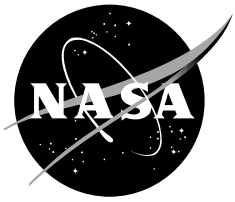
NASA/TP–2008–214759



Risk Assessment of Acute Mountain Sickness in the Crew Exploration Vehicle

Johnny Conkin, Ph.D.
Universities Space Research Association

January 2008

THE NASA STI PROGRAM OFFICE . . . IN PROFILE

Since its founding, NASA has been dedicated to the advancement of aeronautics and space science. The NASA Scientific and Technical Information (STI) Program Office plays a key part in helping NASA maintain this important role.

The NASA STI Program Office is operated by Langley Research Center, the lead center for NASA's scientific and technical information. The NASA STI Program Office provides access to the NASA STI Database, the largest collection of aeronautical and space science STI in the world. The Program Office is also NASA's institutional mechanism for disseminating the results of its research and development activities. These results are published by NASA in the NASA STI Report Series, which includes the following report types:

- TECHNICAL PUBLICATION. Reports of completed research or a major significant phase of research that present the results of NASA programs and include extensive data or theoretical analysis. Includes compilations of significant scientific and technical data and information deemed to be of continuing reference value. NASA's counterpart of peer-reviewed formal professional papers but has less stringent limitations on manuscript length and extent of graphic presentations.

- TECHNICAL MEMORANDUM. Scientific and technical findings that are preliminary or of specialized interest, e.g., quick release reports, working papers, and bibliographies that contain minimal annotation. Does not contain extensive analysis.

- CONTRACTOR REPORT. Scientific and technical findings by NASA-sponsored contractors and grantees.

- CONFERENCE PUBLICATION. Collected papers from scientific and technical conferences, symposia, seminars, or other meetings sponsored or cosponsored by NASA.

- SPECIAL PUBLICATION. Scientific, technical, or historical information from NASA programs, projects, and mission, often concerned with subjects having substantial public interest.

- TECHNICAL TRANSLATION. English-language translations of foreign scientific and technical material pertinent to NASA's mission.

Specialized services that complement the STI Program Office's diverse offerings include creating custom thesauri, building customized databases, organizing and publishing research results . . . even providing videos.

For more information about the NASA STI Program Office, see the following:

- Access the NASA STI Program Home Page at http://www.sti.nasa.gov

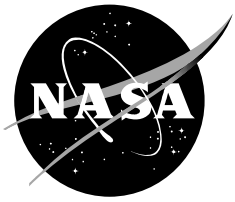
- E-mail your question via the internet to help@sti.nasa.gov

- Fax your question to the NASA Access Help Desk at (301) 621-0134

- Telephone the NASA Access Help Desk at (301) 621-0390

- Write to:
  NASA Access Help Desk
  NASA Center for AeroSpace Information
  7121 Standard
  Hanover, MD 21076-1320

NASA/TP–2008–214759



Risk Assessment of Acute Mountain Sickness in the Crew Exploration Vehicle

Johnny Conkin, Ph.D.
Universities Space Research Association

National Aeronautics and
Space Administration

Lyndon B. Johnson Space Center
Houston, Texas 77058

January 2008

Acknowledgment

I sincerely appreciate the thorough manuscript review by Mr. James H. Wessel, III. His effort improved my review of what is a complex interdisciplinary topic. Special thanks to Dr. Noah Walman, an October 2006 Aerospace Medicine Clerk, and Dr. Wyche T. Coleman, III, an April 2007 Aerospace Medicine Clerk, for educating NASA Flight Surgeons on this topic. Drs. Jeffrey A. Jones, Richard A. Scheuring, and Michael L. Gernhardt contributed substantially to the Executive Summary. My views and opinions do not reflect official NASA policy. This work was possible through the NASA Cooperative Agreement NNJ06HG25A with the Universities Space Research Association.

Abstract

To limit the risk of fire, reduce the risk of decompression sickness and reduce the prebreathe (denitrogenation) time to support frequent extravehicular activities on the moon and later Mars, a hypobaric and mildly hypoxic living environment is considered for the Crew Exploration Vehicle (CEV), the Lunar Surface Access Module, and long-term surface habitats. Superimposed on physiological adjustments to living in a hypobaric hypoxia (HH) environment are also physiological adjustments associated with adaptation to microgravity (μG). The outward manifestations of these physiological adaptations may present as unexpected signs and symptoms of Acute Mountain Sickness (AMS). There is a medical concern that combining these stresses will degrade the health and performance of astronauts who must maintain a high level of proficiency to accomplish mission goals. The concern comes from a lack of mechanistic understanding of the changes induced by each of the above conditions. Therefore, there is a lack of mechanistic understanding of the integrated response. In particular, signs and symptoms of AMS are undesirable, as they would impact crew health and performance. A review of the research literature suggests that: (1) there is an absolute pressure (P_B) effect *per se* on AMS, so the higher the altitude for a given computed hypoxic alveolar oxygen (O_2) partial pressure (P_AO_2) the greater the AMS response; (2) about 25% of adults would experience AMS near 2,000 m (6,600 ft, P_AO_2 = 75 mmHg) altitude; (3) there is no direct evidence from 6 research reports that HH synergizes with adaptive changes during simulated μG to dramatically increase hematocrit (HCT) and blood viscosity, and (4) only susceptible astronauts would develop mild and transient AMS with exposure to 8.0 pounds per square inch, absolute (psia) (16,000 ft) while breathing 32% O_2 (P_AO_2 = 77 mmHg) and simultaneously adapting to μG. No clinically significant increase in HCT or blood viscosity is expected as red blood cell mass, plasma, and total body water volumes adjust to the combined HH and μG environment. Good operational experience with the shuttle staged denitrogenation protocol at 10.2 psia (10,000 ft) while breathing 26.5% O_2 (P_AO_2 = 85 mmHg) in μG-adapted astronauts suggests that a similar good experience is expected for the proposed CEV environment. The uncertainties in the above conclusions due to limited research data require a risk mitigation plan that includes some of the following: (1) developing the rationale and procedures to increase P_B as needed in the CEV, plus using medications, including supplemental O_2, to effectively treat AMS; (2) consider pre-selection of astronauts who are resistant to AMS; (3) pre-adapting the crew to a hypoxic environment prior to launch; (4) considering breathing 100% O_2 at prescribed intervals, or as needed, during the initial adaptive phase to the new environment to prevent AMS; (5) developing an acclimatization plan through a gradual reduction in P_AO_2 during the initial phase of the mission; or (6) conducting a detailed validation test of the extreme limit of the proposed CEV living environment (7.8 psia with 30% O_2, P_AO_2 = 68) in a large representative sample of subjects during 6-deg head down bedrest over several days to characterize the risk of anticipated AMS.

Contents

Tables

Figures

Acronyms and Nomenlature

ADH	antidiuretic hormone
ALD	aldosterone
AMS	Acute Mountain Sickness
ANP	atrial naturetic peptide
AOE	alveolar oxygen equation
ATA	atmosphere pressure absolute
AZ	acetazolamide
BBB	blood brain barrier
BR	bedrest
BTPS	body temperature, pressure, saturated with water vapor
C	Celsius
C_{cr}	creatinin clearance
CA	carbonic anhydrase
CEV	crew exploration vehicle
Cl-	chloride ion
CNS	central nervous system
CO	cardiac output
CO_2	carbon dioxide
CSF	cerebrospinal fluid
DBP	diastolic blood pressure
DCS	decompression sickness
EAA	Equivalent Air Altitude
EP	erythropoietin
EPI	epinephrine
EVA	extravehicular activity
F_EN_2	expired nitrogen fraction
F_ICO_2	inspired carbon dioxide fraction
F_IO_2	inspired oxygen fraction
F_IN_2	inspired nitrogen fraction
ft	feet
GRF	glomerular filtration rate
H+	hydrogen ion
HACE	high altitude cerebral edema
HAPE	high altitude pulmonary edema
HB	hemoglobin
HCT	hematocrit

HCO_3-	bicarbonate ion
HH	hypobaric hypoxia
HN	hypobaric normoxia
HR	heart rate
hr	hour
HVR	hypoxic ventilatory response
JSC	Johnson Space Center
K+	potassium ion
kg	kilogram
LSAM	lunar surface access module
m	meter
MAP	mean arterial pressure
ml	milliliter
μG	microgravity
min	minute
mmHg	millimeter of mercury
N_2	nitrogen
Na+	sodium ion
NH	normobaric hypoxia
NN	normobaric normoxia
NOR	norepinephrine
O_2	oxygen
P_aCO_2	arterial blood carbon dioxide partial pressure
P_ACO_2	alveolar carbon dioxide partial pressure
P_aO_2	arterial blood oxygen partial pressure
P_AO_2	alveolar oxygen partial pressure
P_aN_2	arterial blood nitrogen partial pressure
P_B	atmospheric pressure
PB	prebreathe
$P_{CSF}N_2$	cerebrospinal fluid nitrogen partial pressure
$P_{CSF}O_2$	cerebrospinal fluid oxygen partial pressure
pH	hydrogen ion concentration
P_ECO_2	end-tidal carbon dioxide partial pressure
P_EO_2	end-tidal oxygen partial pressure
P_ICO_2	inspired carbon dioxide partial pressure
P_IN_2	inspired nitrogen partial pressure

P_IO_2	inspired oxygen partial pressure
ppO_2	oxygen partial pressure
ppN_2	nitrogen partial pressure
psia	pounds per square inch absolute
P(VGE)	probability of venous gas emboli
PV	plasma volume
Q	cardiac output, pulmonary perfusion rate
RBC	red blood cell
RER	respiratory exchange ratio
$SaO_2\%$	arterial blood oxygen saturation
SBP	systolic blood pressure
SMEAT	Skylab Medical Experiments Altitude Test
STPD	standard temperature (37 c), pressure (760 mmHg), dry gas
V_A	alveolar ventilation rate
VCO_2	carbon dioxide production rate
V_E	minute ventilation rate
VO_2	oxygen consumption rate
VGE	venous gas emboli
V_t	tidal volume

Executive Summary

This is a summary of a longer report that was written for medical operations, specifically the Flight Surgeons. It will summarize an analysis of risk of crew symptoms associated with the proposed Constellation vehicle oxygen (O_2) partial pressure (ppO_2). The goal of any trade process is an integrated product, and each stakeholder accepts a less than ideal outcome. Each stakeholder then develops a strategy to minimize the impacts of their less than ideal outcome. From the medical and physiological perspective, we need to minimize any risk of altitude transition symptoms, otherwise known as Acute Mountain Sickness (AMS).

To limit the risk of fire, reduce the risk of decompression sickness and reduce the prebreathe time to support frequent extravehicular activities (EVAs) on the moon and Mars, a hypobaric and mildly hypoxic living environment is proposed for the Crew Exploration Vehicle (CEV), the Lunar Surface Access Module (LSAM), and long-term planetary surface habitats.

Two living environments recommended by the Exploration Atmospheres Working Group at the Johnson Space Center in 2006 are seen in Table I.

Table I. Range of Atmospheric Conditions in Proposed Living Environments

Environment	P_B		F_IO_2	P_IO_2	P_AO_2*	Actual Altitude		Equivalent Air Altitude (EAA)	
	psia	mmHg	(%)	mmHg	mmHg	m	ft	m	ft
CEV + LSAM									
normal	**8.0**	**414**	**32.0**	**117**	**77**	**4,877**	**16,000**	**1,829**	**6,000**
best case	8.2	424	34.0	128	86	4,816	15,800	1,158	3,800
worse case	7.8	403	30.0	107	68	5,029	16,500	2,438	8,000
Habitat									
normal	**7.6**	**393**	**32.0**	**111**	**71**	**5,182**	**17,000**	**2,286**	**7,500**
best case	7.8	403	34.0	121	80	5,029	16,500	1,524	5,000
worse case	7.4	383	30.0	101	63	5,364	17,600	2,895	9,500

P_B is ambient pressure; P_IO_2 is inspired oxygen partial pressure, computed as (P_B mmHg – 47) $*$ F_IO_2 (as decimal percent); and F_IO_2 is inspired oxygen fraction.

* computed alveolar oxygen partial pressure (P_AO_2) is for an ***acute*** altitude exposure with a "typical" adult exhibiting a "typical" response to mild hypoxia. When breathing an atmosphere that does not contain F_IO_2 = 20.9% O_2, it is helpful to determine the EAA by using the Alveolar O_2 Equation since most experience with hypoxia is with ascent to altitude while breathing air.

The expected EAAs of 1,829 and 2,286 m (6,000 and 7,500 ft) do not reflect the complete hypoxic stress since current literature indicates that AMS results from a complex interaction between both P_AO_2 and P_B. Therefore, there is uncertainty as to how to fully evaluate the combination of the 2 components of hypoxic stress to estimate the true risk of AMS.

Superimposed on physiological adjustments to living in a hypobaric hypoxia (HH) environment are physiological adjustments associated with adaptation to microgravity (μG). The outward manifestations of these physiological adaptations may present as unexpected signs and symptoms of AMS. There is some uncertainty about the full impact that the combination of these stresses will have on the health and performance of astronauts who must maintain a high level of proficiency to accomplish exploration mission goals. Therefore, it is prudent to recommend operational ppO_2 that do not fall into a physiological area of uncertainty, and to have a risk mitigation strategy for cases when operations push towards the limits of the known safe operational range.

Concerns Relevant to Constellation Vehicles

There is a P_B effect *per se* on the risk of AMS, in addition to the AMS risk induced by the HH, but to what degree is uncertain.

There may be an increased risk of AMS when HH is combined with adaptations to μG.

Associated with 2 above, there may be an amplified increase in blood viscosity when HH is combined with adaptation to μG.

Since significant uncertainties exist to resolve these concerns, a risk mitigation plan should be developed to minimize the impact of mild hypoxia combined with adaptation to μG.

The Risk of Acute Mountain Sickness

Quick ascent to altitudes over 2,590 m (8,500 ft) often results in symptoms of AMS. Nearly 25% of individuals are affected from a rapid ascent (< 24 hrs), even to 2,000 m (6,600 ft). Many factors modify the risk of AMS between 2,000 and 3,048 m (6,600 and 10,000 ft), particularly the rate of ascent to altitude, the activity level at altitude, and individual susceptibility.

AMS is a constellation of signs and symptoms including headache, nausea, dizziness, fatigue, and sleeplessness that develops over a 6 to 24 hr stay in a hypoxic environment, usually from rapid ascent to altitude while breathing ambient air. The headache, for example, is usually throbbing, bitemporal or occipital, typically worse during the night and on awakening, and made worse by Valsalva's maneuver; when combined with nausea, it can be likened to an alcohol hangover. Additional clinical findings that confirm a diagnosis of AMS include changes in mental status, ataxia, peripheral edema, or changes in performance. A change in performance means that any of the above symptoms or clinical findings have caused a reduction in normal activities.

Quality and Quantity of Research Data

Any factor that could reduce crew health and performance should be minimized. There is not an abundance of data specific to that required for the spaceflight AMS risk assessment. There are only 4 reports about a P_B effect *per se* on the risk of AMS induced by HH and 6 reports on the combined effects of HH and simulated μG adaptation that have some application here. So, all of the conclusions listed in this summary are based on extrapolation or interpolation from limited information.

Although initial signs and symptoms of AMS in *susceptible* subjects are expected after acute exposure to between 2,000 m (6,600 ft at P_AO_2 = 75 mmHg) and 2,590 m (8,500 ft at P_AO_2 = 67 mmHg) while breathing air, it is likely that these would be self-limiting once acclimatization occurs.

At 8.0 pounds per square inch, absolute (psia) (4,876 m or 16,000 ft) with a nominal P_AO_2 = 77 mmHg, it is likely that *susceptible* astronauts breathing O_2-enriched air and simultaneously undergoing adaptation to μG will experience signs and symptoms of AMS.

No clinically significant increase in hematocrit or blood viscosity is expected as red blood cell mass, plasma, and total body water volumes adjust to the combined HH and μG environment. A transient increase to a mean hematocrit of about 50%, possibly as high as 55% in a particular crewperson, would be predicted based on the data for the combined effects of HH and adaptation to μG as envisioned for the CEV program. However, typical μG-adapted spaceflight hematocrit values are in the low normal range, from 36 to 40% depending on gender.

The repeatedly validated operational experience with the shuttle staged denitrogenation protocol at 10.2 psia (10,000 ft) while breathing 26.5% O_2 (P_AO_2 = 85 mmHg) in μG-adapted astronauts suggests that a similar low risk of AMS can be expected for the proposed CEV environment.

On balance, there is no definitive evidence for an exaggerated (negatively synergistic) response to the combination of HH and adaptation to μG. On the contrary, the limited evidence suggests that one stressor tends to counteract the other.

All events associated with the CEV/LSAM mission to the moon are on a short timescale compared to weeks and months needed to achieve a new steady state adaptation. So, physiological compensation, accommodation, or acclimatization processes are under way in the CEV immediately after orbital insertion, on the way to the moon, during EVA on the moon, and during the return to Earth over a 10 to 15 day mission. Individual susceptibility to μG adaptation in a HH environment will likely play a role in mission success (including an absence of medical problems) in these short-term missions with high EVA-rate scenarios. Some peak performance degradation could be expected in crewmembers, if ppO_2 is reduced acutely to less than 2.8 psia, until

compensation occurs. The magnitude of the performance affect will depend on the ppO_2, the metabolic demands of the task, and individual (genetic) factors. Current threshold for mandatory supplemental O_2 during spaceflight operations is 2.2 psia. For lunar outpost missions (approximately 6 months surface stays), full acclimatization to reduced ppO_2 can be expected after 30 to 45 days, allowing crews to function at high performance levels in the face of reduced O_2 tension.

Risk Mitigation Plan

There is no single study that addresses the exact conditions for the proposed nominal Constellation vehicle environment: adaptation to μG with a breathing environment at 8.0 psia (16,000 ft altitude) with 32% O_2 and 68% N_2, resulting in an acute P_AO_2 of about 77 mmHg. Therefore, the recommendations that follow are not only based on extrapolations and judgment from an exhaustive literature review, but also from tests that differ from the proposed CEV, LSAM, and long-duration surface habitat environments.

We expect no significant negative synergistic interaction between HH exposure with μG adaptation for the proposed CEV environment. Any AMS signs and symptoms would be mild, and transient.

Develop the rationale and procedures to easily increase ambient P_B plus use medications such as prophylactic or, as-needed, acetazolamide, dexamethasone, and supplemental O_2 to reduce AMS risk or provide effective treatment if required. Caution is warranted here for several reasons: acetazolamide may be prescribed for diagnosed AMS when, in fact, signs and symptoms are from motion sickness. Or, medication for motion sickness may be incorrectly prescribed for AMS. AMS and motion sickness share many of the same signs and symptoms, and may appear along a similar time course. Often sleep medication is prescribed due to the many distractions in a small space vehicle. However, sleep medications may be contraindicated if AMS is suspected. A sleep medication would likely worsen the signs and symptoms of AMS.

Consider preflight testing to identify astronauts who are susceptible to atmospheric changes in the CEV environment, and provide special training and risk mitigation plans for those who are identified as susceptible, versus reassignment to a different mission.

Pre-adapt crews to a hypoxic environment prior to launch to blunt any combined negative effects of HH exposure with μG adaptation shortly after launch. But, this intervention to reduce the risk of AMS is contraindicated if the resulting increase in HCT significantly adds to the increased HCT transiently observed during the acute phase of μG adaptation, possibly leading to impaired circulation and O_2 delivery. Consider phlebotomy, if warranted.

Develop an acclimatization plan through the gradual reduction in P_AO_2 during the initial phase of the missions, which should significantly reduce the likelihood of AMS signs and symptoms.

Consider inclusion of a plan to breathe 100% O_2 by mask over several intervals of time during the acclimatization to the μG plus HH exposure. Breathing 100% O_2 is shown to blunt the negative physiological effects of subsequent HH exposure.

Risk Assessment of Acute Mountain Sickness in the Crew Exploration Vehicle

Introduction

This report was written for the medical operations community at the Johnson Space Center (JSC), specifically the Flight Surgeons. It summarizes an analysis of risk of crew symptoms associated with the proposed Constellation vehicle oxygen (O_2) partial pressure (ppO_2). Extended exposures to even mild hypoxic stress can lead some to signs and symptoms of Acute Mountain Sickness (AMS). This is a concern in any aerospace application where mild hypoxia is deemed an acceptable trade. The goal of any trade process is an integrated product, and each stakeholder accepts a less-than-ideal outcome. Each stakeholder then develops a strategy to minimize the impacts of their less-than-ideal outcome. Our goal is to understand the risk of AMS, and then develop strategies to minimize any perceived risk.

The brain and spinal cord, which are the central nervous system (CNS), constitute 2% of body mass in adults. Yet, this organ system under basal conditions commands 14% of the cardiac output (CO) and consumes 20% of the O_2 at any given time. The CNS is the system to preserve in a crisis and at some point hypoxia caused by a reduction in breathing gas ppO_2 becomes a crisis. O_2 is not stored in the body, so a reduction in supply quickly becomes apparent. For example, the rods of the eye lose the ability to respond in dim light with ascent to as little as 1,524 m (5,000 ft) altitude.

In situations that threaten O_2 supply to the CNS, compensatory measures are taken to maintain adequate cerebral blood flow. Cerebral blood flow appears to be regulated almost entirely by local mechanisms. The brain initiates various actions in response to peripheral and central detection of a changed O_2 and acid-base environment. The long-term adjustments (adaptation) to hypoxia either return the internal environment to near normal or various organ systems tolerate (accommodation) the new hypoxic conditions with some loss of function. Hypoxic stress impacts the function of any aerobic tissue, and a common first response is to consider the changes in the peripheral lungs, kidneys, or even gut. But, the brain is central and an understanding of the integrated response to hypoxia is no small task. In this vein, it is ultimately necessary to focus on the CNS as the target of and responder to hypoxic stress.

Purpose

This report addresses, through a comprehensive literature search and evaluation of those data, 3 important questions related to AMS. These questions were raised during the development of 2 proposed living environments for continued space exploration, as recommended by the Exploration Atmospheres Working Group at JSC in 2006 (Campbell 2006).

Is there evidence for an absolute pressure (P_B) effect *per se* on the risk of AMS induced by hypobaric hypoxia (HH)?

Is there evidence for an increased risk of AMS when HH is combined with adaptations to microgravity (μG)?

Is there evidence for an amplified increase in blood viscosity when HH is combined with adaptations to μG?

Since significant uncertainties do exist to resolve the above questions, a risk mitigation plan must be developed to minimize the impact of mild hypoxia combined with adaptation to μG.

The 2 proposed living environments are in the (1) Crew Exploration Vehicle (CEV) plus Lunar Surface Access Module (LSAM), and (2) long-duration moon and Mars surface habitats. The proposed nominal living environment for the CEV and LSAM are at 8.0 pounds per square inch, absolute (psia) (16,000 ft) with 32% O_2 compared to 7.6 psia (17,000 ft) and 32% O_2 for the long-duration moon and Mars surface habitats. The environmental control and life support system will operate within a control range; the minimum, normal, and maximum control range for P_B and O_2 concentration (the inspired oxygen fraction, F_IO_2), plus an estimate of the acute alveolar oxygen partial pressure (P_AO_2) from the alveolar oxygen equation (AOE) are shown in Table I.

Table I. Range of Atmospheric Conditions in Proposed Living Environments

Environment	P_B		F_IO_2	P_IO_2	P_AO_2*	Actual Altitude		Equivalent Air Altitude (EAA)	
	psia	mmHg	(%)	mmHg	mmHg	m	ft	m	ft
CEV + LSAM									
normal	**8.0**	**414**	**32.0**	**117**	**77**	**4,877**	**16,000**	**1,829**	**6,000**
best case	8.2	424	34.0	128	86	4,816	15,800	1,158	3,800
worse case	7.8	403	30.0	107	68	5,029	16,500	2,438	8,000
Habitat									
normal	**7.6**	**393**	**32.0**	**111**	**71**	**5,182**	**17,000**	**2,286**	**7,500**
best case	7.8	403	34.0	121	80	5,029	16,500	1,524	5,000
worse case	7.4	383	30.0	101	63	5,364	17,600	2,895	9,500

P_B is ambient pressure; P_IO_2 is inspired oxygen partial pressure, computed as (P_B mmHg – 47) ∗ F_IO_2 (as decimal percent); and F_IO_2 is inspired oxygen fraction.

* computed alveolar oxygen partial pressure (P_AO_2) is for an ***acute*** altitude exposure with a "typical" adult exhibiting a "typical" response to mild hypoxia. The exact value for P_AO_2 seen in the table would not likely be measured in a small sample of adults exposed to the conditions listed in the table. When breathing an atmosphere that does not contain F_IO_2 = 20.9% O_2, it is helpful to estimate the EAA since most experience with hypoxia is with ascent to altitude while breathing air. With a given P_AO_2 from the AOE one can consult published "altitude tables" (DeHart 1996 in Appendix) to find the altitude while

breathing air that corresponds to the acute P_AO_2 value, regardless of the combination of P_B and F_IO_2 that is used to achieve the value.

Rationale for Mild Hypoxic Spacecraft Atmosphere

Future vehicles for space exploration will have less than atmospheric P_B, with a ppO_2 less than a sea level equivalent of 3.07 psia, or 160 mmHg. What is the rationale for this statement? A hypobaric and mildly hypoxic environment will be the product of a complex integration of safety, engineering, operational, and medical concerns where the goal is *routine and safe* exploration of the lunar and martian surfaces. An efficient exploration program requires that extravehicular activity (EVA) be efficient. The time to prepare for EVA should be minimal, and the suit pressure should be low to accommodate EVA tasks without undue fatigue, physical discomfort, or even suit-related trauma. Currently, a long prebreathe (PB) time is used prior to EVA from the shuttle and the International Space Station to prevent decompression sickness (DCS) and significant venous gas emboli (VGE) insult of the lungs at 4.3 psia. To shorten the PB time, the habitat atmosphere should not have a high nitrogen (N_2) partial pressure (ppN_2). One practical approach to reduce the ppN_2 is to increase the ppO_2 while also reducing the P_B. A balance must be achieved between the increased risk of fire at high O_2 concentration and the decreased risk of DCS as ppN_2 is reduced in the habitat. The concentration of O_2 and, therefore, the risk of fire for a given P_B can be reduced further if P_IO_2 is less than 149 mmHg, but not so low as to cause significant hypoxia. A candidate atmosphere for the CEV is 8.0 psia (414 mmHg) with O_2 concentration between 30% and 34% (ppO_2 = 124 to 140 mmHg), with balance N_2. So, for good reasons, a modest HH environment with crews adapted to μG is one option for future moon and Mars exploration. How will the body accommodate or adapt to this new living environment? Will the accommodation or adaptation lead to a new functional state for the crew and, therefore, a significant change in health and performance?

It is known that deconditioning and fluid redistribution occurs during extended bedrest (BR), BR with head down tilt, and exposure to μG. There is a decrease in total blood volume through a combined loss in plasma volume (PV) and red blood cell (RBC) mass (Alfrey 1996, Buckey 2006, Bungo 1989, Johnson 1977). Hematocrit (HCT) transiently changes during this period of adaptation, but returns to near-baseline values over several weeks in a normobaric normoxia (NN) environment. Exposure to significant HH leads to an increase in RBC mass with an expected increase in HCT (Ge 2002, Murray 1986) and blood viscosity (Martin 1986, Neuman 1976). An increase in HCT above 55% increases blood viscosity where the decrease in CO more than offsets the gain in O_2 capacity of the blood. This combination leads to a decrease in O_2 transport (Murray 1986, Burton 1972).

A small environmental perturbation is expected to produce a small transient physiological change until the original equilibrium or new equilibrium condition is

established. There are situations where several small physiological adjustments, which by themselves are inconsequential, synergize to induce an amplified positive feedback change. For example, hyperventilation is a CNS-mediated response to increase P_AO_2 to preserve CNS function. But this action also reduces arterial blood carbon dioxide (CO_2) partial pressure (P_aCO_2) that, in turn, leads to vasoconstriction of cerebral blood vessels and that further exacerbates O_2 delivery to the CNS that in turn leads to a greater CNS-mediated drive to increase hyperventilation. In the short term, the new condition may not be favorable to the organism but buys time so that longer-term adjustments can bring a new functional equilibrium. So, time is taken to survey the literature to understand the integrated physiological response to HH and adaptation to μG. Our interest is primarily during the acute physiological compensatory phase, the first 3 or 4 days of a 15-day sortie mission back to the moon.

Our physiology, with individual sensitivities, has the ability to integrate multiple environmental changes to achieve a new "functional" sustained balance. As long as this new functional balance does not degrade significant health and performance, then engineers should take advantage of human adaptability when designing life support systems. The key is to understand what is meant by a "significant decrease in health and performance".

First Issue: Hypoxia and Acute Mountain Sickness

Ascent to altitude without supplemental O_2 results in decreased P_IO_2 and P_AO_2 along with a decrease in gas density. Alveolar hypoxia is immediately sensed by the lungs, leading to increased pulmonary vasoconstriction with a corresponding increase in pulmonary artery pressure (McMurtry 1982, Hultgren 1982, Moudgil 2005). Peripheral (carotid and aortic bodies) and CNS (medulla) respond to arterial oxygen (P_aO_2) and P_aCO_2 partial pressure, and hydrogen ion (H+) concentration (pH). O_2 delivery must fundamentally match tissue demand, leading to increased pulmonary ventilation as a means by which to increase O_2 supply to the body. This is a breath-by-breath response on the order of seconds since the body needs an uninterrupted source of O_2. The CNS consumes about 20% of available O_2, and is exquisitely sensitive to the lack of O_2. Hyperventilation in response to significant hypoxia simultaneously reduces alveolar carbon dioxide partial pressure (P_ACO_2), leading to transient alkalosis. The body's response to the alkalosis and hypoxic milieu triggers numerous physiological adjustments: rapid responses in the blood buffer system and pulmonary mechanics to increase P_AO_2 with adjusted acid-base and fluid balance by the kidneys much later to reestablish homeostasis. AMS signs and symptoms are ultimately linked to poorly understood disruptions of the CNS.

This report covers a substantial amount of physiology on adaptation to hypoxia and μG even before addressing adaptation to the combination of these stressors. But, it is necessary to limit the scope of this report since decades of interest in hypoxia, from many

perspectives, has led to thousands of reports and hundreds of books. Humans now routinely live in space for long periods, and a substantial amount of information has accumulated about adaptation to μG from simulated μG as well as actual exposure. Without precisely defining the terms below (see Fulco 1988 for additional discussion), this report is restricted to the conditions between the brackets.

seconds – [minutes – hours – days] – weeks – months – years

responses – [adjustments – acclimatization] – adaptation

[acute]---------- chronic

AMS is a constellation of signs and symptoms including headache, nausea, dizziness, fatigue, and sleeplessness that develops over a 6 to 24 hr stay in a hypoxic environment, usually from rapid ascent to altitude while breathing air. The headache, for example, is usually throbbing, bitemporal or occipital, typically worse during the night and on awakening, and made worse by Valsalva's maneuver; when combined with nausea, it can be likened to an alcohol hangover. In one of the earliest efforts to understand the interaction between prolonged BR and HH, Lynch (1967) and Stevens (1966) exposed young men to 3,658 m (12,000 ft) in an altitude chamber for 28 days. Lynch writes, "In the altitude subjects, headache of moderate severity was not uncommon during the first 24 hrs of BR at simulated altitude, particularly in the 3,658 m groups". This was at a time when AMS was not well characterized. In retrospect, it appears to this reviewer that an acute P_AO_2 = 54 mmHg at 3,658 m altitude is sufficient to precipitate a necessary symptom for a diagnosis of AMS.

Roach (1998) says that a quick ascent to altitudes over 2,590 m (8,500 ft) often results in symptoms of AMS. Nearly 25% of people are affected even at 2,000 m (6,600 ft) (Roach 1998, Houston 1982, Montgomery 1989). Montgomery (1989) observes that half of the 12% of tourists afflicted with symptoms of AMS at 2,000 m (6,600 ft) seek relief of symptoms through medication. Others (Vardy 2006) find no significant symptoms below 3,048 m (10,000 ft). Many factors modify the risk of AMS between 2,000 to 3,048 m (6,600 to 10,000 ft), particularly the rate of ascent to altitude, activity level at altitude, and individual susceptibility. One reality about NASA space vehicles is that depressurization to a final hypobaric P_B is on the order of minutes and not hours or days.

AMS, as opposed to the immediate response to hypoxia, evolves over a time-course that suggests changes in hormones are also involved in its final expression. There is a wide range of susceptibility to AMS. If you are susceptible, then the risk of AMS increases the longer you stay and the higher you go, until you adapt to the new conditions or return to higher P_B. Mild forms of AMS are transient but can impact crew health and performance, certainly on short missions. Serious manifestations of AMS lead to high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE), both

debilitating and life threatening conditions. This report considers only the milder forms of AMS that may impact the success of a mission more so than threaten life. The operation of the environmental control and life support system, even at the extreme of the control range, will not place the crew in an extreme hypoxic environment.

The "normal" response to acute hypobaric exposure is extremely variable but is characterized by an increase in the rate and depth of respiration as compensation for detected hypoxemia. But, the resulting respiratory alkalosis stimulates the CNS to reduce respiration as a means to preserve the pH in the cerebrospinal fluid (CSF). There is also an expected hypoxia-induced diuresis through the loss of bicarbonate (HCO_3-) and sodium (Na+) ions from the plasma through the kidneys as compensation for the respiratory alkalosis and through activation of the peripheral chemoreceptors. In those individuals who go on to experience AMS, the normal hyperventilation response to HH is modified such that the minute ventilation rate (V_E) is reduced relative to the V_E of someone who will not go on to develop AMS (Roach 1992 and 1994). It appears that a reduced sensitivity to the HH environment effectively increases the deadspace ventilation with all of the attending disruptive consequences of those who go on to develop AMS, but there are contrary interpretation of data (Savourey 2003, Loeppky 1997). Those who are prone to subsequent AMS have a slightly greater hypoxemia compared to those who have acclimatized well. A greater alveolar-arterial O_2 difference (P_AO_2 - P_aO_2) is associated with AMS, suggesting that impaired gas exchange due to pulmonary edema begins prior to the onset of clinical symptoms. Also, there is an absence of the typical hypoxia-induced diuresis and natriuresis. PV moves into the interstitial space leading to edema in those who go on to develop AMS (Auerbach 1995, Sutton 1976, Hackett 1982, Hildebrandt 2000). In severe exposures, the resulting pulmonary and cerebral edema can lead to death if either a return to higher P_B or supplemental O_2 is delayed (Severinghaus 1995). Finally, no one knows the integrated physiological mechanisms that precipitate signs and symptoms of AMS, but progress is being made (Leaf 2006).

The diagnosis of AMS has been standardized using the Lake Louise AMS Scoring System (Roach 1993, The Lake Louise consensus 1992). You have AMS if you have been at altitude for an extended period greater than 2 hrs and you develop a headache plus one or more of the following conditions: nausea, dizziness, fatigue, or sleeplessness. Additional clinical findings that confirm a diagnosis of AMS include changes in mental status, ataxia, peripheral edema, or changes in performance. A change in performance means that any of the above symptoms or clinical findings have caused you to reduce your normal activities.

Carbonic Anhydrase and Action of Acetazolamide

The prevention and treatment of AMS with acetazolamide (AZ, DIAMOX), a potent carbonic anhydrase (CA) inhibitor, is very effective. Some understanding of this interaction is helpful to grasp the multiple causes and effects from hypoxia leading to AMS. Carbonic anhydrase in its several isozyme forms is a ubiquitous and highly conserved enzyme that is found in RBCs, pulmonary endothelial cells, the kidney, acid

secreting cells in the stomach, the brain, and even within the peripheral chemosensors. The isozyme form CAIV is located on the luminal aspect of nearly all capillary beds.

Carbonic acid formed by the hydration of CO_2 quickly dissociates to H+ and HCO_3- ions, but this reversible reaction is too slow to process the 13 to 20 moles of CO_2 (volatile acid) produced per day.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H+ + HCO_3-$$

Valtin (1983) shows that the hydroxylation of CO_2 through the action of CA is the significant reversible reaction that moves CO_2 into its main transportable form.

$$\begin{array}{l} \quad HOH \leftrightarrow H+ \\ \quad \uparrow\downarrow \\ CO_2 + OH- \leftrightarrow HCO_3- \\ \quad\quad CA \end{array}$$

Inhibiting this reaction prevents CO_2 from being managed by the lungs and kidneys leading to global tissue metabolic acidosis, so proper dosing of AZ is key to efficacy. The inhibition of CA in RBCs and vascular endothelial cells increases CO_2 retention in all tissues, which is an additional stimulus to increase V_E associated with CA inhibition.

As tissue CO_2 diffuses into plasma and then into RBCs, the reactions shown previously are driven to the right, and about 63% of the CO_2 is carried to the lungs as plasma bicarbonate, with 7% carried as dissolved CO_2 and 30% as CO_2 bound to hemoglobin (HB). The reactions are reversed in the lungs, and HCO_3- moves from the plasma into the RBCs and CO_2 leaves the body. Bicarbonate from CO_2 in the parietal cells of the stomach is conserved while the H+ and Cl- ions are pumped into the gastric lumen. The similar action in the brain returns H+ ions to the circulation, leaving HCO_3- in the CSF. CA in the membrane and cytosol of cells in the proximal tubules of the kidney promotes about 99.9% of HCO_3- reabsorption and H+ secretion.

The main action of AZ is the reversible inhibition of CA. However, Swenson (2006) shows that AZ also reduces hypoxic pulmonary vasoconstriction independent of CA inhibition. AZ can, to a limited degree, cross the blood brain barrier (BBB). In the brain, the effect is to reduce the production of CSF and the HCO_3- content in the CSF. This is certainly beneficial if cerebral edema is present. The reduction of HCO_3- tends to restore the H+ concentration, returning CSF toward its near-normal pH of 7.33 compared to 7.40 for arterial blood. This then reduces the hypoventilation response mediated by the medullary respiratory center due to high CSF HCO_3- concentration. Ventilation is improved, particularly during sleep, leading to enhanced O_2 delivery in a hypoxic environment. Inhibition of CA in the proximal tubules of the kidneys prevents the

reabsorption of HCO_3- and distal tubular H+ secretion (Swenson 1998). An osmotic diuresis with natriuresis ensues, reducing the magnitude of tissue edema seen in AMS.

The extent of AZ interaction with several isozyme forms of CA (I, II, IV, XII, XIV) in central and peripheral tissues is not known, so how it reduces the signs and symptoms of AMS is unclear. Leaf (2006) provides a review and summary figure for the known and suspected actions of AZ on the physiology and how these actions reduce the consequences of hypoxia. Much of what he summarizes in his figure 5, which is shown below, is now described.

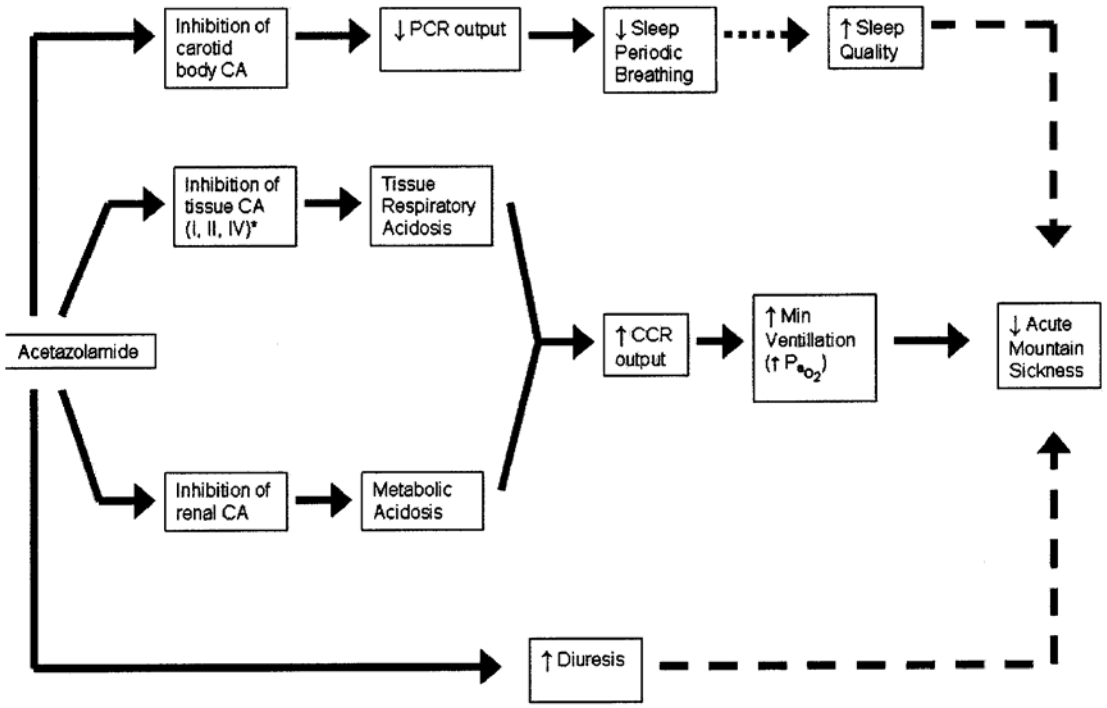


Figure 5. Proposed model for acetazolamide's reduction of AMS. Solid lines represent well-established connections; broken lines represent less-well established connections. *CA I and II are located intracellularly in RBCs and tissues; CA IV is located on the luminal aspect of nearly all capillary beds. PCR=Peripheral Chemoreceptor; CCR=Central Chemoreceptor.

The metabolic acidosis that results from HCO_3- loss from the kidneys due to AZ counters the respiratory alkalosis from increased V_E in response to hypoxia detected by peripheral and central chemosensors. In effect, the resulting metabolic acidosis increases V_E for a given P_aCO_2, improving O_2 supply to the tissues. There is a leftward shift in the ventilation-CO_2 response curve after AZ administration. A critical observation is that AZ actually inhibits the sensitivity of the carotid body chemoreceptor response to CO_2. A decreased sensitivity of the peripheral chemosensors is thought to reduce periodic breathing during sleep at high altitude, thus increasing blood O_2 saturation. Inhibition of

the CO_2 hydration reaction within the carotid body would limit the increase in H+ following a hypercapnic stimulus. Since V_E is increased at any P_aCO_2 under hypoxic stress given AZ, the effect is principally mediated by central chemosensors. This mediation appears to be indirect in that AZ does not cross the BBB to a significant degree. So, interaction with CA within the central chemosensors or the CNS is limited. However, metabolic acidosis from the action of AZ on the kidneys ultimately reduces HCO_3- in the CSF over many hrs since a diffusion gradient for HCO_3- from the CSF to plasma is established. The restricted movement of ions through the BBB is a hallmark of this system, so a mechanism that depends on diffusion would certainly be slow to reach equilibrium – much like the slow onset of AMS. The reduction in CSF HCO_3- plus the increase in CO_2 due to global tissue respiratory acidosis effectively reduces the inhibition to respiration, and V_E increases. The central chemosensors profoundly change V_E given their high CO_2 ventilatory responsiveness (1 to 3 L/min/mmHg, Swenson 1998).

There are side effects to AZ that may be as significant in some individuals as the symptoms of AMS. In those sensitive to sulfonamide drugs, a severe allergic reaction is possible. There are reports of tingling of the lips and fingertips, blurred vision, malaise, anorexia, weakness, nausea, diarrhea, and alteration of taste, just to list a few. The medical management of AMS with AZ and the efficacy of this drug in μG are not the thrust of this report, but deserve serious consideration.

Is Acute Mountain Sickness a Function of Absolute Pressure and Hypoxic Stress?

The complex cardiovascular-pulmonary-cerebral-renal-hematological-endocrine response to a hypoxic environment is *assumed* to be identical whether you are hypoxic while at altitude in an altitude chamber or whether you breathe an equivalent hypoxic mixture at sea level P_B. It is also *assumed* that if you maintain sea level equivalent conditions at all altitudes given the correct supplemental O_2, no AMS signs and symptoms are expected. The first assumption (accepted truth) is called into question with data in this report, and the second assumption has not been systematically tested as of 2008.

For example, in an experiment where the subjects are their own controls, the hypothesis is that there are no signs or symptoms of AMS if P_AO_2 is made equivalent to sea level conditions (P_AO_2 = 103 mmHg from AOE if ppO_2 = 160 mmHg) at any reduced P_B. So, a subject exposed to 5.45 psia (282 mmHg, 25,000 ft altitude) in an altitude chamber would have no signs or symptoms of AMS if the atmosphere was 63% O_2 (177 mmHg/282 mmHg = 63%) for P_AO_2 = 103 mmHg from the AOE. All other variables would be identical to the sea level control in the altitude chamber, except the density of the atmosphere would decrease from 1.177 g/liter to 0.431 g/liter at 50% relative humidity, using 25° C for ambient temperature and 15° C for dew point.

To eliminate the confounding influence of DCS and VGE, the subject would PB 100% O_2 for 4 hrs prior to a slow 1,000 ft/min ascent to 5.45 psia. Noninvasive monitoring for VGE in the pulmonary artery using an ultrasound Doppler bubble detector would verify that no gas phase is present in the venous return due to the depressurization. If signs or symptoms of AMS or a change in any physiological measurement are observed while exposed to 5.45 psia, then the explanatory variables associated with the observations are the changes in breathing gas density and decrease in absolute P_B. It is stated this way because gas density could be reduced (changed) independent of P_B by substituting helium for N_2; for example, in the breathing mixture. Other physical changes occur with a change in P_B beyond a change in breathing gas density, such as changing the capacity of a fluid to hold gas in solution.

The AOE (DeHart 1996) will be referenced and used often in the remainder of this report. It is the key physiological variable to associate changes in the breathing environment to changes in other physiological systems. Acute respiratory changes, such as hyperventilation that increases the respiratory exchange ratio (RER), make it difficult to understand the resulting P_AO_2 without the aid of an equation. Also, the disproportionate contribution of water vapor toward decreasing P_AO_2 as P_B decreases is managed in the AOE:

$$P_AO_2 = F_IO_2 * (P_B - 47) - P_ACO_2 * [F_IO_2 + ((1 - F_IO_2)/RER)] \quad (1)$$

where P_AO_2 is alveolar oxygen partial pressure (mmHg), F_IO_2 is inspired oxygen fraction (decimal percent), P_B is atmospheric pressure (mmHg), 47 is the vapor pressure of water at 37 C (mmHg), P_ACO_2 is alveolar carbon dioxide partial pressure (mmHg), and RER is the respiratory exchange ratio (unitless), which is equal to 1.0 when breathing 100% O_2. The contribution of RER to P_AO_2 and P_ACO_2 is complex when P_B, for example, changes. This important topic is explored in the section entitled "Partial Pressure of Nitrogen, Oxygen, and Carbon Dioxide in the Cerebrospinal Fluid" but for now we move forward as if RER is a particular value fixed in time, but modified by at least hypoxia-induced hyperventilation. Another often reported variable is the inspired oxygen partial pressure (P_IO_2) defined as $F_IO_2 * (P_B - 47)$.

Algebraic manipulation of the AOE provides a useful form where ppO_2 is computed for a particular constant P_AO_2 plus other inputs to the equation. Since engineers deal with the control of a life support system with O_2 sensors that monitor the cabin environment, it is convenient to express a desired P_AO_2 in terms of ppO_2, which can easily be measured in the breathing environment.

Since $F_IO_2 = ppO_2/P_B$, you can rearrange the AOE to solve for ppO_2:

$$ppO_2 = [P_AO_2 + (P_ACO_2/RER)]/[1 - ((47 + P_ACO_2 - (P_ACO_2/RER))/P_B)]. \quad (2)$$

As an example, the medical community at JSC decides, after various engineering, operational, and medical trades, that a long-term exposure to a mild hypoxic condition in a hypobaric living environment for astronauts is desirable for mission efficiency. The target P_AO_2 is 77 mmHg. The habitat P_B is 414 mmHg (8.0 psia). Physiological acclimatization and adaptation will occur, so average P_ACO_2 and RER return to near-normal sea level values of 40 mmHg and 0.85 after a period of respiratory compensation where mild hyperventilation resulted in a P_ACO_2 = 37 mmHg and an RER = 0.88. Given the inputs after adaptation, the life support engineer computes a ppO_2 of 137 mmHg, meaning that the concentration of O_2 in the 8.0 psia habitat should be no lower than 33% (137/414 = 33%) to maintain P_AO_2 at 77 mmHg under resting, steady state conditions.

Another helpful equation computes P_B in mmHg for an altitude exposure expressed in kilometers (H):

$$P_B = 760 * [288.15/(288.15 - 6.5 * H)]^{-5.256}. \quad (3)$$

Concept of Equivalent Air Altitude Exposure

Figure 1 is an example of the application of the AOE, which demonstrates the concept of EAA exposure. The concept of an EAA exposure is that there is no difference in hypoxic response at any altitude as long as the same P_AO_2 is achieved at 2 different altitudes by breathing the proper supplemental O_2. It also follows that there should be no hypoxic response at all as long as sea level equivalent P_AO_2 is maintained at any altitude. The routinely applied notion of an EAA exposure is invalid for higher altitude if it is true that there is an absolute P_B effect on the risk of AMS. The validity of an absolute P_B effect on the risk of AMS would be easier to confirm if the 2 different test altitudes are supposedly equivalently hypoxic. For example, a P_AO_2 of 77 mmHg in people just arriving from sea level to 1,829 m (6,000 ft) could induce a low incidence of mild AMS symptoms. These same people breathing 100% O_2 at 11,278 m (37,000 ft) would have the same P_AO_2 but the incidence of AMS might double. This P_B effect on AMS would not likely be observed when a P_AO_2 of 103 mmHg for air breathing at sea level is compared to the same P_AO_2 while breathing 100% O_2 at 10,211 m (33,500 ft), even though the difference in P_B is substantial. In the second example, a degree of hypoxia was not initially present, so a P_B effect could not manifest itself.

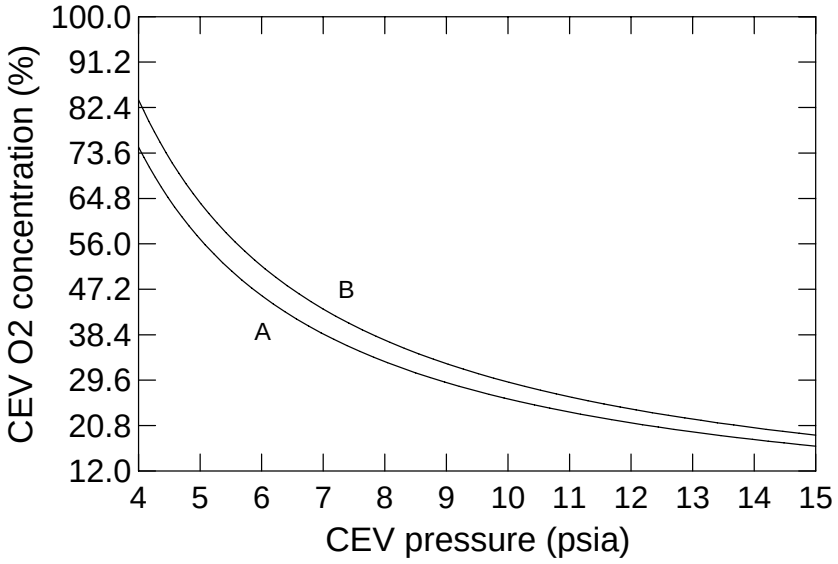


Fig. 1. Two examples of EAAs as a function of CEV atmospheric pressure. Curve A is the minimum required inspired oxygen fraction (F_IO_2) for a specific CEV atmosphere P_B for a 5,000 ft EAA exposure. Curve B is the minimum F_IO_2 for a specific CEV atmosphere P_B for a 2,000 ft EAA exposure. The further left you go from Curve A the more hypoxia you accept; and the further right you go, the less hypoxia you accept. For Curve A, P_AO_2 = 81 mmHg, P_ACO_2 = 37 mmHg, and RER = 0.87, all for the 5,000 ft EAA condition. For Curve B, P_AO_2 = 94 mmHg, P_ACO_2 = 39 mmHg, and RER = 0.86, all for the 2,000 ft EAA condition (see Appendix for these data).

The earliest known record of altitude sickness was a report by Chinese official Too Kin in 37 to 32 BCE. He described the perils of a route over or near the Karakoram Range of the western Himalya: "Next one comes to Big Headache and Little Headache Mountains … They make a man so hot that his face turns pale, his head aches, and he begins to vomit… Even the donkeys and swine react this way". Big Headache Mountain is believed to be the apex of the Kilik Pass at an altitude of 4,827 m (15,837 ft). Paul Bert, as long ago as 1878, is recognized as the first person to show that AMS is prevented at any altitude if P_AO_2 is maintained at a sea level EAA (ppO_2 = 160 mmHg and P_AO_2 = 103 mmHg). But, there are recent data to suggest there could be a P_B effect that works independent of the change in P_AO_2 that contributes to the signs and symptoms of AMS (Roach 1996, Tucker 1983). So, the question is: Is absolute P_B *per se* an explanatory variable for AMS? But, even this question is not specific enough since the majority of the information in this report has an overlay of hypoxic stress. The more appropriate question is, therefore: Is absolute P_B *per se* an explanatory variable for AMS on the

condition that significant hypoxic stress is present? The assumption here is that there is no absolute P_B effect if P_AO_2 under all hypobaric conditions is $\geq$ 103 mmHg. This question deserves serious attention since we move forward with habitat atmosphere selection for moon and Mars exploration on the assumption that P_AO_2, and not P_B and P_AO_2, is the only consideration to avoid the signs and symptoms of AMS.

Variability to Acute Mountain Sickness

The challenge to understanding AMS, regardless of additional complicating factors from μG adaptation, is that there is no single predictive variable associated with AMS. There is no one dominant cause associated with one dominant effect; even the most significant environmental stress of hypoxia affects some individuals more than others. By definition, AMS has a component of hypoxia that itself produces signs and symptoms that are included in the description of AMS; for example, headache, nausea, dizziness, fatigue, and sleeplessness are sure signs and symptoms of AMS. But, many would be dizzy and fatigued while breathing 12% O_2 at sea level if they also scaled a flight of stairs. In fact, it is not possible to induce AMS unless hypoxia is a factor. But there does seem to be a component to AMS that is in addition to just chronic hypoxic stress. A component of AMS is that it takes from 6 to 24 hrs to manifest (Milledge 1984). Changes secondary to the immediate effects of hypoxia suggest that hormones such as renin, aldosterone (ALD), atrial naturetic peptide (ANP), catecholamines, and antidiuretic hormone (ADH), which change fluid balance and microvascular function, are linked to AMS (Loeppky 2005a, Loeppky 2005b, Hackett 1982).

Yet individual variability to AMS makes this a difficult malady to study, even when studied in a controlled laboratory setting where cold, fatigue, variable ascent rates, dehydration, etc., from mountain trekking are not confounding factors. AMS seems to be a cluster of many subtle physiological changes in response to the ambient P_B *per se* and the degree of hypoxic stress that, by themselves, are meaningless to the malady. But, in combination these subtle physiological changes drive susceptible people to modest signs and symptoms under modest HH conditions. Extreme HH conditions drive susceptible and not-so-susceptible people all the way to serious pulmonary and cerebral edema, leading to cardiopulmonary and neurological collapse, and even death.

Figures from Schoene (1984), on the following pages, show a wide range of integrated physiological response between subjects to significant hypoxia where exercise while hypoxic is an additional stress. Schoene's figure 6 shows the extreme range of the integrated physiological reaction to hypoxic stress, expressed as the hypoxic ventilatory response (V_E/VO_2) to exercise. As O_2 consumption and CO_2 production increase with exercise, the pattern of integrated response expressed as the ratio of V_E/VO_2 is consistent across the 3 subjects at sea level P_B and under extreme hypoxic stress. But, it is clear that the low responder (L) is very insensitive to hypoxic stimulation of the peripheral and CNS at low and higher exercise intensity. Figure 7, also from Schoene (1984), is another example of the extreme variability between subjects in their response to hypoxia. Subject CP increases ventilation in response to breathing 10% O_2 at 750 mmHg (computed

P_AO_2 = 49 mmHg for resting condition) while at rest and during mild exercise much more than subject RS. As a result, the HB saturation for subject CP shows a modest decrease compared to subject RS under a significant hypoxic stress.

A lower ventilatory response to HH is linked to AMS (Schoene 1984, King 1972, Sutton 1976), so this between-subject variability can be the basis of a selection protocol if AMS is to be avoided when exposure to a significant hypoxic environment is unavoidable. However, Sutton (1976) found no relation between the degree of ventilatory response to hypoxia at site P_B and the development of AMS at 5,364 m (17,600 ft). He did not control for P_ACO_2, and the test was done at site P_B, both of which could mask a better relationship between the decreased hypoxic ventilatory response and the subsequent AMS.

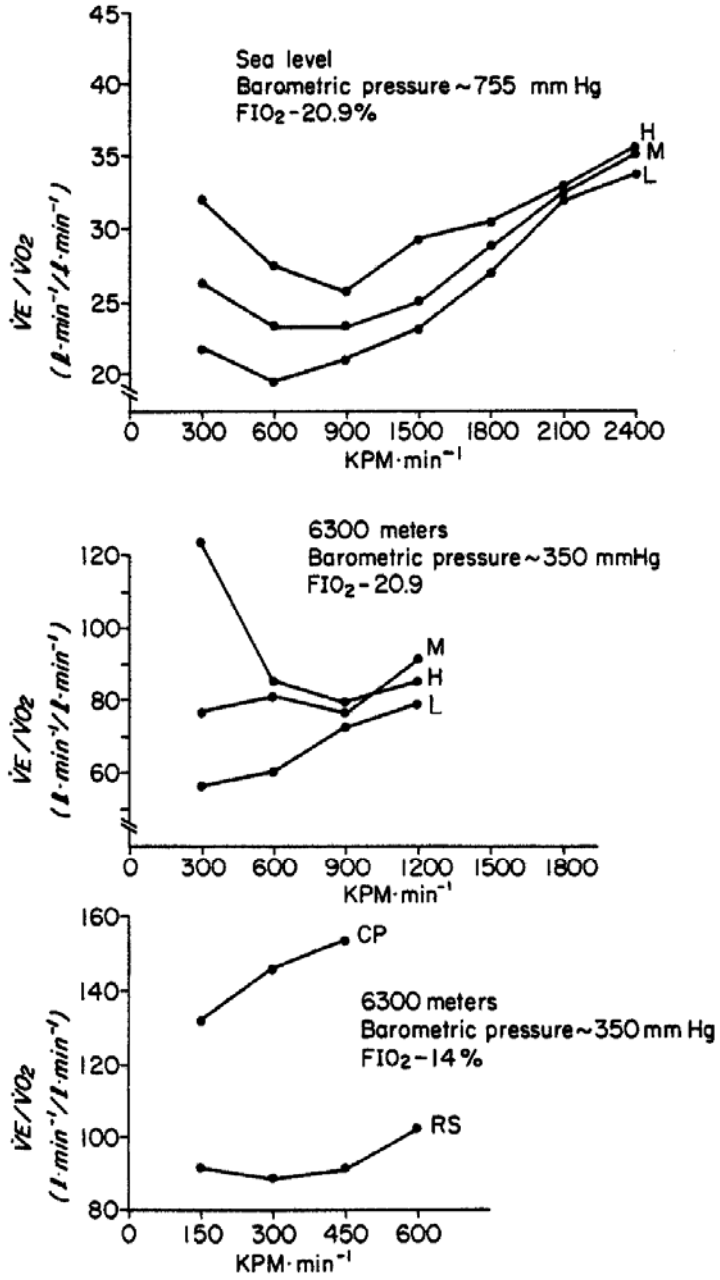


FIG. 6. Work load vs. $\dot{V}_E/\dot{V}_{O_2}$) of the high (H), moderate (M), and low (L) hypoxic ventilatory responders at sea level (*top panel*) and 6,300 m (*middle panel*). Subjects *CP* and *RS* are shown in *bottom panel* during exercise at 6,300 m, breathing a fractional concentration of O_2 in dry inspired gas ($F_{I_{O_2}}$) of 0.14.

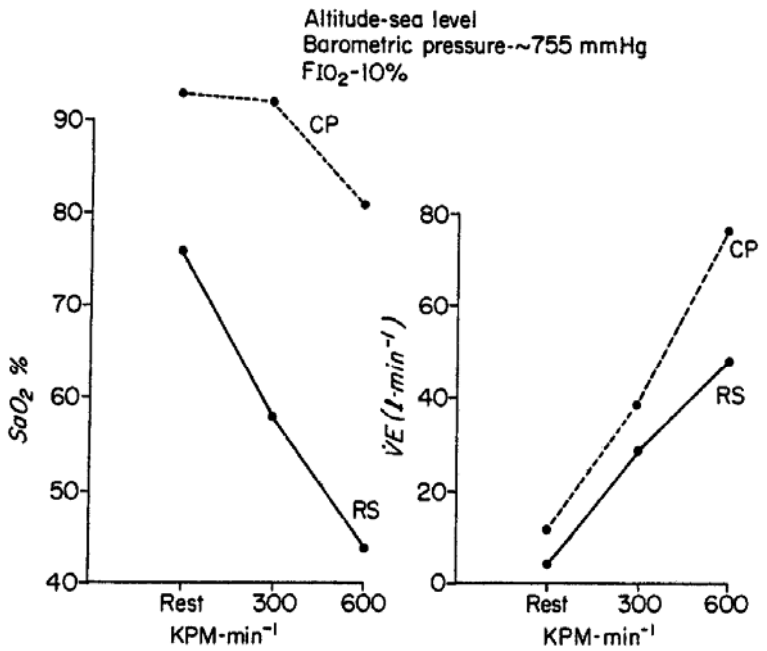
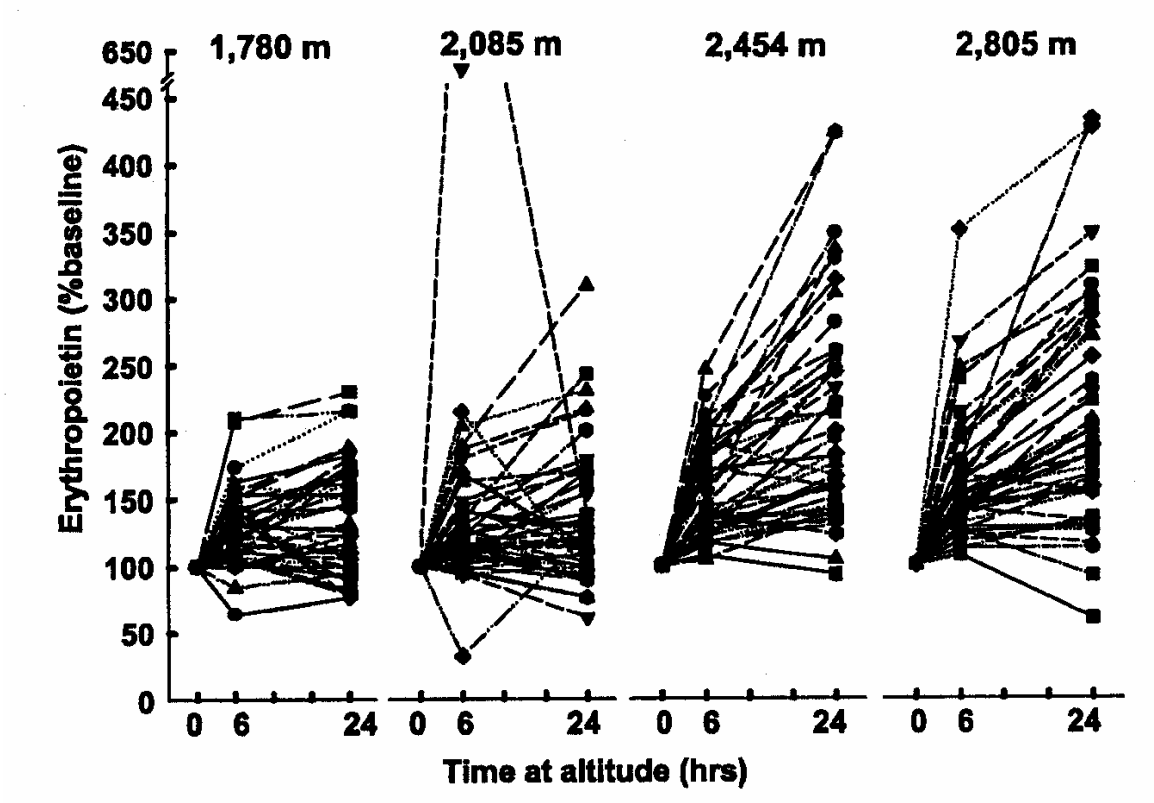


FIG. 7. Work load vs. Sa_{O_2} % (*left panel*) and $\dot{V}_E$ (*right panel*) in subjects *CP* and *RS* while breathing a hypoxic FI_{O_2} of 0.10.

Finally, the figure below from Ge (2002) provides an excellent example of the variability in erythropoietin (EP) change after 24 hrs of mild (1,780 m or about 5,850 ft) to modest (2,805 m or about 9,200 ft) hypoxic challenge from ascent in an altitude chamber. Ge makes the point that individual variability to increased EP production increases with increasing altitude.



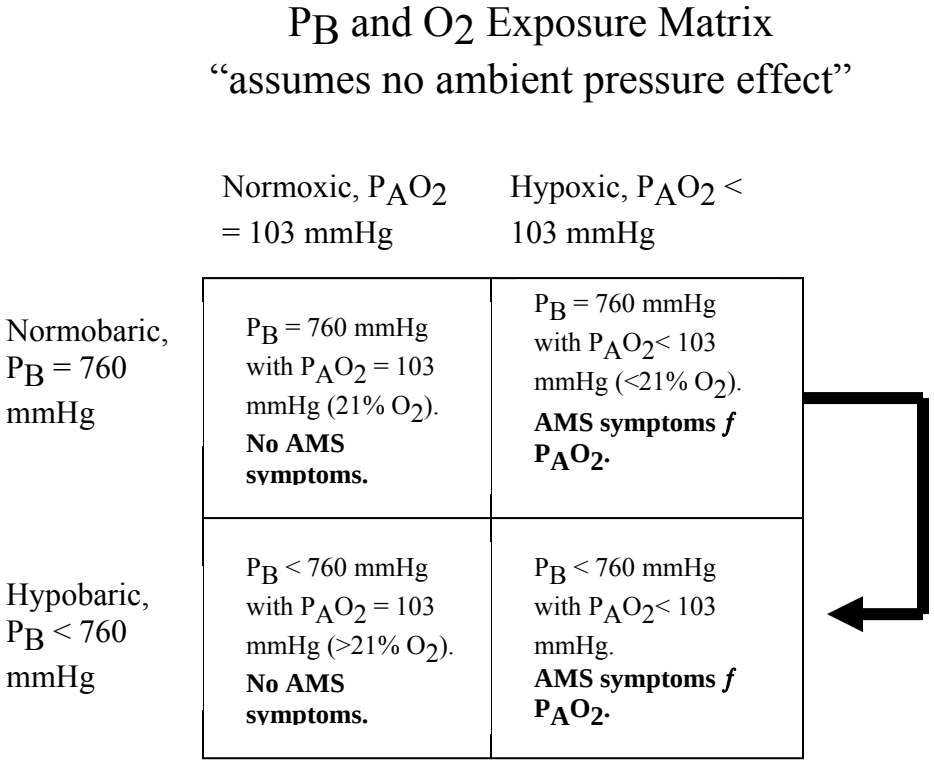
Data for Pressure Effect *per se* on Acute Mountain Sickness

There are hundreds of reports about HH and hundreds of reports about NH, but unfortunately there are fewer than 9 reports where the combination of HH and NH was tested together or HH, NH, and HN were tested together to specifically look for a P_B effect on AMS. The sum total are listed here in ascending chronological order: Tucker (1981 [abstract] and 1983), Grover (1982), Levine (1988), Roach (1995), Roach (1996), Loeppky (1996), Loeppky (1997), Savourey (2003), and Leoppky (2005a).

Three of these report: Grover (1982), Leoppky (1996), and Savourey (2003), were looking for a mechanism to account for a decreased V_E response under HH compared to NH conditions. Their tests were of very short duration of less than 120 min, so AMS was not the primary focus. One study was with sheep (Levine 1988), so no direct application here. Only 4 of these studies (Tucker 1983, Roach 1996, Loeppky 1997, and Loeppky

2005a) have some direct application here. The others, plus Epstein's (1972) evaluation of HN, provide helpful insight into mechanisms.

Figures 2 and 3 show a data presentation format used extensively for the remainder of this report. The P_B and O_2 exposure matrix (4 quadrant box) provides a convenient way to summarize the main experimental conditions and to show selected data. It is not possible to summarize all available data, so only data that show magnitude and direction deemed relevant to this report are shown. This is a practical, although incomplete, approach to show what would otherwise be an unmanageable amount of information.



NN – normobaric normoxia, NH – normobaric hypoxia, HN – hypobaric normoxia, HH – hypobaric hypoxia

Fig. 2. Matrix of combinations of P_B and O_2 concentration that have been evaluated. Hyperbaric P_B exposures are not covered here. The higher the altitude, the greater the O_2 concentration needed to provide a particular P_AO_2 < 103 mmHg. So, there are infinite combinations of altitudes and O_2 concentrations that can set a particular P_AO_2 < 103 mmHg, with the assumption that the consequences are equivalent to ascent on air (21% O_2) to a particular P_AO_2 < 103 mmHg; a notion accepted, since the time of Paul Bert in 1878, about AMS symptoms.

P_B and O_2 Exposure Matrix
"assumes an ambient pressure effect"

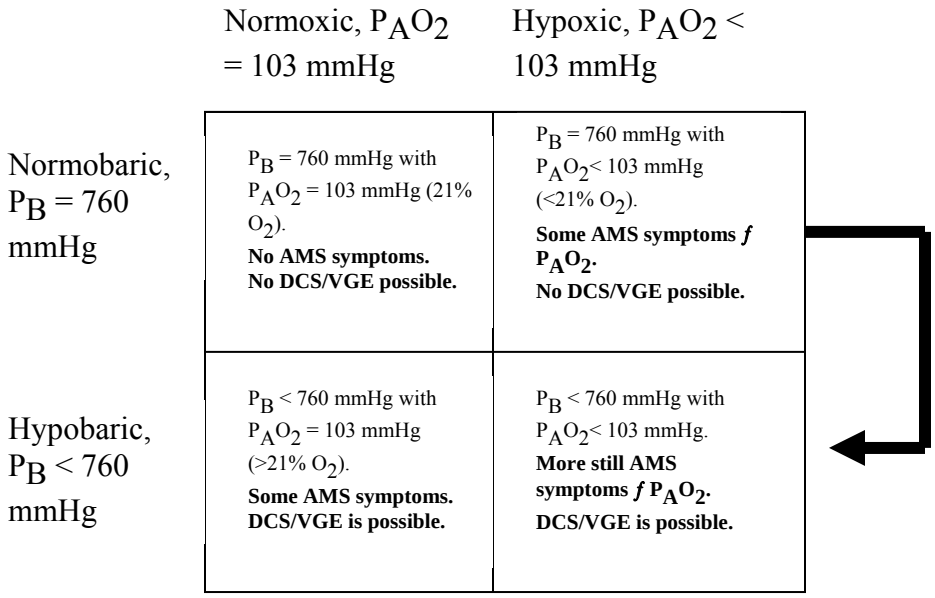


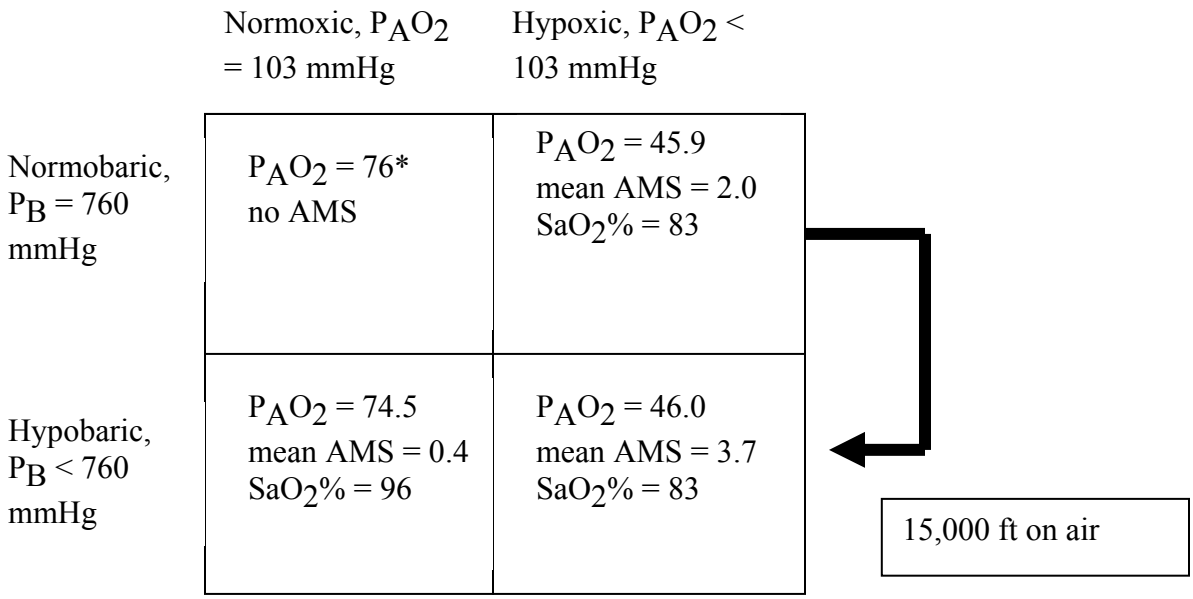
Fig. 3. A P_B effect *per se* appears at work on physiological responses and signs and symptoms of AMS based on a review of literature from 1980 to the present. Notice that this statement is "conditional" on the fact that hypoxia is present. The current research says that you should not assume all AMS outcomes would be equivalent given only equivalent hypoxic P_IO_2 or P_AO_2. This confirms anecdotal observations that the most effective treatment for AMS is the application of increased P_B to achieve a particular treatment P_AO_2 instead of increasing the percentage of O_2 at the current lower P_B to achieve the same treatment P_AO_2 (Kasic 1991). What is needed are data that show little or no physiological changes when ambient P_B is reduced but $P_AO_2 \geq 103$ mmHg. These data, and there are thousands of exposures to altitude while breathing 100% O_2, would indirectly support the idea that both hypoxia and hypobaria have a negative synergistic effect on the body. One confounding reality that has not been carefully controlled in early studies was the potential for bubble formation and subsequent embolization of the lungs due to HN and HH exposures.

Notice that under steady state conditions, data in the 2 verticals of the P_B and O_2 exposure matrix allow you to understand the contribution of changes in P_B (physics about gas density, gas viscosity, work of breathing, etc.) on the data, irrespective of the physiology. Data in the 2 horizontals allow you to understand the physiology of hypoxia, irrespective of the P_B. The data in the 2 diagonals combine gas physics and the

physiology of hypoxia, allowing you to understand the interaction of both variables. The interactions can be additive in the same direction, additive in opposite directions, cancel each other, or some other complex nonlinear interaction.

By way of introduction, and for economy of space, we list several related figures now that display summary data about a P_B effect on AMS. Figure 4 shows results from Roach (1996), figure 5 is Tucker (1983), figures 9 and 10 are Grover (1982), figures 11 to 13 are Levine (1988), figure 14 is Leoppky (2005a), figure 15 is Savourey (2003), figure 16 is Loeppky (1996), figure 17 is Loeppky (1997), figure 18 is Meehan (1986), Swenson (1995), and Knight (1991), and figure 19 is Epstein (1972).

Summary of Roach (1996) Results (acute P_AO_2)



*See Note 1 at end of report.

AMS – Acute Mountain Sickness score using the Lake Louise system (Roach 1993).
SaO_2% - arterial blood oxygen saturation (%).

Fig. 4. The average Lake Louise AMS score from 6 and 9 hrs of hypoxic exposure in 9 subjects associated with the computed P_AO_2 from the AOE. These data are from figure 1 in Roach (1996); see next page. An earlier review by Roach (1995) expands on data from others that he references in the 1996 paper. Roach concludes that symptoms of AMS are less severe and occur later during NH compared to HH, given the same inspired ppO_2. Based on the data above, there appears to be a P_B effect at work on the signs and symptoms of AMS. Note that there was no clear cause-and-effect relationship between SaO_2% and AMS with P_B, except that hypoxia reduces SaO_2%. Results in this report suggest that you should not assume that all AMS outcomes would be equivalent given only equivalent P_AO_2.

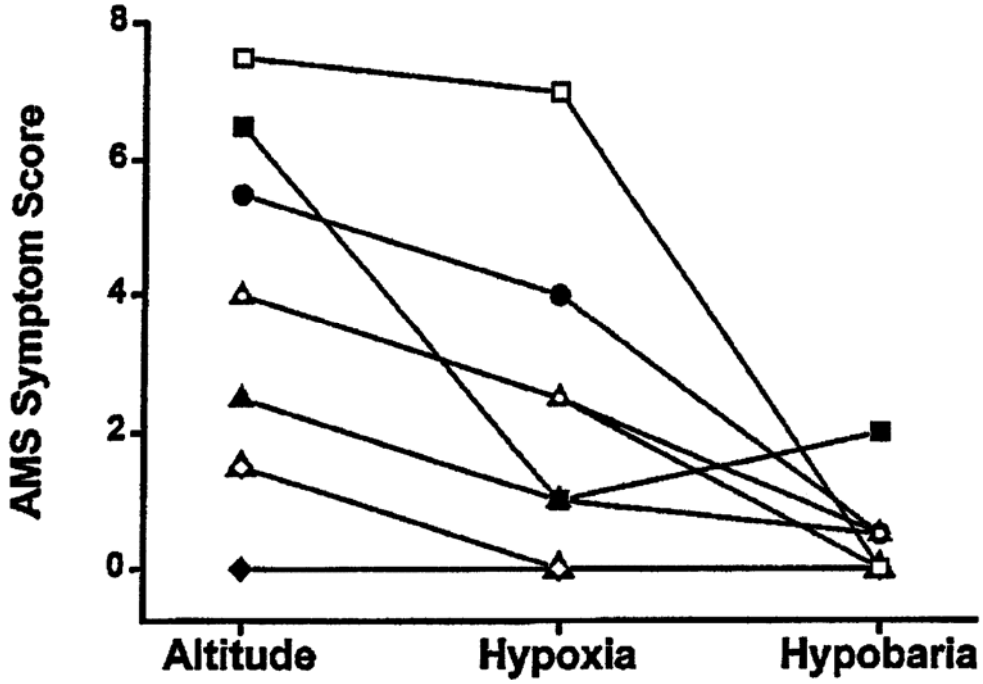
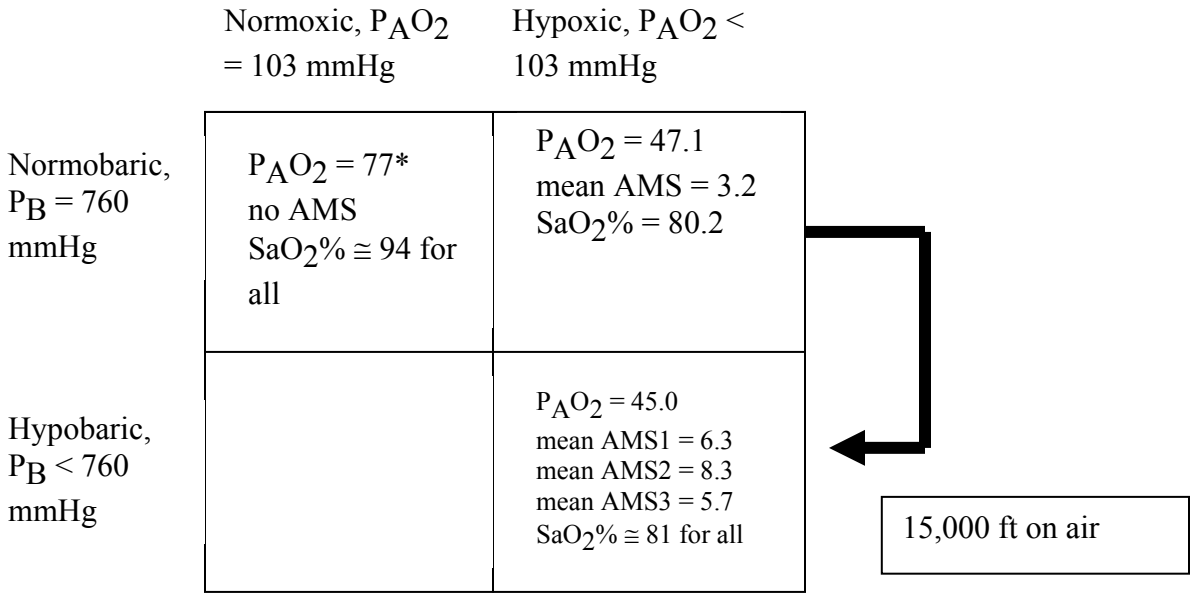


Fig. 1. Individual Lake Louise acute mountain sickness (AMS) scores (average for *hours 6* and *9*) are presented for simulated altitude, normobaric hypoxia, and normoxic hypobaria. Each symbol represents a different subject (n = 9). During simulated-altitude exposure, AMS scores were significantly higher than during either normobaric hypoxia or normoxic hypobaria ($P < 0.01$); during normobaric hypoxia, AMS symptoms were not significantly different from normoxic hypobaria.

Summary of Tucker (1983) Results (acute P_AO_2)



*See Note 2 at end of report.

AMS – Acute Mountain Sickness score not based on the Lake Louise system.
SaO_2% - arterial blood oxygen saturation (%).

Fig. 5. Tucker's (1983) summary results supports a P_B effect at work on the signs and symptoms of AMS (see his figures 1 and 2 below). A 2-hr exposure time was sufficient to measure acute changes, but not sufficient enough to track any adaptive changes in V_E seen by Grover (1982) in 4 hrs. AMS1 was with subjects in a normal water balance, AMS2 was with subjects in a positive water balance (no statistical difference between AMS1 and AMS2), and AMS3 was with subjects in a normal water balance plus a 1.5-hr PB prior to ascent (no statistical difference between AMS1 and AMS3).

There was no significant difference in any measured variables between normal and overhydrated subjects. Prior PB did not change the AMS score between NH and HH (3.2 vs. 5.7). The difference between an AMS of 3.2 for NH and 8.3 for HH in subjects with positive water balance was not statistically evaluated. But PB did reduce hyperventilation and alkalotic response to HH. This was a reduction in V_E relative to what was observed under NH. There was a 27% greater V_E in NH relative to HH in 6 subjects, a change similar to that reported by Loeppky (1997) in 9 subjects over a longer measurement period. The smaller increase in V_E response under HH relative to NH was further reduced (blunted) when O_2 was breathed for 1.5 hrs in 11 subjects. Since

subjects maintained arterial O_2 saturation after PB, despite the relative hypoventilation at 4,572 m (15,000 ft), the gas exchange must have improved, possibly through an improved ventilation - perfusion (V_A/Q) matching. Increased ppO_2 during PB may also decrease ADH secretion from the pituitary gland. This would, in turn, encourage a diuresis, which is associated with fewer signs and symptoms of AMS. It appears that there is renal dysfunction leading to fluid shifts and water retention as an important component of AMS with both hypoxic stress (Hackett 1982) and hypobaria (Epstein 1972) implicated in this dysfunction.

Heart rate (HR) did not increase as much with prior PB and subsequent HH exposure compared to just HH exposure. Systolic and diastolic blood pressure (SBP, DBP) were actually lower than control values with prior PB and subsequent HH exposure compared to just HH exposure. HH by itself increased both SBP and DBP from baseline. PB tended to "blunt" the classic cardiopulmonary response seen in HH exposure. Tucker (1983) proposes a decrease in chemosensitivity to hypoxia due to 100% O_2 PB at site P_B, and it persisted for the 2-hr duration of his test. O_2 can be considered a drug with dose-response relationships. During a 3 hr PB, Conkin (1984) measured an increase in DBP with a reduction in CO, and no change in SBP. These changes increased mean arterial pressure (MAP) and computed peripheral vascular resistance. One atmosphere ppO_2 has a vasoconstrictive effect on the vasculature, and the persistent reduction in SBP and DBP during subsequent hypoxic exposure following O_2 PB in Tucker's experiment is curious.

The decrease in V_E, increase in pH and end-tidal CO_2 partial pressure (P_ECO_2), and decrease in urine flow with expected increase in urine osmolality in the HH exposure relative to the NH exposure is consistent with a hypobaric P_B effect, given that hypoxia is present. SBP and DBP were also higher in the NH exposure compared to the HH exposure. So, Tucker also proposes a decrease in chemosensitivity caused by just the hypobaric exposure since V_E was actually higher in the NH exposure. There appears to be some benefit to PB above and beyond reducing the chance of VGE as a confounder. Periods of PB prior to and following ascent are easy to implement and should make the acclimatization to HH easier.

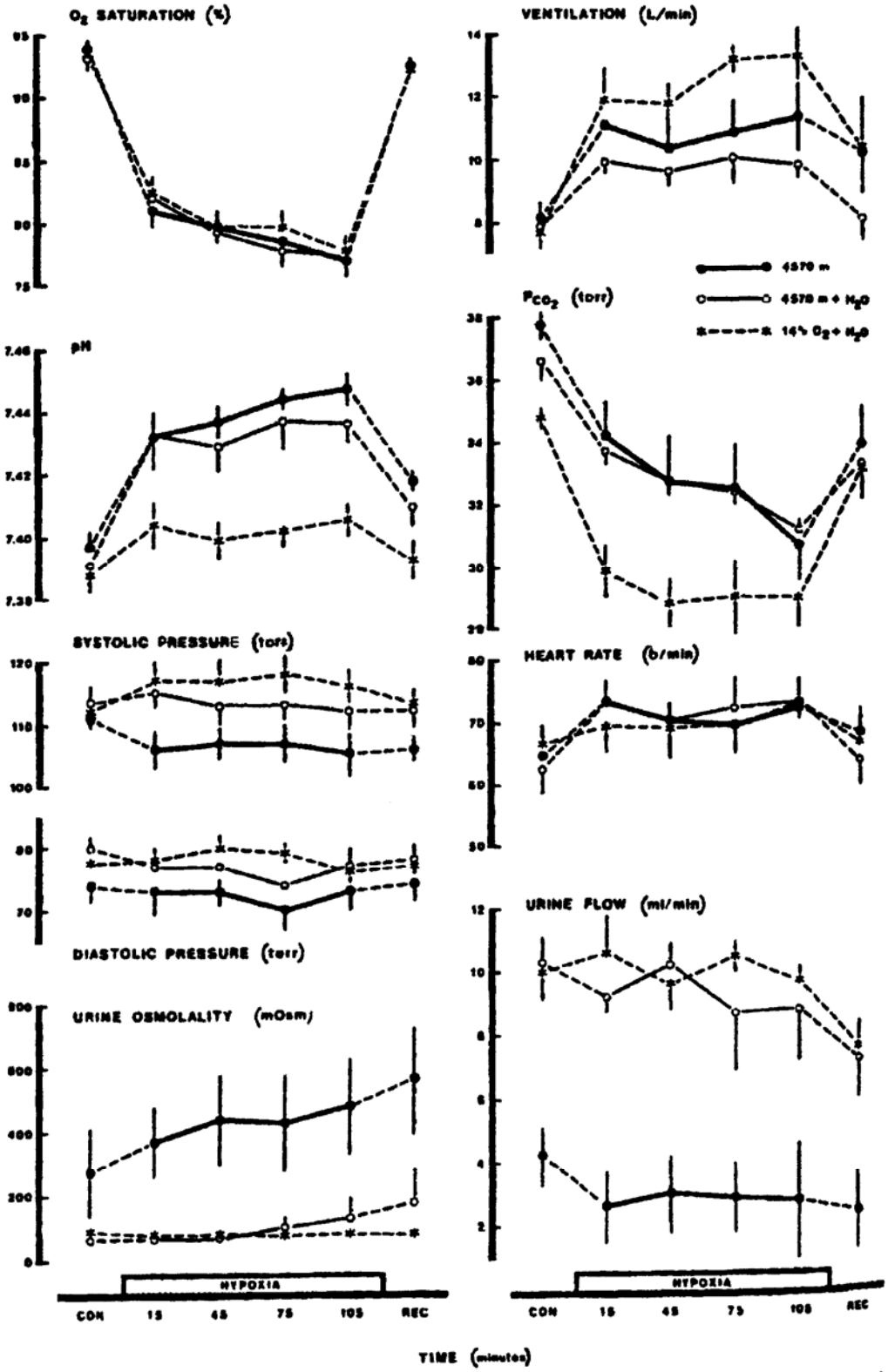


Fig. 1. Cardiopulmonary and urinary changes in subjects (n = 6) exposed to 4570 m with (O) and without (●) water loading and breathing 14% O_2 (*) under normobaric conditions. Mean ± SE.

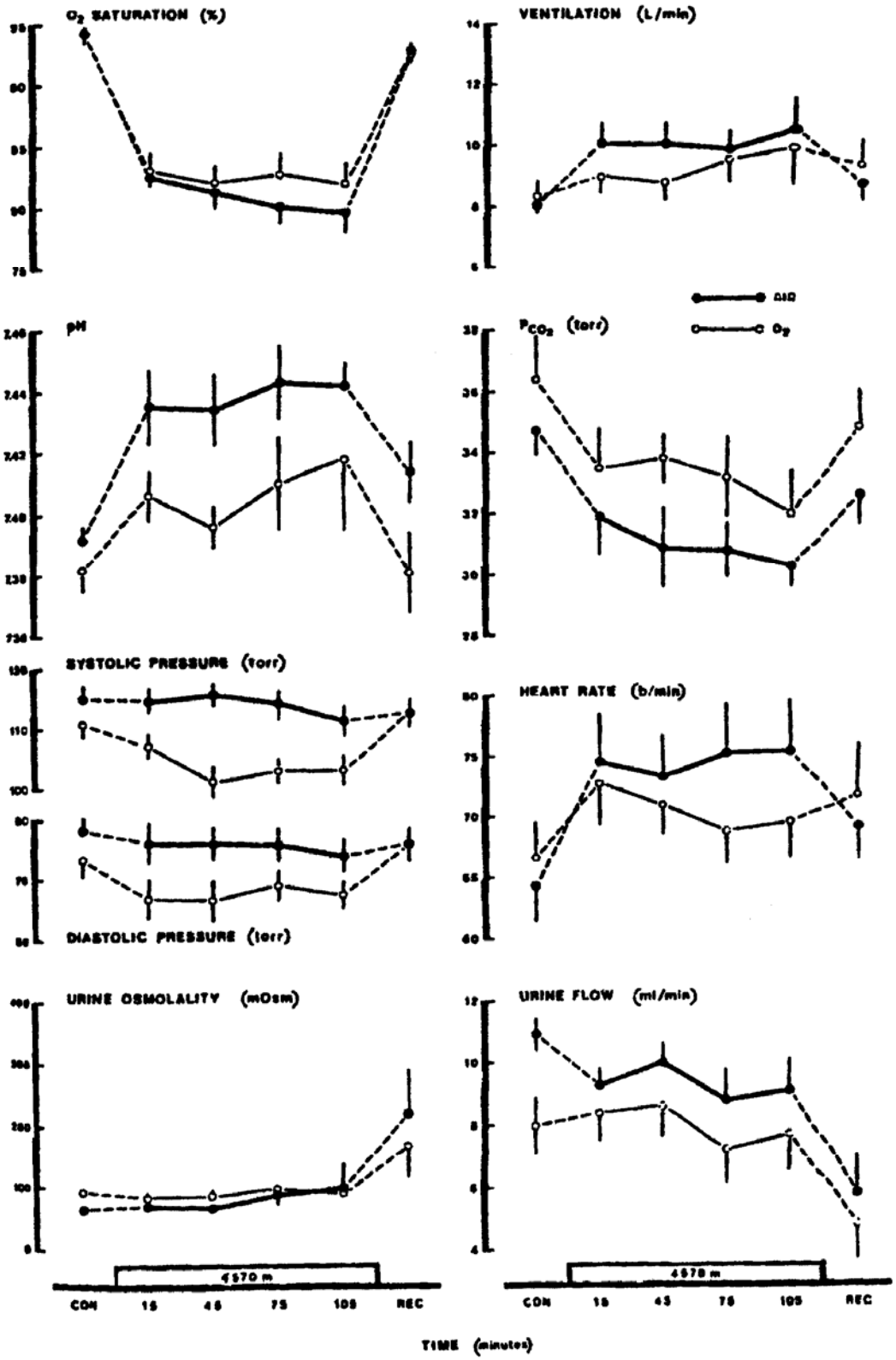


Fig. 2. Cardiopulmonary and urinary changes in subjects (n = 11) exposed to 4570 m with (O) and without (●) prior O_2 breathing. Mean ± SE.

Do Venous Gas Emboli have a Role in Acute Mountain Sickness?

The topic of VGE, in conjunction with O_2 PB and subsequent HN or HH exposures, needs some discussion. The lungs are an excellent filter of bubbles in the venous return. The microscopic to macroscopic impacts that VGE have on modifications to pulmonary blood flow, subsequent pulmonary vasoreactivity, and gas exchange is not covered here. It is certain that VGE form with very little provocation during ascent to even modest altitudes; especially if the ascent to a final P_B is within minutes, there is little or no O_2 PB, subjects are physically active at altitude, and the altitude exposure is longer than a couple of hours. All of these conditions are present in most of the research on AMS performed in altitude chambers. In addition, hypoxia is present that may or may not contribute to the incidence or consequences of VGE.

Figure 6 shows the probability of venous gas emboli [P(VGE)] as a function of the DCS dose (Conkin 1994). The figure is helpful to show the magnitude of the "VGE potential" given some of the exposure conditions documented in the reports on HH. But, the data shown in the figure were collected in experiments about DCS where subjects routinely performed hours of PB, breathed 100% O_2 from a mask while at altitude, and were physically active during the 3 to 6-hr tests. In the case of Tucker's experiment, a 1.5 hr PB reduces the computed ppN_2 in a theoretical tissue compartment with a 380 min half-time from 9.7 to 8.2 psia. Tucker performed his experiment with subjects living at 12.2 psia, so the initial tissue ppN_2 is simply taken as $12.2 * F_IN_2$ (0.79) = 9.7 psia. The DCS dose on the x-axis is defined as [(PN_2380/P2) - 0.95], where PN_2380 is the computed 8.2 psia, and P2 is the final exposure altitude of 8.3 psia (15,000 ft) used in Tucker's experiment. The DCS dose is therefore computed as 0.037, indicating a very low probability of VGE from figure 6.

Discounting the influence of hypoxia on the incidence of VGE, the computed P(VGE) for Tucker's experiment with PB is $[0.037^{1.576}/(0.037^{1.576} + 0.48)] = 0.01$, or 1%. A direct ascent to 8.3 psia without the benefit of O_2 PB gives a DCS Dose of [(9.7/8.3) - 0.95] = 0.218, and a computed P(VGE) of $[0.218^{1.576}/(0.218^{1.576} + 0.48)] =$ 0.16, or 16%. There is a potential for VGE to influence the lungs of subjects exposed for 2 hrs, but the impact is unclear on how this might affect gas exchange in hypoxic subjects. There is a latency time for the onset of detectable VGE in the pulmonary artery and a response pattern (Conkin 1996) that is a function of the DCS dose, and in most studies about HH the DCS dose is small. This is because ascents in altitude chambers without supplemental O_2 are limited because of hypoxia. Changes in pulmonary gas kinetics ascribed to VGE in HH occur on time scales that do not match the latency times or response patterns for VGE embolization of the lung. So, it is unlikely that VGE are the "magic bullets" to understand differences between NH and HH. Other HH experiments to be described are similar to Tucker's except O_2 PB was never considered, so the confounding role of VGE in those results must be acknowledged.

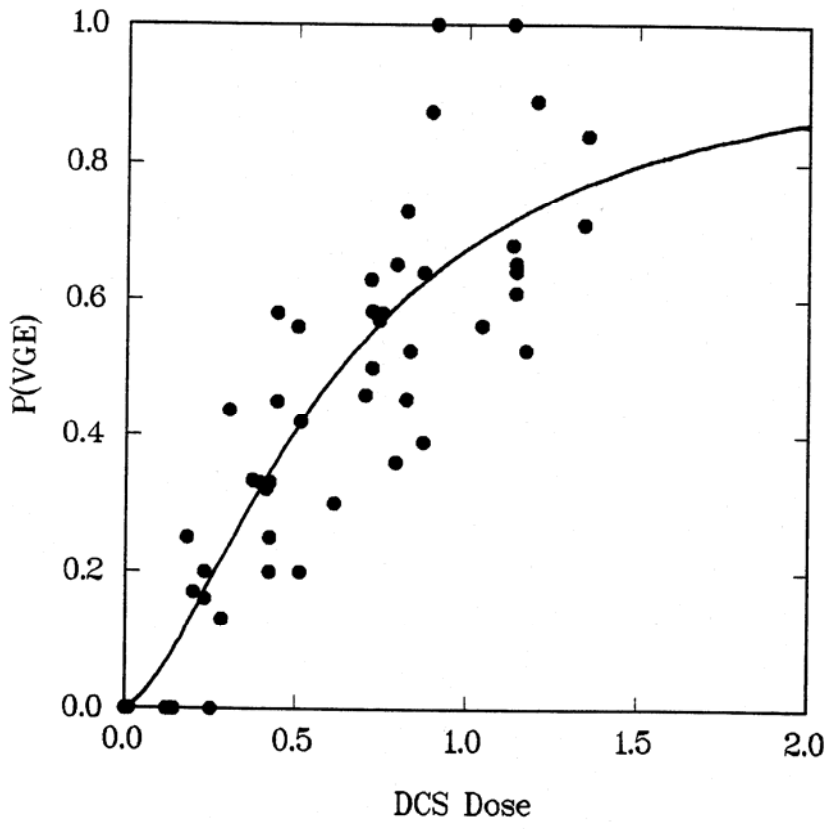


Fig. 6. Best-fit statistical DCS dose - VGE response curve for 52 different tests at altitude that involved 1,009 men who were physically active at altitude. The duration of exposures was greater than 1 hr, but usually less than 6 hrs. VGE were or were not detected in the pulmonary artery during the test using a Doppler ultrasound bubble detector with the sensor placed in the precordial position. The presence of any VGE, regardless of Doppler signal intensity, was coded as a "yes (1)" response for VGE. The absence of VGE was coded as a "no (0)" response, and a DCS dose and dichotomous VGE response curve was constructed for the 1,009 records. See explanation above for the definition of DCS dose.

Partial Pressure of Nitrogen, Oxygen, and Carbon Dioxide in the Cerebrospinal Fluid

As just described, evolved N_2 contributes to VGE that could alter V_A/Q in the lungs or cause the release of vasoactive compounds from pulmonary endothelium under both HH and HN. But, the movement of dissolved N_2 under HH and NH should also be discussed. Differences in the outward manifestations of hypoxia, such as the incidence or severity of AMS, in what is an identical hypoxic stress as defined by P_IO_2 for both NH and HH would be reconciled if there is a true difference in hypoxic stress within the CNS. An understanding of this difference defines the P_B effect.

The mechanism for a P_B effect on AMS starts with the transport of O_2 from the atmosphere to the blood. The effectiveness of alveolar ventilation is influenced by the density of the breathing gas since flow is proportional to the reciprocal of the square root of gas density, the work of breathing is proportional to the relative density times the minute volume cubed, and the diffusivity of a gas, including water vapor, is inversely proportional to the density of the breathing gas. These effects are small in resting subjects in our circumstances. Logic dictates that even subtle changes in the breathing environment affects physiology, as most investigators conclude. Gas density in conjunction with other factors about a change and rate of change in P_B contributes to differences in the body that do matter.

One could reason, farther into the body, that both the numerator and the denominator of the V_A/Q ratio are affected differently under NH and HH conditions. Alveolar ventilation is affected by gas density, while pulmonary perfusion is affected by regional time-varying responses to hypoxia within the lung. Careful measurements show lower V_E with HH relative to NH in some subjects. But, there is disagreement concerning whether these data support a decrease or an increase in alveolar deadspace (wasted ventilation) under the HH condition. Savourey (2003) speaks of the "specific response to HH" and concludes the lower tidal volume and higher breathing rate in his HH condition supports an increase in deadspace ventilation. Loeppky (1997), in contrast, used fewer subjects but collected data over several hours compared to Savourey, says there is a decrease in deadspace ventilation in his HH results. There was a suspected decrease in O_2 consumption and CO_2 production rate of about 80 ml/min attributable to a decreased work of breathing in HH. Loeppky shows no difference in SpO_2 from finger oximetry between NH and HH conditions, about 83%, while Savourey shows an SaO_2 from arterial blood of 88% for NH and 85% for the HH condition. Even though in both experiments HH was from an ascent on air in an altitude chamber to 4,572 m (15,000 ft), subjects in Loeppky's study lived in Albuquerque, New Mexico at an altitude of about 1,524 m (5,000 ft).

We will now go farther into the body, to the system that interprets, integrates, and responds to peripheral and central chemoreceptors. The premise to explore is that differences in AMS to identical hypoxic P_IO_2 under NH and HH conditions are due to proper responses of the CNS to the true hypoxic condition. The proper CNS response is due to different constituents of the CSF that are due finally to the different metabolic rate and N_2 kinetics leading to different quantities of dissolved O_2 and CO_2 in the CSF under NH and HH conditions. The differences in these gases within the CSF are our hypothesized cause-and-effect of the P_B effect on AMS. We focus on the role of the CSF as an acellular capacitance reservoir through which the medulla senses H+ and a medium through which O_2 and CO_2 interact with brain cells. The medulla as a central chemoreceptor has been established (Leaf 2006, Murray 1986). Small pockets of CSF are found within the subarachnoid space, particularly around the base of the brain. The largest of these pockets is the cisterna magna between the inferior surface of the cerebellum and the medulla.

The solubility of N_2, O_2, and CO_2 in CSF is 0.01, 0.02, and 0.5 ml (STPD)/ml CSF $*$ ATA^{-1} respectively, with CO_2 about 25 times more soluble than O_2. The absolute quantity (moles) of these gases is small owing to the small volume (130 to 150 ml) of the CSF and the low solubility of O_2 and N_2. CSF is an extension of the extracellular fluid of brain cells; a unique system that transiently buffers extremes in P_aO_2 (Kazemi 1968). Depending on the conditions, the CSF is either a sink or a source of dissolved O_2. An increase in P_aO_2 moves excess O_2 from brain cells into the acellular CSF until a new, higher equilibrium is established. A decrease in P_aO_2 moves excess (relative) O_2 from the CSF into brain cells until a new, lower equilibrium is established. The flux is large for O_2 (about 50 ml/min) and CO_2 (about 50 ml/min) to meet the high metabolic demand of brain cells at 3.5 ml/100 gm/min. So, small differences in P_AO_2 and P_ACO_2 between non-equivalent NH and HH conditions combined with the required flux rate through the CSF have the potential for large effects in the brain, particularly the cerebral blood flow. There would be no hindrance to the diffusion of gases through the BBB. The barrier serves to protect the CNS from ionic disturbances in the plasma, and protects the brain and vascular smooth muscle cells in brain vessels from circulating hormones.

A study by Tucker (1983) points to the importance of N_2 in the development of AMS. Depending on the duration of 100% O_2 breathing, the ppN_2 gradient across the alveoli is less compared to the gradient when a hypoxic mixture is breathed at the start of a NH or HH exposure. The reduction in the N_2 diffusion gradient across the alveoli due to a 1.5 hr denitrogenation at site pressure correlated with a reduction in AMS scores between the NH and HH conditions where SpO_2 from ear oximetry was about 81% for both conditions. As in Loeppky's studies (1996, 1997), subjects in Tucker's study lived at about 1,524 m (5,000 ft), but in Fort Collins, Colorado, prior to ascent to 4,570 m (15,000 ft). The score (Environmental Symptoms Questionnaire) for the NH condition was 3.2 compared to 5.7 after denitrogenation under HH conditions, which was lower compared to 6.3 and 8.3 units in 2 other HH experimental conditions that did not include prior denitrogenation. We will focus on the movement of dissolved gases as opposed to evolved gas, as Tucker suggested, and how this movement influences hypoxic stress within the CNS.

The transient ppN_2 concentration gradient in NH causes N_2 to diffuse from the alveoli into oxygenated blood, and this gradient is reversed in HH. The small change in volume affects other alveolar gases as a function of the direction and amount of N_2 movement through time. The effect must be small since the removal of N_2 from the body after about 90 min of resting denitrogenation with 100% O_2 breathing is in the range of 2 to 3 ml/min. In NH the F_EN_2/F_IN_2 ratio is initially less than one as N_2 enters the tissues, and then increases toward one, modified by actual VO_2 and VCO_2, as a new equilibrium P_aN_2 is established. The combination of a changing metabolic rate and N_2

kinetics, reflected in the RER and F_EN_2/F_IN_2 ratio, change P_AO_2 and P_ACO_2 through time between NH and HH; both Savourey (2003) and Loeppky (1997) show trends in lower end-tidal O_2 partial pressure (P_EO_2) and P_ECO_2 in HH relative to NH.

We propose that P_AO_2 and P_ACO_2 in NH are *always initially higher* relative to HH given that P_IO_2 is identical in both conditions when metabolic rate and N_2 kinetics are considered. P_AO_2 and P_ACO_2 in NH falls to a final steady state value reflected through a stable F_EN_2/F_IN_2 ratio. P_AO_2 and P_ACO_2 in HH are *always initially lower* than in NH, and increases to a final steady state value, again reflected through a stable F_EN_2/F_IN_2 ratio. For the same hypoxic P_IO_2, the N_2 gradient is larger in the HH condition. Therefore it takes longer to come to the new P_aN_2 equilibrium thus keeping P_AO_2 and P_ACO_2 lower in HH than NH. By our reasoning, investigators who rely on P_IO_2 to establish identical hypoxic equivalency between NH and HH exposures should instead refer to this method as establishing similar hypoxic equivalency.

Figure 7 is our conceptual construct for the cause of the differences in CNS hypoxic stress between NH and HH. P_IO_2 is 80 mmHg at both 760 mmHg for the NH case with RER of 0.92 and 428 mmHg (15,000 ft altitude) for the HH case with RER of 0.86 (see Loeppky 1997).

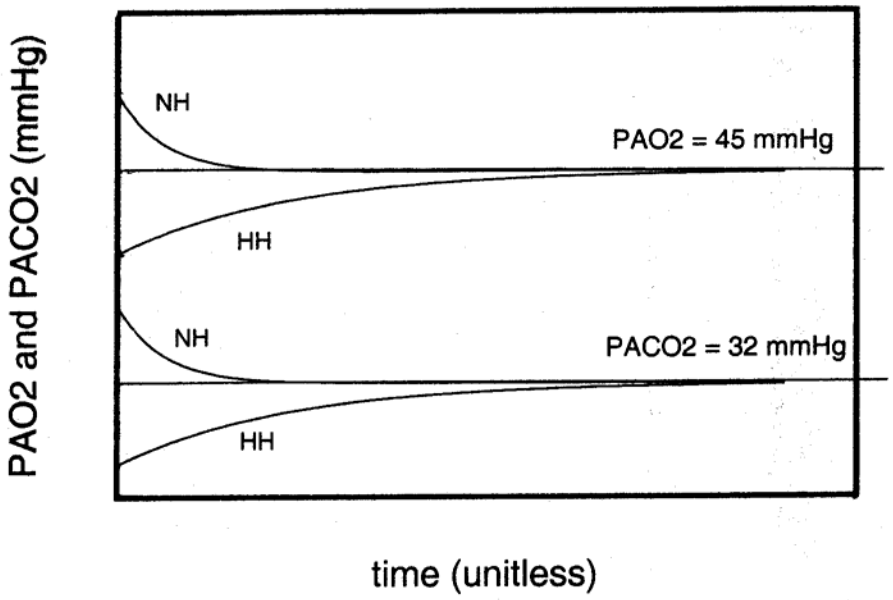


Fig. 7. Change in metabolic rate due to work of breathing and N_2 kinetics within the lung modifies P_AO_2 and P_ACO_2. At some future time both situations approach a steady state P_AO_2 of 45 mmHg and P_ACO_2 of 32 mmHg. But the outcome for AMS between

NH and HH is not the same due to earlier differences in the transport of O_2 and CO_2 to and from the CNS.

The concept, but not the magnitude of the effect, applies to other comparisons at different P_IO_2s. Note that there is no unit for time and only steady state P_AO_2 and P_ACO_2 is shown since only the direction, but not the magnitude or duration of this effect is clear. The time to reach a new equilibrium for the P_aO_2 and $P_{CSF}O_2$ gradient following a switch to a hypoxic condition depends how quickly the O_2 partial pressure in the CSF falls and how quickly the reduced supply at a reduced partial pressure can diffuse through out the CSF as an extension of the extracellular fluid of neural tissues. P_B does not change in NH but P_IN_2 increases in the breathing gas, by 74 mmHg in our example where 88.8% N_2 is breathed at sea level to simulate a hypoxic ascent to 4,572 m (15,000 ft) on air. $P_{CSF}O_2$ falls to match the new reality of an acute P_AO_2, about 45 mmHg after a new steady state F_EN_2/F_IN_2 is established. Oxygen, N_2 and CO_2 reach equilibrium gradients with the arterial source once the capacity of the CSF to accept these gases is reached. The hypothesis is that NH provides medullary tissues in contact with the CSF a greater net flux of O_2; the gradient between $P_{CSF}O_2$ and mixed venous ppO_2 from the jugular vein is larger for a time in NH than in HH. There is a shorter delay to achieve the lower steady state $P_{CSF}O_2$ in NH compared to HH. In concert with this process is a slower decrease in CSF H+ since there is a higher P_aCO_2 in NH compared to HH. This delays a change in CSF pH thus delays hypoxia-induced hypoventilation caused by the alkalization of the CSF. There is less inhibition on the ventilatory drive to hypoxia due to the alkalization of the CSF, so V_E is higher in NH relative to HH. A higher P_aCO_2 also increases cerebral blood flow relative to HH at a time when local autoregulation is active.

P_B is reduced in HH leading to a lower P_IN_2 and P_IO_2 in the lungs, a large decrease of 262 mmHg for N_2 in our example. P_AO_2 decreases to 45 mmHg after a new steady state F_EN_2/F_IN_2 ratio is established. The CSF at a lower P_B initially has N_2 in excess of what can be held in solution, so a greater amount of N_2 leaves the CSF and body tissues than enters the body in NH. It takes longer to achieve a new P_aN_2 equilibrium in our HH example where P_IO_2 is 80 mmHg in both conditions. The O_2 in excess of what is held in solution in the CSF is quickly consumed by neural tissues, or lost to the venous return. The HH condition provides medullary tissues in contact with the CSF a reduced net flux of O_2; the gradient between $P_{CSF}O_2$ and mixed venous ppO_2 from the jugular vein is smaller for a time in HH than in NH. There is a longer delay to achieve the lower steady state $P_{CSF}O_2$ in HH compared to NH. There is also a faster decrease in CSF H+ since there is a lower P_aCO_2 in HH compared to NH. This leads to a faster alkalization of the CSF, a potent stimulus within the CNS to transiently suppress (Grover 1982) the ventilatory response to hypoxia, so V_E is lower in HH relative to NH. A lower P_aCO_2 would suppress cerebral blood flow relative to NH.

In summary, the change in metabolic rate and opposite direction of N_2 movement and different times to achieve a new P_aN_2 equilibrium have the net effect of making more O_2 and a slower decrease of H+ transiently available to the CSF in NH relative to HH. Savourey (2003) shows a mean P_aO_2 of 6.90 kPa (47.5 mmHg) and P_aCO_2 of 5.06 kPa (34.9 mmHg) for an NH condition in 15 subjects after a 40 min exposure compared to significantly lower ($p \leq 0.05$) values of 6.38 kPa (43.0 mmHg) and 4.65 kPa (32.0 mmHg) for the HH condition where P_IO_2 was 81 mmHg for both experiments. This result is consistent with Loeppky's observations on how changes in O_2 consumption and CO_2 production influences the partial pressure of gases in the alveoli and, by extension, the partial pressure of gases in the CSF. It follows from this hypothesis that under NH the onset of signs and symptoms of AMS occur later, the incidence of AMS is lower, and the severity of signs and symptoms is less compared to HH. In effect, the body is responding properly under both NH and HH but the responses are not equivalent.

To achieve the same AMS response as in NH the P_AO_2 and P_ACO_2 must increase in HH by an amount computed from a precise model (not yet available) that quantifies how changes in metabolic rate, P_IN_2, and direction of movement of N_2 affects O_2 and CO_2 in the CSF. Figure 8 shows our application of a iso-hypoxic model through a range of hypobaric and hyperbaric pressures. A contrast is made between the current EAA (iso-P_IO_2) model and a future iso-hypoxic model using an example for an atmosphere currently selected for the NASA CEV where F_IO_2 is 0.32 at a P_B of 414 mmHg (P_IO_2 = 117 mmHg).

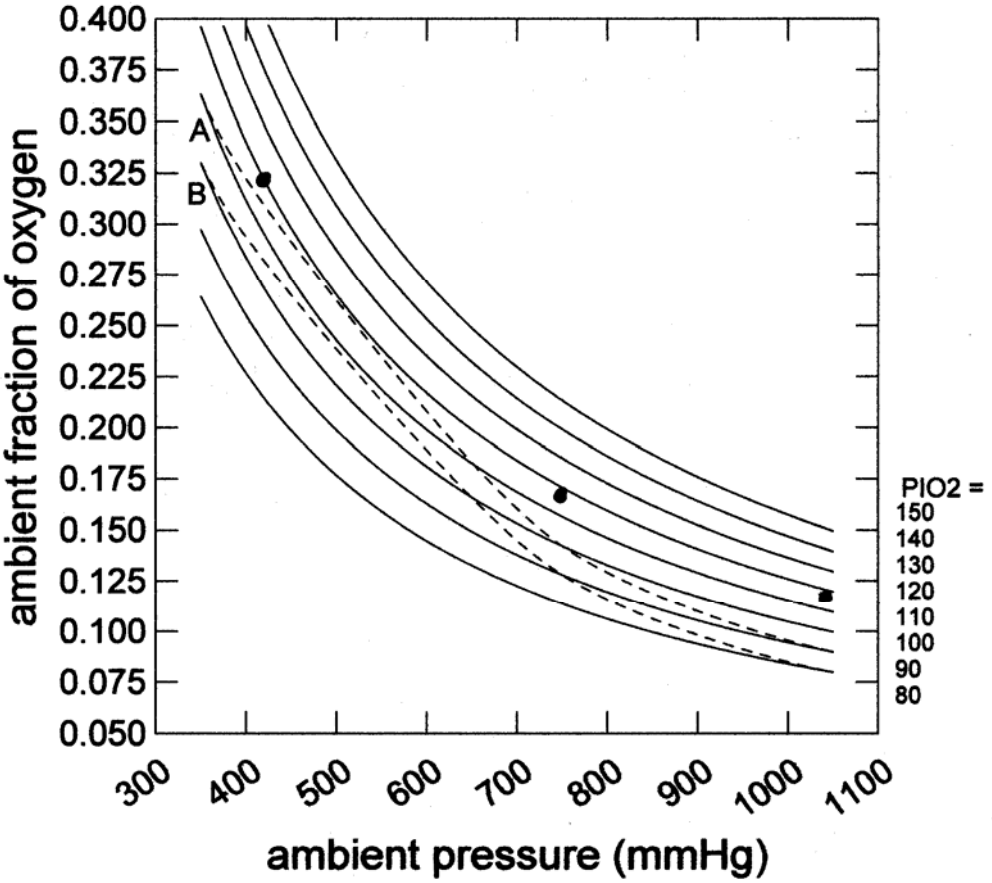


Fig. 8. Eight P_IO_2 isopleths from 80 to 150 mmHg. Dashed curve A is the x% AMS isopleth and dashed curve B is the larger y% AMS isopleth; the actual incidence of AMS for the true isopleths is unknown. Each curve demonstrates that an increasingly larger P_IO_2 is needed to achieve the same probability of AMS as ambient pressure decreases, or conversely a smaller P_IO_2 is needed as ambient pressure increases. Upper point near the x% AMS isopleth is P_IO_2 of 117 at a CEV pressure of 414 mmHg, middle point further from the x% AMS isopleth is also P_IO_2 of 117 at a sea level pressure of 760 mmHg, and finally lowest point farthest from the x% AMS isopleth is again P_IO_2 of 117 at 1,050 mmHg (1.38 ATA). Therefore, the signs and symptoms of AMS are not identical (hypothesis) between the 3 conditions. Difference in time to achieve a new equilibrium F_EN_2/F_IN_2 ratio is a factor that defines the AMS isopleth.

A point at P_B of 609 mmHg and F_IO_2 of 0.209 on figure 8 represents an ascent on air to 1,829 m (6,000 ft), and is also a P_IO_2 of 117 mmHg. This point is slightly further from the x% AMS isopleth than the upper most point representing the CEV breathing environment. Therefore, we hypothesize that the CEV breathing environment has

slightly more hypoxic stress than would otherwise be observed for a direct ascent on air to 1,829 m, but how much more hypoxic stress is unclear. A future iso-hypoxic model that creates precise AMS isopleths would be a refinement to the current EAA (iso-P_IO_2) model, which empirical data suggests needs to be refined.

Kazemi (1968) measured $P_{CSF}O_2$ in dogs breathing 14% O_2, a typical NH condition evaluated in humans, and showed a rapid reduction and equilibration of $P_{CSF}O_2$, on the order of 30 minutes. Our working hypothesis requires that $P_{CSF}O_2$ and pH be effective inputs to the medulla and other brain cells over an extended period, certainly hours, roughly matching the different times it takes for F_EN_2/F_IN_2 to come to a new equilibrium under NH and HH conditions where hypoxic P_IO_2 are identical. Kazemi also shows that an increased cerebral blood flow accelerated the equilibration of the P_aO_2 - $P_{CSF}O_2$ gradient by using 30% CO_2 and 70% O_2 in mechanically ventilated dogs to induce vasodilatation of cerebral blood vessels. In humans, hyperventilation in response to hypoxia leads to hypocapnia that, in turn, causes vasoconstriction of cerebral blood vessels. So, the combination of hypoxia and hypocapnia in spontaneously breathing humans under both NH and HH conditions is expected to increase the time to reach an equilibration of the P_aO_2 - $P_{CSF}O_2$ gradient; there would be a significant difference in time to reach an equilibrium O_2 gradient in a comparison of NH and HH.

We conclude that there is a P_B effect on AMS. It is the difference in P_IO_2 and P_ICO_2 needed to achieve the same AMS response in a large number of subjects between HH and NH. This difference changes as a function of the imposed hypoxic stress, the P_B, and rate of change of P_B. One only needs to measure $P_{CSF}O_2$ and pH through time, given identical P_IO_2 in both NH and HH, to test the basic hypothesis.

Summary of Grover (1982) Results (acute P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg	P_AO_2 = 140 to 40, HVR = 133	
Hypobaric, P_B < 760 mmHg		P_AO_2 = 140 to 40, HVR = 53 after 30 min, and 124 after 240 min

12,000 ft

HVR - hypoxic ventilatory response. Values shown above are coefficients (A) that relates the HVR (l/min, BTPS) to P_EO_2 under isocapnic rebreathing in the equation: V_E (BTPS) = V_o + A/(P_AO_2 - 32), and BTPS is body temperature, pressure, saturated with water vapor.

Fig. 9. Grover's (1982) summary results. He had subjects breathe supplemental O_2 at 750 mmHg such that P_EO_2 was at 140 mmHg at the start of the HVR measurement. The O_2 concentration in the rebreather system decreased over 10 min so that P_EO_2 fell from 140 to 40 mmHg. As hyperventilation ensued, he increased CO_2 concentration in the rebreather to maintain constant P_ECO_2. The resulting HVR was compared to the response at 480 mmHg (12,000 ft) after 30- and 240-min exposures in an altitude chamber. Subjects breathed 40% O_2 during ascent to 3,657 m (12,000 ft), which provides a computed P_AO_2 of 129 mmHg from the AOE for the start of the experiment. But during the time at site P_B (750 mmHg) on 40% O_2, the P_AO_2 is estimated at 237 mmHg. The time from the end of the first experiment to the second while at 3,657 m was spent breathing ambient air (P_AO_2 = 54 mmHg) before once again breathing 40% O_2 for the 10-min duration of the HVR measurement. During the first measurement, HVR was suppressed; but by the second measurement, the HVR had returned to a pre-test response (see figure 10 below for the HVR curves).

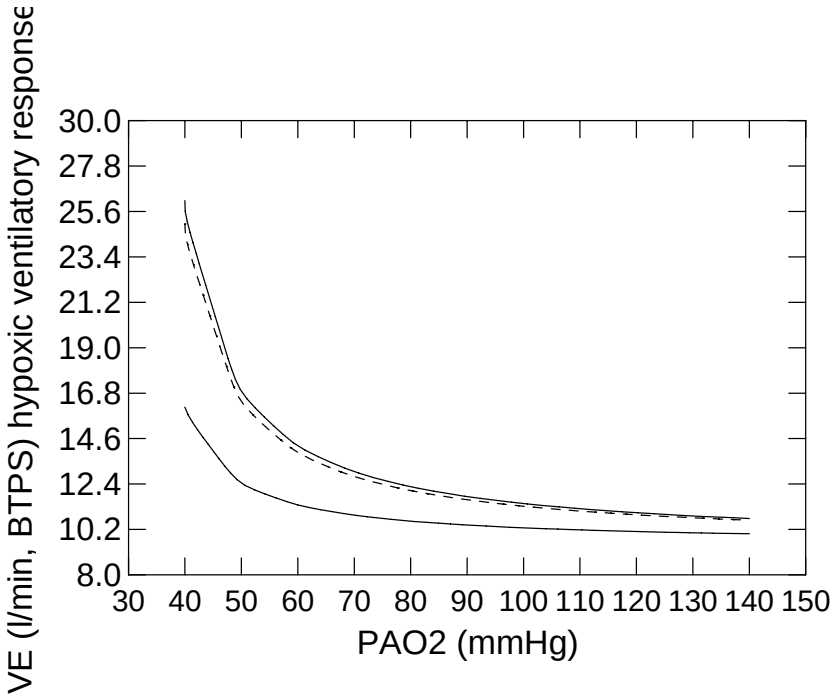


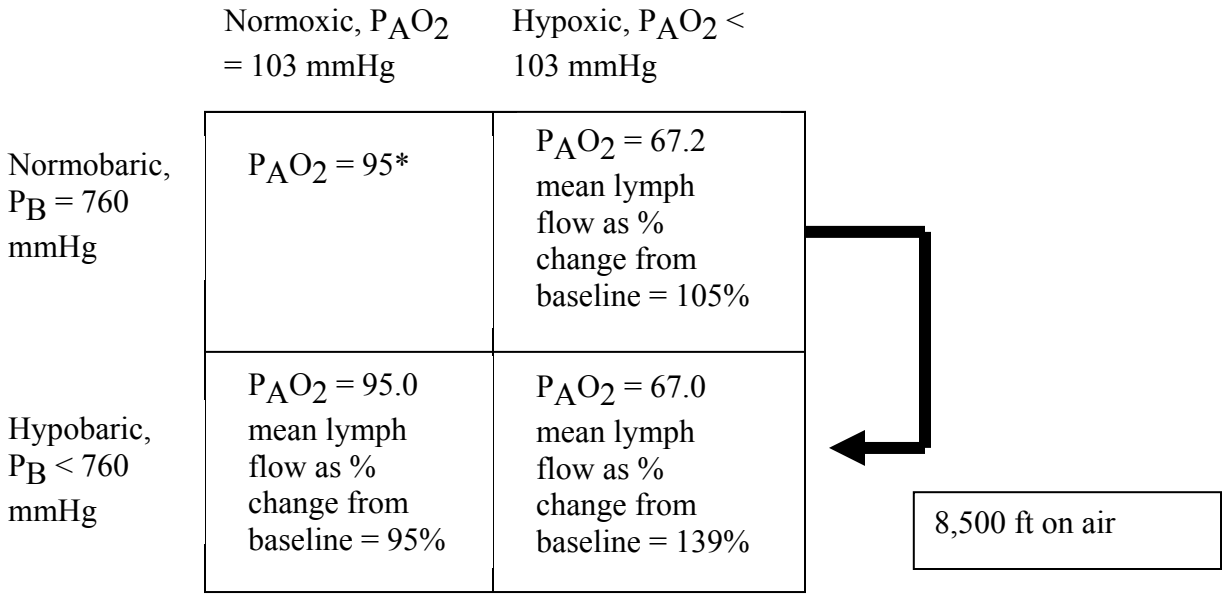
Fig. 10. Curves created from an equation published by Grover (1982). Upper solid curve shows the increase in V_E as P_EO_2 (similar to P_AO_2) is reduced at a total P_B of 750 mmHg by subjects breathing a hypoxic mixture with P_ACO_2 held constant at about 40 mmHg. So, this curve shows just the hypoxic ventilatory response at 750 mmHg without the confounding interaction of a decreasing P_ACO_2 in the face of increased V_E. The lower solid curve is the same experiment performed at 480 mmHg (12,000 ft altitude) during the first 30 mins of the altitude exposure. Note the decreased response in V_E caused by a decrease in absolute P_B (or other factors) over the same change in P_AO_2. A mechanism to describe what appears to be a transient reduced sensitivity to hypoxic challenge at altitude is not known. The dashed curve shows the change in V_E in response to a normocapnic hypoxic challenge after 4 hrs at 480 mmHg. The change seen after the first 30 mins is not evident after 4 hrs, and the changes after 4 hrs at 480 mmHg are no different than the changes at 750 mmHg.

Grover (1982) concludes that hypobaria *per se*, at least transiently, was the cause of blunted respiratory chemosensitivity to hypoxia. Since air enriched with O_2 was used at site P_B and at 3,657 m to achieve an initial P_EO_2 of 140 mmHg, it is likely that the brief exposures to enriched O_2 equally desensitized the respiratory chemoreceptors in both experiments, so the effect of hypobaria could be understood without a bias from the procedure. But, the use of O_2-enriched air does add some uncertainty as to the cause of the blunted HVR immediately on arrival at 3,657 m altitude. He discusses earlier work that he and Tucker (1981 and 1983) performed where 1.5 hrs of 100% O_2 PB were

performed before an exposure to 430 mmHg. Tucker shows that the smaller increase in V_E response after 2 hrs under HH relative to NH was further reduced (blunted) when O_2 was breathed for 1.5 hrs in 11 subjects. So, it is strange that Grover does not discuss that his brief period of hyperoxia (40% O_2 at site P_B) was not a contributor to his blunted HVR response after 30 min at 3,657 m. He attributes his observation only to a hypobaric P_B effect. Finally, Loeppky (1996) conducts a pilot test of a P_B effect for only 30 min at 430 mmHg to understand whether sensitivity (chemoresponsiveness) to hypoxia was altered by hypobaric exposure. He measured pulmonary changes the last 2 mins of a 30-min exposure, and then had subjects breathe 100% O_2 for 1 min. He shows, on a short time scale, that there was no decrease in hypoxic sensitivity, which did not accord with Grover (1982). Tucker (1983) and even Loeppky (1997) show a greater V_E in NH than HH. The reduction in V_E with 100% O_2 suggests that reduced P_B did not markedly alter hypoxic chemosensitivity within 30 mins.

Before leaving the discussion of HVR by Grover (1982), it is helpful to include observations from Prisk (2000) to understand more about factors that modify HVR. Prisk shows that sustained μG and supine body position in normal gravity reduce the ventilatory response to hypoxia but not to hypercapnia under NH conditions. The HVR response, as measured from the slope of ventilation against arterial O_2 saturation from a rebreather device that maintained normocapnia, was reduced about 50% compared to subjects in a standing position. Prisk concludes that inhibition of the hypoxic drive, but not the hypercapnic drive, was mediated through stimulation of carotid baroreceptors in response to an increase in blood pressure. The point being that there could be a combined reduction in HVR due to μG exposure and hypobaria anticipated in the CEV, leading to a greater risk of AMS.

Summary of Levine (1988) Results for 8,500 ft exposure (acute P_AO_2)



*See Note 3 at end of report.

Fig. 11. Levine's (1988) summary results for 8,500 ft exposure. It was expected that any effect of HN and NH on increased pulmonary lymph flow would be additive in the results from the HH condition. This was not the case, however, suggesting that there was a complex negative synergy between HN and NH leading to the HH results. See figure 13 description for more information.

Summary of Levine (1988) Results for 15,100 ft exposure (acute P_AO_2)

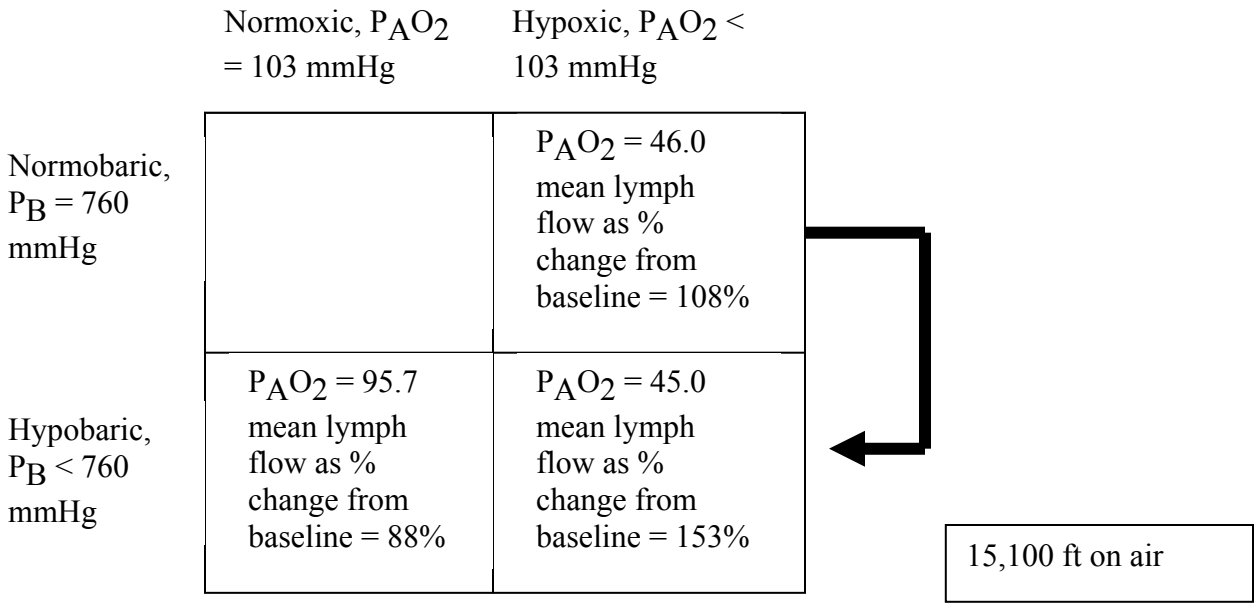


Fig.12. Levine's (1988) summary results for 15,100 ft exposure. Again, the HH results far exceed the combined effects of the HN and the NH conditions. See figure 13 description for more information.

Summary of Levine (1988) Results for 21,500 ft exposure (acute P_AO_2)

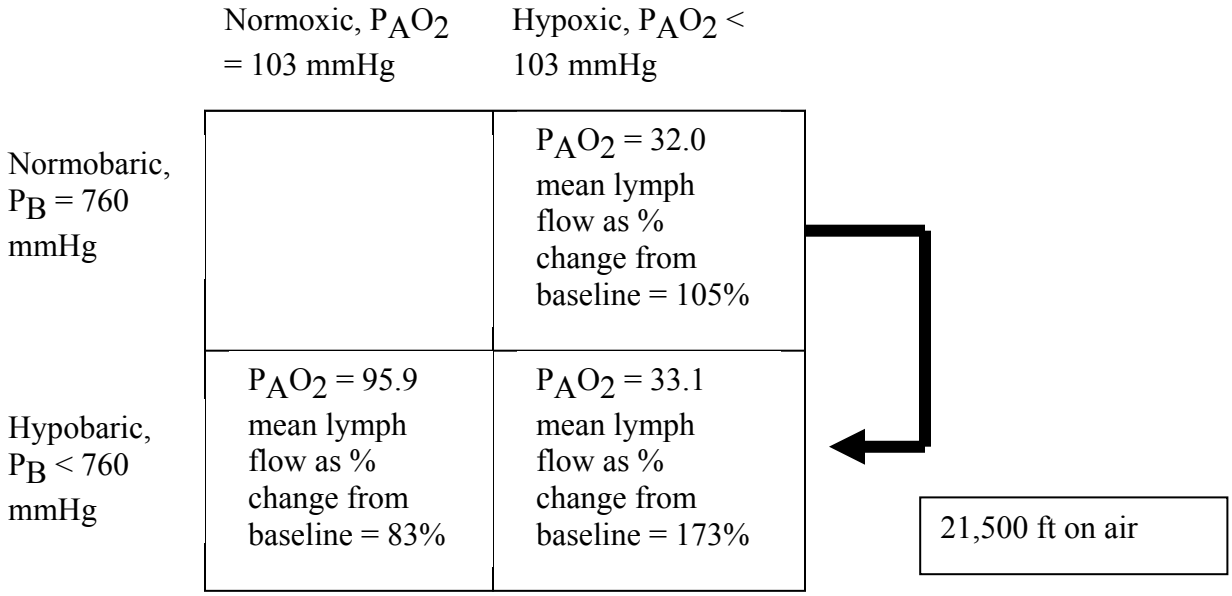


Fig. 13. Levine's (1988) summary results for 21,500 ft exposure. Figures 11, 12, and 13 show important results from Levine (1988) taken from his figure 3 (see below). He used a sheep model to understand pulmonary edema caused by substantial hypoxic insult. Classic pulmonary edema formation in HH AMS is evident. Pulmonary and cerebral edema in extreme cases leads to death. There appears to be a P_B effect at work. Since no change in lymph flow occurred under HN conditions, he concludes that hypobaria is a necessary, but not sufficient, condition for change in pulmonary fluid balance under HH conditions. He demonstrates an increased lymph flow and protein clearance (not shown here) only under conditions of combined (synergized) HH, not under equivalent degrees of alveolar hypoxia or hypobaria alone. Only under HH was there a clear and highly significant increase in lymph flow. Levine hypothesizes that ambient P_B in the alveoli significantly alters the Starling forces (delta hydrostatic pressure and delta oncotic pressure) governing transcapillary fluid flux in the lung, which in turn may affect the P_AO_2 - P_aO_2 gradient for O_2 diffusion.

Levine's results logically lead to this conclusion, but it is completely contrary to the dogma that absolute P_B is communicated equally throughout the body. In essence, the body can be considered a bag of water. Any P_B applied to the bag is equally distributed. This is easy to visualize if the bag is taken 30 m underwater. The additional hydrostatic P_B is transmitted through the bag of water such that there is no pressure

difference at any location. So, the bag maintains the original shape. The same applies if the increase in P_B is caused by compressing gas. If this were not so, we would certainly notice significant effects with just a few mmHg change in pressure, such as you experience when trying to equalize pressure across the ear drum when going from a low-pressure airplane cabin to the higher pressure at the airport. So, in the absence of additional hypoxic stress leading to some change in epithelial or endothelial membrane properties, it is not reasonable to accept that P_B over a few hundred mmHg can influence membrane permeability to water. If this were so, a simple SCUBA dive should always cause some significant fluid imbalance in the lungs, and this is certainly not the case. The amount of extravascular liquid in the lung depends on the balance between the rate of fluid formation and the rate of its removal.

Levine suggests that P_B is *not* communicated equally within the lungs and the body such that there are areas of significant pressure difference (delta or transmural pressure) that would affect the balance of Startling forces. This hypothesis is suspect. The alternative is to think that oncotic pressure, or the filtration coefficient, is somehow modified after hypoxic stress, but to a greater extent when ambient P_B is reduced, or to a lesser extent when ambient P_B is increased. The fact that Levine shows no change in lymph flow under NH condition equivalent to 6,553 m (21,500 ft) altitude is compelling evidence that high P_B, *even in the presence of hypoxic stress*, is protective.

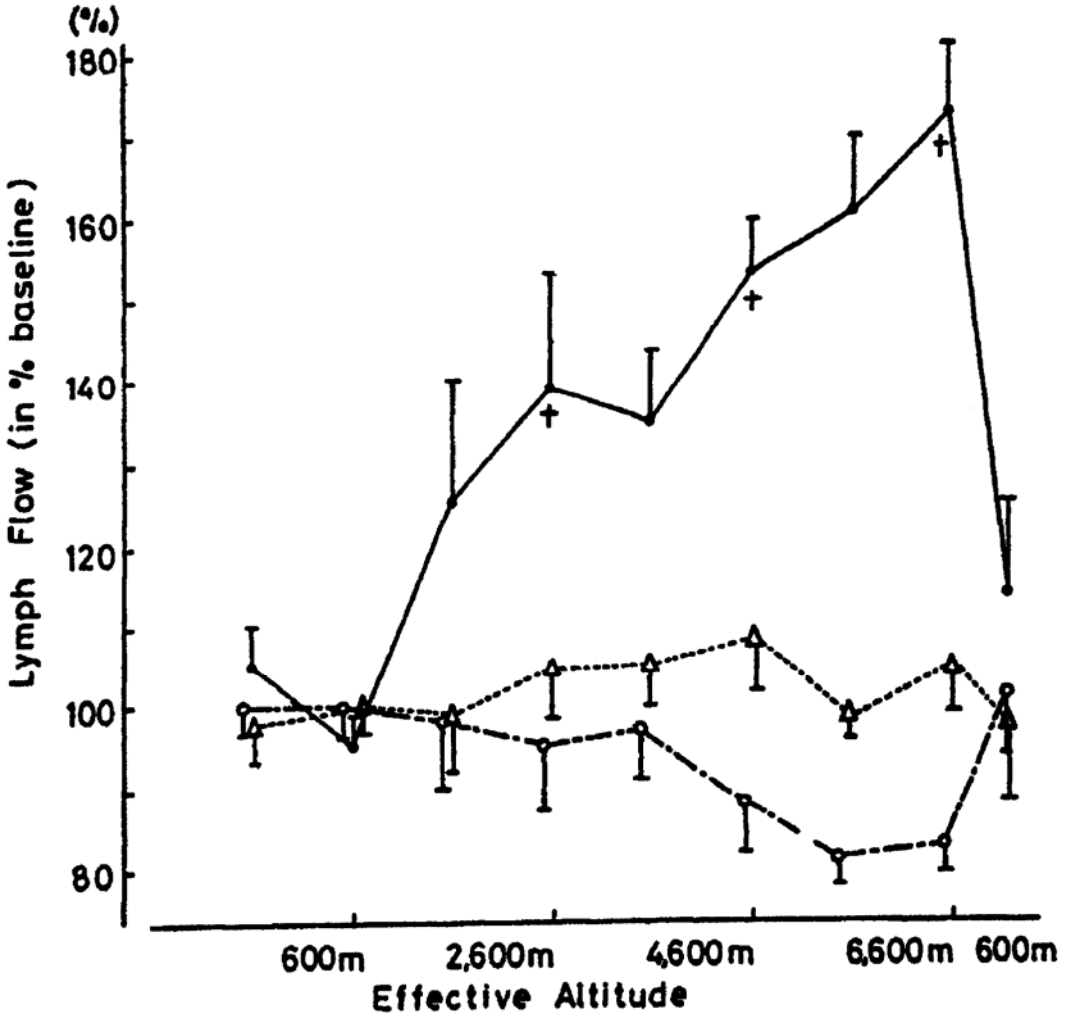
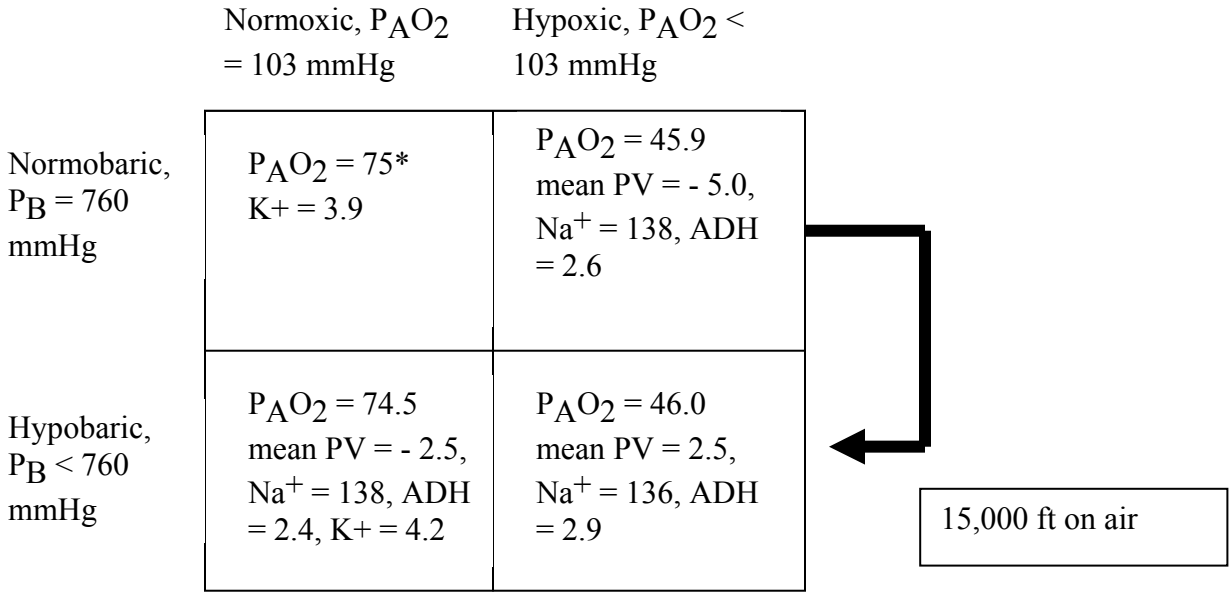


FIG. 3. Effect of hypobaric hypoxia (●——●), normobaric hypoxia (△- - -△), and normoxic hypobaria (○- - -○) on lymph flow. Lymph flow is expressed as percent of mean of 8 base-line lymph flow measurements from each experiment. Each point represents mean grouped data ± SE from all sheep, divided into hourly segments. Statistical analysis was performed on data after steady-state conditions were achieved, during 2nd h of each stage of effective altitude. * $P < 0.05$; + $P < 0.01$.

Summary of Loeppky (2005a) Results (acute P_AO_2)

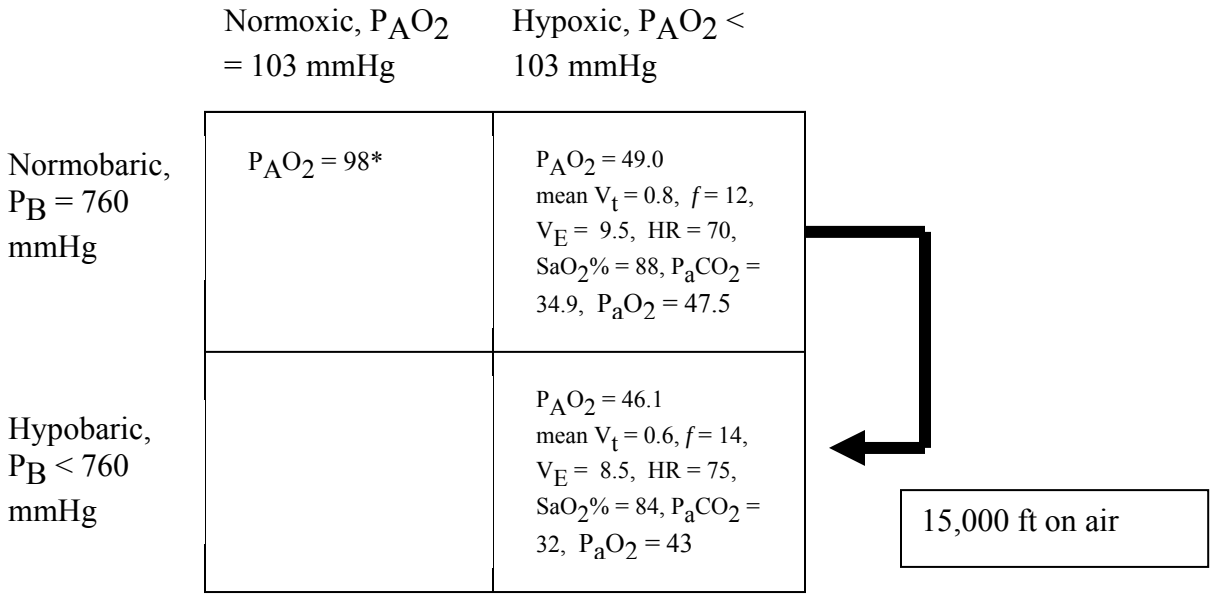


*See Note 1 at end of report.

PV - plasma volume as % change from baseline
K+ - potassium ion concentration in plasma (mmol/l)
Na+ - sodium ion concentration in plasma (mmol/l)
ADH - antidiuretic hormone in plasma (pg/ml)

Fig. 14. Loeppky (2005a) summary results describe classic edema formation with AMS. Urine volume decreased over 10 hrs in HH while PV increased relative to NH. Plasma Na+ decreased at HH due to increased PV, and ADH was greatest in HH even in the presence of increased PV. Loeppky concludes that fluid retention under HH conditions in AMS-susceptible subjects appears related to a synergistic interaction between reduced P_B and ADH and ALD. Plasma K+ was significantly elevated in HN compared to NN. This peculiar observation was noted by Epstein (1972) and Leach (1973) while testing the NH environment proposed for Skylab, which each attributed to increased ALD production while living normoxic at 5.0 psia. Glomerular filtration rate (GFR), through creatinine clearance, did not decrease over just 9 hrs under HN as it did progressively over 9 days from Epstein (1972). But GFR was reduced transiently in HH. The changes cited above are modest, but pulmonary and cerebral edema in extreme cases lead to death. There appears to be a P_B effect at work. More AMS was reported in HH (3.7 mean score) than NH (2.0 mean score), and even symptoms in HN (0.4 mean score) as reported by Roach (1996) for these same experiments.

Summary of Savourey (2003) Results (acute P_AO_2 only 40 min)



*See Note 4 at end of report.

V_t - tidal volume (l/min, BTPS)
f - breathing rate (breaths/min)
V_E - min ventilation (l/min, BTPS)
HR - heart rate (beats/min)
SaO_2% - arterial blood oxygen saturation (%)
P_aCO_2 - arterial blood carbon dioxide partial pressure (mmHg)
P_aO_2 - arterial blood oxygen partial pressure (mmHg)

Fig. 15. Savourey's (2003) summary results. This example shows changes in pulmonary mechanics for the same P_AO_2 under NH and HH conditions (see Savourey's figures 1 and 2 below). There appears to be a P_B effect at work in the control of pulmonary mechanics. Others also show a decrease in V_E at altitude given the same degree of hypoxic stress as simulated at sea level with a hypoxic breathing mixture. The author concludes that the lower V_t and higher breathing rate in HH results indicates an increase in deadspace ventilation (Van Liew in a personal communication says that there is a decrease in deadspace ventilation in HH, but warns there are different definitions for deadspace), and Loeppky (1997) says that there is a decrease in deadspace ventilation in his HH vs. NH results; his experiment was over 10 hrs, not 40 min seen with Savourey.

Loeppky (1997) used half the subjects (9) and started the experiment with subjects living at 636 mmHg (5,270 ft) compared to 733 mmHg (1,000 ft) in Savourey's work.

Compared to NH, HH leads to a greater hypoxemia, hypocapnia, and blood alkalosis, and to lower O_2 arterial saturation.

A working hypothesis to account for these and similar observations is that there is an increased alveolar deadspace through a mismatch in V_A/Q secondary to regional pulmonary vasoconstriction as a function of gas density plus hypoxic stress. And, both synergize to create a greater response than either in isolation of the other. You must have both at once, not just hypoxic stress and not just reduced gas density. Savourey refers to this as a "specific response to HH" in that it is a unique response, one that is not possible to simulate with an NH analog.

It is difficult to reconcile only small changes in gas density as a significant contribution to these changes, since the magnitude of differences in breathing gas density routinely encountered in normoxic and even hyperoxic SCUBA diving does not lead to any clinical consequences. It must be a synergistic interaction through a poorly understood mechanism between gas density and hypoxic stress within the CNS (see Partial Pressure of Nitrogen, Oxygen, and Carbon Dioxide in the Cerebrospinal Fluid).

One could hypothesize that a direct ascent to 4,572 m (15,000 ft) while breathing 100% O_2 or a mixture that brings P_AO_2 to a normoxic 103 mmHg (39.0% O_2) will not elicit the changes seen during Savourey's HH exposure, even though the breathing gas is at the same lower density. One caveat to this test is that there is some risk of forming VGE that embolize the lung given the magnitude of this depressurization if some prior denitrogenation is not done and the exposure time exceeds about 60 mins (see Do Venous Gas Emboli have a Role in Acute Mountain Sickness?).

Another interesting experiment would be to repeat the work done by Savourey, except to provide the identical hypoxic stress under hyperbaric conditions. Take the same pressure difference used in his study (740 mmHg - 430 mmHg = 310 mmHg) and add the difference to his 740 mmHg ambient P_B to produce a modest hyperbaric P_B of 1,050 mmHg. Have the subjects breathe 7.9% O_2, which provides a computed P_AO_2 of 45 mmHg, to produce the same hypoxic stress in his 2 comparisons.

The results from the 2 experiments above would help to understand a P_B effect on the physiological response to hypoxia.

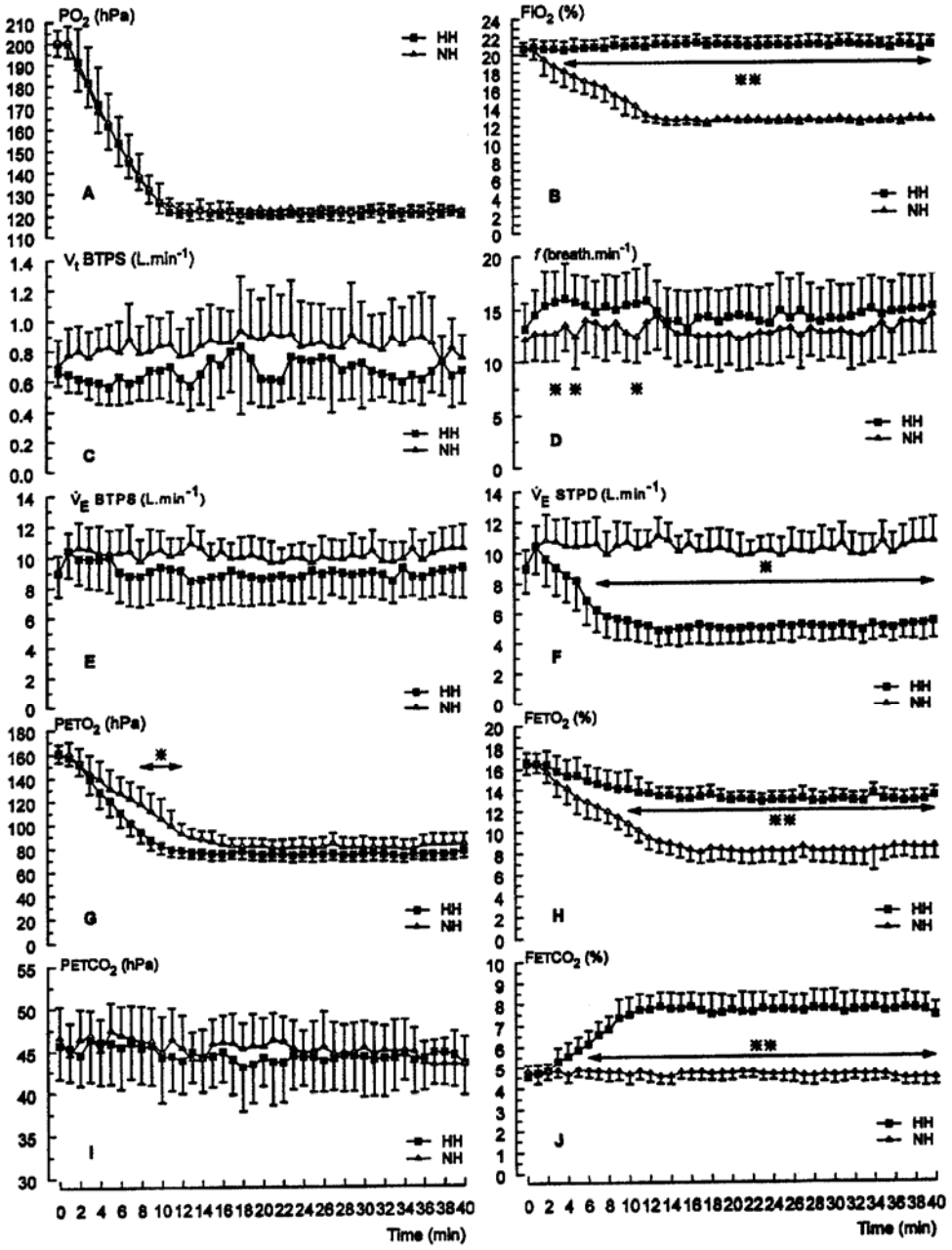


Fig. 1I–J Ventilatory measurements observed in 18 subjects during hypobaric (*HH*) or normobaric (*NH*) hypoxic tests. A Ambient oxygen partial pressure (PO_2) and B oxygen inspired fraction (FIO_2) versus time. C Tidal volume (V_t) under body temperature pressure saturated (BTPS) conditions. D Breathing frequency (f). E, F Minute ventilation ($\dot{V}_E$) in BTPS and standard temperature pressure dry (STPD) conditions, G end tidal O_2 pressure (PET_{O_2}), I end tidal CO_2 pressure (PET_{CO_2}), H end tidal O_2 fraction (FET_{O_2}), J end tidal CO_2 fraction (FET_{CO_2}) versus time. $^{*}P<0.05$, $^{**}P<0.01$, level of statistical significance between means observed during HH and NH at the same time

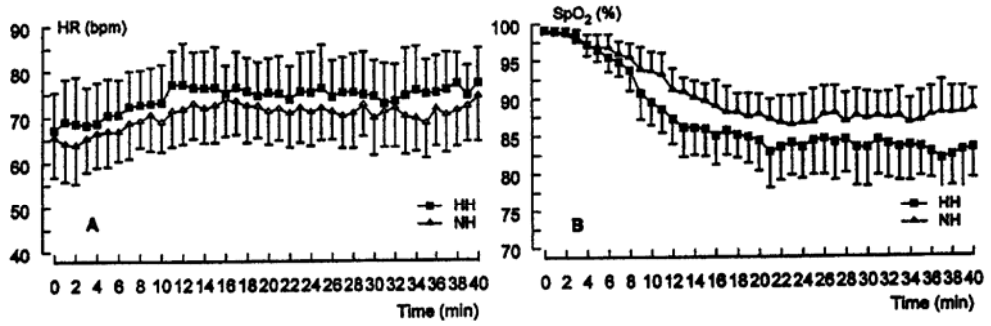
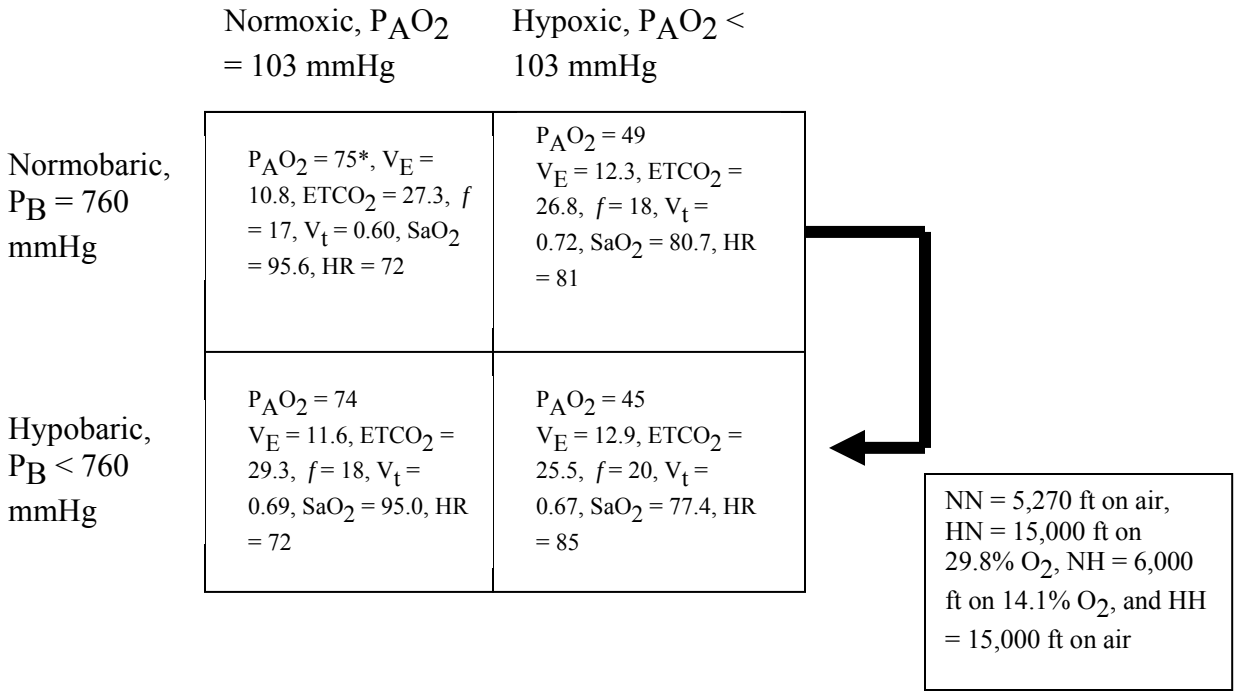


Fig. 2A, B Cardiovascular measurements observed in 18 subjects during HH or NH hypoxic tests. **A** Heart rate (*HR*). **B** O_2 blood saturation measured by finger pulse oxymetry (SpO_2)

Summary of Loeppky (1996) Results (acute P_AO_2 only 30 min)

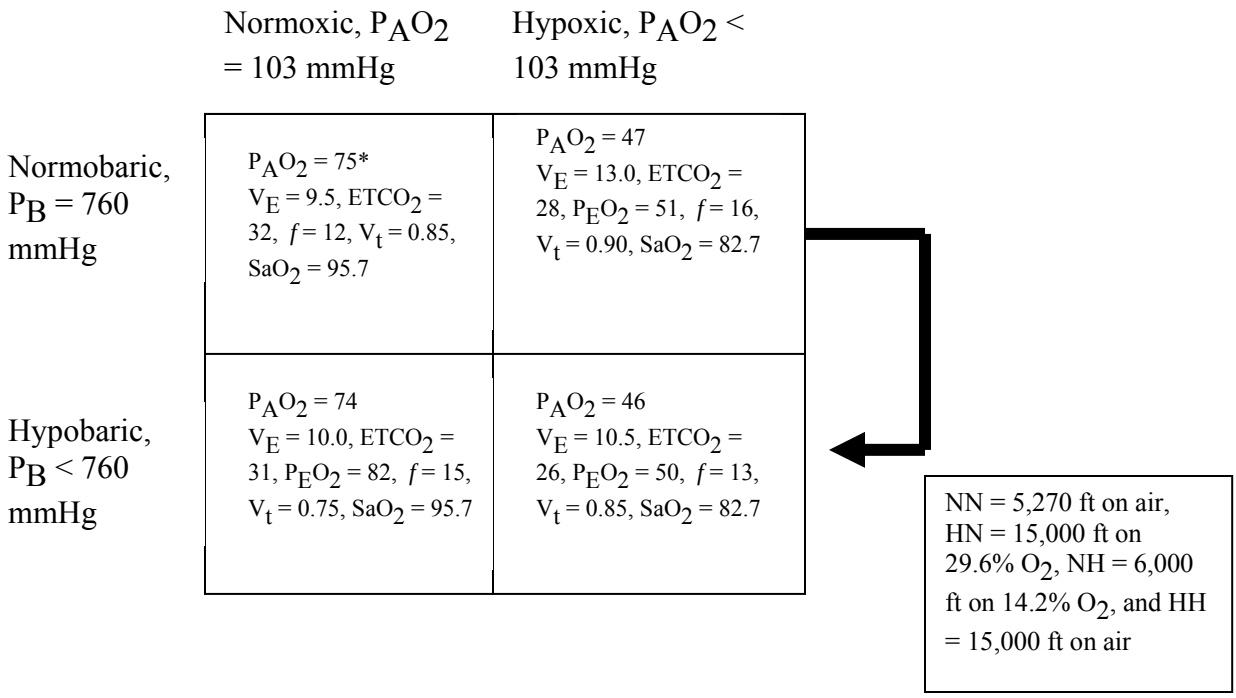


*See Note 1 at end of report.

V_E - min ventilation (l/min, BTPS)
$ETCO_2$ - partial pressure of end-tidal carbon dioxide - inspired oxygen - P_ECO_2 - P_ICO_2 (mmHg)
f - breathing rate (breaths/min)
V_t - tidal volume (l/min, BTPS)
HR - heart rate (beats/min)
SaO_2% - arterial blood oxygen saturation (%)

Fig. 16. Loeppky's (1996) summary results. He conducted a pilot test of a P_B effect for only 30 min at 430 mmHg to understand whether sensitivity (chemoresponsiveness) to hypoxia was altered by hypobaric exposure. He measured pulmonary changes the last 2 mins of a 30 min exposure, and then had subjects breathe 100% O_2 for 1 min. He shows, on a short time scale, that there was no decrease in hypoxic sensitivity, which did not accord with Grover (1982). Tucker (1983) and even Loeppky (1997) show a greater V_E in NH than HH. The reduction in V_E with 100% O_2 suggested that reduced P_B did not markedly alter hypoxic chemosensitivity within 30 mins.

Summary of Loeppky (1997) Results (acute P_AO_2)



*See Note 1 at end of report.

V_E - min ventilation (l/min, BTPS)
$ETCO_2$ - partial pressure of end-tidal carbon dioxide - inspired oxygen = P_ECO_2 - P_ICO_2 (mmHg)
P_EO_2 - partial pressure of end-tidal oxygen (mmHg)
f = breathing rate (breaths/min)
V_t - tidal volume (l/min, BTPS)
SaO_2% - arterial blood oxygen saturation (%)

Fig. 17. Loeppky's (1997) summary results. He conducted a detailed analysis of a P_B effect on respiratory dynamics by comparing results for all 4 O_2 and P_B options (see Loeppk's figures 1 and 2 below). Nine subjects had pulmonary measurements taken about 1, 4, 7, and 10 hrs into each of the 3 experimental conditions, plus baseline values for the NN condition about 2 hrs after the experimental conditions. Shown above are the means for his 4-, 7-, and 10-hr experimental results and his 2-hr post-test controls at 636 mmHg (5,270 ft).

It is best to list Loeppky's main results and conclusions:

1. There was a greater V_E and higher $P_{ET}CO_2$ during NH as compared to HH, about a 31% increase for NH and a 20% increase for HH for V_E when compared to the NN baseline. A high $P_{ET}CO_2$ in relation to a high V_E for NH suggested that there was

an increased physiological deadspace in NH relative to HN and HH, assuming no change in O_2 consumption and CO_2 production. If you assume there was a change in O_2 consumption and CO_2 production in NH relative to HN and HH, the work of breathing and not an increase in physiological deadspace could explain the observations.

2. There was no difference between NN and HN, so a decrease in P_B (gas density) without hypoxic stress did not affect the pulmonary measures even when the physics of gas density and gas flow is present. You need the combination of reduced gas density and hypoxic pulmonary vasoconstriction to get a better V_A/Q matching, which manifests as a reduced alveolar deadspace in HH relative to NH.
3. Loeppky posits that a decreased work of breathing (less CO_2 production and less O_2 consumption) and/or an improved V_A/Q in HH relative to NH would explain the HH results relative to NH, but you still need hypoxic stress to make this conclusion.
4. What seems plausible is that respiratory dynamics do change as a function of P_B since dense gas requires more respiratory effort for the same flow. As the dynamics of respiration change as a function of P_B, maybe V_A/Q changes. But, only in the presence of hypoxic stress do the synchronized effects of decreased P_B and altered V_A/Q plus pulmonary vasoconstriction explain the differences seen in all 3 experimental conditions.
5. Loeppky says an increase in physiological deadspace in NH due to a less ideal V_A/Q relation relative to HH could be an explanation for the results if you assume CO_2 production was constant over all experiments.
6. A reduced gas density does reduce the pressure swings (driving delta pressure for ventilation) to ventilate the lungs, so ventilation dynamics change. These changes coupled with pulmonary vasoconstriction due to hypoxic stress may improve V_A/Q, which manifests as a reduced alveolar deadspace relative to NH. V_E is not stimulated to increase relative to NH. In NH, the pulmonary vasoconstriction is not associated with a reduced gas density, so V_A/Q is not improved as much, which manifests as an increased alveolar deadspace relative to HH. V_E is stimulated to increase relative to HH.
7. Loeppky (1997) was the first to rigorously evaluate mechanisms to account for his observations, so a portion of his important Discussion is paraphrased here as follows:

> Perhaps more interesting and important in considering these results is how alveolar deadspace may be altered by the change in V_A/Q ratio to account for the difference in V_E between HH and NH. The reduction in P_IO_2 was essentially identical in these two situations. A number of acute measurements in humans have demonstrated that the initial increase in mean pulmonary arterial pressure is approximately 5 mmHg within 10 min. If this response is equal under both conditions, then at altitude this would be associated with a synchronous and significant reduction in the airway or alveolar pressure swing during the breathing cycle because of

the reduction in gas density. This reduction in alveolar pressure at a given air flow at altitude was impressively demonstrated by Otis (1949) in humans breathing 100% O_2. An increase in pulmonary artery pressure (due to hypoxia) simultaneous to a reduction in airway pressure at altitude would be expected to (through a better matching of ventilation to perfusion) result in an improved V_A/Q distribution and a reduction in equivalent alveolar deadspace (because pulmonary artery mean pressure exceeds alveolar pressure) as compared to NH, where an increase in pulmonary artery pressure is not associated with changes in airway pressure. The P_aO_2 would fall and P_aCO_2 rise more in the case of a synchronous enlargement of alveolar deadspace, this would stimulate V_E by chemoreceptors. In HN, the reduction in density was not accompanied by hypoxic pulmonary vasoconstriction and no change in deadspace or V_E resulted.

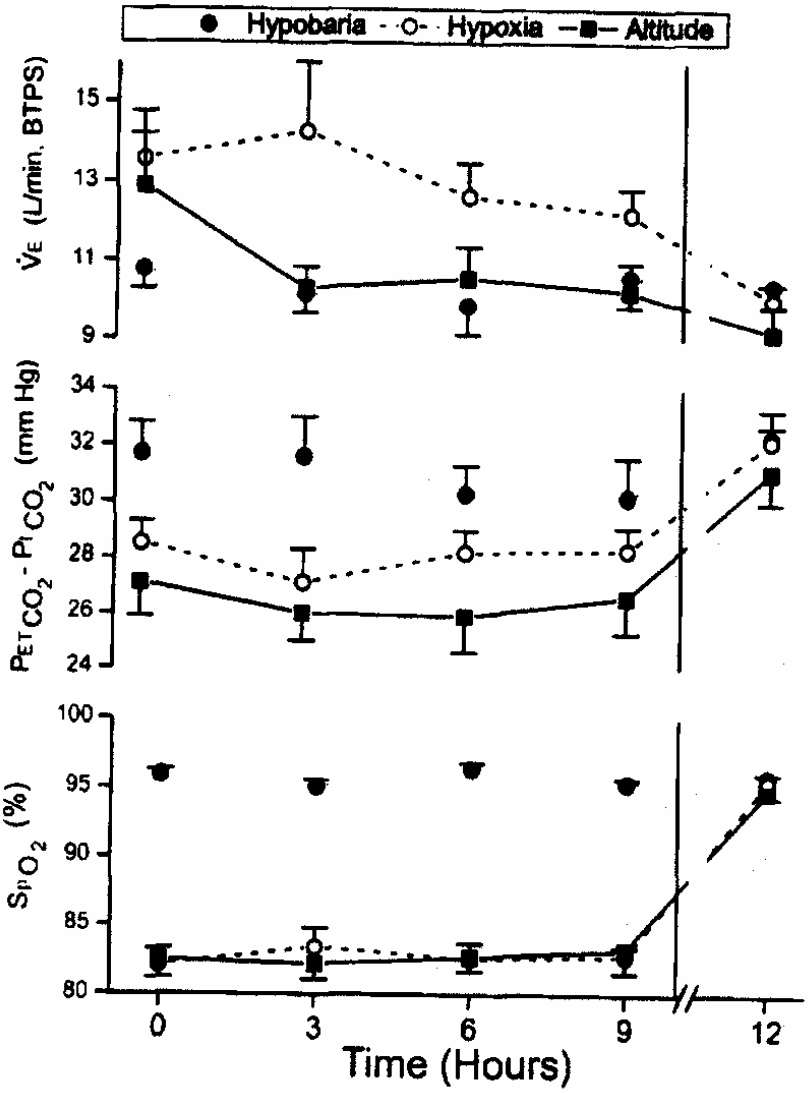


Fig. 1. Mean values ($\pm$ 1.0 SE) for nine subjects for $\dot{V}_E$, end-tidal minus inspired P_{CO_2} and arterial O_2 saturation in three environments in the chamber and after exposure (vertical line). $\dot{V}_E$: greater in hypoxia than altitude and hypobaria overall in chamber ($p < 0.01$) and at t_3 ($p < 0.05$); greater in hypoxia ($p < 0.05$) and altitude ($p < 0.06$) at t_0 compared to t_{12}. $P_{ET_{CO_2}}$: higher in hypobaria than altitude and hypoxia ($p < 0.01$) at each time in chamber; lower in hypoxia and altitude ($p < 0.01$) at each time in chamber compared to t_{12} ($p < 0.01$); higher overall in chamber in hypoxia than altitude ($p < 0.02$, paired t-test). S_pO_2: greater in hypobaria than altitude and hypoxia ($p < 0.01$) at each time in chamber.

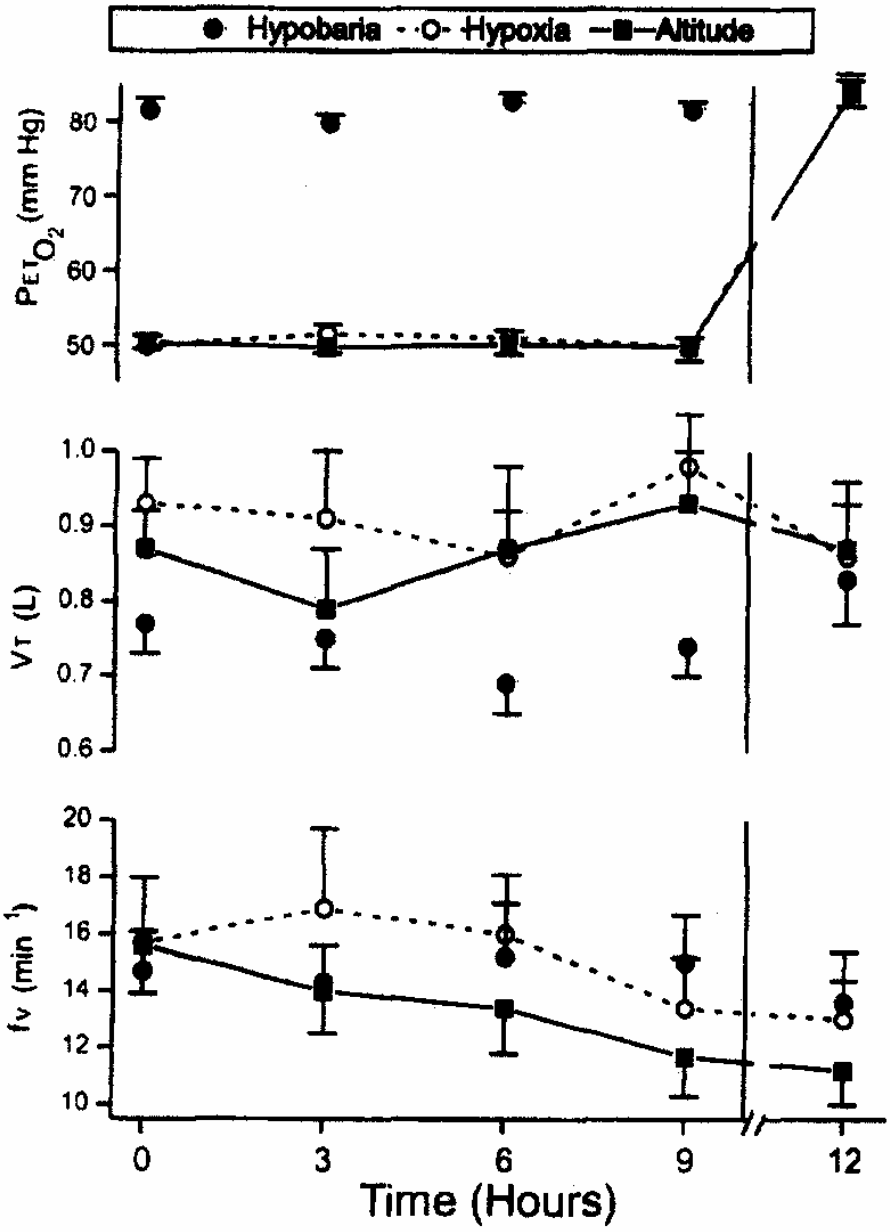


Fig. 2. Mean values ($\pm$ 1.0 SE) for nine subjects for end-tidal P_{O_2}, tidal volume and ventilatory frequency. $P_{ET_{O_2}}$: greater in hypobaria than altitude and hypoxia ($p < 0.01$) at each time in chamber. V_T and f_v: no differences among conditions in chamber or compared to t_{12}.

Summary of Meehan (1986), Swenson (1995), and Knight (1991) Results (acute P_AO_2)

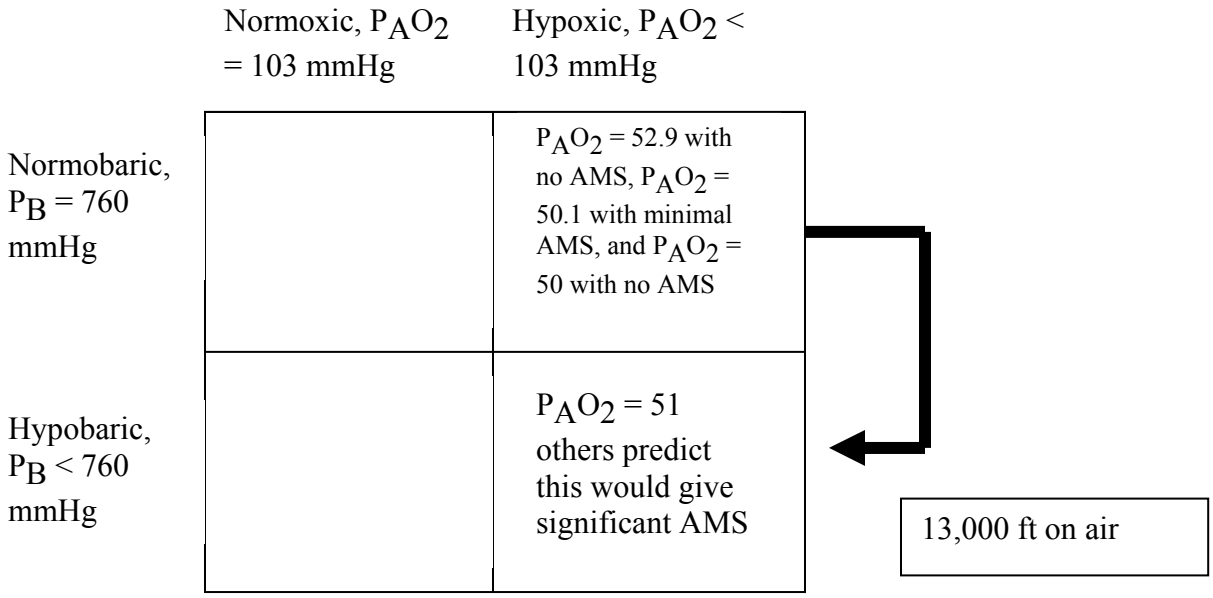


Fig. 18. There appears to be a consensus of opinion of a P_B effect at work on the signs and symptoms of AMS, but no one knows a mechanism as of 2008. No one knows why AMS occurs, except that the trigger is hypoxia. Hypoxia affects every system in the body instantly, since you need O_2 on a breath-by-breath basis. There appears to be direct peripheral effects on the kidneys and the pulmonary vasculature in response to hypoxia as well as a centrally-mediated response from the CNS as it receives a plethora of inputs about changes induced by hypoxia. There is a decreased hypobaric diuresis, an increased edema, and a decreased hypoxic ventilatory response in subjects that go on to exhibit AMS. No mechanism for AMS is available from which to interpolate or extrapolate to a new set of environmental conditions. Meehan (1986), Swenson (1995), and Knight (1991) published results from NH exposures where computed P_AO_2 was about 51 mmHg, and there was little or no AMS. Based on observations of significant AMS with HH exposures that produce P_AO_2 around 50 mmHg (13,000 ft), it is reasonable to conclude, although indirectly, that there is a P_B effect at work on the signs and symptoms of AMS.

Summary of Epstein (1972) Results (chronic P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg	P_AO_2 = 102, ALD = 74, BW = -2.6, Na $t_{1/2}$ = 0.70, HR = 70, C_{cr} = 100	
Hypobaric, P_B < 760 mmHg	P_AO_2 = 105.6, ALD = 82, BW = -1.1, Na $t_{1/2}$ = 0.57, HR = 62, C_{cr} = 57	

Na+ - sodium ion concentration in plasma or urine
K+ - potassium ion concentration in plasma or urine
ALD - aldosterone concentration (μg/24 hr)
BW - body weight (% change in body weight following dietary Na+ restriction)
HR - heart rate (beats/min)
Na $t_{1/2}$ - half-time in days to achieve a new lower urinary Na+ balance following dietary Na+ restriction.
C_{cr} - Creatinin clearance (ml/min), a measure of kidney glomerular filtration rate (GFR)
Note: Comparison data between NN and HN shown in table are generally after 7 or more days after the start of the restricted Na+ diet (see Epstein 1972 for details).

Fig. 19. Epstein's (1972) summary results. He shows a P_B effect on Na+ balance in subjects with significant dietary Na+ restriction. He reproduced the 70% O_2 at 5.0 psia (258 mmHg) Skylab atmosphere in an altitude chamber for 9 days. He wanted to understand the effect of hypobaria alone without the confounding role of hypoxia on the responsiveness of the renin-angiotensin-ALD system given a diet deficient in Na+ as a means to stimulate Na+ conservation.

About 99.5% of the filtered load of Na+ is reabsorbed by the kidneys. Given a normal dietary intake of about 155 mEq per day, any change in the GFR or in the rate of tubular Na+ reabsorption could seriously threaten Na+ balance and, hence, the maintenance of body fluid compartments. Or, a change in the dietary intake of Na+ would pose a similar threat unless the GFR or tubular reabsorption rate were quickly adjusted. Plasma Na+ is carefully maintained between 136 and 146 mEq/L. Plasma

sodium chloride is sensed by the kidney, specifically the juxtaglomerular apparatus, where renin is secreted when Na+ is reduced, ultimately leading in several steps to the production of ALD. As plasma Na+ decreases, ALD concentration increases, leading to increased tubular reabsorption of Na+. Epstein reduced Na+ in the diet of 8 men from a 10-day control period of 200 mEq to 10 mEq over 9 days to understand how the renin-angiotensin-ALD system would respond to the HN in the absence of μG.

There was a small, but insignificant, decrease in plasma Na+ in pooled data from days 7 through 9 in both NN and HN (142 mEq/L vs. 145 mEq/L) compared to the first day of Na+ restriction. So, plasma Na+ concentration was preserved. The increase in plasma renin activity was the same for NN and HN. Urinary ALD excretion over days 7 and 9 was significantly greater in HN compared to NN over days 8, 9, and 10 (82 μg/24 hr vs. 74 μg/24 hr). The significant decrease in body weight of 1.1% over 9 days for HN was less than the decrease of 2.6% in NN. So, more body water was retained relative to controls during a diet restricted in Na+. As expected, urinary Na+ fell. Subjects under NN lost 134 mEq of Na+ during the 3.1 days required to achieve a new, lower Na+ balance after the start of Na+ restriction. The half-time to achieve a new lower Na+ balance under NN was 0.70 day. Subjects under HN lost 100 mEq of Na+ during the 2.6 days required to achieve a new, lower Na+ balance after the start of Na+ restriction. The half-time to achieve a new lower Na+ balance under HN was 0.57 days So, it appears that the conservation of Na+ under HN responds faster than under NN conditions. Creatinine clearance (C_{cr}) decreased progressively from about 100 ml/min to 57 ml/min (a 40% reduction) after 8 days in HN compared to NN, and returned to pre-test level after about 3 days after the test (see Epstein's figure 2 below). Although serum creatinine increased from a mean of 1.22 to 1.46 on day 8 of HN, the decrease in C_{cr} was primarily attributed to the decrease in urinary creatinine excretion.

Epstein says the highly significant decrease in C_{cr} during HN suggests that the changes in renal Na+ handling may have been mediated by changes in the filtered load of Na+, and points to the decrease in HR as evidence that CO may have decreased during HN. Blood pressure did not change under NN or HN conditions in the Na+ deprived matched subjects, but HR was consistently lower in HN compared to NN (see Epstein's figure 4 below). If you assume that renal blood flow was constant between HN and NN, then an increase in afferent renal arteriolar resistance or a decrease in efferent renal arteriolar resistance would decrease C_{cr} (GFR). This does not explain the difference in C_{cr} between HN and NN, but it does offer a possible effector site in the kidneys to account for this interesting observation.

Epstein concludes that subjects exposed to HN attained Na+ balance more rapidly, with a smaller decrement in body weight, in response to dietary Na+ deprivation. The early positive Na+ balance in HN may be related to reduced P_B, but he offers no mechanism whereby reduced P_B alters renal Na+ handling. HH-induced diuresis is associated with less risk of AMS while antidiuresis is associated with more risk. Epstein shows that reduced P_B alone may contribute to antidiuresis, at least in a situation where Na+ is being conserved due to a restricted Na+ diet.

Finally, in contrast to the above, Leach (1973) reports very modest changes in fluid and electrolyte balance in 3 subjects over 56 days during the Skylab Medical Experiments Altitude Test (SMEAT). These 3 subjects did not change body weight over the first 10 days of a HN environmental exposure that was identical to Epstein (1972). Urinary ALD and plasma Angiotensin I, which was used as a direct measure of renin activity, showed increases in the 3 subjects. There was a slight, but significant, decrease in K+ excretion attributed to the slight increase in plasma ALD; Epstein (1972) also reports a positive K+ balance. It is possible that the dietary Na+ restriction by Epstein (1972) revealed a subtle contribution of P_B in the HN condition that otherwise goes unnoticed given a normal diet, even after 56 days in a HN environment.

This ends the summary of data for our first issue, Hypoxia and Acute Mountain Sickness. Figures 20 and 21 compare and contrast the P_AO_2 and P_B in some past, present, and future NASA vehicles. A comparison is started between the literature results about a P_B effect on AMS and the mild hypoxic atmospheres proposed for the CEV, LSAM, and surface habitats.

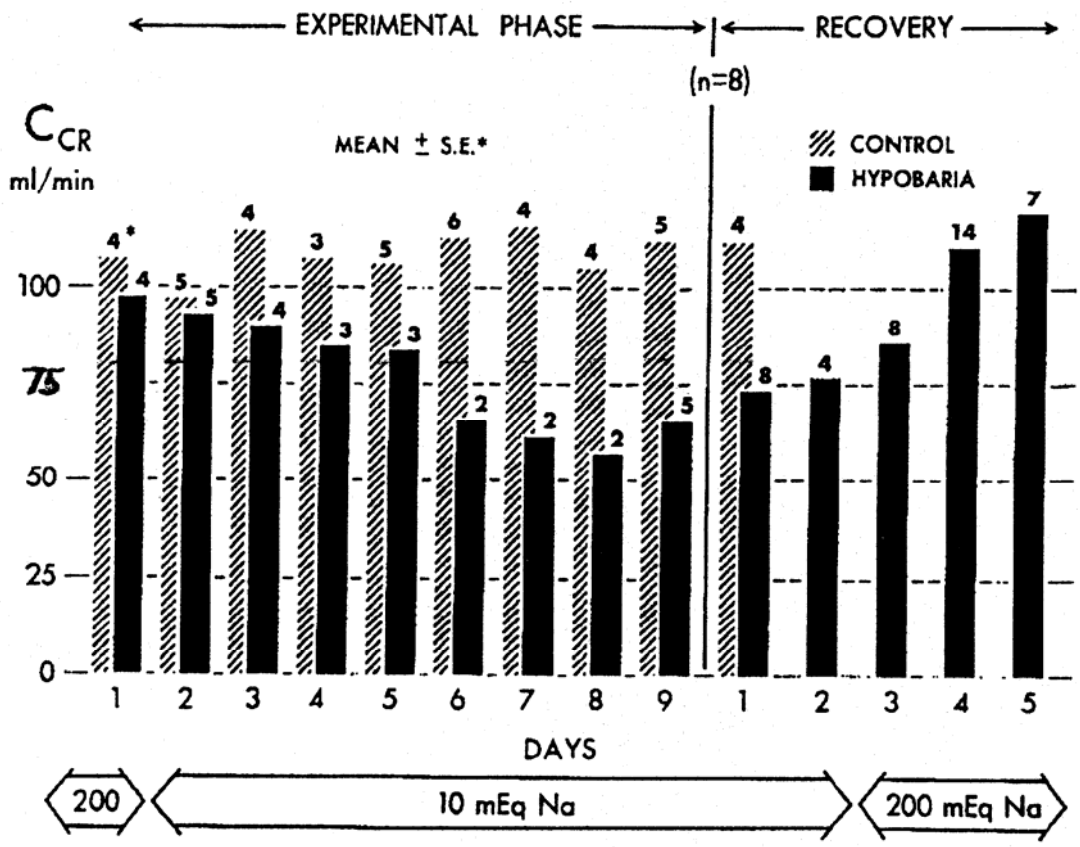


FIG. 2. Effect of chronic exposure to a reduced barometric pressure (hypobaria) on creatinine clearance. There was a progressive decrease in C_{Cr} compared to mean C_{Cr} on *day 1*, beginning on *day 3* ($P < 0.05$). By *day 8*, C_{Cr} had decreased by 40% ($P < 0.001$). During recovery, there was a progressive increase in C_{Cr} with attainment of prehypobaria levels by *day 3*. Numbers above each bar represent SEM.

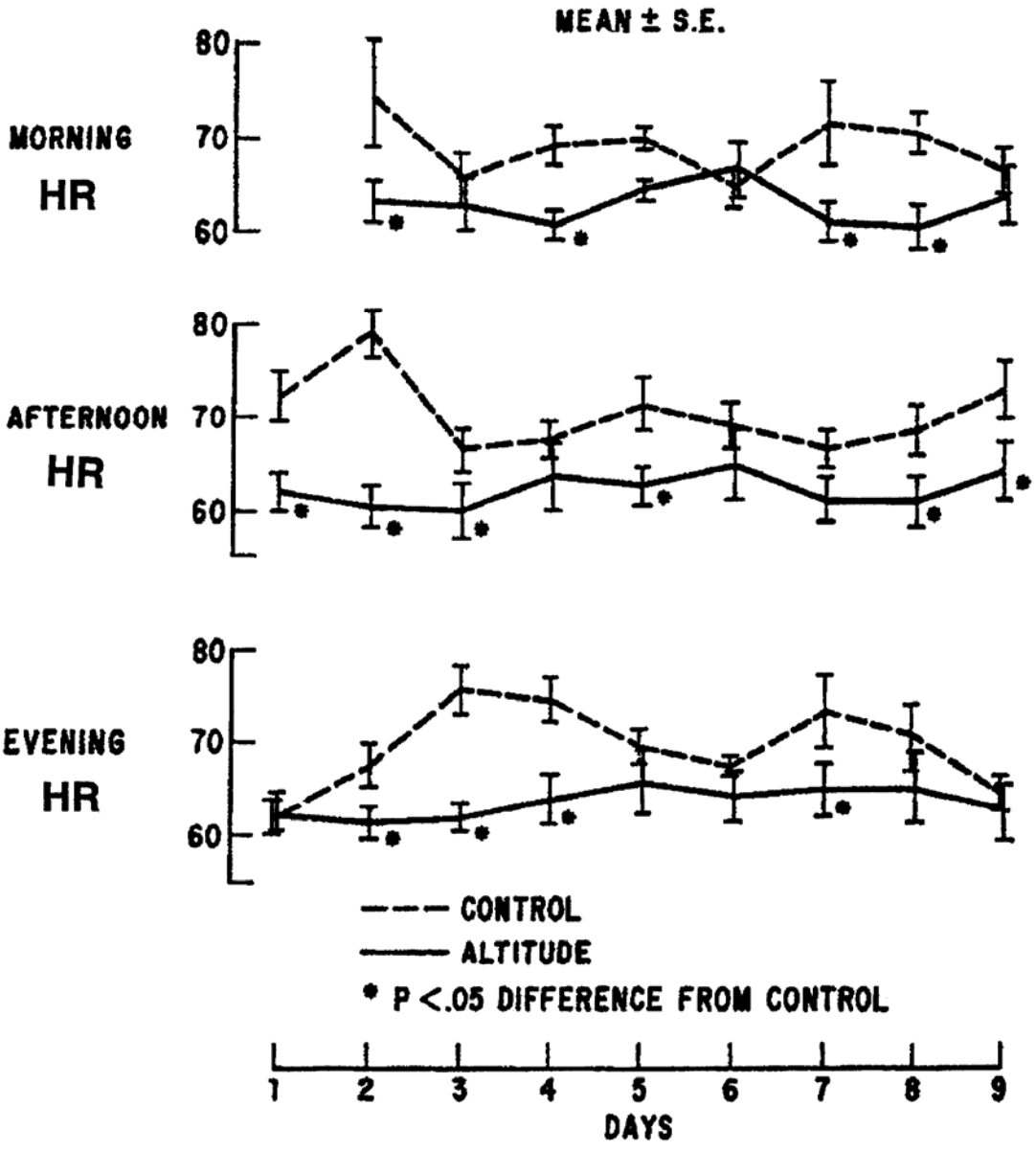


FIG. 4. Changes in heart rate during chronic exposure to a reduced barometric pressure (hypobaria). Thrice daily measurements disclosed significant decreases during hypobaria, compared with control, on 14 of 26 determinations. Of these, 8 occurred during initial 4 days of study.

Skylab, Shuttle, and Proposed Crew Exploration Vehicle, Lunar Surface Access Module and Habitat Results (acute P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg		
Hypobaric, P_B < 760 mmHg	P_AO_2 = 105.6 For Skylab	P_AO_2 = 85.2 for Shuttle, P_AO_2 = 77.0 for CEV nominal, and 68.0 for CEV extreme

Skylab - 70.0% O_2 at 5.0 psia (27,000 ft, 8,229 m)
shuttle - 26.5% O_2 at 10.2 psia (10,000 ft, 3,048 m)
CEV/LSAM nominal - 32.0% O_2 at 8.0 psia (16,000 ft, 4,877 m)
CEV/LSAM extreme - 30.0% O_2 at 7.8 psia (16,500 ft, 5,029 m)
Habitat nominal - 32.0% O_2 at 7.6 psia (17,000 ft, 5,181 m)
Habitat extreme - 30.0% O_2 at 7.4 psia (17,600 ft, 5,364 m)

Fig. 20. The experimental data presented allow comparisons and then conclusions about the risk of AMS given the nominal and extreme breathing gas environment on the CEV. With 10.2 psia P_B (10,000 ft) and 26.5% O_2 on the shuttle, the ppO_2 is 140 mmHg with P_AO_2 = 85 mmHg from the AOE. For the proposed nominal CEV, LSAM, and moon habitat with an 8.0 psia P_B (16,000 ft) and 32.0% O_2, the ppO_2 is 132 mmHg with P_AO_2 = 77 mmHg from the AOE. These conditions are equivalent to an ascent on 21% O_2 to 11.8 psia. Since AMS signs and symptoms do not start at less than 11.5 psia (6,500 ft, ppO_2 = 125 mmHg with P_AO_2 = 75 mmHg from the AOE), it is unlikely that anyone on the shuttle would experience AMS. The conditions on the CEV, especially the worse case extreme of the control box for the life support system, could drop P_AO_2 to about 68 mmHg. Months of living in the moon and Mars habitats will likely be well tolerated even when the worse case *acute* P_AO_2 to about 63 mmHg. See Conclusions for a

summary of expectations about this degree of HH plus adaptation to μG on the risk of AMS.

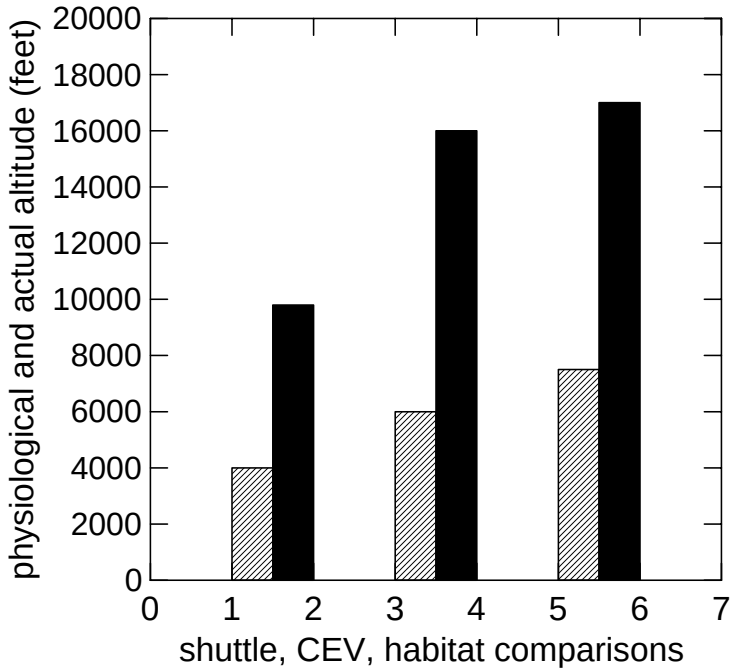


Fig. 21. A visual comparison of the difference in physiological and actual altitude in 3 vehicles: the shuttle, the proposed CEV and LSAM, and the proposed moon and Mars habitats. The increase in physiological altitude from 4,000 (1) to 6,000 (3) to 7,500 (5) ft shows a desire to exploit mild hypoxia as a means to reduce denitrogenation time and reduce the risk of DCS during EVAs from these vehicles. The increase in actual altitudes from 9,800 (2) to 16,000 (4), to 17,000 (6) ft is possible because the O_2 concentration is increased from 26.5% in the shuttle to 32.0% in the other vehicles. One goal of this report is to understand whether the difference between physiological and actual altitude significantly increases the risk or nature of AMS.

Second Issue: Body Fluid Balance and Red Blood Cell Changes in Microgravity

The adaptive response to μG exposure is a rapid reduction in total body fluid (Leach 1977), followed by a gradual reduction in RBC mass, but with little change in HCT in the absence of hypoxic stress (Johnson 1977). Prior to the reduction in body fluid, there is a cephalic shift of fluid leading to a loss of leg fluid volume, with excess fluid distributed into the face and chest. Pulmonary capillary blood volume increases by about 25%. The initial fluid shift increases stroke volume. Stretch receptors in the arterial circulation and the heart sense changes in the central blood volume, so water immersion, supine or head down BR, and exposure to μG are all sensed as an increase in central blood volume. In response, there is a decreased renal sympathetic drive, a decrease in renin activity from the kidneys leading to decreased ALD secretion (Buckey 2006).

Although urine output does not appear to increase on the first day in orbit, PV drops rapidly by about 17% (Buckey 2006). Part of this reduction is due to the loss of fluid to the extravascular space. There is a transient increase in HCT that would reduce EP secretion, which does decrease in space (Srinivasan, 1996). The net result in a normoxic environment is a reduction in RBC mass. In a significant hypoxic environment, EP production would be stimulated. EP secretion requires an altitude of about 2,500 m (8,200 ft) or greater, and exposures longer than 6 hrs (Ge 2002). Figure 22 is a summary from Ge (2002) that shows EP production as a function of P_B. The combined PV and RBC mass loss contribute to a reduction in total blood volume of about 11%. This new fluid volume appears to provide a central blood volume similar to what is seen on Earth in an upright posture. The HN condition during SMEAT was not expected to, and did not, down-regulate RBC production (Johnson 1973). Total blood volume in 3 subjects after 56 days in the SMEAT did not change. So, the loss of RBCs in Skylab was attributable to μG adaptation and not to a HN environment of 70% O_2 at 5 psia (Johnson 1977). Erythrocytes are the most abundant cells in the body, and their numbers are exquisitely regulated in a normal physiology to match O_2 supply with O_2 demand.

Summary of Ge (2002) Results (acute P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg	P_AO_2 = 103 EP = 14.3 mU/ml	
Hypobaric, P_B < 760 mmHg		P_AO_2 = 77, 19.6 EP P_AO_2 = 73, 19.4 EP P_AO_2 = 69, 25.4 EP P_AO_2 = 65, 27.2 EP

6,000 ft on air
7,000 ft on air
8,000 ft on air
9,000 ft on air

EP - plasma erythropoietin (mU/ml) under 1 atmosphere pressure absolute (ATA) control, or after 24 hrs at altitude

Fig. 22. Ge's (2002) summary results. EP is dose-dependent on a renal hypoxia trigger. It is expected to increase at > 2,100 m (7,000 ft). Since the nominal CEV environment is close to P_AO_2 = 77, there is some HH-induced increase in EP expected even in the face of fluid redistribution and reduction in μG adaptation. We used discrete data published in Ge (2001) in a regression model to summarize the mean response to EP over the tested range of altitude and time. The model computes the central tendency in these data, well within the standard error of tabulated data. The regression is: EP concentration (μm/l) = $14.3/(1 - 0.000091 * \text{altitude (meters)} * \text{time (hrs)}^{0.2104})$. If time = 0 hr regardless of altitude, the function computes 14.3 μm/l, the mean EP concentration at 1 ATA in 32 men and 16 women.

A dysfunction in the body's handling of water is proposed as one factor in the development of AMS. Individuals who show diuresis upon arrival at high altitude fare better than those who exhibit an antidiuresis response. The most affected subjects show a marked reduction in urine flow associated with elevated levels of ADH (Loeppky 2005a, Loeppky 2005b). It is unclear whether the increase in ADH is a response to net fluid loss into the extravascular space or whether the cause is initiated by an unknown mechanism triggered by HH. Fluid shifts from the intravascular space to the extravascular space leads to edema, with significant problems if the result is cerebral edema or pulmonary edema. As mentioned in the previous section, there is a hypoxic component as well as a hypobaric component to AMS. There is no mechanism available to pull all of the observations together about changes in the neural, cardiopulmonary, renal, and endocrine systems.

Certainly fluid retention and redistribution leading to edema seen in AMS could be exacerbated (synergized) if these processes were superimposed on fluid redistribution and net fluid loss seen in early adaptation to μG. It is not possible to practically alter fluid changes during μG adaptation; but with the judicious use of O_2 and/or AZ, it may be possible to reduce any negative synergy by reducing the risk of AMS. Periods of breathing 100% O_2 prior to and following orbital insertion of the CEV and reduction of cabin P_B to 8.0 psia with 32% O_2 would be needed to avoid VGE formation, and would also ease the transition to the hypobaric and mild hypoxic environment during the early stages of μG adaptation. Two hours of PB would be effective to reduce the risk of VGE, thus removing one confounding condition that some suggest contributes to AMS. Breathing 100% O_2 for 30 mins every 8 hrs for 2 days during early adaptation to μG may be effective to reduce the risk of AMS. Previous studies show the benefits of O_2 breathing above and beyond the benefit through denitrogenation to reduce the risk of VGE.

Tucker (1983) shows that O_2 prebreathing reduced sympathoadrenal sensitivity. If hypoxia-induced secretion of epinephrine (EPI) and norepinephrine (NOR) were reduced, the cardiovascular response to these hormones would be reduced. He observed less tachycardia and no increase in systemic blood pressure in those who breathed O_2 (see Tucker's figure 2 in this report). There was also more diuresis with the accompanying decrease in urine osmolarity. His observations were similar to those of Hesse (1981), who showed a decreased NOR response during 100% O_2 breathing at sea level compared to breathing 21% O_2. Hesse (1981) concludes that these data demonstrated a causal relationship between O_2 and sympathetic nervous activity. During exercise, a reduced HR and plasma EPI concentration was additional evidence that the sympathetic nervous system was responding to 100% O_2 breathing. It does appear that prebreathing O_2 modifies some physiological responses to subsequent HH in the results from Tucker (1983) and Grover (1982). There was an improvement in pulmonary gas exchange implicating less V_A/Q mismatching, plus antidiuresis was prevented. The 1.5

hr dose of O_2 at sea level P_B appears to have a protracted benefit for several hours, which makes it viable as a therapeutic intervention to reduce the risk of AMS.

A concern with any decrease in PV, with or without an accompanying edema, is that the rheological properties of the blood will change, ultimately leading to impaired cardiopulmonary performance. So, a brief discussion about HCT and blood viscosity is provided.

Viscosity is a property of fluid related to the internal friction of adjacent fluid layers sliding past one another as well as the friction generated between the fluid and the wall of the vessel. This internal friction contributes to resistance to flow. The viscosity of plasma is about 1.8 times the viscosity of water (termed relative viscosity) at 37° C and is related to the protein composition of the plasma. Whole blood has a relative viscosity of 3 to 4, depending upon HCT, temperature, and flow rate.

HCT is an important determinant of blood viscosity. Figure 23 shows that as HCT increases, there is a disproportionate increase in viscosity. For example, at a HCT of 40%, the absolute viscosity is 2.3 centipoise. At an HCT of 60%, the viscosity is 3.7 centipoise. Therefore, a 50% increase in HCT from a normal value increases absolute blood viscosity by 63%. Such changes in HCT and blood viscosity occur in patients with polycythemia.

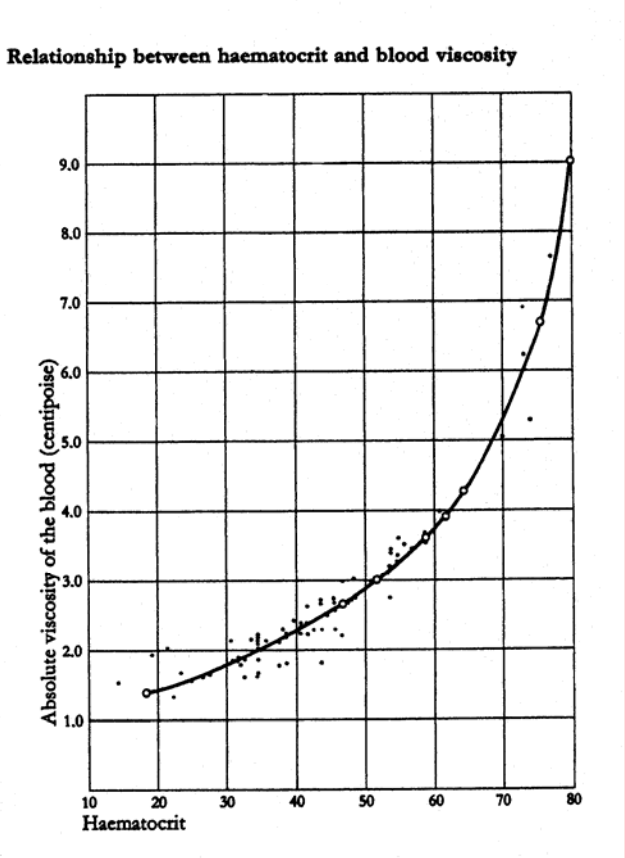


Fig. 23. Increase in absolute viscosity of blood with an increase in HCT. A 63% increase [(3.75 – 2.30)/2.3] in absolute viscosity by a 50% increase in HCT from 40 to 60 [(60 – 40)/40]. A second-degree polynomial curve fit for absolute viscosity as a function of HCT is: viscosity (centipoise) = $1.803 - 0.032 * HCT + ((1.071 * HCT^2)/1000)$.

Temperature also has a significant effect on viscosity. As temperature decreases, viscosity increases. Viscosity increases approximate 2% for each °C decrease in temperature. This effect has several implications. For example, when a persons hand is cooled the increase in blood viscosity contributes to the decrease in blood flow, along with neural-mediated thermoregulatory mechanisms that constrict the vessels.

Blood flow rate also affects viscosity. At very low flow states in the microcirculation, as occurs during circulatory shock, the blood viscosity can increase significantly. This occurs because at low flow states, there are increased cell-to-cell and protein-to-cell adhesive interactions that can cause erythrocytes to adhere to one another and increase the blood viscosity.

An example is helpful to understand the optimal HCT for O_2 transport per unit time by the circulation. The size, shape, and flexibility of RBCs are different for different species, and evolution has set an optimum ratio of RBC volume to PV to deliver O_2 to the tissues. The optimal HCT for a camel is 27%, 32% for a sheep, and 47% for a man (Burton 1972). Figure 5-5 below from Burton (1972) shows the curves of relative viscosity versus HCT for a camel and a man in panel A and the rate of flow of HB through a glass tube with a constant driving pressure for a camel and a man in panel B. The highest HB flow is associated with the optimum HCT for each species. Crowell (1967), with a different methodology, places the optimal HCT for a man at 40%.

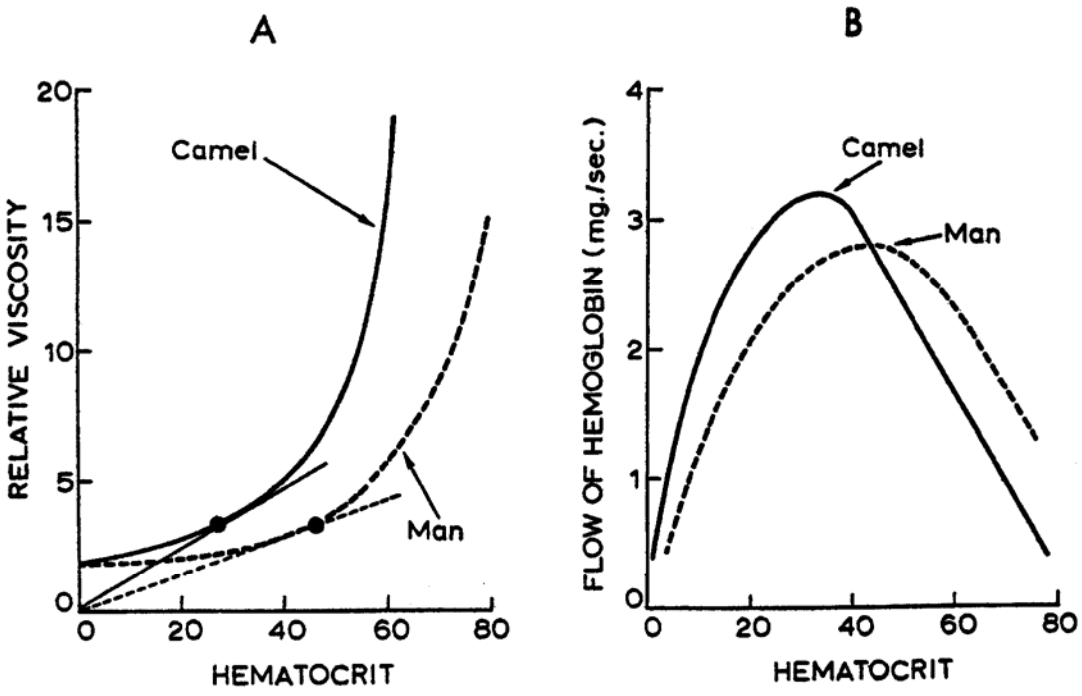


Fig. 5-5.—A, relative viscosity vs hematocrit for human blood and camel blood. B, the transport of oxygen through a glass tube vs hematocrit, with a constant driving pressure.

Papers by Martin (1986) and Neuman (1976) are helpful to understand the change in blood and plasma viscosity in relation to changes in HCT and plasma protein content. Results from Martin (1986) are shown in the next section as an introduction to the "typical" changes expected during NN extended 6-deg head down BR.

Third Issue: Potential Integrated Response

There are hundreds of reports about HH without μG simulation, and hundreds of reports about μG simulation under NN conditions. But, the unfortunate reality is that there are fewer than 10 reports in the United States where the combination of HH and adaptation to μG were tested together. And in some of these reports, the degree of μG adaptation was limited to just hours on a tilt table, so have limited application here. The sum total are listed here in ascending chronological order: Stevens (1966), Lynch (1967), Waligora (1982), Fulco (1985), Loeppky (1990), Loeppky (1993a), Loeppky (1993b), and Whitson (1994). Two of these reports have minimal application here: (Loeppky (1990), Whitson (1994), since the μG simulation was from short-duration tilt table studies with subjects breathing a hypoxic mixture through a mask.

Before providing a summary about these reports, it is helpful to understand the "typical" changes expected during NN extended 6-deg head down BR, as reported by Martin (1986). His figure 1 below is very descriptive. Data during BR 1 and BR 2 intervals are from day 6 of a 10-day BR. The intervening control period was 14 days.

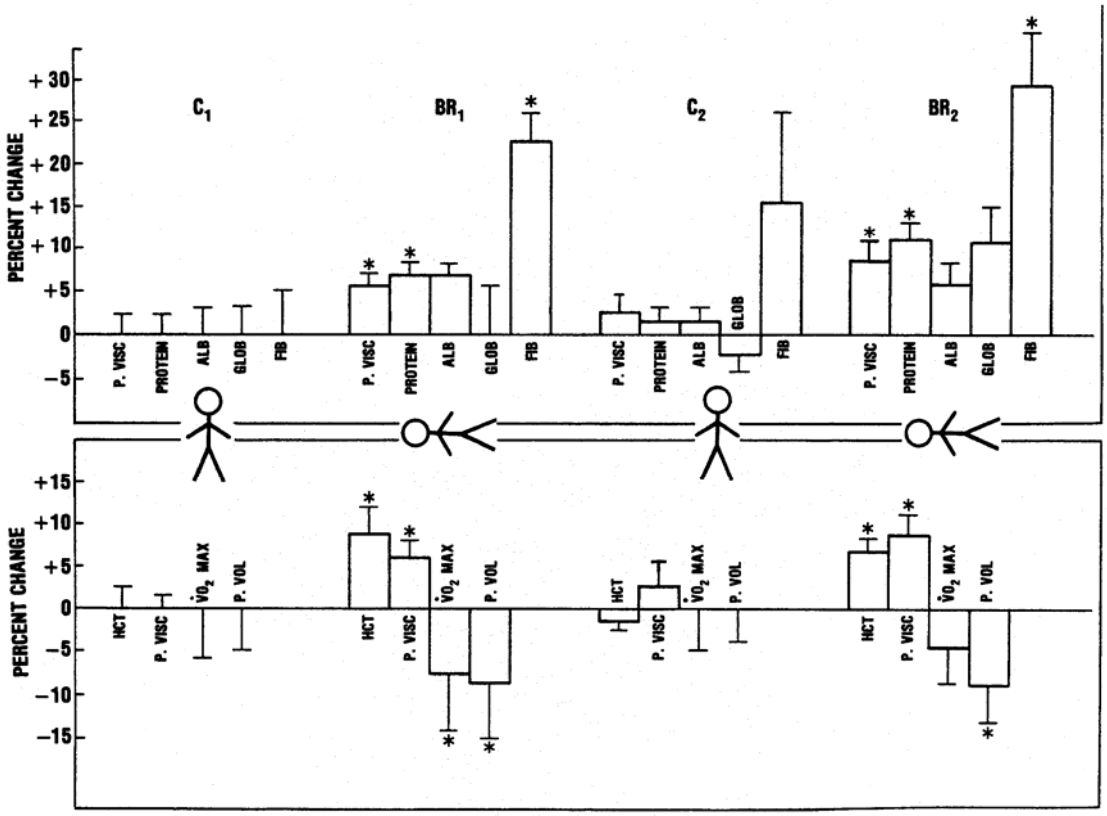


Fig. 1. Percent change with bed rest for plasma viscosity (P. VISC), total plasma protein concentration (PROTEIN), albumin concentration (ALB), globulin concentration (GLOB), fibrinogen concentration (FIB), hematocrit (HCT), aerobic exercise capacity ($\dot{V}O_{2\ max}$), and plasma volume (P. VOL) for eight subjects. Standard error bars for the first control period C1 represent the variability around the mean control measurements. BR1, C2, and BR2 represent the percent change from C1 ±S.E.M. Asterisks (*) represent significant difference p >0.05 from C1.

The data from Martin (1986) shows changes after 6 days of BR simply by taking an active person moving in a gravity field and making that person less active by placing them in 6-deg head down BR. Total plasma protein increased from 7.2 to 7.7 g/dl with the decrease in PV from 3,704 to 3,271 ml. HCT increased from 42.0 to 45.7%, and plasma viscosity increased from 1.32 to 1.39 centipoise after 6 days in the first 10-day BR period. Martin says that the increase in plasma fibrinogen from 324 to 396 mg/dl is greater than can be explained by hemoconcentration alone, so the increase in blood viscosity is without an enhancement of O_2 carrying capacity that you would expect if the increase in HCT was due to new RBC production. The changes seen after 6 days in the second 10-day BR period after the intervening 14 days of recovery were similar to the first BR results.

Martin (1986) was the first to directly measure changes in plasma viscosity during simulated μG, so a portion of his important Discussion is paraphrased here as follows:

> Viscosity of blood is a function of several factors: RBC concentration (HCT), plasma viscosity, RBC aggregation, and RBC deformability. HCT is the single most important determinant of blood viscosity. At a constant plasma viscosity and shear rate (vessel size and flow rate), an exponential increase in blood viscosity is observed with elevations in HCT. At an HCT of 20%, plasma viscosity is the primary determinant of blood viscosity. As shown in this study, there is a strong relationship between plasma viscosity and total plasma proteins, with fibrinogen having the greatest influence. Because of their marked axial asymmetry, fibrinogen molecules produce a greater hydrodynamic effect on fluid streamlines and influence plasma viscosity more than albumin and globulins. The final two determinants of whole blood viscosity, RBC deformability and aggregability were not directly measured in this study. RBC aggregability is dependent on shear rates, inter-cellular bridging by fibrinogen molecules as well as packing or closeness of the cells, a function of HCT. In vitro a 20% elevation in fibrinogen concentration results in elevations in RBC aggregability and whole blood viscosity of 70 - 85 centipoise at low shear rates ($0.1\ s^{-1}$). Thus, the increases in fibrinogen concentration and HCT we observed in this study should markedly elevate viscosity in low shear fields. Given the > 20% elevation in fibrinogen concentration and the 5 - 8% increase in HCT in this study, it is reasonable to suspect that RBC aggregability and whole blood viscosity in venous beds may have risen markedly in our volunteers during BR. This suggests a potential for increased venous stasis during BR.

By way of introduction, and for economy of space, we list several related figures now that display summary data about the potential integrated response between HH and adaptation to μG. Figure 24 shows results from Stevens (1966) and Lynch (1967), figure 25 is Waligora (1982), figure 26 is Fulco (1985), figure 27 is Loeppky (1990) and Whitson (1994), and figure 28 is Loeppky (1993a and 1993b).

Summary of Stevens (1966) and Lynch (1967) Results (chronic P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg	
Normobaric, P_B = 760 mmHg	P_AO_2 = 103 PV = 2928, HCT = 43.6, RBC = 2265, TBV = 5193		
Hypobaric, P_B < 760 mmHg		P_AO_2 = 58 PV = 2318, HCT = 50.9, RBC = 2396, TBV = 4716	10,000 to 12,000 ft plus extended BR, use 11,000 ft average for combined data. Data are from day 26.

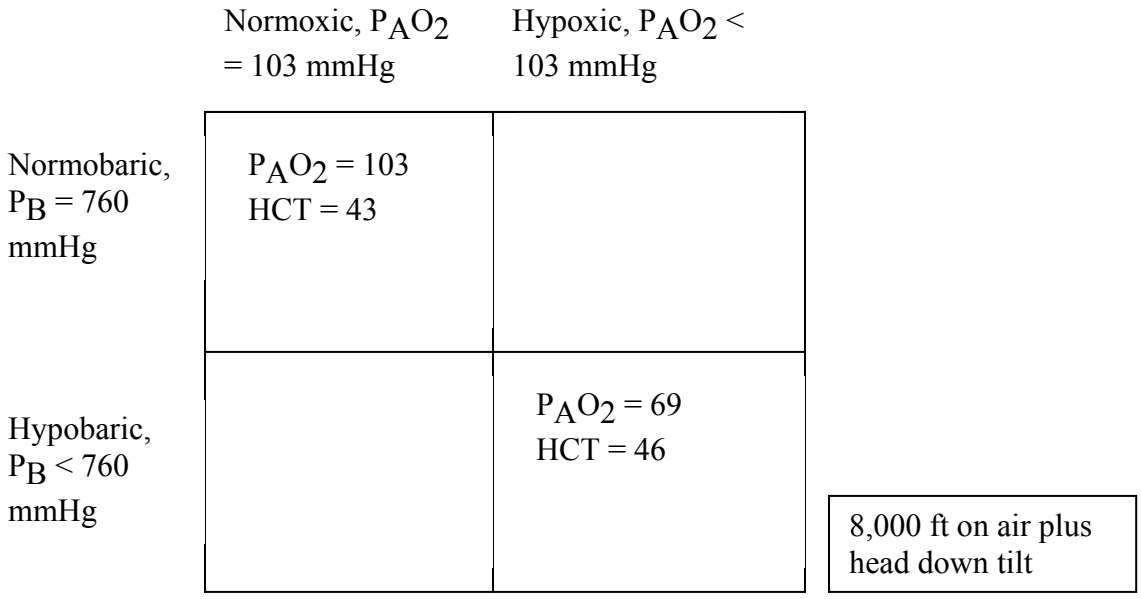
PV - plasma volume (ml)
HCT - hematocrit (%)
RBC – red blood cell volume (ml)
TBV - total blood volume (ml)

Fig. 24. Summary results from extended BR for 28 days in very young men (19 years old average). No difference in results from 10,000 ft and 12,000 ft exposures allowed the author to combine his data. He wanted to understand the benefit of lower body negative pressure to reverse the deconditioning effects of BR, and possibly the benefits of a HH exposure to counter the effects of BR. The study detected the expected changes in respiration and fluid redistribution and regulation associated with extended BR plus exposure to 3,353 m (11,000 ft) altitude (P_AO_2 = 58 mmHg). The issue was a potential negative synergistic effect of HH exposure and fluid redistribution during a 28 day simulated μG adaptation. There was no negative synergy over 28 days of exposure, which included modest exercise during BR. HCT increased from 44% to 51% over 28 days. Hypoxia prevented the loss in RBC mass experienced in extended BR, but the augmented RBC mass induced by hypoxia was less than anticipated. So, Stevens suspected that BR interfered with the response to increased RBC mass by hypoxia.

This study suggests that the proposed nominal CEV operating environment (16,000 ft with P_AO_2 = 77 mmHg) would be acceptable from an AMS perspective and increased blood viscosity perspective. HCT increased to 51% on average, with 54% at the extreme range. Lynch writes, “In the altitude subjects, headache of moderate severity

was not uncommon during the first 24 hrs of BR at simulated altitude, particularly in the 12,000 ft groups". This was at a time when AMS was not well characterized. In retrospect, it appears that an acute P_AO_2 = 54 mmHg at 3,657 m (12,000 ft) altitude is sufficient to precipitate AMS.

Summary of Waligora (1982) Results (acute P_AO_2)



HCT - hematocrit (%)

Fig. 25. Waligora's (1982) summary results. The study detected the expected changes in respiration associated with an 8 hr exposure to 2,438 m (8,000 ft) altitude (P_AO_2 = 69 mmHg). Waligora detected the expected changes in fluid redistribution seen in extended head down BR. The issue was a potential negative synergistic effect of HH exposure and fluid redistribution during a 28 hr simulated μG adaptation (6-deg head down BR). There was no negative synergy over 8 hrs of resting exposure with these 2 interventions; in particular, there was no difference in effective O_2 transport across the lungs with the combination of stressors. HCT increased from 43% to 46% over 28 hrs in 6-deg head down BR; the control group started with 46%, and this did not change during 8 hrs at altitude. Hemoglobin O_2 saturation decreased 6.8% in BR and 4.1% in control, P_aO_2 decreased 25.8 mmHg in BR and 27.4 mmHg in control (absolute value of 60 mmHg for the combined BR and control at altitude), and P_aCO_2 decreased 3.1 mmHg in BR and 5.5 mmHg in control. The P_EO_2 - P_aO_2 difference was 20 mmHg for the combined BR and control at altitude.

CEV will be at a lower absolute P_B of 4,876 m (16,000 ft) compared to this study at 2,438 m (8,000 ft), but P_AO_2 will be higher at 77 mmHg compared to 69 mmHg. If 6-deg head down BR is a reasonable analog for early changes and adaptation to μG, then it is reasonable to expect, based on the observations from Waligora (1982), that negative synergy between HH exposure plus μG adaptation might not be anticipated for the CEV.

Summary of Fulco (1985) and Results (chronic P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg	P_AO_2 = 103, CO = 5.7, TPR = 15.2, MAP = 83, HCT = 42, HB = 15.1, TBV = 100, PV = 100, NOR = 227	
Hypobaric, P_B < 760 mmHg		P_AO_2 = 48, CO = 4.6, TPR = 20.9, MAP = 94, HCT = 48, HB = 16.8, TBV = 90, PV = 81, NOR = 334

14,000 ft plus extended supine BR, used 60-deg head up tilt as challenge, 1, 18, 66, and 114 hrs. Data from 114 hrs, except NOR at 66 hrs.

PV - plasma volume (%)
HCT - hematocrit (%)
TBV - total blood volume (%)
HB - hemoglobin (g/dl)
NOR - norepinephrine (pg/ml)
CO - cardiac output (l/min)
TPR - total peripheral resistance (mmHg/l/min)
MAP - mean arterial pressure (mmHg)

Fig. 26. Fulco's (1985) summary results. Changes show typical magnitudes for combined supine and HH, with no exacerbated negative synergy. Fulco hypothesized that pre-activation of the sympathetic drive through hypoxia-induced increased catecholamine release would decrease subsequent changes elicited by 60-deg head up tilt from supine position. This response should change as "adaptation" to supine and hypoxia continues from 1 to 114 hrs. With continued altitude exposure, the difference between supine and upright values for stroke volume, CO, TPR, and calf blood flow decreased. Less response to tilt at altitude was attributed to 10% less BV and a 40% increase in NOR release. There is an increased sympathetic (adrenergic) drive relative to parasympathetic (cholinergic, Vegas nerve) on exposure to HH as evidenced by increased catecholamines (Malhorta 1976, 1977), particularly NOR (Fulco 1988). Even mild hypoxia while breathing 15% O_2 at sea level for 10 mins increases HR without a significant increase in respiration rate (Iwasaki 2006).

Summary of Loeppky (1990) Results (acute P_AO_2)
Summary of Whitson (1994) Results (acute P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg
Normobaric, P_B = 760 mmHg	P_AO_2 = 75* SaO_2 = 95.5, V_A = 5.69, $P_AO_2 - P_aO_2$ = 16	P_AO_2 = 48 SaO_2 = 80.6, V_A = 6.18, $P_AO_2 - P_aO_2$ = 8
Hypobaric, P_B < 760 mmHg		

14,828 ft with 13.9% O_2 at 5,000 ft plus 28-deg head down tilt for both reports. Data from 51 min into head down tilt from Loeppky.

*See Note 5 at end of report.

SaO_2 - arterial blood oxygen saturation (%)
V_A - alveolar ventilation rate (l/min, BTSP)
$P_AO_2 - P_aO_2$ - alveolar - arterial ppO_2 difference (mmHg)

Fig. 27. Loeppky's (1990) summary results. Loeppky found no exacerbated reaction to the changes expected with 28-deg head down tilt and the changes expected with acute NH. The 2 combined conditions did not create any unexpected synergistic outcomes.

Short-duration 28-deg head down tilt is an extreme input to initiate fluid and hormone changes, and the addition of a hypoxic breathing mixture by mask adds another variable. But this type of experimental intervention is not similar to the conditions expected on the CEV, so these results have limited application here. Loeppky noted that there were no gross indications of pulmonary congestion or interstitial edema with this level of hypoxia in subjects who were pre-adapted to 1,649 m (5,400 ft). The increase in HR, decrease in SBP, DBP, MAP, increase in CO, and decrease in systemic resistance with NH and 60 mins of 28-deg head down tilt is different from what you expect from just NH or HH. The combination of stresses seems to decrease systemic resistance more than expected, such that Loeppky feels the risk of orthostatic intolerance is increased. An acute exposure to NH or HH is expected to increase sympathetic drive (Malhorta 1976, Fulco 1988, Iwasaki 2006).

Whitson (1994) continues the work on ANP that Loeppky started. Loeppky (1993b) shows twice the ANP in a 5-deg head down BR after 4 days at 3,261 m (10,700 ft) compared to altitude exposure without head down BR. HH decreases plasma renin activity and ALD levels (Bouissou 1989). Bouissou (1989) shows no change in ANP on initial exposure to 4206 m (14,000 ft) with a computed P_AO_2 = 48 mmHg. Whitson also shows an increase in ANP with NH and head down tilt. The acute exposure to NH *did not* significantly alter the ANP response to head down tilt, but suggested attenuation during the NH.

Summary of Loeppky (1993a and b) Results (acute P_AO_2)

	Normoxic, P_AO_2 = 103 mmHg	Hypoxic, P_AO_2 < 103 mmHg	
Normobaric, P_B = 760 mmHg	P_AO_2 = 75*, HB = 16.5, HCT = 47		
Hypobaric, P_B < 760 mmHg		P_AO_2 = 59, HB = 17.5, HCT = 49, PV = -5, PaO_2 = 67 with HH HB = 19.0, HCT = 52, PV = -20, PaO_2 = 62 with HH + BR	10,700 ft on air and HH plus head down tilt BR

* See Note 1 at end of report.

HB - hemoglobin (g/dl)
HCT - hematocrit (%)
PV - plasma volume (% from baseline)
P_aO_2 - arterial oxygen partial pressure (mmHg)

Fig. 28. Loeppky's (1993a and 1993b) summary results. The study detected the expected changes in respiration associated with an 8 day exposure to a 3,254 m (10,678 ft) altitude (P_AO_2 = 59 mmHg) with subjects pre-adapted to 1,646 m (P_AO_2 = 75 mmHg). These results should be considered conservative since subjects exposed to 3,254 m from sea level would be expected to show greater changes. The study detected the expected changes in fluid redistribution seen in extended head down BR. The issue was a potential negative synergistic effect of HH exposure and fluid redistribution during 8 days of simulated μG adaptation (5-deg head down BR). HH plus head down BR did show an additive effect on changes over 8 days.

Changes associated with adaptation to mild hypoxia include an increased HB from 16.5% to 17.5%, an increased HCT from 47% to 49%, and a decrease in PV over the 8 days of about 5%. This compared to adaptive changes caused by mild hypoxia plus head down BR with an increased HB from 16.5% to 19.0%, an increased HCT from 47% to 52%, and an impressive decrease in PV over the 8 days of about 20%. He mentions from another study that the decrease in PV just from head down BR at sea level is about

10%. P_aO_2 in BR plus hypoxia after 7 days was 62 mmHg compared to 67 mmHg for hypoxia only. The P_EO_2 - P_aO_2 difference in BR plus hypoxia was 6 mmHg compared to 4 mmHg for hypoxia only. An elevated ANP and catecholamines together account for the enhanced fluid shift with head down BR during HH exposure.

Loeppky concludes that head down BR and HH exposure accentuated the loss of fluids and electrolytes and reduced PV. There were no negative impacts resulting from these fluid changes in terms of pulmonary mechanics or gas exchange, suggesting no evidence of pulmonary interstitial edema. He notes that symptoms of AMS were more prevalent, but not marked, and arterial blood gases and oxygenation were not seriously affected by the fluid shifts associated with adaptations to head down BR given that HH exposure was present.

CEV will be at a lower absolute P_B of 4,877 m (16,000 ft) compared to this study at 3,254 m (10,678 ft) with subjects pre-adapted to 1,646 m (5,400 ft), but P_AO_2 will be higher at 77 mmHg compared to 59 mmHg in this study. It is assumed that extended 5-deg head down BR is a reasonable analog for changes and adaptation to μG, so it is reasonable to expect, based on the observations from Loeppky (1993), that there would be no negative synergy between HH exposure plus μG adaptation anticipated for CEV.

The increase in HCT from about 42 to 45% during 10 days of 6-deg head down BR from Martin (1986) was similar to the increase from 43 to 46% for 6-deg head down BR after 28 hrs reported by Waligora (1982) with subjects exposed to 2,438 m (8,000 ft) altitude for 8 hrs, and the increase from 42 to 48% for supine subjects after 114 hrs at 4,300 m (14,000 ft) reported by Fulco (1985). The results from Fulco (1985) are similar to Stevens (1966) and Loeppky (1993a, 1993b). They show increases from 43.6% to 50.9% and from 47% to 52% when head down BR over many days was combined with HH from ascent to between 3,048 and 3,657 m (10,000 and 12,000 ft). It is important to note that the baseline data from Loeppky with 47% HCT are from subjects pre-adapted to living at about 1,524 m (5,000 ft), but the difference of 5% from the combined head down BR and HH is comparable to the 6% difference from Stevens (1966) and the 6% difference from Fulco (1985).

In summary, there is no obvious negative synergistic interaction between HH exposure with μG adaptation that appears across the experimental conditions in 6 applicable reports. There was no test done under the specific conditions proposed for the CEV. In light of the limited research data, the good operational experience from the 10.2 psia staged denitrogenation protocol from the shuttle is considered relevant to this discussion since it is close to the living environment proposed for the CEV.

Conclusions

Quality and Quantity of Research Data

Any factor that reduces crew health and performance should be minimized. *But, we now measure smaller changes with better instruments and, at the end of the day, are left to decide how much change is acceptable.* There was not an abundance of data or even a small amount of data specific to our needs. There were only 4 reports about a P_B effect on the risk of AMS induced by HH, and 6 reports on the combined effects of HH and simulated μG adaptation that have some application here. *The absence of information is not proof that a problem does not exist.* So, all conclusions made here are based on extrapolation or interpolation from limited information. *Knowing that you do not know something is often as important as knowing something.* In this regard, it was verified, with confidence, that there is an absence of data specific to our needs. Even the small amount of best data is not directly applicable. Data from Roach, Loeppky, and Tucker are specific to subjects who lived for years at about 1,524 m (5,000 ft) altitude in New Mexico and Colorado prior to tests conducted at 3,261 and 4,572 m (10,700 and 15,000 ft). Changes associated with these tests are certainly less than expected if applied to subjects who ascend from sea level to 4,572 m (15,000 ft) altitude. In addition to the lack of applicable data, there is also a lack of data for women exposed to HH, to simulated μG adaptation, and to the combination of HH and simulated μG adaptation.

There are extensive data, not summarized here, about good outcomes from ascent to altitude while breathing 100% O_2. The Apollo and Skylab missions, as well as associated ground-based validation and baseline data collection, showed that weeks to months could be spent at an altitude of 27,000 ft (5.0 psia) while breathing 100% O_2 (Apollo) or 70% O_2 (Skylab), certainly without gross indications of hypoxic stress in astronauts adapting to μG. So, it appears that as long as normoxic or slight hyperoxic conditions are maintained, the absolute ambient P_B is a secondary concern. It is only when a hypoxic condition is combined with a hypobaric condition that an ambient P_B become a concern.

All the reports here used 21% O_2 in air plus hypobaric P_B or less than 21% O_2 at site P_B to achieve a degree of hypoxia. It is important to point out that the atmosphere – one that is mildly hypoxic to reduce the risk of fire - proposed for the CEV, LSAM, and long-duration surface habitats will be enriched with O_2 to between 30 and 34%. This method to produce HH may have some net advantage to the body than by producing the same HH using 21% O_2 in air. But, there is an absence of data to evaluate hypoxia produced through the combination of enriched O_2 (>21%) under hypobaric conditions (P_B <760 mmHg). If the effort is made to enrich the breathing gas with O_2, then the goal is often to provide a normoxic environment, such as was done with the breathing environment for Skylab.

There is one example where mild hypoxia is produced through the combination of enriched O_2 (>21%) under hypobaric conditions (P_B <760 mmHg) and has been used with hundreds of subjects over several days, with and without adaptation to μG. These data are from the ground testing and good operation experience of the shuttle staged denitrogenation protocol. The data are marginally applicable here since good operational experience is not equivalent to quality research data, and the shuttle conditions are not identical to those currently planned for the CEV and beyond. Subjects in an altitude chamber and later astronauts on the shuttle spent hours to days at 10.2 psia (10,000 ft) breathing 26.5% O_2 as a means to partially denitrogenate body tissues prior to depressurization to 4.3 psia with 100% O_2. The P_AO_2 is computed at 85 mmHg during the staged protocol, which is equivalent to breathing air at 1,219 m (4,000 ft) if we discount the current discussion about the validity of applying the idea of an EAA exposure. The point is that the good testing and operational experience with this protocol suggests that there is no significant negative synergy between *very mild* HH and μG. But, it is an extrapolation to conclude anything about the worse case P_AO_2 of 68 mmHg at 5,029 m (16,500 ft) in astronauts adapted to μG in the CEV based on the literature reviewed for this report.

It is unlikely that being restricted to the fourth box in the P_B and O_2 exposure matrix (see figure 20 for example) will provide enough difference in exposure conditions to show a difference in AMS outcomes given the same P_AO_2 but different ambient P_Bs. The shuttle and future habitat atmospheres are contained in this fourth box. With 10.2 psia P_B and 26.5% O_2 on the shuttle, the ppO_2 is 140 mmHg with P_AO_2 = 85 mmHg from the AOE. For the proposed nominal CEV, LSAM, and moon habitat an 8.0 psia P_B and 32.0% O_2 the ppO_2 is 132 mmHg with P_AO_2 = 77 mmHg from the AOE. These conditions are close to an ascent on 21% O_2 to 11.8 psia. Since AMS signs and symptoms do not begin at less than 11.5 psia (6,500 ft, ppO_2 = 125 mmHg with P_AO_2 = 75 mmHg from the AOE), it is unlikely that anyone on the shuttle will experience AMS. The conditions on the CEV, especially the worse case extreme of the control box for the life support system, could drop P_AO_2 to about 68 mmHg.

Although initial signs and symptoms of AMS in *susceptible* subjects are expected after prolonged exposure to between 2,000 m (6,600 at P_AO_2 = 75 mmHg) and 2,590 m (8,500 ft at P_AO_2 = 67 mmHg), it is likely that these would be self-limiting once acclimatization proceeds (Roach 1998). Roach (1996) and Tucker (1983) have the best data from which to conclude that AMS is very likely for some people who are exposed to 4,572 m (15,000 ft) with a P_AO_2 of about 45 mmHg and who are pre-adapted to living at 1,524 m (5,000 ft). Therefore, at 8.0 psia (4,877 m or 16,000 ft) with a nominal P_AO_2 = 77 mmHg in astronauts not pre-adapted to living at 1,524 m altitude, it is likely that susceptible astronauts simultaneously undergoing adaptation to μG (Loeppky 1993a and 1993b) will experience the signs and symptoms of AMS. It is unlikely that a clinically significant increase in HCT will occur. A transient increase to a mean HCT of about 50%, possibly as high as 55% in a particular crewperson, would be predicted based on

the data (Stevens 1966, Loeppky 1993a, 1993b) for the combined effects of HH and adaptation to μG as envisioned for the CEV program. However, typical μG adapted spaceflight HCT values are in the low normal range, from 36 to 40% depending on gender.

There are several examples where the physiological changes initiated by HH and adaptation to μG are in opposite directions. Therefore, the net effect is a blunted response when both conditions occur simultaneously. For example, HH increases sympathetic drive through the release of catecholamines (Fulco 1985, 1988, Malhotra 1976, 1977) while supine or head down BR reduces sympathetic drive (Volicer 1976). HH increases RBC mass that is opposite the decrease seen in extended BR and exposure to μG (Alfrey 1996). Some even propose that the compensations for HH provide a beneficial therapy for cardiovascular deconditioning associated with extended BR (Lamb 1965, Lynch 1967, Shvartz 1990). One example for a negative synergy is a possible enhanced reduction of the ventilatory response to hypoxia. The classic response to hypoxia is to increase V_E, but the increase is slightly less if the hypoxia is caused by a hypobaric exposure compared to the same hypoxia caused in a normobaric condition (Savourey 2003). Prisk (2000) shows a reduction in ventilatory response to hypoxia in normocapnic subjects during supine and μG exposure compared to standing subjects. The notion is that increase in blood pressure due to body position modifies the ventilatory response to hypoxic challenge. The 2 studies are not directly comparable, but this may be a case where HH and adaptation to μG lead to a greater reduction in ventilatory response to hypoxia that either in isolation would cause. This is not an ideal situation if the goal is to avoid AMS associated with a suppressed ventilatory response to hypoxia. Rahn (1954) shows that hyperventilation on standing after being supine increases P_AO_2 as P_ACO_2 drops from about 42 mmHg to 37 mmHg in response to the hyperventilation. So, body position modifies P_AO_2, and it is unclear how μG influences P_AO_2, given that body position is irrelevant. Finally, you can argue from the work of Loeppky (1993a and 1993b) that HH and μG simulation produced changes that are additive. He shows an additional loss of PV, with an additional increase in HB and HCT given a P_AO_2 = 59 mmHg at 3,261 m (10,700 ft) altitude in subjects exposed 8 days to 5-deg head down BR compared to the loss of PV and increase in HB and HCT in subjects just exposed to 3,261 m altitude. On balance, there is no definitive evidence for an exaggerated (negative synergistic) response to the combination of HH and adaptation to μG. On the contrary, the limited evidence suggests that one stressor tends to counteract the other.

All events associated with the CEV mission to the moon are on a short time scale compared to the weeks and months needed to achieve a new steady state adaptation. So, physiological compensation, accommodation, or acclimatization processes are underway in the CEV immediately after orbital insertion, on the way to the moon, during EVA on the moon, and during the return to Earth over a 10 to 15 day mission. It is unclear how the cyclical pattern of mild hyperoxia (EVA environment) and mild hypoxia (habitat environment) caused by an ambitious EVA schedule on the moon would influence physiology. The up and down regulation of various antioxidant enzyme systems due to the changing ppO_2 may exhaust the ability to scavenge reactive O_2 species.

Individual susceptibility to μG adaptation in a HH environment will likely play a role in mission success (including an absence of medical problems) in these short-term missions with high EVA-rate scenarios. Some peak performance degradation could be expected in crewmembers if ppO_2 is reduced acutely to less than 2.8 psia until compensation occurs. The magnitude of the performance affect will depend on the ppO_2, the metabolic demands of the task, and individual (genetic) factors. The current threshold for mandatory supplemental ppO_2 during spaceflight operations is 2.2 psia. For lunar outpost missions (approximately 6 months surface stays), full acclimatization to reduced ppO_2 can be expected after 30 to 45 days, allowing crews to function at high performance levels in the face of reduced O_2 tension. Figure 29 is a plot of several tests in this report by the test altitude and computed P_AO_2 compared to the position of successful NASA human space programs and the proposed CEV program.

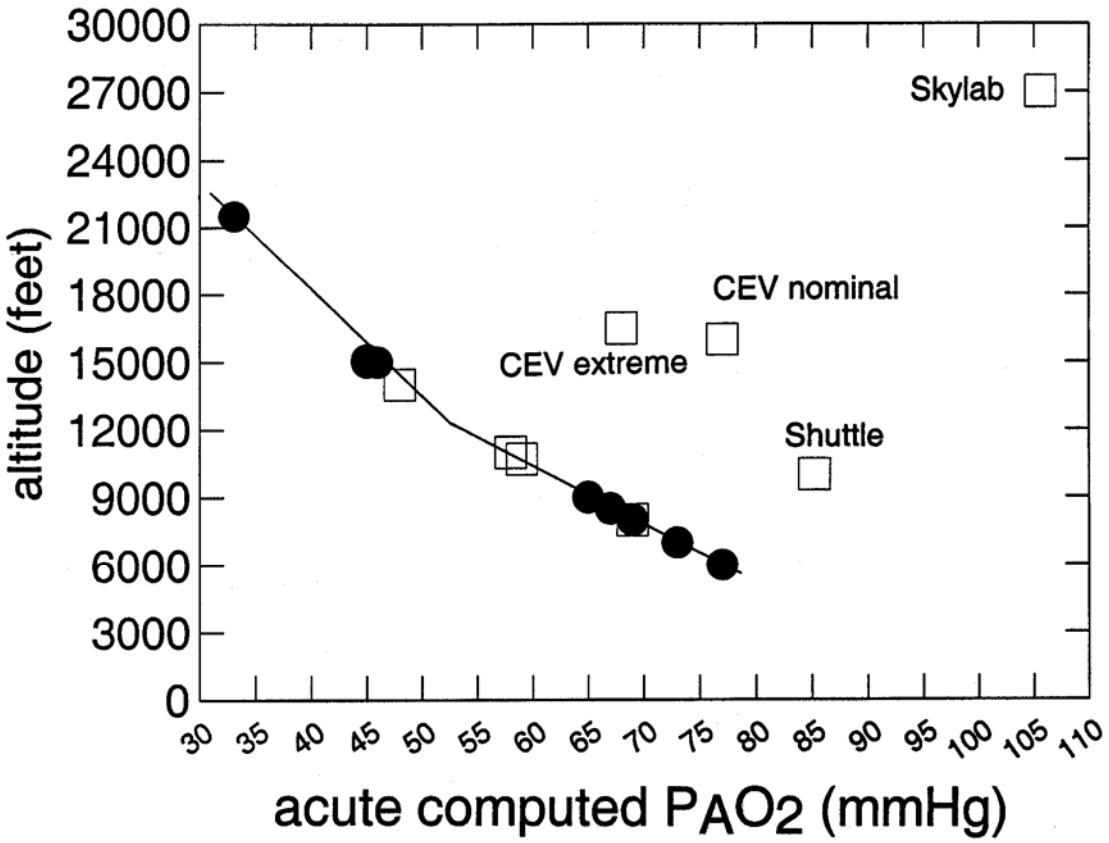


Fig. 29. Plot shows the position of several tests in this report by the test altitude and computed P_AO_2 compared to the position of successful NASA human space programs and the proposed CEV program. Solid circles connected by the curve are studies done where HH was induced by ascent to altitude on air, but are HH exposures without simulated μG. The open boxes are exposures where μG adaptation through simulation or actual exposure is present as part of the HH. The 2 least stressful points along the curve at 6,000 and 7,000 ft are from Ge (2002) where he shows a slight increase in plasma EP concentration. The third point at 8,000 ft from Ge (2002) is within the open box from Waligora (1982). Ge showed a substantial increase in plasma EP concentration at this altitude after 24 hrs. Waligora had subjects in 6-deg head down BR for 28 hrs with 8 of the hours spent at 8,000 ft. No differences were noted that could not be attributed to those expected for acute exposure to 8,000 ft and those attributed to acute head down BR. The most stressful point along the curve is from Levine (1988) and his work with sheep that produced significant pulmonary edema. If you accept that mission-impact AMS after hours of exposure to HH can start at altitudes between 2,000 and 2,590 m (6,600 and 8,500 ft) (Roach 1998) given a mean P_AO_2 of 71 mmHg for 2,286 m (7,500 ft), then the question to ponder is whether the risk of AMS dramatically increases in the CEV given a worse case P_AO_2 of about 68 mmHg, and with an additional 2,743 m (9,000 ft) altitude (5,029 – 2,286 = 2,743 m) in astronauts adapting to μG.

Risk Mitigation Plan

There is no single study that addresses the exact conditions for the proposed nominal Constellation vehicle environment: adaptation to μG with a breathing environment at 8.0 psia (16,000 ft altitude) with 32% O_2 and 68% N_2, resulting in an acute P_AO_2 of about 77 mmHg. Therefore, the recommendations that follow are not only based on extrapolations and judgment from an exhaustive literature review, but also from tests that differ from the proposed CEV, LSAM, and long-duration surface habitat environments. No global mechanism yet exists to describe the observations from these experiments, so you cannot predict changes expected for CEV based on an understanding of a mechanism that describes the empirical data. So, uncertainty prevails; and at least 7 options are offered as part of an integrated risk mitigation plan:

Accept a conclusion based on a literature review that no significant negative synergistic interaction between HH exposure with μG adaptation is expected for the proposed CEV environment. Any AMS signs and symptoms would be mild, and transient.

Develop the rationale and procedures to easily increase ambient P_B plus use medications such as prophylactic or, as-needed, AZ, dexamethasone, and supplemental O_2 to reduce AMS risk or provide effective treatment if required. Caution is warranted here for several reasons: AZ may be prescribed for diagnosed AMS when, in fact, the signs and symptoms are from motion sickness. Or, medication for motion sickness may be incorrectly prescribed for AMS. AMS and motion sickness share many of the same signs and symptoms, and may appear along a similar time course. Often sleep medication is prescribed due to the many distractions in a small space vehicle. However, sleep medications may be contraindicated if AMS is suspected. A sleep medication would likely worsen the signs and symptoms of AMS.

Consider preflight testing to identify astronauts who are susceptible to atmospheric changes in the CEV environment, and provide special training and risk mitigation plans for those who are identified as susceptible, versus reassignment to a different mission.

Pre-adapt crews to a hypoxic environment, either NH or HH, prior to launch to blunt any combined negative effects of HH exposure with μG adaptation shortly after launch. But, this intervention to reduce the risk of AMS is contraindicated if the resulting increase in HCT significantly adds to the increased HCT transiently observed during the acute phase of μG adaptation, possibly leading to impaired circulation and O_2 delivery. Consider phlebotomy, if warranted.

Develop an acclimatization plan through the gradual reduction in P_AO_2 during the initial phase of the mission, which should significantly reduce the likelihood of AMS signs and symptoms.

In addition to 100% O_2 PB to prevent VGE on initial depressurization to 8.0 psia in the CEV, consider a plan to breathe 100% O_2 by mask over several intervals of time during the acclimatization to the μG plus HH exposure. Breathing 100% O_2 is shown to blunt the negative physiological effects of subsequent HH exposure.

Perform a 5-day study in 10 subjects representative of the astronaut corps simulating the extreme control box environmental parameters of the CEV (7.8 psia with 30% O_2, P_AO_2 = 68) plus a head down BR analog for μG adaptation after a 2-hr O_2 PB. Collect some or all of the following measurements to characterize the risk of AMS:

- Hematology: HCT, RBC mass, plasma globin, HB, plasma EP, total plasma protein, plasma albumin, plasma fibrinogen, PV
- Endocrinology: ADH, ANP, ALD
- Renal: Fluid intake, urine output
- Serum and Urine Electrolytes: Na+, K+, Ca++, Cl-, PO_4-, H+ (pH)
- Performance measures: AMS score, visual acuity, 75% VO_2 max
- Pulmonary: Oximetry for SaO_2 (expect about 93% saturation), P_aO_2, P_aCO_2, P_AO_2, P_ACO_2, $ETPO_2$ and $ETPCO_2$, V_t (l/min, BTPS), V_E (l/min, BPTS), breathing frequency, a measure of pulmonary edema, a measure of effective O_2 transport, i.e., P_AO_2 - P_aO_2
- Compute V_A/Q, alveolar and physiological deadspace
- Cardiovascular Measures: Stroke volume, HR, SBP, DBP, CO via echocardiography, and ECG
- Body Weight
- Other: Precordial VGE monitoring with a Doppler ultrasound bubble detector, or transthoracic echocardiography

Notes

1. Roach and Loeppky performed their extensive research on AMS at the University of New Mexico in Albuquerque. The average P_B in this city is 630 $\pm$ 10 mmHg, or equivalent to an altitude of about 1,524 m (5,000 ft); they quote closer to 1,646 m (5,400 ft). So, physiological changes for subsequent HH, NH, or HN exposures, when compared to other studies that started at sea level, must be considered "conservative". Their observations are conservative since subjects were pre-adapted to living at about 1,524 m (5,000 ft) before the experiment began.

2. Tucker performed his research on AMS at Colorado State University in Fort Collins. The average P_B in this city is 632 mmHg, or equivalent to an altitude of about 1,524 m (5,000 ft). So, physiological changes for subsequent HH, NH, or HN exposures, when compared to other studies that started at sea level, must be considered "conservative". His observations are conservative since subjects were pre-adapted to living at about 1,524 m (5,000 ft) before the experiment began.

3. Levine performed his research in Matsumoto, Japan. The average P_B in this city is 708 mmHg, or equivalent to an altitude of about 579 m (1,900 ft).

4. Savourey performed his research in La Tronche, France. The average P_B in this city is 733 mmHg, or equivalent to an altitude of about 305 m (1,000 ft).

5. Loeppky and Whitson did their research at the University of New Mexico in Albuquerque. The average P_B in this city is 630 ± 10 mmHg, or equivalent to an altitude of about 1,524 m (5,000 ft). So, physiological changes for subsequent NH exposures, when compared to other studies that started at sea level, must be considered "conservative". Their observations are conservative since subjects were pre-adapted to living at about 1,524 m (5,000 ft) before the experiment began.

References

1. Alfrey CP, et al. Control of red blood cell mass in spaceflight. J Appl Physiol 1996; 81:98-104.

2. Auerbach PS (ed). Wilderness Medicine: Management of wilderness and environmental emergencies (3ed Ed). St. Louis, MO: Mosby Year Book, Inc., 1995, pp. 1 - 37.

3. Bert P. Barometric Pressure: Researches in experimental physiology. Bethesda, MD: Undersea Medical Society, 1978.

4. Bouissou P, et al. Effect of beta-adrenoceptor blockade on renin-aldosterone and alpha-ANF during exercise at altitude. J Appl Physiol 1989; 67:141-46.

5. Buckey JC, Jr. Space physiology. New York: Oxford University Press, 2006, pp. 140 - 163.

6. Bungo MW. The cardiopulmonary system (Chap. 10). In: Nicogossian AE, et al (ed). Space Physiology and Medicine (ed. 2). Philadelphia: Lea and Febiger1989, pp. 179 - 199.

7. Burton AC. Physiology and biophysics of the circulation (ed. 2). Chicago: Year Book Medical Publications, 1972, pp. 42.

8. Campbell P. Recommendations for Exploration Spacecraft Internal Atmospheres: The final report of the NASA exploration atmospheres working group. JSC-63309, Johnson Space Center: Houston, TX, January 2006.

9. Conkin J, et al. Increase in whole-body peripheral vascular resistance during three hours of air or oxygen prebreathing. NASA Technical Memorandum 58261, Johnson Space Center, Houston, TX, August 1984.

10. Conkin J. Probabilistic Modeling of Hypobaric Decompression Sickness. Doctoral Dissertation. State University of New York at Buffalo, 1994.

11. Conkin J, et al. Relationship of the time course of venous gas bubbles to altitude decompression illness. Undersea Hyperbaric Med 1996; 23:141-49.

12. Crowell JW, Smith EE. Determinant of the optimal hematocrit. J Appl Physiol 1967; 22:501-04.

13. DeHart RL (ed). Fundamentals of Aerospace Medicine (2nd. Ed). Baltimore, MD: Williams and Wilkins, 1996, pp.90-91.

14. Epstein M, et al. Effects of simulated high altitude on renin-aldosterone and Na homeostasis in normal man. J Appl Physiol 1972; 33:204-10.

15. Fulco CS, et al. Hemodynamic responses to upright tilt at sea level and high altitude. Aviat Space Environ Med 1985; 56:1172-76.

16. Fulco CS, et al. Human performance and acute hypoxia (Chap. 12). In: Pandolf KB, et al (ed). Human performance physiology and environmental medicine at terrestrial extremes. Carmel, IN: Cooper Publishing Group, 1988, pp. 467 - 95.

17. Ge R, et al. Determinants of erythropoietin release in response to short-term hypobaric hypoxia. J Appl Physiol 2002; 92:2361-67.

18. Georgopoulos D, Walker S, Anthonisen NR. Increased chemoreceptor output and ventilatory response to sustained hypoxia. J Appl Physiol. 1989; 67:1157-63.

19. Grover RF, et al. Hypobaria: an etiologic factor in acute mountain sickness? In: Loeppky JA and Riedesl ML (ed.). Oxygen transport to human tissues. New York:Elsever/North-Holland, 1982, pp. 223 - 30.

20. Hackett PH, et al. Fluid retention in acute mountain sickness. Respiration 1982; 43:321-29.

21. Hesse B, et al. Reduced norepinephrine response to dynamic exercise in human subjects during O2 breathing. J Appl Physiol 1981; 51:176-78.

22. Hildebrandt W, et al. Diuretic effect of hypoxia, hypocapnia, and hypernea in humans: relation to hormones and O2 chemosensitivity. J Appl Physiol 2000; 88:599-610.

23. Houston CS. Altitude illness: manifestations, etiology, and management. In: Loeppky JA and Riedesl ML (ed.). Oxygen transport to human tissues. New York:Elsever/North-Holland, 1982, pp. 255 - 64.

24. Hultgren HN. Pulmonary hypertension and pulmonary edema. In: Loeppky JA and Riedesl ML (ed.). Oxygen transport to human tissues. New York:Elsever/North-Holland, 1982, pp. 243 - 54.

25. Iwasaki K, et al. Cardiovascular regulation response to hypoxia during stepwise decreases from 21% to 15% inhaled oxygen. Aviat Space Environ Med 2006; 77:1015-19.

26. Johnson PC, et al. Blood volume changes (Chapt 26). In: Johnston RS, Dietlein LF (ed.). Biomedical Results from Skylab, NASA SP-377, Washington, D.C.: U.S. Government Printing Office, 1977, pp. 235 - 41.

27. Johnson PC. Part C: Blood volume and red cell life span (M113). In: Skylab Medical Experiments Altitude Test (SMEAT). Bio Technology, Inc., NASA, TM X-58115, October 1973, pp. 6-15 to 6-18.

28. Kasic JF, et al. Treatment of acute mountain sickness: Hyperbaric versus oxygen therapy. Ann Emerg Med 1991; 20:1109-12.

29. Kazemi H, et al. Dynamics of oxygen transfer in the cerebrospinal fluid. Resp Physiol 1968; 4:24-31.

30. King AB, et al. Ventilation response to hypoxia and acute mountain sickness. Aviat Space Environ Med 1972; 43:419 - 21.

31. Knight DR, et al. Effect of hypoxia on psychomotor performance during graded exercise. Aviat Space Environ Med 1991; 62:228-32.

32. Lamb LE. Hypoxia - an antideconditioning factor for manned space flight. Aerospace Med 1965; 36:97-100.

33. Leach CS, et al. Bioassay of body fluids - experiment M073 (Chap. 11). In: Skylab Medical Experiments Altitude Test (SMEAT). Bio Technology, Inc., NASA, TM X-58115, October 1973, pp. 11-1 to 11-14.

34. Leach CS, et al. Biochemical responses of the skylab crewmen: an overview (Chapt 23). In: Johnston RS, Dietlein LF (ed.). Biomedical Results from Skylab, NASA SP-377, Washington, D.C.: U.S. Government Printing Office, 1977, pp. 204 - 15.

35. Leaf DE, et al. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness: a review. J Appl Physiol 2006; in press.

36. Levine BD, et al. Role of barometric pressure in pulmonary fluid balance and oxygen transport. J Appl Physiol 1988; 64:419-28.

37. Loeppky JA, et al. Role of hypobaria in fluid balance response to hypoxia. High Altitude Med and Biol 2005a; 6:60-71.

38. Loeppky JA, et al. Ventilation during simulated altitude, normobaric hypoxia, and normoxic hypobaria. Respir Physiol 1997; 107:231-39.

39. Loeppky JA, et al. Acute ventilatory response to simulated altitude, normobaric hypoxia, and hypobaria. Aviat Space Environ Med 1996; 67:1019-22.

40. Loeppky JA, et al. Effects of prolonged head-down bedrest on physiological responses to moderate hypoxia. Aviat Space Environ Med 1993a; 64:275-86.

41. Loeppky JA, et al. Body fluid alterations during head-down bedrest in men at moderate altitude. Aviat Space Environ Med 1993b; 64:265-74.

42. Loeppky JA, et al. Effect of acute hypoxia on cardiopulmonary responses to head-down tilt. Aviat Space Environ Med 1990; 61:785-94.

43. Loeppky JA, et al. Early fluid retention and severe acute mountain sickness. J Appl Physiol 2005b; 98:591-97.

44. Lynch TN, et al. Metabolic effects of prolonged bedrest: their modification by simulated altitude. Aerospace Med 1967; 38:10-20.

45. Malhorta MS, et al. Changes in orthostatic tolerance in man at an altitude of 3500 meters. Aviat Space Environ Med 1977; 48:125-8.

46. Malhorta MS, et al. Responses of the autonomic nervous system during acclimitization to high altitude in man. Aviat Space Environ Med 1976; 47:1076-9.

47. Martin DG, et al. Plasma viscosity elevations with simulated weightlessness. Aviat Space Environ Med 1986; 57:426-31.

48. McMurtry IF, et al. The mechanism of hypoxic pulmonary vasoconstriction: a working hypothesis. In: Loeppky JA and Riedesl ML (ed.). Oxygen transport to human tissues. New York:Elsever/North-Holland, 1982, pp. 77 - 89.

49. Meehan RT. Renin, aldosterone, and vasopressin response to hypoxia during 6 hrs of mild exercise. Aviat Space Environ Med 1986; 57:960-65.

50. Milledge JS. Renin-aldosterone system (Chap. 5). In: West JB and Lahiri S (ed.). High altitude and man. Baltimore, MD: Williams and Wilkins, 1984, pp. 47 – 57.

51. Montgomery AB, et al. Incidence of acute mountain sickness at intermediate altitude. JAMA 1989; 261:732-34.

52. Moudgil R, et al. Hypoxic pulmonary vasoconstriction (review). J Appl Physiol 2005; 98:390-403.

53. Murray JF. The normal lung (ed. 2). Philadelphia:W.B. Saunders Company, 1986, pp. 206.

54. Neuman TS, et al. Blood viscosity in man following decompression: correlations with hematocrit and venous gas emboli. Aviat Space Environ Med 1976; 47:803-07.

55. Otis AB, et al. Effect of gas density on resistance to respiratory gas flow in man. J Appl Physiol 1949; 2:300-6.

56. Prisk GK, Elliot AR, West JB. Sustained microgravity reduces the human ventilatory response to hypoxia but not to hypercapnia. J Appl Physiol 2000; 88:1421-30.

57. Rahn H, Fenn WO. A graphical analysis of the respiratory gas exchange: the O_2 - CO_2 diagram (second ed.). Washington, D.C.: The American Physiological Society, 1956, pp. 25-26.

58. Rahn H. The sampling of alveolar gas (Chap. 3). In: Boothby WM (ed.). Handbook of respiratory physiology. Air University, USAF School of Aviation Med, Randolph AFB, Texas, 1954, pp. 29 - 37.

59. Roach RC, et al. The Lake Louise acute mountain sickness scoring system (Chap. 26). In: Sutton JR, et al (ed). Hypoxia and Molecular Biology. Burlington, VT: Queen City Press, 1993, pp. 272-74.

60. Roach RC, et al. Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. J Appl Physiol 1996; 81:1908-10.

61. Roach RC, Loeppky JA. Does hypobaria play a role in the development of the high altitude illness (Chap. 24). In: Sutton JR, et al (ed). Hypoxia and the Brain. Burlington, VT: Queen City Press, 1995, pp. 297-303.

62. Roach RC, et al. Arterial oxygen saturation for prediction of acute mountain sickness. Aviat Space Environ Med 1998; 69:1182-85.

63. Roach RC. Hypoxic ventilatory response and performance at high altitude (Chap. 12). In: Wood SC, et al (ed). Sports and Exercise Med. New York, New York: Marcel Dekker, Inc., 1994, pp. 211-224.

64. Roach RC, et al. Hyperbaria and high altitude illness. In: Sutton JR, et al (ed). Hypoxia and Mountain Medicine. New York, New York: Pergamon Press, 1992.

65. Savourey G, et al. Normo- and hypobaric hypoxia: are there any physiological differences? Eur J Appl Physiol 2003; 89:122-26.

66. Schoene RB. Hypoxic ventilatory response and exercise ventilation at sea level and high altitude (Chap. 2). In: West JB and Lahiri S (ed.). High altitude and man. Baltimore, MD: Williams and Wilkins, 1984, pp. 19 – 30.

67. Severinghaus JW. Hypothetical role of angiogenesis, osmotic swelling, and ischemia in high-altitude cerebral edema. J Appl Physiol 1995; 79:375-79.

68. Shvartz E. Advantages of a low-oxygen environment in space cabins. Aviat Space Environ Med 1990; 61:272-76.

69. Srinivasan RS, et al. Mathematical modeling of physiological states (Chap. 26). In: Huntoon CS, Antipov VV, Grigoriev AI (ed.). Space Biology and Medicine III. Reston, VA: American Institute of Aeronautics and Astronautics, 1996, pp. 559-92.

70. Stevens PM, et al. Effects of lower body negative pressure on physiological changes due to four weeks of hypoxic BR. Aerospace Med 1966; 37:466-74.

71. Sutton JR, et al. Pulmonary gas exchange in acute mountain sickness. Aviat Space Environ Med 1976; 47:1032 - 37.

72. Swenson ER, et al. Diuretic effect of acute hypoxia in humans: relationship to hypoxic ventilatory responsiveness and renal hormones. J Appl Physiol 1995; 78:377-83.

73. Swenson ER, et al. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. Eur Respir J 1998; 12:1242-47.

74. Swenson ER, et al. Carbonic anhydrase inhibitors and hypoxic pulmonary vasoconstriction. Respir Physiol Neurobiol 2006; 151:209-16.

75. Tucker A, et al. Cardiopulmonary response to acute altitude exposure; water loading and denitrogenation. Respir Physiol 1983; 54:363-80.

76. Tucker A, et al. Improved ventilatory, hemodynamic, and renal responses to acute altitude exposure in denitrogenated subjects [Abstract]. Fed Pro 1981; 40:609.

77. Valtin H. Renal Function: mechanisms preserving fluid and solute balance in health (ed. 2). Boston, MS: Little, Brown and Company, Inc., 1983, pp. 195 – 248.

78. Van Liew HD, personal communication (2007).

79. Vardy J, et al. Acute mountain sickness and ascent rates in trekkers above 2500 m in the napali himalaya. Aviat Space Environ Med 2006; 77:742-44.

80. Volicer L, et al. Effects of head-down tilt on fluid and electrolyte balance. Aviat Space Environ Med 1976; 47:1065-68.

81. Waligora JM, et al. Investigation of the combined effects of bedrest and mild hypoxia. Aviat Space Environ Med 1982; 53:643-46.

82. Whitson PA, et al. Acute effects of head-down tilt and hypoxia on modulators of fluid homeostasis. J Clin Pharmacol 1994; 34:427-33.

83. The Lake Louise consensus on the definition and quantification of altitude illness. In: Sutton JR, et al (ed). Hypoxia and Mountain Medicine. Burlington, VT: Queen City Press, 1992.

Appendix: Standard Atmosphere

When breathing an atmosphere that does not contain 20.9% O_2, it is helpful to estimate the EAA since most experience with hypoxia is with ascent to altitude while breathing air (F_IO_2 = 20.9%). With a given P_AO_2 from the AOE one can consult a published "altitude table", like the one reproduced here from DeHart (1996) to find the altitude while breathing air that corresponds to the acute P_AO_2 value, regardless of the combination of P_B and F_IO_2 that is used to achieve the value.

Table 5.12.
Respiratory Gas Pressures and Gas Exchange Ratios

Altitude		Pressure		Ambient P_{O_2}	$P_{A_{O_2}}$	$P_{A_{CO_2}}$	P_{H_2O}	Respiratory Exchange Ratio (R)
(m)	(ft)	(PSIA)	(mm Hg)	(mm Hg)	(mm Hg)	(mm Hg)	(mm Hg)	
				Breathing Air				
0	0	14.69	759.97	159.21	103.0	40.0	47.0	0.85
305	1000	14.17	733.04	153.57	98.2	39.4	—	—
610	2000	13.66	706.63	148.04	93.8	39.0	—	—
914	3000	13.17	681.23	142.72	89.5	38.4	—	—
1219	4000	12.69	656.34	137.50	85.1	38.0	—	—
1524	5000	12.23	632.46	132.50	81.0	37.4	47.0	0.87
1829	6000	11.77	609.09	127.60	76.8	37.0	—	—
2134	7000	11.34	586.49	122.87	72.8	36.4	—	—
2438	8000	10.91	564.64	118.29	68.9	36.0	—	—
2743	9000	10.50	543.31	113.82	65.0	35.4	—	—
3048	10,000	10.10	522.73	109.51	61.2	35.0	47.0	0.90
3353	11,000	9.72	502.92	105.36	57.8	34.4	—	—
3658	12,000	9.34	483.36	101.26	54.3	33.8	—	—
3962	13,000	8.99	464.82	97.38	51.0	33.2	—	—
4267	14,000	8.63	446.53	93.55	47.9	32.6	—	—
4572	15,000	8.29	429.01	89.88	45.0	32.0	47.0	0.95
4877	16,000	7.96	411.99	86.31	42.0	31.4	—	—
5182	17,000	7.65	395.73	84.50	40.0	31.0	—	—
5486	18,000	7.34	379.73	79.55	37.8	30.4	—	—
5791	19,000	7.05	364.49	76.36	35.9	30.0	—	—
6096	20,000	6.76	349.50	73.22	34.3	29.4	47.0	1.00
6401	21,000	6.48	335.28	70.24	33.5	29.0	—	—
6706	22,000	6.21	321.31	67.31	32.8	28.4	47.0	1.05
7010	23,000	5.95	307.85	64.49	32.0	28.0	—	—
7315	24,000	5.70	294.89	61.78	31.2	27.4	—	—
7620	25,000	5.46	282.45	59.17	30.4	27.0	47.0	—
				Breathing 100% Oxygen*				
10,058	33,000	3.81	197.10	197.10	109	40	47.0	—
10,973	36,000	3.30	170.94	170.94	85	38	47.0	—
11,887	39,000	2.86	148.08	148.08	64	36	47.0	—
12,192	40,000	2.73	141.22	141.22	—	—	—	—
12,802	42,000	2.48	128.27	128.27	48	33	47.0	—
13,716	45,000	2.15	111.25	111.25	34	30	47.0	—
14,021	46,000	2.05	105.92	105.92	30	29	47.0	—

* Data from Holmstrom FMG. Hypoxia. *In* Aerospace Medicine. Edited by Randall HW. Baltimore: Williams & Wilkins, 1971.[6]

Notice that to achieve a normoxic P_AO_2 of about 103 mmHg, a person can breathe 100% O_2 at 10,058 m (33,000 ft). However, the ambient ppO_2 must be about 200 mmHg compared to 160 mmHg at sea level to achieve this equivalency. This is due to the greater contribution of water vapor pressure toward total pressure as pressure is reduced. The P_IO_2 defined as $(P_B - 47) * F_IO_2$ is 150 mmHg in the first case and 149 mmHg for the second case. So to use this table to determine the EAA you must first compute P_IO_2 for the breathing gas where $F_IO_2 \neq 0.209$, and then find the P_IO_2 that corresponds to your computed value. Unfortunately, the table above does not show P_IO_2, only ppO_2. So, you must compute several P_IO_2s from the P_Bs and the F_IO_2 of 0.209 until you find the P_IO_2 that matches your P_IO_2. For example, the P_IO_2 for breathing 32% O_2 at 413 mmHg (about 16,000 ft altitude) is $(413 - 47) * 0.32 = 117$ mmHg. Through trial and error you find that the entry for an EAA of 6,000 ft gives a P_IO_2 of 118 mmHg [$(609 - 47) * 0.209 = 118$ mmHg], so you conclude that breathing 32% O_2 at 16,000 ft altitude is equivalent to breathing air at 6,000 ft altitude.

Since the AOE accounts for water vapor pressure, you can also use this equation to compute P_AO_2 and find the corresponding P_AO_2 in the above table to determine the Equivalent Air Altitude. Using the same example, the Alveolar Oxygen Equation computes a P_AO_2 of 77 mmHg given the P_ACO_2 of 37 mmHg, the RER of 0.88, the P_B of 413 mmHg, and the F_IO_2 of 0.32. The P_AO_2 of 77 mmHg is compared to the 77 mmHg seen in the table, so you once again conclude that breathing 32% O_2 at 16,000 ft altitude is equivalent to breathing air at 6,000 ft altitude.

A final caveat. A large portion of this report evaluates results from tests where P_IO_2 or *computed* hypoxic P_AO_2 were very similar between 2 tests with different P_Bs. Two assumptions are that identical hypoxic P_IO_2 or P_AO_2, computed between 2 different tests, results in an equivalent hypoxic response, and that computed P_AO_2 is the correct P_AO_2 experienced by the subjects. So, if an equivalent hypoxic response is not observed, and we accept the 2 assumptions, it follows that the differences in hypoxic response must be linked to something in addition to a reduced P_AO_2. But, Rahn (1954, 1956) shows us that P_AO_2 is extremely dynamic, even when people change posture, certainly when they go to altitude, when they change the composition of the breathing gas, if they exercise, if they stay for short or long periods at altitude, etc. And then, there is individual variability in how the CNS in conjunction with the respiratory system reacts to mild hypoxia, both during an acute and chronic exposure. So, the caveat is to consider computed P_AO_2 as a "best estimate" not as an absolute. Always consider the possibility that there is a true difference in P_AO_2 in 2 experiments that purport to be equivalent hypoxic exposures when identical P_IO_2 or computed P_AO_2 are offered as evidence of their equivalency.

REPORT DOCUMENTATION PAGE	Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave Blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 2008	NASA Technical Paper

4. TITLE AND SUBTITLE
Risk Assessment of Acute Mountain Sickness in the Crew Exploration Vehicles

5. FUNDING NUMBERS

6. AUTHOR(S)
Johnny Conkin, Universities Space Research Association

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Lyndon B. Johnson Space Center
Houston, Texas 77058

8. PERFORMING ORGANIZATION REPORT NUMBERS
S-1009

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
National Aeronautics and Space Administration
Washington, DC 20546-0001

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
TP-2008-214759

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Unclassified/Unlimited
Available from the NASA Center for AeroSpace Information (CASI)
7121 Standard
Hanover, MD 21076-1320 Category: 52

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

To limit the risk of fire and reduce the risk of decompression sickness and prebreathe time to support frequent activities on the moon and Mars, a hypobaric and mildly hypoxic living environment is considered for the Crew Exploration Vehicle, Lunar Surface Access Module, and long-term surface habitats. Superimposed on physiological adjustments to living in a hypobaric hypoxia (HH) environment are those associated with adaptation to microgravity (μG). Outward manifestations of physiological adaptations may present as signs and symptoms of Acute Mountain Sickness (AMS). The signs and symptoms of AMS are undesirable, as they would impact crew health and performance. A literature review suggests that: (1) there is an absolute pressure effect per se on AMS, so the higher the altitude for a given computed hypoxic alveolar oxygen (O2) partial pressure (PAO2) the greater the AMS response; (2) about 25% of adults would experience AMS near 2,000 m altitude; (3) there is no direct evidence that HH synergizes with adaptive changes during simulated μG to dramatically increase hematocrit and blood viscosity, and (4) only susceptible astronauts would develop mild and transient AMS with exposure to 8.0 psia (16,000 ft) while breathing 32% O2 and simultaneously adapting to μG.

14. SUBJECT TERMS	15. NUMBER OF PAGES	16. PRICE CODE
decompression sickness, extravehicular activity, Crew Exploration Vehicle; Lunar Surface Access Module; long-term surface habitats; microgravity, impacts of	114	

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unlimited	Unlimited