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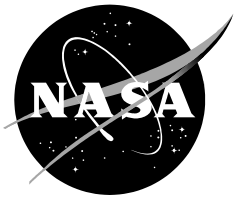

Chronic Exposure to Moderately Elevated CO_2 during Long-Duration Space Flight

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March 2012

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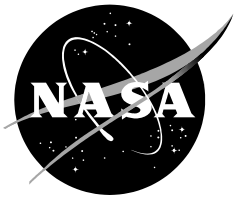

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Acronyms

CBF cerebral blood flow

CDM carbon dioxide monitor

CSF cerebrospinal fluid

EPA Environmental Protection Agency

ICP intracranial pressure

ISS International Space Station

LiOH Lithium-Hydroxide

MCA Major Constituent Analyzer

NRC National Research Council

SMAC Spacecraft Maximum Allowable Concentration

Abstract

Out of operational necessity, space platforms function with ambient carbon dioxide (CO_2) concentrations in excess of normal atmospheric conditions (0.03% or partial pressure of 0.23 mmHg). NASA's long-duration Spacecraft Maximum Allowable Concentration for CO_2 is 0.7% (pp CO_2 of 5.3mmHg). Extensive terrestrial studies support this level as safe and unlikely to cause adverse effects; however, International Space Station crews routinely report symptoms of acute CO_2 toxicity (e.g., headaches, lethargy) that correlate with relative elevations of cabin CO_2 below the permissible level. It is unclear if the unique environment of space results in increased sensitivity to CO_2 or if other confounding factors are present. Regardless, acute symptom presentation at levels significantly lower than expected prompts the need to reevaluate the potential for adverse effects from long-term exposure. NASA's continued commitment to long-duration space flight makes it imperative to evaluate the impact of chronic exposure on the mission and astronaut health. With no definitive research to provide insight into current symptoms, potential avenues of action include incorporating quantifiable methods of measuring crew CO_2 burden, developing a robust study to examine various low-to-moderate CO_2 concentrations on human subjects in microgravity and/or implementing design requirements for reduced CO_2 levels on future space platforms.

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1.0 Introduction

It is impractical to reduce carbon dioxide (CO_2) concentrations on space platforms to those experienced on Earth (0.03% CO_2, pp CO_2 0.23 mmHg). Determining an acceptable level of CO_2 requires consideration of spacecraft capability, resource consumption, and the performance and long-term health of the crew. Current operations on board the International Space Station (ISS) are maintained within permissible levels of CO_2 based on time of exposure (See Table 1). Despite careful consideration of these limits, flight crews are reporting symptoms below these predefined acceptable limits. This paper will examine the current understanding of environmental CO_2 exposure as it relates to space flight and recommend areas for further investigation.

Table 1. Spacecraft Maximum Allowable Concentration (SMAC) for CO_2

Exposure Time	SMAC (%)	Equivalent SMAC (mm Hg)
1 hour	2.0%	15
24 hours	1.3%	10
7 to 180 days	0.7%	5
1000 days	0.5%	4

Reference: James 2008.

For the purpose of this paper, CO_2 will be presented in percent concentration (%CO_2) and partial pressures (millimeters of mercury [mmHg]) as referenced to the standard day sea level pressure of 14.7 psi (also the nominal pressure on the ISS). The terms "crew" and "astronaut" will be used interchangeably and may refer to any human in space without intending to imply nationality or level of training. The intent of this paper is to briefly identify specific aspects of CO_2 exposure as it pertains to space flight and suggest areas of further study. An exhaustive literature review or formal recommendations are beyond the scope of this paper.

The original Spacecraft Maximum Allowable Concentration (SMAC) for CO_2 were developed by K. Wong Ph, D. and reviewed by the National Research Council (NRC) in 1996. A large body of research existed on concentrations of CO_2 exceeding 1% CO_2 (7.5 mmHg); however, much of that research did not meet current standards, and measured disparate concentrations, durations, environments, and endpoints. Little research focused on levels below 1% CO_2 (7.5 mmHg); as such, there was no definitive study available to guide standards. After exhaustively reviewing the available literature, Wong set the standards of permissible levels that were eventually accepted by the NRC (James 2008).

ISS crews have repeatedly reported symptoms associated with acute CO_2 exposure at levels of 0.66% CO_2 (5 mmHg), well below the expected symptom threshold of 2.0% CO_2 (15 mmHg) (Environmental Protection Agency [EPA] 2000). Headache is typically the first symptom reported by crew, although ground medical personnel anecdotally note changes in mood at levels as low as 0.5% CO_2 (4 mmHg). Reported symptoms were successfully correlated to ISS CO_2 levels by Christopher Carr, M.Sc (2006) (discussed in section 3.1). Thorough reviews of these reports are documented in *In-Flight Carbon Dioxide Exposures and Related Symptoms: Association, Susceptibility, and Operation Implications* (Law et al. 2009), and *Assessments of Crew Reports on ISS Carbon Dioxide Symptoms* (Felker 2003). Symptom

presentation at levels nearly a third of what is expected raises the concern that chronic or adverse effects also may be occurring at permissible levels.

The following sections will address CO_2 capabilities on spacecraft, a brief review of pertinent literature, specific aspects of CO_2 metabolism, the role microgravity may play in exacerbating CO_2 sensitivity, mission impact, and recommendations for future study and design.

2.0 Carbon Dioxide in Spacecraft

CO_2 is a by-product of metabolism, as metabolic loads increase more CO_2 is produced. At rest, a person generates approximately 200ml of CO_2 per minute. Under maximal exercise, CO_2 production can exceed 4.0L/Min (Williams 2009). If expired CO_2 is allowed to accumulate, it can have adverse effects on health and performance. Although CO_2 also can be generated by combustion, fire suppression equipment, or organic matter decay, this paper will focus on the nominal CO_2 burden experienced by flight crew.

Terrestrial studies suggest that initial symptoms develop at or above 2% CO_2 (15 mmHg), with headache and dyspnea upon exertion. Visual disturbances and tremor appear at 6% CO_2 (45 mmHg), unconsciousness at 7 to 9% CO_2 (53-68 mmHg), and eventually death with the lowest published concentration at 9% (68 mmHg) in 5 min or 17% CO_2 for 1 min (128 mmHg) (EPA 2000). (See Table 2.)

2.1 Spacecraft removal capability

Space platforms have unique challenges in providing habitable environments. They are essentially closed systems with significant power, mass, and volume constraints. CO_2 must be selectively removed from the cabin's ambient air, or the air itself must be voided and replaced continuously. The latter method is an impractical model for long-duration flights.

Spacecraft used for short-duration missions, such as those in the Mercury, Gemini, Apollo, and Space Shuttle programs, operated with nonregenerable Lithium-Hydroxide (LiOH) canisters to remove CO_2. Relatively low concentrations of 0.15 to 0.3% CO_2 (1 to 2 mmHg) were achieved, with discrete periods of up to 1.0 % (7.6 mmHg) during canister change out (Waligora 1994).

Use of disposable canisters, other than for contingency use, is logistically prohibitive on long-duration missions. Regenerable methods typically have lower affinity for CO_2 and more extensive power requirements. A balance between engineering requirements and ideal environmental conditions must be determined. The Skylab Program incorporated a regenerable molecular sieve system. Although this was not as efficient as the LiOH canisters, CO_2 levels were effectively managed, averaging 0.66% CO_2 (5 mmHg) for the three Skylab missions (Waligora 1994).

Initial requirements for the ISS cabin environment targeted conservative concentrations of 0.4% CO_2 (3 mmHg). Justification for this level included U.S. submarine operational limits, the longer crew rotation cycle on the ISS, potential for renal calculi or loss of bone mass exacerbation and to support on-board scientific research (Waligora 1994). Engineering requirements and overall design changes eventually led to the selection of higher operating CO_2 concentrations consistent with the 1996 SMAC limits of 0.7% CO_2 (5.3 mmHg) (Waligora 1994).

The typical operating CO_2 level on the ISS ranges 0.3 to 0.7% O_2 (2.3 to 5.3 mmHg) with a mean of 0.5% CO_2. Fluctuations dependent on location and environmental loads can raise the hourly mean up to 0.7% CO_2 (James 2008, Carr 2006). The primary CO_2 removal system is the Vozdukh in the Russian-built Service Module. The Vozdukh system uses regenerable desiccant and sorbent beds that can vent collected CO_2 when exposed to a vacuum (Carr 2006). Two Carbon Dioxide Removal Assemblies aid the Vozdukh system, also incorporating desiccant and sorbent beds. These assemblies may be run at higher levels as needed, but power and service life concerns regulate this use. Nonregenerable LiOH canisters are available for contingency use.

2.2 International Space Station carbon dioxide monitoring capability

Two primary systems monitor ppCO_2 on the ISS: the Service Module gas analyzer and the Major Constituent Analyzer (MCA) in the U.S. modules. The Service Module gas analyzer is biased low by approximately 1 mmHg to 2.5 mmHg based on data from air sampling. The MCA, while less rugged, is accurate and samples via collection vents from each U.S. module (Felker 2003). A limiting factor in both of these systems is their fixed sampling locations. The lack of air convection in microgravity makes ventilation and accurate monitoring difficult as the recorded value at fixed sampling sites may not reflect the environment immediately surrounding the crew. This topic will be discussed further in section 4.3. Additional capability to monitor CO_2 is available with two portable carbon dioxide monitors (CDMs) and routine air samples that are returned for detailed analysis on the ground. The portable CDMs are periodically deployed to sample CO_2 levels at fixed locations and have been donned by crew members for mobile monitoring (Felker 2003, Law et al. 2009).

3.0 Pertinent Literature Review

To assess the long-term implications of CO_2 exposure during space flight, an ideal study would evaluate long-duration (>30 days) exposures to moderately elevated CO_2 (<1%) in microgravity. Finding appropriate studies is challenging as research in microgravity is limited and terrestrial studies predominantly focus on CO_2 exposure at much higher concentrations with brief exposure periods. No studies were found addressing the specific criteria mentioned above; therefore, this paper focuses on terrestrial studies lasting greater than 20 days at less than 2.0% CO_2, selected research at higher concentrations or shorter durations as applicable, and any research conducted in microgravity that may provide insight into CO_2 metabolism.

Of note, although there are partial analogs to microgravity such as head-down tilt and parabolic flight, the material reviewed did not provide further insight as to whether the analogs meet stated criteria for CO_2 concentration and duration.

3.1 Research conducted in microgravity

The ability to conduct research in space is limited by multiple factors. No published research was found specifically focusing on moderate elevations of CO_2; however, two studies in particular provided insight into CO_2 symptoms experienced by the ISS crew. Christopher Carr, in a 2006 retrospective study, correlated astronaut reports of headache and other CO_2 symptoms with periods of elevated CO_2 on the ISS. Based on recorded CO_2 levels and symptoms documented in weekly private medical conferences

from ISS Expeditions I-VII, Carr identified symptom complaints with a positive predictive value of 50% and negative predictive value of 90% when CO_2 concentrations exceeded 0.63% CO_2 (4.8 mmHg). G. Kim Prisk evaluated the pulmonary function of 10 astronauts on board the ISS at monthly intervals and was able to evaluate lung function over a 130- to 196-day period. Although the elevated CO_2 environment on board the ISS was not addressed in the study, the pulmonary data collected provide insight into pulmonary function in microgravity (Prisk et al. 2006). This study will be discussed further in section 4.3.

3.2 Terrestrial research

Research of long-duration exposure (>20 day) to moderately elevated CO_2 levels (<2%) originates from three basic sources: animal models, submarine patrol studies, and a limited number of dedicated experiments on humans.

3.2.1 Animal Models and Patrol Studies

The closed-circuit environmental conditions on nuclear submarines, with the exception of microgravity, are grossly analogous to space cabins. From 1960 to the mid 1980s, multiple studies evaluating submariners on extended patrols and in dive chamber simulations were performed. One of the experts in this field, Karl Schaefer from the U.S. Naval Medical Research Laboratory and the Naval Submarine Research Laboratory, published numerous articles on both animal models and submariners. The submarine patrol studies predominantly corroborated earlier animal studies, and Schaefer intended to conduct dedicated long-term manned diving chamber studies to evaluate CO_2 concentrations up to 1%. However, with the advent of new naval technology reducing CO_2 levels below 0.5%, the proposed studies were deemed too costly and no longer pertinent (Waligora 1994).

W. A. Tansey, working with Schaefer in 1979, compiled a retrospective epidemiological evaluation of submariners analyzing medical records from 7,650,000 man-days. Tansey evaluated two time periods from 1965-67 and 1968-73. Between those two time periods, substantial improvements were made in atmospheric controls, most notably a decrease in exposure time to CO_2 concentrations greater than 1% (70 to 90% during 1963-67, <20% during 1968-73). As a retrospective study, no causal relationship could be established, although the data demonstrated reductions in genitourinary (renal calculi), respiratory, and gastrointestinal illnesses as measured in lost workdays.

3.2.2 Dedicated Studies

Two notable studies, Radziszewski (Radziszewski et al. 1988) and a joint NASA-ESA-DARA study (1998), evaluated exposure to moderately elevated CO_2 concentration over multiple days. Radziszewski evaluated 56 subjects in 11 experiments ranging from 6- to 46-day exposures at various CO_2 levels. He noted little impairment at 1% CO_2, and described performance at 1.9% CO_2 as "without noticeable changes of physiological function at rest and during exercise." Despite this, he eventually concluded that the 0.5% CO_2 (3.8 mmHg) limit adopted by the U.S. Navy for long-duration exposure "appears justified."

The Joint NASA-ESA-DARA study evaluated four university students in a diving chamber over two 23-day periods of exposure to 0.7% and 1.2% CO_2, respectively. The study was limited by a small population, a poor control group (students who continued normal activity with periodic testing), and two exposure periods repeated 3 months apart on the same subjects. The authors noted an increase in cerebral

blood flow, lactic acid build up under exercise, and mild performance impairment (Sliwka et al. 1998, Hoffmann et al. 1998, Manzey et al. 1998). No significant effect on sleep, circadian rhythm, or peak oxygen (O_2) consumption during exercise was noted (Gundel et al. 1998 #2, Samel et al. 1998, Hoffmann et al. 1998). Cardiorespiratory response, as measured by heart and breathing rate, varied over the duration of the experiment. The variation was presumed to be due to cycles of mild compensated and uncompensated respiratory acidosis. A steady state was never achieved over the 23-day exposure (Gundel et al. 1998). Specific areas of these studies will be discussed later in section 4.2 Prolonged Effects of CO_2 Exposure.

4.0 Carbon Dioxide-Related Physiology

Crew reports of acute CO_2 symptoms appear credible; astronauts are trained to recognize these symptoms, they correlate with ISS CO_2 levels (Carr 2006), and by anecdotal report, symptoms are observable by crew surgeons in mission control during communication exchange with the crew. Given that these symptoms occur at levels significantly lower than terrestrial studies predict, it can be hypothesized that either an environmental or a physiological condition is sensitizing the astronaut. Many factors may play a role—factors such as stress, sleep, or diet—but the most impressive physiological stimulus experienced by the flight crew is microgravity. This section will identify the known response to elevated CO_2 and review the physiological aspects of microgravity that may potentiate that response.

4.1 Carbon dioxide acute toxicity

The effects of CO_2 toxicity can include dyspnea, increased respiratory and heart rate, headache, decreased alertness, anxiety, dizziness, muscle twitching, coma, or death. Symptom severity is related to the concentration of CO_2 and the length of the exposure. Headache is the symptom most commonly reported by ISS flight crew, typically when levels reach 0.7% CO_2 (5 mmHg) (Carr 2006). The SMAC for Selected Airborne Contaminants Vol. 2 (1996) cites Radziszewski et al. (1988) in setting 3% CO_2 (23 mmHg) as the threshold for headaches, and 2% CO_2 (15 mmHG) as rarely producing headache during exercise. The Environmental Protection Agency references 2.0% (15 mmHg) as the threshold for headache after several hours of exposure. To put this in perspective, the highest level recorded in a manned U.S. spacecraft was 14.9 mmHg or 2.0% CO_2 on Apollo 13 (Michel et al. 1975). A detailed list of acute CO_2 toxicity symptoms can be found in Table 2.

Table 2. Physiological Tolerance Time for Various Carbon Dioxide (CO_2) Concentrations and Acute Health Effects of High Concentrations of CO_2

PHYSIOLOGICAL TOLERANCE			ACUTE HEALTH EFFECTS	
$ppCO_2$		Maximum Exposure		
mm Hg	%	Limit (min)	Duration of Exposure	Effects
3.8	0.5%	Indefinite		
7.5	1.0%	Indefinite		
11	1.5%	480		
15	2.0%	60	Several hours	Headache, dyspnea upon mild exertion
23	3.0%	20	1 hour	Headache, sweating, dyspnea at rest
30	4.0%	10	(4-5%)	
38	5.0%	7	Within few minutes	Headache, dizziness, increased blood pressure, uncomfortable dyspnea
45	6.0%	5	1-2 minutes ≤16 minutes Several hours	Hearing, visual disturbances Headache, dyspnea Tremors
53	7.0%	<3	(7-10%)	
68	9%	N/A	Few minutes 1.5 minutes to 2 hours 9% for 5 minutes	Unconsciousness, near unconsciousness Headache, increased heart rate, shortness of breath, dizziness, sweating, rapid breathing Lowest published lethal concentration
75	10%	N/A	(>10-15%)	
113	15%	N/A	1 minute to several minutes	Dizziness, drowsiness, severe muscle twitching, unconsciousness
128	17%	N/A	(17-30%) Within 1 minute	Loss of controlled and purposeful activity, unconsciousness, convulsions, coma, death

Adapted from EPA 2000 by Law 2009.

All U.S. astronauts participate in CO_2 toxicity recognition training. The trainee inhales from a 15L 100% O_2 reservoir with expired gases (CO_2) recirculated into the reservoir. Pulse oximetry (SpO_2), heart rate, respiratory rate, % CO_2 inspired and % CO_2 expired are displayed. The process continues until inspired CO_2 reaches 8% CO_2 (61 mmHg) or the subject experiences significant symptoms and training objectives are met. NASA flight surgeons are present during this evaluation to ensure safety. Characteristic symptoms, per ISS Environmental Health System instructor David Stanley, begin with air hunger at approximately 5.5% CO_2, followed by facial flushing, increased respiration and heart rate, sweating and tingling in distal extremities. About 40% of the crew report headache and 60% heavy headedness. Smaller numbers note visual disturbances and dizziness. While these data are recorded in each astronaut's medical record, the training is designed to aid symptom recognition, not scientific analysis (D. Stanley, personal conversation).

4.2 Prolonged effects of carbon dioxide exposure

The following section reviews specific physiologic responses to increased CO_2 concentrations. While potentially pertinent, the impact on immunological depression, cellular response, and cerebral metabolism is not well understood.

4.2.1 Respiratory Acidosis

Respiratory acidosis begins within a few minutes of exposure to elevated concentrations of CO_2. Despite the body's compensatory mechanisms, a mild acidosis will persist until the exogenous CO_2 is removed (Schaefer 1980). Respiratory acidosis ensues when the body is unable to effectively expel CO_2 secondary to inadequate ventilation or environmental exposure. Excess CO_2 in blood plasma and erythrocytes is reversibly converted to bicarbonate and H+ by carbonic anhydrase. Therefore CO_2 that cannot be expired raises the body's concentration of H+, lowering the pH. The body has two basic responses to this acidosis. It can neutralize the H+ load with bicarbonate from cellular response and renal absorption or it can reduce CO_2 through increased ventilation.

The chemical reaction below demonstrates how this mechanism works:

(HYPERCAPNIA) $2\ H_2O + CO_2 \leftrightarrow H_2CO_3 + H_2O \leftrightarrow H_3O^+ + HCO_3^-$ (ACIDOSIS)

If respiration is inadequate to eliminate CO_2, the equation is driven to the right and acidosis ensues. $PaCO_2$, PaO_2, and pH chemoreceptors, located in the brain stem and aortic arch, stimulate respiration in an effort to rid the body of CO_2 and drive the equation back to the left.

4.2.2 Pulmonary Response

As described above, $PaCO_2$ and pH influence respiratory drive. Exposure to concentrations of 0.5 to 1.5% CO_2 (3.8 to 11 mmHg) result in arterial CO_2 ($PaCO_2$) increases of 1 to 4 mmHg and reduction in pH by 0.02 to 0.05 (Schaefer et al. 1963, Pingree 1977). These values fluctuate during various phases of compensation but remain elevated through the exposure.

The pulmonary response to this acidosis is increased ventilation volume and rate. Specifically Pingree (1977) described a 3.5L/min increase in volume and a 1.5 breaths/min rate increase at 1.0% CO_2. Although respiratory rate and minute volume tend to return to baseline values by the second to third week of exposure, $PaCO_2$ and pH do not (Schaefer 1963). This suggests that the pH and CO_2 dependent set point for respiratory drive may readjust to the chronic exposure.

4.2.3 Vascular

CO_2 is a potent vasodilator of cerebral blood vessels. Cerebral blood flow (CBF) was monitored by Silwka (1998) in 0.7% and 1.2% CO_2 environments over 23 days. On days 1-3, there was a 35% increase in cerebral blood flow as measured at the middle cerebral artery. After day 3, the blood flow steadily decreased to about 12 to 15% above pre-exposure levels. Sliwka reasoned that brain extracellular bicarbonate ($H\ CO_3$-) increases in response to the increased [H+], slowly lowering, but not normalizing, the stimulus during exposure. Unexpectedly, CBF did not return to baseline after return to ambient CO_2 levels remaining elevated through the end of evaluation period, 2 weeks post-exposure. He was unable to explain this persistence of increased CBF post-exposure.

The impact of increased CBF and its persistence post-exposure is not known. A current area of interest in space medicine is case reports of persistently elevated cerebrospinal fluid (CSF) pressures and papilledema in long-duration flight crew. Increased CBF secondary to CO_2 exposure has not been studied as a potential contributor, but should be considered for further investigation.

4.2.4 Calcium and Bone Changes Secondary to Respiratory Acidosis

Calcium loss from CO_2 exposure and its impact on bone density is controversial. Calcium balance during long-duration space flight is concerning for reductions in bone mass and promotion of renal calculi. Wong (1996) in the Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants Vol. 2, concluded that calcium loss secondary to CO_2 was either not present or not of significant magnitude. His conclusion was based on the inconsistencies of terrestrial studies and measurements of Skylab flight crew's urinary calcium excretion. Terrestrial studies presented conflicting data on the presence of CO_2-induced urinary excretion of calcium. Measurements of Skylab crews' urinary calcium levels were equivocal to patients in terrestrial bed rest studies. These findings suggested to Wong that increased calcium excretion was due to microgravity and not significantly affected by CO_2 levels. In contrast, using rat, rabbit, and guinea pig models along with submarine patrol data, Schaefer portrayed a complex process of cyclical phases of respiratory and metabolic acidosis resulting in periods of both Ca2+ release and deposition in bone. This cyclical process could help explain the conflicting results mentioned above. To promote a more thorough understanding of the processes involved, Schaefer's 1980 conclusions are summarized here.

Schaefer noted that renal regulation of acid base disorders was dependent upon the level of acidosis. Renal regulation via bicarbonate reabsorption is fully active when exposed to high levels of CO_2 (>3%, 23 mmHg); however, at lower levels of hypercapnia (experienced at 0.5 to 1.5% CO_2), renal regulation becomes less effective and paradoxically the time required for compensation increases with decreasing CO_2 concentrations (Schaefer 1979). At these lower levels, "bone buffering" becomes the primary compensatory method, and cyclic periods of respiratory acidosis followed by metabolic acidosis develop in roughly 20-day cycles. In contrast, during higher levels of hypercapnia (experienced at >3% CO_2, 23 mmHg), a pattern of respiratory acidosis with cyclical compensated and uncompensated periods predominates (Schaefer 1980).

Bone has a huge capacity to absorb CO_2. Five of the six moles of total body CO_2 reserves reside in bone. The body can use this reserve to regulate H+ and CO_2 levels. CO_2 is released or deposited in bone as either bicarbonate or calcium carbonate. Bicarbonate is the more easily exchanged form and causes no breakdown of the bone. Bicarbonate and a positive ion (Ca2+, K+, Na+) are exchanged for H+. Over chronic periods of acidosis, carbonate can be released, though it does result in bone breakdown. This process is established in chronic metabolic acidosis but is less well understood in chronic respiratory acidosis. Schafer, in his studies, explored the process of chronic respiratory acidosis secondary to environmental CO_2 exposure.

Schaefer describes a unique variation of the bone buffering process in which excess CO_2 is converted to H+ or alternatively deposited in or released from bone as bicarbonate and carbonate. Over an 8-week period of exposure to 1% CO_2, he saw three distinct phases of alternating cycles of fluctuations in bone bicarbonate and carbonate. During Phase 1 and 3 (centered around weeks 1 and 6), calcium and phosphorus peaks in the plasma and troughs in the bone. Phase 2 (weeks 2 to 4) shows bone deposition of calcium and phosphorus with corresponding drops in the plasma. During phase 2, CO_2 is released with bicarbonate from the bone resulting in increasing $PaCO_2$. The cyclical nature of the calcium balance described by Schaefer may explain the range of findings reported in other studies.

After investigating this process in animal studies, Schaefer (1979) noted a greater than 25% increase in renal tubule and cortex calcification of guinea pigs following an 8-week exposure to 1% and 1.5% CO_2 (7.5 and 11.4 mmHg). Likewise, there was a significant decrease in bone calcium compared to control animals. These levels remained depressed 8 weeks after removal from the elevated CO_2 environment (Schaefer 1980, 2).

4.2.5 Renal Calculi

Many factors are thought to contribute to stone formation in space, among those are reduced urine pH, increased urine Ca2+, and decreased urine output (Whitson et al. 1997). In the third phase (peaking at week 6) of the process described above by Schaefer (1980), plasma Ca2+ is at its highest during a period of metabolic acidosis where renal regulation reabsorbs bicarbonate and acidifies the urine. If Schaefer's observations are accurate, this process could promote renal calculi. However, in contrast, Wong (1996), in the Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants Vol 2, concluded that there is no consistent evidence for increased Ca2+ excretion and urine acidification secondary to carbon dioxide exposure.

In a 10-year retrospective epidemiological review of submarines exposed to two distinct periods of known CO_2 concentration, Tansey et al. (1979) observed an overall reduction in workdays lost to illness when CO_2 concentrations were reduced. In particular, he noted a threefold reduction in workdays lost to renal calculi when exposure to >1% CO_2 was reduced to <20% of the time on patrol. As a retrospective study, causality could not be proven, and potentially confounding factors were present. Of note, the increased risk of renal calculi at the higher exposure percentage is only $2.9x10^{-4}$. No evidence was found to validate or contradict the conclusions of Schaefer or Tansey.

4.3 Microgravity

"The immediate effects of weightlessness on the human are not known….The absolute effects of weightlessness on the human are not known" *-Ellen S. Baker*

Barratt's Principals of Clinical Medicine for Space Flight

Initial adaptation to microgravity impacts nearly every system of the body. Long-duration space flight on board the ISS has revealed complex interactions as the body adapts to its new environment. Analysis of these processes is complicated by a small population of subjects, poor analogs to prolonged microgravity, and a limited ability to collect data in this environment. Microgravity's effect on CO_2 may include lack of air convection, internal fluid shifts, cardiovascular adaptations, and changes in pulmonary function. In addition, physiological response to elevated CO_2 may potentiate musculoskeletal, renal, and vascular responses to microgravity. The following is intended to suggest potential areas of further investigation; it is not an exhaustive study of the impact of microgravity as it pertains to CO_2.

4.3.1 Lack of Air Convection

Isolated pockets of CO_2 or other gases can form in spacecraft and remain undetected by fixed environmental monitors such as the MCA. On Earth, gravity-driven convection allows for effective circulation of expired gases. In microgravity, exhaled gases do not readily disperse and may create *pockets* of CO_2. In a computational fluid dynamics study, Chang Son concluded that without exogenous

ventilation, a sleeping crew member in the ISS Service Module could experience a localized CO_2 concentration of > 9 mmHg or 1.2% CO_2 in 10 minutes (Son et al. 2002) (see figure 1). Although this phenomenon does not alter CO_2 metabolism, an inability to dissipate expired CO_2 could contribute to the symptoms reported.

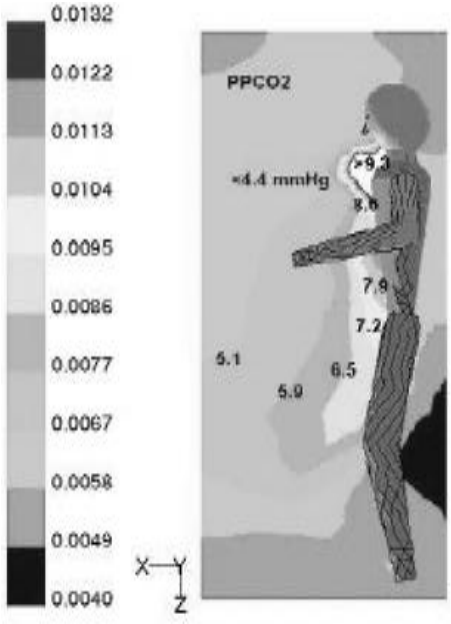

Fig. 1: Carbon dioxide (CO_2) molar concentration an partial pressure in the crew quarters 10 minutes after fa off (x-z plane) (Son et al. 2002).

In Station Detailed Test Objective #25007, two ISS crew members donned CDMs to measure CO_2 levels in the immediate vicinity of the crew members. The CDMs revealed periodic CO_2 spikes during exercise. These spikes were not observed by the MCA (fixed) sensor, supporting the hypothesis that localized areas of elevated CO_2 may be generated during periods of increased metabolic activity (James 2008). Anecdotal reports also identify mild CO_2 toxicity symptoms near the crew dining area and when conducting work in confined or poorly ventilated areas. Further investigation into individual CO_2 burden through noninvasive monitoring may be warranted.

4.3.2 Cardiovascular and Fluid Shift

When standing in a 1G environment, venous pooling in the lower extremities generates a vascular pressure gradient of approximately 200 mmHg from head to heel. Upon entering a microgravity environment, the vascular hydrostatic gradient is lost. When this occurs, a cephalad fluid shift redistributes blood volume in the lower extremities throughout the body. This redistribution results in increased right atrial filling pressure and cardiac output. Mean arterial pressure, however, is preserved, presumably through a decrease in peripheral vascular resistance (Buckey 1996). It is not clear whether cardiac output returns to preflight levels while under the influence of microgravity (Prisk 2005).

Eventually, a new hemodynamic homeostasis is achieved via a 1 to 2L loss of intravascular volume achieved though extravasations into the intracellular space and a relative diuresis (Leach et al. 1996,

Barrett et al. 2008). By flight day 9 in microgravity, a new euvolemic state develops with a 10 to 15% reduction of plasma volume and a 10% reduction in erythrocyte mass (Lane et al. 1996).

How this reduction and redistribution of plasma volume affects CO_2 metabolism is unknown. Blood plasma, proteins, and erythrocytes are responsible for CO_2 transport from tissues to the lungs and are the primary site of action, via carbonic anhydrase, for respiratory acidosis/alkalosis. Providing a glimpse into the possible adverse effects of this hypovolemic state, Burnley (Burnley et al. 2006) investigated terrestrial peak exercise performance following a 450-ml blood donation. In that study, he found significant reductions in O_2 carrying capacity, peak rate of O_2 uptake, and exercise tolerance. Further investigation into CO_2 tolerance and performance in this unique hypovolemic state is recommended.

The effects of long-duration space flight on cerebral blood flow, venous congestion and increased cerebral pressure are not well researched. As presented in section 4.2.3, cerebral blood flow is increased in the presence of 0.7% CO_2 by as much as 35%. How the cephalad fluid shift described above may potentiate any adverse effect from this increased cerebral blood flow is unknown.

4.3.3 Pulmonary Function

Recent studies suggest fewer deficits in lung function from long-duration exposure to microgravity than previously assumed. Studies examining pulmonary function in flight crew reveal that vital capacity returns to near preflight levels by flight day 9 (Prisk 2006 #2). Furthermore, over extended periods of microgravity, pulmonary gas exchange, and muscle strength are preserved (Prisk et al. 2006). Interestingly, though it had been theorized that ventilation and perfusion gradients (Va/Q) of the lung would normalize and improve in microgravity, Va/Q remains effectively unchanged over the normal range of tidal volume, thus suggesting that gravity plays a minimal, possibly even beneficial role in normalizing the Va/Q gradient (Prisk et al. 2006).

G. Kim Prisk ‘s (2006) long-duration study monitored the pulmonary performance of 10 ISS crew members at monthly intervals over a 136- to 196-day period. Measured end-tidal pp CO_2 ($PETCO_2$) revealed an average 2 mmHg elevation above preflight standing values but matched supine preflight values (see Table 4). The only notable variation from preflight values was a 12% decrease in metabolic rate, as measured by oxygen consumption and CO_2 production. This reduced metabolic rate was attributed to disuse of antigravity muscles and work load (Prisk et al. 2006). Based on this analysis, it is unlikely that pulmonary adaptations to microgravity significantly alter pulmonary function, but it is unclear if the 2 mmHg $PETCO_2$ elevation and decreased metabolic rate in the ISS environment are significant.

4.3.4 Renal Calculi

Renal calculi have the potential to seriously impact mission performance and, in one case, nearly resulted in mission termination and unscheduled deorbit (Pietrzyk et al. 2007). While stone formation is multifactorial, several factors experienced in microgravity can be pro stone forming; including reductions in urinary pH, increases in urinary calcium, decreased urinary output, and decreased urinary citrate (stone inhibitor) (Whitson et al. 1997).

5.0 Operational Implications and Recommendations

The known physiological responses to CO_2 exposure and microgravity were reviewed in the previous sections. Based on that review of available literature, three areas with the most potential for mission impact or astronaut health are noted: bone demineralization and renal calculi formation; cerebral blood flow and its impact on increased intracranial pressures; and mission performance.

5.1 Renal calculi and bone reabsorption

Renal calculi symptoms almost resulted in an unscheduled deorbit of a symptomatic ISS crew member (Pietrzyk et al. 2007). An unscheduled deorbit would create a severe impediment to mission success and incur considerable financial and safety consequences. The situation would become more complicated if the symptomatic crew member were the Soyuz commander, or if the situation occurred when transport to definitive care was not possible.

Schaefer (Schaefer et al. 1980) depicts a complex cycle of acidosis and bone reabsorption/deposition leading to varying plasma calcium levels over an 8-week exposure. The SMAC for Selected Airborne Contaminants Vol 2 (Wong 2006) in its discussion of subchronic and chronic toxicity of CO_2 reveals the lack of definitive data to determine the impact on electrolyte levels, kidney, and bone. Given the severity of the consequences, the potential for CO_2 to alter calcium metabolism may need to be reviewed.

Recommendations for further evaluation:

1. Conduct an extended human study (greater than 8 weeks), preferably in microgravity, with multiple levels of CO_2 concentrations from control to 1.0% (7.5 mmHg) to evaluate changes in bone mass, arterial and urinary pH, and calcium and phosphorous levels in bone, plasma, and urine. These studies could be conducted in conjunction with the cerebral blood flow and performance studies suggested in 5.2 and 5.3.

2. Continue current renal calculi prophylaxis of potassium citrate supplementation in astronauts. Magnesium citrate or potassium citrate supplementation may decrease the risk of renal stone formation during and after space flight (Whitson et al. 2009). The potential for increased calciuria secondary to CO_2 exposure may be mitigated by this practice.

3. Consider reduction in environmental CO_2 concentration in future spacecraft. Without further study, however, selection of a practical concentration would only be speculative.

5.2 Cerebral blood flow

Increased intracranial pressure (ICP), increased intraocular pressure and papilledema in space flight are emerging areas of concern, and were the subject of summits at the NASA Glenn Research Center in February 2010 and at Space Life Sciences at Johnson Space Center in February 2011. During the February 2010conference, a case study was presented describing an astronaut with acute visual symptoms in space. The astronaut was found on return to have mild intracranial hypertension, optic nerve sheath dilation, and posterior scleral flattening (Rubin et al. 2007). Furthermore, detailed analysis demonstrating

near vision changes in 23% of short-duration and 48% of long-duration crew members was later published in Ophthalmology Ocotober 2011 (Mader 2011) following those summits.

The etiology of increased ICP and visual impairment is still being evaluated. One theory is that elevated venous pressures may disrupt efficient reabsorption of CSF via the arachnoid granulations. As presented above, exposure to 0.7% CO_2 (5.3 mmHg) results in an immediate (days 1-3) 35% increase in cerebral blood flow. This increased flow partially corrects but does not return to baseline while exposed to elevated CO_2 and it is unknown how long normalization takes once CO_2 levels are returned to ambient levels (Sliwka et al. 1998). The impact of increased CBF in combination with the cephalad fluid shift experience in microgravity should be evaluated in further studies with regard to increased ICP.

Finally, the physiology of increased CO_2 concentrations on the brain and its related structures is unknown. The blood brain barrier is highly permeable to CO_2 and is susceptible to acid/base shifts associated with CO_2 exposure. J. M. Clark (Clark et al. 1969) evaluated four subjects exposed to 3.9% CO_2 (30 mmHg) noting a twofold increase in CSF PCO_2 (6 mmHg) compared to arterial PCO_2 (3 mmHG). In a 5-day exposure, the CSF pH and PCO_2 remained elevated for 2 days longer than arterial PCO_2 and pH. A more complete understanding of CO_2's effects on CSF may be beneficial in understanding the etiology of increased ICP.

Recommendations for further evaluation:

1. Conduct an extended human study (greater than 8 weeks), preferably in microgravity, with multiple levels of CO_2 concentrations from control to 1.0% (7.5mmHg) to evaluate changes in arterial and CSF pH, arterial and CSF pp CO_2, ICP, cerebral arterial and venous pressures. These studies could be conducted in conjunction with calcium and performance studies suggested in 5.1 and 5.3.

2. Incorporate CO_2 and/or increased CBF in the ongoing evaluation of ICP elevation.

3. Consider reduction in environmental CO_2 concentration in future spacecraft.

5.3 Mission performance

With documented physical symptoms reported by astronauts at one-third the expected level of CO_2 (Carr 2006), it is reasonable to hypothesize that performance impairment may also present at lower concentrations. Terrestrial studies suggest that mild performance impairment should begin at elevations of 1.2% CO_2 (Manzey et al. 1998). However, how the relative hypovolemia post-cephalad fluid shift may diminish the body's ability to handle increased CO_2 burdens or acidosis is unknown. Additionally this diminished capacity may become more pronounced during increased physical or neural metabolic activity.

Recommendations for further evaluation:

1. Develop methods for noninvasive monitoring of flight crew's CO_2 burden. It is important to understand if symptoms are related to localized "CO_2 pockets," a physiological sensitization of

microgravity or both. Continuous monitoring of astronauts' immediate CO_2 environment, $PaCO_2$, arterial pH and end tidal CO_2 would be preferred, although noninvasive methods are limited.

Two portable monitors are currently available on the ISS. Wearing the CDMs near the level of the head may provide more specific environmental data. Continuous monitoring of arterial pH and end tidal CO_2 is problematic; however, commercially available transcutaneous $PaCO_2$ monitors are available. Both the TOSCA 500 and V-sign Sentec sensor monitor $PaCO_2$ ($PcCO_2$), SpO_2 and pulse rate. Critical evaluations of these sensors suggest good capability in trend analysis with some overall accuracy concerns (Bernet-Buettiker et al. 2005, Baulig et al. 2007, Bernet et al. 2008, McVicar 2009). Both systems use heated (42 to 45°C) ear clips that may require evaluation for accurate measurements in microgravity. Further investigation of these sensors may be warranted if $PaCO_2$ accuracy can be evaluated.

2. Conduct an extended human study (greater than 8 weeks), preferably in microgravity, with multiple levels of CO_2 concentrations from control to 1.0% (7.5 mmHg) to evaluate performance during continuous stressful activity similar in intensity to ISS missions. If a microgravity environment is not feasible, a method to simulate fluid shift should be incorporated. These studies could be conducted in conjunction with calcium and cerebral blood flow studies suggested in 5.1 and 5.2.

3. Consider reduction in environmental CO_2 concentration in future spacecraft.

6.0 Conclusion

Reliable reports of acute CO_2 symptoms on the ISS are occurring at levels lower than terrestrial studies predict. It is logical to postulate that either an environmental or physiological condition is sensitizing the astronauts. After review of the pertinent literature, three potential areas of operational impact were identified: renal calculi and bone reabsorption; cerebral blood flow; and mission performance. With no definitive research to provide insight into these areas, further evaluation of the following is recommended:

- Incorporating quantifiable methods of measuring crew CO_2 burden through noninvasive continuous motoring of selected astronauts.
- Developing a robust study (>8 weeks) examining various low-to-moderate CO_2 concentrations on human subjects, preferably in microgravity.
- Implementing design requirements for reduced CO_2 levels on future space platforms.

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13. ABSTRACT *(Maximum 200 words)*
Out of operational necessity, space platforms function with ambient carbon dioxide (CO2) concentrations in excess of normal atmospheric conditions (0.03% or partial pressure of 0.23 mmHg). NASA's long-duration Spacecraft Maximum Allowable Concentration for CO2 is 0.7% (pp CO2 of 5.3mmHg). Extensive terrestrial studies support this level as safe and unlikely to cause adverse effects; however, International Space Station crews routinely report symptoms of acute CO2 toxicity (e.g., headaches, lethargy) that correlate with relative elevations of cabin CO2 below the permissible level. It is unclear if the unique environment of space results in increased sensitivity to CO2 or if other confounding factors are present. Regardless, acute symptom presentation at levels significantly lower than expected prompts the need to reevaluate the potential for adverse effects from long-term exposure. NASA's continued commitment to long-duration space flight makes it imperative to evaluate the impact of chronic exposure on the mission and astronaut health. With no definitive research to provide insight into current symptoms, potential avenues of action include incorporating quantifiable methods of measuring crew CO2 burden, developing a robust study to examine various low-to-moderate CO2 concentrations on human subjects in microgravity and/or implementing design requirements for reduced CO2 levels on future space platforms.

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