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Evidence-Based Approach to Establish Space Suit Carbon Dioxide Limits

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ACRONYMS AND ABBREVIATIONS

ATA	atmosphere pressure absolute
ATM	atmosphere pressure
ACFM	actual cubic feet per minute
ALARA	as low as reasonably achievable
BTU	British thermal unit
BTPS	body temperature, pressure, saturated
C	Celsius
CA	carbonic anhydrase
CBF	cerebral blood flow
CFM	cubic feet per minute
Cl^-	chloride ion
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
CSF	cerebrospinal fluid
δ/α	ratio of delta wave power to alpha wave power
DCS	decompression sickness
D_{LCO}	pulmonary diffusion capacity
D_m	membrane diffusion capacity
EEG	electroencephalogram
EVA	extravehicular activity
f	breathing frequency
F_ICO_2	dry-gas decimal fraction of carbon dioxide
ft	feet
g	gram
1G	Earth gravity
H^+	hydrogen ion
$[H^+]$	hydrogen ion concentration
$[H^+]_a$	arterial blood hydrogen ion concentration
Hb	hemoglobin
HCO_3	bicarbonate ion
$[HCO_3^-]$	bicarbonate ion concentration
$[HCO_3^-]_v$	venous blood bicarbonate ion concentration
HDT	head-down tilt
HR	heart rate
h	hour

ACRONYMS AND ABBREVIATIONS

ICP	intracranial pressure
ISS	International Space Station
JSC	Johnson Space Center
L	liter
LEA	launch, entry, and abort
m	meter
MAP	mean arterial pressure
MCA	mid-cerebral artery
μG	microgravity
mM	millimolar
mEq	milliequivalent
mmHg	millimeter of mercury
min	minute
mL	milliliter
mph	miles per hour
N_2	nitrogen
nM	nanomolar
NO	nitric oxide
O_2	oxygen
P_AAr	alveolar partial pressure of argon
P_aCO_2	arterial blood partial pressure of carbon dioxide
P_AH_2O	alveolar partial pressure of water vapor
P_AO_2	alveolar partial pressure of oxygen
P_ACO_2	alveolar partial pressure of carbon dioxide
P_AN_2	alveolar partial pressure of nitrogen
P_B	ambient pressure
PCO_2	partial pressure of carbon dioxide
$P_{CSF}CO_2$	cerebrospinal fluid partial pressure of carbon dioxide
$P_{ET}CO_2$	end-tidal carbon dioxide partial pressure
pH	potential hydrogen ion
PH_2O	partial pressure of water vapor
P_ICO_2	inspired partial pressure of carbon dioxide
P_IO_2	inspired partial pressure of oxygen
PN_2	partial pressure of nitrogen
PO_2	partial pressure of oxygen
ppm	parts per million

ACRONYMS AND ABBREVIATIONS

psia	pounds per square inch absolute
P_VCO_2	venous blood partial pressure of carbon dioxide
$\dot{Q}$	cardiac output rate
RBC	red blood cell
RER	respiratory exchange ratio, modified by respiration
R	respiratory exchange ratio, modified by respiration
rpm	revolutions per minute
RQ	respiratory quotient, modified by metabolism
RR	respiration rate
S_aO_2	arterial hemoglobin oxygen saturation through blood sample
SMAC	spacecraft maximum allowable concentrations
STPD	standard temperature, pressure, dry
S_pO_2	arterial hemoglobin oxygen saturation through pulse oximetry
$\dot{V}_A$	alveolar ventilation rate
$\dot{V}_A/\dot{Q}$	ventilation-perfusion ratio
V_C	pulmonary capillary blood volume
$\dot{V}CO_2$	carbon dioxide production rate
V_D	physiologic dead space volume
$\dot{V}_E$	minute volume (ventilation, exhaled) rate
$\dot{V}_I$	minute volume (ventilation, inhaled) rate
$\dot{V}O_2$	oxygen consumption rate
$\dot{V}O_2max$	maximum aerobic oxygen consumption rate
$\dot{V}O_2peak$	peak aerobic oxygen consumption rate
V_T	tidal volume
wk	week

EXECUTIVE SUMMARY

A literature survey was conducted to assess if published data (evidence) could help inform a space suit carbon dioxide (CO_2) limit. The search identified more than 120 documents about human interaction with elevated CO_2. Until now, the guiding philosophy has been to drive space suit CO_2 as low as reasonably achievable. NASA's EVA Office requested an evidence-based approach to support a new generation of exploration-class extravehicular activity (EVA) space suits. Specific literature data about CO_2 are not available for EVA in microgravity because EVA is an operational activity and not a research platform. However, enough data from ground-based research are available to facilitate a consensus of expert opinion on space suit CO_2 limits. The compilation of data in this report can answer many but not all concerns about the consequences of hypercapnic exercise in a space suit. Inspired partial pressure of CO_2 (P_ICO_2) and not dry-gas partial pressure of CO_2 (PCO_2) is the appropriate metric for hypercapnic dose to establish space suit CO_2 limits. The reduction of inspired gas partial pressures by saturation of the inspired gases with water vapor at 37°C is a significant factor under conditions of hypobaric space suit operation. Otherwise healthy EVA astronauts will exhibit wide variability in responses to acute hypercapnia while at rest and during exercise. What is clear from the literature is the absence of prospective (objective) accept or reject criteria for CO_2 exposure in general, and no such criteria exist for operating a space suit. There is no absolute "Gold Standard" for an acceptable acute hypercapnic limit, just a gradual decrease in performance as CO_2 increases. Acceptable CO_2 exposure limits are occupation, situation (learned or novel tasks), and person-specific. Investigators who measured hypercapnic physiology rarely correlated those changes to neurocognitive symptoms, and those that measured hypercapnic neurocognition rarely correlated those changes with physiology. Some answers about changes in neurocognition and functional EVA performance during hypercapnic exercise in a space suit await new research.

1.0 INTRODUCTION

Humans function properly with a steady-state store of carbon dioxide (CO_2), mostly in the form of bicarbonate ions (HCO_3^-), and too much or too little CO_2 is disruptive to homeostasis. The body exquisitely regulates tissue CO_2 and oxygen (O_2) tensions. CO_2 regulation maintains hydrogen ion concentration [H^+, pH] compatible with efficient cell function. CO_2 is a product of cellular metabolism of carbohydrates, fats, and proteins and must be removed from the tissues by the integrated cardiopulmonary system at a rate that matches CO_2 production or the steady-state balance is disrupted. At rest, steady-state production of CO_2 is about 250 $mL_{(STPD)}$/min and at steady-state maximum exercise is about 4,000 $mL_{(STPD)}$/min. CO_2 concentration is controlled locally at the tissue level by adjusting blood perfusion and broadly by chemoreceptors in the carotid bodies, arch of the aorta, and within the medulla oblongata with cardiopulmonary response integrated by the central nervous system (CNS). On average, combining rest with modest activity, the body effortlessly eliminates about 20 moles of CO_2 (880 g) per day of this volatile acid to preserve a normal alkaline pH of 7.40.

Vascular reactivity, particularly cerebral blood flow (CBF), is sensitive to changes in arterial blood CO_2 partial pressure (P_aCO_2) (Ainslie and Duffin 2009), (Sliwka, Krasney et al. 1998), (Halpern, Neufeld et al. 2003). CO_2 mediates its effect on CBF through alteration of [H^+] of the cerebrospinal fluid (CSF). Over a wide range of P_aCO_2 from 20 to 80 mmHg, the CBF changes 1–2 mL/100 g brain/min for each 1 mmHg change in P_aCO_2. During sustained alterations of P_aCO_2, CBF returns to baseline over several hours due to a correction of brain extracellular pH (Brian 1998), (Sliwka, Krasney et al. 1998). Sliwka insonated the middle cerebral arteries of 4 males exposed to 23 days of 0.7% CO_2 and another 23 days of 1.2% CO_2. CBF was elevated by 35% during the first 1–3 days of both exposures but then returned to pre-test levels. Despite similar CBF responses, headache was only reported during the initial phase of exposure to 1.2% CO_2. Performance of muscles, even respiratory muscles like the diaphragm, is influenced by acute respiratory acidosis when P_aCO_2 exceeds 54 mmHg (Juan, Calverley et al. 1984). The lung itself is a target organ for changes in respiratory CO_2 and O_2. Smooth muscle in terminal bronchioles and pulmonary arterioles contract under either hypercapnia or hypoxia and relax under hypocapnia or hyperoxia (Balanos, Talbot et al. 2003), (Sheehan and Farhi 1993). More on this later, but clearly CO_2, O_2, and even nitric oxide (NO) (Stamler, Jia et al. 1997), have critical roles in modulating the distribution of alveolar ventilation rate ($\dot{V}_A$) and blood perfusion rate (cardiac output, $\dot{Q}$) in the lung and modulating perfusion rate through all vascular beds to preserve homeostasis.

During rest and exercise, the inhalation of extraneous CO_2 opposes the exhalation of metabolic CO_2. Acidified venous blood needs to transport CO_2 for removal and return as pH-normal arterial blood. If this is hindered, then there are physiologic and therefore neurocognitive and performance consequences to hypercapnia. Heavy exercise during hypercapnia will place excessive demands upon ventilation that will limit exercise capacity. Retention of CO_2 occurs when alveolar ventilation does not increase sufficiently to compensate for its reduced effectiveness in CO_2 elimination.

During extravehicular activity (EVA), astronauts will rebreathe CO_2, particularly during periods of physical activity, because helmet CO_2 washout is never perfect. In addition, any compromised suit ventilation and degradation of CO_2 removal capacity will also increase inspired CO_2 partial pressure (P_ICO_2). Therefore, we will assess from a literature review the human physiologic, neurocognitive, and functional performance responses across a range of CO_2

partial pressure (PCO_2) from 0 to 20 mmHg and a range of O_2 consumption from 250 $mL_{(STPD)}$ O_2/min to 2,500 $mL_{(STPD)}$ O_2/min (from 300 to 3000 BTU/h). These ranges of PCO_2 and metabolic rates are possible during EVA and to a lesser degree during launch, entry, and abort (LEA) scenarios where astronauts are in a pressurized suit. Our analysis of the literature data may provide enough evidence to establish operational limits that assures safety and maintains health and performance during EVA and LEA with PCO_2 >0 mmHg. Ultimately, a consensus of opinion after a review of evidence by medical, operational, and life science experts will establish limits.

As a point of departure from previous reviews, in 1993 Seter (Seter 1993) provided an extensive literature review titled, "Allowable Exposure Limits for Carbon Dioxide during Extravehicular Activity". He recommended a PCO_2 limit of 3.8 mmHg for nominal operations in a space suit with 7.6 mmHg for heavy exertion. This reduced by half the NASA limit of 7.6 mmHg for nominal and 15.2 mmHg for heavy exertion, which was a consensus opinion extending back to 1969 (Michel, Sharma et al. 1969), (Roth 1968). Other reviews since 1969 consistently recommended 7.6 mmHg as an upper limit for nominal EVA, and then added conditions (time limits or corrective actions) if PCO_2 was >7.6 mmHg (Furr, Monson et al. 1988), (Waligora 1979). Furr, in his 1988 review, says "*The question addressed here is: During EVA, what level of carbon dioxide should be tolerated?"* In 2018 we are still asking this question. Glatte (Glatte Jr and Welch 1967) provided an extensive review in 1967, extending back into the 1920s. His early review is mentioned here because he parsed data into acute and chronic exposure to CO_2 and further stratified responses into 6 major groupings: a) lung [tidal volume (V_T), minute volume rate ($\dot{V}_E$), alveolar CO_2 partial pressure (P_ACO_2)], b) arterial blood (pH and CO_2 content), c) kidney, d) CNS, e) overt symptoms, and f) performance. He defined acute exposure as 4 hours, which is not unreasonable for an EVA, and covered a range of PCO_2 from 4 to 21 mmHg in his Table III. He identifies increased V_T, $\dot{V}_E$, P_ACO_2, and blood content of CO_2, with decreased arterial pH, few symptoms of dyspnea, and no performance degradation at a PCO_2 of about 15 mmHg, a conclusion worthy of note.

A literature review by Knafelc (Knafelc 2000) titled, "Physiological Basis for CO_2 Limits within Semiclosed and Closed-Circuit Underwater Breathing Apparatus" concluded that underwater work and cognitive performance were not significantly affected at PCO_2 <15.2 mmHg. However, the prevailing Navy standard of 3.8 mmHg for these breathing devices was still recommended because divers also have the additional stressors of decompression sickness (DCS), nitrogen (N_2) narcosis, O_2 toxicity, and CO_2 retention due to high-resistance breathing equipment (Henning, Sauter et al. 1990). All these stressors are exacerbated by hypercapnia. An EVA astronaut in a low-pressure space suit is exempt from N_2 narcosis, O_2 toxicity, and has no CO_2 retention due to breathing resistance; however, he or she is at some risk for DCS. Finally, in 1992 Wong (Wong 1992) of the Johnson Space Center (JSC) Toxicology Group provided an exhaustive review of CO_2 exposure in humans and animals as part of a National Research Council Subcommittee review of Spacecraft Maximum Allowable Concentrations (SMAC) for airborne spacecraft contaminants. The goal was to set SMAC values for space habitation in general; however, literature about CO_2 exposure was cited that has application to EVA. Dr. Wong provided a Toxicity Summary Table specific for human CO_2 exposures that we include in the Appendix. Simply scanning down the table from the lowest (0.5% CO_2) to highest (30% CO_2) CO_2 concentrations provides the reader with an impression of the physiologic, neurocognitive, and performance impacts of normobaric hypercapnia in 1G. It appears to this

reviewer that acute exposure to PCO_2 <22.8 mmHg (3% CO_2) during EVA would be operationally acceptable, assuming that μG and 1G exposures are otherwise equivalent. His numerous references are also provided and the ✓ symbol indicates data from humans, as a resource.

It follows from above that a PCO_2 limit for a diver, an office worker, an airline passenger, a coal miner, a fire fighter, a submersible operator and a different PCO_2 limit for an aviator or astronaut would be justified, as the PCO_2 limit is occupation-specific and situation-specific. This is the challenge when evaluating current requirements by various regulatory agencies. Each requirement is correct within the context that it applies. There is no one "Gold Standard". For example, the American Society of Heating, Refrigeration, and Air Conditioning Engineers, the American Conference of Governmental Industrial Hygienists, and the U.S. Occupational Safety and Health Administration all dictate standards for air quality in different work environments that usually incorporate a significant safety factor for CO_2 exposure. NASA, the European Space Agency, and the Deutsche Agentur fur Raumfahrtangelegenheiten sponsored research to set limits for ambient CO_2 levels for extended space habitation. This research produced 10 papers based on 4 subjects covering physiologic and mental performance, including sleep quality and exercise performance (Frey, Sulzman et al. 1998). The general conclusion was that no serious medical concerns emerged with PCO_2 <9 mmHg (1.2%) for exposures lasting about 3 weeks, but this was based on research in 1G.

2.0 SPECIFIC AIMS

This effort is to evaluate compiled evidence (data) from a comprehensive literature review of changes in physiologic, neurocognitive, and performance in response to increased PCO_2 with specific application to EVA and LEA events with astronauts in pressurized suits. Astronauts during EVA will breathe elevated levels of CO_2, particularly during periods of physical activity, because helmet CO_2 washout is never perfect and compromised suit ventilation and degradation of CO_2 removal capacity will also increase PCO_2. There is no single *a priori* acceptable limit for PCO_2 exposure; any proposed limit is occupation-specific, situation-specific, and even person-specific. However, there is a philosophy that states breathing gas free of CO_2 is preferred. As low as reasonably achievable (ALARA) with an upper acceptable limit for EVA seems a practical approach to move forward with human exploration of space. The model for EVA is similar to that for setting exposure limits for a toxicant in a work environment (8 h/day and 40 h/wk) given that the toxicant in the living environment is absent or present in a significantly lower concentration.

3.0 MAJOR GOALS OF LITERATURE REVIEW

1. Quantify interactions between ambient pressures (P_B), PO_2, PCO_2, exercise, and gravity to provide specific space suit PCO_2 limit(s) applicable to EVA and LEA.
2. Define acceptable deviation(s) in physiology as a function of PCO_2 and recommend space suit PCO_2 limit(s) for EVA/LEA.
3. Define acceptable deviation(s) in neurocognition as a function of PCO_2 and recommend space suit PCO_2 limit(s) for EVA/LEA.
4. Define acceptable deviation(s) in functional performance as a function of PCO_2 and recommend space suit PCO_2 limit(s) for EVA/LEA.

5. Identify health effects from repeated, acute hypercapnic exposures and recommend space suit PCO_2 limit(s) for repeated EVAs.

Does a focused review of the literature about acute exposure to CO_2 combined with exercise provide adequate evidence (data) to establish operational limits for EVA and LEA under hypobaric conditions in <1G environments? If yes, then operational limits will be defined based on a Delphi-method review of literature evidence. If no, then does the absence of data from the literature suggest a clear research protocol to achieve the goal of establishing operational limits for EVA and LEA, given that the majority of testing is limited to 1G? A second related question is do these literature data eliminate the need to validate operational limits in a ground-based study before implementation?

4.0 LITERATURE SEARCH SPECIFIC TO ACUTE EXTRAVEHICULAR ACTIVITY CONDITIONS

To limit the scope of the literature review, we focus mainly on acute exposure to CO_2 combined with rest and exercise. There is a vast literature on chronic exposure to low-level CO_2. For example, exposure to 1.5% CO_2 for 42 days in active submariners induced respiratory acclimatization and CO_2 retention but was well tolerated and reversible on reexposure to fresh air (Schaefer, Hastings et al. 1963). We would prefer to review only specific data about hypercapnia combined with exercise with physiologic, neurocognitive, and performance responses in a hypobaric, hyperoxic space suit in a μG environment. However, no comprehensive data set collected under these conditions currently exists in the literature even after 60 years of EVA experience with astronauts and cosmonauts. Also, no data exists about chronic exposure to low-level PCO_2 followed by acute exposure to higher-level PCO_2, as one might expect during exploration EVA activity from a habitat. The operational philosophy has been to minimize, rather than accommodate hypercapnia. Therefore, recommendations for EVA and LEA will necessarily come from extrapolations of literature evidence and the assumption that all extrapolations are valid.

The responses to hypercapnia are modified by other gases like O_2 and N_2, depending on their partial pressures. But to stay focused, we do not cover to a great extent the interactions between CO_2 and hyperbaric hyperoxia (O_2 toxicity, (Lambertsen, Hall et al. 1963), (Bitterman and Bitterman 1998)) or CO_2 and increased PN_2 (N_2 narcosis, (Fothergill, Hedges et al. 1991)), or CO_2 and risk of DCS, or CO_2 and hypoxia (Nielsen and Smith 1952), (Cormack, Cunningham et al. 1957), or CO_2 and CO_2 retention due to high breathing resistance (Warkander, Norfleet et al. 1990). Our focus is primarily on acute hypercapnia in normobaric normoxia at rest and exercise and in acute hypobaric normoxia at rest and exercise. Establishing chronic CO_2 exposure limits in spacecraft (Gemini, Apollo, Skylab, Space Shuttle, Neurolab, International Space Station (ISS)) is not our focus; however, this process has relevance to EVAs because they occur in μG. Waligora (Waligora 1992) briefly reviewed the history of spacecraft CO_2 limits in 1992 and offered a recommendation of ≤3 mmHg for the then Space Station Freedom.

Fresh air at sea level pressure (760 mmHg) has about 0.03% CO_2 (300 ppm), a PCO_2 of about 0.23 mmHg. A chronic exposure to 1% CO_2 (7.6 mmHg at 760 mmHg, 10,000 ppm) does not significantly limit human health or performance on Earth (Frey, Sulzman et al. 1998). However, with sensitive instruments it is possible to show measurable changes in cognition and physiology even with respired PCO_2 <7.6 mmHg (James 2007), (Satish, Mendell et al. 2012),

(Cronyn, Watkins et al. 2012), (Frey, Sulzman et al. 1998). The current NASA operational approach to limit chronic PCO_2 exposure on the ISS is to maintain 24-hour levels to ≤3 mmHg. It is not possible with current space suit engineering to match this goal during EVA. A distinction is made between chronic and acute CO_2 exposure, with the avoidance of acute symptoms as the primary consideration for limits in a space suit.

Limiting exposure time permits a greater PCO_2. During EVA, currently no corrective action is required until the inlet PCO_2 from the CO_2 scrubber exceeds 3 mmHg; however, at 8 mmHg or if symptoms are present, the helmet purge valve must be opened and at 12.4 mmHg, which corresponds to a P_ICO_2 of 9.8 mmHg, the helmet purge valve must be opened even in the absence of symptoms. This action corrects for the higher but unknown PCO_2 in the helmet that is causing symptoms or instances in which CO_2 removal capability is near exhaustion, or both. In contrast, Mekjavic (Mekjavic IB 1992) references a 1990 requirement from the Norwegian Petroleum Directorate that submersibles and atmospheric diving suits not exceed 3.8 mmHg in a 6-hour working dive, with allowance to 15.2 mmHg over the next 48 hours in the event the recovery is delayed.

In the case of the astronaut, it is uncertain what the actual helmet PCO_2 is because the free volume (dead space) of the helmet depends on the volume of the head and communication equipment, the CO_2 washout efficiency for a given helmet ventilation flow rate, the position of the head at any moment, and the minute-by-minute metabolic rate of the astronaut. A concerted effort is underway to standardize helmet CO_2 washout measurement methodology (Bekdash, Norcross et al. 2017). Historically, Michel (Michel, Sharma et al. 1969) used PCO_2 at the end of inhalation and found it increased 1–2 mmHg for rest, 3.5 mmHg at 1000 BTU/h, and about 7 mmHg at 2000 BTU/h during suited (Apollo A-5L) treadmill exercise at 18.4 psia with helmet ventilation at about 6 actual cubic feet per minute (ACFM). He concedes this approach underestimated the actual P_ICO_2 because it ignored rebreathing helmet CO_2 during initial inhalation. However, it was adequate to evaluate a range of helmet ventilation rates combined over a range of exercise intensity. Wick (Wick 1966) evaluated different sampling methods in an unpressurized Gemini (G2C) suit where 0%, 1%, 2%, or 3% CO_2 was delivered to the suit at 11 cubic feet per minute (CFM) with subjects at rest on a chair or while walking at 3 mph on a treadmill. This was the first and only time that arterial blood for P_aCO_2 assesment was collected during suited exercise. Mean P_aCO_2 in 10 males increased to 57 mmHg during the brief exercise (mean 2,050 BTU/h) with inlet CO_2 at 3%.

A goal with a standard methodology is to provide a standard method to assess P_ICO_2, to be discussed next. P_ICO_2 is a practical measure of hypercapnic dose in a suit environment. P_ICO_2 as hypercapnic dose is applicable to all subjects. It comes before P_ACO_2 or P_aCO_2 and so is not modified by the individuals' ventilatory response to hypercapnia. Thus, P_ICO_2 is superior to PCO_2 for development of CO_2 limits in a space suit.

5.0 DEFINING A PRACTICAL HYPERCAPNIC DOSE

We avoid discussing CO_2 concentration as a percentage and instead use dry-gas PCO_2 as mmHg. We also frequently refer to the inspired wet-gas P_ICO_2, P_ACO_2, and P_aCO_2. The action of CO_2 in the central nervous system is through the partial pressure of CO_2 and resulting change in $[H^+]$ within the cerebrospinal fluid ($P_{CSF}CO_2$).

Atmospheric CO_2 eventually reaches the lung. During this transition, the inspired gas becomes saturated with water vapor at 37°C, a PH_2O of 47 mmHg or 0.909 psi since 1 psi = 51.7 mmHg (Conkin 2011). The following 4 related equations are helpful:

1. $F_ICO_2 = PCO_2/P_B$, where F_ICO_2 is the dry-gas decimal fraction of CO_2, PCO_2 is dry-gas atmospheric CO_2 partial pressure as mmHg from a sensor, and P_B is atmospheric pressure absolute as mmHg.
2. $P_ICO_2 = (P_B–47) \times F_ICO_2$, where 47 is the vapor pressure of H_2O as mmHg at 37°C body core temperature.
3. $F_ICO_2 = P_ICO_2/(P_B–47)$
4. $PCO_2 = P_B \times [P_ICO_2/(P_B–47)]$ or $P_B \times F_ICO_2$

The critical explanatory variable for physiologic, neurocognitive, and performance responses is P_aCO_2, which is assumed equivalent to P_ACO_2 in a healthy astronaut. Therefore the transition from dry-gas PCO_2 in the breathing atmosphere to water saturated P_ICO_2 at 37°C in the lungs is necessary for a precise dose-response approach to inspired CO_2, much the same as for P_IO_2 in terms of hypoxic dose (Conkin 2016).

Figure 1 shows that for the same dry-gas PCO_2, say 20 mmHg, the appropriate "dose" of CO_2 transferred to arterial blood depends on the ambient pressure, in this case the space suit pressure. At 4.0 psia suit pressure (207 mmHg) a PCO_2 of 20 mmHg equates to a P_ICO_2 of 15.5 mmHg while at 6.0 psia suit pressure (310 mmHg) the same PCO_2 is a P_ICO_2 of 17.0 mmHg. At sea level a PCO_2 of 20 mmHg is a P_ICO_2 of 18.76 mmHg. The ultimate goal is to define the equivalent P_ICO_2 hypercapnic dose at any pressure. For example, to compute the equivalent P_ICO_2 of 15.5 mmHg at 4.0 psia for sea level pressure, the PCO_2 must be 16.52 mmHg, through Eq. 4 (above). Once an acceptable limit for P_ICO_2 is established, then the PCO_2 limit is computed for any suit pressure. Note that a PCO_2 limit defined from testing at sea level will always produce a lower P_ICO_2 when applied at reduced pressure. For example, an 8 mmHg PCO_2 suit sensor limit at 14.7 psia (760 mmHg) results in a P_ICO_2 of 7.5 mmHg. The same 8 mmHg PCO_2 suit sensor limit at 4.3 psia (222 mmHg) results in a lower P_ICO_2 of 6.3 mmHg. Therefore, a practical measure of hypercapnic dose should be P_ICO_2. It is reasonable to expect that the same P_ICO_2 under different test conditions will produce the same performance outcomes in those conditions, within a reasonable range of P_ICO_2.

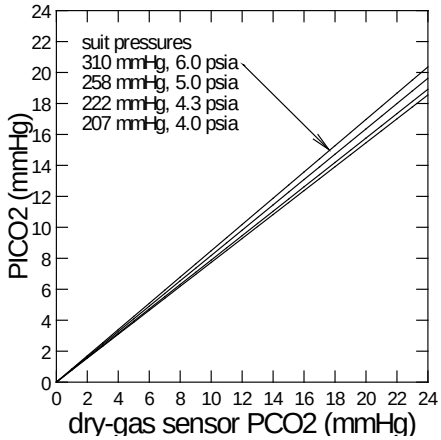

Figure 1 Dry-gas PCO_2 measured with a sensor that monitors the atmospheric breathing gas becomes saturated with water vapor on the way to the lungs. P_ICO_2 at 760 mmHg for PCO_2 of 5, 10, 15, and 20 mmHg are 4.7, 9.3, 14.0, and 18.7 mmHg, respectively.

6.0 BASIC PHYSIOLOGIC RESPONSE TO BREATHING CARBON DIOXIDE

Figure 2 (White 1954) shows how an increase in the dry-gas decimal fraction of CO_2 (F_ICO_2) at sea level increases the P_ICO_2 and therefore the P_ACO_2 (on y-axis) and in-turn the P_aCO_2 that stimulates physiologic responses to hypercapnia. At 0% F_ICO_2 (0 mmHg PCO_2), the P_ACO_2 is normal at 40 mmHg. At an F_ICO_2 of about 4% (30 mmHg PCO_2), the P_ICO_2 is 28.5 mmHg and when combined with the CO_2 in the alveoli then becomes a P_ACO_2 of about 45 mmHg. A small increase in P_aCO_2 even while breathing 1% and 2% CO_2 is expected along with a small decrease in arterial blood pH (Ellingsen, Sydnes et al. 1987), (Brackett Jr, Cohen et al. 1965). Ellingsen explained that the increase in $\dot{V}_E$ provides only incomplete compensation for exposure to CO_2 since P_aCO_2 remains above normal during the event. In other words, the body does not hyperventilate past what is needed to manage an increase in P_aCO_2, so some increase in P_aCO_2 is accomodated even when breathing a low level of CO_2 (Jones, Levine et al. 1971). What is not seen on Figure 2 is the increased rate and depth of respiration in response to the increased hypercapnia.

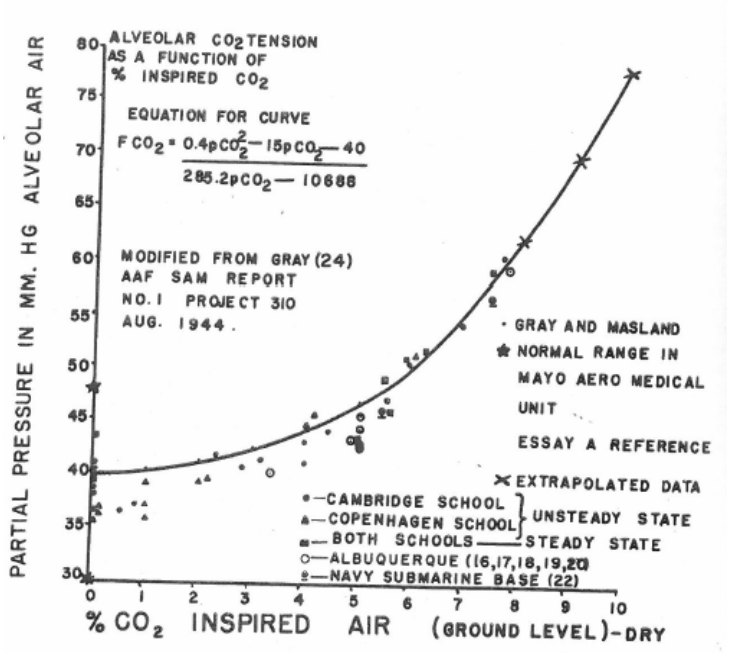

Figure 2 An increase in the dry-gas decimal fraction of CO_2 (F_ICO_2) at sea level increases the P_ACO_2 that initiates physiologic responses.

Figure 3 (Roth 1968) appears in many sources to describe a normal response to breathing CO_2 at sea level in resting subjects. Note the wide variability to human response in pulse rate, respiration rate, and $\dot{V}_E$ even when breathing air free of CO_2. These measures and variability in the measures increase when breathing CO_2, particularly when exceeding 2% (PCO_2 = 15.2, P_ICO_2 = 14.2 mmHg at sea level).

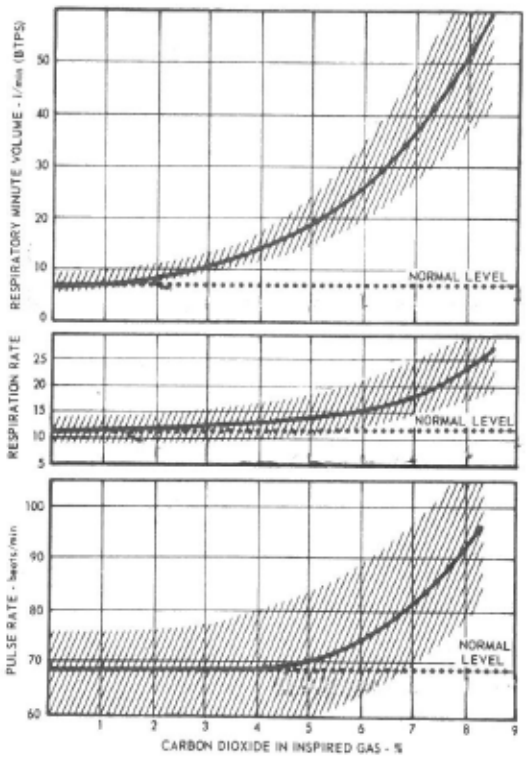

Figure 2–12. Immediate effects of increased CO_2 on pulse rate, respiration rate, and respiratory minute volume for subjects at rest. Hatched areas represent one S.D. on each side of the mean. To convert percentage of CO_2 to partial pressure, multiply percent by 760 mm Hg. (Adapted from Schaefer et al., 1952; & Dryden et al., 1956)

Figure 3 Large sample population response to breathing CO_2 while resting at sea level. Range of standard deviation about the response variable is a measure of between-subject variability.

The single best description of the basic physiologic response to breathing CO_2 comes from a classic 1955 publication by Rahn and Fenn (Rahn and Fenn 1955). A brief example is provided for the case of a resting person breathing CO_2. Then an example is provided to compare and contrast a ground-based exposure with a person breathing air at 4.3 psi above sea level in a space suit (19.0 psia) and a person breathing 100% O_2 at 4.3 psia, both breathing a P_ICO_2 of 20 mmHg.

Figure 4 (Rahn and Fenn 1955) shows equilbrium P_ACO_2 (y-axis) and P_AO_2 (x-axis) for a person at rest breathing CO_2. The curve that intersects the R (Respiratory Exchange Ratio [RER] $\dot{V}CO_2/\dot{V}O_2$) isopleths quantifies the resulting $\dot{V}_A$ in response to breathing CO_2. At sea level (normoxia), the P_IO_2 is 150 mmHg (point H). On the RER isopleth of 0.8 the P_ACO_2 is 40 mmHg with a resulting $\dot{V}_A$ of 1.73 $L_{(BTPS)}$/min. A vertical line from this point to the x-axis shows the normal P_AO_2 of about 100 mmHg for this resting, equilibrium condition. If $\dot{V}_A$ was infinitly large, P_ACO_2 would decrease to 0 mmHg and P_AO_2 would equal the P_IO_2 of 150 mmHg (point H again). Notice that as P_ICO_2 increases the $\dot{V}_A$ curve dramatically increases and P_ACO_2 equilibrates at a higher value. We are only concerned with point G because the upper limit for P_ICO_2 breathing during an EVA will not likely exceed 20 mmHg [$P_ICO_2 = (P_B–47) \times F_ICO_2$], where F_ICO_2 at point G is 0.028 and P_B is 760 mmHg. Point B shows that P_ACO_2 will increase from 40 mmHg to about 41 mmHg with a resulting increase in $\dot{V}_A$ from 1.73 to about 3.0

$L_{(BTPS)}$/min if RER is 0.8. Even if RER is 1.0 the P_ACO_2 increases to 42 mmHg with $\dot{V}_A$ of about 3.5 $L_{(BTPS)}$/min. Notice in this case that P_AO_2 increases from about 100 mmHg without breathing CO_2 to about 125 mmHg when breathing a P_ICO_2 of 20 mmHg. The increase in $\dot{V}_A$ in response to a small increase in P_ACO_2 has effectively shifted the equilibrium point in the lung to allow for a higher P_AO_2.

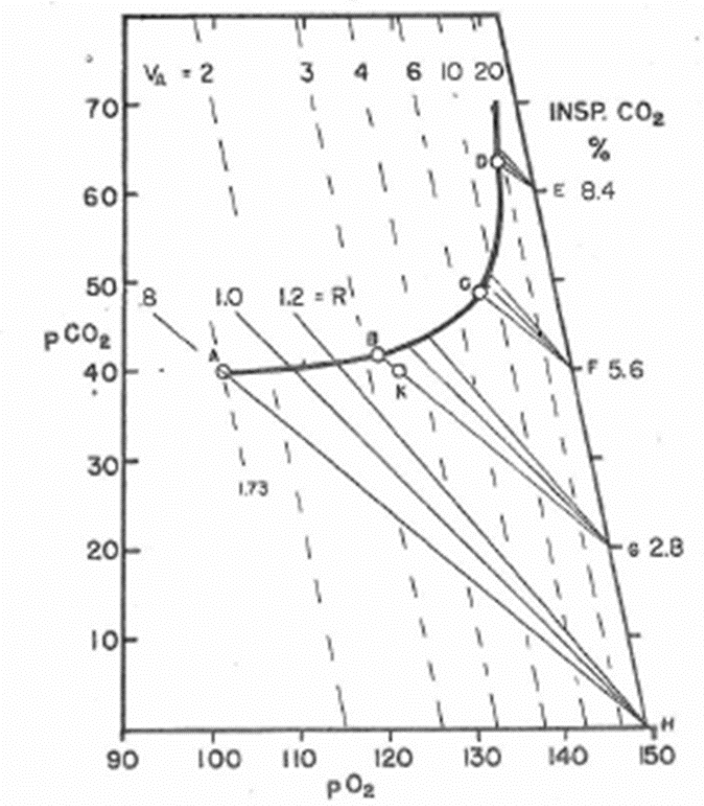

FIGURE 19. The effect of inspiring various CO_2-air mixtures upon the steady state alveolar gas composition.

Figure 4 Effect of inspiring CO_2 on P_ACO_2 (y-axis) and P_AO_2 (x-axis) over a range of R (RER) under steady-state conditions while at rest. Solid curve for alveolar ventilation rate: $\dot{\mathbf{V}}_A = 1.73 \times (0.4 \times P_ACO_2 - 15)$. The 2.8% inspired CO_2 is P_IO_2 of 20 mmHg. Examples are provided using $P_AO_2 = [P_IO_2 \times RER + P_ACO_2 \times [F_IO_2 \times (1 - RER)] + P_ICO_2 - P_ACO_2]/[F_ICO_2 \times (1- RER) + RER]$ from (Rahn and Fenn 1955). In the first example RER is 0.8, P_ACO_2 is 40 mmHg, F_IO_2 is 0.210, F_ICO_2 is 0 at sea level, providing a P_ICO_2 of 0 mmHg, P_IO_2 at sea level breathing air is about 150 mmHg, with a resulting computed P_AO_2 of about 102 mmHg, as seen on the x-axis above by extending a vertical line from point A. In the second case, RER is still 0.8. P_ACO_2 has increased to 42 mmHg given an F_ICO_2 of 0.028 at sea level, providing a P_ICO_2 of 20 mmHg. The resulting F_IO_2 is 0.204; P_IO_2 at sea level, breathing air containing CO_2 is about 145 mmHg. The resulting computed P_AO_2 of about 119 mmHg, as seen on the x-axis above by extending a vertical line from point B.

Summary data from 1955 in Tables 1 and 2 are from Alexander (Alexander, West et al. 1955) to show the typical physiologic responses to hypercapnia. Twelve resting subjects (3 females) breathed 0%, 3%, and 5% CO_2 for about 28 minutes. We assume the experiment was done at sea level pressure so the P_ICO_2 was 0, 21.4, and 35.6 mmHg, respectively. Steady-state respiratory measurements and arterial blood were taken after 25–35 minutes.

Table 1. Means and Standard Deviations of Respiratory Data from Resting Condition

P_ICO_2 mmHg	*f* breaths /min	V_T $mL_{(BTPS)}$ /min	$\dot{V}_E$ $L_{(BTPS)}$ /min	$\dot{V}_A$ $L_{(BTPS)}$ /min	$\dot{V}_A$ * ❶	V_D $mL_{(BTPS)}$	V_D/V_T**
0	15.5	412	5.90	3.47	3.58	162	0.39
$\sigma_{(n-1)}$	5.0	103	1.00	0.50		27	
21.4	19.4	651	11.64	7.67	7.79	215	0.33
$\sigma_{(n-1)}$	5.4	202	1.91	1.40		70	
35.6	20.8	962	18.84	13.13	13.40	278	0.29
$\sigma_{(n-1)}$	6.0	291	4.13	2.85		125	

*computed by Conkin from mean data, independent of author.
** from means of V_D and V_T.
❶$\dot{V}_A = \dot{V}_E \times [1 - V_D/V_T]$

Table 2. Means and Standard Deviations of Remaining Data from Resting Condition

P_ICO_2 mmHg	$\dot{V}O_2$ $mL_{(STPD)}$ /min	$\dot{V}CO_2$* $mL_{(STPD)}$ /min	RER	P_aCO_2** mmHg	P_aCO_2 mmHg ❷	pH_a	P_AO_2 mmHg ❸
0	213	167	0.78	41.5	41.5	7.42	96.5
$\sigma_{(n-1)}$	33	26	0.05	2.4		0.016	4.2
21.4	221	184	0.83	43.6	42.1	7.40	117.2
$\sigma_{(n-1)}$	39	25	0.09	2.10		0.012	3.2
35.6	234	182	0.77	46.5	47.5	7.38	125.0
$\sigma_{(n-1)}$	51	38	0.05	1.83		0.017	2.6

*based on $\dot{V}O_2 \times$ RER.
**from arterial blood sample.
❷$P_aCO_2 = (\dot{V}CO_2/\dot{V}_A) \times 863 + P_ICO_2$
❸ $P_AO_2 = [P_IO_2 \times RER + P_ACO_2 \times [F_IO_2 \times (1 - RER)] + P_ICO_2 - P_ACO_2]/[F_ICO_2 \times (1- RER) + RER]$, given $P_ACO_2 = P_aCO_2$.

The first point is that variation in human response to increasing hypercapnia is evident in the increase in standard deviation across most measurements. The author did not show how physiologic dead space volume (V_D, $mL_{(BTPS)}$) was calculated but probably through $V_T \times [(P_aCO_2 - P_{ET}CO_2)/(P_aCO_2 - P_ICO_2)] - V_{Dvalve}$ (the 60 mL dead space of the breathing valve) since arterial blood was sampled. $P_{ET}CO_2$ is end-tidal CO_2 partial pressure. V_D increased from about 160 mL to 280 mL in resting subjects breathing 5% CO_2. He mentions in the Discussion that his results about V_D have "long been recognized". So increase in V_D with comparable increase in V_T is observed in hypercapnic resting subjects and also in subjects that exercise while hypercapnic, see (Clark, Sinclair et al. 1980). But notice that the ratio of V_D to V_T, called wasted ventilation, decreased from 0.39 to 0.29. Wasted ventilation from another source (Murray 1986) for a resting subject breathing air is about 0.25, and computed from $[(P_aCO_2 - P_{ET}CO_2)/P_aCO_2]$, where P_aCO_2 is 40 mmHg and $P_{ET}CO_2$ is 30 mmHg. It appears that V_D increases and V_D/V_T decreases in hypercapnic resting subjects and in subjects that exercise with increasing CO_2, at least in data from Clark. The reasons offered for an increase in V_D include both a greater number of well ventilated alveoli and poorly perfused alveoli due to the vasoconstrictive action of CO_2 in the pulmonary vasculature, both related to alterations in $\dot{V}_A/\dot{Q}$.

Table 3 shows a comparison of estimated pulmonary gas partial pressures in a resting person breathing air in a space suit pressurized to 4.3 psi above sea level (19.0 psia) and a resting astronaut breathing 100% O_2 at 4.3 psia, both breathing a P_ICO_2 of 20 mmHg. Even though P_ICO_2 is the same in both cases, the gases within a representitive "perfect" alveolus are different. Note that RER is 1.0 for the astronaut because in 100% O_2 there is no N_2 dilution effect possible. The N_2 dilution effect is described in detail elsewhere (Rahn and Otis 1949), (Rahn and Fenn 1955) and is only summarized here. When breathing 100% O_2, however, many molecules of O_2 are taken out of the blood and an equal number is free to flow in from the trachea to maintain equality of pressure. While breathing 100% O_2, the RER is 1.0 even if one hyperventilates (hypocapnia) or hypoventilates (hypercapnia). The combined P_AO_2 and P_ACO_2 pair is set by the ratio of $\dot{V}_A$ to $\dot{V}CO_2$ and will always be on the 1.0 RER isopleth. However, when breathing a gas with an inert gas component, the removal of O_2 by the blood causes an equal volume of gas to flow from the trachea to maintain equality of pressure; however, this volume contains a fraction of inert gas. Partial pressures of all gases present (P_ACO_2, P_AN_2, P_AO_2, P_AAr, P_AH_2O) must sum to the total ambient pressure (Dalton's Law of Partial Pressures). Because of the dilution, there is a unique RER for the unique P_AO_2 and P_ACO_2 pair depending on the volume of O_2 taken into the blood and the CO_2 delivered from the blood. Even though the pulmonary gas partial pressures differ in Table 3 because absolute pressures are 4.5 times different, the P_ACO_2s only differ by 1 mmHg as estimated from Figure 4. In both cases, P_AO_2 is slightly hyperoxic and would have minimum impact on ventilatory response to hypercapnia. At least in the resting case, we conclude that a P_ICO_2 of 20 mmHg during EVA at 4.3 psia will not create a physiologic response significantly different when compared to the extreme of testing on Earth at 19 psia. The case of hypercapnic exercise is covered next and followed by the case of hypercapnic exercise and adaptive changes in μG.

Table 3. Alveolar Gases at Rest for Ground Test and for EVA with P_ICO_2 of 20 mmHg

	Ground Test – 1G Standing 19 psia (982 mmHg) 20.0% O_2 + 77.9% N_2+Ar + 2.1% CO_2	**EVA - μG "free-falling" 4.3 psia (222 mmHg) 88.6% O_2 + 11.4% CO_2**
Total pressure (P_B) Σ P_{AX}	982 mmHg	222 mmHg
P_ICO_2	20 mmHg	20 mmHg
P_IO_2 =	187 mmHg	155 mmHg
P_AO_2 ≅	163 mmHg	133 mmHg
P_ACO_2 ≅	41 mmHg	42 mmHg
P_AH_2O =	47 mmHg	47 mmHg
P_AN_2 ≅	731 mmHg	0 mmHg
RER	0.85	1.0
$\dot{V}_A$ ≅ (BTPS)	2.4 L/min	3.1 L/min
gas density P_AN_2	greater not equilibrated	lesser near equilibrated

From: $P_AO_2 = [P_IO_2 \times RER + P_ACO_2 \times [F_IO_2 \times (1 - RER)] + P_ICO_2 - P_ACO_2]/[F_ICO_2 \times (1- RER) + RER]$, where F_ICO_2 is either 0.021 for the 19.0 psia case or 0.114 for the 4.3 psia case, both providing a P_ICO_2 of 20 mmHg. For reference, P_IO_2 at sea level breathing air is about 149 mmHg with a resulting P_AO_2 of about 103 mmHg. $\dot{V}_A = 1.73 \times (0.4 \times pCO_2 - 15)$.

7.0 OXYGEN AND CARBON DIOXIDE INTERACTIONS

Changes in PO_2 combined with changes in PCO_2 at rest and during exercise have complex physiologic interactions to set ventilation and cardiovascular responses because both O_2 and CO_2 stimulate peripheral and central chemoreceptors differently (Dahan, DeGoede et al. 1990), (Lambertsen, Hall et al. 1963), (Ainslie and Duffin 2009), (Ainslie and Poulin 2004), (Koyal, Whipp et al. 1976). The control of $\dot{V}_A$, and by extension $\dot{V}_E$, depends on P_aCO_2, P_aO_2, and arterial H^+. An important feature of the blood-brain barrier is the low permeability to ions such as H^+ and HCO_3^- and high permeability to lipid-soluble molecules such as CO_2. This selective permeability dictates how ventilation changes in response to changes in P_aO_2, P_aCO_2, and H^+ with peripheral chemoreceptors primarily responsive to changes in P_aO_2 and H^+ and central chemoreceptors exquisitely responsive to P_aCO_2 and H^+. Hyperoxia stimulates increased ventilation (Becker, Polo et al. 1996), (Dean, Mulkey et al. 2004); however, those details are not relevant to review here because the EVA environment is near-normoxic. However, the extent of the hyperoxic-induced hyperventilation is attenuated by a decrease in P_aCO_2 caused by the hyperventilation, so is somewhat self-correcting. But hypercapnia would add to the hyperoxic-induced increase in ventilation. Ainslie (Ainslie and Poulin 2004) presents a comprehensive study in resting subjects where ventilation, CBF, and mean arterial pressure (MAP) are evaluated from hypoxia to hyperoxia combined with normal and hypercapnic $P_{ET}CO_2$. Slopes of ventilation, CBF, and MAP responses with arterial blood O_2 saturation (S_PO_2) were greater in hypercapnia. The following case is made to argue that hyperoxia during EVA is minimal with regard to the control of ventilation.

A significant amount of basic physiologic and applied research has been done by the military to describe combined hyperoxia and hypercapnia because hyperoxic rebreather systems tend to accumulate CO_2 during energetic diving. For example, Gill (Gill, Natoli et al. 2014) showed a protective effect of high PO_2 (989 mmHg) against symptoms of PCO_2 up to 65 mmHg as compared to a normoxic PO_2 of 160 mmHg. The increase in $\dot{V}_E$ associated with hyperoxia resulted in less $P_{ET}CO_2$ during rest or exercise irrespective of hypercapnia. Fothergill (Fothergill, Hedges et al. 1991) examined the interaction of hypercapnia and increased P_IN_2 thinking that the threshold for N_2 narcosis would decrease with hypercapnia – it did not. They concluded that high $P_{ET}CO_2$ and P_IN_2 are additive in their effects on impaired cognitive and psychomotor performance in resting subjects. Results from both Gill and Fothergill are confounded in that Gill did not control for N_2 narcosis at 6 ATA and Fothergill did not control for hyperoxia at 6 ATA. Fortunately, neither of these issues are relevant during EVA.

In relation to specific EVA or LEA conditions, the difference in P_IO_2 between breathing air at sea level and breathing 100% O_2 during EVA at 4.3 psia is only about 25 mmHg (175 $mmHg_{EVA}$ – 150 $mmHg_{sea\ level}$). This small difference will not significantly modify response variables (Henning, Sauter et al. 1990), (Sheehy, Kamon et al. 1982), (Vercruyssen, Kamon et al. 2007), (Lambertsen, Hall et al. 1963) over our limited PCO_2 range from 0 to 20 mmHg and exercise from 250 to 2,500 $mL_{(STPD)}$ O_2/min as seen in Figure 5. Literature data regarding hypercapnia during rest and exercise with near-normoxic P_IO_2 will apply without modification to EVA and LEA conditions.

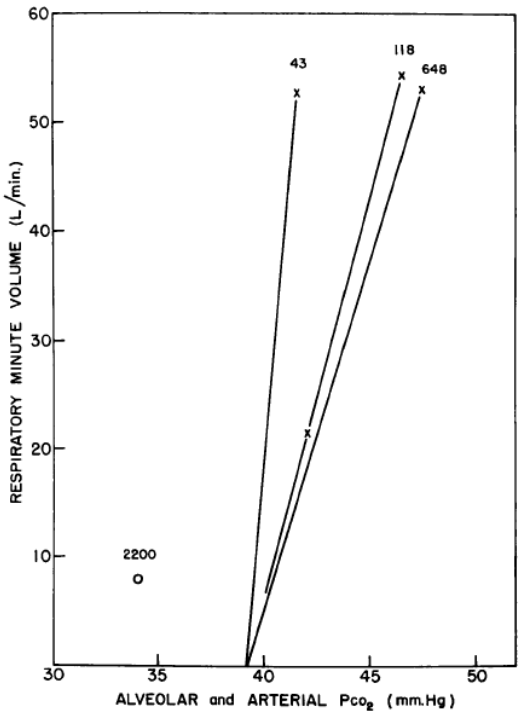

FIGURE 2. This diagram, showing pulmonary ventilation at different levels of alveolar or arterial P_{O_2}, is a composite of data obtained by Cunningham *et al.* and by this laboratory.[9,10] The numbers above the plotted points represent alveolar P_{O_2} in mm. Hg. *x* indicates measurements in a single subject studied at one atmosphere at the indicated level of alveolar P_{O_2},[9] and *o* indicates the average resting relationship of arterial P_{CO_2} and ventilation in a group of subjects during oxygen breathing at 3.0 atmospheres ambient pressure.[10] The diagram shows that decreased alveolar P_{O_2} causes a marked increase in response to carbon dioxide, while increased P_{O_2} may either decrease[9] or increase[10] ventilation, depending upon the circumstances (after Cunningham *et al.*[9]).

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Figure 5 Increase in $\dot{\mathbf{V}}_E$ as P_aCO_2 increases in hypoxic or hyperoxic conditions, from (Lambertsen, Hall et al. 1963). $\dot{\mathbf{V}}_E$ in response to an increasing P_aCO_2 is not significantly increased as P_ACO_2 increases from normoxic (118 mmHg) to hyperoxic (648 mmHg) condition. However, the combination of hypoxic P_AO_2 (43 mmHg) with increased P_aCO_2 dramatically increases $\dot{\mathbf{V}}_E$.

We conclude from this section that the difference between an exposure with a P_IO_2 of about 145 mmHg using room air diluted with CO_2 and an exposure with a P_IO_2 of 175 mmHg (EVA-like) with 100% O_2 at 4.3 psia mixed with CO_2 will not significantly impact adequate O_2 delivery to tissues nor will it significantly hinder CO_2 removal from tissues. Hb will be nearly saturated (98%) with O_2 under either condition. CO_2 transport by Hb from tissues will not be significantly influenced by O_2 binding onto Hb over the range of our EVA conditions. The use of normoxic or even mildly hyperoxic breathing gas will not hinder the ability of Hb to deliver O_2 to the tissues given mild hypercapnia nor to transport CO_2 from the tissues given mild hypercapnia because the allosteric Hb molecule is adaptive and CO_2 transport is not solely tied to Hb.

8.0 HYPERCAPNIA AND MANAGEMENT OF HYDROGEN IONS

Much is known about acid-base regulation through rapid respiratory and slower renal compensations. The goal is to preserve a normal alkaline pH of 7.4, within a range from 7.0 to 7.8 compatible with life. The combination of hypercapnia and exercise is a challenge to the buffering and compensation mechanisms. For a complete treatment about whole-body buffering of H^+ in response to hypercapnia consult Valtin (Valtin 1983), his Figure 9-7 in 2nd edition. In simple terms, the blood in the pulmonary capillaries in the presence of hypercapnia responds the same way as the blood in the systemic capillaries in terms of H^+ buffering and CO_2 transport; however, the ultimate goal is to remove CO_2 from the tissues and not to transport CO_2 to the tissues. Hb and the red blood cell (RBC) is uniquely suited to deliver O_2 and remove CO_2 in concert with H^+ buffering, even when modified by the presence of hypercapnia combined with exercise.

Hb is a large (64,500 Daltons molecular weight) 4-chain polypeptide allosteric protein. The 2 α-chains and 2 β-chains each contain an iron porphyrin heme ring able to reversibly bind a molecule of O_2 while CO_2 binds reversibly at the N terminus valines of both α and β chains. As each O_2 molecule binds to Hb, it increases the affinity of the remaining heme sites for additional O_2 molecules, which results in the nonlinear S-shape of the O_2 dissociation curve. Metabolically produced carbon monoxide (CO) does compete for heme sites and has 250 times the affinity for these sites compared to O_2 (carboxyhemoglobin). Also a small fraction of heme sites contain iron in a ferric ($Fe\ III^+$) form instead of the normal ferrous ($FE\ II^+$) form, so they cannot bind O_2 molecules (methemoglobin). The affinity of Hb for O_2 is modified by several factors (ligands): H^+, CO_2, temperature, and 2-3-diphospoglycerate. All substances that exert an interdependent effect on the chemical binding properties of Hb are termed ligands. This means that the concentration within RBCs of any ligand affects the ability of Hb to combine with the remaining ligands. Then there are the interactions between Hb and NO and how these interactions result in enhanced perfusion when Hb delivers O_2 to the tissues – clearly complex interactions occur (Yonetani, Park et al. 2002), (Stamler, Jia et al. 1997) that are too numerous to summarize here.

Refer to Figure 6 for this discussion. At the systemic capillaries, CO_2 diffuses from the tissue into the plasma and into the RBCs. Very little CO_2 is converted to HCO_3^- in the plasma, and the H^+ that is released is buffered by nonbicarbonate plasma buffers. A small amout of CO_2 is dissolved in the plasma and RBCs, which is removed at the pulmonary capillaries through diffusion. The majority of CO_2 from rest or exercise is converted to HCO_3^- within the RBC by the action of intracellular carbonic anhydrase (CA). This HCO_3^- is transported into the plasma as a chloride ion (Cl^-) is transported into the RBC through a membrane ion exchange pump. CO_2 within the RBC also binds to Hb, now called carbamino Hb, and the release of H^+ from this reaction and the release of H^+ from the CA reaction are taken up (buffered) by Hb. A conformational change to Hb as a result of H^+ binding reduces O_2 affinity for Hb and enhances the removal of O_2 for use by the tissues. These processes are then reversed in the pulmonanry capillaries. The binding of O_2 to Hb in the pulmonary capillaries results in the displacement of bound CO_2. With the aid of CA in pulmonary endothelial cells, the HCO_3^- in the venous blood is reconverted to CO_2 and removed by respiration. Thus the methods by which Hb handles O_2 and CO_2 reciprocally augment the uptake and release of both gases in the lungs and tissues (Murray 1986), (Hlastala and Berger 2001).

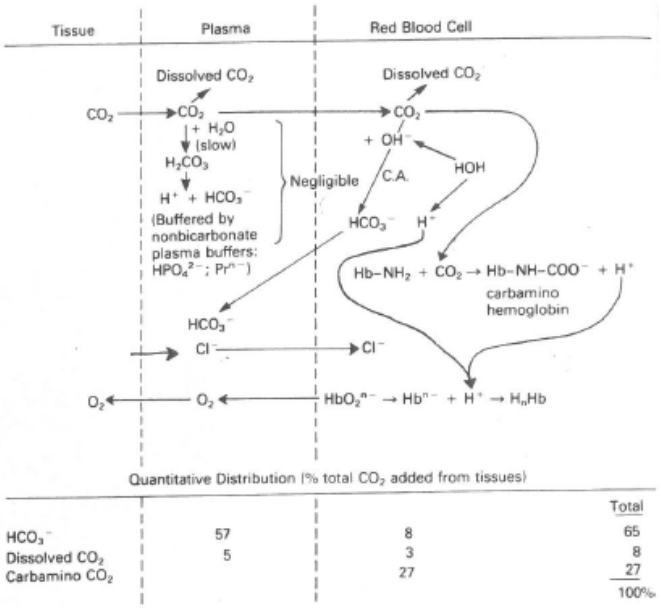

Figure 6 The transport of CO_2 and buffering of H^+ by the blood, from Figure 9-2 in (Valtin 1983).

Any physiologic description of CO_2 uptake, transport, and removal requires at least a brief description of CA. Enzymes increase the rate of reactions. If CA was not present, then the amount of transportable CO_2 as HCO_3^- would be inadequate to meet metabolic production of CO_2, leading to hypercapnia (Hlastala and Berger 2001). CA in its many isozyme forms, is located in RBCs, on all capillary endothelium, in the kidney, brain, and other tissues. CA facilitates the conversion of CO_2 to HCO_3^- (hydration reaction) and HCO_3^- to CO_2 (dehydration reaction), depending on its location in the tissues and the prevailing reactant concentrations. Much has been learned about the role of CA through blocking its action with acetazolamide and benzolamide. CA makes the carriage and evolution of CO_2 possible across small gradients, otherwise large PCO_2 gradients form in tissues and the lung (Swenson and Maren 1978). In brief, inhibiting CA leads to an increase in $\dot{V}_E$, mostly through an increase in V_T and not an increase in breathing frequency (*f*). The drive to increase $\dot{V}_E$ is through an immediate tissue respiratory acidosis as CO_2 is retained in all tissues and a slower metabolic acidosis due to renal HCO_3^- diuresis through inhibition of CA in the kidneys. The increase in CO_2 in place of HCO_3^- and the increase in H^+ are sensed by central chemoreceptors leading to the increase in $\dot{V}_E$ as a compensation to augment CO_2 removal (Ringelstein, Van Eyck et al. 1992). It is a common clinical practice to breathe CO_2 as a means to monitor cerebral vasomotor reactivity in those with compromised cerebral circulation (Leaf and Goldfarb 2007). Hypercapnia induces vasodilation of the mid-cerebral artery (MCA), which is also achieved through inhibiting CA with acetazolamide.

In the case of hypercapnia, the blood in the pulmonary capillaries is “forced” to respond the same as the blood in systemic capillaries, which is clearly inefficient because the goal is to remove CO_2 from the body and not transport CO_2 to the body. Excess CO_2 would be transported to the tissues to add to what is produced by the tissues, an additional burdon to CO_2 removal and H^+ buffering. The H^+ produced from the CO_2 of hypercapnia cannot be buffered by the

bicarbonate system. When H^+ is buffered by HCO_3^- the carbonic acid (H_2CO_3) formed quickly dissociates back to CO_2 and H_2O. Because CO_2 and H_2O are the starting substrates, when CO_2 is added to the body, the reaction $H^+ + HCO_3^- \leftrightarrows H_2CO_3 \leftrightarrows CO_2 + H_2O$ is being driven to the left, and cannot simultaneously be driven to the right as would be required if the H^+ were to be buffered by HCO_3^-. Instead, the H^+ must be buffered by the nonbicarbonate buffers available to the body, in particular Hb. A large proportion of the added volatile acid is buffered by RBCs, which rapidly convert the added CO_2 to HCO_3^- carried in the plasma to the tissues. Lambertsen (Lambertsen, Hall et al. 1963) clearly shows the increase in venous bicarbonate concentration $[HCO_3^-]_v$ as P_aCO_2 increases during hypercapnia.

In summary, CO_2 is transported in venous blood in physical solution (6%), bound to proteins that include Hb (carbamino, 7%), and as HCO_3^- (87%) through the action of CA within the RBCs (Klocke 1987). Increased CO_2 reduces O_2 affinity for Hb even though there is not a direct competition between CO_2 and O_2 for heme sites. Hb is an effective buffer to supplement other buffer systems in the body. When P_aCO_2 is increased or decreased, the changes in plasma HCO_3^- are not equal to changes in $[H^+]$ due to the action of Hb as a component of the total extracellular fluid compartment. The dissociation constant for Hb is 6.8 as compared to 6.1 for H_2CO_3 so is closer to normal pH and Hb O_2 saturation alters the buffering capacity of Hb. When PO_2 is low in the systemic capillaries the affinity for H^+ is high and is reversed in the pulmonary capillaries where PO_2 is high. The proton released from the hydration of CO_2 through CA is buffered by Hb, and the resulting HCO_3^- moves into the plasma in exchange for Cl^-. Hb is less efficient at removal of CO_2, H^+ buffering, and O_2 transport when CO_2 is provided externally, but additional buffer capacity is available to preserve pH. Excess arterial blood HCO_3^- eventually returns to the normal 24 mEq/L as excess CO_2 is eventually exhaled when the hypercapnia is removed. This complex give-and-take can accommodate hypercapnia combined with exercise if either is not excessive and that astronaut physiology is otherwise normal.

Brackett (Brackett Jr, Cohen et al. 1965) exposed 7 resting men to 7% CO_2 over 90 minutes and then 10% CO_2 on another day. Serial arterial blood samples showed the increase in P_aCO_2 and associated generation of HCO_3^- by body buffers, and the increase in $[H^+]_a$. All 7 tolerated the 7% CO_2 for the requested 40–90 minute exposure; however, all mentioned heavy breathing and some complained of mild headache and burning of eyes. During the 10% CO_2 exposure, hyperventilation was extreme and most subjects became restless and confused to the point where the experiment was discontinued earlier than planned. Brackett concluded that the increase of only 3 mEq/L HCO_3^- above the normal 24 mEq/L at a P_aCO_2 of 80 mmHg was a modest compensation for respiratory acidosis with pH still falling to 7.20; there was only a modest generation of HCO_3^- from endogenous buffer stores during this acute respiratory acidosis. The HCO_3^- buffer system alone is a poor buffer but, fortunately, other buffer systems, such as the Hb buffer system, have better buffer value to preserve pH and was active during this experiment. Over a range of P_aCO_2 from 40-50 mmHg in a resting EVA astronaut the $[HCO_3^-]_a$ would show a modest increase and pH would decrease from 7.4 to about 7.3. The preservation of pH during exercise combined with hypercapnia is covered later in greater detail through the work of other investigators (Clark, Sinclair et al. 1980), (Graham, Wilson et al. 1982), (Menn, Sinclair et al. 1970).

9.0 BASIC PHYSIOLOGY OF EXERCISE COMBINED WITH HYPERCAPNIA

Figure 7 (Hlastala and Berger 2001) is used to introduce and summarize physiologic responses to normocapnic exercise, next we review hypercapnic exercise. The healthy body is exquisitely tuned to match cardiopulmonary response to exercise. As O_2 consumption increases and CO_2 production increases, $\dot{V}_E$ and $\dot{Q}$ increase to meet the demand. The control is so precise that P_aCO_2, P_aO_2, and $[H^+]$ remain stable over a large range of $\dot{V}O_2$ as shown in Figure 7. Exercise can be performed at different P_Bs and under different PO_2 and/or PCO_2. Rate and depth of respiration increase as P_ICO_2 increases (Jacobi, Iyawe et al. 1987), (Reynolds, Milhorn et al. 1972), which is integrated with an increase in heart rate (HR) and stroke volume (Dahan, DeGoede et al. 1990). The chemical control of breathing is an expansive topic and best left to a textbook on respiratory physiology (Hlastala and Berger 2001). Others even posit additional CO_2 sensing in the lung (Forster, Klein et al. 1982), but that diverts our focus. Also, the way the CNS integrates the increase in $\dot{V}_E$ by increasing V_T and *f* in response to exercise and hypercapnia is yet another layer of complexity; mainly through an increase in V_T with an increase in *f* playing a lesser role (Sackner, Nixon et al. 1980), (Bussotti, Magrì et al. 2008), (Jones, Robertson et al. 1979). This also diverts our focus and will not be covered in any detail. The simplest interpretation for the hypercapnic EVA case is that P_aCO_2 increases in response to respiratory and metabolic acidosis over a range of exercise possible during EVA, which is countered through several person-specific physiologic responses.

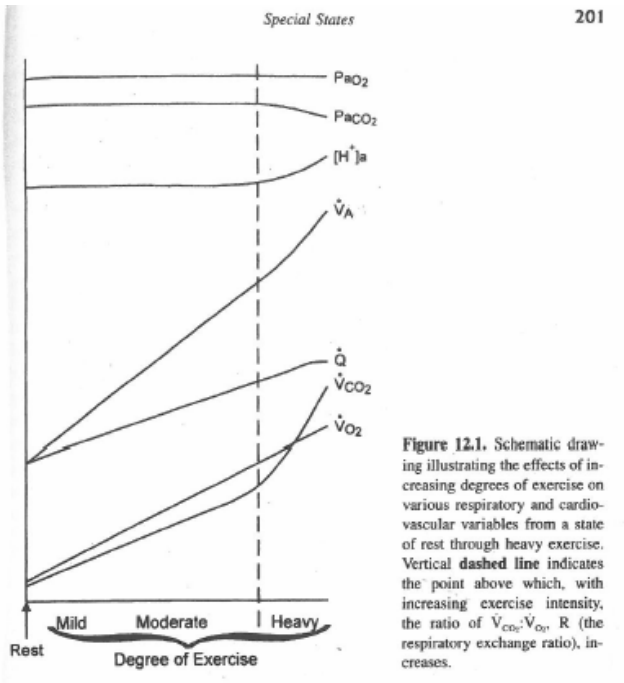

Figure 7 Human responses to exercise.

Several publications regarding exercise combined with hypercapnia are available under different ambient pressure and PO_2 conditions (see Table in Appendix) and provide information that can be extrapolated to exercise during a hypobaric EVA with astronauts breathing 100% O_2. In particular, understanding the synergy between exercise and hypercapnia on the ventilatory response over the EVA range of P_ICO_2 and $\dot{V}O_2$ is our goal.

Exercise increases both the rate and depth of respiration and $\dot{Q}$ in response to metabolic acidosis. Hypercapnia has the same effect working through respiratory acidosis, so both exercise and hypercapnia have a positive effect on ventilation and HR (Liu, Liu et al. 2015), (Koyal, Whipp et al. 1976), (Luft, Finkelstein et al. 1974). However, the increase in $\dot{V}_E$ and HR, and other measures, with hypercapnia and exercise are not simply additive; there are interactions such that the combined effect is less than one might expect (Clark, Sinclair et al. 1980), (Poon and Greene 1985). In addition, there is a wide range of aerobic capacity in otherwise healthy men and women that would dictate performance under hypercapnic conditions (Bishop, Lee et al. 1999). Clark showed that with more severe workload that increased CO_2 sensitivity declined progressively as maximum ventilation was approached. Poon did not impose as severe workloads and showed that controlled hypercapnia enhances exercise hyperpnea by augmenting not only resting ventilation but also the ventilatory sensitivity to exercise. The resulting increase in slope and intercept of the $\dot{V}_E$–$\dot{V}CO_2$ curve were proportional to the rise in P_aCO_2. The body can accommodate for a short time the increase in P_aCO_2 caused by hypercapnia superimposed on exercise (Loeppky 1998), (Luft, Finkelstein et al. 1974). Just as you can temporarily reduce the body store of CO_2 with conscious hyperventilation, you can increase the body store by rebreathing CO_2 even while exercise is performed (Fan and Kayser 2013), his Figure 2, (Menn, Sinclair et al. 1970), his Table 5, and (Sinclair, Clark et al. 1971), his Figure 2.

The same control system that responds to hypercapnia also responds to increased P_aCO_2 during exercise. Ventilation and perfusion are matched such that P_aCO_2 and pH are stable through a wide range of aerobic exercise. We expect respiration rate (RR), HR, V_T, and $\dot{V}_E$ to increase as P_ICO_2 and O_2 consumption increase. We expect P_aCO_2 to increase in a dose-response manner to the increase in P_ICO_2. The combinations of exercise and increased PCO_2 will be tolerated by astronauts based on the experiments described by Menn (Menn, Sinclair et al. 1970). Table 4 shows target metabolic rates possible during EVA given a P_ICO_2 of 15 mmHg.

Table 4. Estimated O_2 Consumption and CO_2 Production Rates Given P_IO_2 of 15 mmHg

BTU/h	kcal/min	$L_{(BTPS)}$ $\dot{V}_E$/min*	$L_{(STPD)}$ O_2/min	$L_{(STPD)}$ CO_2/min
300 (resting)	1.26	13	0.26	0.22
1000	4.2	31	0.86	0.73
2000	8.4	53	1.72	1.46
3000	12.6	75	2.59	2.20

Computed O_2 consumption and CO_2 production based on the following: 100 BTU/h = 0.42 kcal/min and at RQ = 0.85 there is 4.862 kcal/liter$_{(STPD)}$ O_2.* Based on estimates from Menn (Menn, Sinclair et al. 1970) for P_ICO_2 of 15 mmHg.

Research by Krasnogor (Krasnogor, Wempen et al. 1968) in 1968 is noteworthy in that continuous modest ergometer work (100 watts at 60 rpm) for 3 hours with a PCO_2 of 7.6 mmHg was done in a space suit-like environment, simulated in a hypobaric chamber at 180 mmHg (3.45 psia, 35,000 ft altitude) with F_IO_2 of about 0.90 resulting in a P_IO_2 of 120 mmHg. Arterial blood gas, ventilation, and metabolic rate data indicated no significant impact of this acute mild

hypercapnic and mild exercise at altitude and no significant difference when compared to same protocol at 700 mmHg. The consumption of O_2 was about 1.2 l $_{(STPD)}$/min for each protocol with no significant change in P_aCO_2 of about 36 mmHg during the rest or exercise interval at 180 mmHg or at 700 mmHg. Mean $\dot{V}_E$ during exercise at 180 mmHg was about 34 l $_{(BTPS)}$/min and mean arterial pH was never lower than 7.39 under all conditions. Arterial blood saturation (S_aO_2) was about 96% under all conditions. This was convincing evidence in 1968 that modest continuous work combined with modest hypercapnia could be performed under space suit EVA conditions.

In general, $\dot{V}O_2$ and $\dot{V}CO_2$ during exercise are not changed by breathing CO_2 when either exercise intensity or P_ICO_2 is low (Fan and Kayser 2013). However, there are exceptions that we now summarize. Most agree that the increase in $\dot{V}O_2$ with exercise is not inhibited by hypercapnia. Menn (Menn, Sinclair et al. 1970) found a difference (change) in $\dot{V}CO_2$ but no difference in $\dot{V}O_2$ (change) with exercise at 2/3 $\dot{V}O_2$max and increasing hypercapnia. He attributed these findings to an increase in CO_2 retention with hypercapnic exercise greater than 1/2 $\dot{V}O_2$max. RER decreased as exercise intensity and P_ICO_2 increased, also seen by Sinclair (Sinclair, Clark et al. 1971). Graham (Graham, Wilson et al. 1982) found similar results at 55% and 65% $\dot{V}O_2$max exercise in hypercapnia but attributed the decrease in RER to a shift in metabolism from carbohydrates to lipids due to combined respiratory and metabolic acidosis that decreased pH secondary to hypercapnia. Mean blood lactate under hypercapnic exercise was reduced from 3.88 mM/l to 2.22 mM/l while breathing 6% CO_2 for 30 minutes at 65% $\dot{V}O_2$max. In contrast, Clark (Clark, Sinclair et al. 1980) provided convincing data for no difference (change) in $\dot{V}O_2$ or $\dot{V}CO_2$ with increasing hypercapnia. RER increased as $\dot{V}O_2$ increased with no modification (decrease) due to hypercapnia, as seen by others. Mean blood lactate increased as $\dot{V}O_2$ increased and was not modified (decreased) with hypercapnia, as seen by others. For example, at $\dot{V}CO_2$ of 3.0 L/min, blood lactate was about 5 mM/L over the range of blood-gas P_aCO_2 from 35 to 60 mmHg.

Luft (Luft, Finkelstein et al. 1974) conducted a particularly detailed investigation relevant to hypercapnic exercise during EVA. The experiments were conducted in Albuquerque at a P_B of about 632 mmHg (5,000 feet altitude). 12 men with mean age of 26.5 years breathed air and air with P_ICO_2 of 15 mmHg during stepped bicycle ergometry to the point where they could not maintain a metronome pedaling rhythm that produced 50 rpm. The stepped protocol required about 15 minutes, then 30 minutes of recovery while still breathing the test gas. The main conclusion was that the combination of metabolic acidosis from anaerobic metabolism in leg muscles combined with incomplete compensated respiratory acidosis from hypercapnia taxed the respiratory response such that CO_2 retention was evident. Hypercapnia resulted in a decrease in RER, an indication of CO_2 retention. Blood gases were collected from 10 of the 12 men. Those breathing air showed a decrease in P_aCO_2 from 37 to 30 mmHg during exercise. Those breathing CO_2 showed an increase from 36 to 41 mmHg during exercise with a critical rise in $[H^+]_a$. Both observations were similar to those reported by Clark (Clark, Sinclair et al. 1980); however, without an indication of CO_2 retention. The inspired ventilation rate ($\dot{V}_I$) was about 45% greater in the hypercapnic subjects across the exercise profile until subjects reached the peak of their performance. Then $\dot{V}_I$ converged to about the same 140 $L_{(BTPS)}$/min. CO_2 loading was most dramatic at this point where further increase in ventilation was no longer possible leading to acute respiratory acidosis at a point where metabolic acidosis was rapidly increasing. O_2 consumption and maximum work was less with CO_2 in the last 2 minutes at work and during the

first minute of recovery. Clearly, the ventilatory compensation for hypercapnia combined with vigorous exercise was taxed. There was an increased $\dot{V}_I$ relative to the controls at all points during the 30 minute recovery. There were no differences in serum electrolyte concentrations, even after corrected for the transient decrease in plasma volume due to exercise.

10.0 HUMAN VARIATION IN RESPONSE TO HYPERCAPNIA

No two humans are physiologically the same, even within the same sex. So the same response to the same level of hypercapnia in different astronauts is not expected. For example, a $P_{ET}CO_2$ range from 36 to 44 mmHg was measured in 9 resting subjects (Bloch-Salisbury, Lansing et al. 2000). Shea (Shea, Walter et al. 1987) measured a range from 29 to 42 mmHg for $P_{ET}CO_2$ in 41 resting subjects, about half were women. It is well known that there is significant variation to the hypoxic ventilatory response (Teppema and Dahan 2010), (Ainslie and Poulin 2004) as well as the hypercapnic ventilatory response (Prisk, Elliott et al. 2000), (Sebert, Barthelemy et al. 1990), (Jones, Levine et al. 1971). Responses to hypercapnia are subject-specific (Lambertsen 1960, Laurie, Vizzeri et al. 2017, Law, Young et al. 2017), (Morelli, Badr et al. 2004), (Haywood and Bloete 1969), (Alexander, West et al. 1955), which in-turn extends to human variability in neurocognitive and performance responses during onset and recovery from hypercapnia superimposed on exercise. Between-subject variability in the acute hypoxic ventilatory response is linked to variability in CBF and MAP responses to hypoxia, which in-turn are sensitive to hypercapnia responses between subjects (Ainslie and Poulin 2004). Increasing age is associated with less ventilatory response to hypoxia and hypercapnia (Kronenberg and Drage 1973). Shea (Shea, Walter et al. 1987) documents a wide range of breathing pattern variability between resting subjects but reproducible breathing patterns within resting subjects. Schaefer (Schaefer 1958) noted that those with a lower *f* and larger V_T also had a reproducibly higher $P_{ET}CO_2$ and a lower ventilator sensitivity to hypercapnia, a potential basis to select for hypercapnia resistance.

Laurie (Laurie, Vizzeri et al. 2017), extending the work by Zwart (Zwart, Gibson et al. 2012) on the mechanisms of ocular change in μG, suggests a specific genetic link as the basis for variations in P_aCO_2 between humans. Sebert (Sebert, Barthelemy et al. 1990) concluded from a single-breathe CO_2 challenge that sensitivity ($\Delta\dot{V}_E/\Delta P_{ET}CO_2$) to transient hypercapnia and its interaction with hyperoxia are weaker in women than in men, suggesting that hormonal status is the likely reason. A single-breathe CO_2 challenge offers only limited insight into hypercapnia and gender response. In contrast, Haywood (Haywood and Bloete 1969) concluded in a study with steady-state hypercapnia in normobaric air that women's $\Delta\dot{V}_E/\Delta P_ACO_2$ response averaged higher than in men as well as respiration rate when breathing 4 and 5% CO_2. Otherwise healthy humans differ in their absolute aerobic capacity in response to exercise and therefore exercise response to hypercapnia (see Exercise Combined with Hypercapnia). We do not review the vast literature about human variation and accommodation to stressors. We do concede that a single space suit PCO_2 limit will likely be too conservative for most and not conservative enough for a few. A program to identify those susceptible or resistant to hypercapnia could be operationalized rather than recommend a very low PCO_2 limit that protects the most responsive astronaut. Those identified might be assigned easier EVA tasks, select greater helmet ventilation, have additional rest intervals during EVA, etc. How such a program is implemented is beyond the scope of this literature review.

11.0 MICROGRAVITY: INTRACRANIAL PRESSURE AND PULMONARY GAS EXCHANGE

A host of changes occur to the human body as a consequence of spaceflight and exposure to μG, broadly classified as "space adaptation syndrome". The EVA astronaut is not immune to these changes and may place the astronaut at greater risk of spaceflight-induced intracranial hypertension in the presence of hypercapnia (Michael and Marshall-Bowman 2015), (James, Meyers et al. 2011). Law (Law, Van Baalen et al. 2014), (Law, Watkins et al. 2010) contends that there may be greater sensitivity to and therefore consequences of hypercapnia in μG. An increased probability of headache with increased PCO_2 may be an indicator of increased intracranial pressure (ICP) due to CO_2-induced vasodilation and decreased venous drainage because of the loss of the hydrostatic gradient in μG. Laurie (Laurie, Vizzeri et al. 2017) investigated this hypothesis further but was limited to about 15 minutes of 6-degree head-down tilt (HDT) with subjects breathing 1% CO_2 in air. Others have extended the duration and degree of HDT and even exposed subjects to 3% CO_2. Marshall-Goebel (Marshall-Goebel, 2018) exposed 6 males to 12-degree HDT for 26 hours with and without 0.5% CO_2. There was no difference in the increased right internal jugular blood volume when 12-degree HDT was combined with 0.5% CO_2 over several hours. She showed no increase in ICP in 9 males subjected to 3.5 hours of 12-degree HDT while breathing 1% CO_2 (Marshall-Goebel, Mulder et al. 2017). Kurazumi (Kurazumi, 2018) concluded with 15 males that the addition of 3% CO_2 and 10-degree HDT for 10 minutes did not increase ICP compared over the increase just due to 10-degree HDT. $P_{ET}CO_2$ increased about 6 mmHg during the brief hypercapnia but the increased ICP was mainly induced by cerebral fluid shift with 10-degree HDT. Just the simple act of transitioning from supine to standing posture in 1G influences the P_ACO_2–P_AO_2 point and respiratory mechanics (Rahn and Fenn 1955) (see Figure 8).

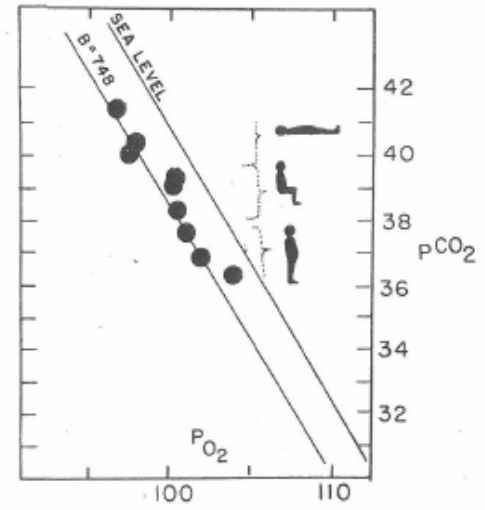

FIGURE 17. The effect of posture upon the steady state alveolar values.

Figure 8 At sea level, breathing air at rest P_AO_2 increases from 100 to about 105 mmHg as P_ACO_2 decreases from 41 to 36 mmHg during the transition from supine to standing posture in 1G.

Now there is good evidence that pulmonary gas exchange is not hindered despite the significant physiologic changes as part of μG adaptation. Much has been learned about gas exchange physiology in μG (Prisk GK 2013). Pulmonary diffusion capacity (D_{LCO}) from single-breath CO breathing and membrane diffusing capacity (D_m) both increase to parallel the increase in pulmonary capillary blood volume (V_c) in μG. The persistent increase in D_{LCO} and D_m is evidence that pulmonary edema does not occur in μG. In addition, gravity imposes a degree of matching between ventilation and perfusion. Prisk concluded that, "… *the increases* (D_{LCO}, D_m, and V_c) *rapidly revert to preflight levels on return to 1g. This in-flight increase was attributed to a transition of the pulmonary circulation from a 1g configuration (ie, zones 1, 2, 3) to a situation in which the lung vasculature is entirely zone 2 or 3. This would result in more uniform filling of the pulmonary capillary bed and an attendant increase in the surface area available for gas exchange*". So an otherwise normal lung with no change in the apparent range of $\dot{V}_A/\dot{Q}$ in μG is expected to have no impediment to gas transfer (Prisk, Elliott et al. 1995, Prisk, Elliott et al. 2000, Prisk, Fine et al. 2006) (Conkin, Wessel et al. 2017). However, this does not mean that hypercapnia does not increase pulmonary vascular resistance (Balanos, Talbot et al. 2003). The ventilatory response to changes in P_aO_2 and P_aCO_2 are mediated through peripheral and central chemoreceptors. In addition to these controls for ventilation, local pulmonary vasculature is modulated through variations in both PCO_2 and PO_2 as part of $\dot{V}_A/\dot{Q}$ matching. Smooth muscle in the pulmonary arterioles contract during hypercapnia and hypoxia and relax during hypocapnia and hyperoxia (Sheehan and Farhi 1993). Balanos (Balanos, Talbot et al. 2003) concludes that CO_2 is a more important regulator of pulmonary blood flow than O_2. The neural activity of peripheral chemoreceptors are also influenced by arterial pressure and adaptation to μG modifies blood pressure. Prisk (Prisk, Elliott et al. 2000) concluded that an increase in blood pressure detected by the carotid baroreceptors in μG resulted in a large reduction of the hypoxic ventilatory response (similar to that seen from supine position in 1G) but that the hypercapnic ventilatory response was unaltered in μG. The opposite vascular response between the pulmonary and systemic circulations in response to both PO_2 and PCO_2 is logical and wonderfully complex. It is linked to the transition from life in water to life in air during mammalian birth, an evolution that required millions of years to perfect (Swenson 2013).

Under EVA conditions we are not concerned about ventilatory response to hypoxia since hypoxia is not present and there appears to be no additional change in ventilatory response to hypercapnia in μG. There are measurements of elevated $P_{ET}CO_2$ in μG, attributed to hypoventilation secondary to a cephalad shift of abdominal contents, rebreathing CO_2 from the ISS atmosphere, or a physiologic change in ventilatory sensitivity to CO_2 (Hughson, Yee et al. 2016). Our literature review is not exhaustive on this subject. But we conclude that an otherwise healthy EVA astronaut can efficiently exchange O_2 and CO_2 through the lung during rest and exercise even if the mechanics (strategy) of breathing are slightly modified in μG (Prisk, Elliott et al. 1995).

Deconditioning in μG and exercise countermeasures to reduce deconditioning combined with exercise response to hypercapnia is beyond the scope of this literature review for the EVA-specific condition. We have no recommendations about P_ICO_2 under chronic conditions to either enhance or retard exercise countermeasures to manage deconditioning in μG.

12.0 EXTRAVEHICULAR ACTIVITY FUNCTIONAL AND COGNITIVE DOMAINS: THE BRAIN AND HYPERCAPNIA

Before proceeding with details, a 2016 comprehensive literature review by Stankovic (Stankovic, Alexander et al. 2016) titled, "A Review of Cognitive and Behavioral Effects of Increased Carbon Dioxide Exposure in Humans" concludes, "*While many studies have thus far addressed the impact of CO_2 concentration on cognition, the inconsistent and contradictory nature of current findings limits the ability to draw firm conclusions about the impact of elevated CO_2 exposure on sleep, cognition, and psychomotor performance. Further research, therfore, remains necessary to provide a clearer understanding of the risks of adverse cognitive and performance effects of acute and chronic high CO_2, particularly at levels relevant to human spaceflight."*

Recent studies about air quality in public spaces, such as offices and schools, suggest that neurocognitive function, as measured through computer-based assesment programs, is reduced at PCO_2 slightly greater than outdoor air (Satish, Mendell et al. 2012), (Allen, MacNaughton et al. 2016), (Bakó-Biró, Clements-Croome et al. 2012), on the order of 1 mmHg PCO_2. Increasing the ventilation in school class rooms decreased PCO_2 from about 1.1 mmHg to 0.34 mmHg (outdoor air is 0.23 mmHg) and resulted in small improvements (about 3%) in measures of cognition, attention, and vigilance in young students (Bakó-Biró, Clements-Croome et al. 2012). Adults working in office environments showed decreased performance using the Strategic Management Simulation (SMS) software tool in several of the 9 tests of higher-order decision making with PCO_2 in the range of 1.1 to 1.9 mmHg (Allen, MacNaughton et al. 2016), (Satish, Mendell et al. 2012). In contrast, Rodeheffer (Rodeheffer, Chabal et al. 2018) could not replicate the results from Satish or Allen at a PCO_2 of 1.9 mmHg in submariners using the same SMS software. He exposed 36 men: 12 each to PCO_2s of 0.4, 1.9, and 11.4 mmHg. After 45 minutes of acclimitization to the condition the resting men completed the 9 neurocognitive elements of the SMS in 80 minutes. There was no difference in the 9 outcomes between the 3 conditions; the submariners did not experience any deficits in decision-making ability. He suggested that prior exposure to hypercapnic conditions in submariners may have pre-adapted this group to hypercapnia. Allen (Allen, MacNaughton et al. 2018) evaluated flight simulator performance during acute mild hypercapnia of 0.5, 1.1, and 1.9 mmHg PCO_2 in 30 experienced commercial pilots. Federal Aviation Administration Designated Pilot Examiners graded performance on 21 flight maneuvers during 180 minute sessions where groups of 2 pilots each flew for 90 minutes. With 1.9 mmHg PCO_2 (2,500 ppm) as reference, the odds of passing a maneuver were 1.52 times higher when the pilots were exposed to 1.1 mmHg (1,500 ppm) and 1.69 times greater than when exposed to 0.5 mmHg (700 ppm), but this difference was not statistically significant. The negative effects of CO_2 on flight performance became more pronounced the longer the pilots were in the simulator. These results, in part, have motivated the National Research Council to investigate standards for flight deck ventilation rates.

Others show that mental performance in an acute 80 minute exposure in resting subjects did not diminish until a PCO_2 of about 34 mmHg was exceeded (Sayers, Smith et al. 1987). Vercruyssen has published extensively about acute hypercapnia from 2% to 4% CO_2 (PCO_2 from 15.2 to 30.4 mmHg) during physical activity with little change in psychomotor and mental performance (Vercruyssen and Kamon 1984), (Vercruyssen, Kamon et al. 2007), (Vercruyssen 2014). In 1984 he showed no change in cognitive and psychomotor performance with 15.2 mmHg (2% CO_2) combined with 75% $\dot{V}O_2$peak exercise for 40 minutes of a 60 minute CO_2

exposure. The results were the same if 50% O_2 was tested or if 50% O_2 plus 2% CO_2 was tested. He then tested CO_2 at 3% and 4% in 50% O_2, keeping his methods the same, and again showed no impairment in cognition or psychomotor performance (Vercruyssen, Kamon et al. 2007). Finally, breathing 4% CO_2 (PCO_2 of 30.2 mmHg) in 50% O_2 for 1 hour in resting subjects did increase information processing time (Vercruyssen 2014); however, changes in other sensitive metrics would seem to have little relevance to EVA performance. Some subjects did report headaches that cleared quickly in fresh air, and were not observed on subsequent test days. Sheehy (Sheehy, Kamon et al. 1982) had similar results with 5% CO_2 (PCO_2 of 38.0 mmHg) combined with exercise, but the treadmill exercise was only 10 minutes. He combined 4% or 5% CO_2 in air or 50% O_2 with 10 minutes of exercise at 80% $\dot{V}O_2max$ and found no deterioration in a multitude of psychomotor and mental performance tests during the 6 minutes of recovery while still breathing the test gases. Some subjects did report headaches and lightheadedness that cleared with fresh air. A 4% CO_2 exposure during bed rest for 2 weeks had no impact on psychomotor performance (Storm and Giannetta 1974). Storm in 1974 performed the first study combining a PCO_2 of 30 mmHg with 2 weeks of bed rest. He provided convincing evidence of no detrimental effect on complex tracking performance, eye-hand coordination, or problem solving ability either with bed rest, hypercapnia, or the combination of both conditions. Manzey (Manzey and Lorenz 1998) concluded that after 26 days of exposure to as much as 1.2% CO_2 (PCO_2 of 9.1 mmHg) that 4 males subjectively perceived reductions in alertness and slight performance decrements in a tracking task. An unstable tracking task showed a greater root-mean-square tracking error (see their Figure 2) when compared to baseline values in both the 0.7% and 1.2% exposures. In contrast to the 0.7% condition, the time course of change under the 1.2% condition seemed related to the CO_2 load and covaried with a loss of subjective alertness. Manzey concluded that at least visuomotor performance might be affected by chronic CO_2 concentrations ≤9.1 mmHg. He says that prolonged exposures to CO_2 concentrations as high as 1.2% appear to be tolerable with regard to their behavioral effects.

Several other investigators also concluded that there was no consistent relationship between CO_2 exposure and cognition or motor function within an operational EVA PCO_2 range <20 mmHg (Bloch-Salisbury, Lansing et al. 2000), (Henning, Sauter et al. 1990), (Sheehy, Kamon et al. 1982), (Selkirk, Shykoff et al. 2010), (Weybrew 1970). The work by Bloch-Salisbury is particularly relevant to EVA with resting astronauts exposed to P_aCO_2 on the order of 47 mmHg. Changes in electroencephalogram (EEG) brain waves with hypercapnia were noted by Bloch-Salisbury, as expected, since the CNS is the integrator of changes in the body. However, the changes in EEG did not affect cognitive function. Thesen (Thesen, Leontiev et al. 2012) tested in 7 subjects acute, cyclic exposure to 5% CO_2 in 21% O_2 and air, increasing $P_{ET}CO_2$ by about 8 mmHg during the cycles. They tested whether mild hypercapnia would decrease the magnetoencphalogram response to auditory pattern recognition and visual semantic tasks. There were decreases in event-related fields without affecting behavioral performance. They advance a homeostatic hypothesis for the observed changes in EEG with hypercapnia based on changes in $[H^+]$. Under normal conditions, low cerebral pH would arise when bloodflow is unable to compensate for neural activity. The observed cortical depression during hypercapnia may reflect a preservation mechanism by which neuronal activity is adjusted to a level that can be sustained by available bloodflow. Even though MCA bloodflow is elevated by hypercapnia (Halpern, Neufeld et al. 2003), the increase in $[H^+]$ from exogenous CO_2 appears to trigger a generalized depressive effect on cortical activity. The universal nature of the neural suppression may explain why, despite its large and widespread effects on neural activity,

hypercapnia did not affect performance speed or accuracy on either task, similar to what was reported by Bloch-Salisbury.

EEG also changes as part of hypercapnia associated in those with sleep disorders (Wang, Piper et al. 2011, Wang, Piper et al. 2014, Wang, Yee et al. 2015). We do not cover the vast literature about linking changes in EEG activity with changes in function. Just a few observations about acute hypercapnia. Wang (Wang, Yee et al. 2015) tested 20 subjects during acute, 5-minute hypercapnia from rebreathing. The procedure increased mean PCO_2 in the breathing circuit from 36 mmHg in control air to about 47 mmHg under hypoxic (PO_2 = 56 mmHg) or hyperoxic (PO_2 = 150 mmHg) conditions. In both cases there was an increase from 7 to 10 in the ratio of delta (δ) wave power to alpha (α) wave power (δ/α) from EEG during the rebreathing. No cognitive or performance measures were taken over this short interval, just a demonstration that hypercapnia but not hypoxia caused EEG slowing, which might indicate a depression of cortical neuroelectrical activity. Patients with sleep disorders had P_aCO_2 near 55 mmHg, which Wang (Wang, Piper et al. 2014) attributed to daytime drowsiness and sleepiness. These patients had slower EEG, as quantified by a higher δ/α ratio. Once nighttime continuous positive airway pressure was started, P_aCO_2 decreased to about 45 mmHg and the δ/α ratio decreased to between 5 and 7 and patients reported greater restful sleep. A lower δ/α ratio indicates a faster, more activated EEG spectral profile. They conclude that sleep hypercapnia resulted in daytime drowsiness secondary to reduced brain neuroelectrical activation and overall depression of cortical activity. Halpern (Halpern, Neufeld et al. 2003) also showed a similar increase in δ/α ratio during CO_2 rebreathing to conclude this cursory discussion.

The U.S. Navy has extensivly researched the causes and consequences of acute hypercapnia in divers, particularly in the performance of CO_2 scrubbers and increased breathing resistance at depth with exercise. A recent 2015 report by Haran (Haran and Lovelace 2015) and a particularly detailed report in 2010 (Selkirk, Shykoff et al. 2010) document minimal changes in neurocognitive and postural stability after execise in 12 feet fresh water with CO_2 exposure up to 3% (PCO_2 of 28.3 mmHg) sea level equivalent either in air or 1.4 ATM O_2. Dives lasted for 3.5 hours with intervals of 30-minute cycle ergometry, otherwise rest. There were many symptoms associated with this testing, including headache, inability to concentrate, and irritability but there was little impairment in sensitive neurocognitive tests. From their abstract, "*Basic cognitive domains of simple reaction time, visual scanning, visuo-spatial processing, and learning were unaffected, while fatigue and the higher cognitive functions of short-term memory, long-term memory, working memory, math processing, and sustained attention produced perplexing results. Most consistent of all differences was a decrease in long-term memory while divers were on CO_2, a decrease that persisted in Phase 1 even after divers were removed from CO_2 and returned to O_2.*" Bacal (Bacal, Beck et al. 2008) provides a table (Table 22.7) that compiles assessment of exercise and mental performance as PCO_2 increases. It appears that PCO_2 <30 mmHg for durations relevant to EVA do not significantly impact physical and mental performance, at least well-learned tasks in a 1G environment.

Clear vision is required for optimal performance. Hypercapnia could influence the retina as well as neurons along the pathway to the visual cortex. Sun (Sun, Sun et al. 1996) and Yang (Yang, Sun et al. 1997) exposed 3 subjects each to 2.5% CO_2 (PCO_2 of 19 mmHg) and measured a decreased stereoacuity and increased stereoscopic threshold, respectively. Stereoacuity is the reciprocal of stereoscopic threshold, so both investigators were reporting similar results in different ways. They concluded that fine detection of the depth of an object and the threshold

detection of motion are influenced by as little as 19 mmHg PCO_2. Each referenced earlier work by Weitzman (Weitzman, Kinney et al. 1969). Weitzman reported in 1 male that repeated exposure over 6 days to as much as 3% CO_2 impaired scotopic and green color detection sensitivity, but several other measures of visual performance were unchanged. Specific research is needed to understand the functional significance of changes to cognition and perception in an operational EVA and LEA environment.

James (James, Meyers et al. 2011) and Law (Law, Van Baalen et al. 2014) confronted the difficulty in defining unacceptable risk of acute hypercapnia. They could not prospectively define an adverse effect of hypercapnia, within the range of CO_2 on the ISS. Their work about hypercapnia on the ISS has some relevance to EVA since they statistically evaluated acute PCO_2 before private medical conferences that included reports of headache. Both used the prevalence of headache as a response variable that could be evaluated. Their analysis concluded that the probability of headache is <1% if PCO_2 is <2.3–2.5 mmHg, but added that headache on ISS is not a serious medical concern. However, a severe headache is debilitating. James used the term "subtle adverse effects" several times as something to avoid with acute hypercapnia, but subtle and adverse are the antithesis of each other. This is a clear indication that defining unacceptable risk in neurocognition, particularly complex decision making, and performance with hypercapnia during EVA is an area of new research. Staal (Staal 2004) provides an extensive review of the many dimensions of how stressors interact with cognition and human performance.

During EVA, there has been only one report of a mild headache lasting 15 minutes with accompanying photophobia in the literature (Vein, Koppen et al. 2009). This headache was not specifically attributed to CO_2. Otherwise, there are no known reports of diminished neurocognitive performance during EVA exposures during flight and training. On the contrary, there are astronaut reports of headaches improving after donning the EMU (Law, Watkins et al. 2010), (Kelly 2017). Research is underway to characterize the CO_2 exposure levels associated with the EMU at various metabolic rates. The expectation is that the levels experienced in the EMU at typical metabolic rates between 500 – 1500 BTU/h would be considered acceptable because of the lack of symptoms reported during hundreds of flight EVAs and thousands of EVA training runs in the Neutral Buoyancy Laboratory.

EVA presents a high stress and high risk environment where astronauts are required to perform mission critical tasks that require a combination of physical demand and high cognitive level. During EVAs astronauts can experience increasing physical and cognitive fatigue due to several factors: suit-fit issues, temperature fluctuations, hypercapnia, and the challenge of the EVA task at hand. As we move from low Earth orbit to exploration class missions EVAs will be more physically and mentally demanding since autonomy and novel (untrained) mission scenarios is the new paradigm. Performance of a new or off-nominal task during EVA with required procedure deviations may be significantly compromised when cognition is impared. Accordingly, the ability to predict and then mitigate acute cognitive changes, predict onset of cognitive deterioration, and most importantly, understand the impacts of cognitive deterioration in specific domains (ie, spatial orientation, abstract reasoning, emotion processing, stability of sustained attention, and risk decision making) on EVA task performance is critical. None of this critical information is in the literature.

13.0 MITIGATION OF AND RECOVERY FROM HYPERCAPNIA DURING EXTRAVEHICULAR ACTIVITY

Unlike many of the exposures to CO_2 described in the literature, the astronaut is the specific source of the CO_2 that they are exposed to and therefore exerts some control on the mitigation of high levels of CO_2. In a space suit, metabolically produced CO_2 is removed through one of several different potential chemical processes in the portable life support systems and then circulated back into the space suit through the ventilation loop. Direction of the inlet gas towards the face is designed to help wash away expired CO_2 and to provide access to air with less CO_2. No CO_2 removal is 100% perfect, and it is expected from past experience (Michel, Sharma et al. 1969), (Bekdash, Norcross et al. 2017) that somewhere between 0.5-2 mmHg remains in the gas supply even after CO_2 removal.

One consistent feature of all studies examining CO_2 exposures in space suits is that P_ICO_2 increases with increased energy expenditure. This is independent of the method used to measure CO_2 in the suit. This is a logical and consistent finding because a space suit is set to operate at a constant flow rate through the ventilation loop. Therefore, assuming a functional space suit, the primary reason an astronaut will be exposed to high levels of CO_2 is due to metabolic production. Therefore, should CO_2 symptoms be experienced during any suited activity, the first step should be for the astronaut to stop the activity and reduce the metabolic CO_2 production. Although this topic has not widely been discussed in the literature, we have seen CO_2 levels in the oronasal area decrease rapidly within 1-2 minutes after test subjects complete high metabolic rate test points at 2000-3000 BTU/h and begin resting.

Even if the P_ICO_2 level can quickly be reduced in the space suit, it has little relevance if the time for an astronaut to recover from a high CO_2 exposure is excessive. Fortunately, this recovery time seems to be fast as well. Reynolds (Reynolds, Milhorn et al. 1972) showed that respiratory variables including $\dot{V}_E$, V_T, RR, P_ACO_2 and P_AO_2 all returned to normal within a few minutes after 25 minute exposures to PCO_2 levels of 22.8, 38, 45.6 and 53.2 mmHg. In another study, P_ACO_2 and pH returned to baseline levels within 5 minutes after a 3 hour exposure, which ramped P_ICO_2 from 7 to 42 mmHg by 7 mmHg increments every 30 minutes (Forster, Klein et al. 1982). Recovery of pH and P_aCO_2 occurred within the 7 minute test period after exposure to PCO_2 levels 7.6 and 15.2 mmHg (Ellingsen, Sydnes et al. 1987). It seems that recovery from hypercapnia is rapid; however, in a space suit environment, one may rapidly recover to a lower P_ICO_2 that is still too high.

14.0 EXTRAVEHICULAR ACTIVITY-SPECIFIC INITIAL CONCLUSIONS

The purpose of this literature review was to provide relevant background information to assist in the evidence-based recommendation of an inspired CO_2 requirement for the xEMU space suit. The xEMU is expected to be used for a maximum of 8 hours EVA preceded by up to 4 hours of in-suit prebreathe. With this application in mind, the following conclusions are provided with respect to healthy astronaut populations, based on review of the literature described herein.

1. A current industry standard [NIOSH/OSHA/ACGIH] of 5,000 ppm, 0.5% dry-gas CO_2 (PCO_2 of 3.8 mmHg with P_ICO_2 of 3.5 mmHg for time weighed average 8-10 h/day, 40 h/wk is documented (https://www.osha.gov/dsg/annotated-pels/tablez-1.html). The standard applies to the general, adult working population with a range of health issues associated with an adult working population. Therefore, the standard applies to an office or school environment, to operators of vehicles, to workers on the factory floor, etc. Short-term exposure to 30,000 ppm (3%) for approximately 15 minutes is also permitted. With this brief background about general-population CO_2 limits, we now summarize EVA-specific conclusions based on our literature review.

2. Otherwise healthy adults can accommodate an acute PCO_2 of 15.2 mmHg at 760 mmHg ambient pressure (2% CO_2 sea level equivalent, P_ICO_2 = 14.2 mmHg) at rest and during exercise anticipated during EVA and LEA operations. This level is associated with acceptable, reversible physiologic alterations like changes in V_T, P_aCO_2, pH, etc. Astronauts sensitive to CO_2 may express symptoms like dyspnea and headache, but these will not be performance limiting. There are no obvious neurocognitive or EVA performance issues expected. While some may not consider this conservative enough for the EVA application, it could be used as a do not exceed target.

3. Exposures to a $P_ICO_2 \leq 7.1$ mmHg would be acceptable for acute exposure based on previous review papers and a long history of spaceflight operations. Literature data indicates no expectation of neurocognitive or physiologic health or performance issues at these levels for this population.

4. Exposures to a PCO_2 of 7.6 to 11 mmHg are still widely considered acceptable [relevant examples include (Bacal, Beck et al. 2008), (Rodeheffer, Chabal et al. 2018), (Clark, Sinclair et al. 1980) for expected EVA durations, based on small physiologic changes and acceptable neurocognitive performance. Symptoms reported at these PCO_2 levels in the literature are limited to small, measurable physiologic responses such as increased $\dot{V}_E$ and decreased pH, but are well within acceptable limits.

5. Careful review of the EMU CO_2 washout test results will help identify the targeted nominal EVA P_ICO_2 levels that have been tolerated without any CO_2 related symptoms reported. These values should weigh heavily on the exposure guidelines.

6. Physiologic changes associated with acute exposures to elevated CO_2 levels return to normal within minutes after return to normal CO_2 levels.

7. P_ICO_2 is a practical measure of hypercapnic dose that accounts for water vapor dilution at any P_B: $P_ICO_2 = (P_B – 47) \times F_ICO_2$, where P_B is ambient pressure as mmHg, 47 is mmHg water vapor pressure at body temperature of 37°C, and F_ICO_2 is dry-gas decimal fraction of CO_2 in breathing

atmosphere. For instance, a P_ICO_2 of 14.2 mmHg would result from an inlet PCO_2 from the scubber for a specific P_B that establishes a constant P_ICO_2 of 14.2 mmHg (see table examples).

Table 5. Examples of IsoP_ICO_2 Conditions

P_B (psia)	P_B (mmHg)	F_ICO_2	PCO_2 (mmHg)	P_ICO_2 (mmHg)
20.0	1034	0.0144	14.88	14.2
14.7	760	0.0200	15.20	14.2
8.0	413	0.0388	16.02	14.2
4.3	222	0.0811	18.00	14.2

8. Otherwise healthy astronauts adapted to μG have no significant physiologic impediments to pulmonary gas exchange that would make them more hypercapnic than expected during EVA if CO_2 is breathed.

9. There were no data on acute, repetitive hypercapnic exposure to understand changes in physiology during cyclical response and recovery.

10. There were no data on acute, repetitive hypercapnic exposure where recovery was in an environment of elevated PCO_2. Therefore, we lack an understanding of physiologic changes during cyclical response and recovery where recovery is in an environment of elevated PCO_2.

11. There is no absolute "Gold Standard" for an acceptable acute hypercapnic limit, just a gradual decrease in performance as P_ICO_2 increases.

12. Otherwise healthy astronauts will exhibit wide variability in responses to acute hypercapnia while at rest and during exercise.

13. No prospective reject criteria currently exits to define unacceptable physiologic, neurocognitive, or performance responses to acute hypercapnia at rest and during exercise. The reality is that an acceptable limit is occupation, situation (learned or novel tasks), and person-specific. Until these criteria are defined, a consensus of expert opinion is the only approach to define an acute hypercapnic limit for a heterogenous population of EVA astronauts.

14. There will always be some uncertainty about application of CO_2 results from normobaric exposure in 1G to hypobaric exposure in μG. Both the physical environment (gas density, total pressure, P_IO_2, method of exercise, etc.) and the physiology (adaptation to μG, including hypercapnia) are differently adapted. But these differences are considered minimal if P_aCO_2, then P_ACO_2, and then P_ICO_2, in that order, are the same between ground testing and EVA. If hypercapnic dose is equivalent between ground testing and EVA, then we hypothesize identical physiologic, neurocognitive, and functional performance responses. Operational EVA experience to date (landing on the moon and building a space station) is evidence that current space suit CO_2 limits established on Earth do apply in μG. In other words, there appears to be no single change or combination of changes associated with "space adaptation syndrome" that invalidates EVA CO_2 limits established in 1G for application in μG.

APPENDIX – LITERATURE EXCERPTS ABOUT ACUTE CARBON DIOXIDE EXPOSURE

A scheme to categorize literature reports is necessary to facilitate an orderly collection and analysis of those reports. We divided reports about hypercapnic exposure as follows:

Hypercapnia; PCO_2 >0.23 mmHg (fresh air @ 760 mmHg)
Normobaric; P_B between 740–770 mmHg
Hypobaric; P_B <740 mmHg
Hyperbaric; P_B >770 mmHg
Normoxic; P_IO_2 between 145–152 mmHg
Hypoxic; P_IO_2 <145 mmHg
Hyperoxic; P_IO_2 >152 mmHg
Normal Gravity; Earth-normal 1G
Abnormal Gravity; <1G (state of free-fall or planetary surface) or bed rest analog.

A-1 Hypercapnia in normobaric normoxia with rest and exercise in 1G.

(Alexander, West et al. 1955)
Provided early comprehensive respiratory and arterial blood gas data from 12 resting subjects after about 30 minutes of breathing air (control), 3%, and 5% CO_2 in air. Showed that physiologic dead space volume (V_D) increased as CO_2 concentration in air increased. He concluded that chronic hypercapnia results in a diminished sensitivity to inhaled CO_2, which is associated with a rise in both P_aCO_2 and $[H^+]_a$.

(Clark, Sinclair et al. 1980)
Evaluated a range of P_ICO_2 from 0 to 40 mmHg over a range of $\dot{V}O_2$max from resting (7% $\dot{V}O_2$max) to extreme exercise (80% $\dot{V}O_2$max, about 3.6 $L_{(STPD)}$ O_2/min) in 9 young men using treadmill at 10% grade with 6 minutes at 1.8, 3.4, 4.8, and 6 mph. No difference (change) in $\dot{V}O_2$ or $\dot{V}CO_2$ with increasing hypercapnia. RER increased as $\dot{V}O_2$ increased with no modification (decrease) due to hypercapnia, as seen by others. Mean blood lactate increased as $\dot{V}O_2$ increased and was not modified (decreased) with hypercapnia, as seen by others. For example, at $\dot{V}CO_2$ of 3.0 L/min, blood lactate was about 5 mM/L over the range of P_aCO_2 from 35 to 60 mmHg. The following data are means from 9 men.

Table A1. RER ($\dot{V}CO_2/\dot{V}O_2$)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}C_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.80	0.80	0.89	0.96	1.03
10	0.78	0.81	0.91	0.98	1.04
20	0.78	0.81	0.94	1.01	1.06
30	0.86	0.86	0.95	1.06	1.07
40	0.75	0.87	0.98	1.02	1.10

TABLE A2. $\dot{V}_E$ $L_{(BTPS)}$/min

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	10.09	27.3	46.5	88.3	124.1
10	12.5	34.6	59.2	109.8	141.0
20	17.2	45.0	73.6	122.9	153.2
30	27.3	65.8	93.0	142.1	161.0
40	46.2	89.4	115.7	151.3	169.0

TABLE A3. V_T $L_{(BTPS)}$

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.712	1.169	1.603	2.266	2.502
10	0.836	1.405	1.860	2.601	2.760
20	0.923	1.734	2.265	2.786	3.018
30	1.361	2.254	2.672	3.083	3.090
40	1.817	2.713	2.901	3.198	3.274

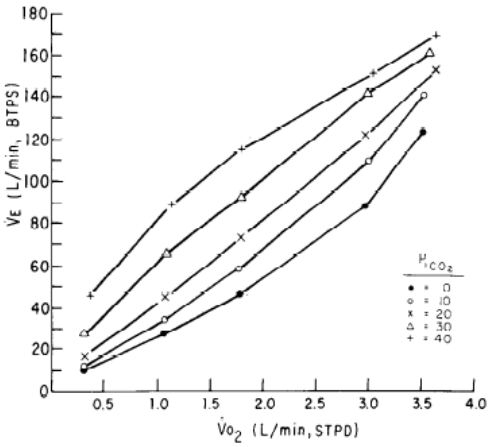

FIG. 1. Relationships of ventilation ($\dot{V}_E$) to O_2 uptake ($\dot{V}_{O_2}$) during exercise at different levels of inspired CO_2 tension ($P_{I_{CO_2}}$). Data in this and all subsequent figures are mean values in 9 subjects. Average values of $\dot{V}_{O_2}$ at rest and at each of 4 work loads were not significantly altered by changes in $P_{I_{CO_2}}$.

Figure A-1

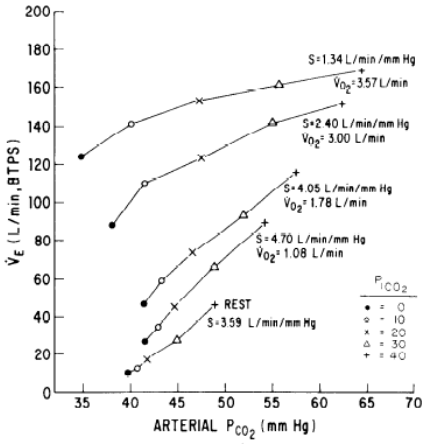

FIG. 7. Relationships of ventilation ($\dot{V}_E$) to arterial P_{CO_2} at different work loads during combined exercise and hypercapnia. Average slopes of the $\dot{V}_E$-Pa_{CO_2} relationships at rest and at 4 levels of exercise are shown. Corresponding average values of O_2 uptake ($\dot{V}_{O_2}$) are also indicated.

Figure A-2

TABLE A4. P_aCO_2 (mmHg) from arterial blood-gas

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	39.7	41.5	41.4	38.1	34.8
10	40.7	42.9	43.3	41.5	40.1
20	41.7	44.6	46.5	47.4	47.2
30	44.9	48.8	51.8	54.8	55.5
40	48.9	54.1	57.3	62.1	64.2

TABLE A5. V_A $L_{(BTPS)}$/min (computed)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	5.41	18.07	33.65	66.59	93.01
10	6.92	23.28	42.67	83.13	108.42
20	9.61	31.44	55.07	94.42	121.72
30	16.47	45.47	68.93	111.27	131.23
40	25.59	59.77	85.47	119.19	140.11

TABLE A6. V_D $L_{(BTPS)}$ (computed)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.325	0.392	0.442	0.553	0.622
10	0.371	0.458	0.518	0.631	0.636
20	0.339	0.524	0.568	0.644	0.617
30	0.543	0.700	0.695	0.662	0.562
40	0.814	0.880	0.742	0.676	0.562

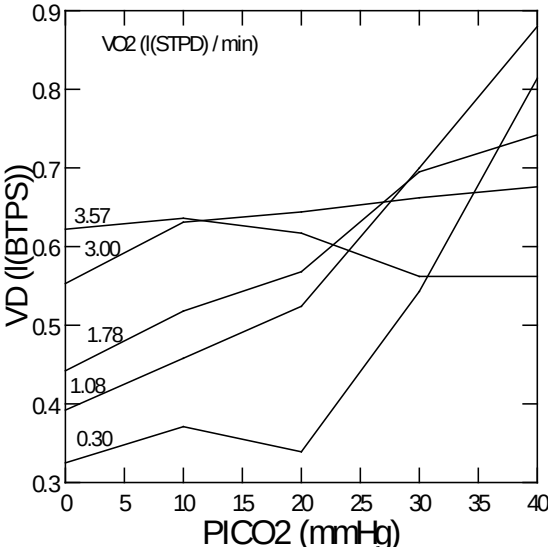

Figure A-3 Plot of Table A-6 data.

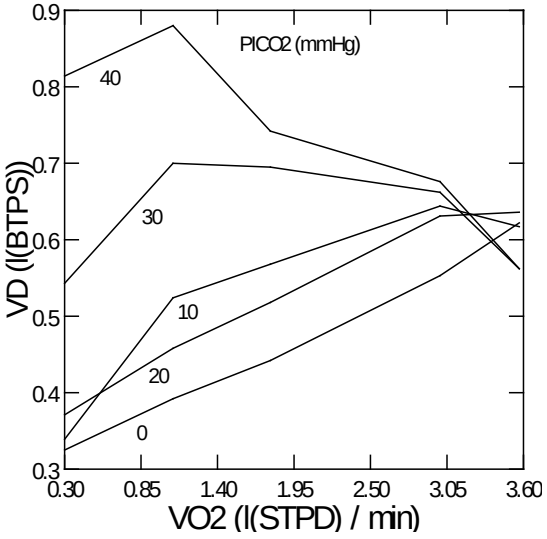

Figure A-4 Plot of Table A-6 data.

Table A7. V_D/V_T $L_{(BTPS)}$ (ratio by Conkin using authors' inputs)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.456	0.335	0.275	0.244	0.248
10	0.443	0.326	0.278	0.242	0.230
20	0.367	0.302	0.250	0.231	0.204
30	0.399	0.310	0.260	0.214	0.182
40	0.448	0.324	0.255	0.211	0.171

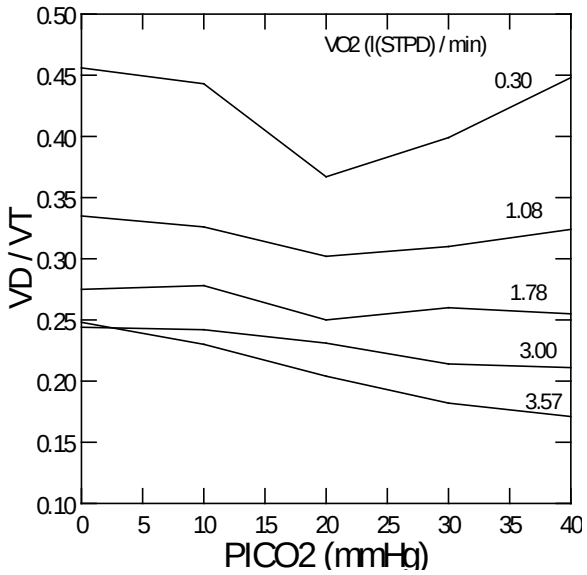

Figure A-5 Plot of Table A-7 data.

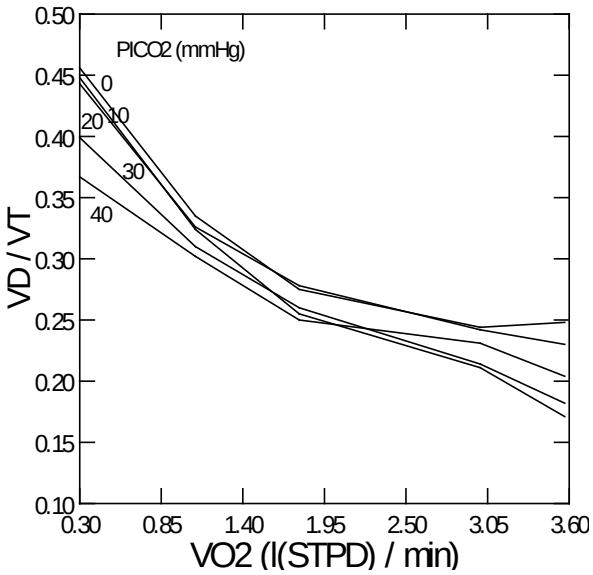

Figure A-6 Plot of Table A-7 data.

TABLĖ A8. VCO_2 $L_{(BTPS)}$/min

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.243	0.849	1.576	2.854	3.608
10	0.233	0.862	1.600	2.937	3.649
20	0.235	0.870	1.657	2.958	3.785
30	0.264	0.936	1.679	3.145	3.822
40	0.263	0.982	1.739	3.062	3.961

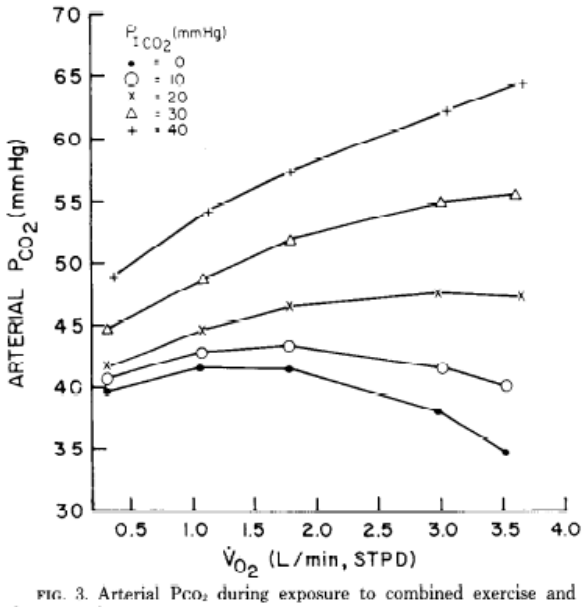

FIG. 3. Arterial P_{CO_2} during exposure to combined exercise and hypercapnia.

Figure A-7

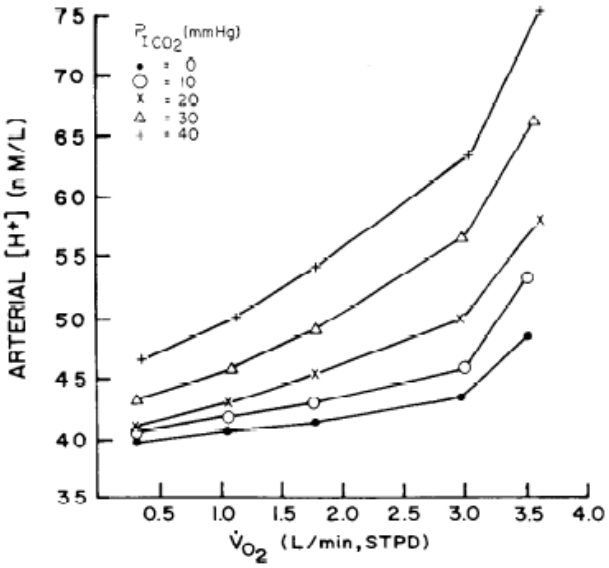

FIG. 4. Arterial [H⁺] during exposure to combined respiratory and metabolic acidosis.

Figure A-8

Table A9. Lactate (mEq/L)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	0.93	0.88	1.71	4.78	9.28
10	1.11	1.09	1.84	5.56	9.67
20	0.85	0.79	1.49	4.25	8.48
30	0.96	0.90	1.53	4.80	9.56
40	0.91	0.95	1.70	5.07	9.47

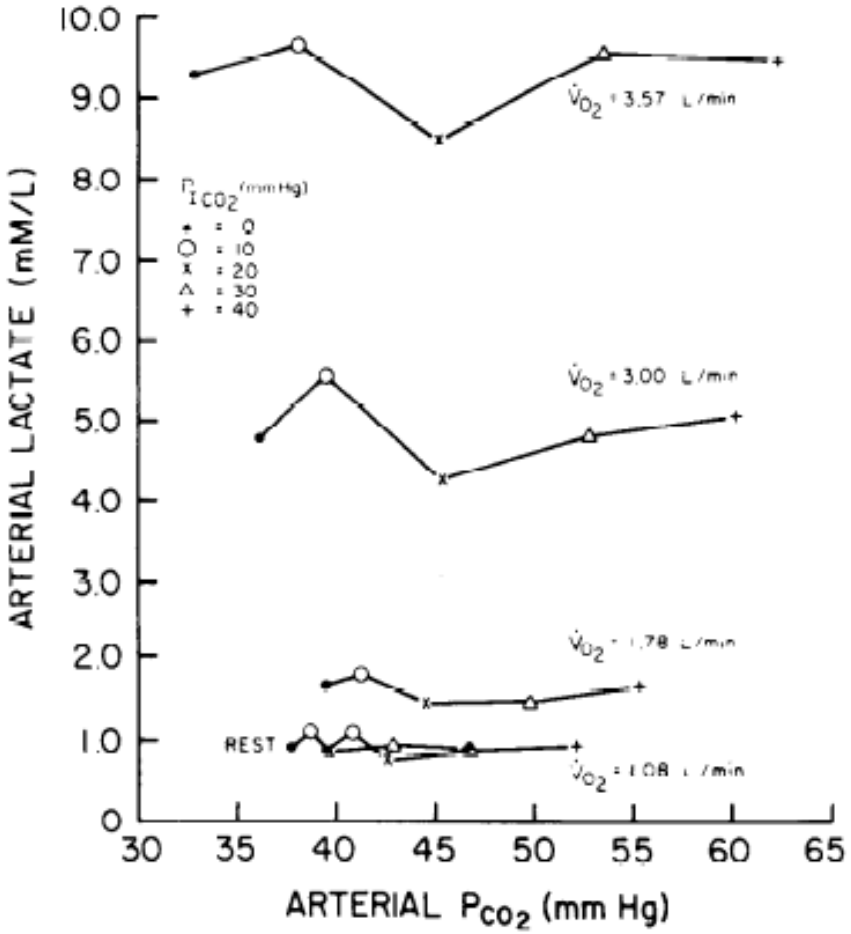

FIG. 5. Arterial lactate concentrations during exposure to combined exercise and hypercapnia.

Figure A-9

Table A10. HCO_3^- (mEq/L)

P_ICO_2 mmHg	0.30 $\dot{V}O_2$ $L_{(STPD)}$/min	1.08 $\dot{V}O_2$ $L_{(STPD)}$/min	1.78 $\dot{V}O_2$ $L_{(STPD)}$/min	3.00 $\dot{V}O_2$ $L_{(STPD)}$/min	3.57 $\dot{V}O_2$ $L_{(STPD)}$/min
0	24.2	24.7	24.3	21.3	17.3
10	24.4	24.9	24.4	21.8	18.1
20	24.6	25.2	24.8	22.9	19.4
30	25.0	25.7	25.4	23.2	19.9
40	25.3	26.0	25.4	23.3	20.2

Table A11. Compilation of Results from Clark Relevant to EVA

P_ICO_2 (mmHg)	$\dot{V}O_2$ $L_{(STPD)}$/min	P_aCO_2 (mmHg)	Lactate (mEq/L)	HCO_3^- (mEq/L)	$[H^+]$ (nM/L)	pH $-\log_{10}$ [H+]	$\dot{V}_E$ $L_{(BTPS)}$/min	RER
0	0.3	39.7	0.93	24.2	40.0	7.398	10.09	0.80
10	0.3	40.7	1.11	24.4	41.0	7.387	12.5	0.78
20	0.3	41.7	0.85	24.6	41.5	7.381	17.2	0.78
0	1.08	41.5	0.88	24.7	41.0	7.387	27.3	0.80
10	1.08	42.9	1.09	24.9	42.0	7.376	34.6	0.81
20	1.08	44.6	0.79	25.2	43.0	7.366	45.0	0.81
0	1.78	42.4	1.71	24.3	42.0	7.376	46.5	0.89
10	1.78	43.3	1.84	24.4	43.0	7.366	59.2	0.91
20	1.78	46.5	1.49	24.8	45.0	7.346	73.6	0.94
0	3.0	38.1	4.78	21.3	43.0	7.366	88.3	0.96
10	3.0	41.5	5.56	21.8	45.0	7.346	109.8	0.98
20	3.0	47.4	4.25	22.9	49.0	7.310	122.9	1.01

Note: nM/L = 10^{-9} Eq/L, so 40 nM/L = 40×10^{-9} Eq/L = $-\log_{10}[40 \times 10^{-9}] = 7.4$

(Jacobi, Iyawe et al. 1987)
Time to reach steady-state during hypercapnic exercise is not universally accepted. As a result, conclusions about respiratory control of $\dot{V}_E$ response to hypercapnic exercise are sensitive to how steady-state is defined.

(Graham, Wilson et al. 1982)
Hypercapnia with 0%, 2%, 4%, and 6% CO_2 in air at 55% and 65% $\dot{V}O_2$max exercise during 30 minutes of steady-state bicycle ergometry increased PCO_2 in arterialized venous blood and decreased pH. No difference (change) in $\dot{V}O_2$ with increasing hypercapnia with exercise but a decrease in $\dot{V}CO_2$ with increasing hypercapnia with exercise. RER was lower at 55% and 65% $\dot{V}O_2$max with hypercapnia. Mean blood lactate under hypercapnic exercise was reduced from 3.88 mM/L to 2.22 mM/L while breathing 6% CO_2 for 30 minutes at 65% $\dot{V}O_2$max. RER results suggest that with hypercapnia and the subsequent decrease in pH that respiratory acidosis and metabolic acidosis during hypercapnic exercise inhibited carbohydrate metabolism in favor of

lipid metabolism. Like Menn et al., 1970, $\dot{V}O_2$ for a given $\dot{V}O_2$max is the same regardless of hypercapnia, but $\dot{V}CO_2$ for a given $\dot{V}O_2$max is decreased in response to hypercapnia. Menn attributes results to CO_2 retention while Graham says CO_2 retention in minimal and suggests a shift from carbohydrate to lipid metabolism in response to decreased pH secondary to hypercapnia.

Table A12. Metabolic Response to Hypercapnic Exercise

CO_2 %	P_ICO_2* (mmHg)	$\dot{V}O_2$ 55% $\dot{V}O_2$ max (STPD)	$\dot{V}CO_2$ 55% $\dot{V}O_2$ max (STPD)	RER 55% $\dot{V}O_2$ max	$\dot{V}O_2$ 65% $\dot{V}O_2$ max (STPD)	$\dot{V}CO_2$ 65% $\dot{V}O_2$ max (STPD)	RER 65% $\dot{V}O_2$ max
0	0	1.85	1.78	0.96	2.37	2.24	0.95
2	14	2.03	1.83	0.89	2.37	2.20	0.92
4	28	1.94	1.70	0.86	2.46	2.16	0.88
6	43	2.09	1.71	0.88	2.39	2.03	0.85

Mean values.
*calculated based on P_B = 760 mmHg

TABLE 1. Group mean data for all subjects.

Measure	Work load +	Inspired CO_2 percentage 0% I	0% II	2% I	2% II	4% I	4% II	6% I	6% II
$\dot{V}_I$ ($l \cdot min^{-1}$) (STPD)	$\bar{X}$	39.2	53.7	52.6	65.8	66.7	80.9	80.6	94.8
	S.E.	4.2	4.2	7.0	4.8	7.9	7.2	8.7	10.0
	V	6.1	8.1	4.4	5.7	8.1	5.1	5.1	5.0
	S.D.	1.3	4.9	1.6	2.0	4.6	2.1	2.6	3.9
$\dot{V}o_2$ ($l \cdot min^{-1}$) (STPD)	$\bar{X}$	1.85	2.37	2.03	2.37	1.94	2.46	2.09	2.39
	S.E.	0.19	0.23	0.29	0.22	0.22	0.22	0.28	0.27
	V	5.2	5.8	5.5	5.1	6.7	3.8	3.5	4.5
	S.D.	1.9	4.1	2.8	3.2	2.6	2.1	2.2	1.7
$\dot{V}co_2$ ($l \cdot min^{-1}$) (STPD)	$\bar{X}$	1.78	2.24	1.83	2.20	1.70	2.16	1.71	2.03
	S.E.	0.21	0.21	0.27	0.20	0.20	0.20	0.18	0.21
	V	5.0	4.5	6.4	3.7	5.1	6.1	8.4	6.5
	S.D.	1.7	3.8	2.8	1.1	2.4	1.4	4.6	3.6
R	$\bar{X}$	0.96	0.95	0.89	0.92	0.86	0.88	0.88	0.85
	S.E.	0.02	0.01	0.02	0.02	0.03	0.02	0.02	0.03
	V	3.1	3.1	5.3	2.7	3.2	4.7	5.3	5.0
	S.D.	0.8	0.9	5.1	1.1	1.7	3.1	3.2	1.4
HR ($bts \cdot min^{-1}$)	$\bar{X}$	138	157	137	155	135	158	146	161
	S.E.	7	6	5	9	6	9	6	8
	V	3.8	5.7	3.1	4.3	4.3	4.7	4.2	3.7
	S.D.	1.3	2.2	1.9	1.4	1.9	1.3	2.3	1.1
$Paco_2$ (mmHg)	$\bar{X}$	35.8	33.8	38.6	39.3	42.8	44.2	51.4	52.0
	S.E.	0.9	0.8	1.1	1.2	1.1	0.9	1.4	1.1
	V	3.4	4.7	3.0	3.7	4.3	3.2	3.1	2.8
	S.D.	1.8	2.2	1.2	1.2	1.5	0.8	1.0	1.6
pH	$\bar{X}$	7.38	7.36	7.36	7.33	7.31	7.28	7.24	7.23
	S.E.	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	V	0.09	0.13	0.13	0.17	0.40	0.43	0.17	0.15
	S.D.	0.03	0.03	0.04	0.12	0.73	0.61	0.09	0.07
Lactate ($mM \cdot l^{-1}$)	$\bar{X}$	1.9	3.9	1.4	3.0	1.2	2.6	1.3	2.2
	S.E.	0.3	0.3	0.2	0.6	0.1	0.6	0.3	0.3
	V	26.7	19.0	23.9	16.1	16.6	20.1	27.2	19.5
	S.D.	24.9	6.7	10.8	5.5	5.5	6.2	13.4	7.7
HCO_3^- ($mEq \cdot l^{-1}$)	$\bar{X}$	20.7	18.5	20.9	20.3	20.9	20.1	21.2	21.1
	S.E.	0.4	0.7	0.5	0.6	0.6	0.6	0.3	0.7
	V	3.0	4.8	3.3	3.9	2.9	4.8	2.2	3.5
	S.D.	1.5	3.0	1.4	3.2	1.3	2.3	0.6	1.2

+I and II = 55 and 65% of $\dot{V}o_{2max}$, respectively.
$\bar{X}$ = mean value for the six subjects.
S.E. = standard error.
V = mean of the coefficients of variation for the six subjects.
S.D. = standard deviation of that mean.

Figure A-10 Note: Means from 6 men with 30 minutes of exercise at 55% (I) and 65% (II) $\dot{V}O_2max$.

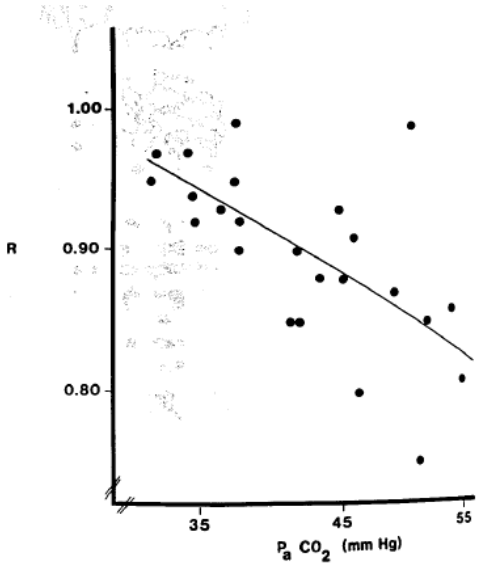

Figure 3—Respiratory exchange ratio (R) and blood P_{CO_2} for the heavy exercise. Each point represents the mean of the six values obtained during the 30-min single exercise test for a single subject. The solid line represents the linear regression equation, $R = 1.14 - 0.0056 (Pa_{CO_2})$, $r = 0.65$, $df = 22$.

Figure A-11 Note: Mean results from 65% $\dot{V}O_2$max exercise over 30 minutes. Data for the no CO_2 condition is from arterialized venous PCO_2 near 34 mmHg (RER ≈ 0.95) and increases to the 6% CO_2 condition for PCO_2 near 52 mmHg (RER ≈ 0.85).

(Menn, Sinclair et al. 1970)
Acute exercise response in 8 men during steady-state bicycle ergometry for 30 minutes to 0, 8, 15, 21, and 30 mmHg P_ICO_2 in air was not difficult at <15 mmHg. RER was similar (about 0.88) with 1/2 $\dot{V}O_2$max over the hypercapnic range but decreased when at 2/3 $\dot{V}O_2$max. There was CO_2 retention during high exercise combined with hypercapnia. There was no difference (change) in $\dot{V}O_2$ during exercise with hypercapnia.

Table A13. Data Showing Hypercapnic CO_2 Retention

P_ICO_2 mmHg	$\dot{V}_E$ rest L/min (BTPS)	P_aCO_2 rest mmHg	$\dot{V}_E$ 2/3 $\dot{V}O_2$ max (BTPS)	P_aCO_2 2/3 $\dot{V}O_2$ max mmHg	$\dot{V}O_2$ 1/2 $\dot{V}O_2$ max (STPD)	$\dot{V}CO_2$ 1/2 $\dot{V}O_2$ max (STPD)	RER 1/2 $\dot{V}O_2$ max	$\dot{V}O_2$ 2/3 $\dot{V}O_2$ max (STPD)	$\dot{V}CO_2$ 2/3 $\dot{V}O_2$ max (STPD)	RER 2/3 $\dot{V}O_2$ max
0	9.9	40.0	75.5	38.9	2.018	1.764	0.88	2.566	2.430	0.95
8	11.4	40.3	78.6	40.8	1.967	1.720	0.87	2.476	2.276	0.92
15	13.7	43.3	80.6	47.8	2.106	1.946	0.92	2.418	2.057	0.85
21	12.8	42.9	86.9	51.5	1.925	1.654	0.86	2.587	2.119	0.82
30	24.2	46.0	103.4	56.6	no data	no data	no data	2.557	1.841	0.72

Note: Mean values.

Table A14. Rest Data – Evaluation of Wasted Ventilation with Resting Hypercapnia

P_ICO_2 mmHg	V_T rest L(BTPS)	P_aCO_2 rest mmHg	$\dot{V}_E$ rest L/min (BTPS)	$\dot{V}CO_2$ rest L/min (STPD)	$\dot{V}O_2$ rest L/min (STPD)	RER rest	$\dot{V}_A$ ❶ rest L/min (BTPS)	V_D❷ rest L (BTPS)	V_D/V_T rest
0	0.62	40.0	9.9	----	----	----	----	----	----
8	0.64	40.3	11.4	----	----	----	----	----	----
15	0.78	43.3	13.7	----	----	----	----	----	----
21	0.81	42.9	12.8	----	----	----	----	----	----
30	1.26	46.0	24.2	----	----	----	----	----	----

Note: Mean values.

Table A15. ½ $\dot{V}O_2$max Exercise Data-Evaluation of Wasted Ventilation with Exercise & Hypercapnia

P_ICO_2 mmHg	V_T ½$\dot{V}O_2$ max $L_{(BTPS)}$	P_aCO_2 ½$\dot{V}O_2$ max mmHg	$\dot{V}_E$ ½$\dot{V}O_2$ max L/min (BTPS)	$\dot{V}CO_2$ ½$\dot{V}O_2$ max L/min (STPD)	$\dot{V}O_2$ ½$\dot{V}O_2$ max L/min (STPD)	RER ½$\dot{V}O_2$ max	$\dot{V}_A$ ❶ ½$\dot{V}O_2$ max L/min (BTPS)	V_D❷ ½$\dot{V}O_2$ max L (BTPS)	V_D/V_T ½$\dot{V}O_2$ max
0	2.04	----	57.1	1.764	2.018	0.88	----	----	----
8	1.81	----	59.0	1.720	1.967	0.87	----	----	----
15	2.06	----	67.4	1.946	2.106	0.92	----	----	----
21	2.32	----	72.3	1.654	1.925	0.86	----	----	----
30	----	----	----	----	----	----	----	----	----

Note: Mean values.

Table A16. 2/3 $\dot{V}O_2$max Exercise Data-Evaluation of Wasted Ventilation with Exercise & Hypercapnia

P_ICO_2 mmHg	V_T 2/3$\dot{V}O_2$ max $L_{(BTPS)}$	P_aCO_2 2/3$\dot{V}O_2$ max mmHg	$\dot{V}_E$ 2/3$\dot{V}O_2$ max L/min (BTPS)	$\dot{V}CO_2$ 2/3$\dot{V}O_2$ max L/min (STPD)	$\dot{V}O_2$ 2/3$\dot{V}O_2$ max L/min (STPD)	RER 2/3$\dot{V}O_2$ max	$\dot{V}_A$ ❶ 2/3$\dot{V}O_2$ max L/min (BTPS)	V_D❷ 2/3$\dot{V}O_2$ max L (BTPS)	V_D/V_T 2/3$\dot{V}O_2$ max
0	2.29	38.9	75.5	2.430	2.566	0.95	54.0	0.65	0.284
8	2.23	40.8	78.6	2.276	2.476	0.92	59.9	0.54	0.242
15	2.29	47.8	80.6	2.057	2.418	0.85	54.0	0.75	0.327
21	2.52	51.5	86.9	2.119	2.587	0.82	60.0	0.78	0.309
30	2.69	56.6	103.4	1.841	2.557	0.72	60.0	1.13	0.420

Note: Mean values.

Decrease in wasted ventilation during exercise without hypercapnia based on Figure 11-5 from Murray (Murray 1986), and analysis of literature data with equations that relate respiratory volumes and gas partial pressures.

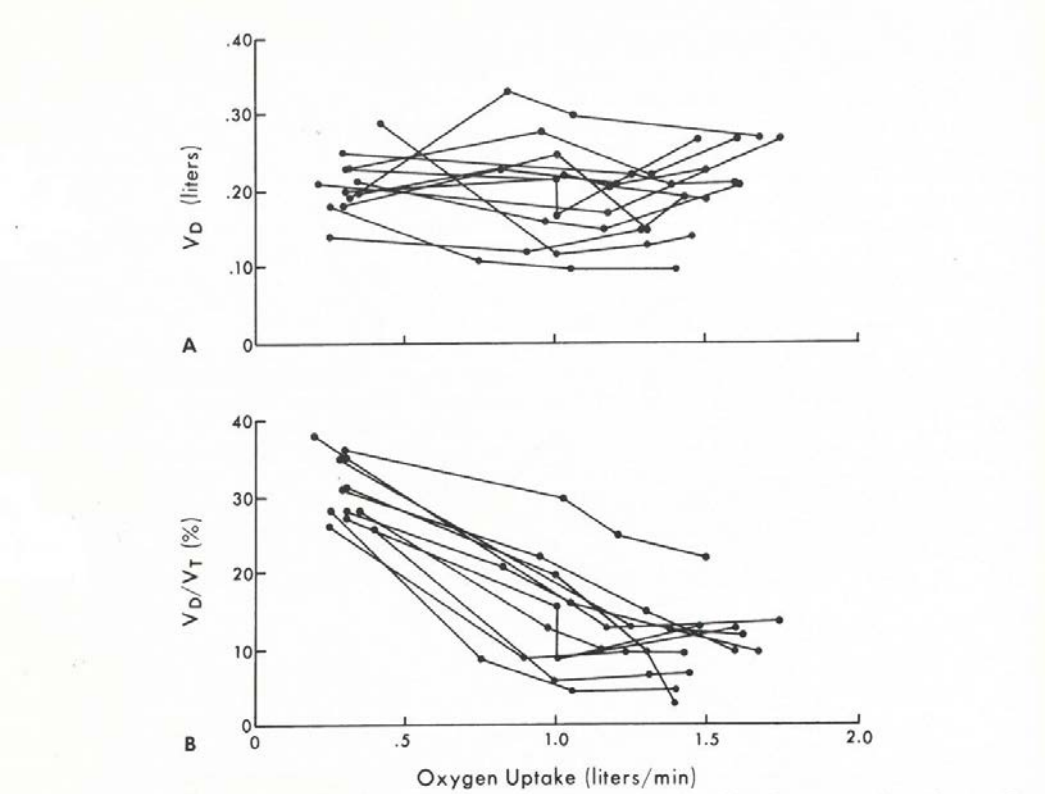

Figure 11–5. Effect of increasing O_2 uptake by exercise (measured with a bicycle ergometer) on *A*, wasted ventilation (V_D) and *B*, wasted ventilation:tidal volume ratio (V_D/V_T). (Data from Glazier, J. B., and Murray, J. F.: Unpublished observations, 1974.)

Figure A-12

❶ $P_aCO_2 = (\dot{V}CO_2/\dot{V}_A) \times 863 + P_ICO_2$

❷ $\dot{V}_A = \dot{V}_E \times [\ 1 - V_D/V_T]$

❸ $V_D/V_T = (P_aCO_2 - P_{ET}CO_2)/P_aCO_2$

❹ V_D, $mL_{(BTPS)} = V_T \times [(P_aCO_2 - P_{ET}CO_2)/(P_aCO_2 - P_ICO_2)] - V_{Dvalve}$ (dead space of the breathing valve) (Murray and Nadel 1988)

❺ $V_D/V_T = [(P_aCO_2 - P_{ET}CO_2)/(P_aCO_2 - P_ICO_2)] - V_{Dvalve}/V_T - V_{Dvalve}$ (Murray and Nadel 1988)

❻ $\dot{V}_A = 0.863 \times \dot{V}CO_2/P_aCO_2$

❼ $V_D/V_T = (\dot{V}_E - \dot{V}_A)/\ \dot{V}_E$

(Sinclair, Clark et al. 1971)
States that healthy men at rest can tolerate acute and chronic PCO_2 up to 30 mmHg, but questions how the contribution of exercise would modify this statement. Four males performed low, moderate, and heavy bicycle exercise on different occasions for 45 minutes while supine. Exercise was during a 1-hour acute exposure to 21 mmHg PCO_2 or later after 15–20 days of chronic exposure to 21 mmHg PCO_2. In the 3 figures that follow, measurements were taken between the 12^{th} and 15^{th} minute of low, moderate, and heavy exercise. It was not clear why the exercise then continued for 45 minutes. Arterial blood samples were collected.

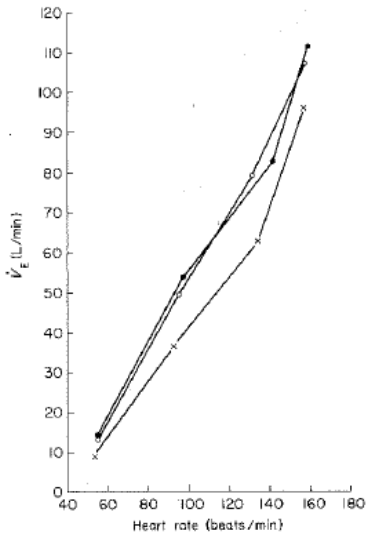

FIG. 1. Effect of graded exercise upon respiratory minute volume in air (×) and in acute (●) and chronic (○) exposure to hypercapnia (21 mmHg). $\dot{V}_E$ values are corrected to BTPS conditions.

Figure A-13 shows that the increase in $\dot{\mathbf{V}}_E$ with increase in HR was not different between the acute and chronic exposure to PCO_2 of 21 mmHg, but was higher than for exercise with air. There is a positive synergy between metabolic and respiratory acidosis, at least with PCO_2 of 21 mmHg**.**

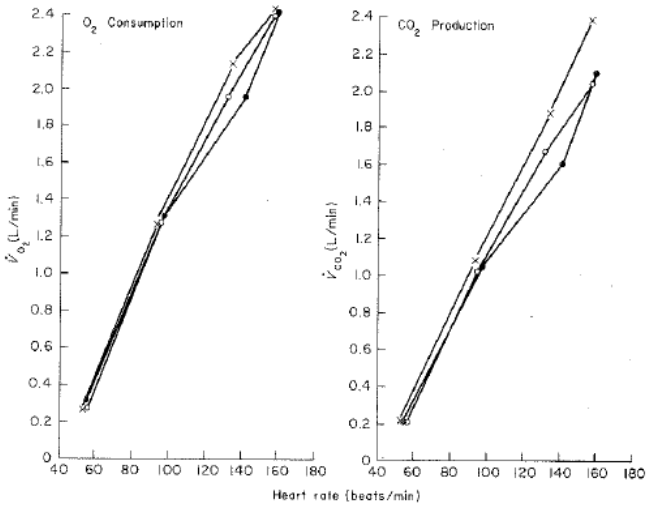

FIG. 2. Effect of graded exercise on respiratory gas exchange in air (×) and in acute (●) and chronic (○) hypercapnia. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ values were corrected to STPD conditions.

Figure A-14 This figure shows that for the same HR the $\dot{\mathbf{V}}O_2$ is no different between the 3 conditions (authors statement); however, the elimination of CO_2 for the same HR at moderate to heavy exercise falls significantly below the line for exercise with air. Mean O_2 consumption with heavy exercise was 2.41 $L_{(STPD)}$ O_2/min. He concludes that CO_2 retention occurred during exercise in hypercapnia that could not be explained by a decrease in metabolism, ie, a decrease in $\dot{\mathbf{V}}O_2$.

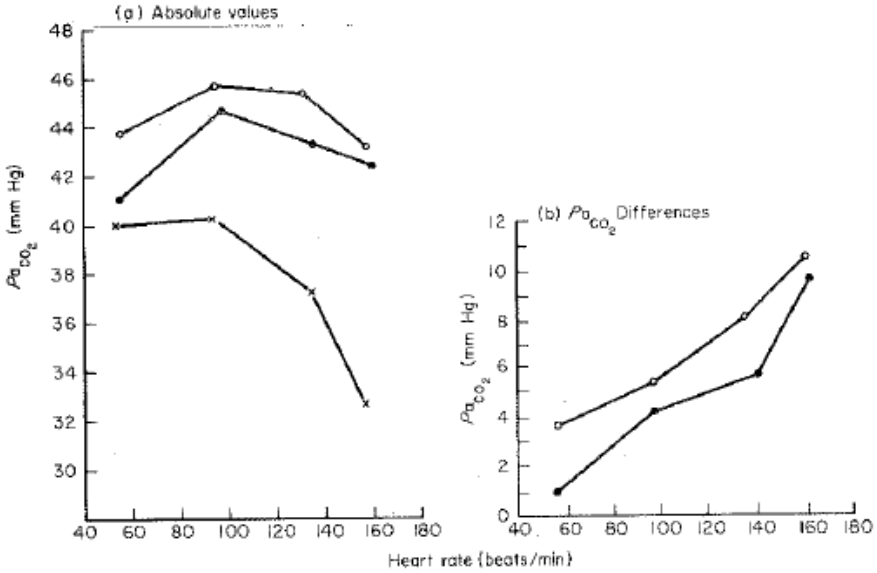

FIG. 3. Effect of graded exercise upon Pa_{CO_2} in air (×) and in acute (●) and chronic (○) hypercapnia. Blood gases were temperature corrected. Pa_{CO_2} *differences* refer to the difference between the absolute Pa_{CO_2} values in acute or chronic hypercapnia and the corresponding Pa_{CO_2} values during air breathing for rest and at each level of work.

Figure A-15 shows P_aCO_2 decreasing with exercise intensity in air; an efficient ventilation is removing CO_2 from metabolism. However, P_aCO_2 further increases from the higher baseline values for both the acute and chronic hypercapnia but does return to baseline values during heavy exercise. The difference between P_aCO_2 for hypercapnic exercise and exercise with air in panel 3b reflects the combined transport of CO_2 in arterial blood. The difference between chronic and acute exercise hypercapnia was statistically significant.

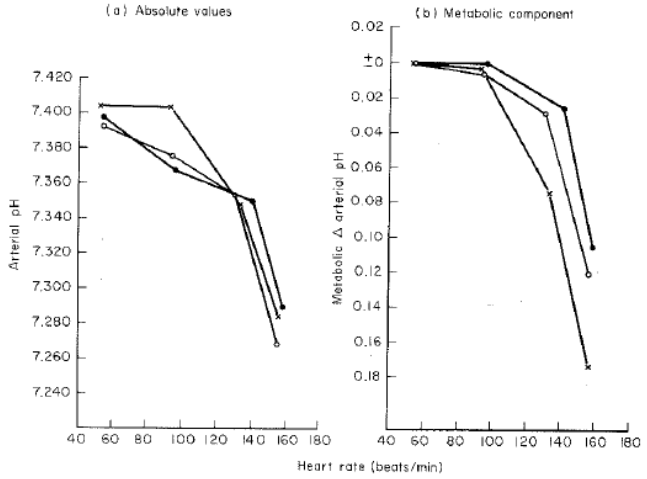

FIG. 4. Effect of graded exercise upon arterial pH in air (×) and in acute (●) and chronic (○) hypercapnia. The pH values were temperature corrected. The *metabolic component* was calculated by subtracting the respiratory component from the total change in pH. The relationship between change in P_{CO_2} and pH has a slope of −0.0075 pH units/1.0 mmHg increase in P_{aCO_2} (12).

Figure A-16 Figure 4 (above) shows the decrease in pH with hypercapnic exercise was similar to exercise with air during moderate and heavy exercise. The metabolic acidosis component of the pH change in panel 4b was greater during exercise while breathing air and smaller in acute hypercapnia. It is not clear how the data in panel 4b were computed.

(Ellingsen, Sydnes et al. 1987)

Acute, resting exposures to 1% and 2% CO_2 resulted in a small increase in P_aCO_2 and small decrease in arterial blood pH. Increase in $\dot{V}_E$ only partially attenuated the increase in P_aCO_2 which is evidence against isocapnic hyperpnea during inhalation of low CO_2. 1 kPa = 7.5 mmHg.

Table 1. Arterial P_{CO_2} in five subjects breathing room air, 1% CO_2, or 2% CO_2 in air

Run	F_{iCO_2}	Subject T.B	V.G.	E.E.	I.A.	F.C.	Mean increase
1	0	5.11	5.35	5.15	5.39	5.01	
	0	5.04	5.48	5.17	5.37	5.21	
	0	5.05	5.28	5.04	5.33	5.21	
2	0	4.95	5.49	5.33	5.67	5.17	
	1	5.04	5.52	5.35	5.73	5.28	
	0	4.96	5.36	5.23	5.61	5.15	
$\triangle P_{a,CO_2}$		0.085	0.095	0.070	0.090	0.120	0.092**
3	1	5.27	5.51	5.04	5.44	5.56	
	0	5.09	5.36	5.11	5.27	5.39	
	1	4.92	5.32	5.07	5.17	5.45	
$\triangle P_{a,CO_2}$		0.005	0.055	−0.055	0.035	0.115	0.031
4	0	4.96	5.41	5.40	5.17	5.32	
	2	5.09	5.51	5.51	5.51	5.59	
	0	4.75	5.33	5.24	5.12	5.33	
$\triangle P_{a,CO_2}$		0.235	0.140	0.190	0.365	0.265	0.239**
5	2	5.00	5.59	5.33	5.51	5.73	
	0	4.89	5.36	5.00	5.37	5.24	
	2	5.15	5.49	5.49	5.71	5.52	
$\triangle P_{a,CO_2}$		0.185	0.180	0.410	0.240	0.335	0.270**

** Significantly different from 0 with $P < 0.01$.

Each subject was exposed to five 'runs' in random sequence, each consisting of three 7-min periods with constant F_{i,CO_2}, the first and third always being equal. The increase in arterial P_{CO_2} caused by CO_2 loading was calculated by comparing the second period with the mean of the first and third period. All values are based on arterial blood samples taken in the seventh min of each period. The values are in kPa.

Figure A-17

(Sayers, Smith et al. 1987)

For acute, resting exposures of 20 minutes there were no changes in mental performance measured in various ways when $P_{ET}CO_2$ was less than 51 mmHg (about 5.5% CO_2). The author concludes a hypercapnic threshold below which mental performance is not affected given the acute condition of his test. Longer 80 minute exposures to 6.5% CO_2 did alter mood assessment: there was increased irritability and discomfort but alertness was unchanged. It took longer to complete subtraction and logic problems with $P_{ET}CO_2$ of about 55 mmHg.

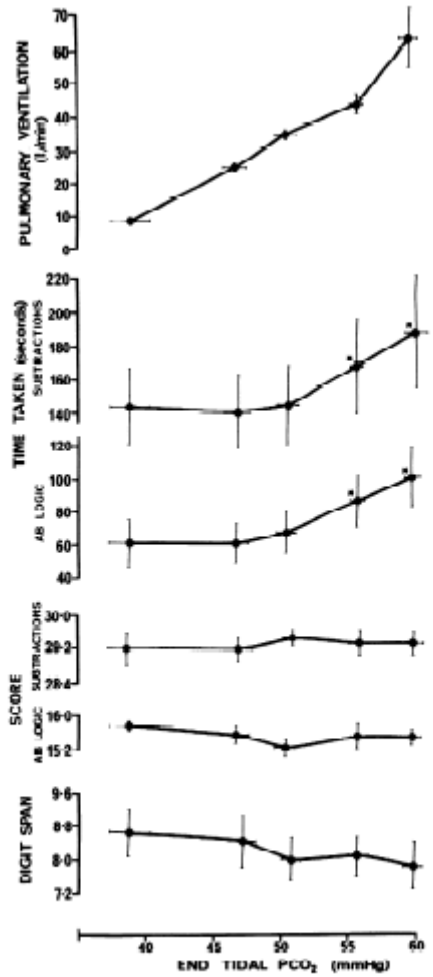

FIG. 1. Effects on pulmonary ventilation and reasoning of breathing (*from left to right*) 0, 4.5, 5.5, 6.5, and 7.5% CO_2 for 5 min. *Points*, means; *brackets*, ± SE. * Differs significantly ($P < 0.01$) from data with 0, 4.5, and 6.5% CO_2.

Figure A-18

(Forster, Klein et al. 1982)

Some investigators have found hypernea associated without a measurable change in P_ACO_2 and suspect chemoreceptors in the lung, independent of the known peripheral or central sensors. Ventilation sensitivity (reactivity) is measured as the ratio of $\Delta\dot{V}_E$ to ΔP_ACO_2, or $\Delta\dot{V}_E/\Delta P_aCO_2$. The point of the study was to determine if this ratio was different under low levels of P_ICO_2 (0.4–21 mmHg) versus higher levels (28–42 mmHg). $\Delta\dot{V}_E/\Delta P_aCO_2$ response is less at low P_aCO_2 and greater at higher P_aCO_2, so they conclude no evidence for additional CO_2 sensing in the lungs.

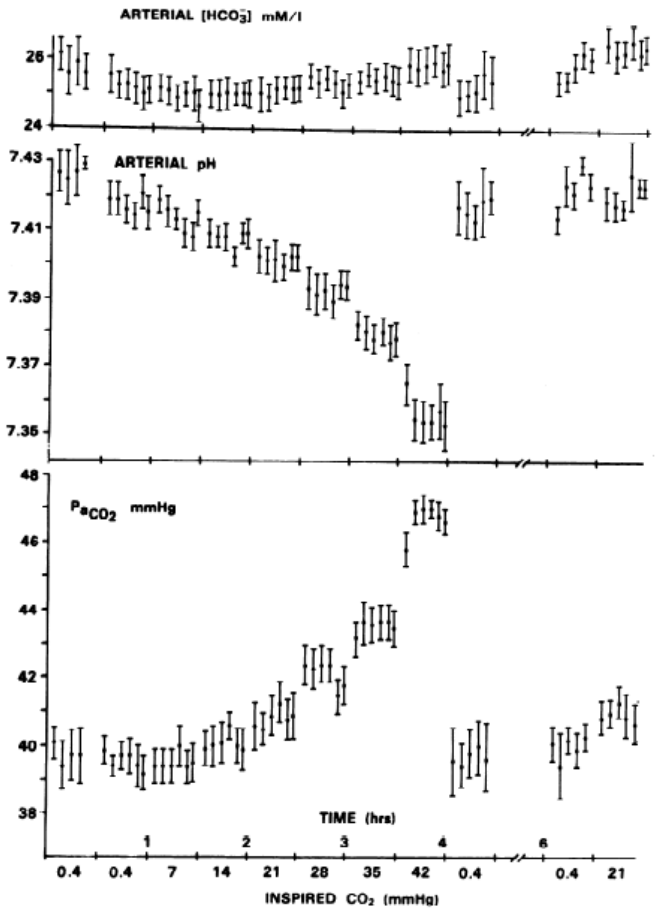

FIG. 2. Mean (± SE) arterial P_{CO_2}, pH, and HCO_3^- of 10 subjects over 7 h during which chamber P_{O_2} was 147 Torr, while chamber P_{CO_2} was altered as indicated (*study 2*). During 5th min at a $P_{I_{CO_2}}$ of 42 Torr, $P_{a_{CO_2}}$ was lower and pH was higher ($P < 0.05$) than during the remainder of the period. During the fourth control period, pH and HCO_3^- gradually increased by 0.015 and 1 meq/l, respectively. There were no systematic variations in any variables during any of the other 0.5-h intervals. Significant differences between conditions are detailed in text. Note that this protocol did not reveal a consistent difference in $P_{a_{CO_2}}$ between room air breathing ($P_{I_{CO_2}} < 0.4$ Torr) and inhalation of gas mixtures with a $P_{I_{CO_2}}$ of 7 and 14 Torr.

Figure A-19

Notice that P_aCO_2 is stable as P_ICO_2 increases to 14 mmHg but pH falls over this interval.

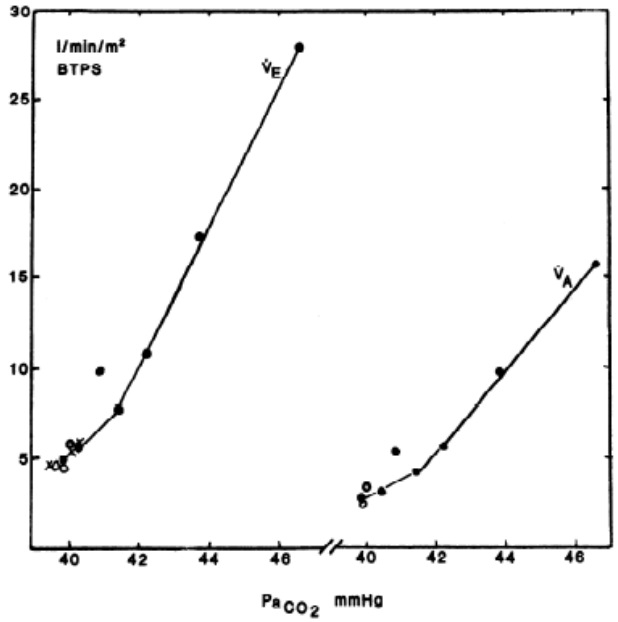

FIG. 3. Relationship between $P_{a_{CO_2}}$ and pulmonary ($\dot{V}_E$, *left*) and alveolar ($\dot{V}_A$, *right*) ventilation. All values represent average data from 8 subjects. Symbol X: values measured during experimental periods of *study 1*; *open* and *closed circles*: *study 2* values during eupnea and CO_2 inhalation, respectively. Note that slopes of the response curves are lowest near eupneic $P_{a_{CO_2}}$. Single value displaced from line represents data obtained on subjects about 2 h after eating a light lunch when $P_{I_{CO_2}}$ was 21 Torr.

Figure A-20 Rest Data – Evaluation of Wasted Ventilation with Resting Hypercapnia

Table A17. Evaluation of Wasted Ventilation with Resting Hypercapnia

V_A rest L/min (BTPS)	P_aCO_2 rest mmHg	$\dot{V}_E$ rest L/min (BTPS)	V_D/V_T❷ rest
3.0	40.0	4.8	0.37
6.0	42.0	11.0	0.45
10.0	44.0	17.5	0.43
14.0	48.0	25.0	0.44

Note: Mean values taken from curves on Figure 3 (above).
❷ $\dot{V}_A = \dot{V}_E \times [\ 1 - V_D/V_T]$, or $V_D/V_T = (\dot{V}_E - \dot{V}_A)/\ \dot{V}_E$

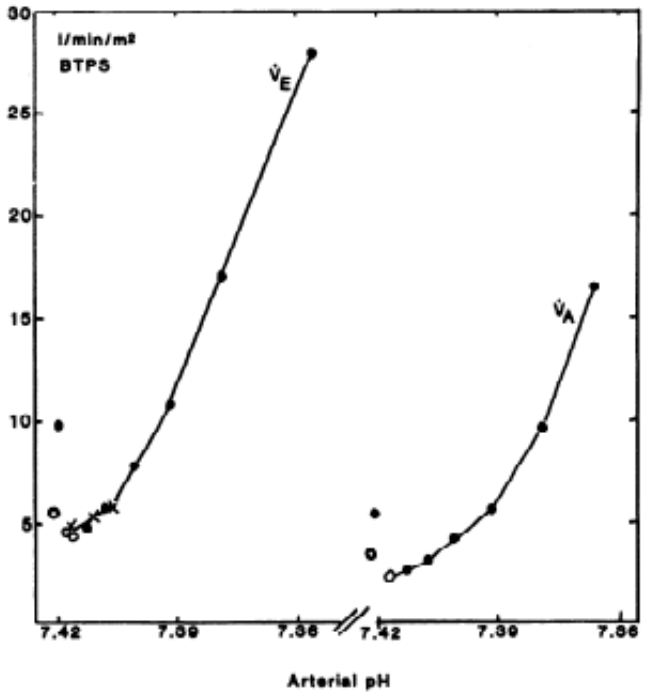

FIG. 4. Relationship between arterial pH and pulmonary ($\dot{V}_E$, *left*), and alveolar ($\dot{V}_E$, *right*) ventilation. See legend to Fig. 3 for explanation of symbols. Note that slopes of response curves are lowest near eupneic pH. The 2 points displaced from line represent data obtained on subjects about 2 h after a light lunch, during eupnea, and while $P_{I_{CO_2}}$ was 21 Torr.

Figure A-21

Notice there is less responsiveness in all responses when with a given ΔP_aCO_2 when P_aCO_2 is low and with a given ΔpH when pH is in the near normal range, the slopes are smaller on the left of the curves compared to the right of the curves.

(Gill, Natoli et al. 2014)
The issue was if hyperoxia exacerbated response to hypercapnia – it did not. Serious symptoms of hypercapnia occurred only during normoxia. Serious symptoms with hyperoxic hypercapnia were absent because of decreased $P_{ET}CO_2$ consequent to increased ventilation. For hyperoxic gases, $P_{ET}CO_2$ was consistently less than for normoxic gases. A limitation of the study is that they did not control for the increase in PN_2 (N_2 narcosis) while at 6 ATA.

Table 6. *Outcome variables and gases for rest and 75 W exercise*

Gas	*A* (*n* = 108)	*B* (*n* = 36)	*P*	*C* (*n* = 36)	*D* (*n* = 36)	*P*
Rest (n = 12)						
$P_{I_{O_2}}$, ata	0.21	1.3	A→B	0.21	1.3	C→D
$P_{I_{CO_2}}$, ata	0.0	0.0		0.065–0.085	0.065–0.085	
$P_{ET_{CO_2}}$, mmHg	36.3 (±3.1)	31.8 (±3.3)	<0.0001	60.7 (±3.9)	57.4 (±4.9)	<0.0001
	31.9–42.6	26.8–37.7		53.5–64.1	49.6–62.8	
$\dot{V}_E$, l/min BTPS	11.9 (±2.7)	14.3 (±3.2)	0.0013	60.3 (±15.5)	59.5 (±16.5)	ns
	7.5–17.8	8.8–20.1		28.5–75.4	28.1–75.9	
RPD (0–10)	0.5 (±0.7)	0.6 (±0.9)	ns	4.6 (±1.5)	3.9 (±1.0)	ns
	0.0–2.0	0.0–2.3		2.3–7.0	2.0–5.0	
n-back, %correct	84.6 (±6.0)	84.4 (±5.8)	ns	70.2 (±9.1)	73.5 (±9.1)	0.003
	73.6–94.2	73.0–93.0		56.0–88.3	59.0–87.8	
Gas	*A* (*n* = 90)	*B* (*n* = 30)	*P*	*C* (*n* = 30)	*D* (*n* = 30)	*P*
Exercise at 75 w (n = 10)						
$P_{I_{O_2}}$, ata	0.21	1.3	A→B	0.21	1.3	C→D
$P_{I_{CO_2}}$, ata	0.0	0.0		0.055–0.085	0.055–0.085	
$P_{ET_{CO_2}}$, mmHg	37.8 (±3.0)	34.8 (±3.2)	0.0003	64.9 (±6.9)	61.6 (±6.7)	0.0081
	33.6–42.0	31.1–40.3		50.8–74.1	46.7–70.7	
$\dot{V}_E$, l/min BTPS	39.5 (±3.9)	42.8 (±4.1)	0.018	82.3 (±11.9)	86.6 (±11.0)	0.0149
	34.1–46.8	37.6–50.7		53.1–96.8	56.8–95,2	
RPD (0–10)	0.7 (±0.9)	0.8 (±1.0)	ns	4.4 (±1.3)	3.9 (±0.9)	0.0192
	0.0–2.7	0.0–3.0		3.0–6.7	2.3–5.0	
n-back, %correct	85.3 (±6.7)	86.3 (±9.6)	ns	69.0 (±8.6)	73.4 (±8.5)	0.0092
	70.1–94.4	61.5–94.4		54.9–83.7	58.1–87.8	

Means, SD, and minimun/maximum values for outcome variables and gases for rest and 75 w exercise. ns, Not significant.

Figure A-22

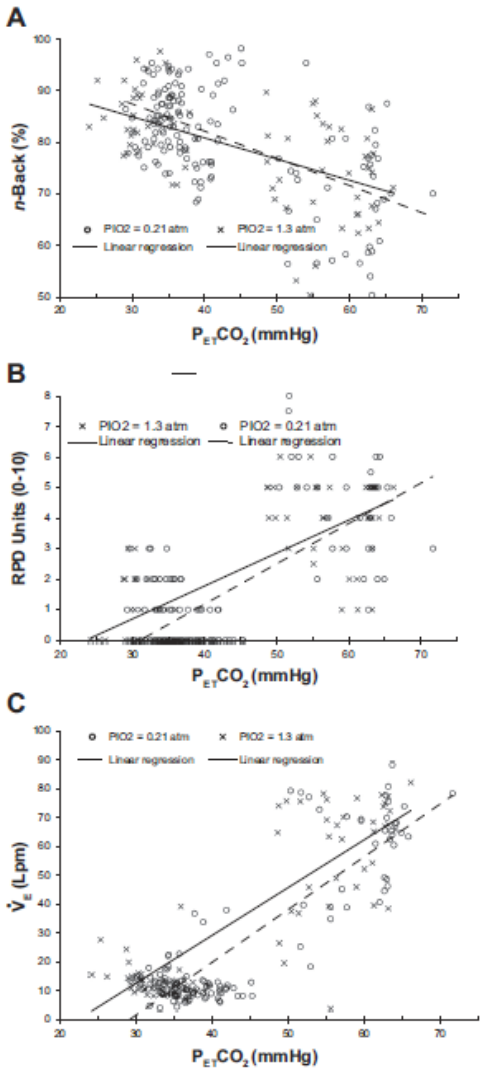

Fig. 2. *A*: individual values of *n*-back as a function of end-tidal CO_2 partial pressure (P_{ETCO_2}) for 12 resting subjects. *B*: individual values of rating of perceived discomfort (RPD) as a function of P_{ETCO_2} for 12 resting subjects. *C*: individual values of expired minute ventilation ($\dot{V}_E$) as a function of P_{ETCO_2} for 12 resting subjects. Lpm, liters per minute.

Figure A-23

(Henning, Sauter et al. 1990)
Acute, resting, normoxic air (21%) with 6% CO_2 – balance N_2 or 94% O_2 with 6% CO_2 was compared in a cross-over design. Mean $P_{ET}CO_2$ was statistically larger for normoxic (49.9 mmHg) compared to hyperoxic (48.1 mmHg). No significant difference in decrements of several measures of performance was assessed by paired comparisons of normoxic versus hyperoxic hypercapnia; both conditions showed equal decrements. N_2 narcosis was not a confounder in this experiment because both conditions were normobaric.

(Fan and Kayser 2013)
Increased F_ICO_2 elevated cerebral blood flow during incremental exercise in normoxia, an issue for EVA, but did not during hypoxia, not an issue for EVA. Neither in normoxic or hypoxic exercise did hypercapnia ($P_{ET}CO_2$ held ≈ 45 mmHg) change the increase in $\dot{V}O_2$ or $\dot{V}CO_2$.

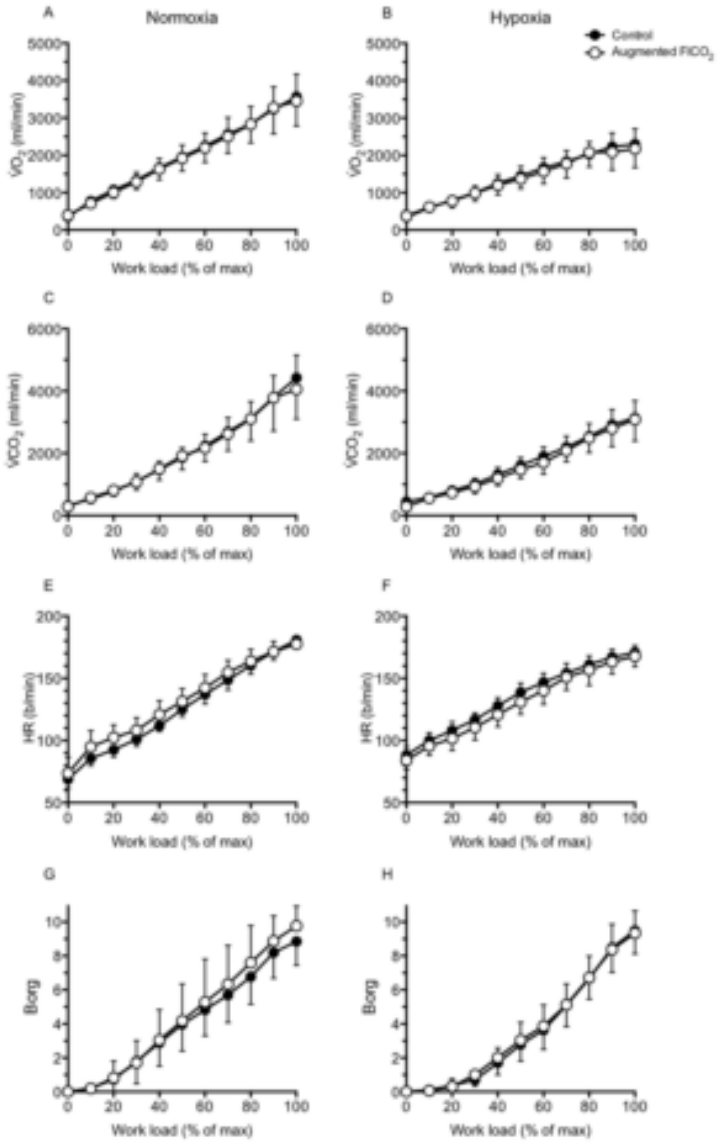

Figure 3. Effect of hypoxia and augmented $FICO_2$ on metabolic variables, heart rate, and perceived effort of exertion during incremental cycling to exhaustion. Left panels: group data in normoxia (mean ± SD); right panels: group data in hypoxia. Note: these graphs are only intended for visualizing the changes in physiological parameters during incremental cycling. Statistical analyses were carried out using the average variable during the exercise session (see Figure 1).
doi:10.1371/journal.pone.0081130.g003

Figure A-24

(Poon and Greene 1985)
Exercise up to $\dot{V}CO_2$ of 1.5 $L_{(BTPS)}$/min with controlled (clamped) hypercapnia from a P_aCO_2 between 46–54 mmHg) increases the slope of $\dot{V}_E$ versus $\dot{V}CO_2$ and increases the intercept. This is an important observation. However, P_aCO_2 during EVA exercise would not be artificially stabilized (clamped).

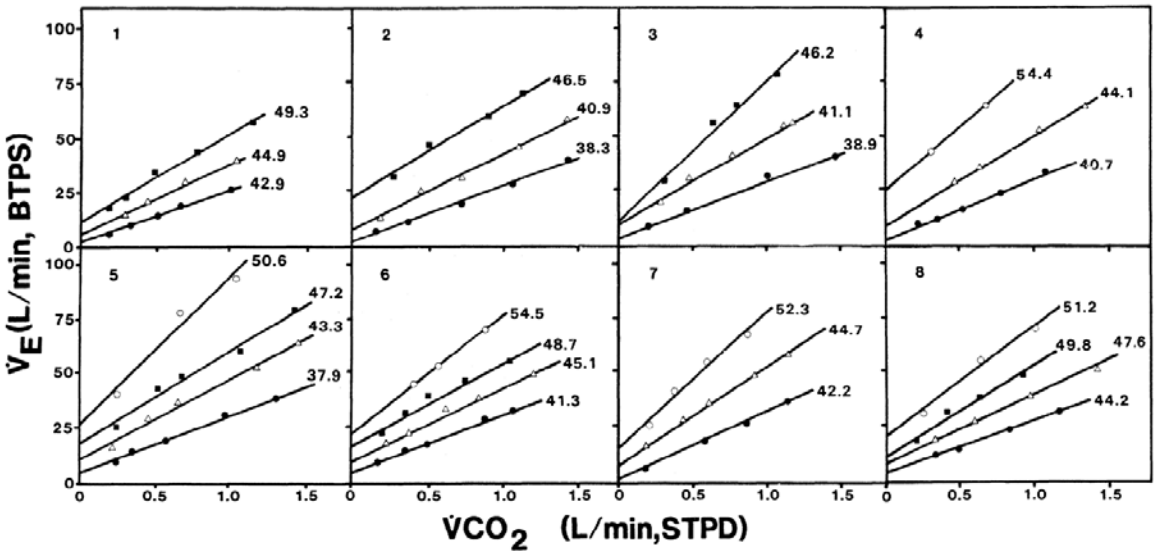

FIG. 1. Relations of steady-state ventilatory response ($\dot{V}E$) to metabolic CO_2 production ($\dot{V}CO_2$) in all subjects at different arterial P_{CO_2} levels (*numerals*, in Torr). *Solid lines* are linear regression fits to data. For comparison of intercepts, response curves were all extrapolated to zero metabolic rate.

Figure A-25

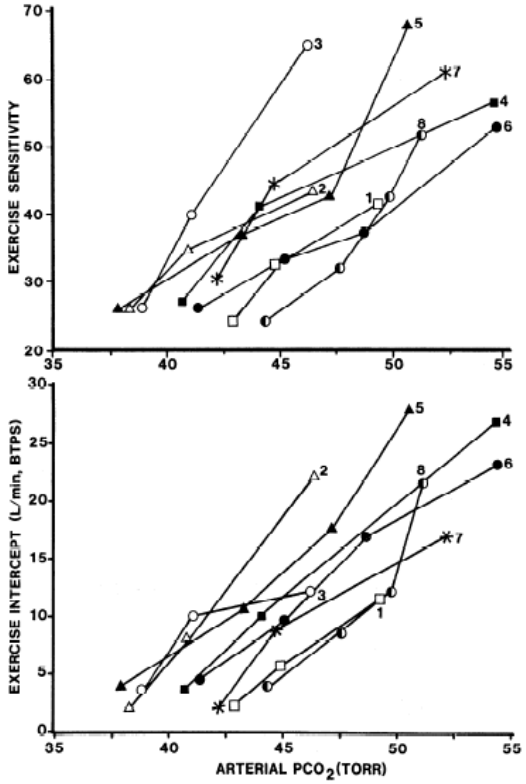

FIG. 2. Effects of hypercapnia on slope (S; exercise sensitivity; *top*) and zero intercept ($\dot{V}_0$; exercise intercept; *bottom*) of exercise response curves. Each *symbol* denotes an individual subject. Regression slopes (means ± SE): $\Delta S/\Delta Pa_{CO_2}$, 2.73 ± 0.28 $Torr^{-1}$; $\Delta\dot{V}_0/\Delta Pa_{CO_2}$, 1.67 ± 0.18 $l \cdot min^{-1} \cdot Torr^{-1}$).

Figure A-26

(Satish, Mendell et al. 2012)
Applied computer-based Strategic Management Simulation software to assess complex cognitive function (decision-making) during three acute 2.5-hour sessions with 600 ppm (0.45 mmHg), 1,000 ppm (0.76 mmHg), and 2,500 ppm (1.9 mmHg) CO_2 with ppm concentrations converted to PCO_2 as mmHg for sea level pressure.

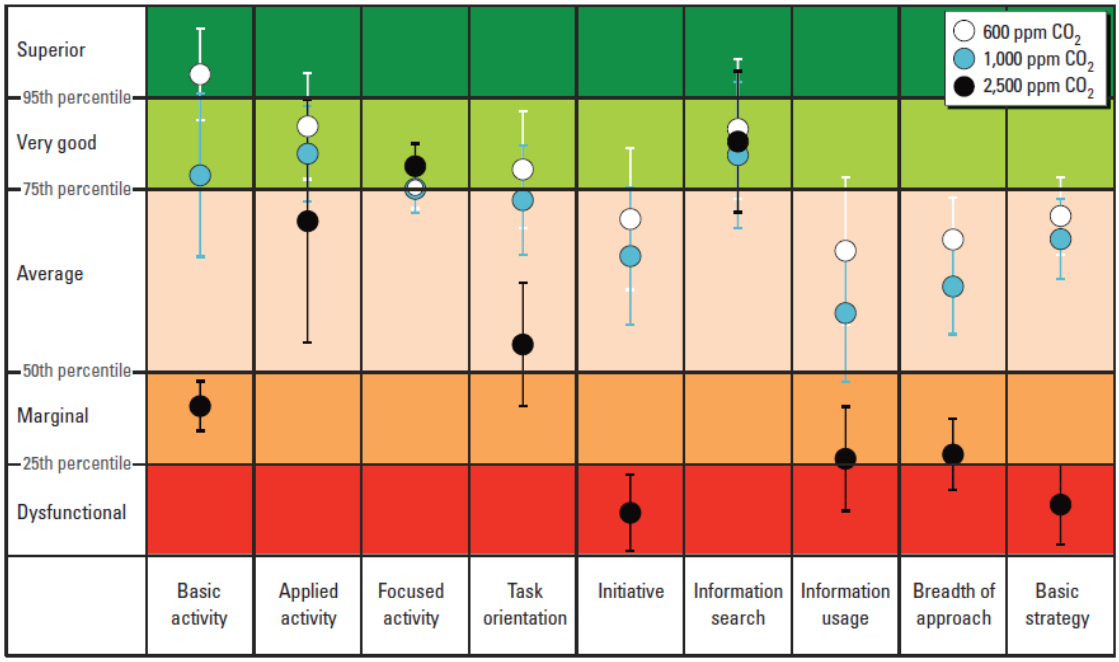

Figure 2. Impact of CO_2 on human decision-making performance. Error bars indicate 1 SD.

Figure A-27
10,000 ppm = 1.0% = 7.6 mmHg at sea level.
2,500 ppm = 0.25% = 1.9 mmHg at sea level.

(Allen, MacNaughton et al. 2016)
Applied computer-based Strategic Management Simulation software to assess complex cognitive function (decision-making) during 6 full work days (9 AM–5 PM) in an environmentally controlled office space with CO_2 concentrations per subject show in their Figure 2 (below).

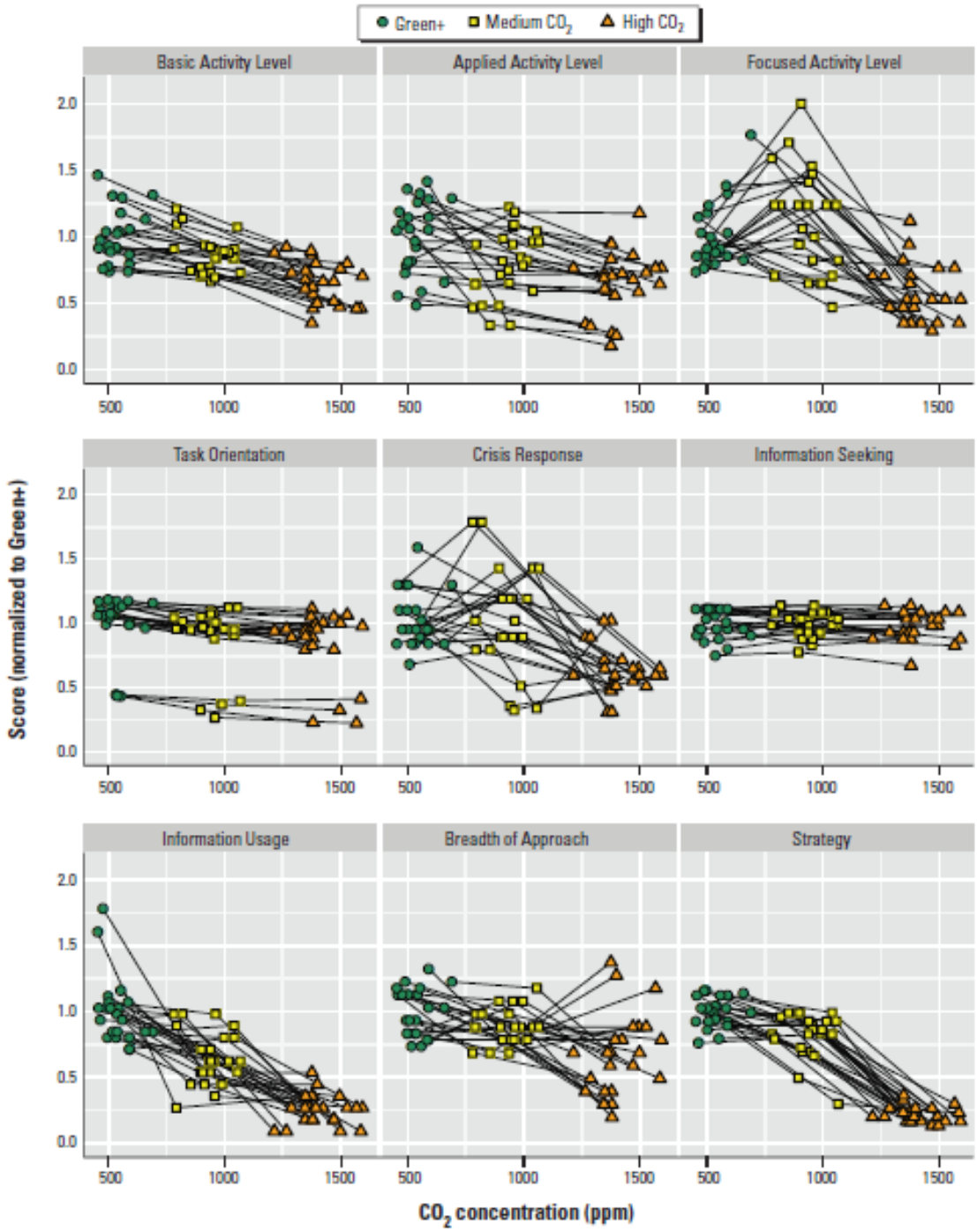

Figure 2. Cognitive function scores by domain and participant and the corresponding carbon dioxide concentration in their cubicles. Each line represents the change in an individual's CO_2 exposure and cognitive scores from one condition to the next, normalized to the average CO_2 exposure across all participants during the Green+ conditions.

Figure A-28 Note: Green condition indicates low concentrations of volatile organic compounds in breathing gas: 10,000 ppm = 1.0% = 7.6 mmHg at sea level, 1,500 ppm = 0.15% = 1.1 mmHg at sea level.

(Allen, MacNaughton et al. 2018)
They used a flight simulator to assess commercial pilot performance during 21 maneuvers in 90 minutes with 30 pilots exposed to 0.5, 1.1, and 1.9 mmHg PCO_2. Groups of 2 pilots were evaluated by FAA Designated Pilot Examiners where each pilot flew the simulator for 90 minutes during a 180 minute session. With 1.9 mmHg PCO_2 as reference, they showed a greater passing scores during simulations with 0.5 and 1.1 mmHg PCO_2. Their Figure 2 shows a reduced passing rate with increasing hypercapnia to about 1.9 mmHg PCO_2, particularly with difficult flight maneuvers.

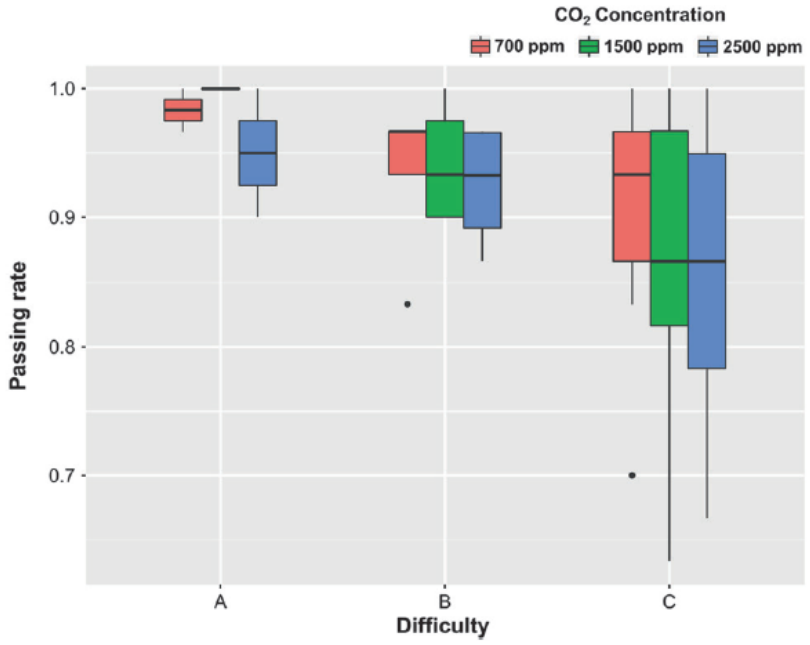

Fig. 2 Passing rates of pilots on each maneuver by maneuver difficulty and CO_2 conditions in the flight simulator

Figure A-29

(Rodeheffer, Chabal et al. 2018)
Applied computer-based Strategic Management Simulation software to assess complex cognitive function (decision-making) during three acute 80 minute sessions with 600 ppm (0.45 mmHg), 2,500 ppm (1.9 mmHg), and 15,000 ppm (11.4 mmHg) CO_2 with ppm concentrations converted to PCO_2 as mmHg for sea level pressure. 12 resting submariners (mean age 30 years) participated in each condition. After 45 minutes of acclimatization to the condition, the resting subjects completed over 80 minutes the 9 tests in the Strategic Management Simulation software. No difference between conditions was found for any of the 9 tests.

Table II. One-Way ANOVA Results.

OUTCOME VARIABLES	CONDITIONS (ppm of CO_2)*			$F(2, 33)$	P	η^2_p
	600 ppm	2500 ppm	15,000 ppm			
Basic Activity	89.92 ± 31.62	83.42 ± 28.28	89.58 ± 21.47	0.21	0.81	0.013
Applied Activity	54.58 ± 24.24	50.33 ± 30.43	51.58 ± 18.20	0.09	0.91	0.005
Focused Activity	12.33 ± 4.48	12.25 ± 4.14	11.50 ± 3.00	0.16	0.85	0.010
Task Orientation	90.33 ± 35.44	75.33 ± 31.84	88.50 ± 28.86	0.78	0.47	0.045
Basic Initiative	13.92 ± 7.19	12.33 ± 8.28	17.58 ± 12.52	0.94	0.40	0.054
Information Orientation	9.08 ± 9.22	5.83 ± 6.02	8.92 ± 7.46	0.68	0.51	0.040
Information Utilization	8.58 ± 5.05	7.58 ± 3.87	8.58 ± 5.43	0.17	0.84	0.010
Breadth of Approach	7.83 ± 1.47	7.75 ± 1.06	7.83 ± 1.03	0.02	0.98	0.001
Basic Strategy	16.58 ± 11.02	16.08 ± 12.13	16.00 ± 11.22	0.01	0.99	0.001

* Means ± SD.

Figure A-30

(Bakó-Biró, Clements-Croome et al. 2012)
Increasing the ventilation in school class rooms decreased PCO_2 from about 1.1 mmHg to 0.34 mmHg (fresh air is 0.23 mmHg) and resulted in small improvements, about 3%, in measures of cognition, attention, and vigilance in young students.

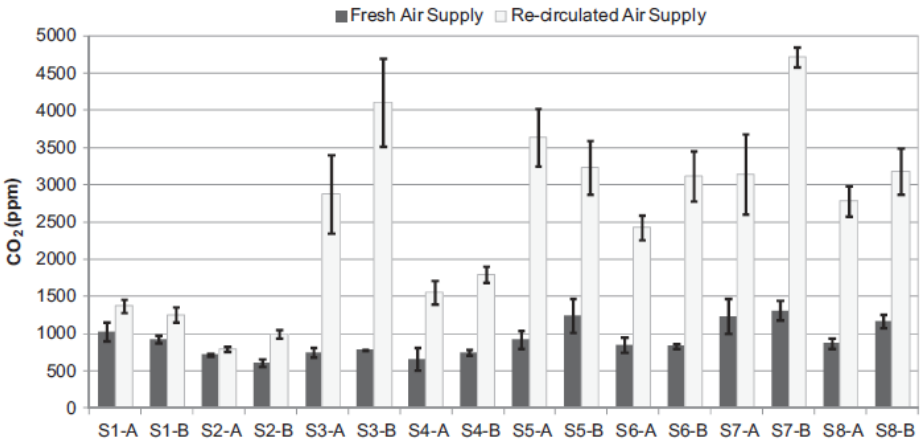

Fig. 2. Mean CO_2 concentrations (±SD) during the computerized performance tests in 16 classrooms at 8 schools. Note: For Schools S1 to S3 no recirculation was carried out; the low ventilation condition was obtained by not changing the windows openings unless the teachers decided so.

Figure A-31

(Frey, Sulzman et al. 1998)
Joint NASA-ESA-DARA study on chronic 3-week exposure with 4 men to 0.7% and then again to 1.2% CO_2 (PCO_2 of 5.3 mmHg and 9.1 mmHg, respectively). The general conclusion was that no serious medical concerns emerged with PCO_2 <9 mmHg (1.2%) for exposures lasting about 3 weeks, based on research in 1G.

(Sliwka, Krasney et al. 1998)
Joint NASA-ESA-DARA study on chronic 3-week exposure with 4 men to 0.7% and then again to 1.2% CO_2 (PCO_2 of 5.3 mmHg and 9.1 mmHg, respectively). Sliwka insonated the middle cerebral arteries of 4 males exposed to 23 days of 0.7% CO_2 and another 23 days of 1.2% CO_2. CBF was elevated by 35% during the first 1–3 days of both exposures but then returned to pre-test levels. Despite similar CBF responses, headache was only reported during the initial phase of exposure to 1.2% CO_2. They conclude that the time-dependent change in CO_2 vascular reactivity might be due either to retention of HCO_3^- in brain extracellular fluid or to progressive increases in ventilation, or both. Cerebral vascular autoregulation was preserved during chronic exposures to low-level CO_2. The attached figure shows the transient increase in CBF over each CO_2 exposure.

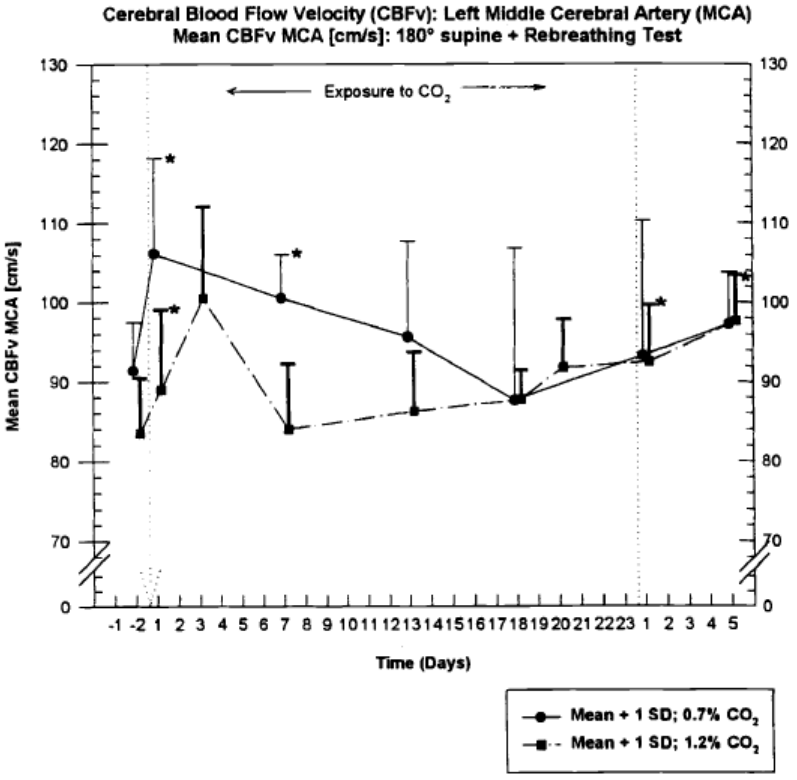

Fig. 3. Mean cerebral blood flow velocity responses for all four subjects in the supine position during rebreathing obtained at various time points in both campaigns.

Figure A-32

(Manzey and Lorenz 1998)
Joint NASA-ESA-DARA study on chronic 3-week exposure with 4 men to 0.7% and then again to 1.2% CO_2 (PCO_2 of 5.3 mmHg and 9.1 mmHg, respectively). Four other subjects served as controls for the 0.7% exposure, identified as filled circles in attached figures. All performed a sequential series of cognitive, visuomotor, and time-sharing performance tasks 7 days before, 26 days during mild hypercapnia, and 3 days of recovery. An unstable tracking task showed a greater root-mean-square tracking error (see Figure 2) when compared to baseline values in both the 0.7% and 1.2% exposures. In contrast to the 0.7% condition, the time course of change under the 1.2% condition seemed related to the CO_2 load and covaried with a loss of subjective alertness. The authors concluded that at least visuomotor performance might be affected by

chronic CO_2 concentrations ≤9.1 mmHg. Figures 1 and 2 below indicate no operationally significant performance deficits, certainly none that would impact acute, repetitive EVA exposures.

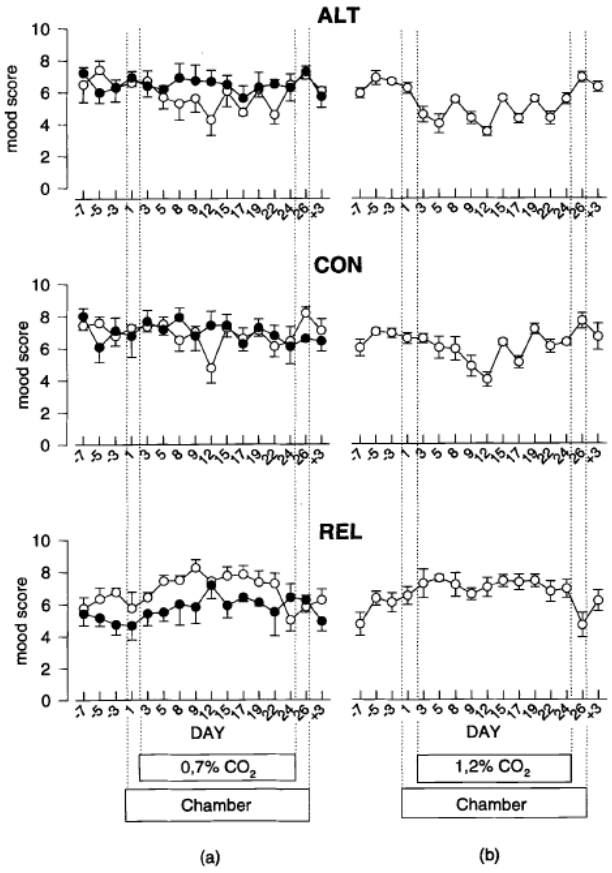

Fig. 1. Mean subjective mood scores and standard errors of means for consecutive sessions during (a) the first experiment (0.7% CO_2) and (b) the second experiment (1.2% CO_2) in the experimental group (n = 4; open circles) and the control group (n = 4; filled circles); ALT: alertness; CON: contentedness; REL: relaxation.

Figure A-33

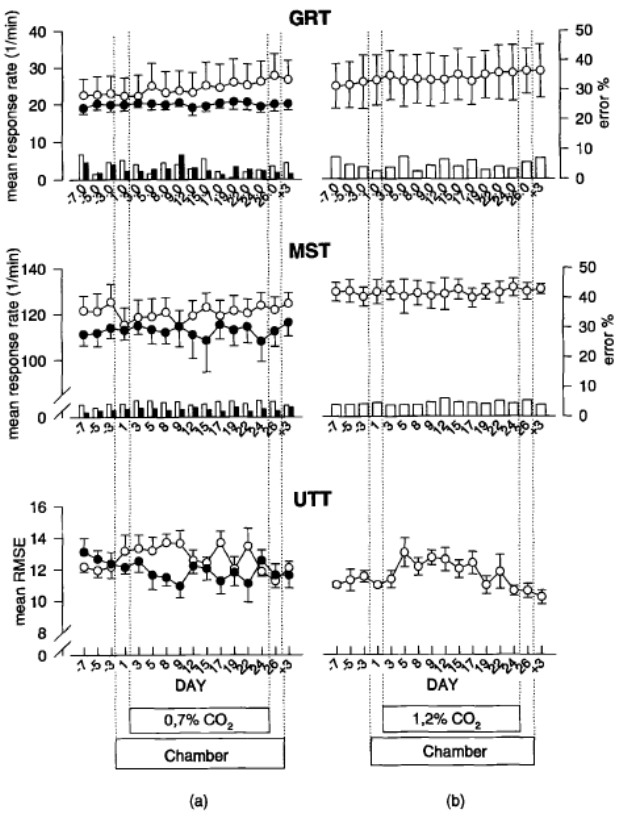

Fig. 2. Mean performance and standard errors of means for consecutive sessions during (a) the first experiment (0.7% CO_2) and (b) the second experiment (1.2% CO_2) in the experimental group (n = 4; open circles) and the control group (n = 4; filled circles); GRT: Grammatical Reasoning Task; MST: Memory Search Task averaged across all difficulty levels; UTT: Unstable Tracking Task averaged across all difficulty levels.

Figure A-34

(Weybrew 1970)
N = 1, 6 days with 3% CO_2 resulted in no significant changes in vigilance, coordination, or simple problem solving ability.

(Reynolds, Milhorn et al. 1972)
Acute resting 25 minute exposure. Conclusion: Breathing 3% CO_2 (PCO_2 = 23 mmHg, P_ICO_2 = 21 mmHg) has an effect on ventilatory response.

Table A18. Resting Ventilatory Response to Hypercapnia

CO_2 %	$\dot{V}_E$ just air $L_{(BTPS)}$/min		P_ACO_2 just air mmHg		P_AO_2 just air mmHg	
3	11	8	45	42	120	95
5	15		48		130	
6	25		49		130	
7	40		55		140	

Note: Data estimated from Figures 3-6.

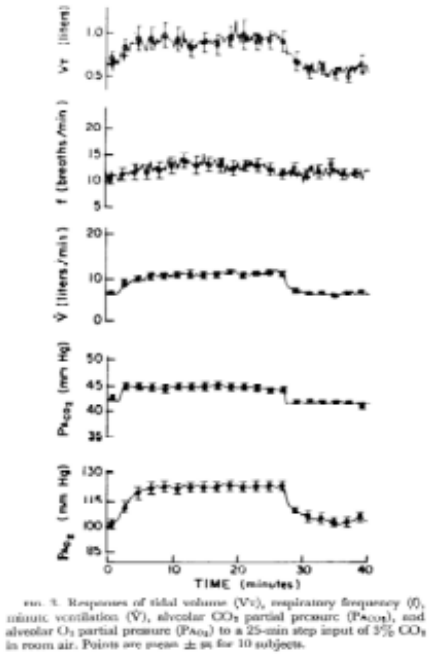

FIG. 8. Responses of tidal volume (V_T), respiratory frequency (f), minute ventilation ($\dot{V}$), alveolar CO_2 partial pressure (P_{ACO_2}), and alveolar O_2 partial pressure (P_{AO_2}) to a 25-min step input of 3% CO_2 in room air. Points are means ± SE for 10 subjects.

Figure A-35
Note: Acute 3% CO_2 exposure while resting at sea level.

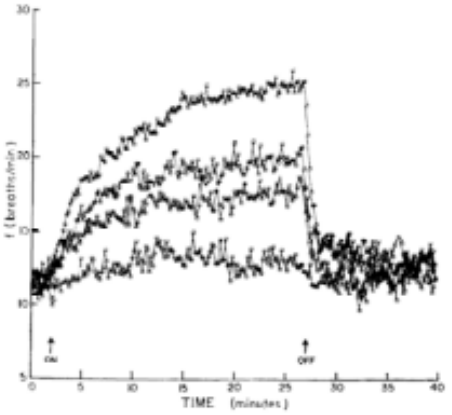

FIG. 9. Respiratory frequency responses to 7, 6, 5, and 3% inspired CO_2 in air. Points shown are means of 10 subjects except for 7% which are means of 14 subjects.

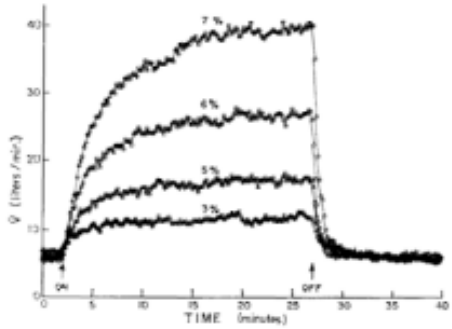

FIG. 10. Minute ventilation responses to 7, 6, 5, and 3% inspired CO_2 in air. Points shown are means of 10 subjects except for 7% which are means of 14 subjects.

Figure A-36
Note: Acute 3%, 5%, 6%, and 7% CO_2 exposure while resting at sea level.

(Balanos, Talbot et al. 2003)
Vascular tone in the pulmonary circulation is substantial and can be increased with hypercapnia and decreased with hypocapnia. Variations in CO_2 and O_2 play a role in matching ventilation to perfusion.

(Fothergill, Hedges et al. 1991)
See summary under #7.

(Ainslie and Duffin 2009)
Extensive review about the control of cerebral blood flow, particularly the role of P_aCO_2. Cerebrovascular reactivity and ventilatory response to P_aCO_2 are tightly linked since the aim is to maintain stable CSF [H^+, pH]. The review covers cerebrovascular CO_2 reactivity during sleep and exercise, as measured by MCA blood flow.

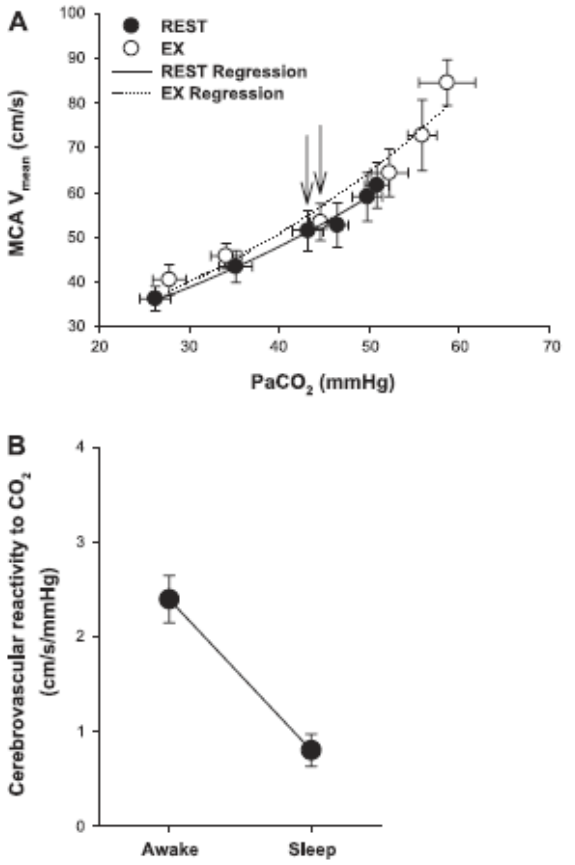

Fig. 4. *A*: characteristics of cerebrovascular CO_2 reactivity at rest and during exercise (EX), with cerebrovascular CO_2 reactivity characterized by an exponential function. Arrows show leftward shift of the operating point with exercise. MCAv, middle cerebral artery blood flow velocity. *B*: changes in cerebrovascular reactivity, assessed using linear regression, in each individual from wakefulness to sleep. Cerebrovascular reactivity to CO_2 from wakefulness to stage 2 sleep is reduced. [Modified from Meadows et al. (124) and Ogoh et al. (144).]

Figure A-37

(Storm and Giannetta 1974)
See summary under #2.

(Dahan, DeGoede et al. 1990)
Complex experiment with 9 resting males breathing CO_2 to set $P_{ET}CO_2$ between 45.0 and 52.5 mmHg during 3 O_2 conditions: $P_{ET}O_2$ at 750 mmHg (hyperoxic), 109 mmHg (normoxic, and 75 mmHg (hypoxic). They were looking for the roles of peripheral and central chemoreceptors in the ventilatory response to CO_2 under hyperoxic, normoxic, and hypoxic conditions. Breath-to-breath data were partitioned into a fast and slow ventilatory component. The influence of hyperoxia on the ventilatory response to CO_2 showed that often a fast component is present. They say this fast component is of peripheral origin. The authors argue that the fast component is due to peripheral chemoreflex loop and the slow component to the central chemoreflex loop. During normoxia and hypoxia there is, besides a peripheral component, only one central component. So apart from peripheral O_2–CO_2 interaction, there is evidence for central O_2–CO_2 interaction.

(Juan, Calverley et al. 1984)
Acute increase in P_aCO_2 in 4 men caused changes in contractility of diaphragm. Contractility was reduced when $F_{ET}CO_2$ was >7.5% CO_2. The diaphragm was influenced by acute respiratory acidosis when P_aCO_2 exceeded 54 mmHg.

(Brackett Jr, Cohen et al. 1965)
Exposed 7 resting men to 7% and then 10% CO_2 on another day in a chamber for about 90 minutes while taking serial arterial blood samples. F_IO_2 maintained at 0.21. Mean HCO_3^- increased from 24.4 to 25.9 mEq/L at 7% CO_2 to 27.3 mEq/L at 10% CO_2. Mean $[H^+]_a$ increased from 38 nM/L (pH 7.42) to 49 nM/L (pH 7.31) to 68 nM/L (pH 7.17) over the same CO_2 increase. He concludes that there is only a modest generation of HCO_3^- from endogenous buffer stores during acute respiratory acidosis. There is a reliance on the renal system for effective buffering mechanisms to defend against extracellular $[H^+]$.

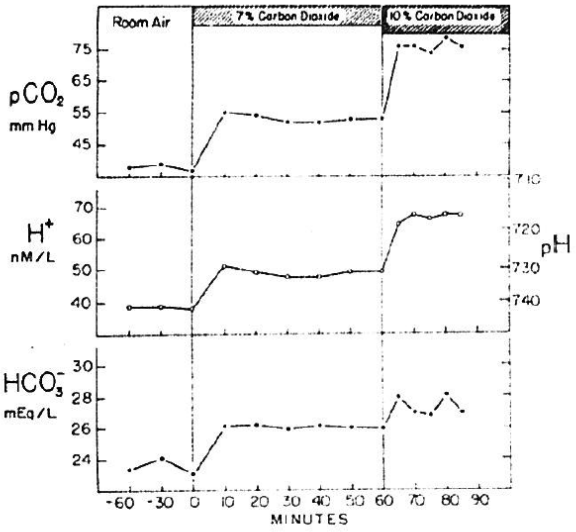

FIGURE 1. *Plasma Hydrogen Ion Concentration, Bicarbonate Concentration and pCO_2 during the Time Course of a Representative Experiment (Subject 2).*
Each point represents a single arterial-blood sample obtained at the time indicated on the abscissa.

Figure A-38

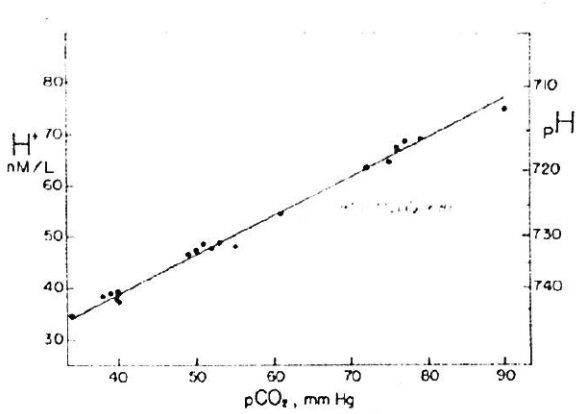

FIGURE 3. *Steady-State Relation between Hydrogen Ion Concentration and pCO_2 during Acute Hypercapnia in Normal Human Subjects.*

Each point is an average of all observations made on a single subject during the steady state at a given carbon dioxide level. Each subject is therefore represented by three points: control and 7 and 10 per cent carbon dioxide. The line drawn through the points was obtained by averaging the slopes and intercepts of the individual regression lines (see Appendix).

Figure A-39

Henderson–Hasselbalch equation for the bicarbonate buffer system is:
$pH = 6.1 + \log_{10} [HCO_3^-, mEq/L]/(0.03 \times P_aCO_2, mmHg)$, also
$pH = - \log_{10} [H^+]$ with concentration as nM/L or nEq/L, where 40×10^{-9} equivalents/L = pH of 7.40.

(Valtin 1983)
Textbook on renal physiology with special treatment of H^+ buffering and compensations for acute respiratory acidosis. Basics of buffering H^+ derived from CO_2 during exercise and hypercapnia to perserve alkaline pH near 7.40. Figures below from: Valtin H (2nd Ed.). Renal Function: Mechanisms preserving fluid and solute balance in health. Little, Brown and Company, Inc., Boston, MA, 1983, pp. 195-218.

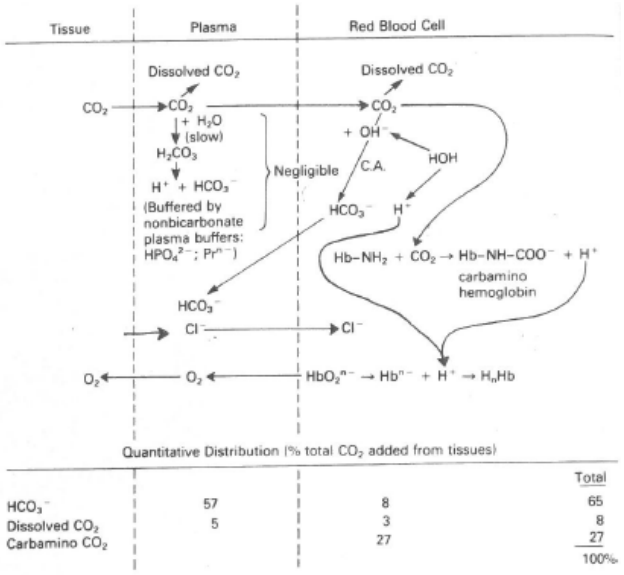

Figure A-40

Adapted from Figure 9-2. CO_2 from tissue metabolism at rest or exercise diffuses into plasma and then RBCs where CA in RBCs produces H^+ and HCO_3^-. HCO_3^- is exchanged for Cl^- through a membrane pump. CO_2 in RBC combines with Hb resulting in H^+ that reduces Hb affinity for O_2 at the tissue.

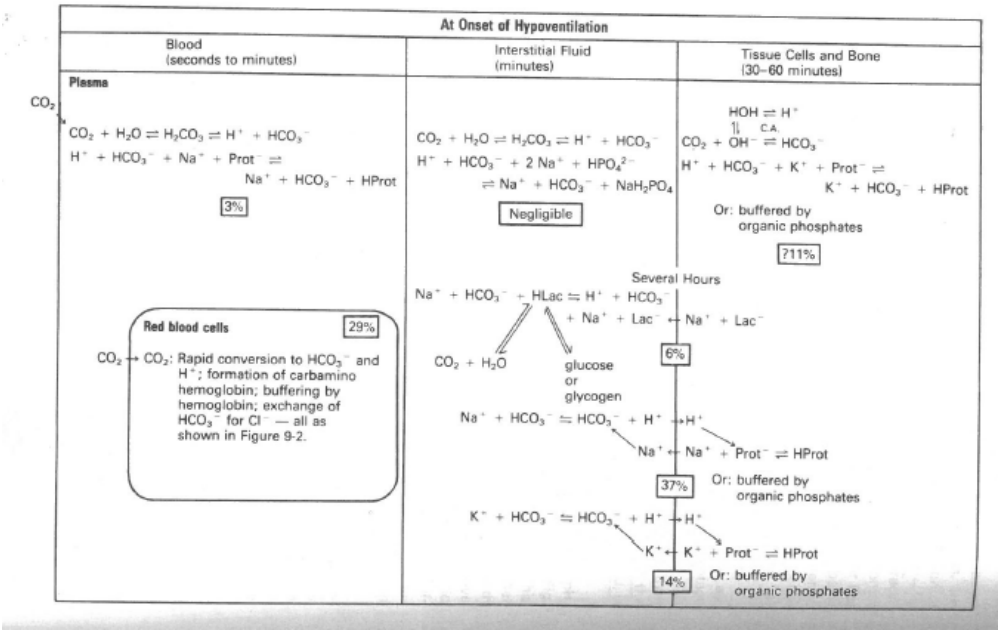

Figure A-41

Adapted from Figure 9-7. CO_2 introduced from outside the body is a volitile acid added to the body as opposed to volitile acid produced by the body. CO_2 produced by the body is removed primarily as HCO_3^-, as diagramed in Figure 9-2 above. The H^+ produced from CO_2 of hypercapnia cannot be buffered by the bicarbonate system. When H^+ is buffered by HCO_3^- the carbonic acid formed quickly dissociates back to CO_2 and H_2O. Because CO_2 and H_2O are the

starting substrates, when CO_2 is added to the body, the reaction $H^+ + HCO_3^- \leftrightarrows H_2CO_3 \leftrightarrows CO_2 + H_2O$ is being driven to the left, and it cannot simultaneosly be driven to the right as would be required if the H^+ were to be buffered by HCO_3^-. Instead, the H^+ must be buffered by the nonbicarbonate buffers available to the body, in particular Hb. A large proportion of the added volitile acid is buffered by RBCs, which rapidly convert the added CO_2 to HCO_3^- carried in the plasma.

(Klocke 1987)
Chapter 10 about CO_2 transport in arterial and venous blood. Provides CO_2 content in arterial and venous blood for a resting person as dissolved CO_2, as HCO_3^-, and as carbamate. Approximate contribution of venous blood to CO_2 transport is physical solution (6%), bound to proteins that include Hb (carbamino, 7%), and as HCO_3^- (87%).

TABLE 4. *Carbon Dioxide Transport in Blood of Resting Human*

	Arterial	Venous
Plasma		
pH	7.40	7.37
P_{CO_2}, Torr	40.0	46.0
Dissolved CO_2, mM	0.68	0.77
HCO_3^-, mM	13.48	14.41
Carbamate, mM	0.30	0.30
Total CO_2 content, mM	14.46	15.48
Erythrocytes		
pH	7.22	7.20
P_{CO_2}, Torr	40.0	46.0
Hb, g/100 ml	15.0	15.0
Hematocrit, %	45.0	45.2
O_2 content, ml/100 ml	20.22	15.22
Dissolved CO_2, mM	0.42	0.49
HCO_3^-, mM	5.65	6.23
Carbamate, mM	1.20	1.44
Total CO_2 content, mM	7.27	8.16

Figure A-42

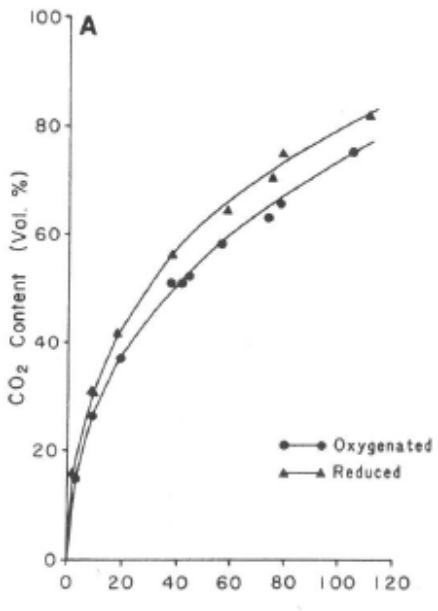

Figure A-43 PCO_2 (mmHg)

(Bacal, Beck et al. 2008)
Provides a recent (Table 22.7) that compiles assessment of exercise and mental performance as PCO_2 increases. It appears that PCO_2 <30 mmHg for durations relevant to EVA do not significantly impact physical and mental performance, at least well-learned tasks.

TABLE 22.7. Symptoms and performance effects of increased atmospheric CO_2.

PCO_2 (mmHg)	Exposure Duration	Symptoms	Exercise performance	Mental performance
≤7.5	3–4 months	No unpleasant sensations, no functional impairments	Possible (all levels)	Possible
<15	Up to 30 days	No perceived symptoms; some increase in respiratory minute volume; slight acidosis	Light and moderate; heavy is difficult	Possible
25–30	Up to 7 days	Discomfort; dyspnea, especially on exertion; respiratory minute volume elevated by 2–2.5 at rest; exposure up to 3 days leads to easily reversible changes in metabolism due to acidosis	Light possible; moderate limited; heavy extremely difficult	Possible, if well learned
35–40	up to 15 h	Dyspnea, even at rest, "heaviness" of head, vertigo; respiratory minute volume elevated by a factor of 3–4; parameters if cardiovascular function relatively stable; respiratory acidosis; impaired cerebral functioning; sleep disorders	Light limited; moderate extremely difficult	Limited, even for familiar tasks
<50	up to 3–4 h	Dyspnea, headache, vertigo, visual impairments, sleep disorders; respiratory minute volume increased by a factor of 4–5, respiratory acidosis; marked changes in cardiovascular function; tachycardia, elevated blood pressure; disruption of central nervous system function	Light limited; moderate and heavy impossible	Difficult
<60	Up to 1 h	Drastic worsening of symptoms	All types impossible	Impossible
>60, <75	None acceptable	Drastic worsening of symptoms	Precluded	Precluded

Source: Malkin [2]. Used with permission.

Figure A-44

(Wick 1966)
Ten males in an unpressurized Gemini (G2C) suit were exposed to 0%, 1%, 2%, and 3% CO_2 with inlet flow at 11 cfm either during rest on a chair (mean 450 BTU/h) or while walking at 3 mph (mean 2,050 BTU/h) on a level-grade treadmill. Subjects sat for 45 minutes to stabilize to the breathing gas condition, then over an unspecified interval various measurements with different gas sampling methods were done while still at rest or during treadmill exercise, estimated total interval from visor down <90 minutes. Arterial blood was drawn during this period. This appears to be the only instance where arterial blood from the radial artery to assess P_aCO_2 and pH was done in a suited subjects. Each subject did the 4 gas conditions at rest and during treadmill walk on separate days; 8 tests per subject.

Figure A-45 Gemini full-pressure space suit.

Table A19. Mean Respiration Data in Gemini Suit at 11 CFM at Rest and Walking at 3 mph with 0% or 3% CO_2

inlet CO_2 (%)	V_T (L^*)	f (breathes/min)	$\dot{V}_E$** (L^*/min)	metabolic rate (BTU/h)
0	0.75	11.1	8.3	460
3	0.92	15.5	14.2	490
0	1.84	17.8	32.7	2,080
3	2.46	20.8	51.7	2,020

*unclear if volume is STPD or BTPS, suspect STPD.
**$\dot{V}_E$ from $V_T \times f$
n = same 10 subjects for each row of results.

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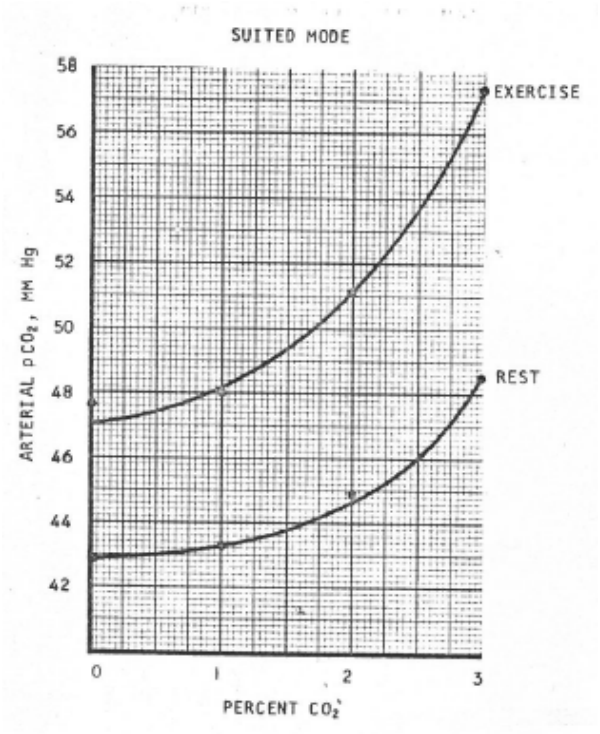


Figure A-46

Figure 4-1. P_aCO_2 as a function of suit inlet CO_2 (adapted)

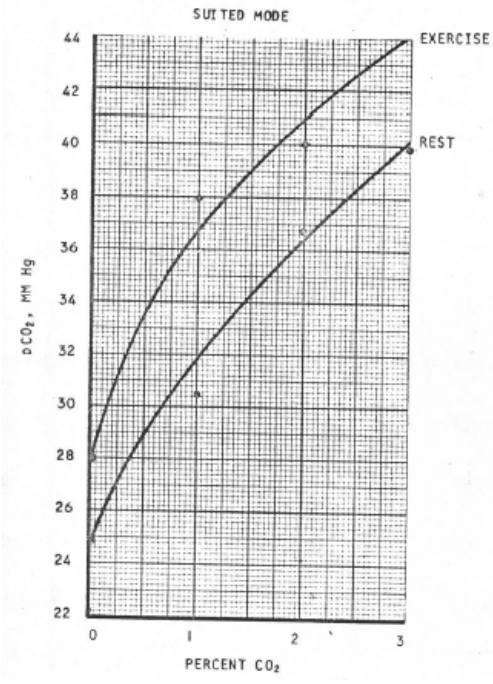


Figure A-47

Figure 4-3. Peak pCO_2 ($P_{ET}CO_2$) at oral-nasal sampler with noseclip as a function of suit inlet CO_2 (adapted).

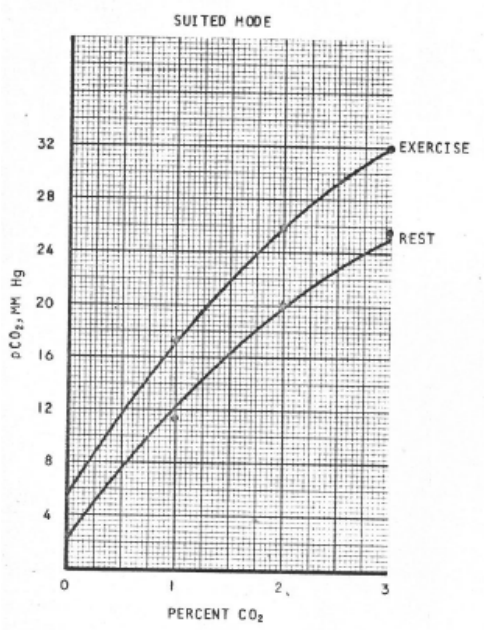


Figure A-48
Figure 4-4. Mean inspired pCO_2 (simultaneous double integration) as a function of suit inlet CO_2 (adapted).

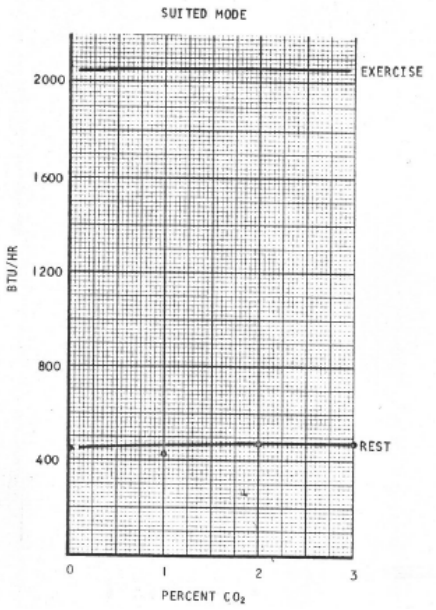


Figure A-49
Figure 4-7. Metabolic rate as a function of suit inlet CO_2 (adapted).

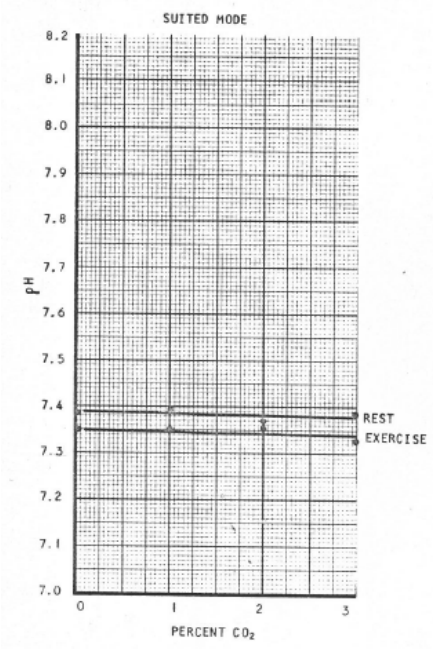


Figure A-50
Figure 4-8. Arterial pH as a function of suit inlet CO_2 (adapted).

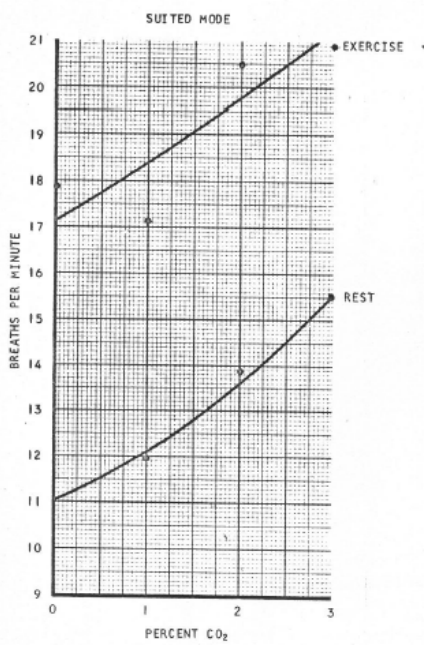


Figure A-51
Figure 4-9. Respiration rate as a function of suit inlet CO_2 (adapted).

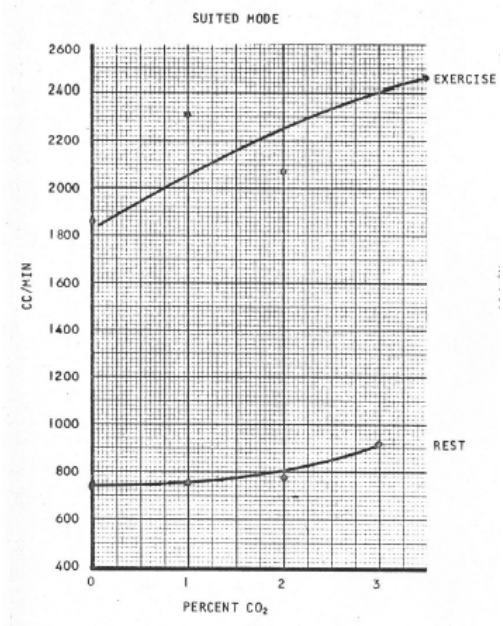


Figure A-52
Figure 4-10. Tidal volume as a function of suit inlet CO_2 (adapted). Note error on y-axis unit because V_T is a volume and not a rate.

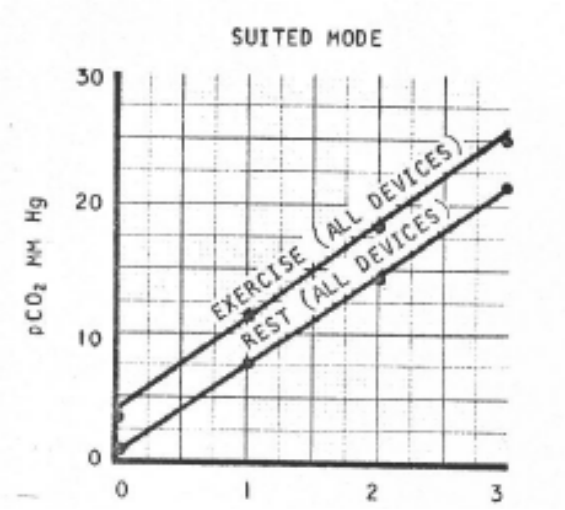
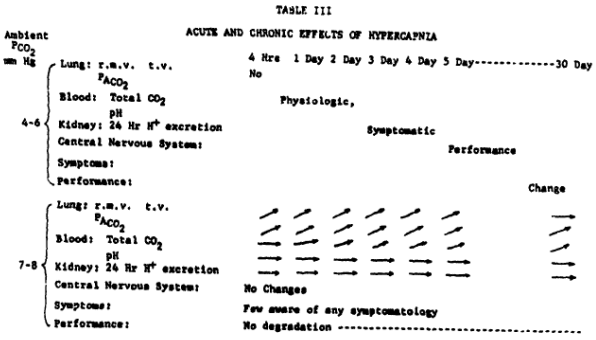


Figure A-53
Figure 4-11. Mean minimal values observed, PCO_2 at the end of inspiration (adapted). Note x-axis is percent CO_2.

(Glatte Jr and Welch 1967)
Early review of human CO_2 exposure from 1967 extending to the 1920's. Compiles his summary and conclusions from literature data into a convenient and novel tabulation (Table III) to assess acute and chronic responses in 6 major categories.



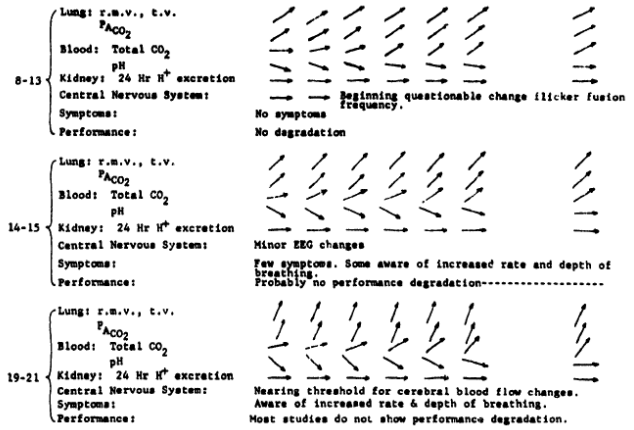


Figure A-54

(Kronenberg and Drage 1973)
Eight young men (22-30 years) and 8 healthy elderly men (64-73) were measured for ventilatory response to hypoxia and hypercapnia. Ventilatory response to hypoxia was measured as the exponential slope constant, *k*, of regression lines relating the logarithm of incremental ventilation to P_AO_2 during isocapnic progressive hypoxia. The ventilatory response to hypercapnia was measured as the slope of the regression lines relating ventilation to P_ACO_2 during rebreathing with P_AO_2 >200 mmHg. Both the ventilatory and HR response were decreased in the elderly men compared to the young men. It decreased by 51% for the hypoxic ventilatory drive and 41% for the hypercapnic ventilatory drive.

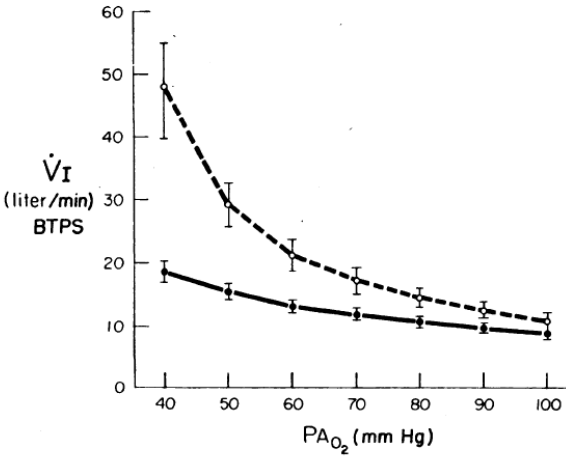


FIGURE 1 Ventilatory response to isocapnic progres hypoxia in eight young normal men (broken line) eight normal men age 64–73 (solid line). Values are m ±SEM. $P_{A_{CO_2}} = 40.9 \pm 0.9$ in the young men and 39.4 in the old men.

Figure A-55

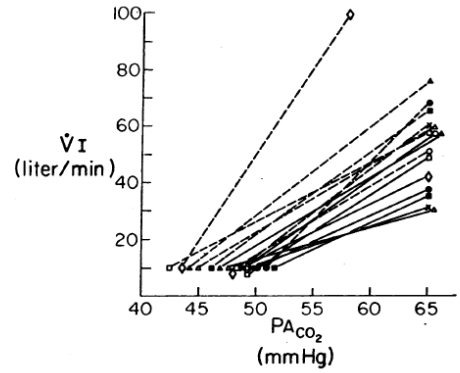


FIGURE 4 Ventilatory response to rebreathing CO_2 ($P_{A_{O_2}}$ > 200 mm Hg) in each of the young (broken lines) and old (solid lines) normal subjects. Symbols for individual subjects are the same as in Fig. 1.

Figure A-56

A-2 Hypercapnia in normobaric normoxia with rest and exercise in μG – Space Shuttle, ISS, Neurolab.

(Laurie, Vizzeri et al. 2017)
Seated, 6-degree head-down tilt (HDT), and then HDT plus 1% CO_2 were compared in in the course of 1 hour. Several measurements related to vision were collected as well as $P_{ET}CO_2$. Analysis of 1-carbon pathway genetics was performed from venous blood. The total experiment was 1 hour, so application of results to chronic μG or EVA are limited. There were no significant differences in hemodynamic variables or ocular variables between HDT and HDT plus 1% CO_2 (see Tables 1 and 2). $P_{ET}CO_2$ increased from 37.7 to 40.4 mmHg from seated to HDT and then to 42.1 mmHg for HDT plus 1% CO_2. When subjects were classified by genotype group, the change in $P_{ET}CO_2$ from seated to HDT plus 1% CO_2 was greater in 4 subjects where both genes expressed alleles previously associated with vision changes in μG (MTRR 66 AG or CG and SHMT 1420 CG), designated SNP+ and 4 subjects where 1 gene or no genes had alleles associated with vision changes, designated SNP-. The change in $P_{ET}CO_2$ from seated to HDT plus 1% CO_2 was significantly greater in SNP+ than SNP- (see Figure 6a). Separation of subjects on the basis of their MTRR 66 genotype suggests that a protective factor against elevated $P_{ET}CO_2$ (surrogate for P_aCO_2) is the AA genotype (see Figure 7).

Table 1. Hemodynamic variables.

Variable	Seated	HDT	HDT+CO_2
Stroke volume, mL	81.9 (71.3–92.6)	101.2 (90.5–111.9)[1]	102.5 (91.8–113.1)[1]
Heart rate, bpm	58 (52–65)	48.3 (42–55)[1]	48 (41–55)[1]
Cardiac output, $mL \cdot min^{-1}$	4631 (4354–4910)	4816 (4539–5095)	4809 (4532–5088)
Mean arterial pressure, mmHg	89 (82–96)	87 (80–94)	88 (80–95)
Systolic blood pressure, mmHg	116 (108–125)	124 (115–133)	123 (115–132)
Diastolic blood pressure, mmHg	73 (66–81)	69 (61–76)	72 (64–79)
Pulse pressure, mmHg	43 (36–51)	55.5 (48–63)[1]	51.4 (44–59)[1]
Common carotid artery flow, $mL \cdot min^{-1}$	680.8 (605.5–756.0)	630.53 (555.3–705.7)[1]	669.3 (594.1–744.5)
Mean MCA_v, $cm \cdot sec^{-1}$	52.2 (45.63–58.70)	62 (55.51–68.58)[1]	62 (55.55–68.62)[1]
Mean MCA_v, % change from seated	–	20.1 (12.1–28.2)	19.7 (11.6–27.7)

HDT, head-down tilt; MCA, middle cerebral artery. Values are mean (95% CI).
[1] $P < 0.05$ versus Seated. There were no significant differences between HDT and HDT + CO_2.

Figure A-57

Table 2. Ocular variables.

Variable	Seated	HDT	HDT+CO_2
Central Macular Thickness, μm	274.2 (265.6–282.8)	273.4 (264.7–282.0)	274.1 (265.5–282.8)
Average RNFL Thickness, μm	104.4 (97.1–111.7)	103.9 (96.6–111.2)	103.5 (96.2–110.8)
BMO area, mm^2	2.09 (1.93–2.25)	2.11 (1.95–2.27)[1]	2.09 (1.93–2.26)
BMO-MRW, μm	365.1 (337.3–392.9)	363.8 (336.0–391.6)	362.7 (334.9–390.5)
Axial Length, mm	24.44 (23.42–25.46)	24.52 (23.50–25.54)	24.54 (23.52–25.57)
ONSD, mm	6.23 (5.71–6.75)	6.58 (6.06–7.10)[1]	6.66 (6.14–7.18)[1]
Choroid Thickness, μm	348.1 (291.1–405.2)	361 (304.0–418.0)[1]	356.7 (299.6–413.7)[1]
Visual Acuity, logMAR	0.10 (−0.11–0.31)	0.14 (−0.06–0.35)	0.09 (−0.12–0.30)

BMO, Bruch's membrane opening; MRW, minimum rim width; ONSD, optic nerve sheath diameter; RNFL, retinal nerve fiber layer. Values are mean (95% CI).
[1] $P < 0.05$ versus Seated. There were no significant differences between HDT and HDT + CO_2.

Figure A-58

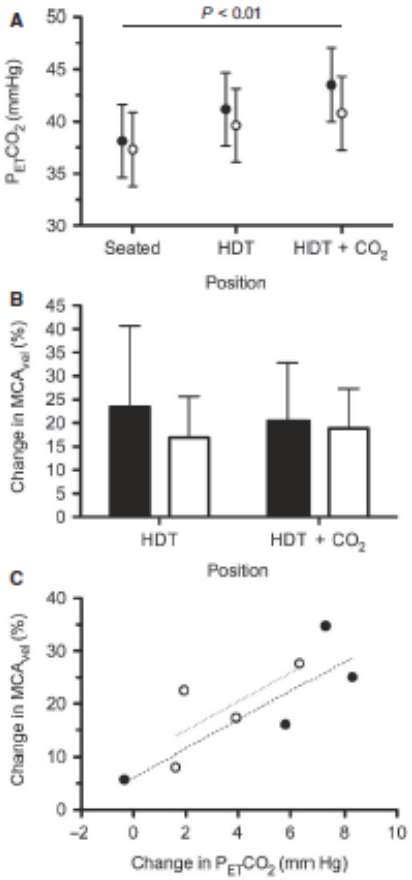


Figure 6. (A) $P_{ET}CO_2$ for SNP+ (filled) and SNP− (open) groups during each condition. (B) Change in MCA_{vel} compared to Seated for SNP+ (filled, n = 4) and SNP− (open, n = 4) groups during head-down tilt (HDT) and HDT + CO_2. (C) Change in MCA_{vel} as a function of the change in $P_{ET}CO_2$ 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.

Figure A-59

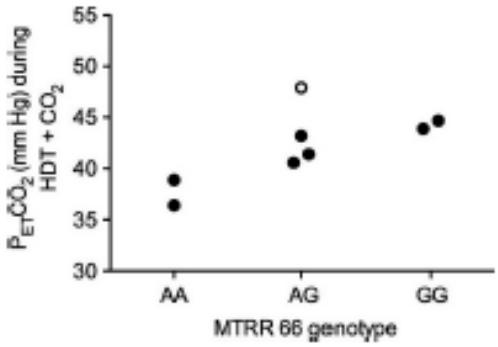


Figure 7. $P_{ET}CO_2$ during HDT + CO_2 by MTRR 66 genotype. The subject indicated by the open circle had a B-12 deficiency which could produce a similar phenotype as the GG subjects.

Figure A-60

(Kurazumi 2018)
Fifteen men had 10-minute exposures to 10-degree HDT with and without 3% CO_2. Data were collected before and after the HDT. Breathing gas was normoxic (21% O_2, 3% CO_2, and 76% N_2). They tested 4 conditions: air breathing plus supine position, air breathing plus HDT, CO_2 breathing plus supine, and CO_2 breathing plus HDT. ICP was computed with 2 methods (see their Methods). The addition of 3% CO_2 had no significant effect on increasing ICP during the HDT.

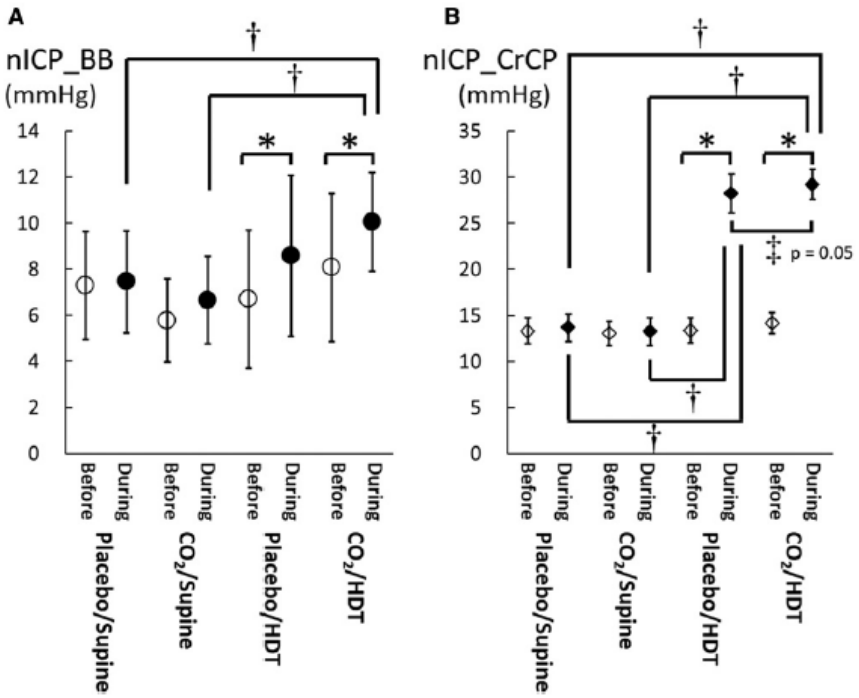


Fig. 1. The mean values of A) nICP_BB and B) nICP_CrCP before and during the interventions. Placebo/Supine, exposure to air in the supine position; CO_2/Supine, exposure to 3% CO_2 in the supine position; Placebo/HDT, exposure to air in a −10° HDT position; CO_2/HDT, exposure to 3% CO_2 in a −10° HDT position. BL, baseline; IV, intervention. Data shown as mean and SD. *$P < 0.05$ compared to before intervention; †$P < 0.05$ compared to other interventions; ‡$P = 0.05$ between the Placebo/HDT and CO_2/HDT interventions.

Figure A-61

(Marshall-Goebel 2018)
Six men had 26 h exposures to 12-degree HDT with and without 0.5% CO_2. The right internal jugular vein was indirectly measured in 4 places for cross-sectional area and contained blood volume (computed) after 26 hours. The addition of 0.5% CO_2 made no contribution to the measured changes.

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

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

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

Figure A-62

(Marshall-Goebel, Mulder et al. 2017)
Nine men had 3.5 h exposures to 12-degree HDT with and without 1% CO_2. ICP was measured with a transcranial Doppler-based noninvasive ICP meter. The addition of 1% CO_2 had no further effect on ICP or intraocular pressure.

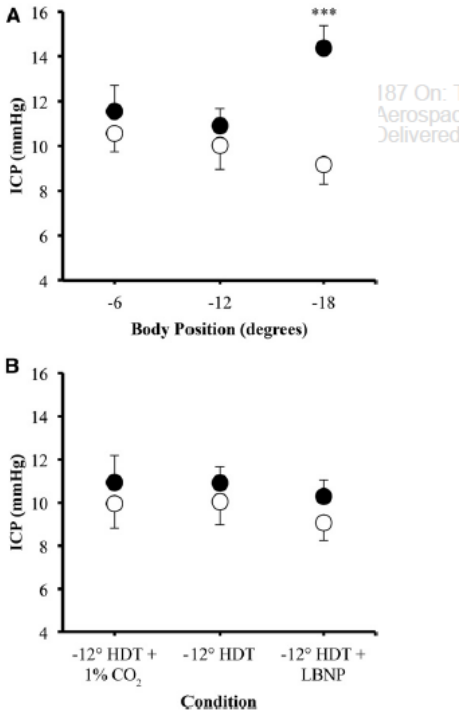


Fig. 1. Intracranial pressure (ICP) before each head-down tilt (HDT) condition at 0° baseline (white circles) and after 3.5 h in the HDT position (black circles) during (A) various degrees of HDT and (B) with the addition of a 1% CO_2 environment and -20 mmHg lower body negative pressure (LBNP) during -12° HDT. Data shown as Mean ± SEM, *** $P < 0.001$

Figure A-63

Table I. The Intraocular-Intracranial Pressure Difference at Baseline (0°) and After 3.5 H Head-Down Tilt (HDT) During Various Conditions.

	INTRAOCULAR-INTRACRANIAL PRESSURE DIFFERENCE (mmHg)	
CONDITION	BASELINE	HDT
-6°	4.7 ± 1.4	4 ± 1.7
-12°	6.3 ± 1.4	7.7 ± 1.4
-12° + 1% CO_2	5 ± 1.8	4.7 ± 1.7
-12° + -20 mmHg LBNP	6.1 ± 1.2	7.4 ± 1.5
-18°	6 ± 1.8	4.5 ± 1.7

Data shown as Mean ± SEM; LBNP = lower body negative pressure

Figure A-64

(Zwart, Gibson et al. 2012)
Some astronauts are genetically predisposed to respond better in μG given the additional stress of adaptation to μG, which includes fluid shifts and mild hypercapnia. Metabolic predisposition can modify intracranial pressure, vascular reactivity, etc., leading to vision changes in some. See summary under #13.

(James, Meyers et al. 2011)
The authors confront the difficulty in defining unacceptable risk of acute hypercapnia. They could not prospectively define an adverse effect of hypercapnia. The incidence of headache on ISS associated with PCO_2 near the time of headache was one response variable that could be evaluated. Their analysis concluded that the probability of headache is <1% if PCO_2 is <2.3 mmHg, but conclude that headache on ISS is not a serious medical concern.

(Law, Van Baalen et al. 2014)
Compilation of previous work from 2010 (Law, Watkins et al. 2010) and 2011 (James, Meyers et al. 2011) to systematically evaluate hypercapnia with a common symptom of headache in μG. But not all headache can be attributed to just hypercapnia. The fundamental question is whether there is a greater sensitivity or greater consequence of hypercapnia in μG. This is still an open question. Analysis of symptom records and associated chronic PCO_2 levels on ISS provided enough data to perform logistic regression. Their analysis concluded that the probability of headache is <1% if PCO_2 is <2.5 mmHg,

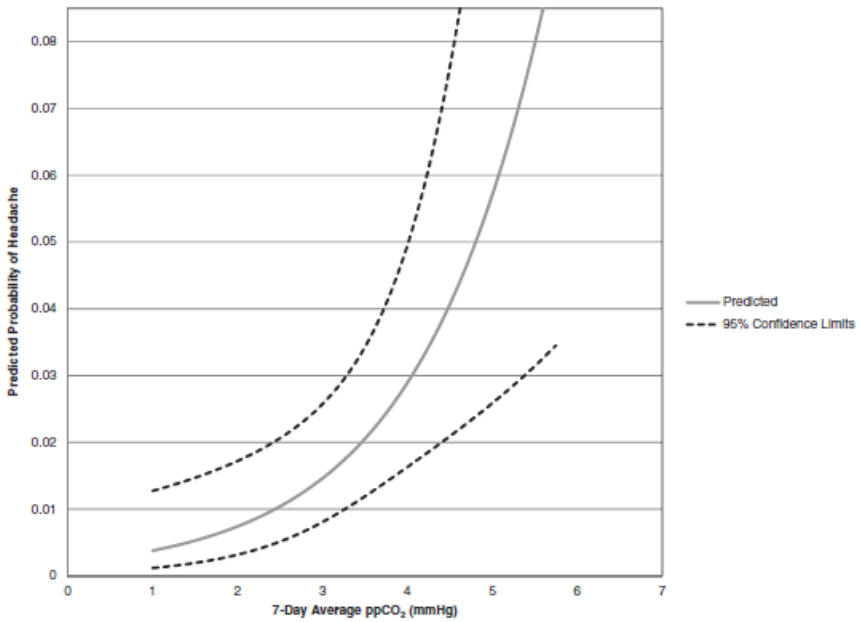


FIGURE 2. Predicted probability of headache on the basis of average 7-day CO_2 levels.

Figure A-65

(Storm and Giannetta 1974)
Two weeks of bed rest with PCO_2 of 30 mmHg had no detrimental effect on complex tracking performance, eye-hand coordination, or problem solving ability. This was the first research to combine hypercapnia with bed rest. 4 groups of 6 subjects were tested under 4 conditions:

Group 1 breathing air without bed rest, Group 2 breathing air with bed rest, Group 3 breathing CO_2 without bed rest, and Group 4 breathing CO_2 with bed rest. Hypercapnia or simulated μG either alone or combined had no significant effect on complex tracking performance, eye-hand coordination, or problem solving ability. A learning effect through time was present in all groups but there was no experimental treatment effect on the repetitive psychometric measures.

TABLE I. MEAN NUMBER OF CORRECT RESPONSES TO RPM TESTS.

RPM Test	Subject Group	Baseline Week 2	Experimental Week 3	Experimental Week 4	Recovery Week 5
Aiming	1	102.8	113.5	110.5	119.6
	2	94.0	108.1	109.6	117.5
	3	112.9	112.6	124.0	125.9
	4	115.8	124.5	129.6	139.0
	Mean	106.4	114.7	118.4	125.5
Flexibility of Closure	1	14.5	18.7	19.5	20.2
	2	12.4	13.2	13.9	16.5
	3	17.3	18.8	21.5	24.0
	4	16.9	18.7	20.7	23.1
	Mean	15.3	17.4	18.9	21.0
Perceptual Speed	1	35.9	37.2	38.3	39.6
	2	39.6	37.6	41.5	43.3
	3	46.5	46.3	52.7	52.7
	4	40.8	39.5	43.7	45.1
	Mean	40.7	40.2	44.0	45.2
Visualization	1	47.5	51.4	51.9	55.3
	2	47.7	49.6	49.2	55.0
	3	55.0	54.7	55.6	60.5
	4	52.8	53.0	54.1	60.1
	Mean	50.7	52.2	52.7	57.7
Number Facility	1	38.6	39.8	41.7	42.7
	2	34.9	35.5	38.2	38.6
	3	33.4	34.0	36.0	36.1
	4	32.9	33.1	36.0	37.2
	Mean	34.9	35.6	38.0	38.7
Speed of Closure	1	37.1	38.1	38.1	46.2
	2	33.7	33.3	32.8	39.2
	3	38.6	40.7	41.8	50.9
	4	36.9	37.6	38.4	45.5
	Mean	36.6	37.4	37.8	45.4

Figure A-66 Note: Group 1 breathing air without bed rest, Group 2 breathing air with bed rest, Group 3 breathing CO_2 without bed rest, and Group 4 breathing CO_2 with bed rest.

(Hughson, Yee et al. 2016)
Nine ISS astronauts had $P_{ET}CO_2$ measured from a seated position (preflight) and in μG. Mean inspired CO_2 increased from 0.6 mmHg for preflight to 3.2 mmHg inflight while $P_{ET}CO_2$ increased from 36.0 mmHg for preflight to 42.1 mmHg inflight. The author concludes that ventilation mechanics due to cephalad shift of organs may result in hypoventilation, or astronauts breathed ambient CO_2 on ISS, or that the ventilatory response to CO_2 is suppressed in the ISS μG environment. Because the inflight data was compared to seated preflight data, the author does concede that a part of the 6 mmHg difference in $P_{ET}CO_2$ may be due to a seated posture versus a supine posture.

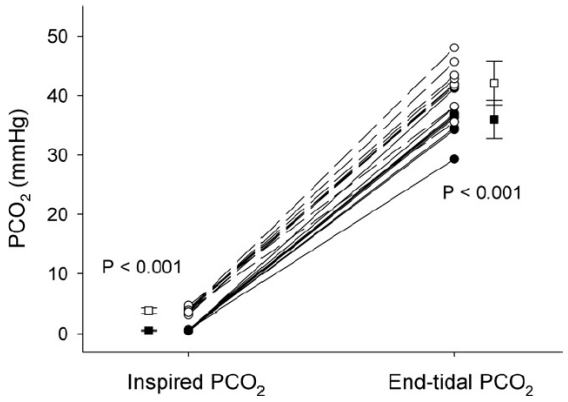


Fig. 2. Individual values for inspired and end-tidal P_{CO_2} are shown for preflight conditions (black circles, solid lines) and in flight (white circles, dashed lines). Offset symbols (squares) with error bars represent mean ± SD. Statistical *P*-values are for comparisons between preflight and in flight.

Figure A-67

(Law, Watkins et al. 2010)
Operational Space Shuttle and ISS experience with management of PCO_2, and descriptions of symptoms associated with particular PCO_2 exposures. The report is a valuable compilation of exposure limits from several organizations and covers both spacecraft and space suit CO_2 limits, as of 2010.

Table 1. Physiological tolerance time for various CO_2 concentrations and acute health effects of high concentrations of CO_2.

PHYSIOLOGICAL TOLERANCE			ACUTE HEALTH EFFECTS	
$ppCO_2$		Maximum Exposure Limit (min)	Duration of Exposure	Effects
mm Hg	%			
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.

Figure A-68 Note: Data applies to normobaric resting subjects breathing air. Application of these results is to hypobaric resting and active astronauts breathing 100% O_2.

Table 2. Key CO_2 concentrations discussed in this paper. 1% = 7.5 mm Hg.

% CO_2	$PPCO_2$ (mm Hg)	Note [Reference]
0.03%	0.23	Ambient outdoor CO_2 level on Earth
	2	Relief of symptoms on Expedition 6 [1]
0.3-0.7%	2.3-5.3	Typical spacecraft CO_2 concentrations [2]
0.5%	3.4	**New NIOSH Recommended Exposure Limit** [3]
	>4	Lethargy, malaise, listlessness, and fatigue on Expedition 6 [1]
	4.9	Derived threshold corresponding to 90% negative predictive value for CO_2-related symptoms [4]
	5	Safe chronic CO_2 level in terms of performance [5] **Empiric threshold established by flight surgeons**
	2.7 to <6	Headaches on STS-112/ISS-9A [1]
	Up to 7.5	Headache on STS-113/ISS-11A [1]
1%	7.5	**NIOSH Permissible Exposure Limit** [6]
	8	**EMU EVA termination limit** with baseline Caution and Warning System [7]
1.2%	9	Slight performance decrement after chronic exposure [5]
	10	**Orlan EVA termination limit** with crew at rest [8]
	12.4	**EMU EVA termination limit** with enhanced Caution and Warning System [7]
1.99%	14.9	Maximum CO_2 concentration on Apollo 13 [9]
2%	15	Headache, exertional dyspnea start [10] **ISS Off-Nominal $ppCO_2$ Level** [11]
	20	**ISS Emergency $ppCO_2$ Level** [11] **Orlan EVA termination limit** [8]
3%	23	Sweating, resting dyspnea start [10] **NIOSH Short-Term Exposure Limit** [3]
4%	30	**NIOSH Immediately Dangerous to Life or Health limit** [3]
4-5%	30-38	Dizziness, lethargy, uncomfortable dyspnea start [10]

Figure A-69 Note: These PCO_2 limits established under normobaric (1 ATA) condition will have larger P_ICO_2 than when the same PCO_2 limits are applied under hypobaric (EVA) conditions. The difference in P_ICO_2 for the same PCO_2 at different ambient pressures (P_B) is due to the presence of constant water vapor partial pressure (PH_2O = 47 mmHg) at reduced total pressures; $P_ICO_2 = (P_B – 47) \times F_ICO_2$, $F_ICO_2 = P_ICO_2/(P_B – 47)$ or $F_ICO_2 = PCO_2/P_B$, and $PCO_2 = P_B \times [P_ICO_2/(P_B – 47)]$.

(Cronyn, Watkins et al. 2012)
Previous ISS limit for chronic PCO_2 of 5.3 mmHg has been challenged based on reports of CO_2-linked symptoms (headaches and lethargy), but living in μG is multivariable. A hypothesis is that adaptation to μG may increase your sensitivity to low PCO_2, but no evidence at present. It is equally likely that crew are exposed to high local CO_2 concentrations that elicit symptoms, which is understandable. The main conclusions are to provide additional monitoring of PCO_2 to understand better the CO_2 exposure and to conduct dedicated research on hypercapnia in μG. There was no discussion about CO_2 and EVA.

(Michael and Marshall-Bowman 2015)
Review of factors that increase intracranial pressure, including hypercapnia combined with μG adaptations, fluid shifts, changes in endothelium, acute exposure to high PCO_2, and chronic exposure to 2–5 mmHg on ISS.

(Prisk, Elliott et al. 2000)
Prisk measured the hypoxic and hypercapnic ventilatory responses before, during, and after 16 days of spaceflight in 5 astronauts. In both μG and in pre-flight supine position the hypoxic ventilatory response was reduced compared to standing. During the hypercapnic ventilatory response test the ventilation at PCO_2 of 60 mmHg was not significantly different in μG and in pre-flight supine position compared to standing. The authors suggest the increase in blood pressure in μG and in supine body position affected the carotid baroreceptors, which modified there response to hypoxia but not hypercapnia.

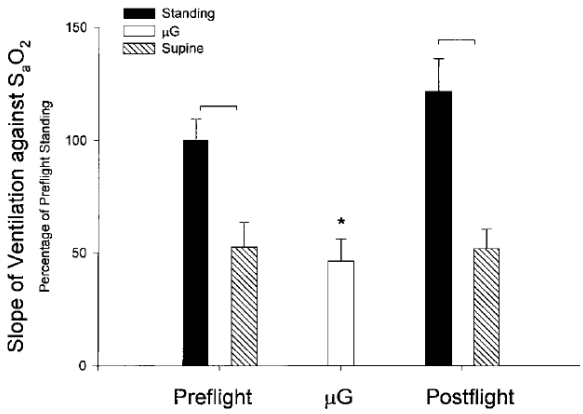


Fig. 2. Slope of ventilatory response to hypoxia calculated as rise ventilation resulting from a decrease in Sa_{O_2}. Data are normalized each subject's preflight standing control. Error bars, SE. Bracke between adjacent bars show $P < 0.05$. $^*P < 0.05$ compared wi preflight study.

Figure A-70

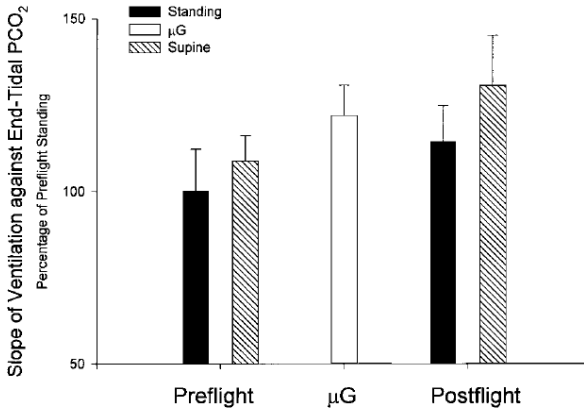


Fig. 4. Slope of ventilatory response to carbon dioxide. Data a normalized to each subject's preflight standing control. Err bars, SE.

Figure A-71

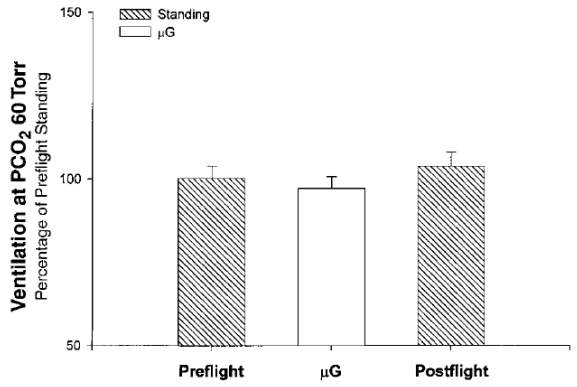


Fig. 6. Ventilation calculated at a P_{CO_2} of 60 Torr from ventilatory response to CO_2 in Life and Microgravity Spacelab crew. Note that that no supine data were collected in these subjects. Error bars, SE.

Figure A-72

A-3. Hypercapnia in normobaric hypoxia with rest and exercise in 1G.

(Fan and Kayser 2013)
See summary under #1.

(Dahan, DeGoede et al. 1990)
See summary under #1.

(Nielsen and Smith 1952)
Provided early evidence on the ventilatory response due to interactions between hypercapnia and hypoxia and hypercapnia and hyperoxia. $\dot{V}_E$ dramatically increases, steep slope on $\dot{V}_E$ versus P_ACO_2 plot, in hypercapnic hypoxia and less so in hypercapnic hyperoxia.

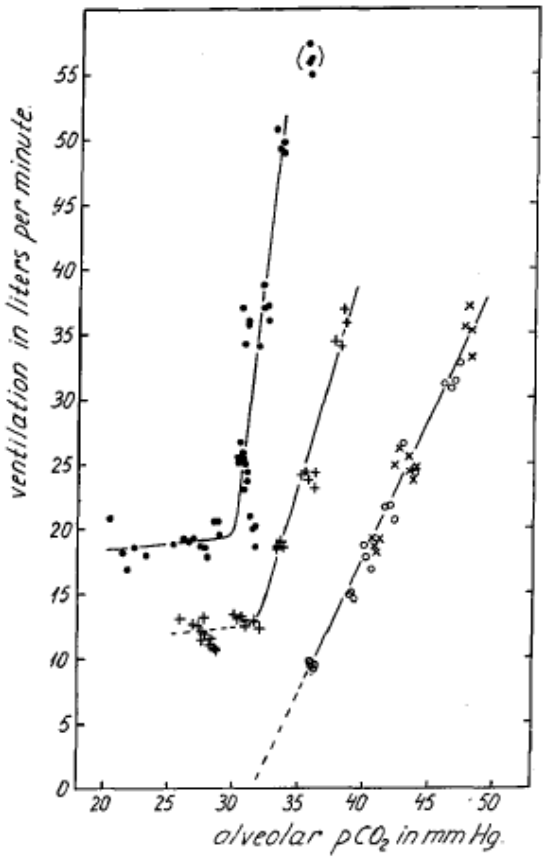


Fig. 4. Subject P. G. Pulmonary ventilation (37°, prevailing bar. pressure, saturat.) in relation to alveolar pCO_2.

● alveolar pO_2 36.9 ± 1.3 mm Hg
\+ » » 47.2 ± 1.5 » »
○ » » 110.3 ± 1.9 » »
× » » 168.7 ± 2.1 » »

Figure A-73

(Ainslie and Poulin 2004)
The acute hypoxic ventilatory response (AHVR) is enhanced by hypercapnia. Ainslie examines the acute effects of high, normal, and uncontrolled $P_{ET}CO_2$ on ventilation, MCA blood flow, and MAP with hyperoxic and hypoxic male subjects. Hypoxia is one stimulus and is combined with hypercapnia. $P_{ET}O_2$ was held at 8 steps between 300 and 45 mmHg and subjects were either hypercapnic (7.5 mmHg above subject normal), isocapnic (1.0 mmHg above subject normal), or poikilocapnic ($P_{ET}CO_2$ freely changed). Slopes of ventilation, MCA, and MAP with S_pO_2 were greater in hypercapnia than the other 2 conditions. Hypoxia plus hypercapnia linked individual sensitivities of ventilation and CBF. Between-subject variability in the AHVR is linked to variability in CBF and MAP responses to hypoxia, which in-turn are sensitive to hypercapnic responses between subjects.

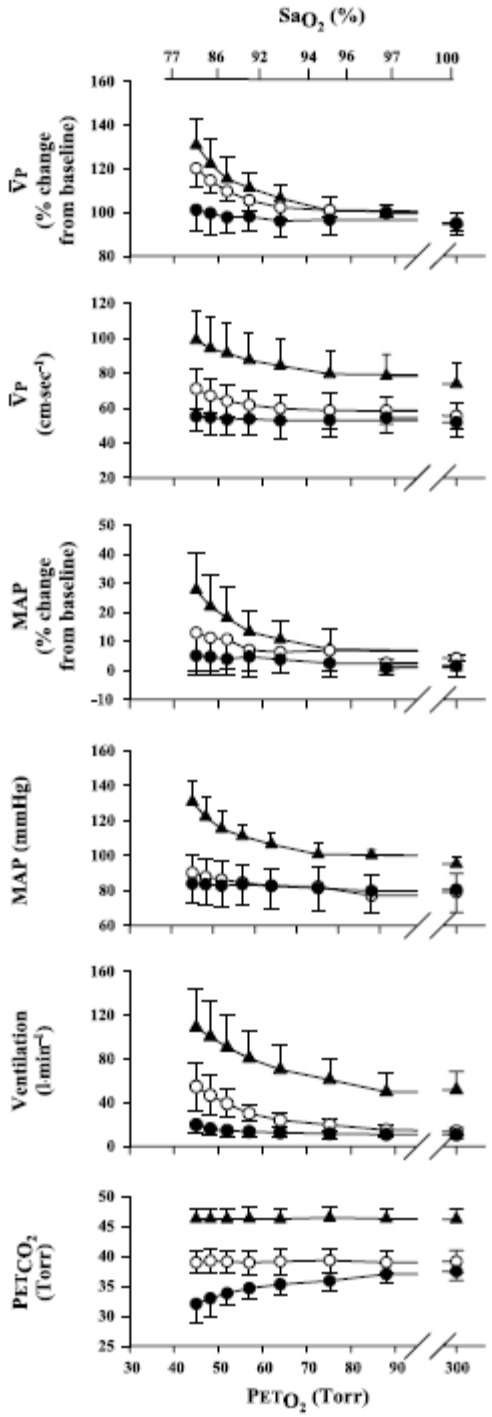


Fig. 2. Ventilatory, peak cerebral blood flow velocity ($\bar{V}_p$), and mean arterial blood pressure (MAP) responses to acute hypercapnic, isocapnic, and poikilocapnic hypoxia. Data are combined from ascending and ascending conditions. Values are means ± SD; $n = 9$. ▲, Hypercapnic protocol; ○, isocapnic protocol; ●, poikilocapnic protocol.

Figure A-74

(Wang, Yee et al. 2015)
See summary under #4.

A-4 Hypercapnia in normobaric hyperoxia with rest and exercise in 1G.

(Bishop, Lee et al. 1999)
Twelve males walked in a Launch and Entry Suit pressurized at 0, 0.5, 1.0, and 1.5 psid above ambient sea level pressure with visor closed and breathing 100% O_2. PCO_2 during inspiration was measured at the end of a resting 6 minute prebreathe followed by 2 minutes of standing and 5 minutes of walking at 1.56 m/sec (3.5 mph). After a 10 minute seated recovery, the 5 minute walk was repeated with visor open so as to measure $\dot{V}O_2$. Suit CO_2 rapidly increased to over 4% during walking and 8 of 12 were not able to complete the 5-minute walk. Aerobic fitness was a factor to complete the 5-minute walk (see summary under #13).

TABLE I. MEAN (±SE) INSPIRED (MINIMUM) %CO_2 FOR THE LAST MIN (MIN 6) OF VISOR-CLOSED PRE-BREATHE (PB), END OF STANDING (MIN 2), AND AT 3 MIN AND 5 MIN (END) OF WALKING AT 1.56 M · S^{-1}, UNDER EACH G-SUIT INFLATION.

G-Suit Inflation	End of PB (%)	End of Stand (%)	3 Min of Walk (%)	End of Walk (%)
0 psi	2.10 ± 0.07	2.06 ± 0.08	3.75 ± 0.15	4.48 ± 0.18 (n = 11)
0.5 psi	2.12 ± 0.08	2.07 ± 0.09	3.99 ± 0.15	4.69 ± 0.19 (n = 10)
1.0 psi	2.25 ± 0.19	1.94 ± 0.09	4.47 ± 0.20*† (n = 11)	4.65 ± 0.21 (n = 4)
1.5 psi	2.10 ± 0.06	1.99 ± 0.12	4.53 ± 0.20*† (n = 8)	4.90 ± 0.21 (n = 4)

Except as indicated, n = 12. * Significantly greater ($p \leq 0.05$) than egress walking at 0.0 psi. † Significantly greater ($p \leq 0.05$) than egress walking at 0.5 psi.

Figure A-75

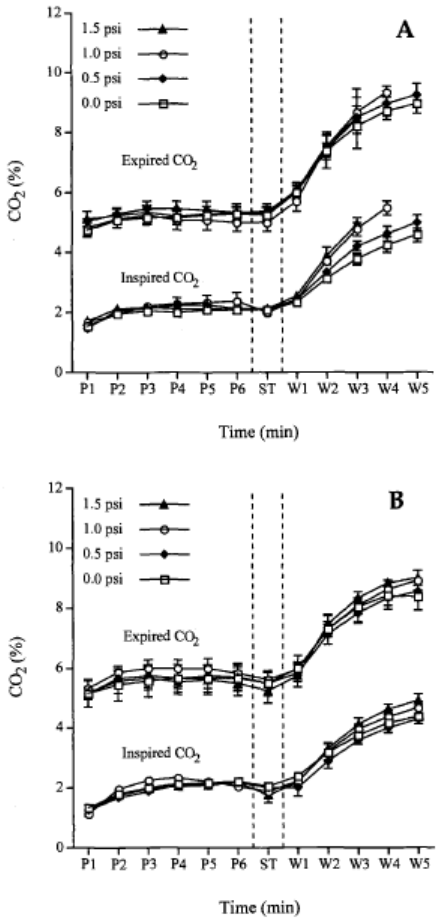


Fig. 2. Mean (± SE) %CO_2 inspired and expired for each min for each G-suit inflation in Non-finishers (A; n = 8) and Finishers (B; n = 4). P is pre-breathe sitting, ST is stand and W is walk. Inspired CO_2 at 3 min was significantly ($p < 0.05$) greater across all subjects at G-suit inflations of 1.0 and 1.5 psi than at G-suit inflations of 0.0 and 0.5 psi.

Figure A-76

(Lambertsen, Hall et al. 1963)
Early work on increased $\dot{V}_E$ in response to hypercapnia in hypoxia and hyperoxia. See summary under #7.

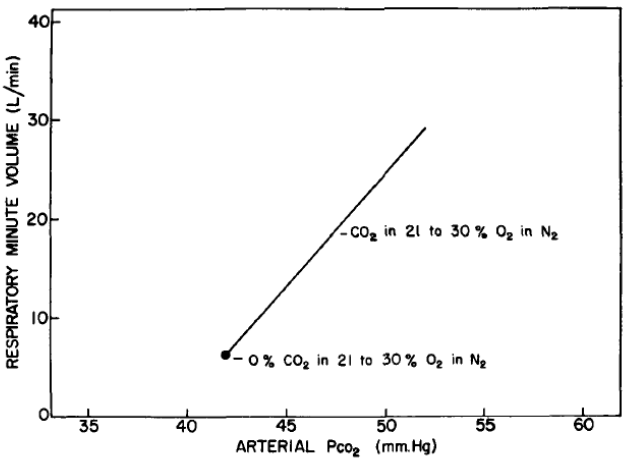


FIGURE 1. This diagram represents the regression of respiratory minute volume on arterial P_{CO_2} in three groups of subjects (mean values in 27 subjects) studied in three different laboratories.[1] The average slope of the ventilatory response to P_{CO_2} elevation ($\Delta\dot{V}/\Delta P_{CO_2}$) is approximately 2.27 l./min. This is probably lower than would be expected in the same subjects at a fixed alveolar P_{O_2} of 100 mm. Hg, since CO_2-induced hyperventilation leads to increased alveolar P_{O_2},[3] and increased alveolar P_{O_2} leads to a decrease in the slope of the respiratory response to CO_2.[3,4]

Figure A-77

(Henning, Sauter et al. 1990)
See summary under #1.

(Sheehy, Kamon et al. 1982)
Breathing 4% (30 mmHg) or 5% (38 mmHg) CO_2 in air or 50% O_2 with 80% $\dot{V}O_2$max treadmill exercise for 10 minutes and 6 minutes of recovery showed no difference between baseline in reaction time, rotor pursuit, short-term memory, and reasoning ability.

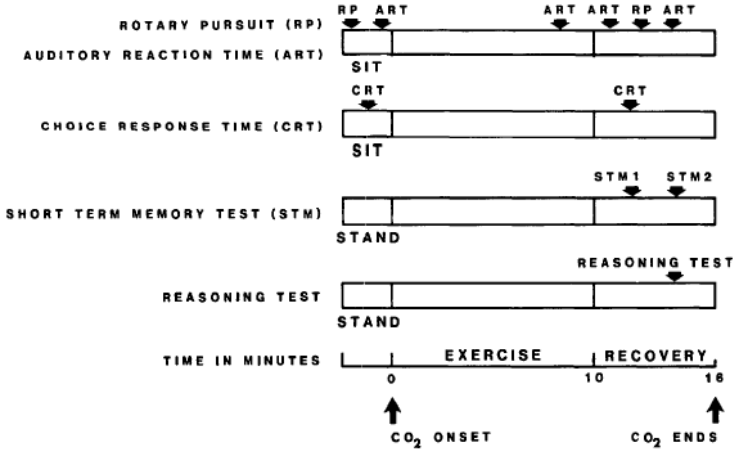


Figure 1. *Graphical description of the time sequence for each of the administered tests.*

Figure A-78

TABLE 5

Means and Standard Deviations for the Number of Statements Completed, Errors per Session, and the Average Response Time per Question (in Seconds)

	Control	*4% CO_2 21% O_2*	*5% CO_2 21% O_2*	*4% CO_2 50% O_2*	*5% CO_2 50% O_2*
Statements Completed	51.50 ± 9.50	42.00 ± 14.7	41.00 ± 11.60	51.50 ± 14.0	43.75 ± 13.30
Number of Errors per Session	1.25 ± 0.96	1.50 ± 0.58	2.00 ± 1.40	2.00 ± 0.82	2.75 ± 2.20
Average Response Time per Question	4.78 ± 0.90	6.36 ± 2.60	6.29 ± 2.10	4.94 ± 1.40	5.80 ± 1.50

Figure A-79 Note: Figure A-77 shows typical presentation of results for several psychomotor and mental performance tests. Note that neither 4% nor 5% CO_2 in air or 50% O_2 had an effect on reasoning tests.

(Vercruyssen 2014)
4% CO_2 in 50% O_2 for 1 hour in resting subjects may slow information processing in the stimulus encoding stage or the response selection stage, or both. Results show increased information processing time by impairing the response selection stage of processing, plus other metrics of information processing.

(Vercruyssen and Kamon 1984)
Six tests about cognition and psychomotor performance did not change while breathing 2% CO_2 in 50% O_2, or just 50% O_2 in subjects working at 75% $\dot{V}O_2$max. The use of 50% O_2 was justified to minimize cerebral hypoxia despite fluctuations in brain blood flow caused by changes in PCO_2.

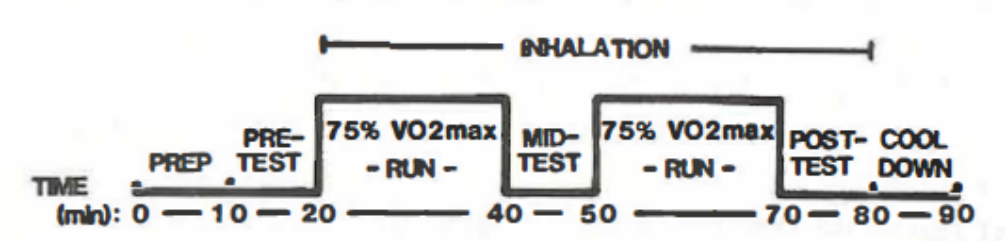


Figure 1. Testing protocol for each testing session. During the 60-min inhalation period subjects breathed either room air (control), high oxygen (50% O2), or high carbon dioxide (2% CO2, 50% O2).

Figure A-80

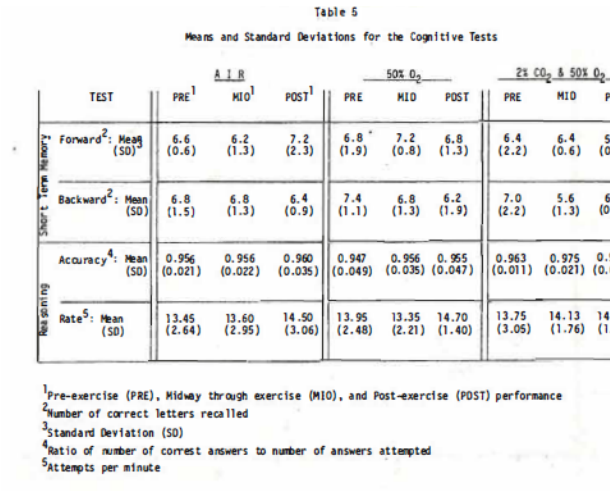


Table 5

Means and Standard Deviations for the Cognitive Tests

	TEST	AIR PRE[1]	AIR MID[1]	AIR POST[1]	50% O_2 PRE	50% O_2 MID	50% O_2 POST	2% CO_2 & 50% O_2 PRE	2% CO_2 & 50% O_2 MID	2% CO_2 & 50% O_2 P
Short Term Memory	Forward[2]: Mean (SD)[3]	6.6 (0.6)	6.2 (1.3)	7.2 (2.3)	6.8 (1.9)	7.2 (0.8)	6.8 (1.3)	6.4 (2.2)	6.4 (0.6)	5 (0
	Backward[2]: Mean (SD)	6.8 (1.5)	6.8 (1.3)	6.4 (0.9)	7.4 (1.1)	6.8 (1.3)	6.2 (1.9)	7.0 (2.2)	5.6 (1.3)	6 (0
Reasoning	Accuracy[4]: Mean (SD)	0.956 (0.021)	0.956 (0.022)	0.960 (0.035)	0.947 (0.049)	0.956 (0.035)	0.955 (0.047)	0.963 (0.011)	0.975 (0.021)	0. (0.
	Rate[5]: Mean (SD)	13.45 (2.64)	13.60 (2.95)	14.50 (3.06)	13.95 (2.48)	13.35 (2.21)	14.70 (1.40)	13.75 (3.05)	14.13 (1.76)	14 (1

[1] Pre-exercise (PRE), Midway through exercise (MID), and Post-exercise (POST) performance
[2] Number of correct letters recalled
[3] Standard Deviation (SD)
[4] Ratio of number of correst answers to number of answers attempted
[5] Attempts per minute

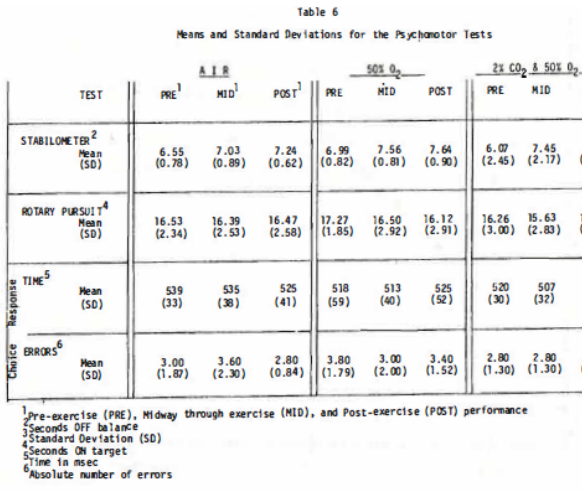


Table 6

Means and Standard Deviations for the Psychomotor Tests

	TEST	AIR PRE[1]	AIR MID[1]	AIR POST[1]	50% O_2 PRE	50% O_2 MID	50% O_2 POST	2% CO_2 & 50% O_2 PRE	2% CO_2 & 50% O_2 MID
	STABILOMETER[2] Mean (SD)	6.55 (0.78)	7.03 (0.89)	7.24 (0.62)	6.99 (0.82)	7.56 (0.81)	7.64 (0.90)	6.07 (2.45)	7.45 (2.17)
	ROTARY PURSUIT[4] Mean (SD)	16.53 (2.34)	16.39 (2.53)	16.47 (2.58)	17.27 (1.85)	16.50 (2.92)	16.12 (2.91)	16.26 (3.00)	15.63 (2.83)
Response	TIME[5] Mean (SD)	539 (33)	535 (38)	525 (41)	518 (59)	513 (40)	525 (52)	520 (30)	507 (32)
Choice	ERRORS[6] Mean (SD)	3.00 (1.87)	3.60 (2.30)	2.80 (0.84)	3.80 (1.79)	3.00 (2.00)	3.40 (1.52)	2.80 (1.30)	2.80 (1.30)

[1] Pre-exercise (PRE), Midway through exercise (MID), and Post-exercise (POST) performance
[2] Seconds OFF balance
[3] Standard Deviation (SD)
[4] Seconds ON target
[5] Time in msec
[6] Absolute number of errors

Figure A-81 **Figure A-82**

(Vercruyssen, Kamon et al. 2007)
Same methods as in 1984 publication but breathing gas was 3% CO_2 in 50% O_2 and 4% CO_2 in 50% O_2. Again, there was no impairment in cognition or psychomotor performance: speed or accuracy of addition, multiplication accuracy, speed or accuracy of reasoning, and stabilometer balance. Headaches were reported by some subjects with rapid resolution on return to fresh air, with fewer cases on subsequent test days. Therefore habituation, desensitization, or acclimatization to CO_2 was evident.

TABLE 2. Performance Means and Standard Deviations

		Air			3% CO_2			4% CO_2		
		Pre-	Mid-	Post-	Pre-	Mid-	Post-	Pre-	Mid-	Post-
Addition	Problems completed in 2 min	13.8 ±3.1	13.7 ±2.9	14.0 ±2.9	13.3 ±3.6	14.5 ±3.0	13.8 ±4.1	13.8 ±4.0	13.3 ±2.4	13.0 ±4.1
	% errors	12.5 ±10.5	14.7 ±9.4	1.2 ±2.9	6.0 ±4.9	9.0 ±8.2	8.8 ±10.7	12.7 ±15.4	7.8 ±7.5	8.3 ±5.0
Multiplication	Problems completed in 2 min	30.0 ±7.7	30.2 ±6.4	30.3 ±7.9	28.3 ±7.9	30.7 ±7.3	31.0 ±7.6	29.7 ±6.3	33.0 ±6.2	28.5 ±7.0
	% errors	9.5 ±8.1	7.8 ±12.5	13.3 ±15.5	16.0 ±16.2	11.8 ±9.6	9.0 ±10.0	6.7 ±6.6	6.0 ±4.8	13.2 ±8.0
Reasoning	Problems completed in 3 min	98.2 ±17.0	101.8 ±14.0	102.3 ±15.2	98.3 ±15.6	102.3 ±16.3	101.0 ±17.0	107.3 ±29.2	104.8 ±30.6	107.2 ±29.1
	% errors	6.7 ±5.4	5.5 ±3.5	5.5 ±4.0	5.2 ±3.0	5.7 ±3.4	7.8 ±7.7	6.2 ±3.7	7.5 ±3.9	7.3 ±6.5
Stabilometer	Trial 1	2.34 ±2.12	5.00 ±3.23	4.69 ±3.49	1.57 ±1.48	3.25 ±1.96	4.36 ±1.77	1.85 ±1.50	4.07 ±2.85	4.67 ±2.90
	Trial 1–3	1.84 ±1.58	4.21 ±2.52	3.62 ±2.38	1.44 ±0.83	3.89 ±2.06	4.00 ±2.10	1.99 ±0.92	4.46 ±2.58	4.26 ±2.82
	Trial 1–5	1.96 ±1.61	3.96 ±2.33	3.41 ±2.21	1.30 ±1.01	3.76 ±2.07	3.74 ±2.10	1.62 ±0.99	3.89 ±2.57	3.94 ±2.76
	Trial 2–5	1.86 ±1.04	3.70 ±1.87	3.07 ±1.54	1.18 ±0.55	3.61 ±1.49	3.40 ±1.71	1.57 ±0.45	3.84 ±2.20	4.15 ±2.62

Figure A-83

(Bloch-Salisbury, Lansing et al. 2000)
Nine subjects (7 female) had a 2 hour exposure to mean hypocapnic ($P_{ET}CO_2$ = 30 mmHg), normocapnic ($P_{ET}CO_2$ = 38 mmHg), and hypercapnic ($P_{ET}CO_2$ = 47 mmHg) breathing in 50% O_2 while at normobaric rest. Changes in EEG were observed, but no effects on several cognitive and vigilance tasks. This work is extremely relevant to at least resting EVA with small increase in P_aCO_2.

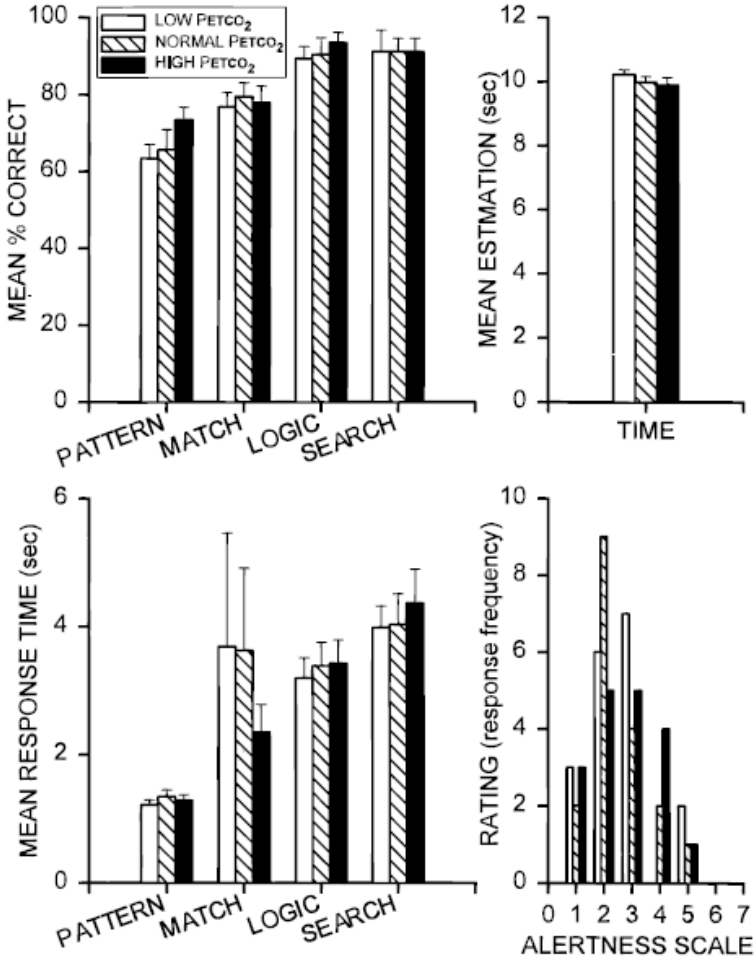


Figure 1. Mean responses to each of the computerized tasks for each end-tidal PCO_2 (PET_{CO_2}) condition: Pattern = pattern recognition; Match = match-to-sample; Logic = logical reasoning; Search = two letter search and recognition; Time = time estimation; Alertness scale = self-assessment of alertness with 1 reflecting most awake to 7 reflecting the struggle to remain awake. Bars = *SEM*.

Figure A-84

(Wang, Yee et al. 2015)

Tested 20 subjects during acute, 5-minute hypercapnia from rebreathing. The procedure increased mean PCO_2 in the breathing circuit from 36 mmHg in control air to about 47 mmHg under hypoxic (PO_2 = 56 mmHg) or hyperoxic (PO_2 = 150 mmHg) conditions. Also tested normocapnic hypoxic condition (PCO_2 = 34 mmHg and PO_2 = 47 mmHg in breathing circuit. In both hypercapnic cases there was an increase from 7 to 10 in the ratio of delta (δ) wave power to alpha (α) wave power (δ/α) from EEG during the rebreathing. There was no change in the ratio of δ/α between control (6.6) and normocapnic hypoxic condition (6.0). No cognitive or performance measures were taken over this short interval, just a demonstration that hypercapnia but not hypoxia caused EEG slowing, which might indicate a depression of cortical neuroelectrical activity.

Table 1
Comparisons of EEG spectral under three hypercapnia and hypoxia protocols.

	Protocol 1		Protocol 2		Protocol 3	
	Control	Hypercapnia Iso-hyperoxia	Control	Hypercapnia Iso-hypoxia	Control	Hypoxia
Total-power, μV^2	41.4±13.7	42.2±17.3	45.2±14.2	45.8±16.4	42.6±14.7	55.8±23.4§
Delta%	58.7±12.8	60.5±14.9	54.7±14.2	59.2±15.6*	54.5±13.6	55.0±13.4
Theta%	9.1±2.3	8.8±1.9	9.8±3.1	9.3±2.5	9.8±3.0	11.6±5.3*
Alpha%	12.2±7.3	9.8±5.6†	14.4±8.9	10.8±7.5**	13.9±7.8	14.3±6.3
Beta%	20.0±8.8	21.0±12.4	21.1±10.2	20.7±11.1	21.8±9.5	19.1±7.9*
D/A ratio	7.9±4.1	9.2±4.5*	6.9±3.7	9.2±5.2‡	6.6±3.9	6.0±3.5
pCO_2, mmHg	36.4±4.5	46.1±3.4	36.7±5.0	47.3±4.0	37.0±4.3	34.5±4.0
pO_2, mmHg	114.2±7.8	150.2±2.9	114.3±8.0	55.9±2.3	112.6±6.6	46.9±2.3

Figures in the table are means and SDs. Cells with shadow indicate significant p values compared to each control session at $^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.005$; $^{\S}p < 0.001$; $^{**}p < 0.0001$. D/A ratio is the primary outcome of interest. Spectral band% was calculated as individual band power/total summed power between 0.5 and 32 Hz × 100. No significance at $p < 0.05$ was found for any spectral band comparison between the Protocol 1 and 2 intervention sessions. No statistical difference was found between the three control sessions in any spectral parameter.

Figure A-85

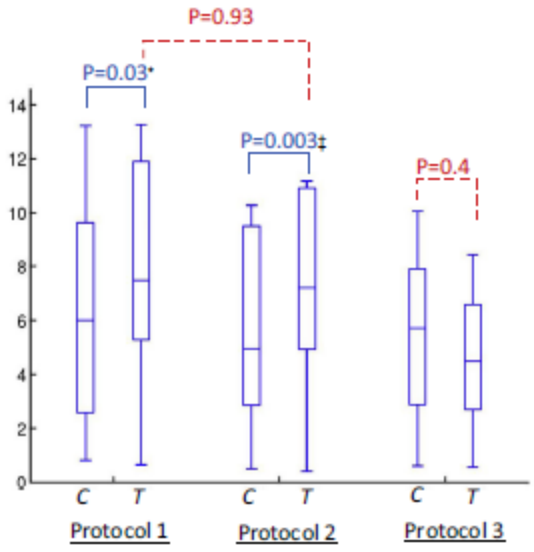


Fig. 1. Box and Whisker Plot of hypercapnia and hypoxia effects on Delta/Alpha ratio of EEG. *C* = Control sessions by breathing room air, *T* = Testing sessions. Protocol 1 Test: response to hypercapnia with pO_2 held constant at 150 mmHg (hyperoxia). Protocol 2 Test: response to hypercapnia with pO_2 held constant at 50 mmHg (hypoxia). Protocol 3 Test: response to hypoxia with CO_2 controlled by a scrubber. Two dashed bars (– – –): compare the effect of hypoxia on D/A ratio, no significant difference was found. Two solid bars (——): compare the effect of hypercapnia on D/A ratio, both showing significant effect. The bottom and top of the box indicates the upper and lower quartile range (IQR) and the middle bar indicates the median value. The whiskers indicate the highest and lowest value after excluding the outliers (>1.5 IQR of the upper and lower quartile). $^{*}p < 0.05$; $^{‡}p < 0.005$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure A-86

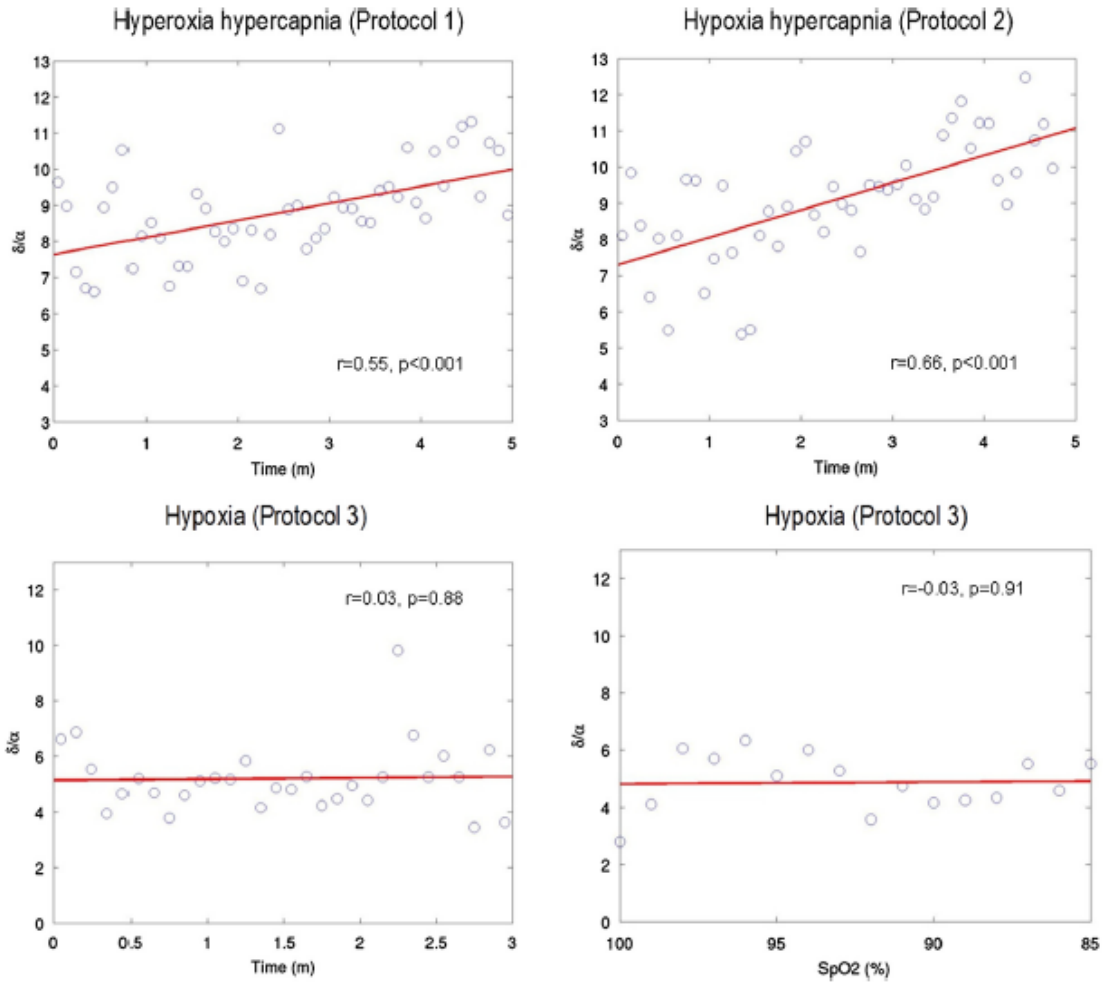


Fig. 2. Average Delta/Alpha ratio change with time under Protocol 1, 2 and 3 in 19 subjects. Pearson's correlation coefficient (r) was used to test the relationships. In the bottom right panel (Protocol 3), each dot represents 1% drop in SpO_2.

Figure A-87

(Dahan, DeGoede et al. 1990)
See summary under #1.

(Becker, Polo et al. 1996)
Isocapnic hyperoxia stimulates ventilation in a dose-response manner. If isocapnia is not maintained, then hyperventilation is attenuated by a decrease in P_aCO_2.

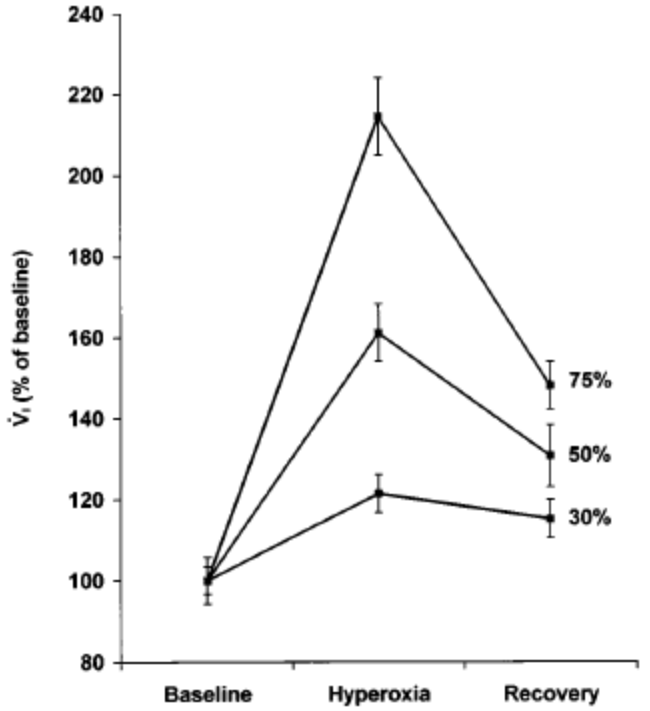


Fig. 1. Minute ventilation ($\dot{V}_I$) during 30, 50, and 75% isocapnic hyperoxia. Values are means ± SE calculated for last 5 min of each period. Previously published results obtained during 50% isocapnic hyperoxia (3) have been included for convenience of comparison.

Figure A-88

(Ainslie and Poulin 2004)
See summary under #3.

A-5 Hypercapnia in hyperbaric normoxia with rest and exercise in 1G.

A-6 Hypercapnia in hyperbaric hypoxia with rest and exercise in 1G.

A-7 Hypercapnia in hyperbaric hyperoxia with rest and exercise in 1G.

(Gill, Natoli et al. 2014)
See summary under #1.

(Lambertsen, Hall et al. 1963)
See summary under #4. Lambertsen covers: O_2 breathing without added CO_2, CO_2 added to O_2 at increased pressure, and inhalation of CO_2 with O_2 at 1 ATA.

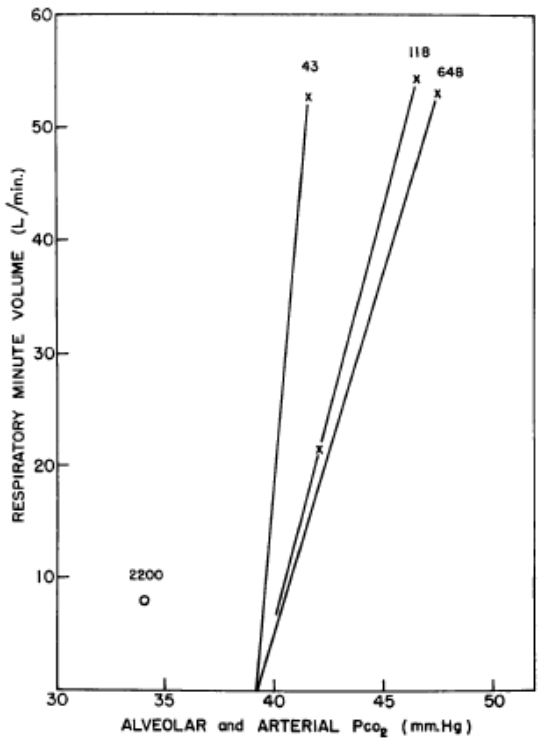


FIGURE 2. This diagram, showing pulmonary ventilation at different levels of alveolar or arterial P_{O_2}, is a composite of data obtained by Cunningham *et al.* and by this laboratory.[5,18] The numbers above the plotted points represent alveolar P_{O_2} in mm. Hg. *x* indicates measurements in a single subject studied at one atmosphere at the indicated level of alveolar P_{O_2}[5] and o indicates the average resting relationship of arterial P_{CO_2} and ventilation in a group of subjects during oxygen breathing at 3.0 atmospheres ambient pressure.[18] The diagram shows that decreased alveolar P_{O_2} causes a marked increase in response to carbon dioxide, while increased P_{O_2} may either decrease[5] or increase[13] ventilation, depending upon the circumstances (after Cunningham *et al.*[5]).

Figure A-89

Figure A-89 shows no significant further increase in $\dot{V}_E$ in response to the mild hyperoxia associated with EVA combined with hypercapnia.

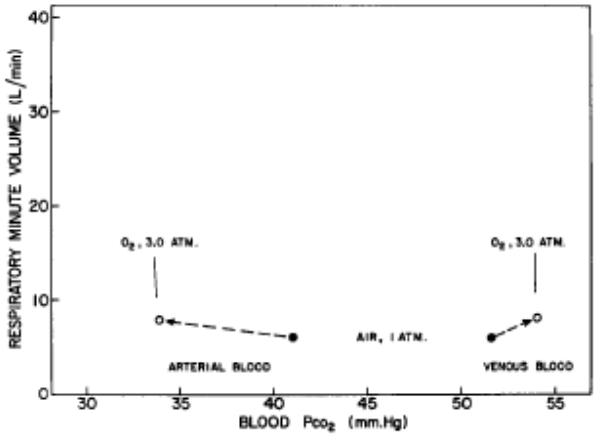


FIGURE 3. Effect of oxygen breathing upon arterial and internal jugular venous P_{CO_2} (mean values in eight subjects[18]): Average values are shown for pulmonary ventilation and blood P_{CO_2} in normal subjects breathing air at 1 atmosphere and oxygen at 3.0 atmospheres. Oxygen breathing, without added carbon dioxide, leads to increased ventilation and lowered arterial P_{CO_2}. The concomitant increase in brain venous P_{CO_2} suggests that one effect of oxygen upon respiration may be by way of an elevation of the central acid-base stimulus. The influence of the secondary arterial hypocapnia upon the magnitude of the respiratory response is uncertain.

Figure A-90

Acute breathing of 3 ATM of PO_2 without hypercapnia is associated with an increase in $\dot{V}_E$, arterial hypocapnia, and venous hypercapnia. Figure 3 shows the increase in $\dot{V}_E$ with hyperoxia. The reason may be that vasoconstriction leads to an increase in P_VCO_2 that may reflect an increase in $P_{CSF}CO_2$. The increase in $P_{CSF}CO_2$ may then stimulate central chemoreceptors to increase $\dot{V}_E$ even in the face of lowered P_aCO_2.

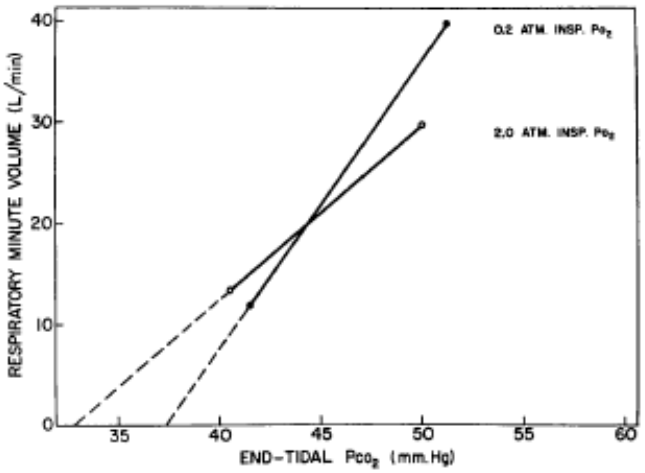


FIGURE 4. 1.5 and 3.0 per cent CO_2 in 10 per cent O_2 in N_2 and in O_2 were administered to normal but nonbasal subjects resting supine at 2.0 atmospheres pressure (mean values in seven subjects). The higher inspired P_{O_2} significantly and prominently reduced the slope of the P_{CO_2}-ventilation response curve. However, while depression of respiration occurred at the higher level of hypercapnia, stimulation of respiration resulted when oxygen was administered with the lower degree of hypercapnia. Probably in each instance both stimulant and depressant actions were in effect. The point of crossover of the curves for high and normal oxygenation indicates a point of equality of stimulant and depressant effects of oxygen.

Figure A-91

Figure A-91 shows the depression of $\dot{V}_E$ to hypercapnia in the presence of hyperoxia. However, while depression of $\dot{V}_E$ occurred at a higher level of hypercapnia, stimulation of $\dot{V}_E$ resulted when the same hyperoxia was administered with lower hypercapnia. So there is a complex interaction between PO_2 and PCO_2 in the chemical control of respiration.

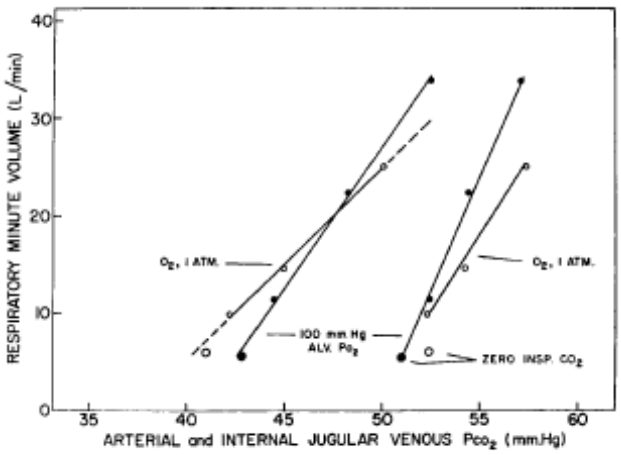


FIGURE 5. Effect of O_2 breathing at 1.0 atm. upon the respiratory response to CO_2 (mean values in four subjects): Respiratory minute volume is related to values of P_{CO_2} determined on samples of arterial and internal jugular venous blood obtained during stable state breathing of carbon dioxide in oxygen (*open circles*) or at an alveolar P_{O_2} controlled near 100 mm. Hg (*solid circles*). The larger circles represent values obtained at 0 per cent inspired CO_2. The arterial and venous lines through the four solid arterial and venous points are the regression of ventilation on P_{CO_2} at normal P_{O_2}. The lines describing oxygen inhalation at various levels of P_{CO_2} are the regressions through three sets of data only. Pure oxygen breathing was not included, since it was associated with a significant degree of arterial hypocapnia which appears to have influenced the pattern of ventilation-P_{CO_2} relationship.
For further description, see text.

Figure A-92

Figure A-92 shows the change in $\dot{V}_E$ for a change in P_aCO_2 and P_VCO_2 either while breathing 1 ATA O_2 or when P_AO_2 is held normal at 100 mmHg. A PO_2 of 1 ATM produced a prominent depression in the slope of the respiratory response to hypercapnia.

(Michel, Sharma et al. 1969)
PCO_2 at the end of inhalation increased in suited subjects at 18.4 psia undergoing exercise at 1000 and 2000 BTU/h. PCO_2 at the end of inhalation is a measure of helmet washout under a range of helmet ventilation rates. A limit of 7.6 mmHg was exceeded in both the Gemini and Apollo suits with helmet ventilation at 6 actual cubic feet per minute when treadmill exercise exceeded 2000 BTU/h.

TABLE I. MEAN CARBON DIOXIDE LEVELS DURING ACTIVITY
Gemini Spacesuit

Metabolic Rate BTU/HR	Flow Rate-CFM			
	8	11.5	18	23
	mm Hg			
801-1200	5.3	4.3	1.7	0.9
1201-1600	7.0	5.7	2.7	1.4
1601-2000	10.1	9.9	5.9	3.8
2001-2800	19.1	12.8	6.2	4.3

TABLE II. MEAN CARBON DIOXIDE LEVELS DURING ACTIVITY
Apollo Spacesuit

Metabolic Rate BTU/HR	Flow Rate-CFM						
	3	4	5	6	7	8	9
	mm Hg						
1-400	6.3	3.9	2.7	2.0			
401-800	7.6	6.0	4.5	2.8			
801-1200	11.0	8.1	5.8	4.3			
1201-1600	15.5	11.7	8.1	5.7			
1601-2000	20.4	13.7	10.7	8.3		8.0	7.6
2001-2400	22.8	16.1	13.8	10.5	8.0	8.8	8.2
2401-2800		22.8	17.0	13.8		9.7	9.0

Figure A-93 Note: Total ventilation in Gemini suit was partitioned between helmet and torso, 11.5 ACFM in Figure A-91 reflects about 6 ACFM in the helmet, see paper for other details.

(Selkirk, Shykoff et al. 2010)
Comprehensive evaluation of cognitive effects of 1.5% and 3% CO_2 (sea level equivalent) on working divers breathing either O_2 at 1.4 ATM or air at 0.3 ATM in 12 feet fresh water. Exercise was with cycle ergometer with three 30 minute exercises and 30 minutes of rests between during which cognition tests were performed while submerged. The test matric was extensive and not possible to succinctly summarize. Basic cognitive domains of simple reaction time, visual scanning, visuo-spatial processing, and learning were unaffected. The author notes “perplexing” results for other cognitive functions but says that long-term memory was decreased while divers were breathing CO_2. Some subjects reported headache, shortness of breath, irritability, and lack of concentration.

(Haran and Lovelace 2015)
Various combinations of 0%, 1%, and 2% CO_2 (sea level equivalent) with high breathing resistance during dives at 12 feet fresh water with high exercise (85% $\dot{V}O_2$peak) for 60 minutes did not impair neurocognitive performance and postural stability. Although there were CO_2-related symptoms that precluded neurocognitive assessments in some subjects.

Table 2. Reported characteristic clinical symptoms associated with CO_2 exposure (from reference 22)

Condition	Clinical symptoms	N	%
R1, 0% SEV CO_2	Headache	2	13%
	Agitated	1	6%
	Nausea	1	6%
	Dizziness	1	6%
R1, 1% SEV CO_2	Headache	4	25%
	Nausea	2	13%
	Dizziness	1	6%
R1, 2% SEV CO_2	Headache	6	38%
	Nausea	1	6%
	Concentration issues	1	6%
	Sleepy	1	6%
	Dizziness	1	6%
R2, 0% SEV CO_2	Nausea	1	6%
	Tunnel vision	1	6%
	Anxious	1	6%
	Concentration issues	1	6%
	Hot	1	6%
	Light-headed	1	6%
R2, 2% SEV CO_2	Headache	7	44%
	Flushed	1	6%
	Feeling 'loopy'	1	6%
	Agitated	1	6%
	Nausea	2	13%
	Anxious	3	19%
	Confused	1	6%
	Hot	1	6%
	Light-headed	1	6%
	Dizziness	1	6%

Note. R1: work of breathing per tidal volume (WOB/V_T) =1.0 kPa at a minute ventilation of 62.5 L/min; R2: WOB/V_T = 1.8 kPa at a minute ventilation of 62.5 L/min; SEV = surface equivalent volume; CO_2 = carbon dioxide; N = number of divers; % = percentage of divers.

Figure A-94

Table 3. Descriptive statistics for the ANAM subtests

Subtest	Breathing Condition	N	Pre-		Post-	
			Mean	Stdev	Mean	Stdev
CDS	R1, 0% SEV CO_2	12	43.18	14.00	44.48	15.23
	R1, 1% SEV CO_2	15	46.41	12.83	42.30	12.58
	R1, 2% SEV CO_2	12	45.50	9.45	45.62	8.35
	R2, 0% SEV CO_2	15	50.26	9.62	47.03	15.16
	R2, 2% SEV CO_2	9	43.60	10.27	42.95	11.28
CDD	R1, 0% SEV CO_2	12	53.37	20.30	47.92	17.73
	R1, 1% SEV CO_2	15	50.82	11.64	43.95	12.97
	R1, 2% SEV CO_2	12	53.70	12.42	45.62	11.02
	R2, 0% SEV CO_2	15	55.53	13.67	52.30	14.80
	R2, 2% SEV CO_2	9	49.09	15.52	47.86	12.72
CDI	R1, 0% SEV CO_2	12	53.22	16.06	47.40	15.23
	R1, 1% SEV CO_2	15	49.21	12.02	43.85	11.52
	R1, 2% SEV CO_2	12	50.86	12.09	45.62	11.55
	R2, 0% SEV CO_2	15	55.11	14.63	50.50	15.43
	R2, 2% SEV CO_2	9	45.23	14.15	50.24	15.61
SWT	R1, 0% SEV CO_2	12	23.28	7.09	25.42	8.80
	R1, 1% SEV CO_2	15	27.43	6.81	27.45	7.27
	R1, 2% SEV CO_2	12	23.99	7.50	45.62	6.71
	R2, 0% SEV CO_2	15	26.18	5.81	26.58	5.72
	R2, 2% SEV CO_2	9	23.04	8.07	26.04	7.30
SRT	R1, 0% SEV CO_2	12	190.55	19.32	203.18	27.87
	R1, 1% SEV CO_2	15	175.86	37.92	186.80	30.39
	R1, 2% SEV CO_2	12	192.64	32.23	186.90	37.75
	R2, 0% SEV CO_2	15	191.04	30.42	181.04	25.31
	R2, 2% SEV CO_2	9	184.81	25.07	180.27	21.18
SRT2	R1, 0% SEV CO_2	12	183.46	20.65	193.54	24.33
	R1, 1% SEV CO_2	15	178.55	38.97	180.20	37.04
	R1, 2% SEV CO_2	12	178.24	23.61	186.90	33.17
	R2, 0% SEV CO_2	15	189.63	35.91	185.57	26.55
	R2, 2% SEV CO_2	9	179.31	23.65	189.71	17.23

Note. N = sample size; CDS = code substation; CDD = code substitution delayed; CDI = code substitution intermediate; SWT = switching task; SRT = simple reaction time; SRT2 = 2nd simple reaction time test; R1: work of breathing per tidal volume (WOB/V_T) =1.0 kPa at a minute ventilation of 62.5 L/min; R2: WOB/V_T = 1.8 kPa at a minute ventilation of 62.5 L/min; SEV = surface equivalent volume; CO_2 = carbon dioxide; stdev = standard deviation. All values in are throughput (correct responses/minute).

Figure A-95

Note: those few subjects who were removed from the study before the end of the 60 minute exercise period due to severe symptoms did not complete post-exercise neurocognitive assessments, so their data was not included in the pre-exercise neurocognitive assessments. This approach seems to bias results to those who were resistant to hypercapnia.

(Fothergill, Hedges et al. 1991)
Resting, 20 minute exposure to $P_{ET}CO_2$ of 26 mmHg (hypocapnic), 47 mmHg (isocapnic), and 57 mmHg (hypercapnic). Cognitive and psychomotor performance decreased at 6 ATA on air and more so at $P_{ET}CO_2$ of 57 mmHg. But no N_2–CO_2 interaction that changed the threshold for CO_2 narcosis. N_2 narcosis lowered performance and disrupted accuracy, while hypercapnia plus N_2 narcosis slowed performance rather than disrupting accuracy. Therefore high $P_{ET}CO_2$ and P_IN_2 are additive in their effects on impairing cognitive and psychomotor performance. A limitation of this study was that they did not control for hyperoxia at 6 ATA.

(Warkander, Norfleet et al. 1990)
Exercise at 6.8 ATA with $P_{ET}CO_2$ of about 62 mmHg increased to 72 mmHg when breathing resistance was rapidly increased and then to 90 mmHg during transition from the experiment, at which time he lost consciousness. Other subjects responded less dramatically but with equally high $P_{ET}CO_2$. The authors conclude that severe hypercapnia does not necessarily correlate with

dyspnea and that severe disturbances in mental function can develop suddenly when high breathing resistance is encountered in diving.

(Bitterman and Bitterman 1998)
Authors explored that increased susceptibility to hyperoxia-induced seizures in the presence of hypercapnia is due to more than cerebral vasodilator effect of CO_2. An increase in CO_2 is also associated with changes in other vasoactive agents, such as nitric oxide (NO). Agents that suppress or enhance NO production were injected into rats and combined with 5% CO_2 in 95% O_2 or just 100% O_2 with hyperbaric exposure to 5 ATA. Inhibition of NO production with or without hypercapnia postponed the appearance of hyperoxic seizures.

A-8 Hypercapnia in hypobaric hyperoxia with rest and exercise in μG – EVA.

A-9 Hypercapnia in hypobaric normoxia with rest and exercise in 1G.

(Glatte Jr, Motsay et al. 1967)
Seven men exposed to 3% CO_2 at about 700 mmHg ambient pressure in a chamber for 5 days. Extensive blood and urine analysis showed little change: P_aCO_2 increased 3–4 mmHg with pH reduced from 7.40 to 7.32, urine HCO_3^- increased from 6.5 to 7.1 mEq/24 h, no remarkable difference to 100 watt exercise over 1 hour with $\dot{V}_E$ increased about 2.5 $L_{(BTPS)}$/min during rest, and no measurable changes in various psychomotor performance compared to baseline. Presentation of extensive results was somewhat confusing.

A-10 Hypercapnia in hypobaric normoxia with rest and exercise in μG – Skylab.

A-11 Hypercapnia in hypobaric hypoxia with rest and exercise in 1G.

(Liu, Liu et al. 2015)
Subjects breathed 25% O_2 at 3,800 m altitude (12,500 ft with $P_IO_2 \approx 118$ mmHg) plus 0.5, 3.0, and 5.0% CO_2 (equivalent to 0.31, 1.89, and 3.14% CO_2 at sea level) on separate days. Each day they exercised 3 times for 3 minutes with 30 minute rest between exercises. Authors concluded in hypobaric, mild hypoxic and hypercapnic environment that the cardiovascular system showed significant responses in heart rate, blood pressure, and cardiac autonomic regulation when breathing 5% CO_2 (3.14% sea level equivalent) compared to other conditions.

(Loeppky 1998)
Exercise to $\dot{V}O_2$max on a cycle ergometer was done with male subjects breathing a P_ICO_2 of 5.4, 7.5, and 15.0 mmHg for 30 minutes. P_B at the laboratory was 630 mmHg (5,400 ft altitude). Author attributes a lower RER with hypercapnic exercise to CO_2 retention. The presence of CO_2 in inspired gas induces a relative ventilation insufficiency under conditions of strenuous exercise. A useful regression equation was provided that shows the change in $\dot{V}_I$ as a function of P_ICO_2 and the ratio of $\dot{V}O_2$ to $\dot{V}O_2$max:

$$\text{Log}_{10}\,\dot{V}_I = 1.174 + 0.00356 \times P_ICO_2^{1.5} + (0.95 - 0.00636 \times P_ICO_2) \times \dot{V}O_2/\dot{V}O_2\text{max}.$$

TABLE I. MEAN RESTING MEASUREMENTS ON AIR AND 7.5 mmHg P_{ICO_2} (2 × 10 SUBJECTS) AND AIR AND 5.7 mmHg P_{ICO_2} (2 × 5 SUBJECTS).

	Air	7.5 mm Hg	Air	5.7 mmHg
$\dot{V}_I$ (L · min^{-1})	6.05	7.15*	6.36	6.99†
f_v (min^{-1})	8.1	8.5	8.4	9.0
V_T (L)	0.83	0.89	0.86	0.87
$\dot{V}_{O_2}$ (L · min^{-1})	0.223	0.230	0.218	0.216
$\dot{V}_{CO_2}$ (L · min^{-1})	0.174	0.174	0.175	0.167
R	0.78	0.76†	0.79	0.77
P_{ACO_2} (mmHg)	36.2	37.7*	35.1	36.4†
P_{AO_2} (mmHg)	79.5	84.2*	81.7	88.6*
$\dot{V}_I/\dot{V}_{O_2}$	27.1	31.0*	28.9	32.0†
$\dot{V}_A$ (L · min^{-1})	4.20	5.01*	4.42	4.83*

* $p < 0.001$ vs. corresponding air measurements.
† $p < 0.01$ vs. corresponding air measurements.

Figure A-96

TABLE II. MEAN CARDIOPULMONARY MEASUREMENTS IN THREE STUDIES, WITH AND WITHOUT ADDED CO_2, DURING THE TIME INTERVAL IN WHICH $\dot{V}_{O_2max}$ WAS ACHIEVED.

	Air	5.4 mmHg	Air	9.4 mmHg	Air	15 mmHg
Work (kpm · min^{-1})	1,228	1,225	1,413	1,438	1,319	1,250†
V_I (L · min^{-1})	128.3	112.6*	135.6	144.1	139.4	142.2
$\dot{V}_{O_2}$ (L · min^{-1})	2.964	2.773†	3.260	3.260	3.102	2.692*
$\dot{V}_{CO_2}$ (L · min^{-1})	3.225	2.978	3.614	3.510	3.444	2.842*
R	1.10	1.09	1.11	1.08	1.11	1.06
HR (bpm)	183	179	182	186	185	180†
SBP (mmHg)	199	192	189	196	204	211†
PP (mmHg)	114	106	107	117	108	111

* $p < 0.001$ vs. corresponding air measurements.
† $p < 0.05$ vs. corresponding air measurements.

Figure A-97

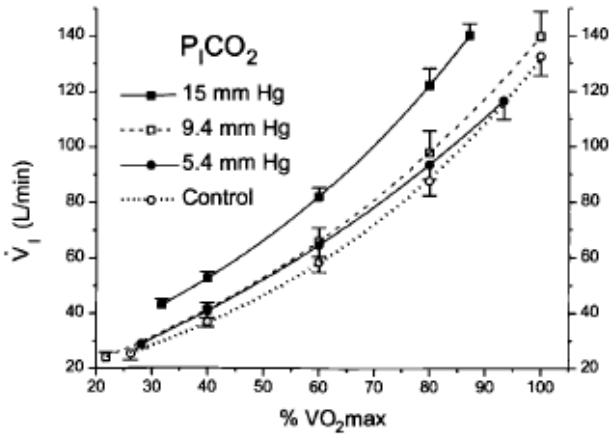


Fig. 1. Ventilation (BTPS) at three levels of inspired P_{CO_2} plotted as a percentage of $\dot{V}O_{2max}$ obtained on air controls. Each point is the mean and SE of $\dot{V}_I$ measured in individual subjects at the lowest, 40, 60, 80 and 100% of $\dot{V}O_{2max}$ in the three studies. The mean and SE of the air curve is the average of the three control studies. The curves with CO_2 are adjusted to deviate from the mean control curve by the same amount as in the three separate studies. The $\dot{V}_I$ values for 5.4 mmHg are significantly higher than controls at 40 and 60% of $\dot{V}O_{2max}$ ($p < 0.02$), as are the values at 9.4 mmHg at 40, 60 and 80% of $\dot{V}O_{2max}$.

Figure A-98

(Krasnogor, Wempen et al. 1968)
Six men exercised on bicycle ergometer at 100 watts 60 rpm for 3 hours while at 180 mmHg (3.48 psia, 35,000 ft altitude) in a chamber with PCO_2 of 7.6 mmHg and F_IO_2 about 0.90. Same men did same protocol at 700 mmHg. Arterial blood gas, ventilation, and metabolic rate data indicated no significant impact of this acute mild hypercapnic and mild exercise at altitude and no significant difference when compared to same protocol at 700 mmHg. O_2 consumption was about 1.2 $L_{(STPD)}$/min for each protocol with no significant change in P_aCO_2 during the rest or exercise interval at 180 mmHg or at 700 mmHg, a P_aCO_2 of about 36 mmHg. Mean arterial pH was never lower than 7.39. This was convincing evidence in 1968 that modest continuous work combined with modest hypercapnia could be performed under space suit conditions.

TABLE I. MEAN ENVIRONMENTAL CONDITIONS

Variable	Phase I 700 mm. Hg Normal P_{CO_2}	Phase II 700 mm. Hg Elevated P_{CO_2}	Phase III 180 mm. Hg Elevated P_{CO_2}
P_B (mm. Hg)	699.7±0.8*	699.9±0.8	180.3±0.7
P_{O_2} (mm. Hg)	150.1±2.9	144.5±7.0	162.4±2.0
P_{CO_2} (mm. Hg)	1.9±1.2	7.3±1.2	7.6±0.4
P_{N_2} (mm. Hg)	534.5±3.5	533.1±5.3	1.6±0.9
P_{H_2O} (mm. Hg)	13.3±2.5	14.8±2.9	8.7±1.5
Temp. (°F.)	75.6±1.2	74.7±1.0	75.2±1.7

*Mean ± S. D.

Figure A-99

TABLE II. P_{AO_2}, ARTERIAL BLOOD, AND ACID-BASE STUDIES

Parameter	Phase	Rest	Exercise*
P_{AO_2}** (mm. Hg)	I	104.0 ±4.3***	106.3 ±1.4
	II	101.1 ±3.8	105.5 ±2.9
	III	95.5 ±3.1	97.0 ±2.6
P_{aO_2} (mm. Hg)	I	93.3 ±2.4	92.9 ±4.6
	II	90.6 ±4.9	92.2 ±3.6
	III	85.1 ±5.3	87.6 ±3.3
A-aD (mm. Hg)	I	10.9 ±5.7	14.2 ±5.3
	II	10.5 ±4.2	13.4 ±3.2
	III	10.4 ±7.2	9.4 ±2.4
S_{aO_2} (Per Cent)	I	96.7 ±0.8	95.6 ±0.7
	II	97.9 ±1.1	95.9 ±1.2+
	III	96.2 ±1.6	95.9 ±1.1
pHa	I	7.41±0.02	7.40±0.01
	II	7.41±0.02	7.39±0.02+
	III	7.40±0.02	7.39±0.02
Total CO_2 (Whole Blood) (mM./1)	I	20.8 ±0.7	19.5 ±0.9++
	II	20.9 ±1.1	20.0 ±0.6
	III	20.7 ±1.3	19.5 ±1.2
P_{aCO_2} (mm. Hg)	I	35.5 ±2.2	37.7 ±3.2
	II	35.9 ±1.6	36.7 ±2.0
	III	36.7 ±2.8	35.3 ±2.1

*Unmarked exercise values were not significantly different from resting values. Exercise bloods were drawn during the last 30 minutes of the three-hour exercise period.

**Calculated from alveolar gas equation.

***Mean ± S.D.

+$P < 0.05$

++$P < 0.001$

Figure A-100

TABLE III. VENTILATION, GAS EXCHANGE AND METABOLISM DURING EXERCISE

Parameter	Phase	Rest	Exercise
$\dot{V}_E$	I	8.92 ± 1.91*	33.28 ± 3.05**
(l. BTPS/min.)	II	10.16 ± 1.52	39.42 ± 5.74
	III	9.75 ± 1.34	33.74 ± 3.87
V_T	I	0.691± 0.238	1.669± 0.392
(l. BTPS)	II	0.795± 0.157	1.790± 0.335
	III	0.719± 0.112	1.489± 0.197
f	I	14.0 ± 4.6	21.0 ± 4.8
(breaths/min.)	II	13.2 ± 3.1	23.1 ± 6.5
	III	13.8 ± 2.8	23.1 ± 3.6
$\dot{V}_{CO_2}$	I	0.236± 0.034	1.15 ± 0.11
(l. STPD/min.)	II	0.254± 0.044	1.18 ± 0.12
	III	0.210± 0.030	0.943± 0.077
$\dot{V}_{O_2}$	I	0.308± 0.046	1.26 ± 0 10
(l. STPD/min.)	II	0.324± 0.056	1.24 ± 0.12
	III	0.292± 0.046	1.16 ± 0.11
RQ	I	0.78 ± 0.15	0.91 ± 0.07
	II	0.79 ± 0.04	0.95 ± 0.08
	III	0.73 ± 0.06	0.82 ± 0.06
Metabolic Rate	I	87.5 ±12.0	370.9 ±29.4***
(kcal./hr)	II	92.5 ±15.9	368.1 ±34.1
	III	82.2 ±12.4	333.1 ±29.4

*Mean ± S.D.

**Exercise means represents 30 observations (5 for each of the 6 subjects taken at approximately 30-minute intervals throughout exercise).

***Exercise values are given as overall metabolic rate (includes the resting metabolism).

Figure A-101

(Luft, Finkelstein et al. 1974)

Experiments conducted in Albuquerque with P_B of about 632 mmHg (5,000 ft altitude). Twelve young men (26.5 years) breathed air and air with P_ICO_2 of 15 mmHg during stepped bicycle ergometry to the point where they could not maintain a metronome pedaling rhythm that produced 50 rpm. The stepped protocol required about 15 minutes, then 30 minutes of recovery while still breathing the test gas. The main conclusion was that the combination of metabolic acidosis from anaerobic metabolism in leg muscles combined with incomplete compensated respiratory acidosis from hypercapnia taxed the respiratory response such that CO_2 retention was evident. Hypercapnia resulted in a decrease in RER (Figure A-105), an indication of CO_2 retention. Blood gases were collected on 10 of the 12 men, showing a decrease in P_aCO_2 during exercise on air while an increase during exercise with hypercapnia (Figure A-106), with a critical rise in $[H^+]a$ (Figure A-107). There were no differences seen in serum electrolyte concentration, even after corrected for the transient decrease in plasma volume due to exercise (Figure A-108 and Figure A-109).

Table A22. Select Means for Exercise EVA with P_ICO_2 of 15 mmHg (Luft 1974)

exer kpm/ min	exer watts	exer kcal/ min	$\dot{V}_I$ $L_{(BTPS)}$/ min	HR bpm	$\dot{V}O_2$ $L_{(STPD)}$/ min	ΔO_2 (e – c)	$\dot{V}CO_2$ $L_{(STPD)}$/ min	ΔCO_2 (e – c)	RER
300	50	5							
cont			27.67	111	0.89	0.04	0.84	-0.180	0.94
exper			41.04	114	0.93		0.66		0.71
600	100	8							
cont			40.00	128	1.31	0.02	1.22	-0.126	0.93
exper			58.70	131	1.33		1.094		0.82
900	150	11							
cont			62.66	152	1.95	0.02	1.94	-0.100	0.99
exper			89.45	155	1.97		1.84		0.94

Note: No difference between experiment and control for O_2 consumption as exercise increases but a decrease in CO_2 production difference, as reflected in lower RER for hypercapnia with exercise.

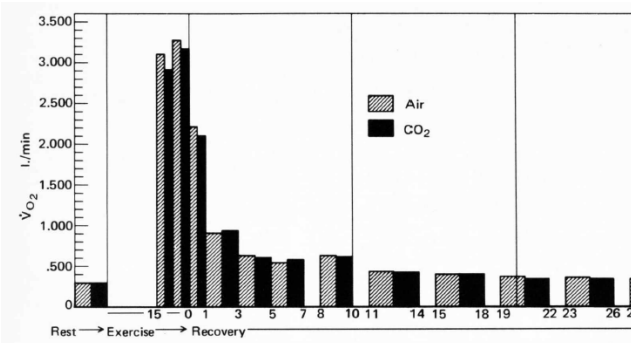


Fig. 1. Oxygen intake at rest before, during the last two minutes of exercise and for 30 mir

Figure A-102

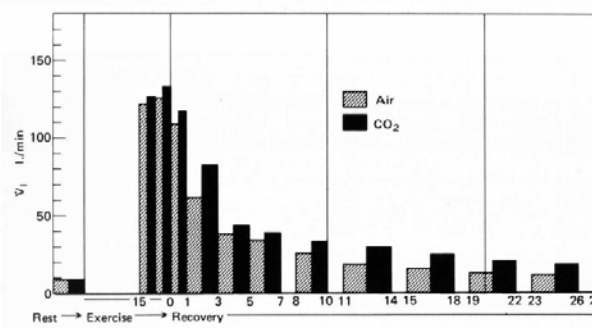


Fig. 2. The same as Figure 1 for ventilation.

Figure A-103

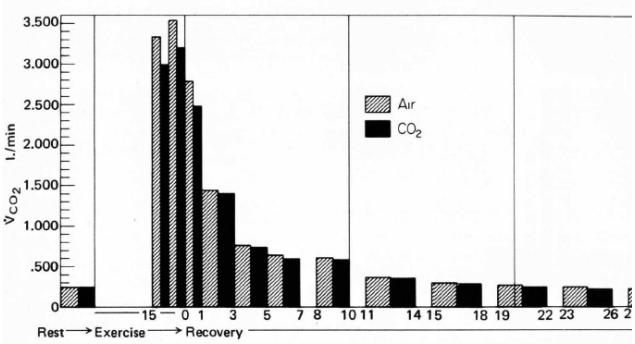


Fig. 3. The same as Figures 1 and 2 for carbon dioxide output.

Figure A-104

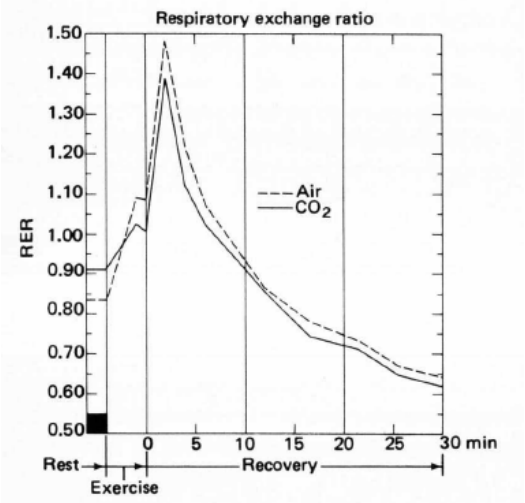


Fig. 4. The same as Figures 1 to 3 for the respiratory exchange ratio.

Figure A-105

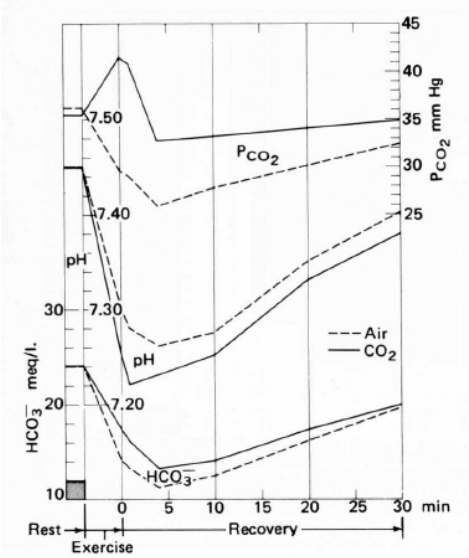


Fig. 6. Acid-base changes during and after exercise with and without 15 mm Hg $P_{I_{CO_2}}$.

Figure A-106

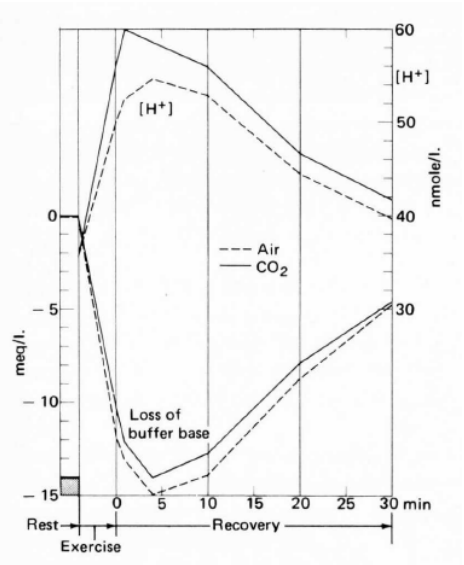


Fig. 7. Hydrogen ion activity and base deficit during and after exercise with and without 15 mm Hg $P_{I_{CO_2}}$.

Figure A-107

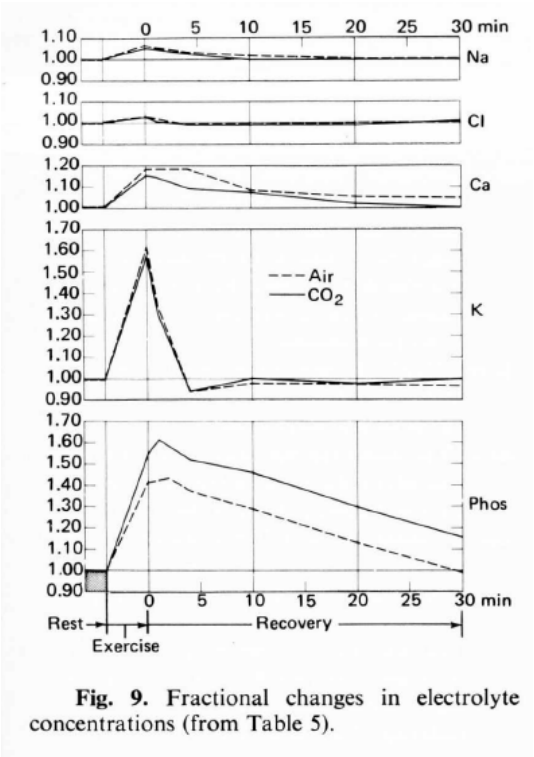


Fig. 9. Fractional changes in electrolyte concentrations (from Table 5).

Figure A-108

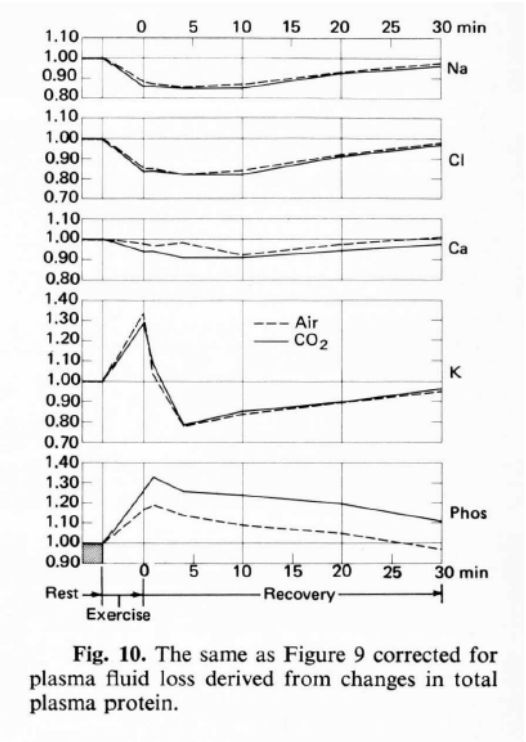


Fig. 10. The same as Figure 9 corrected for plasma fluid loss derived from changes in total plasma protein.

Figure A-109

A-12. Hypercapnia in hypobaric hyperoxia with rest and exercise in 1G.

A-13. Human response variation to hypercapnia/genetics, gender, etc.

(Bishop, Lee et al. 1999)
Aerobic fitness ($\dot{V}O_2max$) of males during hypercapnic exercise correlated with completed walk time in the LAE suit at 16.2 psia (1.5 psid during test at sea level pressure). Finishers had a mean $\dot{V}O_2peak$ of 56.1 mL/kg/min versus non-finishers of 42.1 mL/kg/min. Fit subjects introduced less CO_2 into the helmet space since inspired CO_2 were lower in those that finished after 3 minutes of walking than non-finishers at both 1.0 and 1.5 psid above ambient sea level pressure. Fit people can extract more O_2 (more efficient) to support muscle metabolism through various anatomical and biochemical adaptations, plus differences in genetic endowment. See summary under #4.

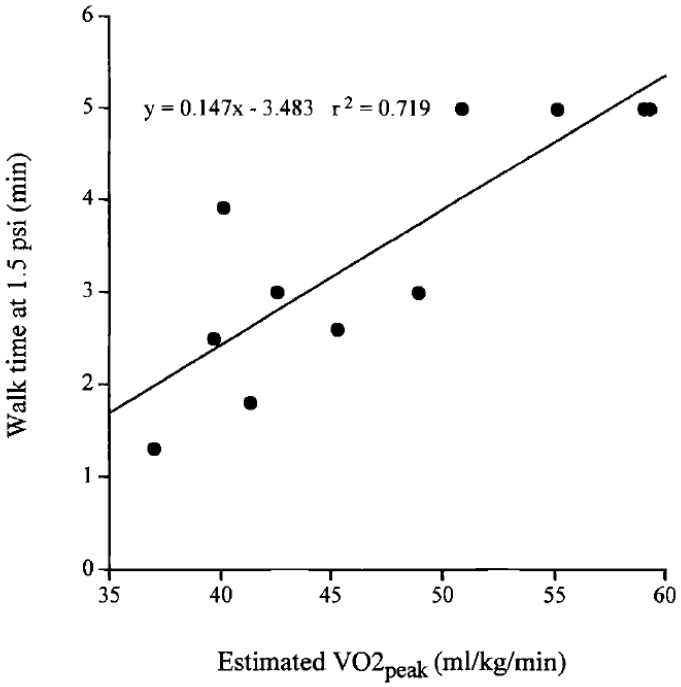


Fig. 5. Regression of walk time with 1.5 psi G-suit inflation against estimated $\dot{V}O_2peak$, (n = 11).

Figure A-110

(Morelli, Badr et al. 2004)
Men and women have different sensitivity (peripheral chemoreflex sensitivity) in ventilation response to hypercapnia, which is modified after exposure to hypoxia. Ventilatory response to CO_2 above a set point was increased in men compared to women before exposure to episodic hypoxia, independent of the PO_2 maintained during the rebreathing trial. Enhancement of the acute ventilatory response to CO_2 after episodic hypoxia is sex dependent.

Table A23. Response Before Episodic Hypoxia Breathing

rebreather PO_2 condition during hypercapnic ventilatory response (HVR)	mean male HVR (L/min/mmHg CO_2)	mean female HVR (L/min/mmHg CO_2)
hypoxic PO_2 of 50 mmHg	5.19	4.70
hyperoxic PO_2 of 150 mmHg	4.37	3.21

Table A24. Response After Episodic Hypoxia Breathing

rebreather PO_2 condition during hypercapnic ventilatory response (HVR)	mean male HVR (L/min/mmHg CO_2)	mean female HVR (L/min/mmHg CO_2)
hypoxic PO_2 of 50 mmHg	9.52	5.97
hyperoxic PO_2 of 150 mmHg	5.73	3.83

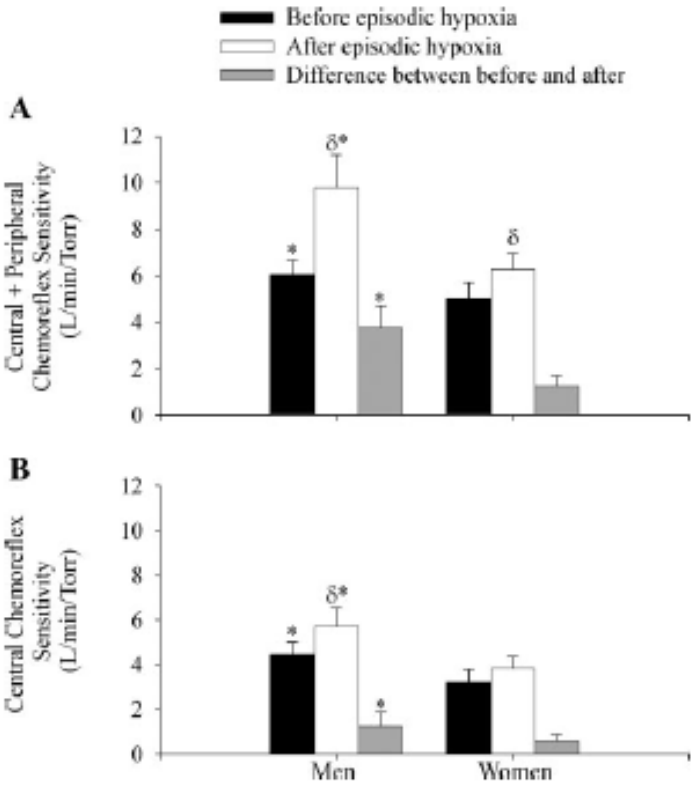


Fig. 2. Histograms showing the average chemoreflex sensitivity obtained from the rebreathing trials completed by men and women while oxygen was maintained at 50 Torr (central + peripheral chemoreflex; *A*) or 150 Torr (central chemoreflex; *B*) before (black bars) and after (white bars) exposure to episodic hypoxia. Moreover, histograms showing the difference between chemoreflex sensitivity measured before and after episodic hypoxia (gray bars) for men and women are shown. Note that before exposure to episodic hypoxia central and central + peripheral chemoreflex sensitivity was greater in men compared with women. Additionally, note that the increase in central and central + peripheral chemoreflex sensitivity after episodic hypoxia was greater in men compared with women. Values are means ± SE. *Significantly different from women, $P < 0.05$. δSignificantly different from baseline $P < 0.05$

Figure A-111

(Laurie, Vizzeri et al. 2017)
See summary under #2.

(Lambertsen 1960)
$\dot{V}_E$ response to 2%, 4%, and 6% CO_2 in normobaric air is not universally the same for all male subjects. There are those that respond with a vigorous increase in $\dot{V}_E$ in response to an increase in P_ACO_2 ($\Delta\dot{V}_E/\Delta P_ACO_2$ ratio) and those that do not.

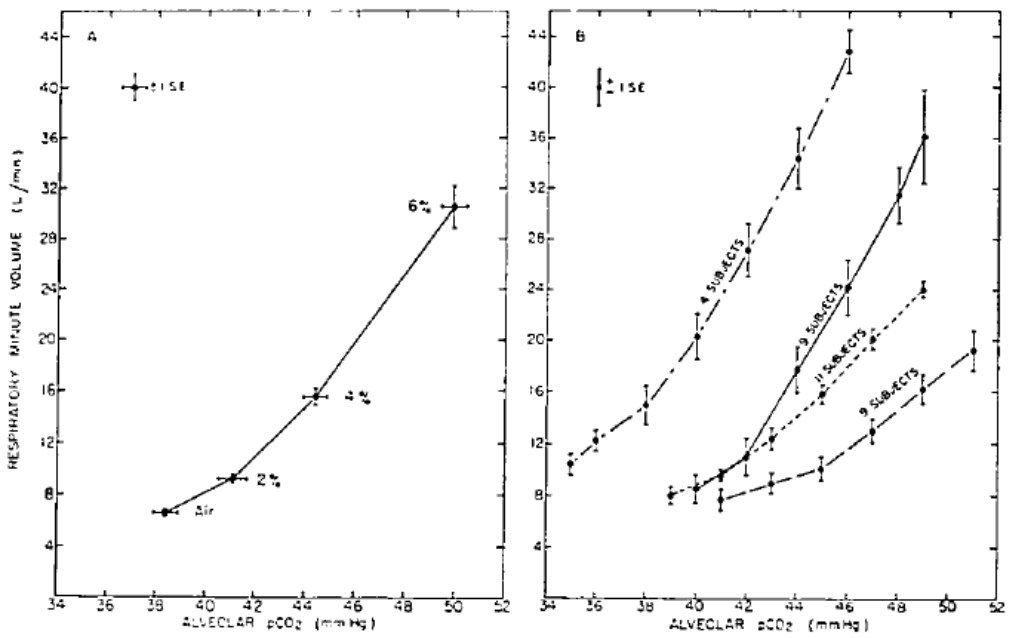


FIG. 1. Variability of the respiratory response of normal subjects to low concentrations of inspired carbon dioxide. In *A*, the responses to approximately 2, 4, and 6 per cent CO_2 in 21 per cent O_2 in N_2 are averaged. For *B*, the individual CO_2 "Response" curves were appraised to obtain interpolated values of respiratory minute volume at selected levels of P_{CO_2}.[2, 12] In the course of this appraisal, it became apparent that the total subject population could be grouped such that at least four statistically different patterns of respiratory response appeared.

Figure A-112

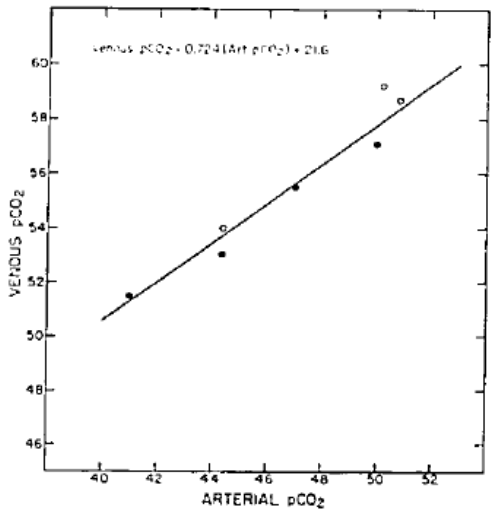


FIG. 3. Regression of the CO_2 tension of internal jugular venous P_{CO_2} upon that in arterial blood in normal subjects exposed to low concentrations of inspired CO_2 in 21 per cent O_2 in nitrogen. Plotted points represent mean values for the 8 and 5 subjects used in the several phases of the two studies selected. ● from reference 10; ○, reference 3. The somewhat smaller rise in central venous than in arterial P_{CO_2} is in large measure related to the influence of hypercapnia upon the rate of brain circulation.[10]

Figure A-113

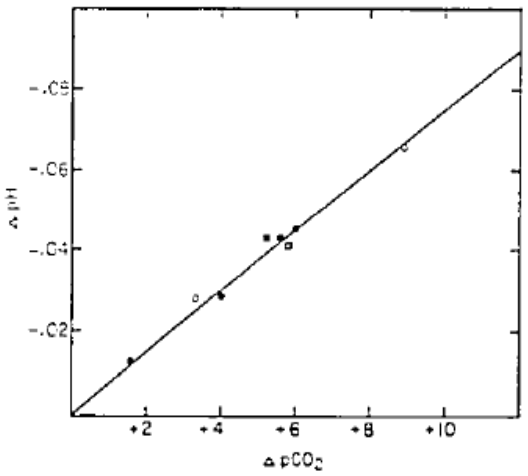


FIG. 4. Relationship of change in P_{CO_2} to change in *p*H in the arterial and internal jugular venous blood of normal subjects. Each plotted point represents the average finding in the 8 or 5 subjects used for the studies which provided the data.[3, 10] The observed slope of this relationship, $-.0075$ ΔpH/mm. Hg ΔP_{CO_2} is identical with that found in 7 other subjects by Loeschcke *et al.*[6] ○ = arterial.[10] ● = venous,[10] □ = arterial,[3] ■ = venous.[3]

Figure A-114

Note: Significance of Figure 4 is that there exists a linear relationship between P_aCO_2 and P_vCO_2 and pH. The relationship between change in PCO_2 and pH has a slope of -0.007 pH units/1.0 mmHg increase in PCO_2. For example, a 10 mmHg increase in P_aCO_2 from 40 to 50 mmHg will reduce normal pH of 7.400 to 7.325.

(Sebert, Barthelemy et al. 1990)
Seven men and 7 women were compared after a single-breath 13% CO_2 hypercapnia in normoxic and hyperoxic normobaric exposures. Mean sensitivity ($\Delta\dot{V}_E/\Delta P_{ET}CO_2$) in normoxia was greater in men (0.37 $L_{(BTPS)}$/min/mmHg $P_{ET}CO_2$) than women (0.15). Sensitivity decreased in hyperoxia for both men and women but was still greater in men (0.19) than women (0.11). A general consensus is that women are less sensitive to chemical stimulation from hypercapnia, hypoxia, and hypercapnic hypoxia, which may be explained by different hormonal status.

Table 1. Ventilation, $\dot{V}_E$, and PET_{CO_2} before (control) and after inhalation of a single breath of a normoxic or hyperoxic gas mixture containing 13% CO_2 (CO_2 SB): S is the peripheral ventilatory CO_2 sensitivity calculated as $S = \Delta\dot{V}_E/\Delta PET_{CO_2}$

	Normoxia: $PIO_2 \approx 150$ Torr		Hyperoxia: $PIO_2 \geqq 600$ Torr	
	men (n = 7)	women (n = 7)	men (n = 7)	women (n = 7)
Control				
$\dot{V}_E$, $L_{BTPS} \cdot min^{-1}$	9.4 ± 0.39	7.0 ± 0.55	9.9 ± 0.62	7.7 ± 0.86
PET_{CO_2}, Torr	30.0 ± 1.30	31.2 ± 0.78	30.5 ± 0.12	29.8 ± 0.99
CO_2 SB				
$\dot{V}_E$, $L_{BTPS} \cdot min^{-1}$	14.2 ± 1.25	8.7 ± 0.66	12.4 ± 0.62	9.1 ± 1.13
PET_{CO_2}, Torr	44.7 ± 3.12	44.7 ± 1.35	43.3 ± 1.28	41.9 ± 1.85
S, $L_{BTPS} \cdot min^{-1} \cdot Torr^{-1}$	0.370 ± 0.0880	0.148 ± 0.0251	0.192 ± 0.0435	0.110 ± 0.0231
	0.270 ± 0.0570 (n = 14)		0.165 ± 0.0249 (n = 14)	

Figure A-115

(Law, Young et al. 2017)
CO_2 training provided by rebreathing for about 10 minutes from an anesthesia bag. The number of symptoms from 130 astronauts reported per session out of the possible 24 was related to age and sex, with those older slightly more likely to report symptoms. Women reported more symptoms on average than men (men: 3.7, women: 4.7). Respiratory symptoms (90%), flushing sensation / sweating (56%), and dizziness/feeling faint/lightheadedness (43%) were the top symptoms. Only headache reached statistical significance in differences between men (13%) and women (37%) after adjustment for multiple testing. Among those with multiple training sessions, respiratory symptoms were the most consistently reported.

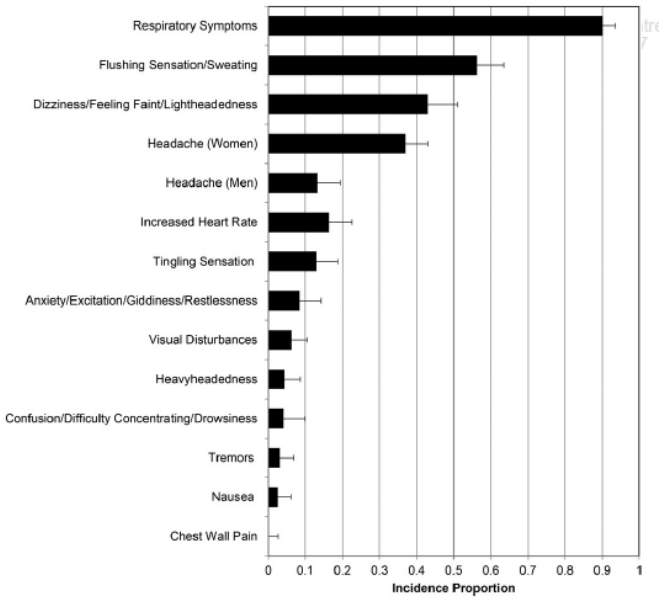


Fig. 3. Incidence of symptoms reported during CO_2 exposure training, adjusted for repeated measures; error bars denote width of the 95% confidence interval.

Figure A-116

(Bloch-Salisbury, Lansing et al. 2000)
See summary under #4.

Table 1. *Subject Characteristics and Mean Ventilatory Parameters Used in the Experimental Tasks*

Subject	Gender	Age (years)	Weight (kg)	V_T (ml)	Rate (bpm)	$\dot{V}_E$ (l/m)	Resting $P_{ET}CO_2$ (mmHg)	Low $P_{ET}CO_2$ (mmHg)	Normal $P_{ET}CO_2$ (mmHg)	High $P_{ET}CO_2$ (mmHg)
1	F	31	62	1400	12	16.8	37	29	37	44
2	F	40	59	1000	16	16.0	41	31	41	51
3	F	24	64	900	18	16.2	40	29	39	47
4	F	26	52	900	13	11.7	44	32	40	50
5	M	43	80	1300	14	18.2	42	31	40	49
6	M	24	77	1150	15	17.3	37	28	37	43
7	F	35	67	1000	13	13.0	37	28	37	46
8	F	27	52	900	16	14.4	36	27	36	44
9	F	23	48	900	10	9.0	38	34	39	46
Mean		30	62	1050	14	14.7	39	30	38	47

Note: V_T = tidal volume; Rate = respiratory frequency; $\dot{V}_E$ = minute ventilation.

Figure A-117

(Dahan, DeGoede et al. 1990)
See summary under #1. The results of their breath-to-breath analysis of the hyperoxic experiments indicate that there is a great diversity between subjects with regard to the magnitude of the peripheral component of ventilatory response to CO_2.

(Haywood and Bloete 1969)
Twenty women breathed 5 to 10 minutes (reaching steady-state ventilation) normobaric air with 0%, 4%, 5%, 6%, and 7.5% CO_2. Results of $\Delta\dot{V}_E/\Delta P_ACO_2$ were compared to previous studies with men. Women's $\Delta\dot{V}_E/\Delta P_ACO_2$ were higher than men as well as respiration rate while breathing 4 or 5% CO_2.

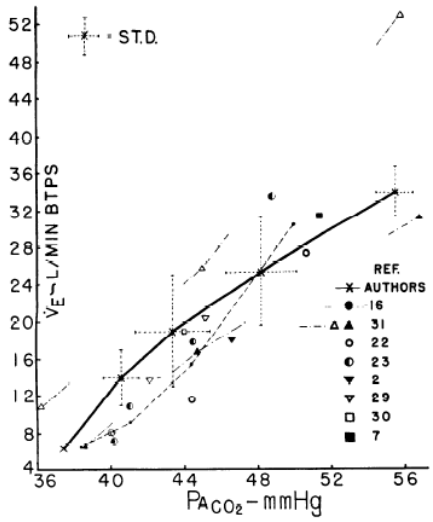


FIG. 3. Comparison of $\dot{V}_E/P_{A_{CO_2}}$ of young women with that of n
Subjects reclining and CO_2 in 21.0 ± 1.0% O_2 unless otherwise sta
N = no. of subjects.—×— Authors' young women: CO_2, 5 min;
(N = 14); 5% (N = 17); 6% (N = 14); 7.5% (N = 3). —●— L
bertsen (16): CO_2, 0, 2, 4, 6%, 8–13 min, increased without ir
mediate recovery periods; N = 33; based upon reports (21, 25,
–·–△–·– Schaefer (31): CO_2, 5.4 and 7.5%, 15 min; high ventila
N = 44. –·–▲–·– Schaefer (31): CO_2, 5.4 and 7.5%, 15 min;
ventilators; N = 21. ○ Lambertsen et al. (22): CO_2, 8–10 min,
creased without intermediate recovery periods; N = 5. ◐ Lerche e
(23): CO_2 in 35% O_2, 15 min; N = 7. ▼ Alexander et al. (2): C
21–32 min; N = 9, at rest. ▽ Rahn et al. (29): CO_2 in O_2, rebreat
10–15 min; N = 4, seated. □ Read et al. (30): CO_2, 30 min; N =
seated. ■ Eldridge et al. (7): CO_2, 10 min; N = 10, seated.

Figure A-118

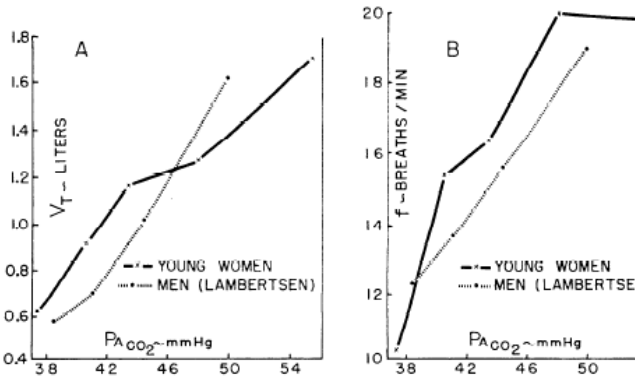


FIG. 4. Average responses of V_T and f to inhaled CO_2. Auth
data on young women, with 0, 4, 5, 6, and 7.5% CO_2. Lamberts
data on men (17) with 0, 2, 4, and 6% CO_2. *A*: V_T; *B*: f.

Figure A-119

(Ainslie and Poulin 2004)
See summary under #3.

(Gill, Natoli et al. 2014)
See summary under #1.

(Zwart, Gibson et al. 2012)
Metabolic variables do not change in μG in response to mild chronic hypercapnia, just that Cystathionine, for example, is higher in those with ocular changes (OC+) than in those without ocular changes (OC-). The hypothesis is that modification in vascular reactivity due to chronic CO_2 combined with fluid changes and other changes associated with μG manifest in ocular changes in a subset of astronauts with genetic alterations in specific metabolic pathways.

TABLE 1 Serum folate– and vitamin B-12–dependent 1-carbon pathway metabolites before, during, and after long-duration spaceflight in crewmembers with (OC+) and without (OC-) ophthalmic changes after flight[1]

	L-180	L-45	L-10	FD15	FD30	FD60	FD120	FD180	R+0	R+30
n										
OC-	14	15	11	15	15	14	10	8	15	15
OC+	5	5	5	5	5	5	5	5	5	5
MMA, *nmol/L*										
OC-	170 ± 66	175 ± 76	193 ± 96	142 ± 40	157 ± 49	161 ± 37	141 ± 32	148 ± 37	161 ± 72	166 ± 48
OC+ **	211 ± 80	212 ± 46	200 ± 92	196 ± 49	221 ± 86	204 ± 53	202 ± 50	197 ± 64	200 ± 59	198 ± 57
2MCA,[a,b] *nmol/L*										
OC-	152 ± 38	152 ± 33	153 ± 30	146 ± 34	133 ± 32	122 ± 27	119 ± 28	137 ± 49	131 ± 37	146 ± 35
OC+ **	195 ± 55	195 ± 58	191 ± 29	169 ± 32	173 ± 37	182 ± 31	160 ± 39	162 ± 30	183 ± 41	193 ± 34
Cystathionine, *nmol/L*										
OC-	141 ± 38	173 ± 71	157 ± 39	151 ± 38	153 ± 42	159 ± 47	137 ± 47	149 ± 35	170 ± 105	170 ± 57
OC+ **	206 ± 49	262 ± 78	206 ± 79	198 ± 27	200 ± 40	247 ± 56	217 ± 64	198 ± 29	342 ± 196	253 ± 80
Hcy, *μmol/L*										
OC-	8 ± 1	8 ± 1	8 ± 2	7 ± 1	8 ± 1	8 ± 1	8 ± 1	8 ± 1	7 ± 2	8 ± 2
OC+ **	10 ± 2	11 ± 1	10 ± 2	9 ± 0	10 ± 1	10 ± 1	9 ± 1	9 ± 0	10 ± 1	9 ± 1
Folate, *nmol/L*										
OC-	44 ± 22	48 ± 29	41 ± 15	39 ± 16	35 ± 10	37 ± 15	36 ± 16	53 ± 56	34 ± 15	36 ± 11
OC+ ***	48 ± 49	44 ± 46	24 ± 8	26 ± 11	26 ± 13	26 ± 16	29 ± 14	28 ± 14	27 ± 16	48 ± 45
Cabin CO_2, *mm Hg*										
OC-				2.6 ± 1.4	2.9 ± 1.3	2.9 ± 0.9	2.6 ± 1.2	2.9 ± 0.6		
OC+ *				3.6 ± 0.7	3.7 ± 0.5	3.8 ± 0.5	3.3 ± 0.8	3.1 ± 1.1		

[1] Untransformed data are presented as mean ± SD. Asterisks indicate different from OC- (group effect): * $P < 0.05$, ** $P < 0.001$, ***Different from OC- when in-flight data were compared and 1 OC+ outlier was removed ($P < 0.01$). The folate data presented here represent all participants (including the outlier). [a]Effect of spaceflight (R+0 < preflight, $P < 0.05$). [b]Effect of spaceflight (in-flight < preflight, $P < 0.05$). FD, flight day; Hcy, homocysteine; L-, launch minus (days before flight); 2MCA, 2-methylcitric acid; MMA, methylmalonic acid; OC+, group of individuals who had ophthalmic changes; OC-, group of individuals who did not have ophthalmic changes; R+0, landing day; R+30, 30 d after landing.

Figure A-120

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Clark, Sinclair et al. 1980)	normo	normo	PCO_2 10 20 30 40	yes	yes	1	yes		1
(Menn, Sinclair et al. 1970)	normo	normo	P_ICO_2 8 15 21 30	yes	yes	1	yes		1

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Graham, Wilson et al. 1982)	normo	normo	PCO_2 15.2 30.4 45.6	yes	yes	1	yes		1
(Jacobi, Iyawe et al. 1987)	normo	normo	hyper see paper	yes	yes	1	yes		1
(Ellingsen, Sydnes et al. 1987)	normo	normo	PCO_2 7.6 15.2	yes		1	yes		1
(Sayers, Smith et al. 1987)	normo	normo	PCO_2 34.2 41.8 49.7 57.0	yes		1	yes	yes	1
(Bishop, Lee et al. 1999)	normo	hyper	hyper see paper	yes	yes	1	yes		4
(Vercruyssen 2014)	normo	hyper	PCO_2 30.4	yes		1		yes	4
(Vercruyssen, Kamon et al. 2007)	normo	hyper	PCO_2 22.8 30.4	yes	yes	1		yes	4
(Vercruyssen and Kamon 1984)	norm	hyper	PCO_2 15.2	yes	yes	1		yes	4
(Liu, Liu et al. 2015)	hypo	hypox	PCO_2 2.3 14.3	yes	yes	1	yes		11

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
			23.8						
(Loeppky 1998)	hypo	hypox	P_ICO_2 5.4 5.7 7.5 9.4 15.0	yes	yes	1	yes		11
(Forster, Klein et al. 1982)	norm	norm	P_ICO_2 7 14 21 28 35 42	yes		1	yes		1
(Sheehy, Kamon et al. 1982)	norm	hyper	PCO_2 30.4 38.0	yes	yes	1		yes	4
(Henning, Sauter et al. 1990)	norm	norm	PCO_2 45.6	yes		1		yes	1
(Henning, Sauter et al. 1990)	norm	hyper	PCO_2 45.6	yes		1		yes	4
(Gill, Natoli et al. 2014)	norm	norm	PCO_2 49 57 65	yes	yes	1	yes	yes	1
(Gill, Natoli et al. 2014)	hyper	hyper	PCO_2 41	yes	yes	1	yes	yes	7

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
			49 57 65						
(Fan and Kayser 2013)	norm	hypox	hyper see paper	yes	yes	1	yes		3
(Fan and Kayser 2013)	norm	norm	hyper see paper	yes	yes	1	yes		1
(Poon and Greene 1985)	norm	norm	hyper see paper	yes	yes	1	yes		1
(Laurie, Vizzeri et al. 2017)	norm	norm	PCO_2 7.6	yes		0	yes		2
(Kurazumi 2018)	norm	norm	PCO_2 22.8	yes		0	yes		2
(Marshall-Goebel 2018)	norm	norm	PCO_2 3.8	yes		0	yes		2
(Marshall-Goebel, Mulder et al. 2017)	norm	norm	PCO_2 7.6	yes		0	yes		2
(Michel, Sharma et al. 1969)	hyper	hyper	hyper see paper	yes	yes	1	methods	methods	7
(Law, Van Baalen et al. 2014)	norm	norm	hyper see paper	yes		0		yes	2
(Law, Watkins et al. 2010)	norm	norm	hyper see paper	yes		0		yes	2

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(James, Meyers et al. 2011)	norm	norm	hyper see paper	yes		0		yes	2
(Cronyn, Watkins et al. 2012)	norm	norm	hyper see paper	yes		0		yes	2
(Lambertsen 1960)	norm	norm	PCO_2 <45.6	yes		1	yes		1
(Lambertsen, Hall et al. 1963)	norm	hyper	PCO_2 11.4 22.8	yes		1	yes		4
(Lambertsen, Hall et al. 1963)	hyper	hyper	PCO_2 11.4 22.8	yes		1	yes		7
(Storm and Giannetta 1974)	norm	norm	PCO_2 30	yes		0		yes	2
(Storm and Giannetta 1974)	norm	norm	PCO_2 30	yes		1		yes	1
(Satish, Mendell et al. 2012)	norm	norm	PCO_2 0.45 0.76 1.90	yes		1		yes	1
(Allen, MacNaughton et al. 2016)	norm	norm	PCO_2 <1.06	yes		1		yes	1
(Allen, MacNaughton et al. 2018)	norm	norm	PCO_2 0.5 1.1	yes		1		yes	1

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
			1.9						
(Rodeheffer, Chabal et al. 2018)	norm	norm	PCO_2 0.45 1.9 11.4	yes		1		yes	1
(Bakó-Biró, Clements-Croome et al. 2012)	norm	norm	PCO_2 <3.8	yes		1		yes	1
(Hughson, Yee et al. 2016)	norm	norm	PCO_2 3.8	yes		0	yes		2
(Michael and Marshall-Bowman 2015)	norm	norm	hyper see paper	yes		0		yes	2
(Bloch-Salisbury, Lansing et al. 2000)	norm	hyper	hyper see paper	yes		1	yes EEG	yes	4
(Wang, Yee et al. 2015)	norm	hyper	hyper see paper	yes		1	yes EEG		4
(Wang, Yee et al. 2015)	norm	hypo	hyper see paper	yes		1	yes EEG		3
(Wang, Yee et al. 2015)	norm	hypo	normo see paper	yes		1	yes EEG		norcapnic hypoxia
(Selkirk, Shykoff et al. 2010)	hyper	hyper	PCO_2 11.4 22.8	yes	yes	1	yes	yes	7
(Weybrew 1970)	norm	norm	PCO_2 22.8	yes		1		yes	1

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Haran and Lovelace 2015)	hyper	hyper	PCO_2 7.6 15.2	yes	yes	1	yes	yes	7
(Glatte Jr, Motsay et al. 1967)	hypo	norm	PCO_2 21	yes	yes	1	yes	yes	9
(Reynolds, Milhorn et al. 1972)	norm	norm	PCO_2 22.8 38.0 45.6 53.2	yes		1	yes		1
(Balanos, Talbot et al. 2003)	norm	norm	hyper see paper	yes		1	yes		1
(Warkander, Norfleet et al. 1990)	hyper	hyper	hyper see paper	yes	yes	1	yes	yes	7
(Fothergill, Hedges et al. 1991)	norm	norm	P_ICO_2 2 38 49	yes	?	1	?	yes	1
(Fothergill, Hedges et al. 1991)	hyper	hyper	P_ICO_2 3 20 29	yes	?	1	?	yes	7
(Nielsen and Smith 1952)	norm	hypo	PCO_2 <38.0	yes		1	yes		3
(Bitterman and Bitterman 1998)	hyper	hyper	hyper see paper	yes		1	yes (animal)		7

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Prisk, Elliott et al. 2000)	norm	hypo	hyper see paper	yes		0	yes		2
(Prisk, Elliott et al. 2000)	norm	hyper	hyper see paper	yes		0	yes		2
(Ainslie and Poulin 2004)	norm	hyper	hyper see paper	yes		1	yes		4
(Ainslie and Poulin 2004)	norm	hypo	hyper see paper	yes		1	yes		3
(Ainslie and Duffin 2009)	norm	norm	hyper see paper	yes	yes	1	yes		1
(Frey, Sulzman et al. 1998)	norm	norm	PCO_2 5.3 9.1	yes	yes	1	yes	yes	1
(Manzey and Lorenz 1998)	norm	norm	PCO_2 5.3 9.1	yes		1		yes	1
(Sliwka, Krasney et al. 1998)	norm	norm	PCO_2 5.3 9.1	yes		1	yes		1
(Zwart, Gibson et al. 2012)	norm	norm	PCO_2 3 mmHg	yes	yes	0	yes		2
(Juan, Calverley et al. 1984)	norm	norm	hyper see paper	yes		1	yes		1
(Brackett Jr, Cohen et al. 1965)	norm	norm	PCO_2 53 76	yes		1	yes		1

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Valtin 1983)	norm	norm	hyper see chapter	yes		1	yes		
(Bacal, Beck et al. 2008)	norm	norm	hyper see chapter	yes		1	yes	yes	1
(Wick 1966)	norm	norm	PCO_2 7.6 15.2 22.8	yes	yes	1	yes		1
(Wong 1992)			hyper see paper	yes	yes	1	yes	yes	
(Glatte Jr and Welch 1967)	norm	norm	PCO_2 4 to 21	yes	yes	1	yes	yes	1
(Sinclair, Clark et al. 1971)	norm	norm	PCO_2 21	yes	yes	1	yes		1
(Krasnogor, Wempen et al. 1968)	hypo	hypo	PCO_2 7.6	yes	yes	1	yes		11
(Alexander, West et al. 1955)	norm	norm	PCO_2 22.3 38.0	yes		1	yes		1
(Kronenberg and Drage 1973)	norm	norm	hyper see paper	yes		1	yes		1
(Luft, Finkelstein et al. 1974)	hypo	hypo	P_ICO_2 15	yes	yes	1	yes		11
(Weitzman, Kinney et al. 1969)	norm	norm	PCO_2 0 to 22.8	yes		1		yes (vision)	1

Table A25. Literature Specific to Acute Space Suit Hypercapnia Limits

reference	P_B	O_2	CO_2	rest	exer	grav	phys	neuro	code
(Sun, Sun et al. 1996)	norm	norm	PCO_2 19	yes		1		yes (vision)	1
(Yang, Sun et al. 1997)	norm	norm	PCO_2 19	yes		1		yes (vision)	1

Note 1: In most cases PCO_2 is estimated from F_ICO_2 provided by the author with the assumption that research was done at sea level pressure. Therefore, the actual as-tested PCO_2 may be slightly lower than tabulated if research was done at <760 mmHg.

Note 2: "see paper" designation often means that CO_2 was added to breathing gas to achieve a specific hypercapnic $P_{ET}CO_2$, P_ACO_2, or even blood-gas P_aCO_2, so no specific PCO_2 is reported by the author.

(Wong 1992)
Extensive review in 1992 about CO_2 exposure to set SMAC limits for long-duration space habitation. Provided a Toxicity Summary Table applicable to consideration of limits for EVA, so is reproduced here along with cited references, as additional resource.

TOXICITY SUMMARY TABLE*

Conc.	Expo. Dur.	Species	Effects	Ref.
0.5%	30 d	Human	No acidosis, hyperventilation, or symptoms. No changes in urinary excretion of potassium, sodium, or calcium.	104
0.6% in d 1-46, 0.8% in d 47-90	90 d	Human	No change in serum calcium level in d 1-53, but it decreased accompanied with an increase in serum phosphorus in d 54-90. No changes in hematological indices & psychomotor performance.	124
0.7%	7 w	Human	Higher serum levels of calcium, magnesium, & inorganic phosphorus. Lower urinary excretions of calcium, magnesium, & inorganic phosphorus. Urinary excretion of acids was lower except during the 3rd & 4th weeks when it was higher than pre-exposure level.	131
0.8-0.9%	20 d	Human	Physiological dead space increased by 50-60%, which returned to normal soon after the exposure.	34
0.85-1.2%	57 d	Human	In plasma: increase in sodium, decreases in K^+ & Ca^{++}, but no change in phosphorus; increased Mg^{++} only on d 51; decrease in Cl^- in w 5-7; decreases in pH, increases in pCO_2 & bicarbonate in w 4 with complete recovery by d 51; In urine: phosphorus & hydroxyproline decreased in w 1-3; Ca^{++} decreased in w 1-3, increased in w 4-5, then decreased in w 6-9. No changes in parathyroid or calcitonin activity.	41
1%	17-32 min	Human	Alveolar ventilation increased by 24%, slight increases of systolic and diastolic blood pressure.	29
1%	30 d	Human (n = 1)	Acidosis. Increases in blood pCO_2 & respiratory ventilation. No change in performance in physical exercise.	70
1%	30 d	Human	Hyperventilation. No symptoms. No changes in urinary excretion of potassium, sodium, or calcium. Increased arterial pO_2.	104

23

Figure A-121.1

1 or 2%	30 min	Human	No symptoms during exercises at two-thirds maximum or maximum oxygen consumption.	72
1.1% TWA with excursions up to 8% for 3 min	8 h/d, 5 d/w	Human (workers)	No change in blood HCO_3^- levels.	77
1.5%	10-15 min	Human	Increases in respiratory rate & tidal volume. The respiratory rate increase was lower & the tidal volume increase was higher in diving instructors than other individuals.	52
1.5%	15 h/d, 6 d	Human (n=1)	Impairment in night vision sensitivity & green color sensitivity. All other visual functions were normal.	87
1.5%	42 d	Human	Alveolar ventilation increased by 8%. Ventilatory response to 5% CO_2 challenges decreased at the end of the 6th w. Increase in anatomic dead space of the lung. O_2 consumption increased in the first 2 w. Plasma Ca^{++} & phosphorus followed the changes in plasma pH. Uncompensated respiratory acidosis in the first 3 w: decreases in blood pH, urine pH, urinary HCO_3^- excretion, & CO_2 exhalation. Compensated respiratory acidosis in the last 3 w: normal blood pH, increases in urine pH, urinary HCO_3^- excretion, & CO_2 exhalation. No effects on weight, pulse rate, blood pressures, oral temperature, adaptation to darkness, visual acuity, visual accommodation, depth perception, pitch discrimination, manual dexterity, letter-cancelling ability, problem-solving ability, mechanical ability, strength, coordination, and immediate memory. Apathy, increased sexual desire, a desire to leave, and uncooperativeness.	50, 51, 65-68, 133
1.8 or 3.5%	11-40 min	Human	No changes in oxygen consumption, pulse rate, & cardiac output. Increase in respiratory ventilation.	61
1.9%	N.S. (until subjects could not exercise	Human	Compared with exercising in normal air: 45% higher ventilation when doing submaximal exercise, but the exposure did	75

Figure A-121.2

	further)		not increase ventilation further when doing maximal exercise (O_2 consumption was even lower).	
2%	30 d	Human	No acidosis. No headaches. No change in psychomotor performance. Hyperventilation (more at 2 h than 24 h). Good ability to exercise.	104
2%	17-32 min	Human	Alveolar ventilation increased by 50%, slight increases of systolic and diastolic blood pressure.	29
2%	Several h	Human	Headache & dyspnea on mild exertion.	55
2%	30 d	Human (n = 1)	Acidosis. Increases in blood pCO_2 & respiratory ventilation. Deterioration in performance in physical exercise.	70
2.5%	2 h	Human	No changes in specific airway conductance.	53
2.5-2.8% CO_2 in 14.6-15% O_2	Several h	Human	No giddiness, headache, dyspnea, or drop in body temperature.	132
2.7%	30 d	Human	Mild headaches only in the first d. Hyperventilation that diminished after the first d.	59
2.8%	1 h or 15-20 d	Human	Acidosis. Abilities to exercise moderately or heavily did not change. During exercise: occasional mild headaches, but no dyspnea, intercostal muscle pain, or EKG changes. No difference between acute & subchronic CO_2 exposures.	74
2.8 or 3.9%	30 min	Human	Intercostal muscle pain & respiratory difficulties during exercises at two-thirds maximum or maximum oxygen consumption, so that ability to do heavy exercise was impaired. Mild to moderate frontal headaches at 3.9% CO_2 occurred near the end of the exercise period. No significant increases in premature atrial or ventricular contractions usually seen with exercise in normal atmosphere.	72
2.9%	8 d	Human	Acidosis & hyperventilation at 2 &	104

Figure A-121.3

			24 h. Slight headaches. Extrasystoles during exercise. No change in psychomotor performance.	
3%	Several h	Human	Dyspnea even at rest, headache (more severe than at 2% CO_2), & diffuse sweating.	55
3%	78 h	Human (n = 2)	Acclimation in the ventilatory effect of CO_2: minute volume was 15.1 l/min at the start & 12.9 l/min near the end of the exposure.	54
3%	5 d	Human	Very slight acidosis in d 1-3, elevated arterial pCO_2 & serum HCO_3^- level in d 3-5. Respiratory ventilation increased by 15-60%, which was easily tolerated. Mild-to-moderate headaches in 4/7 subjects in d 1-2. No changes in vital capacity & 1-sec vital capacity, psychomotor functions (hand steadiness, vigilance, auditory monitoring, memory, arithmetic, & problem solving), urinary levels of Ca^{++}, phosphorus, K^+, Na^+, NH_3, & titratable acidity, serum levels of Ca^{++}, phosphorus, K^+, Na^+, alkaline phosphatase, SGOT, SGPT, direct bilirubin, & indirect bilirubin. No change in the ability to exercise moderately for 1 h daily. No EKG problems.	33
3%	8 d	Human	A slight state of excitement in d 1 (euphoria, troubled sleep with frequent dreams & nightmares), followed by slight depression of the nervous systems in the remainder of the exposure (inattentiveness, erratic behavior, exhaustion, confusion, & decreased manual skills). Uncompensated respiratory acidosis in the first 3 d. The acidosis was then compensated by increases in plasma HCO_3^- level, urinary excretion of acid, & alkali retention by kidneys. When the subjects performed moderate work load, the tidal volume decreased & the respiratory rate increased, leading to higher O_2 uptake & CO_2 excretion.	62, 69
3.0-3.5%	1-2 min	Human	Small loss in hearing threshold.	30,31

Figure A-121.4

3.2% CO_2 in 13.4% O_2	Several h	Human	Giddiness & headache. No dyspnea or drop in body temperature.	132
3.3%	10-15 min	Human	Increases in respiratory rate & tidal volume (diving instructors and other subjects responded similarly). CNS depression: decrease in flicker-fusion threshold, increased latent time of alpha blocking after light stimulus. Increases in blood sugar & oxygen consumption. Decrease in the eosinophil count.	47, 52
3.8%	9 d	Human	Acidosis & hyperventilation at 2 & 24 h. Intense & annoying headaches & gastralgia. Extrasystoles during exercise. Limited exercise capacity. No change in psychomotor performance.	104
3.9%	5 or 11 d	Human	Acidosis in d 1-4, but arterial & CSF pH returned to normal in d 5. Mild headaches in d 1 only. Hyperventilation (it decreased in magnitude starting d 2).	59
4%	5 d	Human	Acidosis. Tidal volume almost doubled, but no change in respiratory rate. Mild-to-moderate, throbbing frontal headaches beginning in the first few hours, but none starting d 3.	71
4%	11 d	Human	Alveolar ventilation increased by 200% in day 1, but the increase dropped to 150% after day 1. Increased pCO_2 in arterial blood & cerebral spinal fluid.	28
4%	2 w	Human	No change in hand-eye coordination, complex tracking performance, & problem-solving ability.	60
4.3%	1 d	Human	Acidosis & hyperventilation at 2 & 24 h. Intense & annoying headaches & gastralgia. Not able to exercise. No change in psychomotor performance.	104
4-5%	17-32 min	Human	Dyspnea.	29
4-5%	About 4 h	Human	Body temperature dropped $1^{o}F$. Deterioration in performance in cancellation test. No effects on the Army Alpha intelligence test, arithmetic test,	132

Figure A-121.5

			muscular coordination, & attention.	
4.5%	30 min	Human	No effect on visual vigilance.	35
4.7%	Several h	Human	Headache and dyspnea.	132
4.7% CO_2,' balance O_2	15 min	Human (emphysema patients)	Alveolar ventilation increased by less than 100% (it increased by 150-300% in normal subjects).	27
5%	N.S.	Human (fighter pilots)	Significant degradation in pilot performance during landing: lengthened flight time between gear down & touch down, and unacceptable increase in touch down sink rates.	42
5%	30 min	Human	Increased renal blood flow, glomerular filtration rate, & renal venous pressure. Decreased renal vascular resistance. In plasma: increase in HCO_3^-, but no increase in NA^+, K^+, & Cl^- levels.	64
5%	17-32 min	Human	Headache, dizziness, hiccoughing	29
5 or 7%	15-30 min	Human	Increases in blood pressure, cerebral blood flow, decrease in cerebrovascular resistance, no changes in cardiac output or cerebral oxygen consumption.	58
5% in 95% O_2	45-90 min	Human (n = 2 psychotic patients)	Arterial pH dropped to 6.9. A-V nodal beats; increases in the amplitude of R & T waves; elevation or depression of S-T segment; & inverted T waves. The EKG changes disappeared within 30 min after the exposure ended.	106
5, 7.5 or 10%	2 h	Human	Decreased specific airway conductance.	53
5-6.75%	37 h	Human	Headaches, increased respiratory ventilation, soreness of the respiratory musculature, heart rate increased by 10 bpm, & slight decrease in hand-arm steadiness. No change in blood pressure, auditory discrimination, ability to stand still, ability to walk an 1-inch rail, hand-eye coordination, abilities to compute, translate, and check number.	109

Figure A-121.6

5%	Several h	Human	CNS depression.	55
5.4 or 7.5%	10-15 min	Human	Increases in respiratory rate and tidal volume. Diving instructors responded less than other subjects. Increases in blood sugar & oxygen consumption. Decrease in the eosinophil count. Increased pulse rate at 7.5% CO_2.	52
6%	1-2 min	Human	Decreased visual intensity discrimination.	32
6%	6-8 min	Human	Decrease in the amplitude of the QRS complex & T wave, especially in 61 year old men than 23 year old men. No change in S-T segments. No T inversion.	57
6%	16 min	Human	Dyspnea, headaches, sweating, hyperventilation, subjective feeling of speech difficulty (but listeners had no problem in understanding the speech), & subjective feeling of movement difficulty. Slightly slower rate of card sorting, but no change in card sorting error rate.	125
6%	20.5-22 min	Human	Considerable discomfort, but tolerable. 9% rise in systolic pressure & 7% rises in diastolic pressure & pulse rate.	36
6%	Several h	Human	Visual disturbances & tremors.	55
7% CO_2, 93% O_2	3 min	Human	Tidal volume, respiratory rate, & ventilation increased by 140, 50, & 250%, respectively.	24
7% CO_2, 93% O_2	5 min	Human	Tidal volume, respiratory rate, & ventilation increased by 150, 60, & 290%, respectively.	24
7%	60 min	Human	Arterial pCO_2, H^+, and HCO_3^- levels were raised in 10 min during exposure and remained at a plateau from min 10-60. Arterial Na^+ level increased by < 1%. No changes in arterial K^+, Cl^-, and phosphate levels. Mild headache & burning of the eyes.	110
7-14% CO_2, balance	10-20 min	Human	Headache, moaning, belligerently complaining, coughing, restlessness, sweating, twitching, tremor, amnesia,	26

Figure A-121.7

O_2			unconsciousness, increased respiratory ventilation, arterial pressure, heart rate, & plasma concentrations of epinephrine, norepinephrine, and corticosteroids. EKG at rest: premature nodal contraction (2/27 test subjects vs 0/27 before CO_2 exposure) & premature ventricular contraction (3/27 test subjects vs 1/27 before CO_2 exposure).	
7.5% CO_2 in 16% O_2	3.25-6 min	Human	Considerable discomfort, but tolerable. 24% & 20% rises in systolic & diastolic pressures, 10% rise in pulse rate.	36
7.5%	4-25 min	Human	Increases in pulse rate, cardiac output, blood pressure, & respiratory ventilation.	61
7.5%	15 min	Human	Headache, dizziness, restlessness, & dyspnea.	47
7.6%	2.5-10 min	Human	Dyspnea, dizziness, headache, head fullness, sweating, increases in respiratory ventilation, systolic & diastolic pressures.	37
8% CO_2, 19% O_2	3-6 min	Human	Total lung resistance increased by 120%. No change in static lung compliance.	25
8%	17-32 min	Human	Tolerance limit.	29
8.8% CO_2 in 39% O_2	7-10 min	Human	Approaching tolerance limit. 22% & 13% rises in systolic 7 diastolic pressures, & 13% rise in pulse rate.	36
10%	1.5 min	Human	Eye flickering, myoclonic twitches, & psychomotor excitation.	45
10%	15-25 min	Human	Restlessness, confusion, and listlessness.	110
10%	Several h	Human	Unconsciousness.	55
10.4%	3.8 min	Human	Dizziness, dyspnea, headache, head fullness, restlessness, hyperventilation, unconsciousness, & increases in systolic & diastolic pressures.	37
10.4%	1-2.25 min	Human	33% & 38% rises in systolic &	36

Figure A-121.8

CO_2 in 14.4% O_2			diastolic pressures. 19% rise in pulse rate.	
12.4%	.75-2 min	Human	Dizziness, drowsiness, near stupor, dyspnea, feeling of fullness in the head, sweating, flushing sensation, sense of impending collapse, throat irritation, & slight choking sensation. 1/7 subjects collapsed. No nausea or throbbing of temples. 55% & 26% rises in systolic & diastolic pressures & 13% rise in pulse rate.	36
15%	3 min	Human	Eye flickering, myoclonic twitches, psychomotor excitation, increased muscle tone, sweating, flushing, dilated pupils, leg flexion, torsion spasms, & restlessness.	45
17% CO_2, 17.3% O_2	20-52 sec	Human	Unconsciousness.	46
18.6%, 17% O_2	<2 min	Human	Dullness, unconsciousness, cyanosis, & throbbing headache.	38
20-22% CO_2, ca. 16% O_2	N.S.	Human (workers)	Death. In survivors: unconsciousness, cyanosis, sluggish reflexes, rattling respiration, & motor unrest.	76
20% CO_2, 80% O_2	3 min	Human	Eye flickering, myoclonic twitches, psychomotor excitation, increased muscle tone, sweating, flushing, dilated pupils, leg flexion, torsion spasms, restlessness, tonic & tonic-clonic seizures.	45
30% CO_2, 70% O_2	38 sec	Human (patients in psychiatry)	Narcosis, EKG: extrasystoles, premature atrial & nodal beats, atrial tachycardia & supraventricular tachycardia.	56
30% CO_2, 70% O_2	50-52 sec	Human (patients in psychiatry)	Unconsciousness & extrasystoles. Consciousness regained at 110 sec after exposure.	44
30% CO_2, 70% O_2	3 min	Human	Eye flickering, myoclonic twitches, psychomotor excitation, increased muscle tone, sweating, flushing, dilated pupils, leg flexion, torsion spasms, restlessness, tonic & tonic-clonic seizures.	45

Figure A-121.9

			Unconsciousness within 2 min.	
30% CO_2, 70% O_2	N.S. (10-15 breaths)	Human (patients in psychiatry)	Auricular extrasystoles, auricular tachycardia, increased P wave voltage, low or inverted P waves, spiked T waves with a broad base, increased T wave voltage, slight increases in PR intervals & QRS intervals, & marked increase in QT interval. Marked increases in systolic & diastolic pressure. Acidosis. No ventricular extrasystole.	105
0.5%	4 w	Guinea pig	No effects on body weight, the levels of calcium in kidneys, bone and plasma, Type II pneumocyte cell size, & the number of lamellar bodies in Type II pneumocytes.	20
0.5%	8 w	Guinea pig	Increased calcium levels in kidneys & plasma. No significant effects on bone calcium level, body weight gain, Type II pneumocyte cell size, & the number of lamellar bodies in Type II pneumocytes.	20
1%	1 w	Guinea pig	Acidosis. Kidney: Ca^{++} increased. Plasma: Ca^{++} & phosphorus increased. Bone: Ca^{++} & phosphorus decreased. No change in body weight gain.	19
1%	1 or 2 w	Guinea pig	Acidosis. No change in arterial pO_2, pCO_2, or HCO_3^- level. No change in the appearance of pneumocytes, alveolar macrophages, ciliated epithelial cells & Clara cells of terminal bronchioles, & endothelial cells in the lung under the electron microscope.	21
1%	2 or 4 w	Guinea pig	Acidosis. Kidney: Ca^{++} increased. Plasma: Ca^{++} & phosphorus levels did not differ from the control levels. Bone: Ca^{++} & phosphorus levels did not differ from the control levels. No changes in body weight gain.	19
1%	3 w	Guinea pig	No change in arterial pH & pO_2. Increased arterial pCO_2. Decreased arterial HCO_3^-. No change in the appearance of pneumocytes, alveolar macrophages, ciliated epithelial	21

Figure A-121.10

EXPOSURE LIMITS SET BY OTHER ORGANIZATIONS

ACGIH's TLV	= 5,000 ppm, TWA
ACGIH's STEL	= 30,000 ppm
OSHA's PEL	= 5,000 ppm, TWA (transitional limit effective till 12-30-92) 10,000 ppm, TWA (final limit effective starting 12-31-92)
OSHA's STEL	= 30,000 ppm (starting 12-31-92)
NIOSH's REL	= 10,000 ppm, TWA 30,000 ppm, Ceiling
NIOSH's IDLH	= 50,000 ppm
ASHRAE Standard 62-1989	= 1,000 ppm
Navy's 90-d Limit	= 5,000 ppm*
Navy's 24-h Limit	= 40,000 ppm
Navy's 1-h Limit	= 40,000 ppm

*According to Navy's Nuclear Powered Submarine Atmosphere Control Manual, S9510-AB-ATM-010/(U), 1988, long-term exposures to 5000-8000 ppm CO_2 probably have no significant health effect.

SPACECRAFT MAXIMUM ALLOWABLE CONCENTRATIONS

	ppm	mg/m^3	Target Toxicity
1-h SMAC	13,000	23,400	CNS Depression, Visual Disturbance
24-h SMAC	13,000	23,400	CNS Depression, Visual Disturbance
7-d SMAC**	7,000	12,600	Hyperventilation
30-d SMAC	7,000	12,600	Hyperventilation
180-d SMAC	7,000	12,600	Hyperventilation

**There was no 7-d SMAC. Space Shuttle Flight Rules require mission termination at 2% or above and flight surgeon's evaluation at 1-2%(88).

Figure A-122

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