

Previous (approved September 2021)

DRM Categories	Mission Type and Duration	LxC OPS	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit	Short (<30 days)	4x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	4x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
Lunar Orbital	Short (<30 days)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
Lunar Orbital + Surface	Short (<0 days)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
Mars	Preparatory (<1 year)	3x3	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Planetary (730-1224 days)	3x3	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring

Current (approved December 2024)

DRM Categories	Mission Type and Duration	LxC OPS	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit	Short (<30 days)	4x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	4x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
Lunar Orbital	Short (<30 days)	4x3	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
Lunar Orbital + Surface	Short (<0 days)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
	Long (30 d-1 yr.)	3x2	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring
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	Planetary (730-1224 days)	3x3	Accepted w/ Monitoring	1x1	Accepted w/ Monitoring

6. Risk Summary

Primary Hazard:

Hostile closed environment

Secondary Hazard(s):

Altered gravity Distance from Earth

Countermeasures in use:

Prevention

Human system integration processes (i.e., implementation of standards) and pre-flight training that teaches crewmembers how to identify symptoms of CO_2 toxicity

Monitoring

Cabin and local area monitoring of CO_2 levels and crewmember symptom monitoring

Intervention

Processes for reducing the levels of CO_2 in the vehicle, protective equipment, protocols for treating symptoms of CO_2 toxicity, operational procedures and responses to occurrences of CO2 levels above limits

Contributing Factors

Sources of CO_2 (from crew, medical oxygen regeneration, payloads, etc.) combined with individual factors, such as CO_2 retention, in balance with CO_2 scrubbing (vehicle design) and convection and ventilation.

Knowledge

Present State:

Adverse effects are mitigated by implementing current standards on the International Space Station (ISS); however, relationships between vehicle design, average CO_2 levels in the cabin, and crew inhalational exposures remain ill defined, and uncertainty exists regarding whether the same standard will remain protective when applied to other vehicles and DRMs. For example, if or when a crewmember experiences symptoms of CO_2 toxicity or elevated CO_2 levels occur on the ISS, additional resources can be employed to reduce the level of CO_2, however, these resources may be unavailable on future vehicles.

Gaps in knowledge

Spaceflight Operations (Ops): Accepted with monitoring: Monitoring of CO_2 levels should prevent symptoms of CO_2 toxicity. However, cabin level monitoring , which provides input to the ECLS system, at this time does not always mitigate symptom onset. Monitoring the level of CO_2 that the crewmembers inhale would provide data to better correlate cabin levels with crew inhalational exposure, which would support the goal of improved cabin ventilation and CO_2 scrubbing capabilities.

Long-term Health (LTH): Accepted with monitoring: On-going evaluation of cerebral changes, such as with magnetic resonance imaging (MRI), is needed to confirm no LTH consequences. However, no demonstrated LTH impacts of CO_2 toxicity have been reported in the literature or operational investigations.

General Assumptions

- Assume that NASA Standards 3001 have been met
- Countermeasures equivalent to current ISS countermeasures are in use

DRM Categories	Mission Type and Duration	Prior Assumptions (2021)	Current Assumptions (2024)
Low Earth Orbit (LEO)	Short (<30 days)	Excludes suited operations	Excludes suited operations
	Long (30 d-1 yr.)	Excludes suited operations	Excludes suited operations
Lunar Orbital	Short (<30 days)	Excludes suited operations	Excludes suited operations Average 6 seconds, max 30-sec comm delay
	Long (30 d-1 yr.)	Excludes suited operations	Excludes suited operations Average 6 seconds, max 30-sec comm delay
Lunar Orbital + Surface	Short (<30 days)	Excludes suited operations	Excludes suited operations
	Long (30 d-1 yr.)	Excludes suited operations	Excludes suited operations
Mars	Preparatory (<1 year)	Excludes suited operations	Excludes suited operations
	Planetary (730-1224 days)	Excludes suited operations	Excludes suited operations

- ***Current countermeasures in use:***
  - ***Monitoring****: Cabin and local area monitoring of CO_2 levels and crew symptom monitoring*
  - ***Prevention****: Human system integration processes (i.e., implementation of standards) and pre-flight training that teaches crewmembers how to identify symptoms of CO_2 toxicity*
  - ***Intervention****: Processes for reducing CO_2 levels in the vehicle, protective equipment, treatment protocols, ops procedures and responses*
- ***Anticipated countermeasures:***
  - ***Prevention:*** *improved modeling of cabin atmospheric dynamics to better inform future ECLS system design and operations*
  - ***Monitoring****: development of local area and inhalational CO_2 monitoring*
  - ***Intervention****: earlier ECLS system response to rising local CO_2 values to increase scrubbing before symptoms develop. Continue to explore physiologic interventions to decrease susceptibility to elevated CO_2 levels.*

7. Risk Postures

DRM	Category	LxC	Disposition	LxC Drivers for Likelihood	LxC Drivers for Consequences	Disposition Rationale	DRM Specific Assumptions	Level of Evidence
LEO (< 30 Days)	Ops	4x2	Accepted with Monitoring	ISS ECLS systems were designed to maintain CO_2 at much higher levels based on requirements at the time. Levels on the ISS are maintained by a CHIT (a form used to exchange information between the MER and flight control center) at a 24-hr average of 3mmHg rather than a 1-hr average of 3 mmHg. Monthly monitoring data indicate that spikes above a cabin average of 3 mmHg can and do occur, scrubber demonstrations fail, etc.	Minor impact to crew performance and operations.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	2 - Moderate
LEO (< 30 Days)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
LEO (30 d - 1 yr)	Ops	4x2	Accepted with Monitoring	ISS ECLS systems were designed to maintain CO_2 at much higher levels based on requirements at the time. Levels on the ISS are maintained by a CHIT at a 24-hr average of 3mmHg rather than a 1-hr average of 3 mmHg. Monthly monitoring data indicate that spikes above a cabin average of 3 mmHg can and do occur, scrubber demonstrations fail, etc.	Minor impact to crew performance and operations.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	2 - Moderate
LEO (30 d–1 yr)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
Lunar Orbital (< 30 Days)	Ops	4x3	Accepted with Monitoring	Assumption: Current levels of countermeasures will be maintained, and standards will be met through program requirements. Evidence: although Orion ECLS systems were designed to maintain CO_2 at higher levels (4 mmHg) based on requirements at the time) it is expected they will be able to maintain CO_2 levels at the current standard. Plans for the Human Landing System (HLS) are to maintain the current standard but accept a higher limit during orbital 'docked ops' with Orion. Actual system performance remains unknown.	CO_2 and humidity control systems are degrading faster than expected, increasing the likelihood of elevated CO_2 levels. The Laser Area Monitor on board Orion cannot be relied on to monitor CO_2, increasing the consequence that elevated CO_2 levels will cause crew symptoms. Unreliable CO_2 scrubbing and monitoring expend crew and operational resources by requiring crewmembers to perform manual portable CO_2 measurements when they experience headaches to verify CO_2 levels prior to further action.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations Average 6 seconds, max 30-sec comm delay	3 - Weak
Lunar Orbital (< 30 Days)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits		2 - Moderate
Lunar Orbital (30 d–1 yr)	Ops	3x2	Accepted with Monitoring	Assumption: Current levels of countermeasures will be maintained, and standards will be met through program requirements. Evidence: Gateway planning to maintain CO_2 levels at current standard. Actual system performance remains unknown.	Minor impact to crew performance and operations.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations Average 6 seconds, max 30-sec comm delay	3 - Weak
Lunar Orbital (30 d–1 yr)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
Lunar Orbital + Surface (< 30 Days)	Ops	3x2	Accepted with Monitoring	Assumption: Current levels of countermeasures will be maintained, and standards will be met through program requirements. Evidence: Plans for the HLS are to maintain CO_2 levels at the current standard. Actual system performance remains unknown.	Insignificant impact to crew performance and operations. Assumes that this DRM includes crewmembers on the planetary surface who will be exposed to partial gravity.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	3 - Weak
Lunar Orbital + Surface (< 30 Days)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
Lunar Orbital + Surface (30 d–1 yr)	Ops	3x2	Accepted with Monitoring	Assumption: Current levels of countermeasures will be maintained, and standards will be met through program requirements. Evidence: Plan for HLS are to maintain CO_2 levels at current standard. Actual system performance remains unknown	Insignificant impact to crew performance and operations. Assumes that this DRM includes crewmembers on the planetary surface who will be exposed to partial gravity.	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	3 - Weak
Lunar Orbital + Surface (30 d–1 yr)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
Mars Prep (< 1 yr)	Ops	3x3	Accepted with Monitoring	Planning to maintain CO_2 levels at current standard. Actual system performance remains unknown.	Significant reduction in crew performance, threatens loss of a mission objective. Assumes no benefit of partial gravity on planetary surface and reduced resources to address issues (ECLS system or crew).	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	3 - Weak
Mars Prep (< 1 yr)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence exists of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate
Mars Planetary (730–1224 d)	Ops	3x3	Accepted with Monitoring	Planning to control to current standard. Actual system performance remains unknown.	Significant reduction in crew performance, threatens loss of a mission objective. Assumes no benefit of partial gravity on planetary surface and reduced resources to address issues (ECLS system or crew).	Monitoring of CO_2 levels and crewmembers' reported symptoms allows for appropriate response to elevated levels or crew concerns.	Excludes suited operations	3 - Weak
Mars Planetary (730–1224 d)	LTH	1x1	Accepted with Monitoring	Currently, LTH consequences are not expected.	Career related short-term self-resolving medical condition. No current evidence of LTH impacts. Thus far data shows that consequences are short term and self-resolving. On-going evaluation of cerebral changes (using MRI) is needed to confirm no LTH consequences, but currently no evidence of LTH impacts.	No LTH consequences associated with CO_2 have been reported even at historical levels much higher than current limits.		2 - Moderate

8. HSRB Risk Likelihood x Consequence Matrix

LIKELIHOOD RATING	In-Mission	Flight Recertification	Long Term Health
5 Very High	More likely to happen than not during the mission or probability (P) >10%	Very likely to happen. Controls are insufficient or P> 10%	Likelihood is very high OR >10% excess risk
4 High	Likelihood is during the mission or 1%<P≤10%	Likely to happen. Controls have significant limitations or uncertainties or 1%<P≤ 10%	Likelihood is high OR 6-10% excess risk
3 Moderate	May happen during the mission or 0.1%<P≤1%	Not likely to happe[n] with some limitatio[ns] uncertainties or 0.1	
2 Low	Unlikely to happen during the mission or .01%<P≤0.1%	Not expected to happen. Controls have minor limitations or uncertainties or 0.01%<P≤0.1%	Likelihood is low OR 1-3% excess risk
1 Very Low	Nearly certain to not occur in-mission or P≤0.01%	Extremely remote possibility that it will happen. Strong controls in place or P≤0.01%	Likelihood is very low OR < 1% excess risk

L x C Matrix

LIKELIHOOD					
5	10	16	20	23	25
4	7	13	18	22	24
3	4	9	15	19	21
2	2	6	11	14	17
1	1	3	5	8	12
	1	2	3	4	5

CONSEQUENCE

Ops: Lunar Orbital Short 4x3

Ops: LEO Short & Long 4x2

Ops: Lunar Orbital Long; Lunar Orbital & Surface Short & Long 3x2

LTH: All DRMs 1x1

Mars Short & Long 3x3

Time frame Expected Need for Mitigation	
Near	0 < 2 Years
Mid	2-7 Years
Far	> 7 Years

Risk Score Card values are constant across all risks and prioritize consequence over likelihood.

CONSEQUENCES		1	2	3	4	5
IN MISSION	Crew Health Impact OR	Temporary discomfort	Minor injury/illness that can be dealt with by crew without ground support, minor crew discomfort	Significant injury/illness or incapacitation that requires diagnosis and/or treatment support from ground, may affect personal safety	Critical injury/illness of one crew member requiring extended medical intervention and support, may result in temporary disability	Death or permanently disabling injury/illness affecting one or more crewmember (LOCL/LOC)
	Mission Objectives Impact	Insignificant impact to crew performance and operations – no additional resources required	Minor impact to crew performance and operations – requires additional resources (time, consumables)	Significant reduction in crew performance, threatens loss of a mission objective	Severe reduction of crew performance that results in loss of multiple mission objectives	Loss of mission due to crew performance reductions or loss of crew
FLIGHT RECERT	Crew Flight Recertification Status	Immediate flight recertification status	Flight recertification status within 3 months with limited intervention	Flight recertification status within 1 year with nominal intervention or restricted flight status	Flight recertification status requires extended medical intervention and takes > 1 year	Unable to be Recertified for Flight Status, premature career end
LONG TERM HEALTH	Health Outcomes OR	Career related short term self-resolving medical conditions	Career related medical conditions manageable with outpatient medical treatments	Treatable career related medical condition that requires hospitalization for management	Chronic career related medical condition requiring intermittent hospitalization or nursing care	Career related premature death or permanent disability requiring institutionalization
	Quality of Life	No impact on quality of life OR independence in activities of daily living	Minor, short-term impact on quality of life OR rare support required for activities of daily living	Moderate long-term impact on quality of life OR may require some time-limited support for activities of daily living	Major long-term impact on quality of life OR requires intermittent support for activities of daily living	Chronic debilitating impact on quality of life OR requires continuous support for activities of daily living

9. Overall Assessment of the Evidence

❖ Operations Evidence (In-flight data remain limited)

- Inflight symptom data are limited to personal observations and subjective reports of symptoms attained through questionnaires, debriefs, and private medical conferences.
- Monitoring of ppCO_2 indicates spikes above a cabin average of 3 mmHg can and do occur.
- It is difficult to correlate symptom timing, crew location, and cabin CO_2 measurements.

❖ Research Evidence

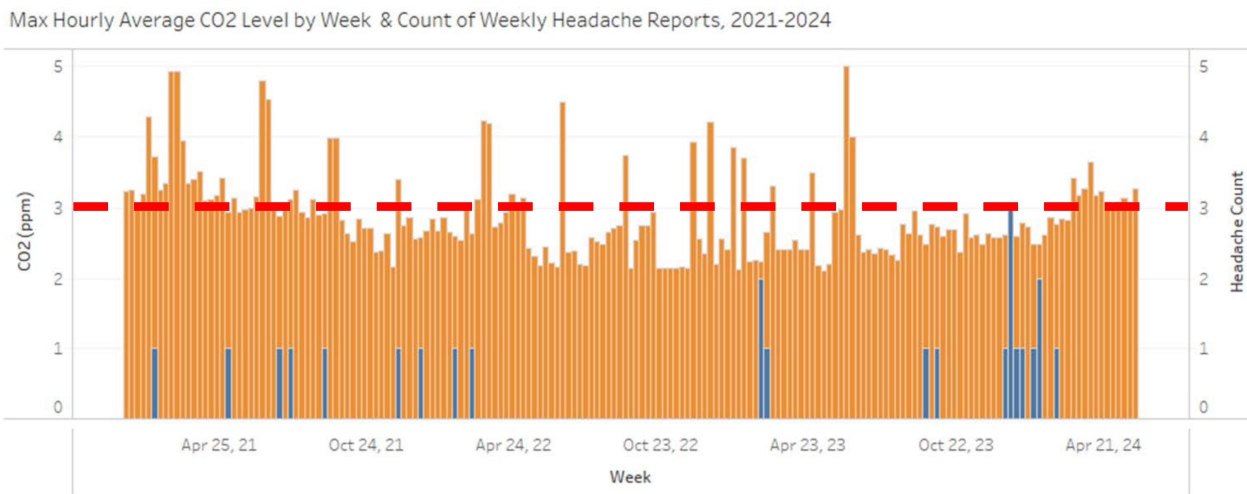
- Interaction of elevated CO_2 levels combined with hypobaric hypoxia (such as exploration atmospheres), fluid shifts in microgravity, and venous stasis are unknown.
- Findings of studies that have assessed the effects of elevated CO_2 on cognition have been inconsistent.
- Genetic analyses identified that the presence of 3–4 risk alleles is associated with an increased risk of developing spaceflight associated neuro-ocular syndrome (SANS) in head down tilt bedrest studies (HDBR), and elevated CO_2 may increase the risk of developing SANS.

10. State of Knowledge

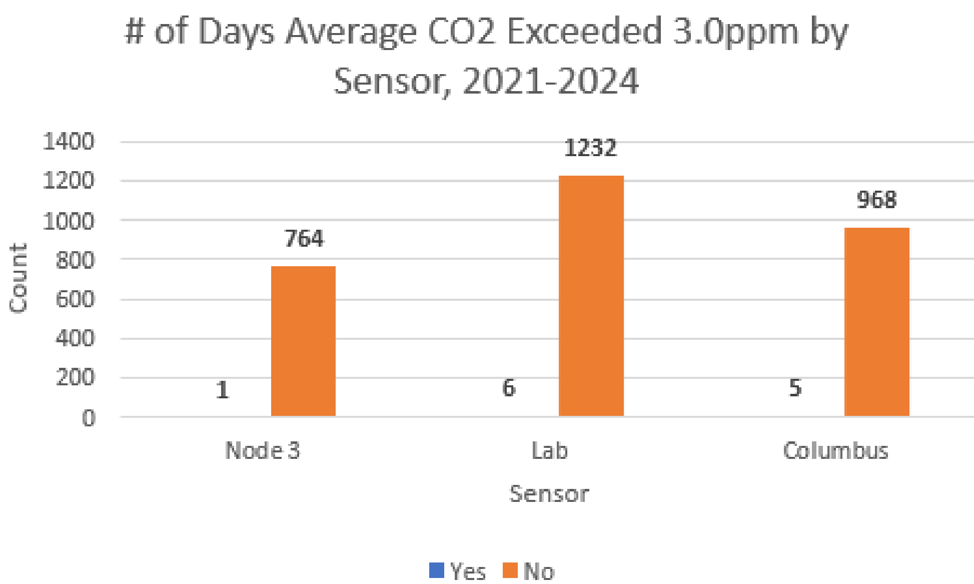
10.1 New Epidemiological Evidence

In 2016 a CHIT (control number 014468) specified the US On-Orbit Segment (USOS) of the ISS will operate with a partial pressure CO_2 of no greater than a 24-hour average of 3 mmHg. During nominal operations, the major constituent analyzer (MCA) on the USOS samples each module hourly and the readings are averaged with values obtained during the previous 24 hours.

In August, 2021 a Mission Control Center Flight Note (F091532E) was released specifying the plan to maintain the USOS 24-hour average ppCO_2 to between 2.8 and 3.1 mmHg when the MCA is available for CO_2 sensing. If the MCA is not available, the plan was to maintain 24-hour average ppCO2 between 2.4 and 3.0 mmHg. If crewmembers develop symptoms of CO_2 toxicity, additional portable CO_2 monitor readings are required.


Max Hourly Average CO2 Level by Week & Count of Weekly Headache Reports, 2021-2024
CO2 (ppm)
Headache Count
Week
Apr 25, 21
Oct 24, 21
Apr 24, 22
Oct 23, 22
Apr 23, 23
Oct 22, 23
Apr 21, 24

10.2 New Literature Evidence



Because CO_2 is an extremely potent cerebrovasculature dilator, it has been investigated as a potential contributor, along with other conditions experienced in microgravity, for inducing changes in cerebrovascular dynamics, the apparent lower threshold for CO_2 induced headaches, the occurrence of SANS, sensorimotor perturbations, sleep loss, and cognitive impairments during space travel. In addition to outcomes influenced by changes to the cerebrovasculature, it is possible that chronic exposure to elevated levels of CO_2 could affect other physiological outcomes, such as altered rates of bone loss or by changes in microbial pathogenesis.

Regarding effects of CO_2 on the **cerebrovasculature**, a recent publication reported that in the presence of gravitational stress (50° head up tilt compared to supine position) with exposure to 5% CO_2 for 9 minutes, impaired anterior cerebral circulation, whereas the posterior circulation was unaffected (Watanabe et al., 2022). These findings are consistent with those of others who have suggested that all parts of the brain may not respond in the same manner to changes in CO_2 levels because flow responses are a mixed result of resistance changes in blood vessels and competition for blood flow between regions of the brain (Bhogal et al., 2015; Fisher et al., 2017). Aebi et al. (2020) evaluated cerebrovascular reactivity to CO_2 (CVR) in 9 human subjects under conditions of normobaric normoxia, hypobaric hypoxia, hypobaric normoxia, and normobaric hypoxia. Measures of partial pressure of inspired oxygen (PIO2) were the same for all the conditions. CVR was measured by plotting sigmoid curves of middle cerebral artery blood velocity (MCAv) versus end tidal CO_2 pressure ($P_{ET}CO_2$). $P_{ET}CO2$ differed under the 3 conditions of hyperventilation, normal tidal breathing, and breathing 5% CO_2 (36 mmHg at 1444 ft) for 3 min. CVR was greater in hypobaric hypoxia conditions than in normobaric normoxia conditions as evidenced by left shift and greater slope of MCAv vs $P_{ET}CO2$. Interestingly, hypobaric hypoxia induced a greater CVR than normobaric hypoxia despite similar PIO2. Hypobaric normoxia conditions also induced greater CVR than normobaric normoxia conditions despite similar PIO2. These data indicate that both low PIO2 and low ambient pressure increase CVR in acute exposures to elevated CO_2.

In studies conducted in human-certified chambers, research on proposed exploration atmospheres has tested human responses to variations in ambient pressure and oxygen partial pressures. Exploration Atmospheres 1 and 2 exposed human subjects to an ambient pressure of 8.2 psia at 34% O_2, whereas the parameters from Exploration Atmospheres 3 and 4 were 9.6 psia at 28.5% O_2. As demonstrated by Aebi et al. (2020) cerebrovascular response to CO_2 varies by both ppO_2 and ambient pressure. The physiologic and symptomatic responses of acute and chronically elevated CO_2 combined with hypobaric hypoxia at fraction of inspired oxygen outside of 21% and 100% require further characterization.

Crewmembers on board the ISS have reported **severe headaches** that do not respond to ordinary treatment but are usually relieved when CO_2 levels are reduced (Law et al, 2014). The threshold for CO_2-associated headaches during spaceflight is well below that on Earth (Law et al, 2014). Recently, a retrospective study of the frequency and clinical features of **headaches experienced by ISS crewmembers** during long-duration missions found that the occurrences of **headaches were not correlated with the weekly means of several variables, including CO_2** (van Oosterhout et al., 2024). However, 3 important limitations were associated with this study that affect interpretation. First, an apparent failure exists in this study to distinguish between CO_2-associated headaches, migraine headaches, and headaches that are often associated with space motion sickness. Migraine-like headaches secondary to another disorder (symptomatic migraine) is coded as a secondary headache attributed to that disorder, but this was not done in the study. Most headaches were mild and lasted less than 4 hours. Frequent accompanying symptoms included nasal congestions and difficulty sleeping. These descriptions are consistent with common issues during spaceflight and are inconsistent with the severe headaches that are unresponsive to typical treatments and that resolve when CO_2 concentrations are lowered. The lack of correlation between headaches recorded in this study and CO_2 is not surprising given that the features of these headaches are inconsistent with those of CO_2-associated headaches. Second, the weekly mean CO_2 levels were not different during weeks when a crewmember had a headache (2.74 +/- 0.38 mmHg, mean +/- standard deviation) versus weeks the crewmember did not have headaches (2.66 +/- 0.46 mmHg). This range of CO_2 measurements were collected from 2011 to 2018 and represents a narrower range of CO_2 levels than those reported in the previous study (Law et al., 2014) that did find a correlation between CO_2 and the incidence of crewmembers' headaches. The previous positive correlation between weekly mean CO_2 and the incidence of headaches spanned 2001 to 2012, which included data from the early days of the ISS program when CO_2 was regulated below 5.3 mmHg, and the period from 2010 when CO_2 was regulated below 4.0 mmHg (Law et al., 2014). The mean 7-day CO_2 ranged from 3.60 mmHg to 2.54 mmHg with the more conservative regulation in place and this resulted in decreased incidence of headaches. It is likely the absence of correlation between headache and weekly mean CO_2 level reported by van Oosterhout et al. (2024) was due to the narrow range of levels in the cabin. Third, mean weekly CO_2 values are possibly less relevant to headache than peak CO_2 values. Notably, Law et al. 2014 found a correlation between headache incidence and all 4 values for CO_2 (average and peak across both 1-day and 7-days).

Several studies have investigated a potential contribution of elevated CO_2 to **SANS**. Laurie et al. (2017) examined visual acuity, intraocular pressure (IOP), ocular structures, cardiovascular measures, intracranial pressure (ICP), and translaminar pressure difference in healthy subjects, who, for one hour, were seated, or reclined at 6^o HDBR while exposed to either ambient or 1% CO_2. One-carbon genetic pathways were also analyzed in these subjects (Zwart et al., 2019). **No significant differences were found between HDBR subjects exposed to ambient or elevated CO_2 for visual acuity, ocular structures, cardiovascular outcomes, ICP or translaminar pressure difference**, however **genetic polymorphisms were associated with differences in IOP, ICP, and end tidal CO_2 (PCO_2)** (Laurie et al., 2017)**.**

In a follow-up study (the vision impairment/intracranial pressure [VIIP] and Psychological :envihab Research Study [**VaPER** study], which was conducted in 2017 at the :envihab facility in Cologne, Germany), Laurie et al. (2020) exposed 11 subjects (5 female) to strict HDBR and 4 mmHg (0.5%) CO_2 for 30 days and found that half of the subjects developed optic disc edema. However, because an increase of 1.4 mmHg in the partial pressure of arterialized CO_2 ($PaCO_2$) that resulted from exposure to CO_2 was not significantly different from the baseline value and cerebrovascular reactivity was unchanged, the **authors suggested that mild hypercapnia may not have contributed to the development of SANS-like symptoms during HDBR**. The relationship of the one-carbon genetic pathways to SANS (Zwart et al., 2019) demonstrated **increases in total thicknesses of the retina and of the retinal nerve fiber layer and the magnitude of optic disk edema** in the VaPER study subjects who had 3–4 risk alleles. Zwart et al. (2023) reported that subjects from the VaPER with 3–4 risk alleles had greater changes in total retinal thickness than subjects with 3–4 risk alleles in the later Artificial Gravity Bed Rest Study (**AGBRESA** study), which was conducted at the same facility and under the same standard conditions as the VaPER study, but without the raised levels of CO_2. In contrast, subjects who had 1–2 risk alleles had similar changes in total retinal thickness in both studies. Zwart et al. (2023) cited the report by Laurie et al. (2020) that detected **no change in arterialized PCO_2 or cerebrovascular reactivity to CO_2** in the VaPER subjects but did not suggest that the differences between the VaPER and AGRESA subjects might be due to the exposure of the former to elevated levels of CO_2. Further evidence of elevated PCO_2 contributing to SANS was provided by Brunstetter et al. (2024) in a case study of a crewmember with 4 SANS risk alleles who developed SANS on the ISS. This individual presented initially with increasing bilateral total retinal thickness, mean choroidal thickness, and surface roughness of choroidal folds all of which subsequently improved during the spaceflight coincident with a lowering of cabin partial pressure CO_2 from a mean of 2.6 to 1.3 mmHg. However, this crewmember also received additional vitamin supplementation (17 days of daily oral vitamin B6, vitamin B12, L-methylfolate, and riboflavin) that may have contributed to the improvements in these SANS markers (Brunstetter et al., 2024). Subjects of the VaPER study were assessed using arterial spin labeling to compare cerebral perfusion before, during, and after HDBR+CO_2 in participants who developed SANS (n = 5) with those who did not (n = 6), and the results indicated that HDBR+CO_2 resulted in reduced cerebral perfusion that varied based on SANS status (Roberts et al., 2012). The SANS group experienced a greater reduction in perfusion (Roberts et al., 2021). A comparison of dynamic changes to the morphology of the perivascular space in VaPER subjects to subjects of a 60-day HDBR study who breathed ambient air **found no significant differences in the quantity or morphology of cerebral perivascular spaces observed with MRI**.

Differences have been noted between the subset of VaPER subjects (HDBR + CO_2) who developed signs of SANS and those who did not (Lee et al., 2019; Mahadevan et al., 2021; Richmond et al., 2024). Subjects with SANS had slower speed but greater accuracy on sensorimotor and cognitive testing (Lee et al., 2019). Richmond et al. (2024) found the subjects who developed signs of SANS during bedrest had significantly greater median volume and width in MRI-visible perivascular spaces (PVS), and diffusion tensor imaging along the PVS (DRIALPS) index than those who did not develop signs of SANS, and the non-SANS group experienced a significant reduction in median volume of the PVS and DTIALPS index during bedrest compared to before bed rest. Brain activities associated with the simultaneous performance of cognitive and motor tasks also differed between the SANS and non-SANS groups, with the former exhibiting slower reaction times during performance of dual tasks (Mahadevan et al., 2021). Investigators remarked that **the role of hypercapnia in SANS is unclear** because some subjects who were not exposed to elevated levels of CO_2 developed signs of SANS, and data collected by Laurie et al. (2020) and by Mahadevan et al. (2021) in the VaPER study demonstrated no significant changes in arterialized $PaCO_2$ with exposure to 3.8 mmHg CO2. However, McGregor et al. (2021) reported finding a greater and statistically significant difference in $PaCO_2$ in the VaPER study. **Additional studies are required to disentangle contributions of HDBR and hypercapnia in the development of symptoms of SANS** (Richmond et al., 2024; Roberts et al., 2021).

Influences of CO_2 on neural functions, including sensorimotor outcomes, examined in the VaPER study, have been widely reported. Lee et al. (2019) found that VaPER subjects had greater **enhancement of processing speed on cognitive tests and decreases in functional mobility** than subjects pooled from an earlier 70-day HDBR study that was conducted in ambient air with 18 male subjects aged 25.8 to 39.8 years who were assigned to either a control group, a group performing aerobic and resistance exercise, or a group exercising with a flywheel. Hupfeld et al.

(2020) also compared VaPER subjects to those of an earlier 70-day HDBR study. The investigators used functional MRI to examine brain activity in response to pneumatic skull taps, which stimulates the vestibular system, and found increased deactivation of certain brain regions was associated with better balance after HDBR. The HDBR + CO_2 induced greater increases in activation of multiple frontal, parietal, and temporal regions during vestibular stimulation over the course of bed rest than HDBR alone, which suggests that elevated levels of **CO_2 may alter vestibular processing and compensation** (Hupfeld et al., 2020). Banker et al. (2021) found that the sensorimotor adaptation in response to mechanical or sensory perturbations was unchanged in VaPER subjects. However, based on findings of earlier studies, improvements had been expected, therefore, elevated levels of **CO_2 may have interrupted potential learning effects**. Changes in resting state functional connectivity and sensorimotor behavior of VaPER subjects (HDBR +CO_2) were compared to these responses in 8 subjects (2 females) who participated in a subsequent 60-day HDBR study in which they breathed ambient air (McGregor et al., 2021). Functional network encompassing bilateral insular cortices and right posterior cingulate cortex, which is thought to be involved in introspection and autobiographical memory retrieval and controlling balance between internal and external attention, exhibited a distinct pattern of changes in functional connectivity during HDBR + CO_2 that differed from the changes observed in the HDBR control group, which suggests that the observed **changes in connectivity were due to the combination of HDBR and elevated CO_2 that** caused HDBR-associated multisensory reweighing and CO_2 affecting vascular perfusion (McGregor et al., 2021). Although Laurie et al. (2020) found no change in $PaCO_2$, or cerebrovascular reactivity in VaPER study subjects, analysis of blood samples collected during the VaPER study as part of NASA's standard measures study showed a significant increase in $PaCO_2$ from after HDBR compared to values before HDBR (McGregor et al., 2021). Salazar et al. (2021) examined brain activation during visuomotor adaptation and performance and found no statistically significant differences between the HDBR+CO_2 group and the HDBR controls, suggesting that effects of **visuomotor adaptation performance were due primarily to bed rest rather than elevated CO_2.** Noting the disparate findings of **interactive or additive effects of HDBR + CO_2 on vestibular processing** (Hupfeld et al., 2020) **and activation of brain regions associated with spatial working memory** (Salazar et al., 2020) **but not visuomotor adaptation**, Salazar et al (2021) suggested that **elevated CO_2 effects may be task-specific**, at least at the level and duration of elevated CO_2 employed in the VaPER study.

Assessments of effects of CO_2 on **cognition and performance** in the VaPER study produced varied findings. Lee et al. (2019) found an enhancement of processing speed indicated by a significant group-by-time interaction for completion time on **the digit symbol substitution task**, where the **completion times were faster for the HDBR + CO_2 group** than the group exposed to HDBR alone. Completion of a **functional mobility task was significantly slower in** the group exposed to **elevated CO_2**. No differences were observed in spatial working memory between the two groups. On the other hand, Basner et al. (2021), who used a battery of cognitive assessments called "Cognition" on the VaPER study subjects reported that elevated **CO_2 neither improved nor deteriorated HDBR effects on cognitive performance**. Assessment of performance in the VaPER study using counting, tapping, and preforming both tasks concurrently (dual task performance), found that HDBR + CO_2 subjects performed tapping less accurately that the HBDR group, but overall, the **data "do not indicate change in cognitive performance with either elevated CO_2 or bed rest**" and no significant brain-behavior correlations were found (Mahadevan et al., 2021). Recently, Flagner et al. (2024) used a sealed respiration chamber with fully controlled environmental variables to expose 20 healthy subjects to pure CO_2 at 900 and 3000 ppm (0.7 mmHg and 2.3 mmHg, respectively) for 8 hours in cross-over single-blinded study and **found no effects of CO_2 on physiological variables, decision-making, or cognition. Findings of studies that have assessed the effects of elevated levels of CO_2 on cognition have been inconsistent** (Fan et al., 2023). The variability in outcomes among the studies could be due to differences in the populations assessed, the sensitivity of assessment methods (Fan et al., 2023; Scully et al., 2019), exposure concentrations, study design, and small sample sizes (De La Torre et al., 2012; Fan et al., 2023).

Effects of exposure to elevated concentrations of CO_2 on bone metabolism during strict 6^{o} HDBR were evaluated by use of dual-energy X-ray absorptiometry (DXA) measures and biochemical analyses of blood and urine collected during the VaPER and AGBRESA studies (McGrath et al., 2022). As was expected, because of the short duration of the study, no changes were detected in bone mineral density or bone mineral content. Biomarkers of bone resorption were increased after bedrest, relative to baseline values but **exposure to CO_2 produced no measurable increase in** the concentration of minerals in serum and urine (McGrath et al., 2022). It is possible that the results were confounded by the control group's exposure to 60 days of bedrest, whereas the bedrest plus 0.5% CO_2 (3.8 mmHg) group's exposure was only 30 days.

During the VaPER study, effects of CO_2 on sleep were gauged using measures of sleep, 24-hour core body temperature, and overnight transcutaneous CO_2 (Christian et al., 2024). None of these variables, when measured during the exposure to CO_2, differed significantly from the baseline values obtained prior to exposure. The normal increase in PCO_2 that occurs during sleep was observed during baseline data collection, but contrary to expectation, the level did not increase during sleep while exposed to 0.5% CO_2. The quality and duration of sleep did not depreciate significantly with exposure to elevated levels of CO_2 (Christian et al., 2024).

A pilot study designed to determine if the elevated concentrations of CO_2 on the ISS could synergistically increase microbial pathogenesis factors found that pathogens grown in a spaceflight analog under elevated CO_2 exhibited no detectable changes in virulence (Ott et al., 2024).

An association exists between dry eye disease and the ISS environment as shown by 30% of ISS astronauts experiencing dry eye disease, possibly because the nominal CO_2 level on ISS higher than nominal terrestrial conditions (Sampige et al., 2024). Further study is needed to better elucidate this potential relationship.

10.3 Figures and Tables

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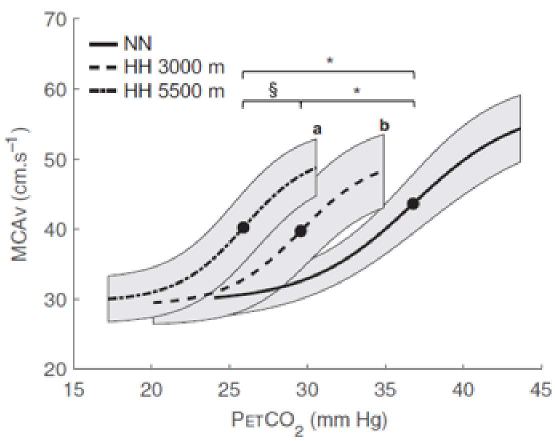

FIGURE 2 Mean sigmoidal curves of all subjects ($n = 9$): In normobaric normoxia (NN, Dübendorf 440 m); 3,000 m and 5,500 m in hypobaric hypoxia (HH) conditions. Bold point represents midpoint. *$p < .05$ midpoint different than NN; §$p < .05$ midpoint different than 3,000 m; (a) $p < .05$ slope different between 5,500 m and NN; (b) $p < .05$ slope different between 3,000 m and NN. Shaded areas surrounding the sigmoid curves represent the 95% confidence interval

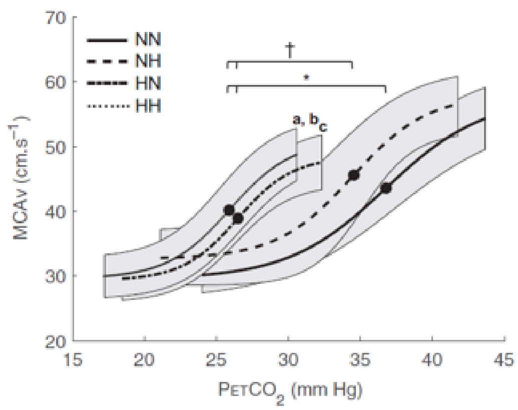

FIGURE 3 Mean sigmoidal curves of all subjects ($n = 9$) in: normobaric normoxia (NN); normobaric hypoxia (NH); hypobaric hypoxia (HH); and hypobaric normoxia (HN) conditions. Bold point represents midpoint. †$p < .05$ midpoint different between HH/HN and NH; *$p < .05$ midpoint different between HH/HN and NN; (a) $p < .05$ slope different between 5,500 m HH and NN; (b) $p < .05$ slope different between 5,500 m HH and NH; (c) $p = .069$ slope tend to be different between HN and NN. Shaded areas surrounding the sigmoid curves represent the 95% confidence interval

	NN	HH 3000 m	HN	NH	HH 5500 m
Midpoint	35.7 ± 3.3	27.3 ± 2.0*	21.6 ± 1.9*	33.7 ± 1.7#	19.6 ± 2.0*§†
Slope	0.23 ± 0.12	0.52 ± 0.27*	0.46 ± 0.12(*)	0.35 ± 0.19	0.66 ± 0.33*†

TABLE 1 Absolute values are means ± *SD* ($n = 9$). Mean sigmoidal curve data: Midpoint (mmHg) and inclination (slope) of the sigmoid curve

Note: In normobaric normoxia (NN, Dübendorf altitude level of 440 m), hypobaric hypoxia (HH, at altitude level of 3,000 m and 5,500 m), hypobaric normoxia (HN, altitude level of 5,500 m in normoxia), and normobaric hypoxia (NH, altitude simulation of 5,500 m in normobaria). Statistical analysis was performed separately for altitude comparison in HH (NN, 3,000 m and 5,500 m HH) and for conditions comparison (NN, HN, NH, and 5,500 m HH). (*) $p = .069$, *$p < .05$ different from NN conditions; §$p < .05$ different from 3,000 m HH; #$p < .05$ different from HN; and †$p < .05$ different from NH.

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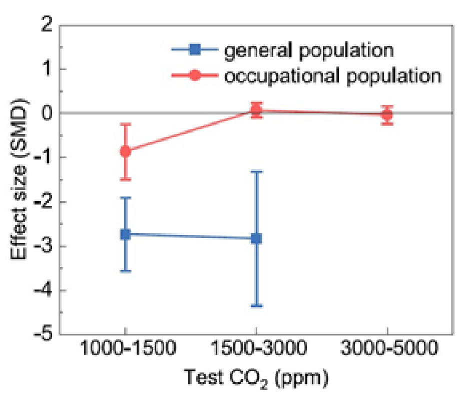
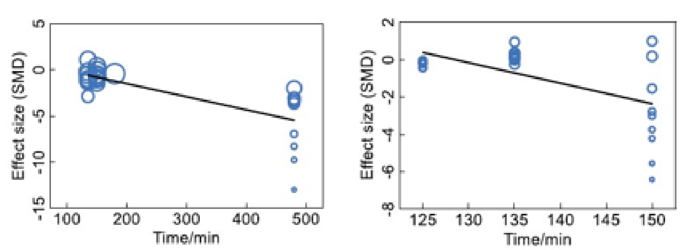


Fig. 5. Subgroup analysis of complex cognitive task performance stratified by population characteristics [8,21–23,29]. (The dots represent the pooled SMDs and the error bars are the corresponding 95%CIs.)



(a) 1000-1500 ppm

(b) 1500-3000 ppm

Fig. 6. Subgroup regression analysis of complex cognitive task performance under different exposure durations [8,21–23,29].

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Table 2
Elevated indoor CO_2 and CANTAB test scores.

	Panel A: Attention & psychomotor control				Panel B: Memory			
	Reaction Time Task		Motor Screening Task		Delayed Matching to Sample		Paired Associate Learning	
High CO_2	3.587	2.025	0.493	4.445	3.550*	4.050	0.500	1.550**
	(4.622)	(6.064)	(12.651)	(16.93)	(1.518)	(2.432)	(0.288)	(0.552)
	[0.871]	[0.798]	[0.968]	[0.798]	[0.200]	[0.501]	[0.483]	[0.056]
High CO_2 x Morning		3.125		−7.905		−1.000		−2.100*
		(8.910)		(7.905)		(3.405)		(0.915)
		[0.960]		[0.960]		[0.960]		[0.184]
Fixed effects								
First test day	Y	Y	Y	Y	Y	Y	Y	Y
Morning	Y	Y	Y	Y	Y	Y	Y	Y
Participant	Y	Y	Y	Y	Y	Y	Y	Y
Observations	80	80	80	80	80	80	80	80
R^2	0.897	0.897	0.625	0.625	0.483	0.484	0.705	0.737
Adj. R^2	0.858	0.855	0.480	0.471	0.284	0.272	0.591	0.628
	Panel C: Executive function							
	Multitasking Test		One-Touch Stocking of Cambridge		Stop Signaling Task		Spatial Working Memory	
High CO_2	−11.037	−9.650	0.450	0.350	6.239	6.437	−0.400	−1,000
	(8.516)	(13.517)	(0.233)	(0.239)	(4.140)	(4.073)	(0.677)	(0.845)
	[0.715]	[0.798]	[0.311]	[0.593]	[0.570]	[0.488]	[0.968]	[0.798]
High CO_2 x Morning		−2.775		0.200		−0.396		1.200
		(14.408)		(0.358)		(8.019)		(1.035)
		[0.960]		[0.960]		[0.960]		[0.960]
Fixed effects								
First test day	Y	Y	Y	Y	Y	Y	Y	Y
Morning	Y	Y	Y	Y	Y	Y	Y	Y
Participant	Y	Y	Y	Y	Y	Y	Y	Y
Observations	80	80	80	80	80	80	80	80
R^2	0.842	0.842	0.712	0.713	0.564	0.564	0.820	0.823
Adj. R^2	0.781	0.778	0.601	0.596	0.396	0.385	0.750	0.751

Note: The table shows the results of the regression analysis as presented in Section 2.5 with regards to the cognitive performance of participants in the Cambridge Neuropsychological Test Automated Battery (CANTAB) tests. For each outcome variable, we show two columns, with the first column containing the estimated treatment parameter δ based on Eq. (1), and column 2 showing δ_1 and δ_2 based on Eq. (2). Fixed effects on whether participants conduct the tests on their first test day independent of the CO_2 condition, if they conduct the test in the morning after 30 min of exposure, and participant fixed effect has been added. See Section 2.3 for a detailed description of the outcome variables. Bootstrapped standard errors based on wild bootstrap clusters with 1,000 replications are shown in (parentheses). Significance levels before multiple hypothesis testing are indicated as *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. In addition, p-values resulting from multiple hypotheses testing, based on the method by Hommel [48] are in [brackets].

Table 3
Elevated indoor CO_2 and economic decision-making.

	Risk aversion α	Discounting ρ	Fechner error μ	Tremble error κ
High CO_2	0.000	0.005	0.116	−0.090
	(0.050)	(0.015)	(0.12)	(0.063)
	[0.998]	[0.998]	[0.984]	[0.616]
High CO_2 x Morning	0.022	0.009	−0.093	−0.030
	(0.061)	(0.010)	(0.144)	(0.093)
	[0.752]	[0.752]	[0.752]	[0.752]
Fixed effects				
First test day	Y	Y	Y	Y
Morning	Y	Y	Y	Y
Sex	Y	Y	Y	Y
Observations	4800	4800	4800	4800
Log likelihood	−1910	−1910	−1910	−1910

Note: The maximum likelihood estimation includes fixed effects controls for the time of the day when the multiple price lists were conducted (120 min and 420 min into the test day), for the sex of the participant, and whether it was the first test day for the participant. Standard errors clustered at the subject level are in (parentheses). Significance levels before multiple hypothesis testing are indicated as *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. In addition, p-values resulting from multiple hypotheses testing based on the method by Hommel [48] are in [brackets].

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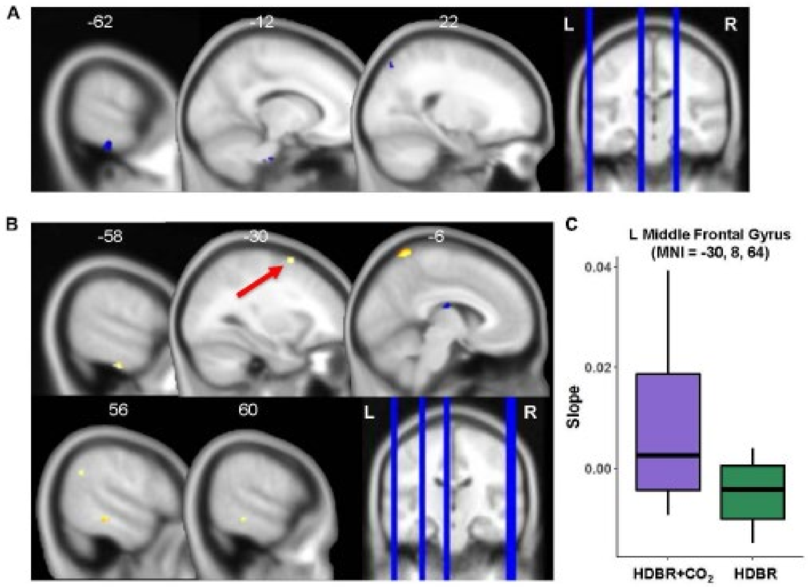

FIGURE 7 | HDBR + CO_2 vs. HDBR group comparisons. **(A)** Regions of intercept differences between HDBR + CO_2 and HDBR groups. **(B)** Regions of slope differences between HDBR + CO_2 and HDBR groups. Results overlaid onto MNI standard template; non-parametric $p < 0.0005$, $k = 10$. Cool colors indicate regions where the intercept or slope for the HDBR + CO_2 group was numerically less than the intercept or slope for the HDBR group. Warm colors indicate regions where the slope for the HDBR + CO_2 group was numerically greater than the slope for the HDBR group. **(C)** Example slope values extracted from L Middle Frontal Gyrus (i.e., the cluster with greatest T value for the HDBR + CO_2 > HDBR contrast). Here, the HDBR + CO_2 group showed *increased activation* of this region across bed rest, while the HDBR group showed *increased deactivation* of this region across bed rest.

- [Laurie SS, Vizzeri G, Taibbi G, Ferguson CR, Hu X, Lee SM, Ploutz-Snyder R, Smith SM, Zwart SR, Stenger MB. Effects of short-term mild hypercapnia during head-down tilt on intracranial pressure and ocular structures in healthy human subjects. Physiological reports. 2017 Jun;5(11):e13302.]

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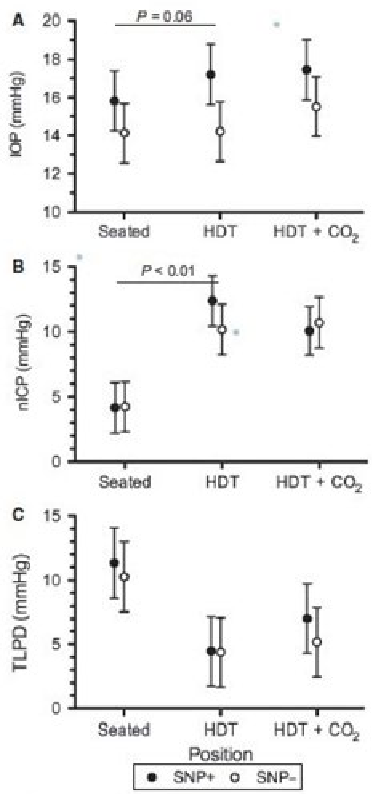

Figure 5. (A) IOP, (B) nICP, and (C) TLPD for SNP+ (filled) and SNP– (open) groups during each condition. Values are means ± 95% confidence intervals. P-value indicates group by condition interaction. n = 4 subjects in each SNP+ and SNP- groups.

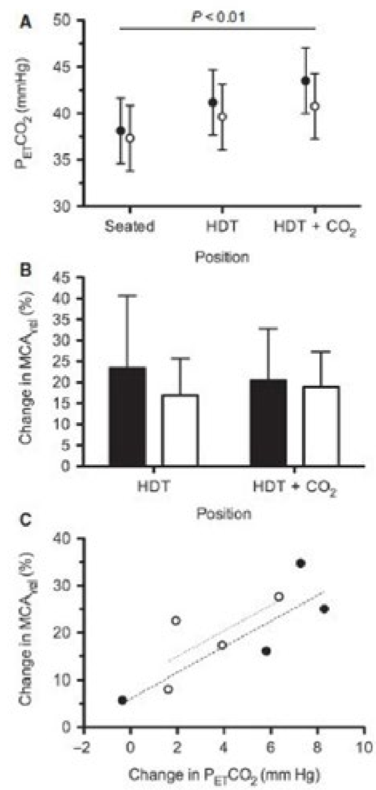

Figure 6. (A) $P_{ET}CO_2$ for SNP+ (filled) and SNP– (open) groups during each condition. (B) Change in MCA_{vel} compared to Seated for SNP+ (filled, n = 4) and SNP– (open, n = 4) groups during head-down tilt (HDT) and HDT + CO_2. (C) Change in MCA_{vel} as a function of the change in $P_{ET}CO_2$ between Seated and HDT + CO_2 for SNP+ (filled, n = 4) and SNP– (open, n = 4) groups. Linear regression slopes for the SNP+ (dashed, r^2=0.7256) and SNP– (dotted, r^2 = 0.5077) groups were not significantly different.

- [Laurie SS, Christian K, Kysar J, Lee SM, Lovering AT, Macias BR, Moestl S, Sies W, Mulder E, Young M, Stenger MB. Unchanged cerebrovascular CO2 reactivity and hypercapnic ventilatory response during strict head-down tilt bed rest in a mild hypercapnic environment. The Journal of Physiology. 2020 Jun;598(12):2491-505.]
    - See Figures 3, 5, 6.

- [Law J, Van Baalen M, Foy M, Mason SS, Mendez C, Wear ML, Meyers VE, Alexander D. Relationship between carbon dioxide levels and reported headaches on the international space station. Journal of occupational and environmental medicine. 2014 May 1;56(5):477-83]
    - See Figures 1 and 2

- [Lee JK, De Dios Y, Kofman I, Mulavara AP, Bloomberg JJ, Seidler RD. Head down tilt bed rest plus elevated CO2 as a spaceflight analog: effects on cognitive and sensorimotor performance. Frontiers in Human Neuroscience. 2019 Oct 17;13:355]
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- [Mahadevan AD, Hupfeld KE, Lee JK, De Dios YE, Kofman IS, Beltran NE, Mulder E, Bloomberg JJ, Mulavara AP, Seidler RD. Head-down-tilt bed rest with elevated CO2: effects of a pilot spaceflight analog on neural function and performance during a cognitive-motor dual task. Frontiers in Physiology. 2021 Aug 25;12:654906]

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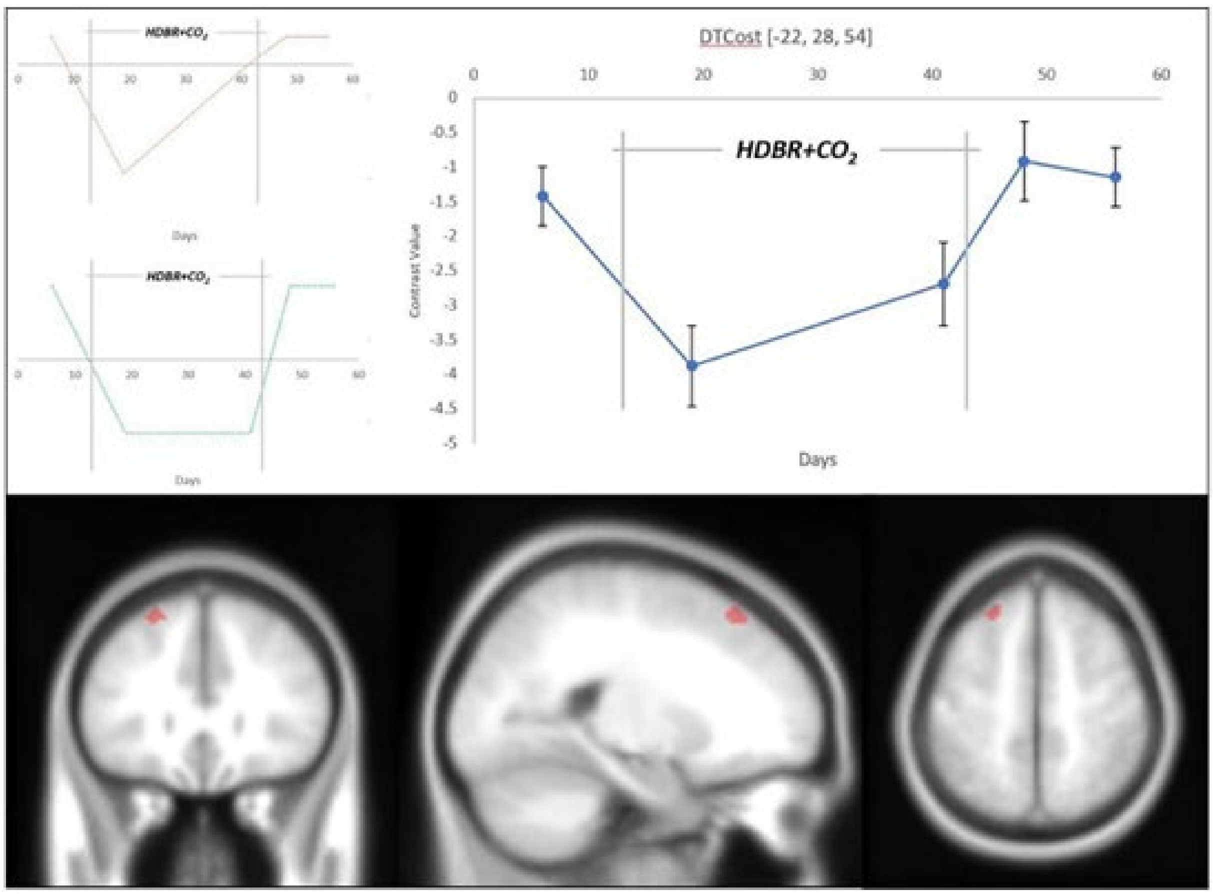

FIGURE 5 | Longitudinal change in DTCost of brain activation associated with HDBR + CO_2. (Top Left) Hypothesized models of longitudinal instant change (orange) and instant change with recovery in-HDBR (green). (Top Right) Exhibited pattern of longitudinal DTCost of brain activation change in the left superior frontal gyrus (blue). Analyses were conducted at an uncorrected alpha level of $p < 0.0001$. (Bottom) Left superior frontal gyrus cluster that showed significant longitudinal change associated with HDBR + CO_2.

- [McGrath ER, Frings-Meuthen P, Sibonga J, Heer M, Clement GR, Mulder E, Smith SM, Zwart SR. Bone metabolism during strict head-down tilt bed rest and exposure to elevated levels of ambient CO2. npj Microgravity. 2022 Dec 16;8(1):57]

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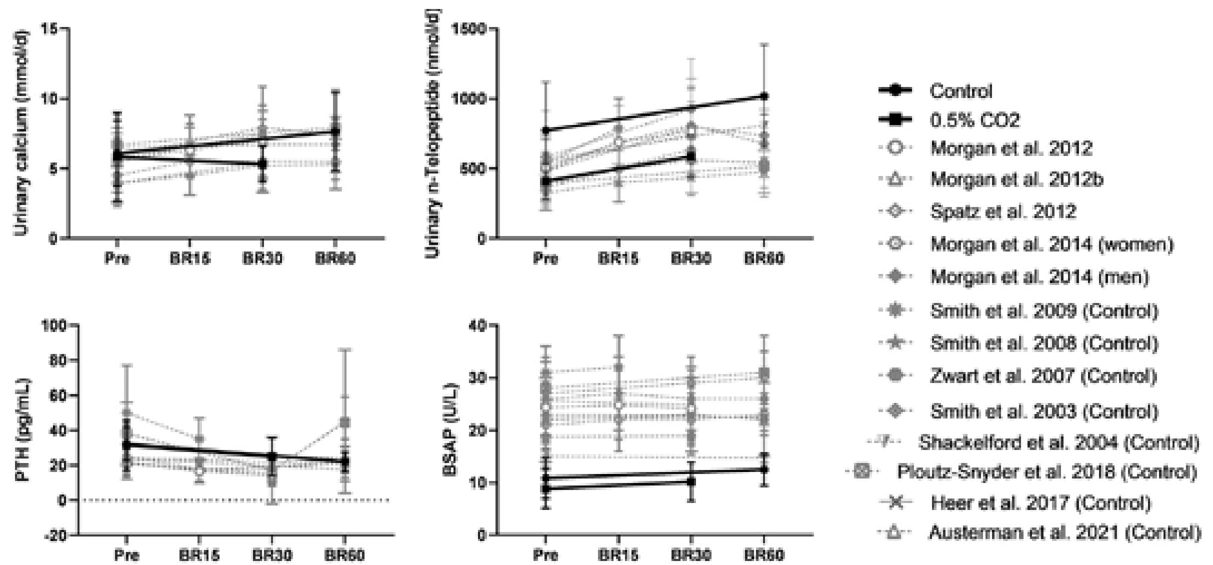

Fig. 1 Bone biochemistry. Urinary calcium, n-telopeptide, parathyroid hormone (PTH), and bone-specific alkaline phosphatase (BSAP) before (Pre), and during bed rest (BR15, BR30, or BR60) comparing several bed rest studies of similar duration. Data are means ± SD. The control data from this study are the solid black line and filled circle (AGBRESA Control) and the subjects exposed to 0.5% CO_2 during bed rest are the solid line with filled squares. Comparable bed rest studies are in gray with dashed lines[9,13,14,16,18,21,33–35,47,65,66].

- [McGregor HR, Lee JK, Mulder ER, De Dios YE, Beltran NE, Kofman IS, Bloomberg JJ, Mulavara AP, Seidler RD. Brain connectivity and behavioral changes in a spaceflight analog environment with elevated CO2. Neuroimage. 2021 Jan 15;225:117450]
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- [Richmond SB, Seidler RD, Iliff JJ, Schwartz DL, Luther M, Silbert LC, Wood SJ, Bloomberg JJ, Mulder E, Lee JK, De Luca A. Dynamic changes in perivascular space morphology predict signs of spaceflight-associated neuro-ocular syndrome in bed rest. npj Microgravity. 2024 Mar 1;10(1):24]()

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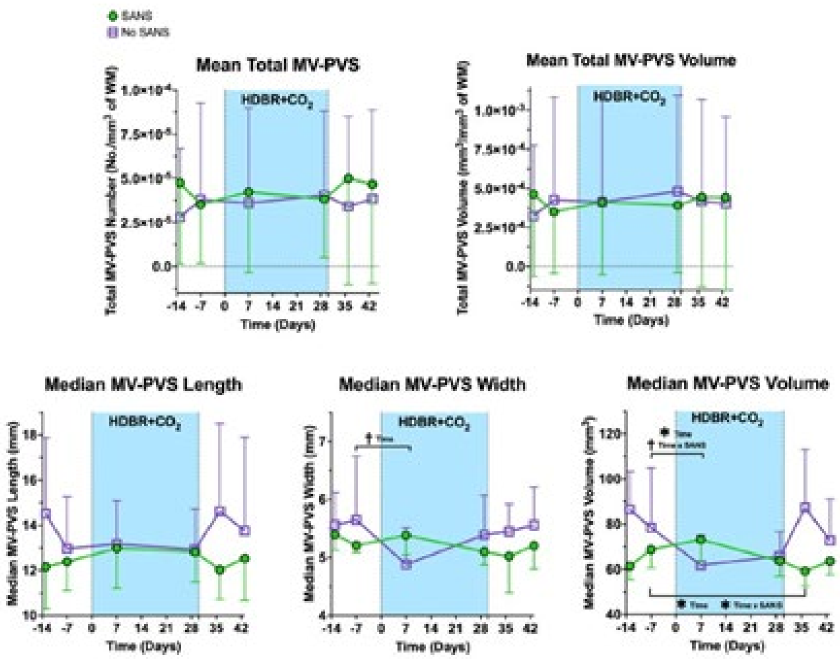

Fig. 1 | **Changes in MV-PVS metrics from pre- to post-bed rest for persons with signs of SANS compared to those without.** The HDBR + CO_2 data are split into SANS (green) and No-SANS (purple) subgroups. Bars represent standard deviation. The width of the blue box indicates the duration of HDBR + CO_2. *Indicates a statistically significant ($p < 0.05$) group difference between the SANS and No-SANS participants for changes in median MV-PVS volume and diffusivity along the PVS with bed rest. †Indicates a statistical trending ($p < 0.10$) change in median MV-PVS width and median MV-PVS volume from pre- to post-bed rest. Significant changes in recovery were examined in instances where significant pre- to post-bed rest changes occurred (i.e., median MV-PVS volume). *SANS* spaceflight-associated neuro-ocular syndrome, *MV-PVS* magnetic resonance imaging-visible perivascular space, *WM* white matter.

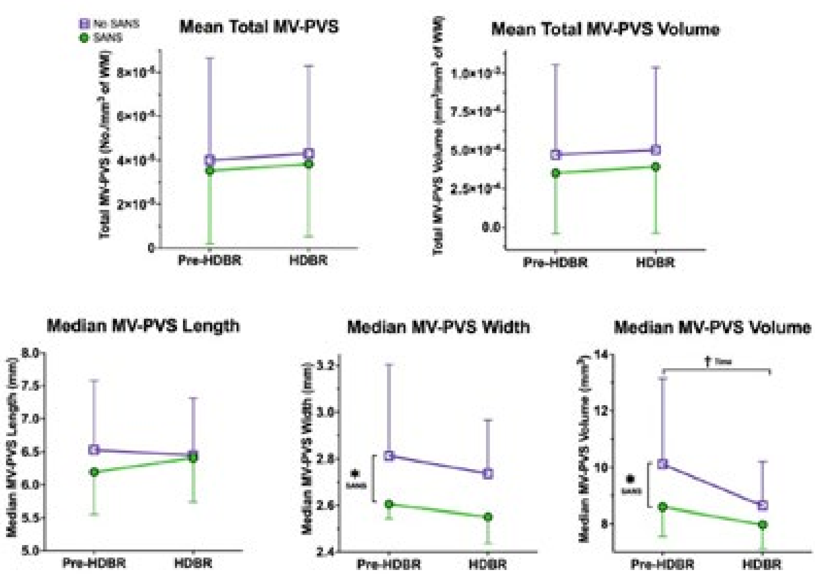

Fig. 3 | **Changes in MV-PVS metrics with bed rest in SANS versus No-SANS.** Here in each plot, we depict the group average MV-PVS characteristics for the total sample (HDBR (controls) and HDBR + CO_2), with error bars representing the standard deviation. The data are split into SANS (green) and No-SANS (purple) subgroups. *Indicates a statistically significant ($p < 0.05$) group difference between the SANS and No-SANS participants for changes in median MV-PVS width and volume with bed rest. †Indicates a statistical trending ($p < 0.10$) time effect for median MV-PVS volume from pre- to post-bed rest. *SANS* spaceflight-associated neuro-ocular syndrome, *MV-PVS* magnetic resonance imaging-visible perivascular space, *WM* white matter.

- Roberts DR, Collins HR, Lee JK, Taylor JA, Turner M, Zaharchuk G, Wintermark M, Antonucci MU, Mulder ER, Gerlach DA, Asemani D. Altered cerebral perfusion in response to chronic mild hypercapnia and head-down tilt Bed rest as an analog for Spaceflight. Neuroradiology. 2021 Aug;63:1271-81.
    - See Figure 4

- Salazar AP, Hupfeld KE, Lee JK, Banker LA, Tays GD, Beltran NE, Kofman IS, De Dios YE, Mulder E, Bloomberg JJ, Mulavara AP. Visuomotor adaptation brain changes during a spaceflight analog with elevated carbon dioxide (CO2): a pilot study. Frontiers in Neural Circuits. 2021 Jun 7;15:659557.

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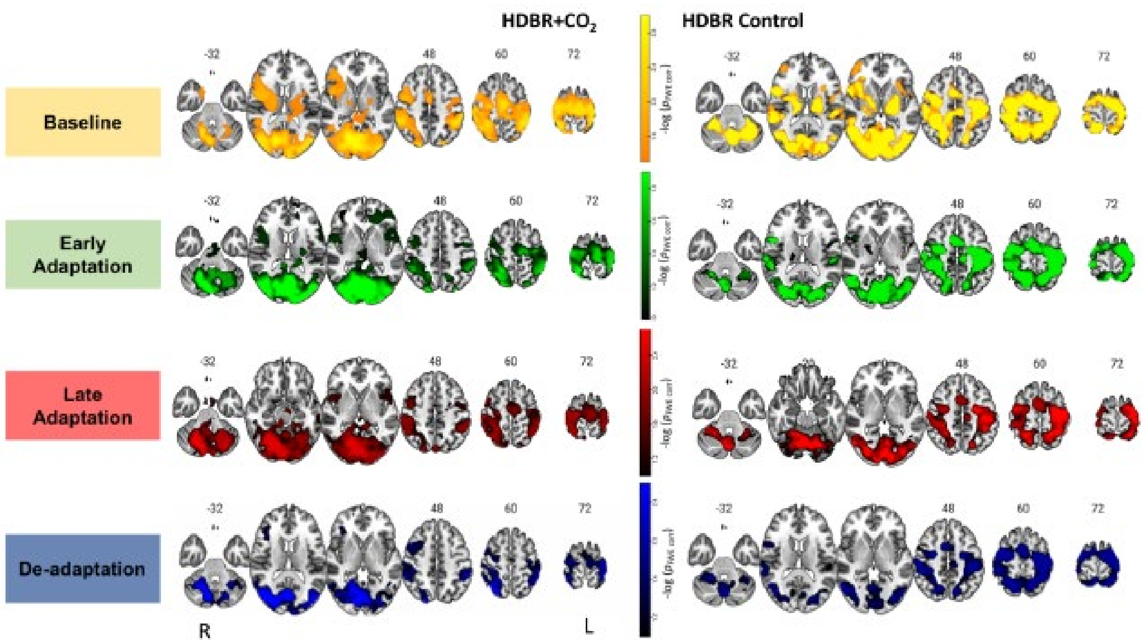

FIGURE 3 | Brain activation during each phase of visuomotor adaptation. Here we depict the main effect for each group HDBR+CO_2 (left) and HDBR Control (right) during each task phase: baseline (yellow-orange), early (green), late (red), and de-adaptation (blue). Whole brain results are overlaid onto an MNI standard template, thresholded at FWE < 0.10 and k = 10 voxels. The color scale depicts the -log($p_{FWE\text{-}corr}$) values in which brighter colors (higher values) represent smaller p-values.

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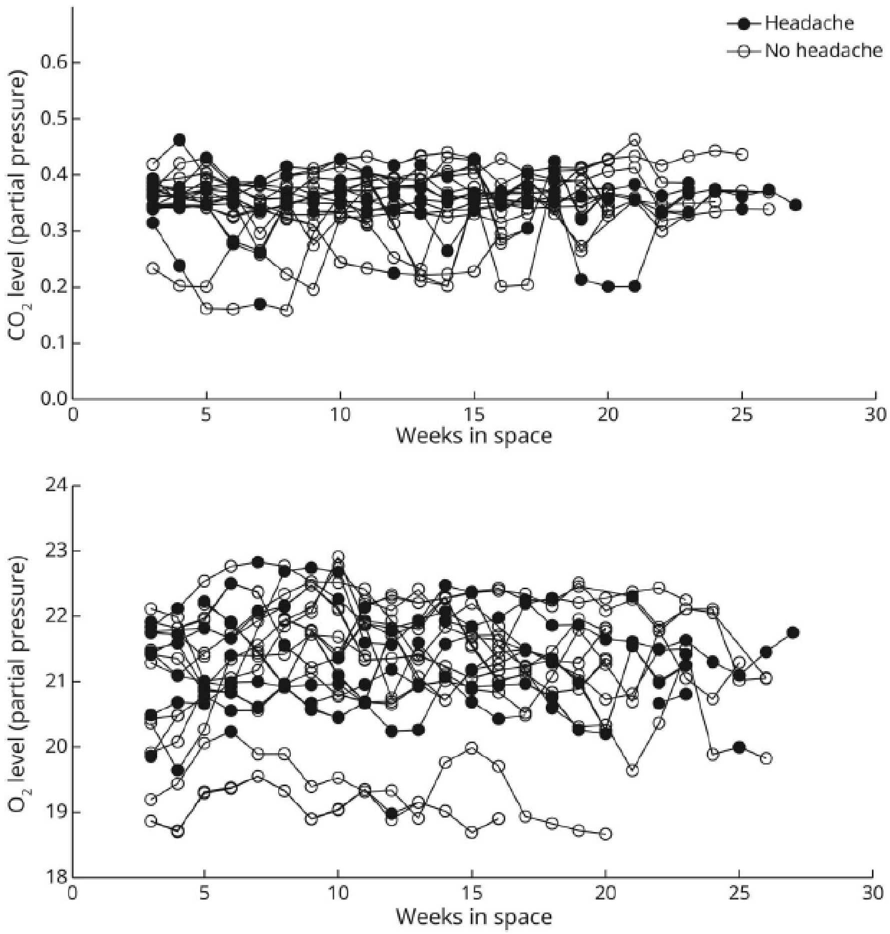
Figure 4 Graph Showing There Was No Relation Between Partial CO_2 and Partial O_2 Levels and Weekly Headache Incidence in Individual Healthy Astronauts During Long-Term Stay at the ISS



Every line reflects data from individual astronaut during space stay, in both figures.

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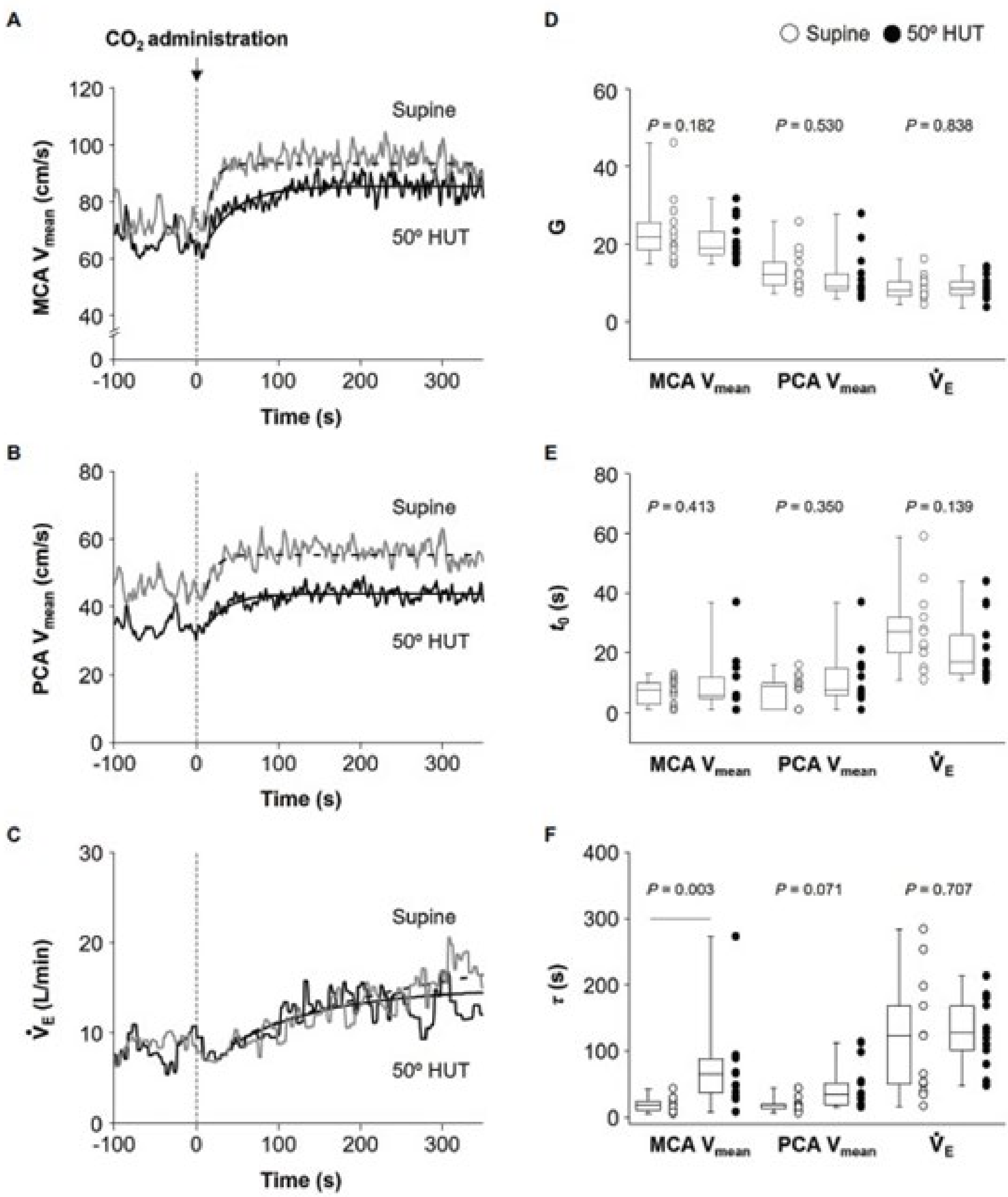

FIGURE 3 | Dynamic cerebrovascular carbon dioxide (CO_2) reactivity and central respiratory chemoreflex were characterized using a single-exponential regression model. Panels **A–C**: Continuous recordings of middle and posterior cerebral artery mean blood velocities (MCA V_{mean}, A and PCA V_{mean}, B) and pulmonary ventilation ($\dot{V}_E$, C) response to CO_2 administration (5% CO_2) during hypercapnia during supine (gray line) and 50° head-up tilt (HUT; black line) in one representative participant. The dash-dotted and smooth curve represent the exponential lines at supine and 50° HUT, respectively. Panels **D–F**: Grouped gain (G, D), CO_2-response delay (t_0, E), and time constant (τ, F) of MCA V_{mean}, PCA V_{mean}, and $\dot{V}_E$ exponential fitting curves during supine and 50° HUT. Grouped data are shown as median and interquartile range with individual data points.

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    - See Figure 1

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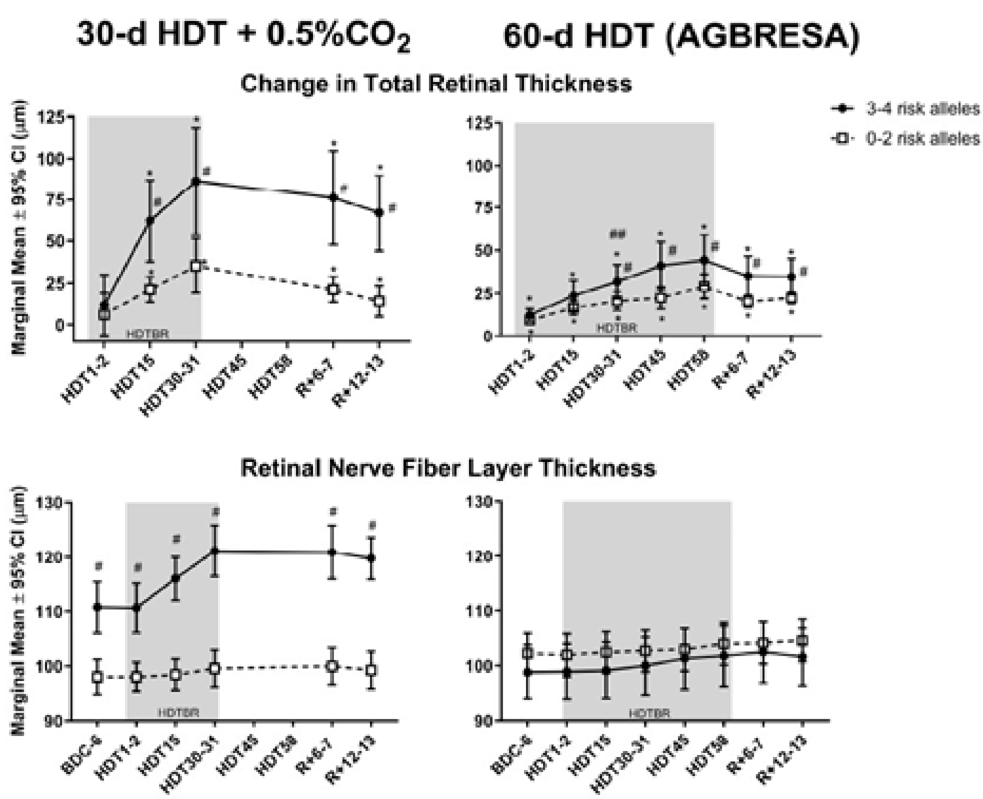

FIGURE 1

The top graphs depict mean (± 95% CI) change in peripapillary total retinal thickness in Artificial Gravity Bed Rest with European Space Agency (AGBRESA) subjects (right panel) with 3–4 (n=9) or 0–2 (n=13) risk alleles, after 2, 15, 31, 45, and 58 days of head-down tilt bed rest (HDTBR) and 6 and 13 days of recovery (R+6–7). Previously published 30-d HDTBR study data where subjects were exposed to 0.5% CO_2 are included for comparison (7) (left panels). The mean thicknesses of the peripapillary retinal nerve fiber layer are presented in the bottom panels. Shading indicates the HDTBR phase of the study. #Significantly different from subjects with 0–2 risk alleles ($P < .05$); *Significantly different from baseline total retinal thickness ($P < .001$); ##3–4 risk allele group significantly different from 3–4 risk allele group in the 30-d HDTBR + 0.5% CO_2 bed rest study ($p = 0.01$)

11. Risk Mitigation Framework – Color Changes

- **How do we know when we go from yellow → green?**
  - LEO Short/Long—reduce frequency and magnitude of excursions
  - Lunar Orbital Short—assurance of accurate CO_2 monitoring and adequate CO_2 scrubbing capability
  - Mars Preparatory/Planetary—assurance of accurate CO_2 monitoring, assurance of adequate control (scrubbing), and robust medical system to respond to symptoms

12. Risk → Standards → Requirements Flow

Risk of Acute and Chronic Carbon Dioxide Exposure

Standard

NASA-STD-3001: NASA Space Flight Human-System Standard Vol. 1, Crew Health, Revision C – September 2023

- [V1 3003] In-Mission Preventive Health Care
- [V1 5001] Medical Training
- [V1 5009] Physiological Exposure Mission Training
- [V1 3004] In-Mission Medical Care
- [V1 5002] Crewmember Training

NASA-STD-3001: NASA Space Flight Human System Standard Vol. 2, Human Factors, Habitability, and Environmental Health, Revision D – September 2023

- [V2 4015] Aerobic Capacity
- [V2 6001] Trend Analysis of Environmental and Suit Data
- [V2 6004] Nominal Vehicle/Habitat Carbon Dioxide Levels
- [V2 6006] Total Pressure Tolerance Range for Indefinite Crew Exposure
- [V2 7041] Environmental Control During Exercise
- [V2 6020] Atmospheric Data Recording
- [V2 6021] Atmospheric Data Displaying
- [V2 6022] Atmospheric Monitoring and Alerting Parameters
- [V2 6107] Nominal Vehicle/Habitat Atmospheric Ventilation
- [V2 6108] Off-Nominal Vehicle/Habitat Atmospheric Ventilation

Handbook

- NASA/SP-2010-3407, Human Integration Design Handbook (June 2014)
- NASA/SP-2015-3709, Human Systems Integration Practitioners Guide (Nov 2015)

Requirements

ISS	MPCV	CCP	HLS	Gateway	EHP	CLDP
SSP 50005: International Space Station Flight Crew Integration Standard SSP 41162 Segment Specification for United States On-Orbit SSP 50808 ISS to COTS IRD	MPCV 70024 Human System Integration Requirements	CCT-REQ-1130 ISS Crew Transportation Requirements Document JSC-65993 CHSIR	HLS-HMTA-001 (Initial) HLS-HMTA-006 (Sustained)	GP10000 Gateway Program System Requirements	xEVAS-SRD-001	

13. Proposed Standard Updates

- None at this time.

14. High Value Risk Mitigation Targets

- Systematically evaluate acute spikes and swings in CO_2 levels (Epidemiology/ Space Medicine Operations Division)
- Systematically evaluate the correlation between cabin average CO_2 levels and crew exposures by developing a method to continuously evaluate inhaled CO_2 levels (human research Project [HRP])
- Off-nominal excursions are beyond the scope of the CO_2 risk but should be investigated (magnitude, frequency, and duration) to support the development of an emergency (cabin) standard for CO_2 level
- Evaluate the physiological impacts of combining proposed exploration atmospheres (altered pressure/O_2) with elevated ambient CO_2 (HRP)
- Suited CO_2 limits are beyond the scope of the CO_2 risk but should continue to be investigated under the Risk of Injury and Compromised Performance Due to EVA Operations
- Monitor additional symptoms related to CO_2 such as sinus congestion (Space Medicine Operations Division 3)
- On-going evaluation of acquired cerebral changes (using MRI) are needed that would indicate LTH impacts, and further MRIs would be required after a mission (HRP)

15. Conclusions

- For all DRMS
    - Reliable CO_2 monitoring
    - Reliable CO_2 scrubbing
- Concerns
    - Implementation of NASA standard 3001 is variable
    - The ISS has ongoing spikes and swings in CO_2 levels and ongoing reports of symptoms (but largely within Flight Note rules)
    - Correlation between cabin CO_2 levels and inspired CO_2 levels are unknown
    - Effects of exploration atmospheres on CO_2 sensitivity are unknown
    - Although no LTH effects from elevated levels of CO_2 exposure in microgravity have been reported, further evaluation (such as brain MRI) is needed to rule out acquired cerebrovascular changes

16. Recommendations Accepted

- The Risk Record for the CO_2 Risk is revised to provide:
  - Likelihood x Consequence (LxC) scores assessed against updated DRMs and the 5x5 Risk Matrix
  - Updated evidence

17. Acronyms and Abbreviations

AGBRESA	Artificial Gravity Bed Rest – European Space Agency
CDRA	Carbon Dioxide Removal Assembly
CHIT	A form used to exchange information between the MER and flight control center
CO_2	Carbon Dioxide
CVR	Cerebrovascular Reactivity to CO_2
CR	Change Request
DAG	Directed Acyclic Graph
DRM	Design Reference Mission
ECLS	Environmental Control and Life Support
HDBR	head down tilt in bed rest
HLS	Human Landing System
ICP	Intracranial Pressure
IOP	Intraocular Pressure
ISS	International Space Station
LEO	Low Earth Orbit
HSRB	Human System Risk Board
LTH	Long-Term Health
LxC	Likelihood and Consequence
MCA	Major Constituent Analyzer
MCAv	Middle Cerebral Artery Blood Velocity
MRI	Magnetic Resonance Imaging
mmHg	millimeters of mercury
Ops	Operations
p	calculated probability
pCO_2m	personal CO_2 monitors
pCO_2	personal CO_2
$P_{ET}CO_2$	End Tidal CO_2 Pressure
PIO2	Pressure inspired oxygen
psia	Pounds per square inch absolute
PVT	Psychomotor Vigilance
SANS	Spaceflight Associated Neuro-ocular Syndrome
SD	Space Medicine Operations Division (Division Code)
SK	Biomedical Research and Environmental Sciences Division (Division

	Code)
TAS	Thermal Amine CO_2 Scrubber
USOS	US On-Orbit Segment
VaPER	Vision Impairment and Intracranial Pressure (VIIP) and Psychological :envihab Research

18. Reference Materials

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- Zwart SR, Laurie SS, Chen JJ, Macias BR, Lee SM, Stenger M, Grantham B, Carey K, Young M, Smith SM. Association of genetics and B vitamin status with the magnitude of optic disc edema during 30-day strict head-down tilt bed rest. JAMA ophthalmology. 2019 Oct 1;137(10):1195- 200.
- Zwart SR, Macias BR, Laurie SS, Ferguson C, Stern C, Suh A, Melin MM, Young M, Bershad E, Smith SM. Optic disc edema during strict 6° head-down tilt bed rest is related to one-carbon metabolism pathway genetics and optic cup volume. Frontiers in Ophthalmology. 2023 Oct 27;3:127983

Appendix – Existing Evidence Base

Existing Evidence – Rev C

Bedrest Studies

❖ **VaPER data (preliminary at last update) indicate no change in the following parameters during 30 days of 6° head-down tilt 'strict' bedrest at 4 mmHg ambient CO_2 in 11 healthy subjects**

- End-tidal personal CO_2 (PCO_2)
- Arterialized PCO_2
- Cerebrovascular reactivity
- Brain blood flow velocity
- Ventilatory response to CO_2


J Physiol 00.0 (2020) pp 1–15 1

Unchanged cerebrovascular CO_2 reactivity and hypercapnic ventilatory response during strict head-down tilt bed rest in a mild hypercapnic environment

Steven S. Laurie[1], Kate Christian[2], Jacob Kysar[2], Stuart M.C. Lee[1], Andrew T. Lovering[2], Brandon R. Macias[1], Stefan Moestl[3], Wolfram Sies[3], Edwin Mulder[3], Millennia Young[4] and Michael B. Stenger[4]


american physiological society | JOURNAL OF APPLIED PHYSIOLOGY.

J Appl Physiol 130: 1235–1246, 2021.
First published February 25, 2021; doi:10.1152/japplphysiol.00865.2020

RESEARCH ARTICLE

Effects of head-down tilt bed rest plus elevated CO_2 on cognitive performance

Mathias Basner,[1*] Alexander C. Stahn,[1*] Jad Nasrini,[1] David F. Dinges,[1] Tyler M. Moore,[2] Ruben C. Gur,[2] Christian Mühl,[3] Brandon R. Macias,[4] and Steven S. Laurie[5]
[1]Division of Sleep and Chronobiology, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; [2]Brain Behavior Laboratory, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; [3]Department of Sleep and Human Factors Research, Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany; [4]NASA Johnson Space Center, Houston, Texas; and [5]KBR, Houston, Texas

❖ **SANS related effects noted in VaPER were also noted in AGBRESA in the control condition without elevated CO_2**

❖ **Strict 6° head-down tilt bedrest resulted in (negative) impacts in several cognitive domains, but these were not impacted by the presence of absence of elevated CO_2 (4 mmHg) nor by the inclusion of artificial gravity**


american physiological society | JOURNAL OF APPLIED PHYSIOLOGY.

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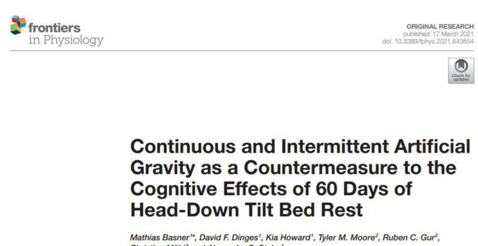

frontiers in Physiology

ORIGINAL RESEARCH
published: 17 March 2021
doi: 10.3389/fphys.2021.643854

Continuous and Intermittent Artificial Gravity as a Countermeasure to the Cognitive Effects of 60 Days of Head-Down Tilt Bed Rest

Mathias Basner[1*], David F. Dinges[1], Kia Howard[1], Tyler M. Moore[2], Ruben C. Gur[2], Christian Mühl[3] and Alexander C. Stahn[1]

In-Flight Data

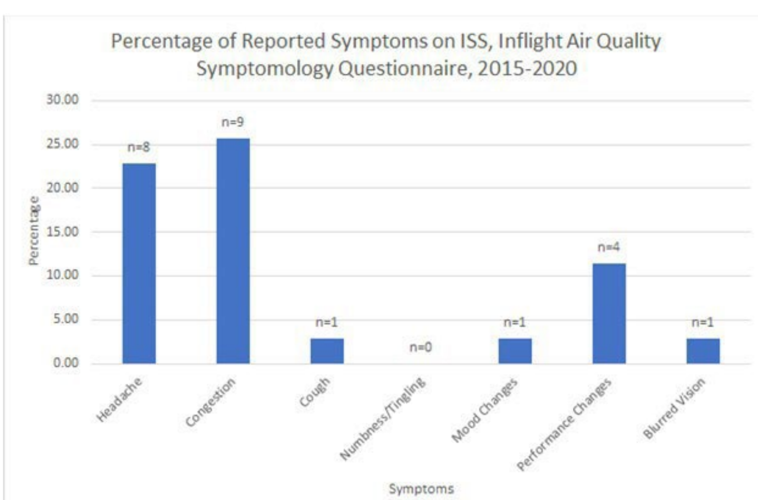
❖ **Basner M, Smith M, Jones C, Riedy S, Stahn A, Shou H, Tu D, Aeschbach D, Romoser A, Ryder V, Williams S, Dinges D. Advanced algorithms for the prediction of adverse cognitive and behavioral conditions in space.** NASA Human Research Program's Investigators' Workshop, Jan 27-30, 2021 Galveston TX.

Determined the following in-flight environmental variables with the highest predictive value for PVT (Psychomotor Vigilance Test) performance:

- Past PVT performance
- Self-reported workload, sleep quality, sleepiness, physical exhaustion, mental fatigue, and stress
- Radiation
- Temperature
- Oxygen (O_2) and Carbon Dioxide (CO_2) levels
- Sleep duration and predicted lapses based on sleep history
- Age

❖ **Air quality symptom questionnaires—recommended when symptoms potentially related to CO_2 are reported by a crewmember**

- Between 2015–2020
  - 35 crewmembers have flown since the Inflight Air Quality Symptomology Questionnaire was implemented in 2015 (data is through 2020 and does not include Russian crewmembers)
  - 14 reports from 10 crewmembers
  - The most consistent report was congestion
  - All symptoms reported through the questionnaire were alleviated by medications (antihistamines or analgesics)
  - Some crewmembers have reported symptoms (in-flight and post flight debriefs) that were NOT documented in this questionnaire.



❖ Evaluation of Congestion

- Analysis conducted on the ISS through 2015
- Logistic regression modeling used to assess the association between reports of congestion and CO_2 levels and age of station
  - $\log\left(\frac{P}{1-p}\right) = \beta\beta 0 + \beta\beta 1 \text{ x } IIIII\text{age} + \beta\beta 2 \text{ x } CCCC2$
  - Adjusted for repeated measures within crew across time
  - Multiple Imputation used to address missing CO_2
- Congestion has been associated with age of station (years) (OR: 1.25) CO_2 (mmHg) (OR: 1.21) (data pending publication)
  - Age of station and CO_2 are confounded, but both contribute to congestion reports
  - After 20+ years, age is the stronger contributor to the predicted probability of congestion reports

❖ Updates to CO_2 Removal Technology Demonstrations

- **Thermal Amine Scrubber (TAS)**
  - Launched in April 2019 on Cygnus NG-11
  - 340 days of cumulative on orbit run time
  - Demonstrated capability to manage CO_2 levels well below current CHIT requirement of 3 mmHg (24-hr average) when combined with single Carbon Dioxide Removal Assembly (CDRA) but has experienced several reliability issues over the past 2 years.
  - TAS recovery expected by end of September 2021, pending SpaceX-23 Launch
  - Small air loss (~0.1 pounds mass per day) limits nominal operating mode equivalent removal for 2 crewmembers

❖ Updates to CO_2 Removal Technology Demonstrations (cont.)

- **4-Bed CO_2 Scrubber**
  - Launched in August 2021 on Cygnus NG-16
  - Based on existing CDRA with the following upgrades
    - New sorbent materials
    - Efficiently designed sorbent beds (packaging & heaters)
    - Robust valves
    - Higher flow rates
    - Robust filters
  - Activation expected by end of September 2021
  - Agreement in place with the Space Medicine Operations Division to operate TAS and 4-Bed simultaneously (or with single CDRA) with expectation to achieve levels at or near 2 mmHg
- **Mini Scrubber**
  - Core technology still in development
  - On orbit demonstration no earlier than Fall 2023

Existing Evidence – Rev B
Terrestrial Evidence (Acute Exposure)

Cognitive Data

❖ Allen JG, MacNaughton P, Satish U, Santanam S, Vallarino J, Spengler JD. 2016. Associations of cognitive function scores with carbon dioxide, ventilation, and volatile organic compound exposures in office workers: a controlled exposure study of green and conventional office environments. Environ Health Perspect 124:805–812; http://dx.doi.org/10.1289/ehp.1510037

This study, which involved controlled exposure of office workers to different building conditions, showed that improved indoor air quality, particularly with lower CO_2 and volatile organic compound (VOC) levels, correlated with better cognitive performance.

- Study Design: 8-hour daily exposure to green (CO_2 = 0.7 mmHg), green+ (CO_2 = 0.4 mmHg) or conventional office environments (CO_2 = 1.0) mmHg.
- Key Results: Participants in green and green+ environments, characterized by higher ventilation rates and lower volatile organic compound (VOC) levels, exhibited significantly better cognitive performance across various domains.
- Study Caveats: Outdoor air quality (particularly ozone) varied over the course of the exposure and although VOCs and CO_2 levels were independently associated with cognitive scores, the effect of CO_2 alone was not studied.
- Questions: What is the functional impact of a 50% decline in cognitive measures? The study suggests that even modest improvements in indoor air quality can lead to substantial enhancements in cognitive abilities such as decision-making but does not indicate if performance is acceptable in conventional environments.

❖ Rodeheffer CD, Chabal S, Clarke JM, Fothergill DM. Acute Exposure to Low-to-Moderate Carbon Dioxide Levels and Submariner Decision Making. Aerosp Med Hum Perform. 2018 Jun 1;89(6):520-525

This study investigated whether submariner decision-making performance is impacted by acute exposure to the levels of CO_2 typically found in the submarine atmosphere.

- Study Design: Subject-blinded balanced design with 36 submarine-qualified male sailors (age 20–47 years) were randomly assigned to one of 3 CO_2 exposure conditions: 0.5, 1.9, or 11.4 mmHg.
- Key Results: No significant differences were detected for any of the 9 strategic management simulation test measures to assess decision making in the different CO_2 exposure conditions.

- Study Caveats: Statistical analysis was not performed *a priori* (lack of available data) and there was no within-subject design.
- Questions: Does chronic exposure (3-month submarine mission or 6–12-month ISS mission induce cognitive deficits that are not capture in this acute study (4 hours)? Do acute peak exposure (spikes) in addition to an elevated background level of $C0_2$ impact cognition?

❖ Allen JG, MacNaughton P, Cedeno-Laurent JG, Cao X, Flanigan S, Vallarino J, Rueda F, Donnelly-McLay D, Spengler JD. Airplane pilot flight performance on 21 maneuvers in a flight simulator under varying carbon dioxide concentrations. J Expo Sci Environ Epidemiol. 2019 Jun;29(4):457-468. doi: 10.1038/s41370-018-0055-8.

This study found that higher CO_2 levels in the flight simulator negatively impacted pilot performance.

- Study Design: Randomized blinded study of commercial airline pilots who completed three 3-hour flight segments in a simulator at different CO_2 concentrations: 0.6, 1.1, or 1.9 mmHg.
- Key Results: Maneuver performance degraded at 1.9 mmHg relative to 0.5 mmHg.
- Study Caveats: Outcome (performance) was subjective and may have varied by evaluator. Evaluators were exposed to the same levels of CO_2. Scenarios did not use realistic flight-like parameters. Ventilation parameters and/or exposure to other volatile compounds were not evaluated. Learning effects may not have been controlled.
- Question: How is this study applicable to more realistic flight/spaceflight operational scenarios?

❖ Scully RR, Basner M, Nasrini J, Lam CW, Hermosillo E, Gur RC, Moore T, Alexander DJ, Satish U, Ryder VE. Effects of acute exposures to carbon dioxide on decision making and cognition in astronaut-like subjects. NPJ Microgravity. 2019 Jun 19;5:17. doi: 10.1038/s41526-019-0071-6.

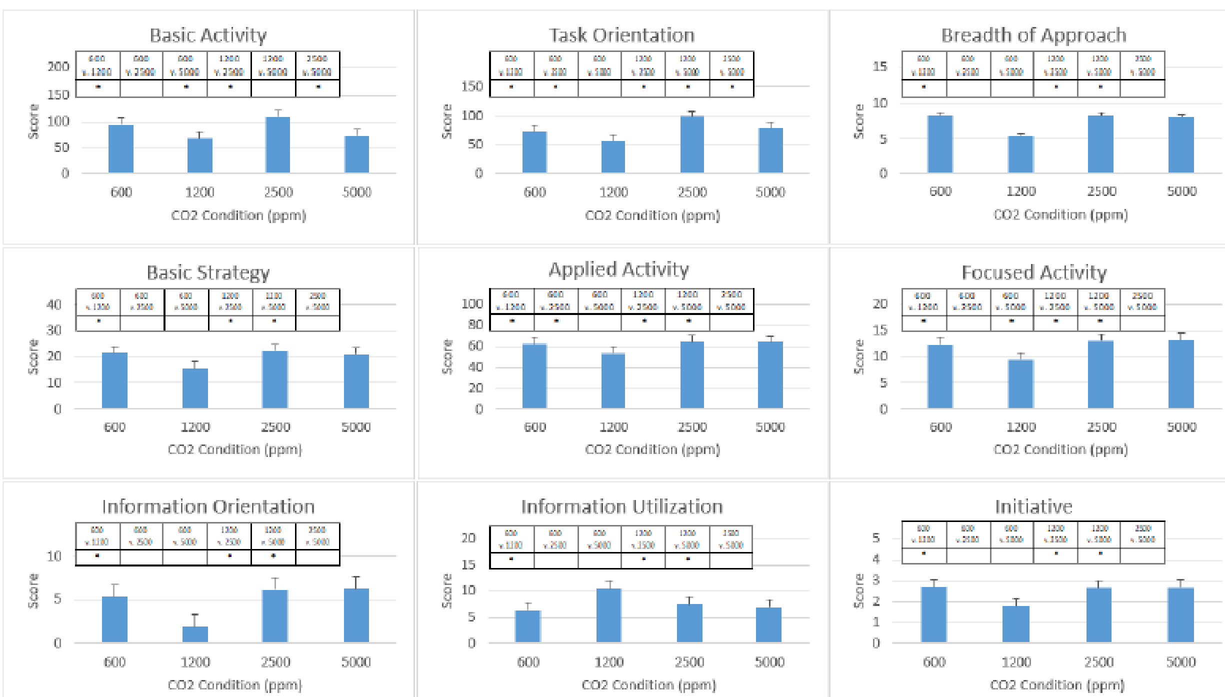
This study found that acute exposure to CO_2 at levels below those typically found on the ISS can negatively impact decision-making and cognitive functions.

- Study Design: Randomized double-blinded, controlled, balanced cross-over study of astronaut-like subjects who were exposed to 0.5, 0.9, 1.9 or 3.8 mmHg for 3 hours per session
- Key Results: Performance decreased for most measures in the strategic measurement simulation test for 0.9 mmHg exposure compared to baseline (0.5 mmHg), however, at higher CO_2 concentrations

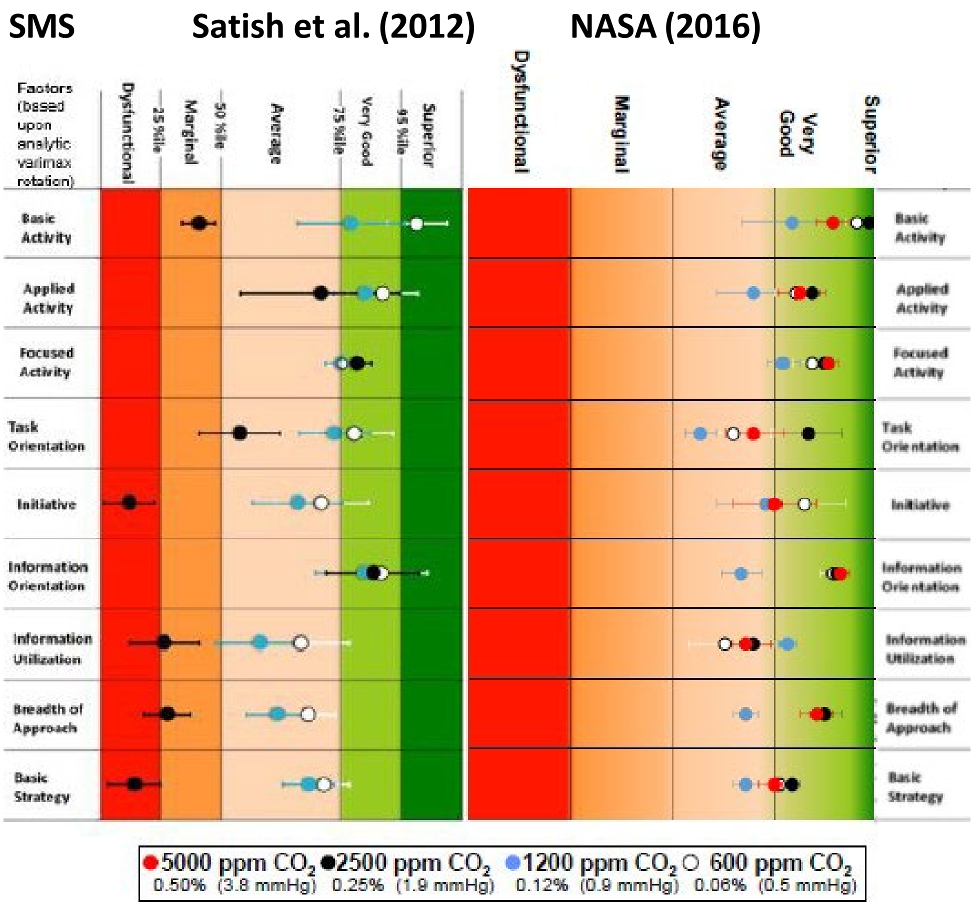
performance was similar to, or exceeded, baseline for most measures. In contrast to a previous study (Satish et al., 2012), performance on the strategic measurement simulation test never declined below average (50–75th percentile). No significant changes were detected on 9 of the 10 tests administered by the Cognition test battery. Accuracy on the visual object learning test (one of the Cognition test battery measures) increased with exposure to 1.9 mmHg CO_2 (similar to reports by Basner et al., 2017). Speed and accuracy over all 10 Cognition tests was reduced for the 0.9mmHg CO_2 exposure compared to performance for the other CO_2 levels.

- Questions: Were the cognitive endpoints measured most relevant for spaceflight contingency operations? Were the effects noted at 0.9 mmHg caused by something other than CO_2? Are these terrestrial data relevant to microgravity conditions, or are thresholds lower in microgravity? Does a chronic exposure of 6–12 months on the ISS induce cognitive effects that are not captured by acute exposure (3 hours)?

Figure 1 from Scully et al. 2019

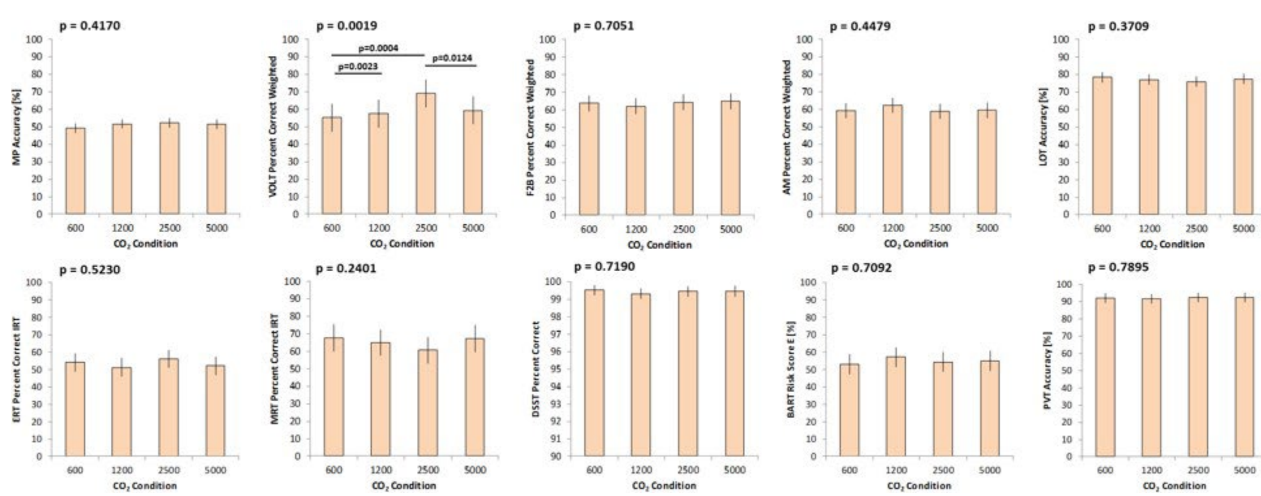


Means ± 95% confidence intervals of SMS measures at each targeted concentration of CO_2. Measures for Initiative represented are the log-transformed values utilized for statistical analysis. * Significant differences $p < 0.008$

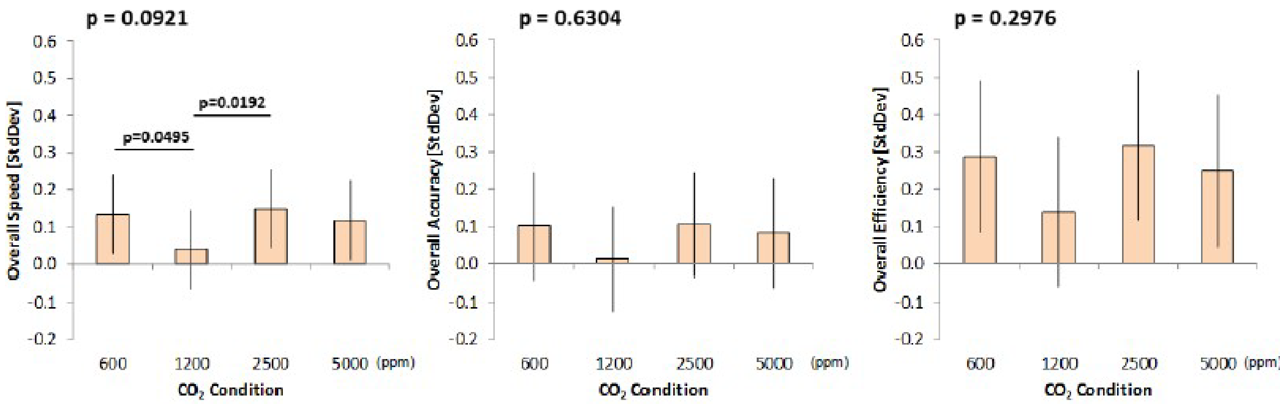


SMS= strategic measurement simulation test

“Cognition” Responses (Mean, 95% FI), taken from Figure 4 Scully et al. 2019



“Cognition” Responses Accumulated Across 10 Tests), Figure 5 Scully et al. 2019



Evaluation of standardized scores of speed, accuracy, and efficiency across tests (higher scores reflect better performance). The P-values for significant differences in overall speed across tests achieved at different CO_2 concentration are given on the graphs for Overall Speed.

Physiological Data

❖ Laurie SS, Vizzeri G, Taibbi G, Ferguson CR, Hu X, Lee SM, Ploutz-Snyder R, Smith SM, Zwart SR, Stenger MB. Effects of short-term mild hypercapnia during head-down tilt on intracranial pressure and ocular structures in healthy human subjects. Physiological reports. 2017 Jun;5(11):e13302

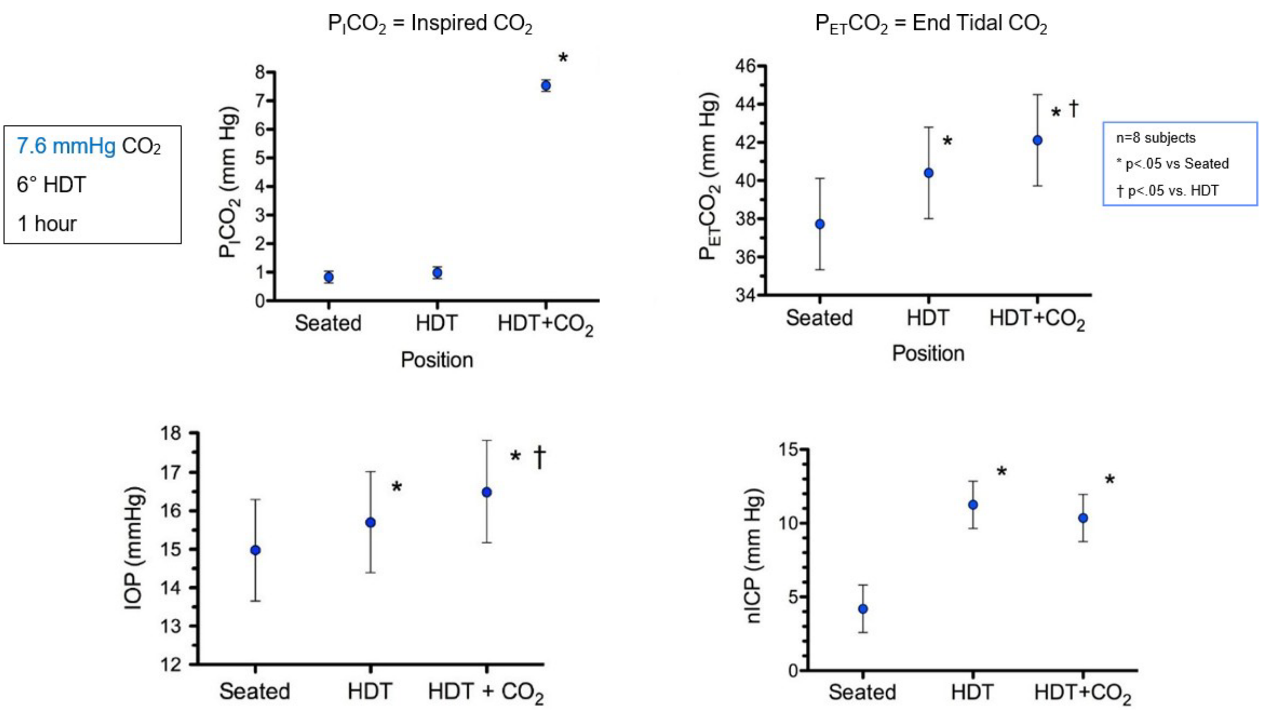
This study investigated how mild hypercapnia (increased CO_2 levels in the blood) combined with a head-down tilt position affects ICP and structures in the eyes of healthy individuals.

- Study Design: Randomized sonographer-blinded, repeat measures study in which noninvasive IOP and ICP, cerebral and ocular ultrasounds, and optical coherence tomography scans of the maula and optic disc were obtained from 8 men during three 1-h sessions in seated, 6° head down tilt (HDT), or HDT with 7.6 mmHg CO_2. Analysis of one-carbon pathway genetics previously associated with SANS was also conducted.
- Key Results: Increased levels of CO_2 did not cause a 1:1 change in arterial pCO_2. HDT also induced IOP that was further exacerbated by elevated levels of CO_2. HDT increased ICP, optic nerve sheath diameter, and choroidal thickness compared to the values obtained in a seated position, but adding mild hypercapnia during HDT did not significantly worsen these changes. Genetic polymorphisms related to one-carbon metabolism were linked to individual differences in IOP, ICP, and end-tidal PCO2.
- Study Caveats: Measures of ICP were indirect, and data regarding accuracy were lacking. Outcome measures were taken sequentially rather than concurrently at the end of each condition. Subjects observed that the

breathing devices were not connected to the breathing reservoir, so the study was not blinded during the control conditions. The number of subjects was small.

- <u>Question</u>: what effects would be observed with longer acute or chronic exposures?

PCO_2 Levels, IOP and ICP



Laurie, *et al*. (2017) *Physiol Rep*. 5(11)

- **Kramer LA, Hasan KM, Sargsyan AE, Marshall-Goebel K, Rittweger J, Donoviel D, Higashi S, Mwangi B, Gerlach DA, Bershad EM; SPACECOT Investigators Group. Quantitative MRI volumetry, diffusivity, cerebrovascular flow, and cranial hydrodynamics during head-down tilt and hypercapnia: the SPACECOT study. J Appl Physiol (1985). 2017 May 1;122(5):1155-1166. doi: 10.1152/japplphysiol.00887.2016**

This study used MRI to measure anatomical and physiological changes in the brain and ocular structures to evaluate the effects of HDT and hypercapnia on brain physiology.

- Study Design: Double blinded, cross-over study of 6 men who were exposed for 26.5 h to 12° HDT with ambient air or with 3.8 mmHg CO_2 and both conditions were followed by 2.5-h exposure to 23 mmHg CO_2.
- Key Results: Cerebrovascular flow was no different under either CO_2 exposure condition. HDT decreased cerebrovascular flow, and this effect was reverse by the exposure to 23 mmHg CO_2. Acute exposure to 23 mmHg CO_2 augments cerebral spinal fluid pulsatility within the cerebral aqueduct and the lateral ventricles. ICP pulsatility during exposure to 23 mmHg CO_2 was more notable after HDT with ambient air then HDT with 3.8 mmHg CO_2. ICP pulsatility may contribute to pathophysiology even in the absence of elevated static ICP.
- Study Caveats: the number of subjects was small. Baseline ICP pulsatility values were not the same for ambient air and CO_2 conditions. Measures of ICP were inferred by cerebrospinal fluid flow characteristics and not measured directly. The effects of exposure to 23 mmHg CO_2 without HDT was not included as a control condition.
- Questions: Is there a synergistic effect on cerebrospinal fluid from combined exposure to HDT and elevated levels of CO_2 that is likely encountered during spaceflight? What are the long-term effects of acute elevations in CO_2 levels in conjunction with reduced craniospinal compliance and exposure to chronically elevated levels of CO_2?

- **Marshall-Goebel K, Mulder E, Bershad E, Laing C, Eklund A, Malm J, Stern C, Rittweger J. Intracranial and Intraocular Pressure During Various Degrees of Head-Down Tilt. Aerosp Med Hum Perform. 2017 Jan 1;88(1):10-16. doi: 10.3357/AMHP.4653.2017.**

  This study investigated the impact of different degrees of HDT on ICP and IOP.

  - Study Design: Experiment I measured ICP and IOP in 9 healthy men (mean age 24 +/- 2.4 yrs) after 3.5 hours of HDT in 5 conditions: -6°, -12°, and -18° HDT with 7.6 mmHg CO_2 and -12° HDT with -20 mmHg lower body negative pressure (LBNP). Experiment II measured IOP in 16 healthy subjects after 5 mins of tilt at +12°, 0°, -6°, -12°, and -24°, at various angles, with and without 40 mmHg LBNP.
  - Key Results: No significant differences were detected in ICP and IOP when HDT was conducted in ambient air or 7.6 mmHg CO_2.
  - Study Caveats: Baseline measurements were taken in supine position; however, it would have been useful for future studies if there was a comparison between the interventions and both the upright and supine postures. Number of subjects was small.
  - Question: Does exposure to elevated levels of CO_2 exacerbate extended exposure (i.e., more than 3.5 h) to HDT-induced ICP and IOP?

- **Lawley JS, Petersen LG, Howden EJ, Sarma S, Cornwell WK, Zhang R, Whitworth LA, Williams MA, Levine BD. Effect of gravity and microgravity on intracranial pressure. J Physiol. 2017 Mar 15;595(6):2115-2127. doi: 10.1113/JP273557.**

  This study found that while ICP is lower in microgravity compared to the supine position on Earth, it is not reduced to the levels seen in the upright posture on Earth.

  - Study Design: ICP was assessed in 5 men and 3 women who had an Ommaya reservoir inserted for delivering prophylactic central nervous system chemotherapy. Subjects were assessed in upright and supine position during acute exposure to microgravity (during parabolic flight) and simulated microgravity during HDT bedrest. The participants breathed increased ambient CO_2 through a face mask during the tests.
  - Key Results: 5.3 mmHg CO_2 had no effect on ICP either during real or simulated microgravity. The addition of 5.3 mmHg CO_2 during parabolic flight slightly increased the fall in ICP. This suggests that the complete removal of gravity prevents the normal lowering of ICP that occurs when standing upright on Earth due to hydrostatic effects.
  - Study Caveats: The number of subjects was small. Only acute durations of microgravity could be induced.

Terrestrial Evidence (Acute Exposure)

VaPER: 30 d 6°HDBR @ 3.8 mmHg CO_2 Conducted in the :Envihab environmental chamber and bedrest facility German Aerospace Center (DLR) in Cologne

Three studies were supported by the HRP's Human Health Countermeasure Element

- **Integrative physiology of SANS/VIIP: cardiopulmonary, sleep, and cognitive function assessment during hypercapnic bed rest;** *PI: Steven Laurie (NASA JSC)*
  - Evaluated if ocular/visual changes developed that were consistent with SANS/VIIP, and correlated those to arterial CO_2 levels, cerebrovascular reactivity, intracranial pressure, cognitive function, mood, sleep quality, sleep fragmentation, and circadian alignment

- **Omics and biochemical markers of cardiovascular and bone health: Relationship with bed rest and standard physiological Measures;** *PI: Carl Ade (University of Oklahoma)*
  - Investigated cardiovascular and bone-specific blood transcriptomic biomarkers and correlated them to cardiovascular and bone outcomes

- **Identification of functional metabolomic alterations during the simulated spaceflight environment;** *PI: Brinda Rana (University of California, San Diego)*
  - Investigated and correlated blood and urine metabolomic biomarkers with cardiovascular, muscle/bone/exercise, and SANS/VIIP measures

Preliminary Results – Presented to HSRB on 2/8/18

- Optic disc edema developed in both eyes in 5 of 11 subjects (3 females).
- Quantification of total retinal thickness (TRT) was significantly greater during the VaPER study compared to previous 14-day and 70-day bedrest studies (Figure 1).
- Retinal nerve fiber layer (RNFL) thickness increased in subjects with optic disc edema, but not in those without. The increased thickness did not resolve within the first 13 days after bedrest (Figure 2).

One study supported by HRP's Human Factors and Behavioral Performance Element.

- **Bed Rest Combined with 3.8 mmHg CO_2 as a Spaceflight Analog to Study Neurocognitive Changes: Extent, Longevity, and Neural Bases;** *PI: Rachel Seidler (Univ of Michigan)*
  - Identification of the underlying neural mechanisms (i.e., brain reorganization, structural remodeling, positive and negative plasticity) and operational risks (i.e., impaired performance, safety) of changes in behavior with a high fidelity spaceflight analog
  - Determination of whether a return to normative behavioral function (i.e., working memory, processing speed, visuospatial abilities) following bed rest is associated with a restitution of brain structure and function or instead is supported by substitution with compensatory processes. This will be done via behavioral tests, and structural and functional MRI neuroimaging assessments.
  - The addition of a CO_2 group enables ability to parse out the multiple mechanisms contributing to any spaceflight induced neural structural and behavioral changes that we observe in our ongoing flight projects (NASA flight project, Seidler PI; ILSRA flight study, Stahn PI)
  - Comparison with recently completed bed rest projects (Seidler and Stahn, PIs) will allow delineation of brain and behavioral changes occurring with long term exposure to slightly elevated CO_2 level

Inflight Evidence (Chronic Exposures)

- Crew Reports indicate that symptoms occur at lower CO_2 levels on orbit than terrestrially - possible due to synergy with fluid shifts
  - Therefore, results from terrestrial studies may not reflect physiological changes associated with microgravity and should be used with caution for establishing in-flight limits and requirements
- There is mounting evidence that human health and performance impacts remain at recent ISS CO_2 levels (≤ 3 mmHg)
  - Current operational limit of 3.0 mmHg is a balance of considerations (crew health versus ECLSS capabilities/resources)
  - Current operational limit of 3.0 mmHg may be below the threshold for non-localized headaches for all but the most sensitive crewmembers; however, it is still likely to be associated with CO_2 symptomatology

CO_2 (mmHg)	Crew Reports (private medical conferences (PMCs) and call-downs)
< 2.3	Fewer reports attributable to CO_2
2.3 - 2.7	Fatigue, full-headedness
2.7 - 3.0	Self-reports of performance decrements, procedure missed steps, procedures going long
> 3.0	Headaches (variable - between 3.0 - 3.4 mmHg) [in addition to the symptoms experienced at lower CO_2]

ISS and Terrestrial Signs and Symptoms Comparison

Row #	% of CO_2	mmHg	Effects
1	0.1	0.76	Acute exposure affects judgment
2	0.3-0.35	2.3-2.7	Subjective fatigue and full-headedness
3	0.35-0.4	2.7-3.2	Self Reports of performance decrements, difficulty concentrating, procedural missed steps and procedures going long
4	0.4-0.45	3.0-3.4	Headache onset
5	0.45-0.48	3.4-4.0	Sensation of ↑ breathing rate and one case of dysesthesia
6	0.5	3.8	International Safety Limits for 8-10 hour days (HSE, OSHA, NIOSH)
7	1	7.6	Rate of breathing increases >37%, increased work of breathing acutely
8	1.6	12.2	Respiratory tidal volume increases (MEL 480 min)
9	2	15.2	1) Rate of breathing increases to >50%, perceived as a shortness of breath 2) ↓ visual stereoacuity (detection of coherent motion), and increase in metabolic rates after 30-60 minutes (MEL 60 minutes)
10	3-5	15.2-38	Feeling of being closed in, feeling of panic in some, HA in some after 20 minutes (MEL 10 min)
11	5	38	Dizziness, HA, Confusion, Dyspnea after 10-20 minutes

Headaches upon arrival to ISS may have a CO_2 component as well as Space Adaptation Syndrome (SAS)

- Crew reports indicate that EVA pre-breathe resolved symptoms of congestion and headache and improved overall well-being
- CO2 has been associated with vertigo terrestrially

Reported symptoms increase in incidence over time

- May be an indicator of vascular dilatation as well as cerebral compliance decompensation
- Chronic CO2 exposure should be considered as disease progression – Rice et al. (2004), Ainsle et al. (2005)
- Symptoms occur based on the individual's tolerance level set point and once the levels rise above the level of cerebral and vascular compliance and compensation, overt symptoms occur which are past the compensatory mechanisms
- Subtle compensated symptoms are occurring at levels below the tolerance set point and this region needs to be explored.
- Based on crew reports of fatigue, full headedness, procedural missteps, and headaches, an operational limit at or below 2.0 mmHg is expected to maintain crew health and performance, which is the basis for the proposed NASA Standard 3001, volume 2 update

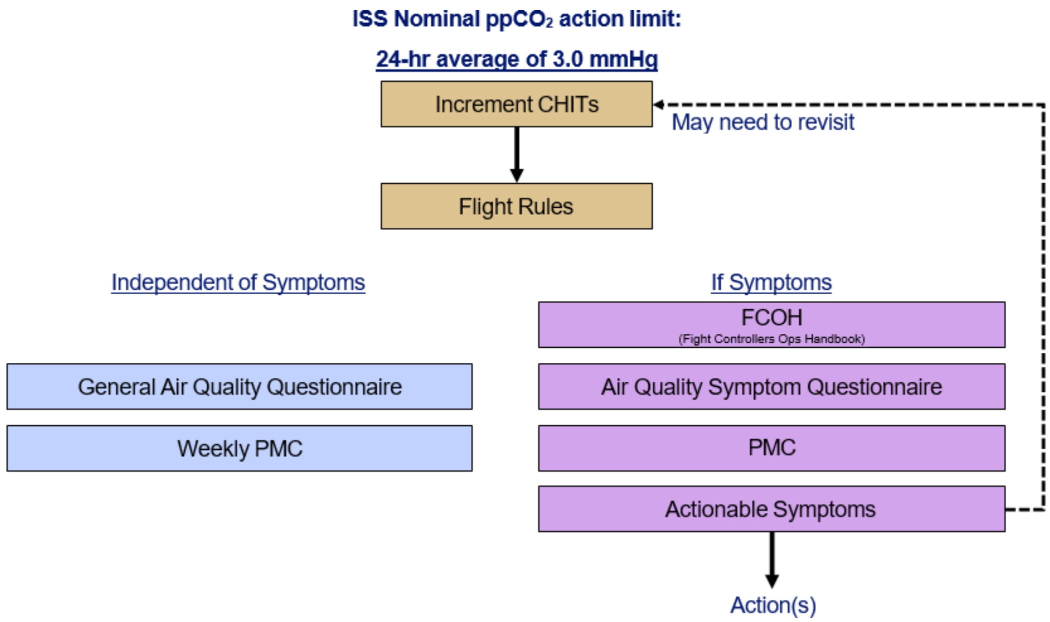
Limitations of Existing Data

- Not all symptoms are reported
- Multiple possible reporting routes
- Symptoms may be multifactorial
- Symptom reports are not homogeneous
- Symptom reports may not be temporally related to the exposure
- Physiological data, such as exercise, may be sparse
- Environmental exposure data from MCA is assumed to represent individual exposures
- Some environmental data are missing (due to limited sensor availability/instrument failure)

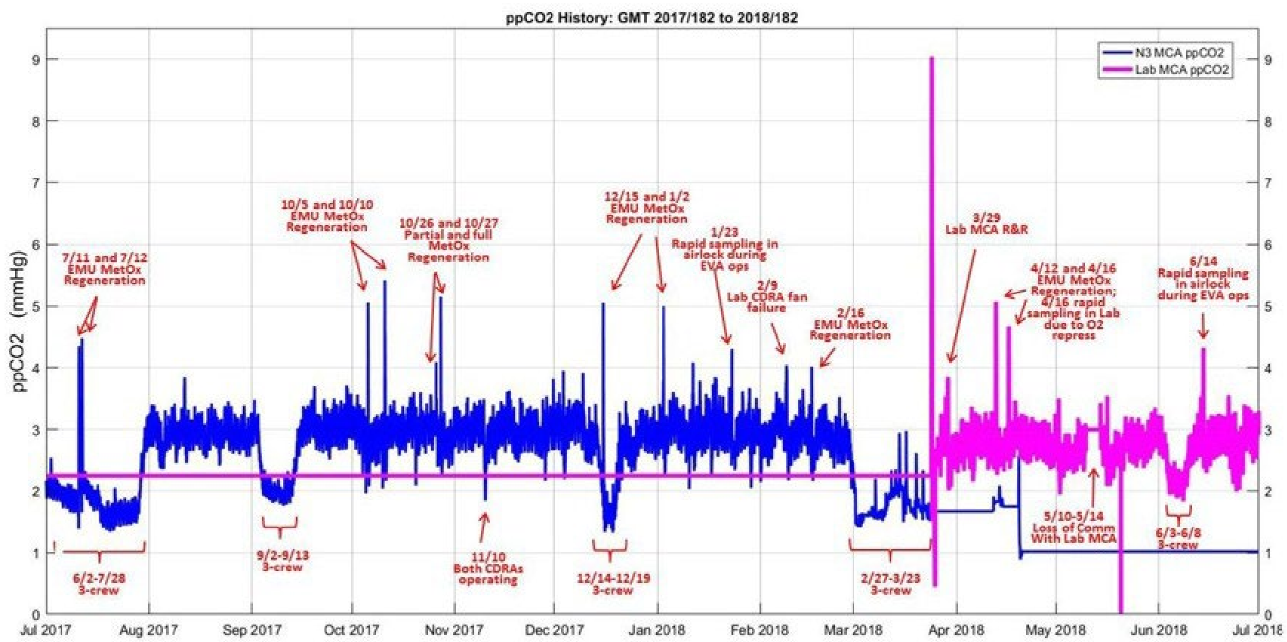
Hypotheses

- Does headward fluid shift in microgravity combined with increased CO_2 levels alter CO_2 sensitivity?
- Are local, individual CO_2 exposures higher than those recorded by the MCA?
  - Localized pockets behind racks
  - Exercise
  - MetOx regen ops
  - SPHERES
- Can individual susceptibility to CO_2 be used to predict at risk crewmembers?

Operational Mitigations: Overall Strategy



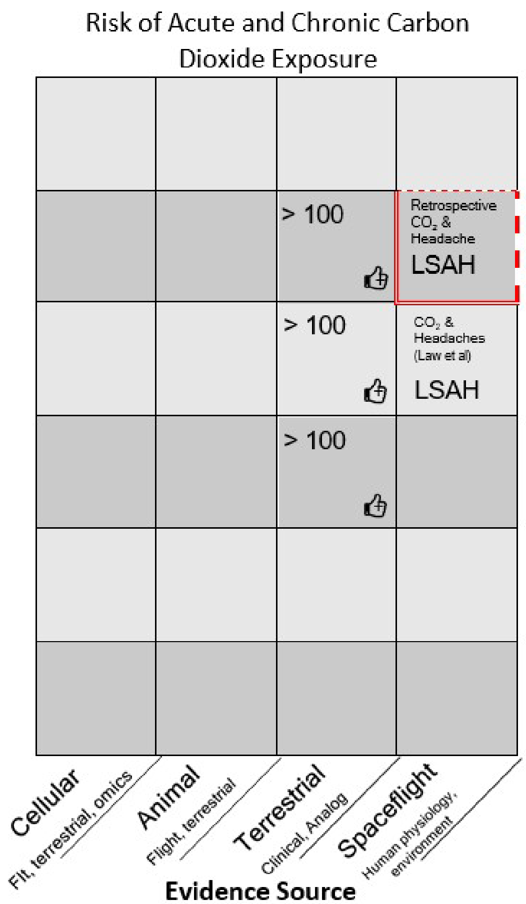
CO_2 levels at ISS Jul 2017 – Jul 2018



NOTES: 1. CO_2 levels controlled by US (CDRA) and Russian (Vozdukh) resources

2. ppCO2 of 3mmHg is represented as a 24-hr Time Weighted Average (TWA)

Human System Risks – Proposed Levels of Evidence



Evidence Description		Impact on Risk Assessment
Direct linkage between hazard, effect on humans & potentially countermeasures	**Causation** Evidence Synthesis	Ultimate impact - defines the ability to understand, mitigate risk & extrapolate to DRMs
Related linkage between hazard, effect on humans & potentially countermeasures.	**Association** Risk Understanding	Significant impact - defines the ability to understand and mitigate
Probability of occurrence of a condition in a population within a specified period of time	**Incidence** Risk Quantification	Further quantifies risk understanding & may impact mission design
Proportion of cases of a condition in a population at a given time	**Prevalence** Risk Assessment	Ability to start to quantify risk assessment
Case study with multiple subjects	**Case Series/ Descriptive Study**	Moderate impact may trigger risk or enhance metric
Detailed examination of an individual, descriptive study design that does not look for cause & effect.	**Case Study** Descriptive	Limited impact may trigger concern

Note: The *"State of Knowledge"* field within the Risk Summary should contain a comprehensive account and overall assessment of the evidence indicated.

Legend
Risk Metric
New Evidence
# of Publications or LSAH data
#
Evidence Assessment
Neutral
vs. Risk Statement

CO2 Monitoring and Scrubbing Technology Development for Spaceflight

Localized/Personal CO2 Monitoring

- In-flight crew exposure data remain limited
- Prisk (2006) reported end tidal CO_2 does not differ significantly between supine ground and in-flight (data collected during Expeditions 3-6)

Prisk et al., J Applied Physiol (2006) 101:439-447.

Portable" CO_2 Monitor

System Plan

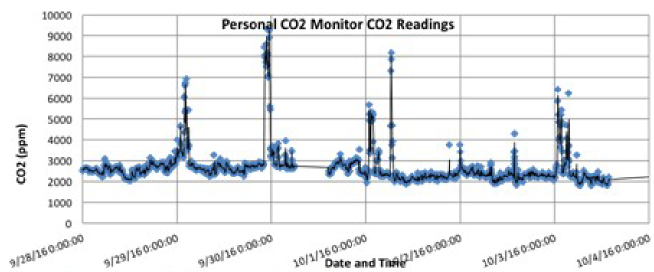
Historical CO_2 exposure data are almost exclusively based on stack level monitoring by the major constituent analyzer (MCA) – **working on steps to better understand local area concentrations and individual crew exposures**

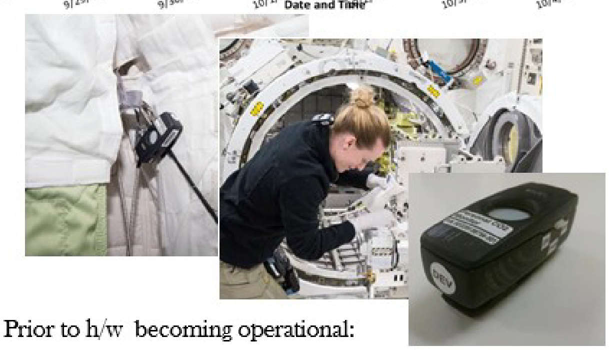
Data from these monitors are expected to help resolved questions about localized areas of higher concentrations (pockets) but will not represent crew inspired levels.

Launched Mar 2016; Flight objectives were met in Dec 2016; currently transitioning to operations

Objectives:

1. Supplement CDM (not replace)
2. Better testing for Measuring Capability
3. Test - Static Measures
4. Test - How crews should wear device (understanding dynamic data collection) and the capability to accurately characterize the environment immediately surrounding the crew





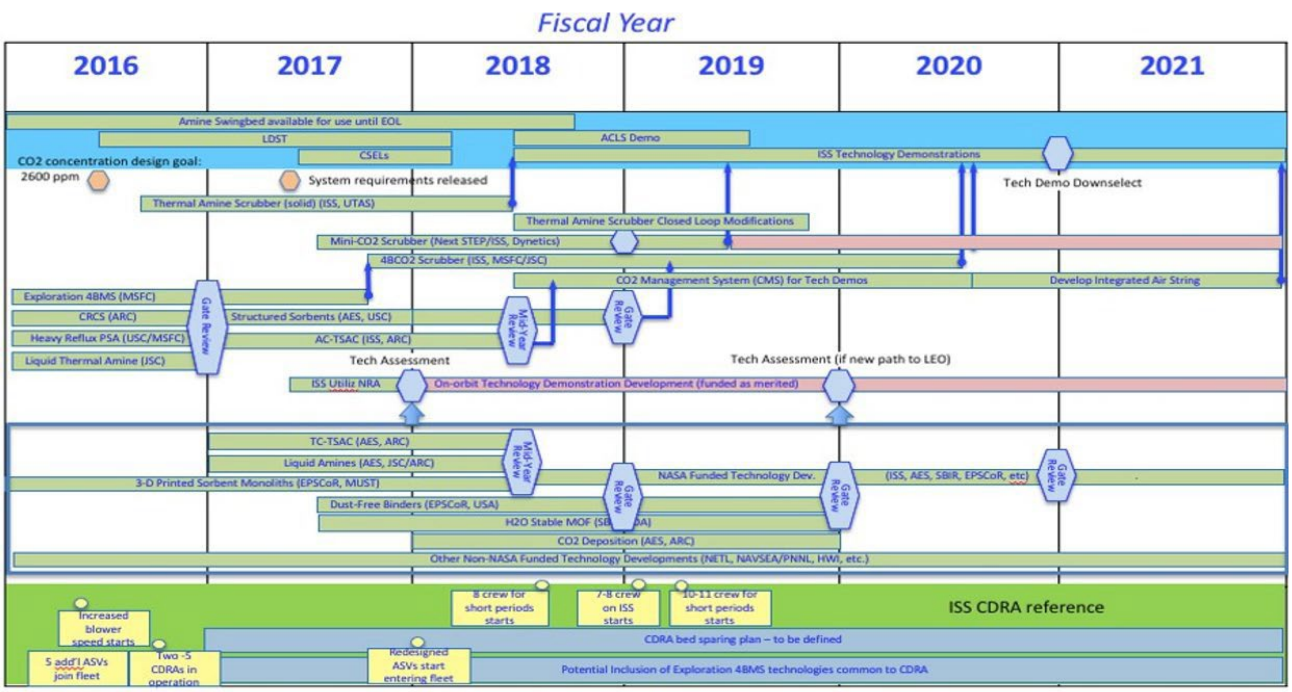
Prior to h/w becoming operational:

- Test Long Term Sensor Stability (1 month)
- Stability of Calibration during Storage
- Inter-Unit Consistency

ECLSS CO_2 Scrubbing Technologies

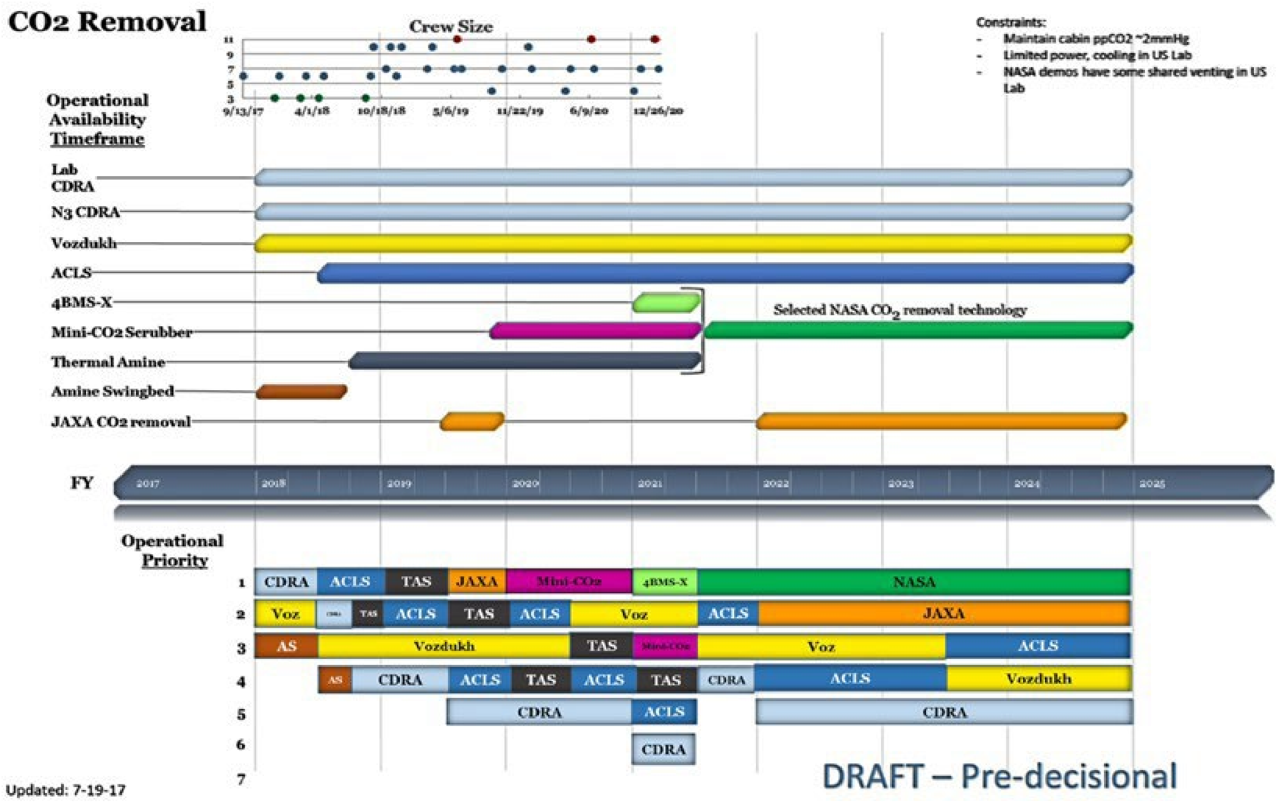
- ECLSS community is working aggressively to get high fidelity CO_2 removal technology demonstrations between 2018 and 2021
  - International partners are also flying demos
  - All demos are initially operated in "open loop" mode, venting CO_2 overboard
  - Best performing CO_2 removal demo system will be integrated with a CO_2 management system to feed to Sabatier
- ISS Demo systems have been developed with design goal of 2 mmHg inlet concentration as a design point, and most are designed to 4 crewmembers size (per Orion metabolic loads)
  - These performance levels are not verified performance before launch, they will be evaluated during use
- ECLSS community continues to small levels of investment in low-TRL technologies that could provide performance or reliability benefits
- Technologies slated for testing:
  - Thermal Amine CO_2 Scrubber (TAS)
  - Mini-CO_2 Scrubber
  - Four Bed Molecular Sieve CO_2 Scrubber

CO_2 Removal Map **(**POCs Jim Knox & Craig Broerman)

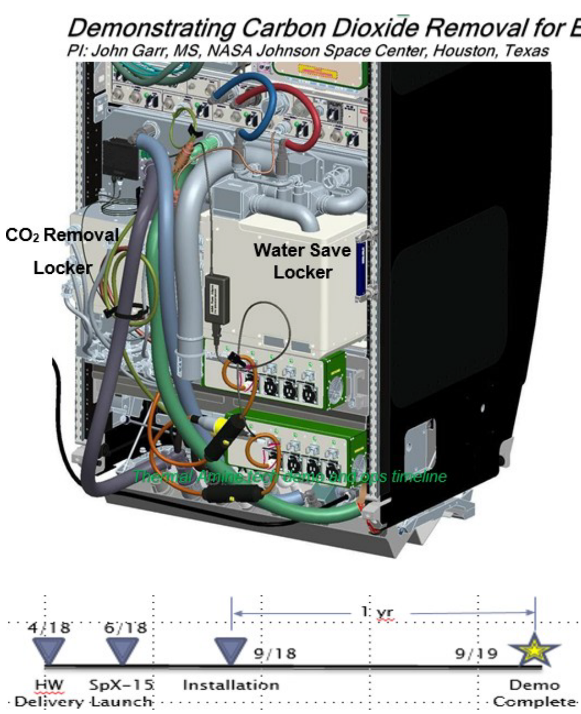


- Objectives/FOMs: Improved reliability (enabling, >3 year between unplanned maintenance), reduced mass/power/volume (enhancing, < 204 kg, 1kW, 0.5 m^3), lower $ppCO_2$ (enhancing, 2600 ppm with 4 crew), microgravity compatible

NASA + International CO_2 Removal & Demos on ISS



Thermal Amine CO_2 Scrubber (TAS)

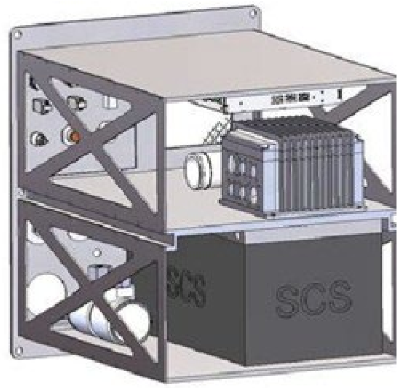


- Tests CO_2 removal using alternately actively heated and cooled solid amine fixed beds
    - Enables closed-loop operation by desorbing with heat and pump
- Removes 4 crew CO_2 load at 2 mmHg CO_2 cabin air
- Lower cabin CO_2 reduces crew symptoms due to ~3 mmHg CO_2 on ISS using existing technology
- Performance and reliability data informs down select to prime CO_2 removal technology for 3 year Exploration Air Revitalization demonstration on ISS from 2021 to 2024.
- Demonstrates more efficient air and water saving technologies compared to Orion system design and "Amine Swing Bed" ISS demonstration
    - Orion/ASB is open-loop only configuration
- First tech demo to utilize new Ku command/telemetry system for MCC-H control of Exploration demonstrations
- Currently targeted for launch late 2018

Mini-Scrubber Status

Dynetics, Inc. – Proprietary Information Micro-Fluid Technology

- Mini CO_2 is a technology demonstration of CO_2 removal on ISS
- Configured for ISS EXPRESS Rack, in packaged in 1 double middeck locker shell
- Delivery planned for June 2019
- Performance requirements set with minimum and target levels
  - Lower TRL start and accelerated dev. that began through Next STEP BAA Public-Private Partnership

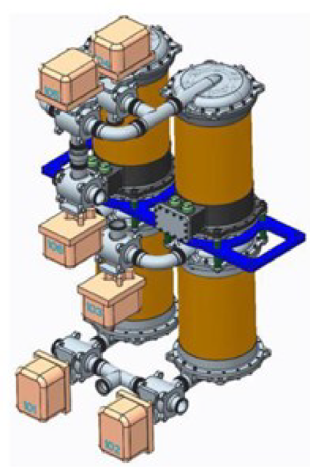


Criteria	Required	Target
CO_2 Removal Rate	2.5 kg/day	4.16 kg/day
Water Recovery (% ingested from cabin air that is not vented overboard)	99%	99.9%
Air Save (lbm of air per day overboard)	≤0.073 kg (≤0.16 lbm)	≤0.01 kg (≤0.02 lbm)

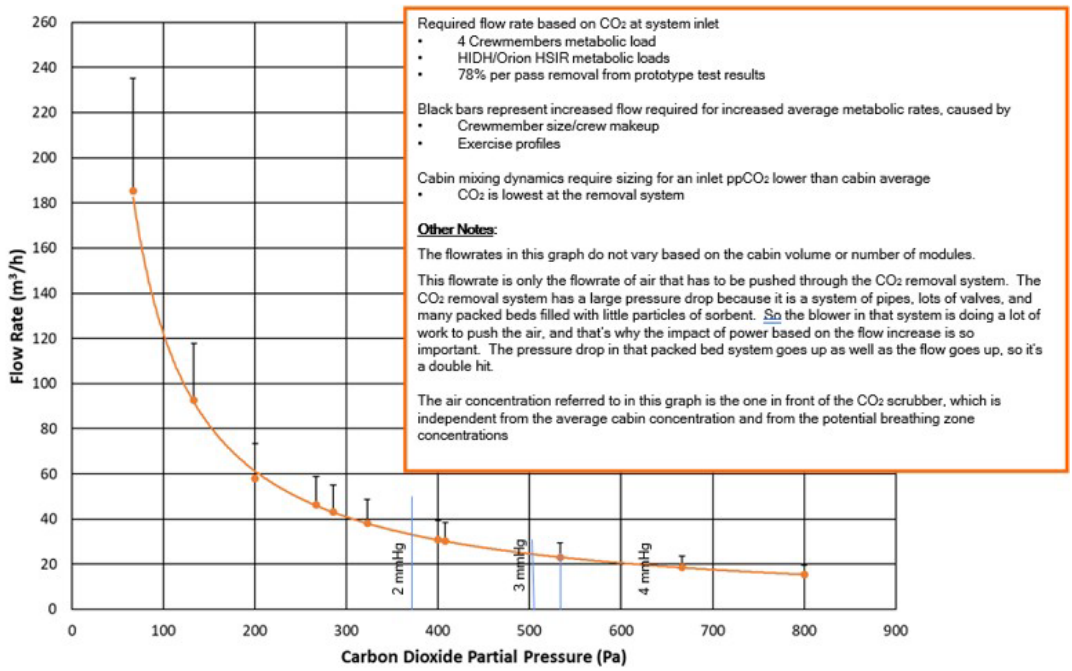
$4BCO_2$ Scrubber Status

Upgraded CDRA to meet 4-Crew & 2mmHg CO2

- MSFC led with JSC participation
- Based on same "Four-Bed Molecular Sieve" overall architecture as ISS CDRA
- Upgrade and redesign of every component to meet new performance (2 mmHg design point, 4 crewmember load) and achieve higher reliability
  - New sorbent materials
  - Efficiently designed sorbent beds (packaging & heaters)
  - Robust valves
  - Higher flow rates
  - Robust filters
- Team goal to complete system buildup by end of FY'2019 for launch and integration and operation in 2021



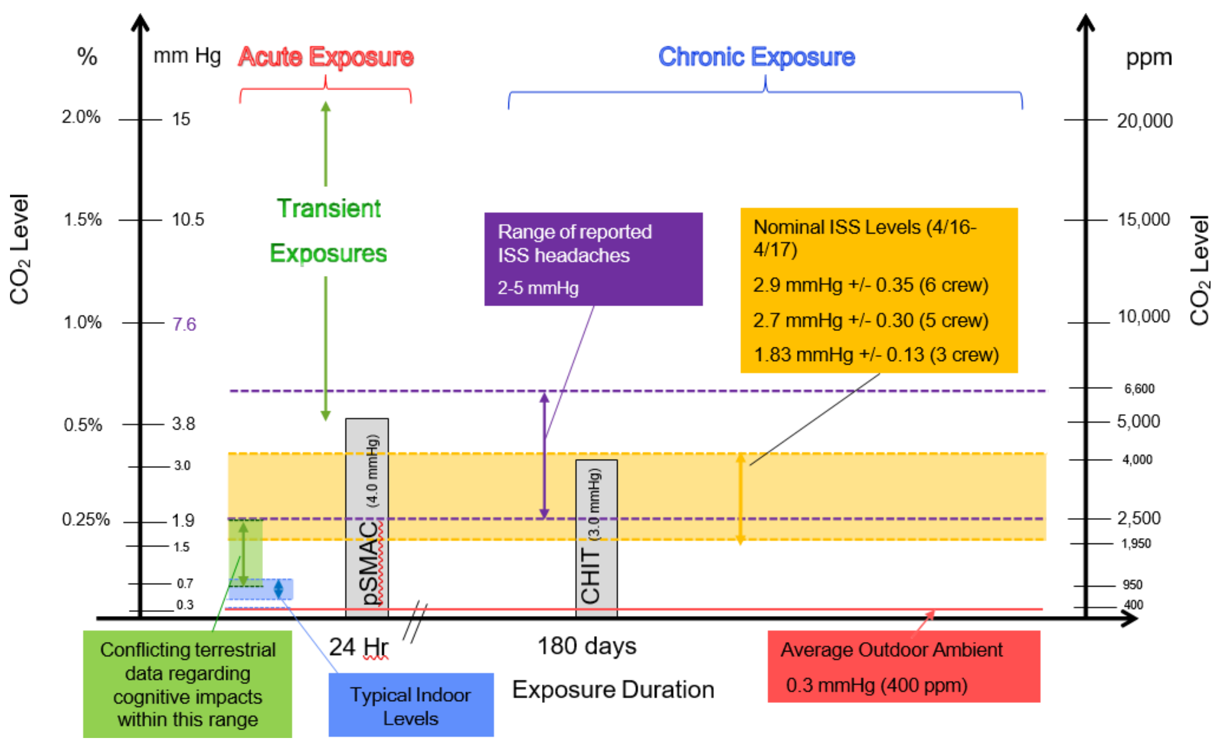
Impacts of 2 mmHg on ECLSS Sizing



- Flow drives system power linearly or worse
- Flow drives some major components size (desiccants, filters) linearly

CO_2 Exposures – Acute, Transient, Chronic

Metric for Risk of Acute and Chronic Carbon Dioxide Exposure



CO_2 Exposures – Chronic

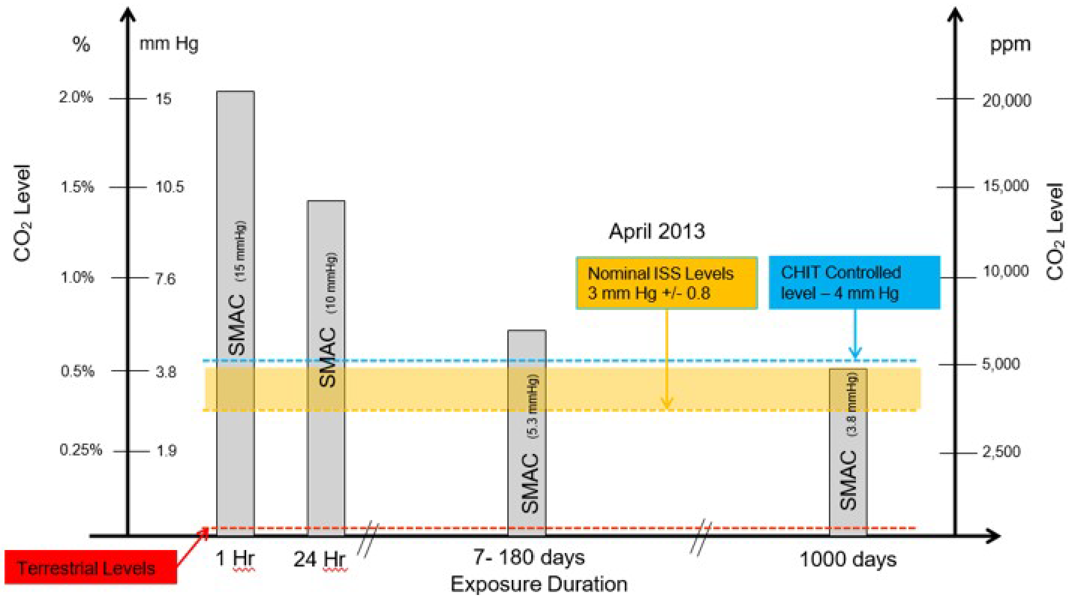
Predicted Probability of Headache (CO_2) : Retrospective Analysis
Metric for Risk of Acute and Chronic Carbon Dioxide Exposure

See Law et al., (2014). J Occupational Environ Med 56: 477-483 Figures 1 and 2. Existing Evidence – Rev A

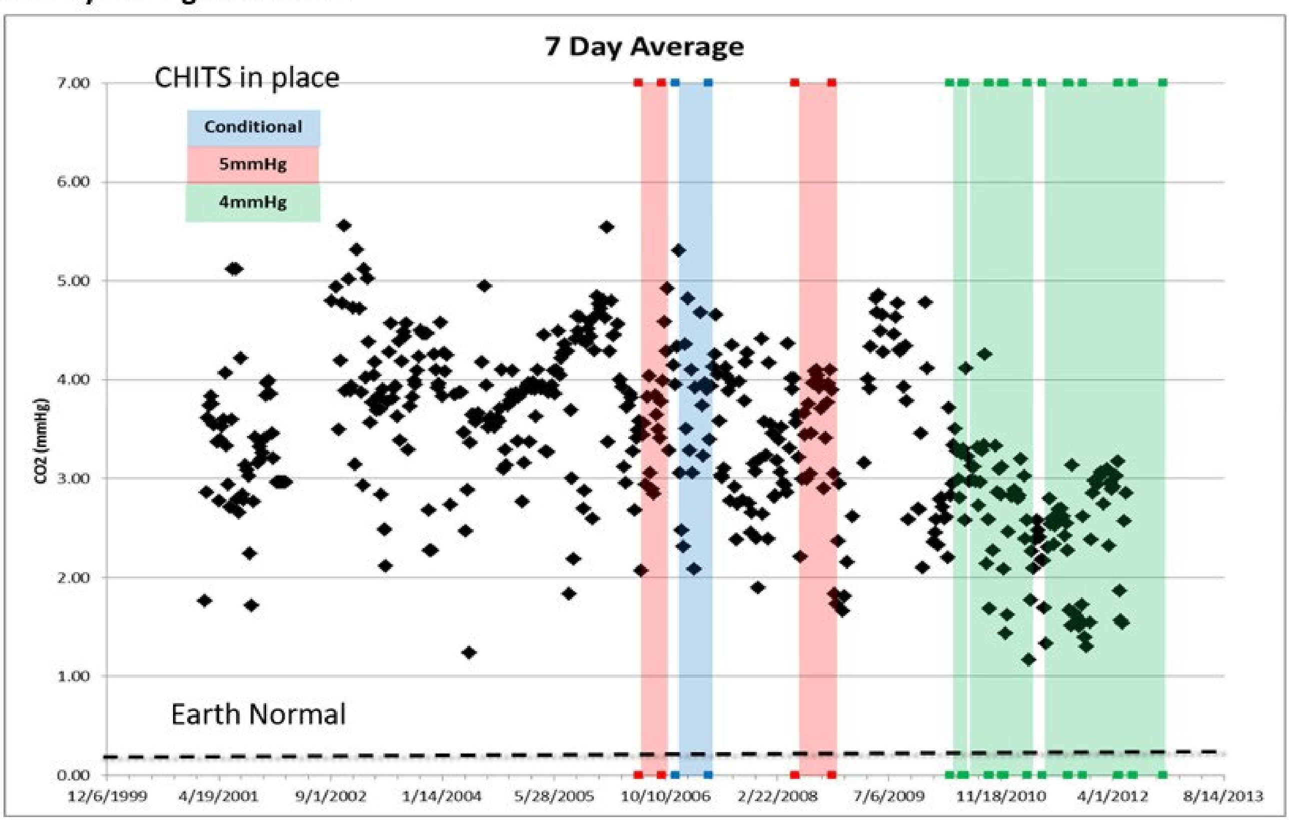
Existing Evidence – Rev A

CO_2 Exposures – Acute, Transient, Chronic

Spacecraft Maximum Allowable Concentrations (SMAC) and CHIT Implemented Levels

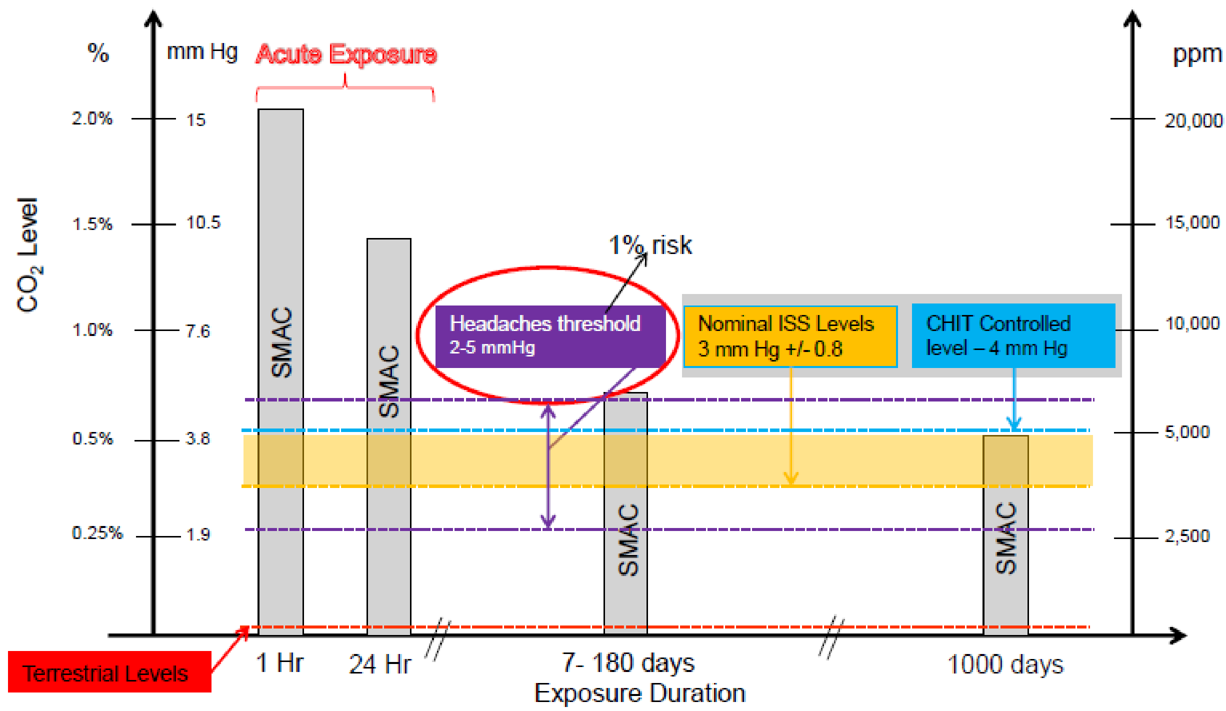


Weekly Average CO2 Level



Acute Exposure to High Concentrations of CO_2

CO2 Exposures – Acute
Spacecraft Maximum Allowable Concentrations (SMAC) and CHIT Implemented Levels



Retrospective Analysis

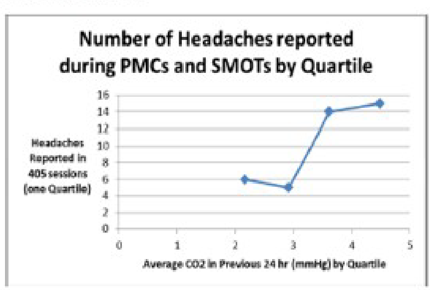
Occurrence of Headaches on ISS

Assessment was performed by LSAH along with Space Medicine and Toxicology to evaluate the occurrence of headaches that were reported by crews on ISS with the following caveats:

- Observations were made via PMC and SMOT*
- Headaches that were not alleviated by analgesics
- Headaches within the first 7 days of flight were not included

The following was observed via since 2001:

- 46 headaches were observed
- 1670 non-headaches were observed
- Prior to the 2010 CHIT
  - 25 headaches were observed
  - 518 non-headaches were observed
  - Rate of 4.6%
- Post 2010 CHIT which lowered the level to < 4 mm Hg
  - 21 headaches were observed
  - 1152 non-headaches were observed
  - Rate of 1.8%



Visual Association

(*) PMC – Private Medical Conference
SMOT – Space Medicine Operations Team notes

CO2 Exposures –Acute–Cognitive Function

Decision-Making Decrements (Satish et al. 2012)

See Satish et al., 2012, Figure 2

Relevance to Operations:

- Decision Making
- Situational Awareness

The Challenge of Aviation Emergency and Abnormal Situations

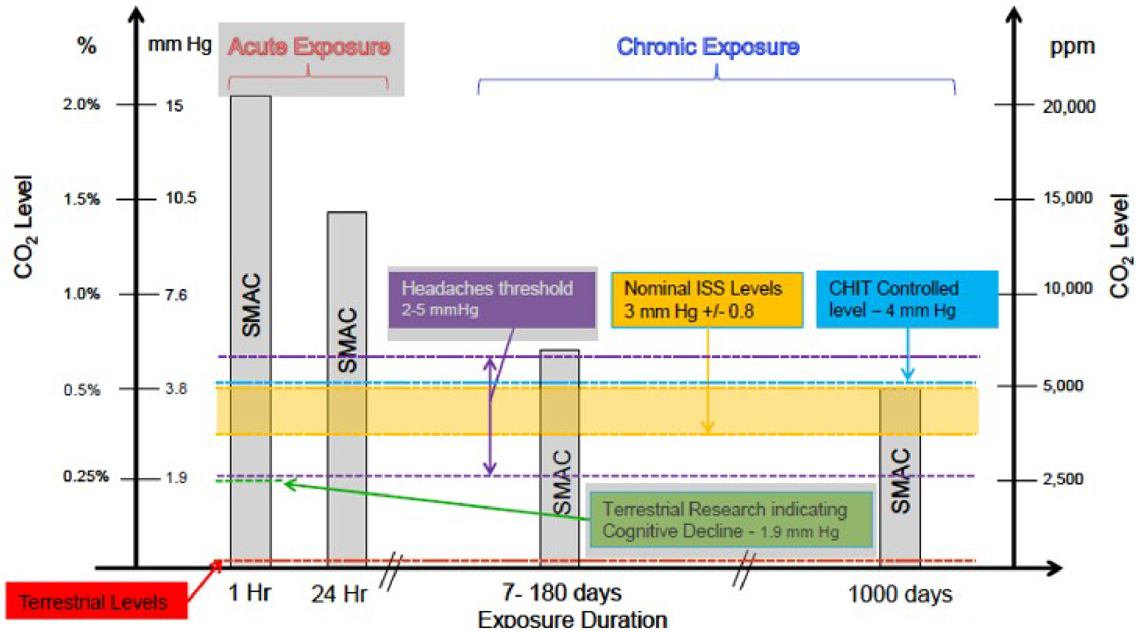
Barbara K. Burian, Immanuel Barshi and Key Dismukes

when experiencing stress and high workload, crews are vulnerable to missing important cues related to their situation and are likely to experience difficulty pulling together disparate pieces of information and making sense of them. This is especially true when some of that information is incomplete, ambiguous, or contradictory. Pilots' problem-solving abilities may be impaired, and they will generally have difficulty performing complex mental calculations (Hendy, Farrell, & East, 2001)… In contrast, well-learned motor skills, such as those demonstrated by experienced pilots when operating flight controls, are quite robust and are much less affected by stress (Cohen & Weinstein, 1981).

See Slides 50 & 51: Skill v. Prob. Solving

Chronic Exposure to High Concentrations of CO_2

Spacecraft Maximum Allowable Concentrations (SMAC) and CHIT Implemented Levels



Spaceflight Evidence

Currently, there is no correlated spaceflight evidence of the effects of chronic CO_2 exposures.

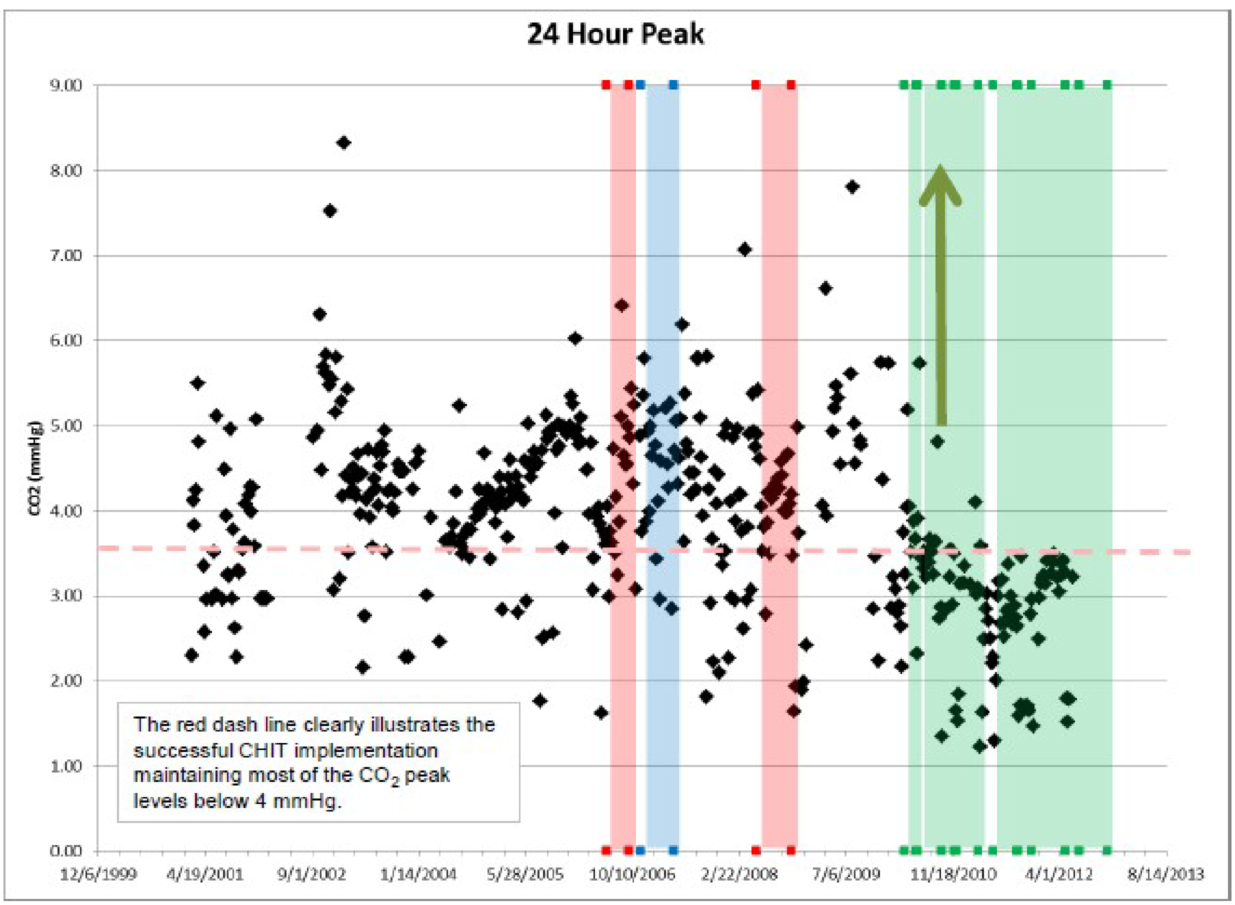
Terrestrially the following is known:

- CO_2 is a potent vasodilator
- Causes increased blood flow – problem in that the cerebral blood vessels are already congested (cephalad fluid shift)
- May be a contributing factor to VIIP
  - Preliminary assessment of spaceflight CO_2 levels and VIIP symptoms have not indicated a correlation. Additional assessments are in work.

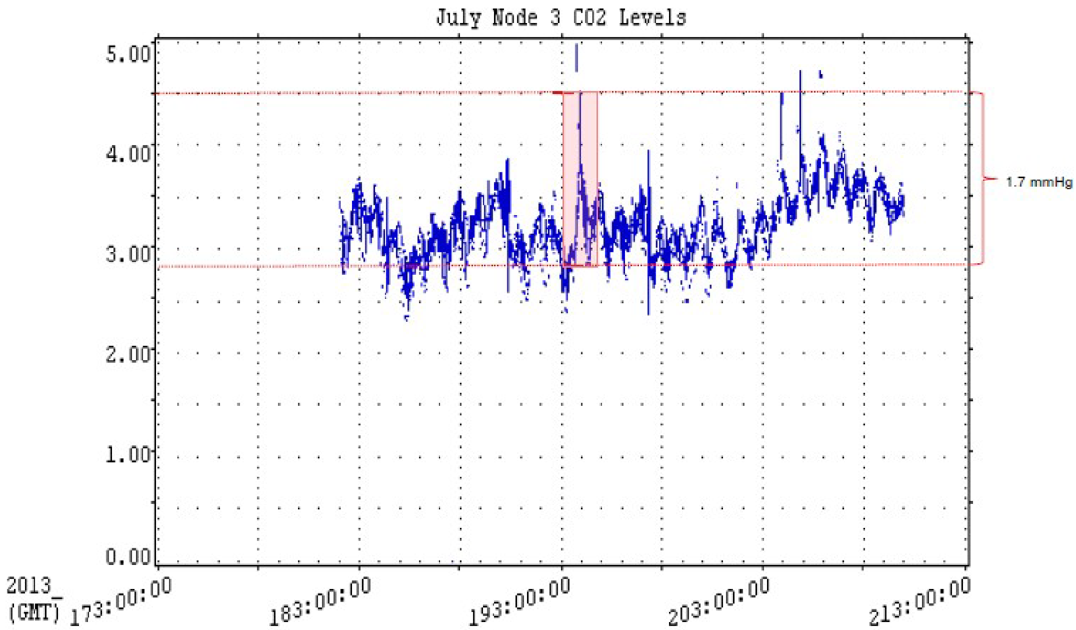
It is anticipated that the fluid shift coupled with the spaceflight CO_2 levels have a compounding effect.

Transient Exposure to High Concentrations of CO_2

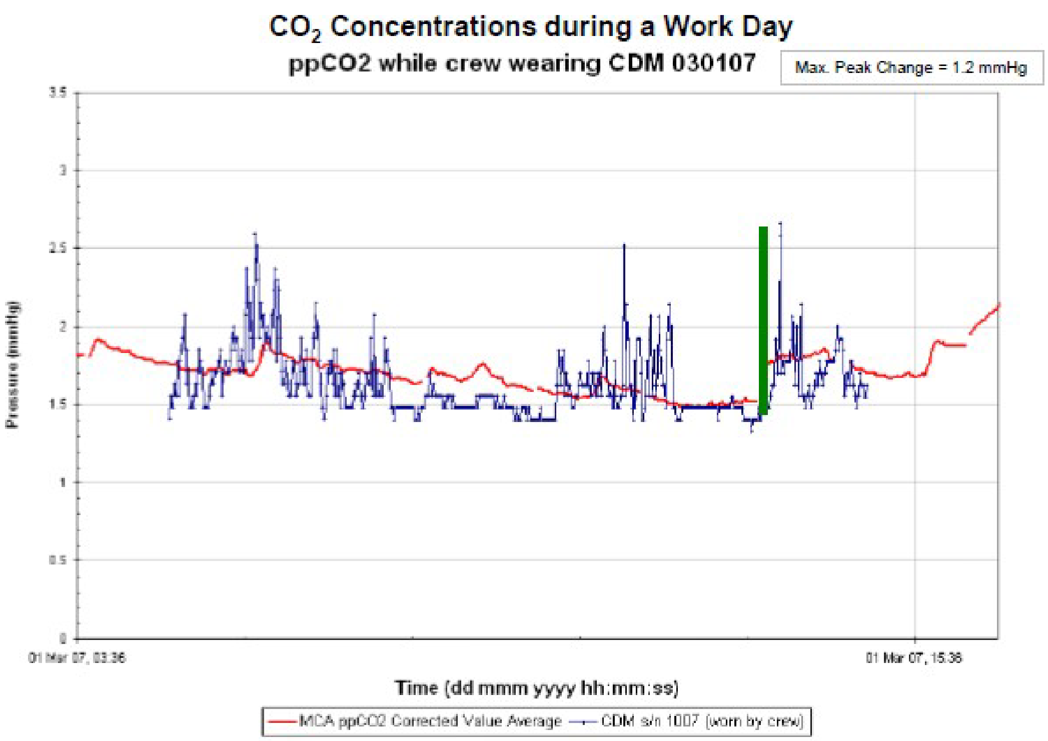
24 Hour Peak CO_2 Level



Time-Based Transient Exposure
Spikes of CO2 Levels During Metox Regeneration

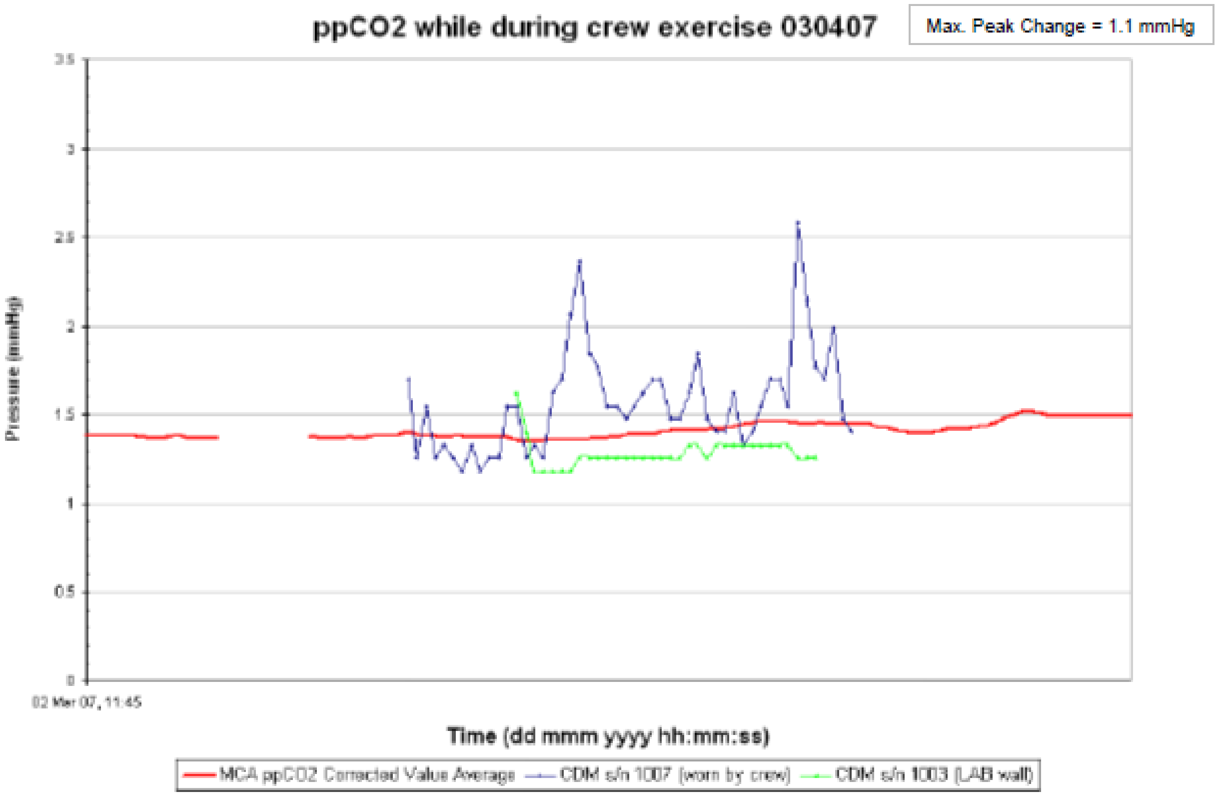


Spatially Based Transient Exposure



Reference: J. Law, S. Watkins, D. Alexander, "In-Flight Carbon Dioxide Exposures and Related Symptoms: Association, Susceptibility, and Operational Implications", NASA/TP-2010-216126, 2010, pp. 1-21

Transient Exposure Event



Reference: J. Law, S. Watkins, D. Alexander, "In-Flight Carbon Dioxide Exposures and Related Symptoms: Association, Susceptibility, and Operational Implications", NASA/TP-2010-216126, 2010, pp. 1-21

Transient Exposure Summary

Summary – transient of + 5 mm Hg may rarely occur on ISS. 1-2 mm Hg transients occur on a regular basis (based on MCA and CDM monitoring).

Aspects of transient levels are in the flight rules, but should be re-assessed based on new information regarding cognitive deficits. Note Flight Rules are presently under a CR.

Station Operations. Flight Rule B13-53 ("PPCO$_2$ Constraints") prescribes required actions when station ppCO$_2$ levels approach or exceed the permissible exposure limit of 7.6 mm Hg.

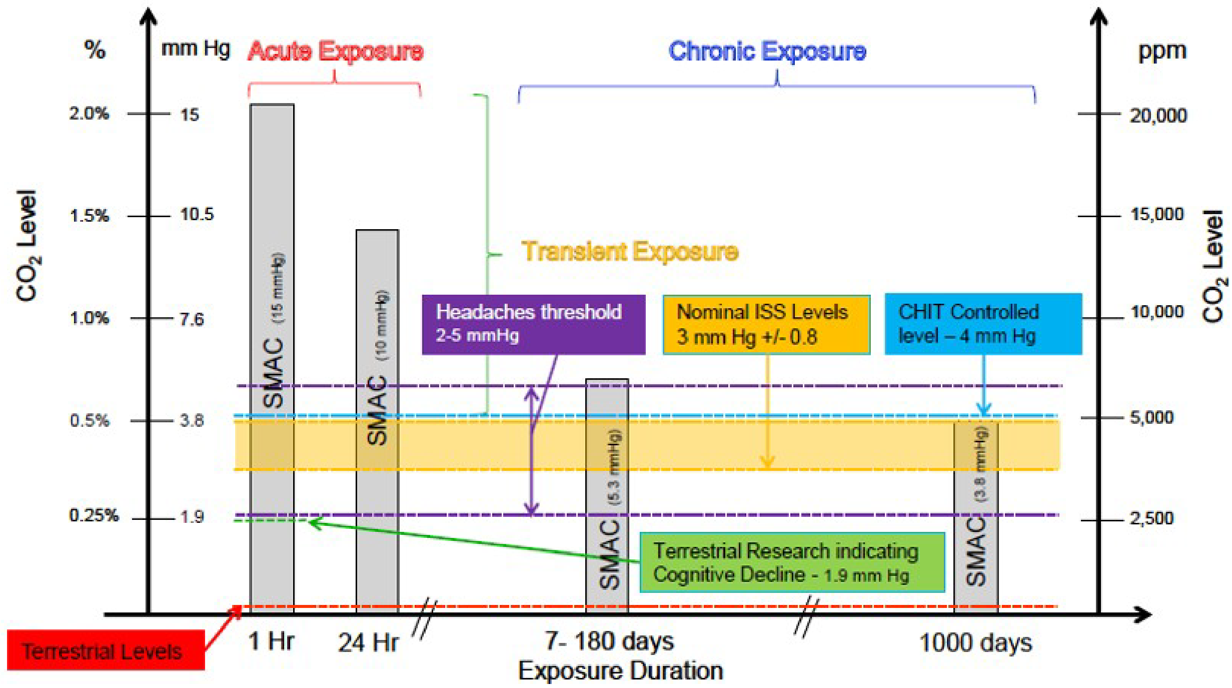
• If ppCO$_2$ levels average higher than 5.3 mm Hg over 5 days or 6.0 mm Hg over 1 day, the flight surgeon must be consulted when planning crew activities.

• If ppCO$_2$ levels reach or exceed 7.6 mm Hg, measures must be taken to lower the ppCO$_2$ to permissible levels per Flight Rule B17-5 ("CO$_2$ Partial Pressure Limits and Actions"), which details specific actions to troubleshoot and scrub CO$_2$. The same corrective actions are required if ppCO$_2$ is 4.5 mm Hg or greater and CO$_2$-related symptoms not attributed to another cause are present.

• Off-nominal situation: Immediate action to minimize adverse CO$_2$ effects on the crew must be taken at CO$_2$ levels of 10 to 15 mm Hg. The gas environment is scrubbed down to allowable CO$_2$ levels. If signs of illness develop, the crew must use individual breathing devices (IBD). If the ppCO$_2$ remains above 7.6 mm Hg or if the IBDs get expended, the crew must evacuate the affected area. Exposure to CO2 levels of 10 to 15 mm Hg are limited to 8 hours or less.

• Emergency situation: Immediate action with the highest priority to prevent crew exposure must be taken at CO$_2$ levels of 15 to 20 mm Hg. The crew is to use IBDs when performing repair operations, scrub down the gas environment, and evacuate the affected area if ppCO$_2$ remains higher than 15 mm Hg or if IBDs become expended.

CO2 Exposures – Acute, Transient, Chronic
Spacecraft Maximum Allowable Concentrations (SMAC) and CHIT Implemented Levels



Existing Evidence – Previously Presented or Complementary Data

Acute Exposure to High Concentrations of CO_2

CO_2 levels aboard the ISS during early expeditions remaining for the most part within 7-d and 30-d SMACs = 0.7% (5.32 mmHg)

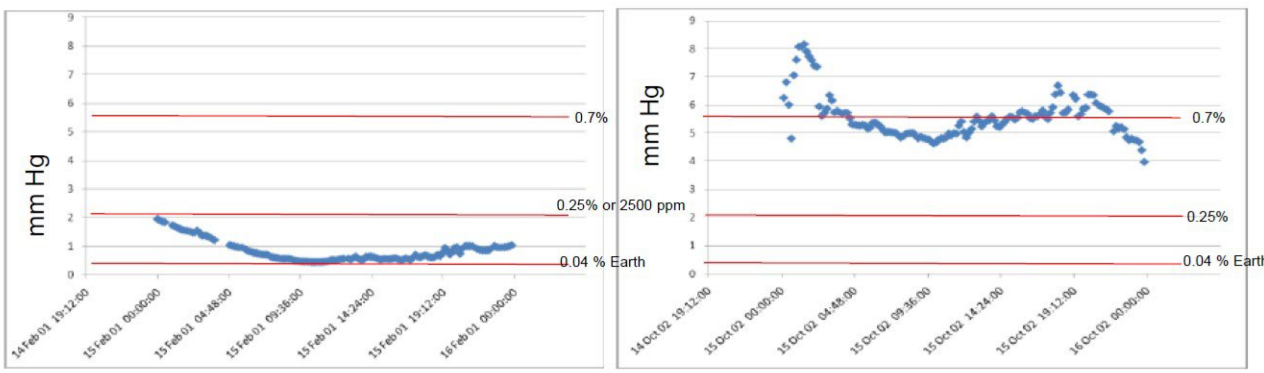
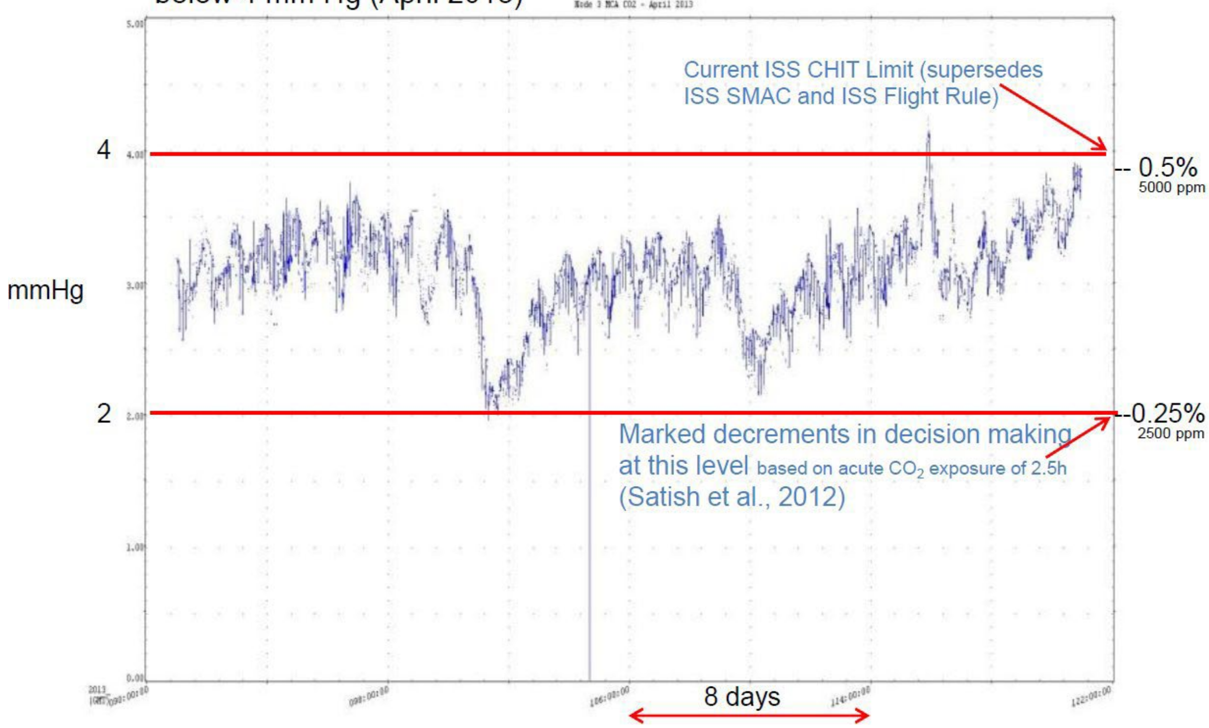


Figure 1a. One day of CO_2 concentrations during a time of relatively low CO_2 concentrations aboard the ISS. CO_2 concentration averages < 2 mmHg

Figure 1b. One day of CO_2 concentrations during a time of relatively high CO_2 concentrations aboard the ISS CO_2 concentration averages > 5 mmHg

CO_2 levels aboard the ISS after CHIT implementation - to maintain levels below 4 mm Hg (April 2013)



Spaceflight Evidence

41st International Conference on Environmental Systems, 2011 publication

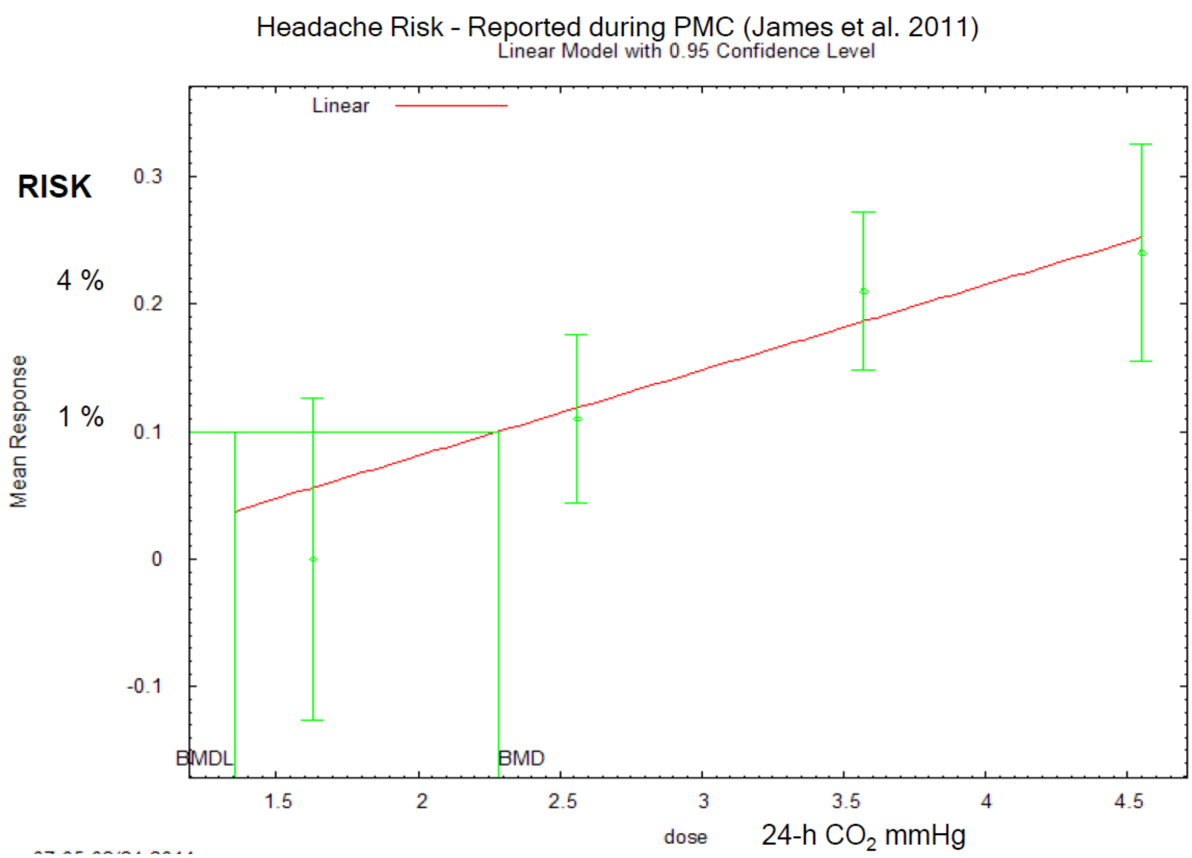
Crew Health and Performance Improvements with Reduced Carbon Dioxide Levels and the Resource Impact to Accomplish Those Reductions

John T. James Valerie E. Meyers, Walter Sipes, Robert R. Scully and Christopher M. Matty

NASA Johnson Space Center, Houston, 77058, USA

American Institute of Aeronautics and Astronautics

- Risk of headache being reported during a PMC increases with increasing 24-hr average levels of CO_2 in the range of 2-5 mmHg aboard ISS
- Occurrence of numerous *"space viscosity"* events aboard ISS*



Ground-based Evidence

Is CO_2 an Indoor Pollutant? Direct Effects of Low-to-Moderate CO_2 Concentrations on Human Decision-Making Performance

Usha Satish,[1] Mark J. Mendell,[2] Krishnamurthy Shekhar,[1] Toshifumi Hotchi,[2] Douglas Sullivan,[2] Siegfried Streufert,[1] and William J. Fisk[2]

[1]Department of Psychiatry and Behavioral Science, Upstate Medical University, State University of New York, Syracuse, New York, USA; [2]Indoor Environment Department, Lawrence Berkeley National Laboratory, Berkeley, California, USA

Environmental Health Perspectives • VOLUME 120 | NUMBER 12 | December 2012

- Decision-making performance (n=22) reaches dysfunctional levels for several measures during 2 ½ hour exposures to CO_2 at 1.9 mmHg
- Visual effects reported in subjects (n=3) exposed for ~30 min to19 mmHg CO_2
- Depth perception decreased (Sun, et al., 1996)
- Motion detection decreased (Yang, et al., 1997)

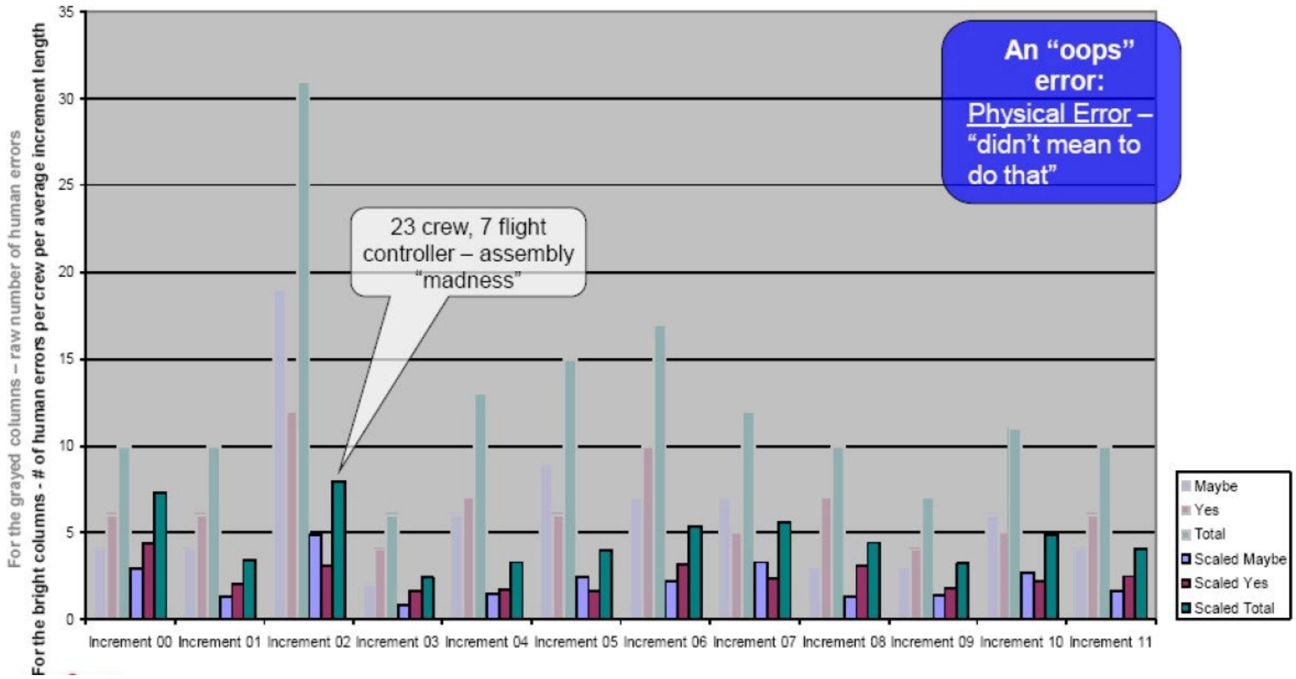
Chronic Exposure to High Concentrations of CO_2

Ground Based Evidence

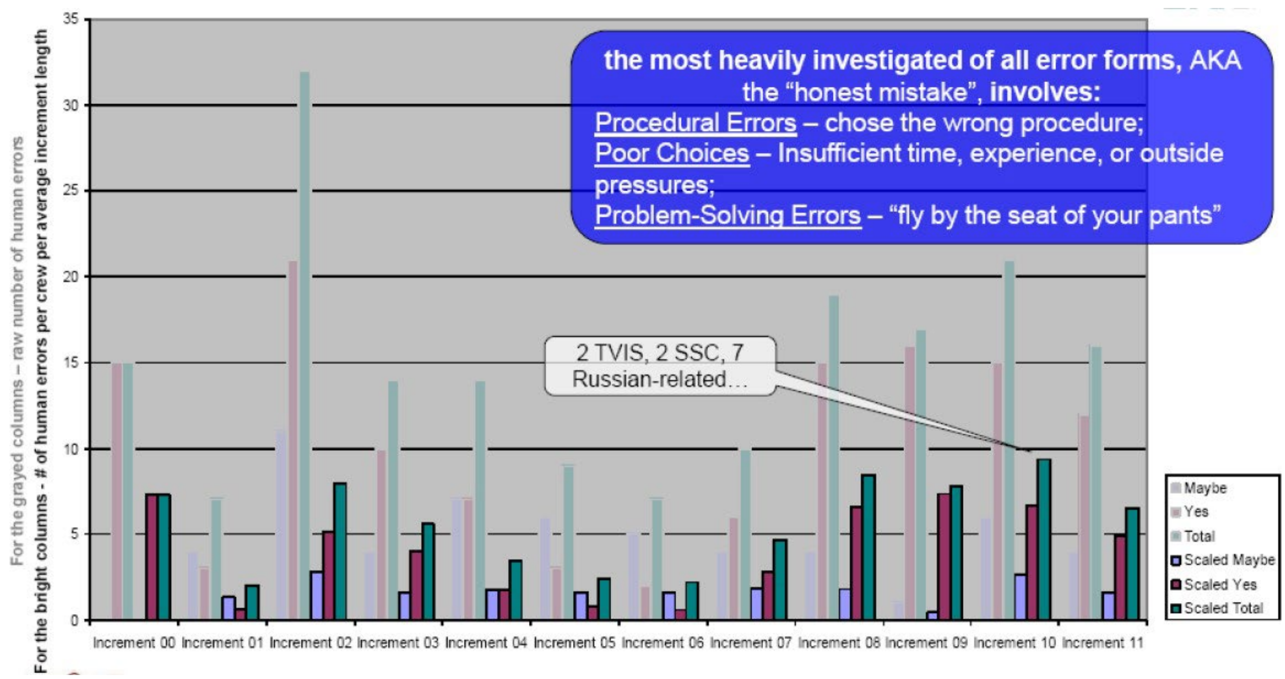
- **Submarine and Equivalent Environment Research**
  - *Tansey and Schaefer -* Submarine Patrol data in comparison with surface vessels. Ten year study showed higher rate of illnesses in the respiratory, GI, urologic (kidney stones), EENT. CO2 > 1% (7.6 mmHg).
  - *Royal Navy, Pingre -* 44 day patrols with 1% (7.6 mmHg) CO_2 - mild uncompensated respiratory acidosis with the respiratory parameters returning to normal.
- **Mental Performance**
  - *Manzey and Lorenz -* showed Visuomotor decreases in performance with concentrations of as small as 1.2% (9.12 mmHg)

- Submarine and Equivalent Environment Research
  - *Schaefer - Naval Submarine Research Center*
    - Animal model- 1.5% (11.19 mmHg) CO_2 increased incidence of focal and tubular kidney calcification
    - Animal model 2 -at 1.5% (11.19 mmHg) showed significant bone loss of calcium and phosphorus with the commensurate increase in bone bicarbonate to compensate for acidosis.
    - Subject Exposure to 1.5% (11.19 mmHg) CO_2 - 42 days increased red cell calcium and renal excretion of Phosphorus. Calcium effect on cell membrane similar to narcosis
- NASA-ESA-DARPA
  - *Silwaka -* Exposed subjects to 0.7% (5.32 mmHg) and 1.2% (9.12 mmHg) for 23 days.
  - Cerebral Blood Flow (CBF) increased 35%. There was no alteration in Heart Rate or mean Arterial Pressure.
  - The CBF decreased after the initial exposure to a higher stabilized baseline. It was also noted that during the CO_2 exposure visual stimulation increased the CBF 30%.

Skill-Based Error (Involving Hardware)



For the grayed columns – raw number of human errors
For the bright columns - # of human errors per crew per average increment length
An "oops" error:
Physical Error – "didn't mean to do that"
23 crew, 7 flight controller – assembly "madness"
Maybe
Yes
Total
Scaled Maybe
Scaled Yes
Scaled Total
Increment 00
Increment 01
Increment 02
Increment 03
Increment 04
Increment 05
Increment 06
Increment 07
Increment 08
Increment 09
Increment 10
Increment 11



Problem Solving, Procedural Errors

- **Problem Solving Impaired in Off-Nominal Situations**
  - When information is incomplete, ambiguous, or contradictory. Pilots' problem-solving abilities may be impaired, and they will generally have difficulty performing complex mental calculations.
  - In contrast, well-learned motor skills, such as those demonstrated by experienced pilots when operating flight controls, are quite robust and are much less affected by stress.

    Burian, B. K., Barshi, I., & Dismukes, K. (2005). The challenge of aviation emergency and abnormal situations. *NASA Technical Memorandum, 213462.*

- **Prediction of Procedural Errors in Operating NASA Spacecraft**
  - Cognitive Reliability Error Analysis Model used to predict human error
  - Applied to ISS Ingress Procedure
    - Under IDEAL conditions risk was 1:88
    - Under COMMON conditions the risk of a procedural error was 1:3
    - Skill training reduced the risk from 1:3 to 1:11

      Calhoun et al., (2013) Quality Reliab Engr DOI: 10.1002/qre.1471

Effect of Training and Complexity?

- **Training May Not be An Effective Countermeasure for types of errors that were related to Cognitive ability.**
  - A recent study by Veridian Corporation revealed that even with upset training many pilots have trouble executing recovery procedures adequately in the real world of surprise, confusion, and stress pilots may have trouble identifying the nature of the upset and selecting the correct recovery procedure.
  - Training did not mitigate error on spaceflight emergency task associated with cognitive ability

    Zhang et al., 2011 Lect Notes in Comp Sci 6777: 436

- **Error rate is related only partially to the Complexity of a task**
  - In spacecraft operation, the average operation time, subjective complexity rating, and subjective workload could be predicted well from the operation complexity value but the error rate could only be partly explained (R = 0.343) by this value.

    Zhang et al., 2009 Intnl J Indust Ergo 39:765