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Allowable Exposure Limits for Carbon Dioxide During Extravehicular Activity

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Table of Contents

Nomenclature

α	solubility coefficient
atm	atmospheres
CBF	cerebral blood flow
Cl	chloride
CO_2	carbon dioxide
CSF	cerebrospinal fluid
ECG	electrocardiogram
EEG	electroencephalogram
EST	electroshock therapy
EVA	extravehicular activity
GI	gastrointestinal
GU	genitourinary
H^+	hydrogen ion
HCO_3^-	bicarbonate
H_2CO_3	carbonic acid
H_2O	water
K	potassium
kcal/hr	kilocalories per hour
LiOH	lithium hydroxide
L/min	liters per minute
MBF	myocardial blood flow
meq/L	milliequivalents per liter
min	minute
ml	milliliter
ml/min	milliliters per minute
mmHg	millimeters mercury
N_2	nitrogen
Na	sodium
NMR	nuclear magnetic resonance
O_2	oxygen
P_{CO_2}	partial pressure of carbon dioxide
pH	$-\log[H^+]$
pK	dissociation constant
psi	pounds per square inch
psia	pounds per square inch absolute
PTH	parathyroid hormone
RMV	respiratory minute volume
V/Q	ventilation/perfusion ratio

Summary

The intent of this paper was to review the research pertaining to human exposure to carbon dioxide (CO_2) and to recommend allowable exposure limits for extravehicular activity (EVA). Respiratory, renal, and gastrointestinal systems may be adversely affected by chronic low dose CO_2 exposure. Ventilation was increased 15% with 1% CO_2 and 50% with 2% CO_2. Chronic exposure to <2% CO_2 led to 20 day cycles of uncompensated and compensated respiratory acidosis. Acid-base changes were small. Histopathologic changes in guinea pig lungs have been noted with long term exposure to 1% CO_2. No changes were seen with exposure to 0.5% CO_2. Cycling of bone calcium stores with associated changes in blood and urinary calcium levels occurs with long term CO_2 exposure. Histologic changes in bone have been noted in guinea pigs exposed to1% CO_2. Renal calcification has been noted in guinea pigs with exposure to as low as 0.5% CO_2. An increase in gastric acidity was noted in subjects with long term exposure to 1% CO_2. Cardiovascular and neurologic function were largely unaffected. A decrease in the incidence of respiratory, renal, and gastrointestinal disease was noted in submariners coincident with a decrease in ambient CO_2 from 1.2% to 0.8-0.9%. Oxygen (O_2) and CO_2 stimulate respiration independently and cumulatively. The addition of CO_2 to high dose O_2 led to the faster onset of seizure activity in mice. Experiments evaluating the physiologic responses to intermittent, repetitive exposures to low dose CO_2 and 100% O_2 mixtures should be performed. A reduction in the current NASA standard for CO_2 exposure during EVA of 1% (7.6 mmHg) for nominal and 2% (15.2 mmHg) for heavy exertion to 0.5% (3.8 mmHg) for nominal and 1% (7.6 mmHg) for heavy exertion may be prudent. At a minimum, the current NASA standard should not be liberalized.

Introduction

Purpose

The intent of this paper is to review the research pertaining to human exposure to carbon dioxide and to recommend allowable exposure limits for extravehicular activity (EVA). Carbon dioxide (CO_2) accumulation within a space suit during EVA must be controlled in order to avoid harm to the astronaut. Carbon dioxide is a natural byproduct of human metabolism and an important mediator of physiologic performance. The total elimination of CO_2 from the space suit is unnecessary, however, from a physiologic viewpoint. Humans can breathe small quantities of CO_2 for prolonged periods without any apparent long term ill effects. The allowable limit of residual CO_2 accumulation in the space suit is a matter of debate.

The environment within the space suit is defined by the interaction between the astronaut and the life support system. Current NASA standards allow for residual CO_2 levels in the space suit of 7.6 mmHg under nominal operation and 15.2 mmHg for periods of heavy exertion. Currently, CO_2 is removed from the suit with a lithium hydroxide (LiOH) absorbent. Relaxation of the current CO_2 standard may lead to a decrease in the quantity of absorbent required and a subsequent weight savings. For long duration space ventures requiring numerous EVAs, such a weight savings may be significant. Relaxation of CO_2 limits may also allow the consideration of technologies which are superior to LiOH absorbents but which cannot achieve the current CO_2 standard.

The effect of carbon dioxide on the body is protean. The maintenance of CO_2 within a specific range is important to maintain proper physiologic function. Carbon dioxide levels that are either too high or too low are of equal concern. The human body is capable of compensating for wide variations in CO_2, however, compensation is time dependent and not complete. Each organ system is effected differently by variations in CO_2. An understanding of each organ system and its inherent response to altered CO_2 levels is necessary in order to recommend exposure limits.

This paper will address the effects of high levels of CO_2 on physiologic performance of the various organ systems of the body. Attention will be paid to the specific level of CO_2 which causes physiologic decrement in each organ system. The highest level of CO_2 which does not adversely impair the function of individual organ systems will be noted when possible.

Since the experiments which will be discussed were conducted in a terrestrial environment, the application of these results to a space suit/EVA environment will be discussed. Recommendations as to allowable CO_2 exposures for portable life support will be made.

Extravehicular Activity Considerations

An awareness of the extravehicular and terrestrial environments is important when addressing CO_2 exposure limits. Terrestrial exposure to CO_2 is minimal. Total atmospheric pressure at sea level is 760 mmHg (14.7 psi). Carbon dioxide exposures have traditionally been represented as a percent of sea level atmospheric pressure. Each 1% CO_2, therefore, represents an increment of 7.6 mmHg. Ambient CO_2 comprises only 0.03% (0.228 mmHg) of atmospheric gases. Exposure to 1%

CO_2 during EVA represents 7.6 mmHg CO_2 which is well above terrestrial norms.

It is important to note that the absorption of a particular gas by the body is dependent on the partial pressure of that gas only (ref. 1). Neither the presence of other gases nor the total pressure of the system has any influence on the absorption of a particular gas. Absorption of CO_2 in the body is dependent on the partial pressure of CO_2 only (P_{CO_2}). Therefore, the operating pressure of the suit will not affect the CO_2 absorption by the body.

Current NASA plans call for operating the space suit at a total pressure of 4.3 psia (222 mmHg) or greater. The breathing gas during EVA is currently 100% oxygen (O_2). Ambient oxygen comprises 20.9% (159 mmHg) of atmospheric gases. Breathing 100% oxygen at greater than or equal to 4.3 psi will expose the individual to a high oxygen (hyperoxic) environment.

Since astronauts will be breathing gas mixtures that have O_2 and CO_2 concentrations above terrestrial norms, this produces a concurrent hyperoxic and hypercarbic (high CO_2) EVA environment. Both O_2 and CO_2 are physiologically active. The individual and interactive effects of each gas on the body are important in establishing exposure limits. The interaction of these two gases at supranormal concentrations may limit the total allowable concentration of each gas.

Currently, EVAs are planned for maximum 8 h durations. The total number of EVAs may prove to be considerable (ref. 2). It is possible that EVAs will need to be performed on a daily basis. The response of the human body to repetitive, 8 h exposures to high CO_2 levels needs to be addressed.

Carbon Dioxide

Carbon dioxide is a natural byproduct of cellular combustion and serves to control the acid-base status of the body. Within a space suit, CO_2 would accumulate to harmful levels quickly. An appreciation of the physiologic significance of CO_2 is required in order to set exposure limits.

Changes in CO_2 concentration directly influence the acid-base status by a mechanism which will be discussed shortly. An excessive accumulation or elimination of CO_2 is physiologically detrimental, largely due to the resultant change in acidity. In order to control acidity, an elaborate control mechanism for CO_2 has developed in the body.

Acute and chronic changes in CO_2 are compensated for in different fashions. An acute accumulation of CO_2 is primarily controlled by an increase in the rate and depth of respiration. The onset of the respiratory response is measured in seconds and can persist indefinitely. With chronic changes in CO_2 levels, the kidneys provide additional compensation. The onset of renal responses is measured in hours and can also persist indefinitely.

The degree of respiratory and renal compensation is limited. In fact, acute and chronic acid-base changes are rarely fully corrected. Once the initial cause of the change in the CO_2 concentration is corrected, respiratory and renal compensation returns to normal.

Given that EVAs may be as long as 8 h in length and perhaps performed daily, the question arises as to whether all the accumulated CO_2 will be vented between excursions. If breathing air for 16 h is not sufficient to eliminate 8 h of accumulated CO_2, repetitive EVAs may lead to the establishment of chronic compensatory mechanisms. If accumulated CO_2 is vented in a shorter period of time, repetitive acute compensatory changes are likely to predominate.

Carbon dioxide also directly influences the function of the body. Carbon dioxide has depressant properties and can act similar to an anesthetic agent. Each organ system possesses a different response to the direct and indirect effects of CO_2. These responses will be discussed within the context of each organ system.

Acid-Base Chemistry

A review of acid-base chemistry reveals the significant role of CO_2 in maintaining acidity (ref. 3). Acidity is defined as the negative logarithm of the concentration of hydrogen ions:

$$pH = -\log\left[H^+\right]$$

Acidity must be maintained within a narrow range to ensure optimum physiologic performance. Enzymes are particularly sensitive to changes in acid-base status. Acid-base derangements can severely limit biologic performance and may even cause death.

In order to avoid wide fluctuations in acidity, the human body has developed a buffered acid-base system. Buffered acid-base systems can withstand large fluctuations of acid or base with only minimal changes in pH. The main acid-base buffer pair in the body involves carbonic acid, H_2CO_3, and bicarbonate, HCO_3^-:

$$[H^+] + \left[HCO_3^-\right] \underset{k_2}{\overset{k_1}{\leftrightarrow}} [H_2CO_3] \leftrightarrow [CO_2] + [H_2O]$$

The constants k_1 and k_2 represent the dissociation rates of the above chemical reaction in each direction. Based on

the mass action principle, Henderson presented a mathematical formulation of the above equation:

$$[H^+] = K[H_2CO_3]/[HCO_3^-], \text{ where } K = k_1 / k_2$$

Hasselbach reported the transformation of the above equation into negative logarithmic form as:

$$pH = pK + \log[HCO_3^-]/[H_2CO_3]$$

The dissociation constant for HCO_3^- / H_2CO_3 is denoted by pK. H_2CO_3 rapidly dissociates into CO_2 and water (H_2O) so that the concentration of H_2CO_3 is related to P_{CO_2} by a solubility coefficient, α. Since HCO_3^- and CO_2 comprise the main physiologic acid-base pair, the overall pH of the human body can be approximated by the modified Henderson-Hasselbach equation as:

$$pH = pK' + \log[HCO_3^-]/\alpha P_{CO_2}$$

The modified Henderson-Hasselbach equation displays the relationship between CO_2 and pH. In plasma at 37°C, the pK' of the HCO_3^- / CO_2 system is 6.1 and α is 0.03. Normal values in the arterial blood are a P_{CO_2} of 40 mmHg, a $[HCO_3^-]$ of 25 mmole/L, and a pH of 7.40.

The pH of the human body is normally maintained between 7.35 and 7.45. The acidity level or acidity is a continuum with humans being able to withstand deviations from this range for short periods of time. An elevation in H^+ or CO_2 is called acidosis and is reflected by a decrease in pH. A decrease in H^+ or CO_2 is called alkalosis and is noted by a rise in pH. Humans can generally withstand a lower pH better than higher pH values. Physiologic decrement is considered likely at pH values <7.20 and >7.50.

It should be noted that many other acid-base pairs are important in the maintenance of pH. The effect of all the acid-base pairs is cumulative so that pH changes can occur without an initial change in CO_2 or HCO_3^-. The majority of the compensation for the underlying change in pH is made via protein binding of H^+ and alterations in CO_2 and HCO_3^-.

Acute elevations in CO_2 are initially compensated for by an increase in pulmonary function. An increase in the rate and depth of ventilation leads to an increase in the elimination of CO_2 directly. Chronic elevations in CO_2 are additionally compensated by the retention of HCO_3^- by the kidneys. Both mechanisms aid in regulating the acid-base status. The time course and capacity of compensation differs for both systems.

Normal Respiratory Parameters

Since the elimination of CO_2 is so intimately tied to the function of the respiratory system, a review of respiratory physiology is appropriate. The lung is composed of millions of tiny air sacs called alveoli. The alveoli are very thin thereby allowing ready gas transport between air and blood.

Air is a mixture primarily composed of 21% oxygen (O_2) and 78% nitrogen (N_2). Carbon dioxide makes up only 0.03% of air. At sea level pressure of 760 mmHg, air contains 158 mmHg of O_2, 597 mmHg of N_2, 6 mmHg of H_2O vapor, and essentially no CO_2.

As air is inhaled into the lung, it mixes with exhaled gases to produce a slightly different mixture of gases (ref. 4) (fig. 1). In the gas exchange between alveoli and blood only P_{H_2O} and P_{N_2} fail to undergo substantial change. Even during air breathing at sea level, a prominent fall in P_{O_2} occurs during the passage of blood through the tissue capillaries, resulting in a reduction of total gas tension

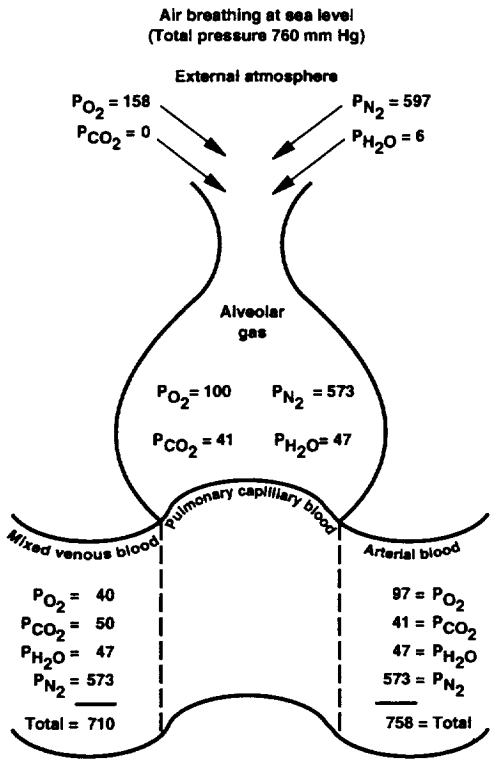


Figure 1. Breathing air at sea level. The partial pressures of each of the major gaseous constituents of the normal external atmosphere are shown as different from the tensions of the same gases in the pulmonary alveoli (from Lambertsen (ref. 4)).

below atmospheric pressure. Inhaled air is humidified in transit to produce a water vapor pressure of 47 mmHg. Carbon dioxide is released raising the alveolar pressure of CO_2 to 41 mmHg. The partial pressure of oxygen is reduced to 100 mmHg and the partial pressure of nitrogen is reduced to 573 mmHg. Total pressure in the alveolus remains at 760 mmHg.

The gas composition of blood exiting the lungs is essentially identical to that of alveolar gas. The blood returns to the heart where it is then pumped into the arterial system for delivery to the tissues of the body.

Within the tissue capillary, oxygen diffuses into the cell as CO_2 diffuses into the blood. Venous blood returning to the lung has a P_{O_2} of 40 mmHg and a P_{CO_2} of 50 mmHg. Within the lung, CO_2 diffuses into the alveolus and oxygen diffuses into the blood, thereby repeating the cycle of gas transport.

The function of the lung can be evaluated by measuring volume flow of gas (ref. 1) (fig. 2). The tidal volume, the amount of gas inhaled with each breath, averages about 500 ml per breath. The respiratory rate, the number of breaths per minute, averages 15 breaths per minute. The respiratory minute volume is the total amount of air ventilated in 1 min and equals the tidal volume multiplied by the respiratory rate. Respiratory minute volume averages 7.5 L/min at rest.

Respiratory

Acute Exposures to CO_2

Ventilation– Respiratory stimulation is noted with acute exposure to elevated CO_2. Respiratory minute volume (RMV) increases steadily with increased concentrations of CO_2 (ref. 5) (fig. 3). RMV increases gradually with CO_2 below 2%, but rises more sharply thereafter (ref. 6). A curvilinear relationship appears to apply with exposures below 5% CO_2. Above 5% CO_2, RMV increases in a more linear fashion (ref. 7). A plateau effect is noted above 10% CO_2 as respiratory responses become taxed. At 25% CO_2, RMV is pushed to its physiologic limit and further increases in CO_2 do not elicit an additional increase in RMV (ref. 5).

Resting RMV is about 7.5 L/min. At 1% CO_2, RMV is increased 15% to 8.5 L/min (ref. 7). Conscious awareness of increased respiration begins at 2% CO_2 as RMV rises 50% to 11 L/min. At 3% CO_2, RMV is doubled and the onset of uncomfortable breathing (dyspnea) is noted. Above 5% CO_2, RMV continues to rise and individuals become increasingly symptomatic.

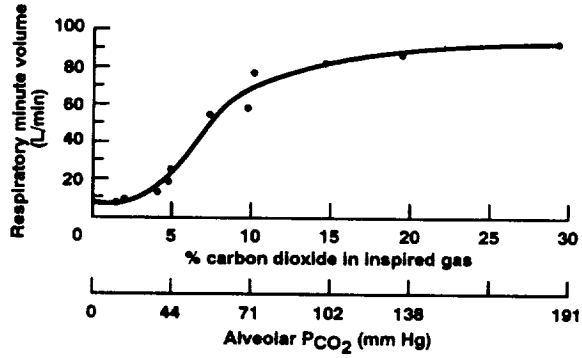


Figure 3. Relationships between respiratory minute volume and inspired CO_2 concentration in man. Points indicate averages of peak values. Solid circles indicate measurements in normal men; open circles are measurements in psychoneurotic patients (from Lambertsen (ref. 5)).

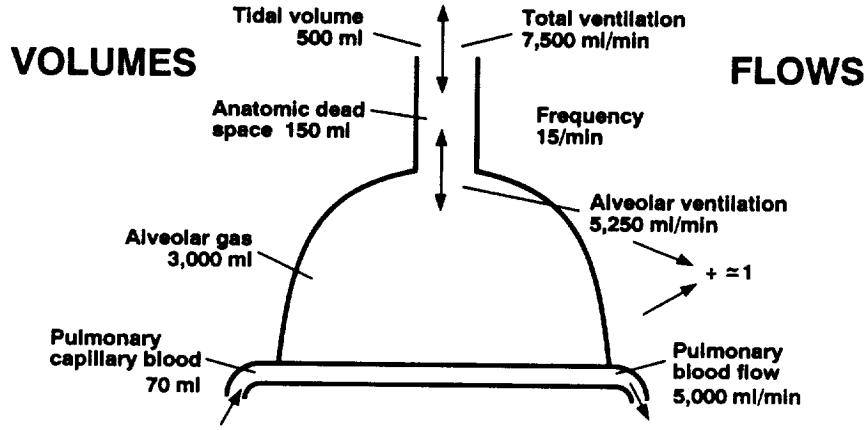


Figure 2. Diagram of a lung showing typical volumes and flows. There is considerable variation around these values. Modified from JB West: Ventilation/Blood Flow and Gas Exchange. Oxford, Blackwell, 1977, p. 3 (from West (ref. 1)).

The increase in RMV below 3% CO_2 is primarily due to an increase in tidal volume. At 2% CO_2, tidal volume increases approximately 50%, comprising the total rise in RMV (ref. 8). Inspiratory time increases slightly and expiratory time decreases slightly so that respiratory rate is unchanged. Above 3% CO_2, a rise in both tidal volume and respiratory rate are noted (ref. 9).

With acute exposure to CO_2 below 5%, respiratory responses stabilize within 15 min (ref. 9). Higher concentrations of CO_2 require longer time periods for stabilization.

The nature of the respiratory response with CO_2 levels below 2% has been the subject of some debate (ref. 10). Several studies have reported a linear relationship (ref. 11) whereas others note a more curvilinear response (ref. 12). Natural respiratory variation complicates the measurement of small changes in RMV (ref. 13). For purposes of this study, the true nature of the respiratory response is not as important as the degree of respiratory stimulation itself.

In spite of increased ventilation, arterial P_{CO_2} (Pa_{CO_2}) rises. The rise in arterial P_{CO_2} indicates that respiratory responses are insufficient to eliminate the additional CO_2. As arterial P_{CO_2} rises, carbon dioxide begins to accumulate in the body above normal levels.

Arterial P_{CO_2} rises steadily with increased CO_2 exposure in a curvilinear fashion (ref. 14) (fig. 4). Arterial P_{CO_2} rises even with CO_2 exposures of 1% (ref. 15). Whether increased RMV is sufficient to keep arterial P_{CO_2} at normal levels even with very small increases in CO_2 is a matter of debate.

The stimulus for the increase in respiration with CO_2 exposure is also open to debate (refs. 11 and 16). Whether it is CO_2 itself or the subsequent acid-base changes caused by CO_2 that stimulate the respiratory center is undetermined. For the purposes of this paper, the underlying mechanism of the respiratory response is not as important as the degree of the response itself.

The function of the diaphragm is adversely affected by CO_2 exposure (ref. 17). Contractility and the time to onset of fatigue were reduced by CO_2 exposure (refs. 18 and 19). The influence of such an effect on ventilatory function is undetermined.

Acid-base changes– Initial exposure to elevated CO_2 leads to the development of an acute respiratory acidosis. As CO_2 levels rise in the body, pH falls. As the diaphragm attempts to return the pH to normal, increased ventilation ensues. As CO_2 is eliminated, the pH begins to return toward normal. Since the primary cause of the

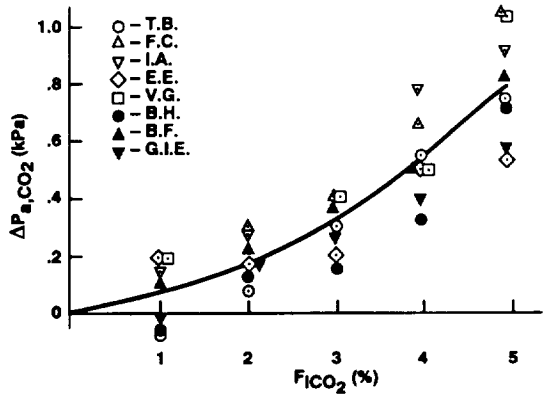


Figure 4. The change in arterial P_{CO_2} ($\Delta P_{a,CO_2}$) at five different levels of inspired CO_2 (F_{i,CO_2}) in eight healthy subjects. Each subject is designated with one symbol. The curve is of the form $(aF_{i,CO_2} + b(F_{i,CO_2})^2)$. H_j, where a and b are common to all individuals, while H_j is a scaling factor which is allowed to differ between individuals (set to 1.0 for FC). Least square fitting gave a = 0.0364 and b = 0.0337, demonstrating clear non-linearity. The value of H_j is 0.740, the average of the values for all individuals (from Ellingsen (ref. 14)).

acidosis is a change in the respiratory state, a respiratory acidosis is said to occur. Both acute and chronic states are possible; however, the current discussion will be limited to the state of acute respiratory acidosis.

Acid-base changes with increased CO_2 are seen quickly. Exposure to 1-2% CO_2 for only 6 min led to a decrease in pH (ref. 15). Progressive exposure to increasing levels of CO_2 (PI_{CO_2}) in 30-min increments showed a steady decrease in pH (ref. 12) (fig. 5). During the fifth minute at PI_{CO_2} of 42 Torr, Pa_{CO_2} was lower and PH was higher ($P < 0.05$) than during the remainder of the period. During the fourth control period, pH and HCO_3^- gradually increased by 0.015 and 1 meq/L, respectively. There were no systematic variations in any variables during any of the other 0.5-h intervals. This protocol did not reveal a consistent difference in Pa_{CO_2} between room air breathing ($PI_{CO_2} < 0.4$ Torr) and inhalation of gas mixtures with a PI_{CO_2} of 7 and 14 Torr. Generally, acute CO_2 exposures less than 3% produced pH changes less than 0.05 below the norm of 7.40 (refs. 12 and 6). Acute exposures above 5% CO_2 led to pH decreases of greater than 0.07 (ref. 20). Within 20 min of exposure, pH had equilibrated at a new but lower steady state. Resumption of normal acidity occurred quickly on return to ambient conditions.

Several sources have reported linear relationships between P_{CO_2} and pH (refs. 20 and 11). Others have reported sharp increases in pH with P_{CO_2} above 2.2% (ref. 6).

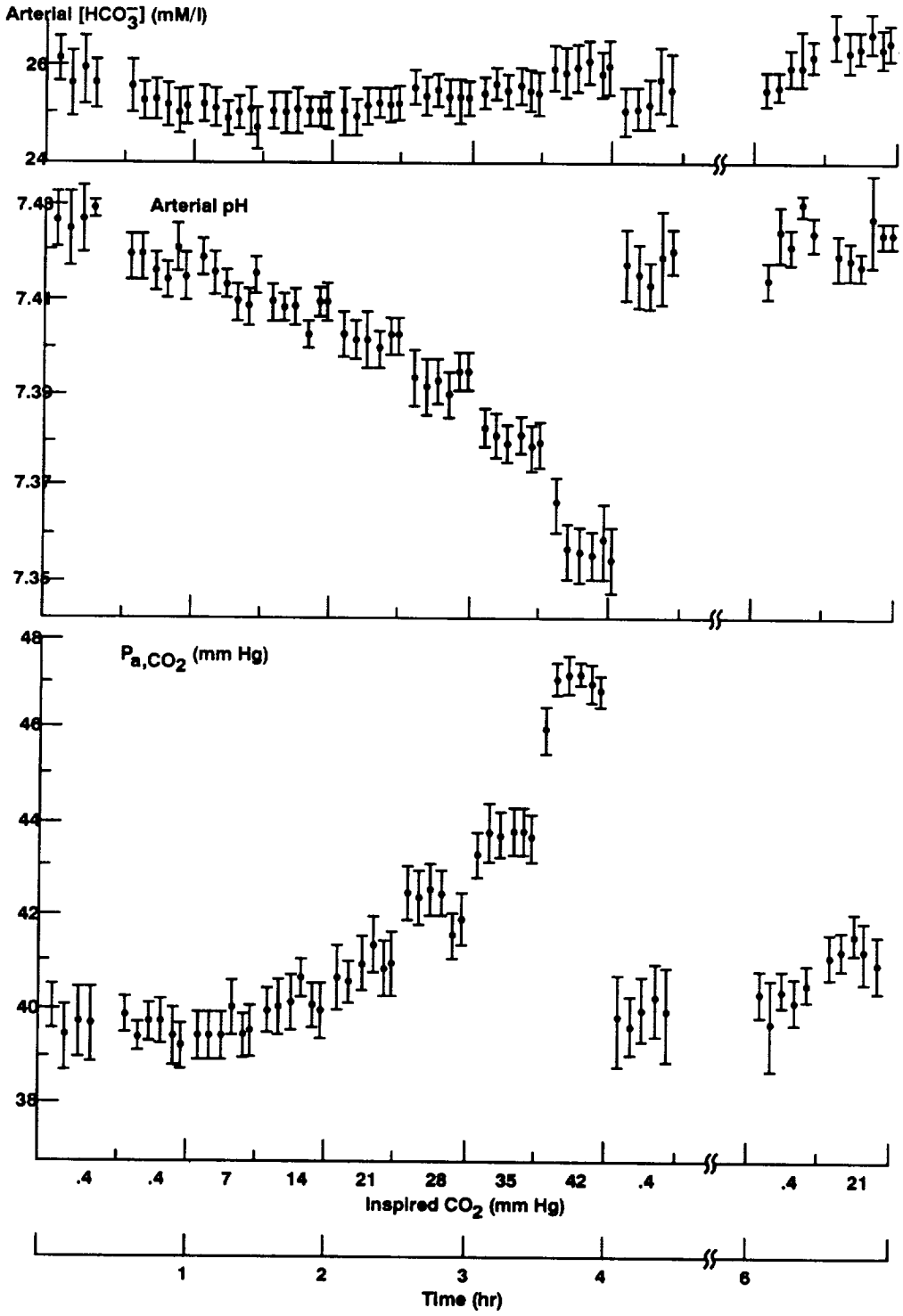


Figure 5. Mean (±SE) arterial P_{CO_2}, pH, and HCO_3^- of 10 subjects over 7 h during which chamber P_{O_2} was 147 Torr, while chamber P_{CO_2} was altered as indicated (study 2) (from Forster (ref. 12)).

Significance bands relating P_{CO_2} to pH have been established (ref. 20). The predictive nature of significance bands is limited by individual variation; however, pH changes are not extreme with CO_2 exposures under 3%.

The responses of various body fluids to pH changes from elevated CO_2 are similar in magnitude (refs. 11 and 6). It is postulated that the acidity of the cerebral spinal fluid (CSF) surrounding the brainstem determines respiratory responses. Although CSF pH has a lower resting value than arterial blood, the responses of both fluids to pH change is similar. Due to the similarity of response, the measurement of central respiratory change to pH is reflected by the acid-base status of arterial blood.

Although pH changes are not great with low dose acute CO_2 exposure, preexistent acid-base disturbances limit the systems' ability to compensate for additional changes in acidity. Exercise is characterized by the accumulation of metabolic acids. An increase in metabolic acids in concert with acute respiratory acidosis may create pH changes of physiologic significance (ref. 21). The issue of exercise will be discussed later in this paper.

Symptoms– A variety of symptoms occur from exposure to CO_2 (refs. 22 and 23) (fig. 6). Symptoms related to the respiratory tract are the first to appear and continue throughout exposure to both high and low dose CO_2.

Acute exposures to CO_2 of less than 2% produce few symptoms. Dyspnea on exertion and conscious awareness of increased respiration begins near 2% CO_2. The onset of dyspnea at rest is noted with breathing 3% CO_2. After termination of exposure to 3% CO_2, respiratory symptoms quickly abate but headaches occasionally occur.

Inhalation of 4-5% CO_2 for 30 min causes dyspnea, sweating, dizziness, and headaches. Breathing 6% CO_2 for 15 min led to dyspnea in all 21 subjects studied (ref. 24). Headaches, sweating, and speech difficulties were also prevalent. Exposure to 7-11% CO_2 led to marked symptomology within minutes (ref. 7). Further increases in CO_2 lead to convulsions and loss of consciousness in minutes.

Variability– The respiratory response to increased CO_2 displays marked individual variability (refs. 25, 11, 5, and 26). Subjects exposed to varying concentrations of CO_2 can be grouped according to their respiratory response (ref. 11) (fig. 7). In the course of this appraisal, it became apparent that the total subject population could be grouped such that at least four statistically different patterns of respiratory response appeared. A somewhat arbitrary designation is to group individuals into high and low ventilation groups. Individuals in the low ventilation group have a lower resting RMV and a higher arterial P_{CO_2}. These individuals may have an inherently decreased sensitivity to CO_2. Individuals in the high ventilation group have a higher resting RMV and a lower arterial P_{CO_2}.

On exposure to elevated CO_2, individuals in the high ventilation group display a greater degree of respiratory stimulation and experience more symptomology than do individuals in the low ventilation group. The inherent difference in sensitivity to CO_2 may account for these observations (ref. 27).

Exposure to low levels of CO_2 tends to exaggerate the differences between the ventilation groups. A progressive rise in CO_2 tends to diminish the difference so that at 7.5% CO_2, no difference is noted (ref. 26). It is likely that

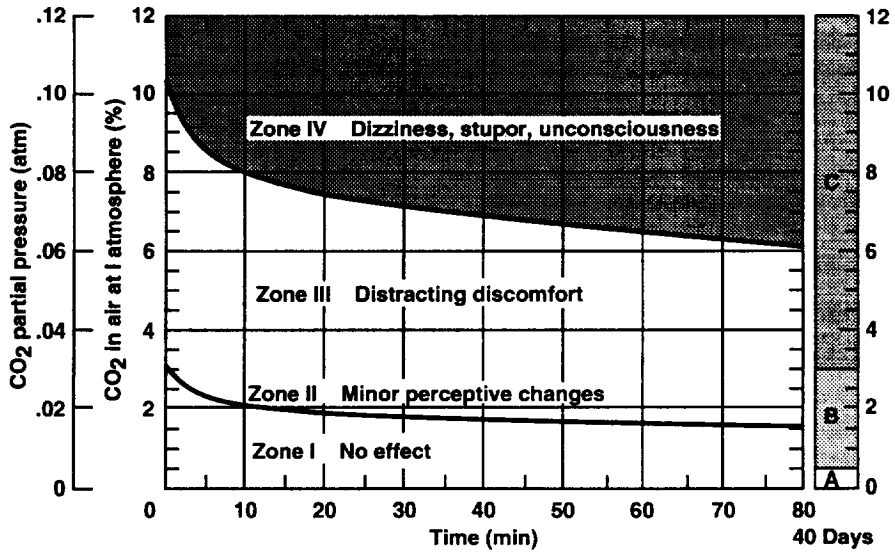


Figure 6. Relation of physiological effects to carbon dioxide concentration and exposure period *(from U. S. Navy Diving Gas Manual (ref. 23)).*

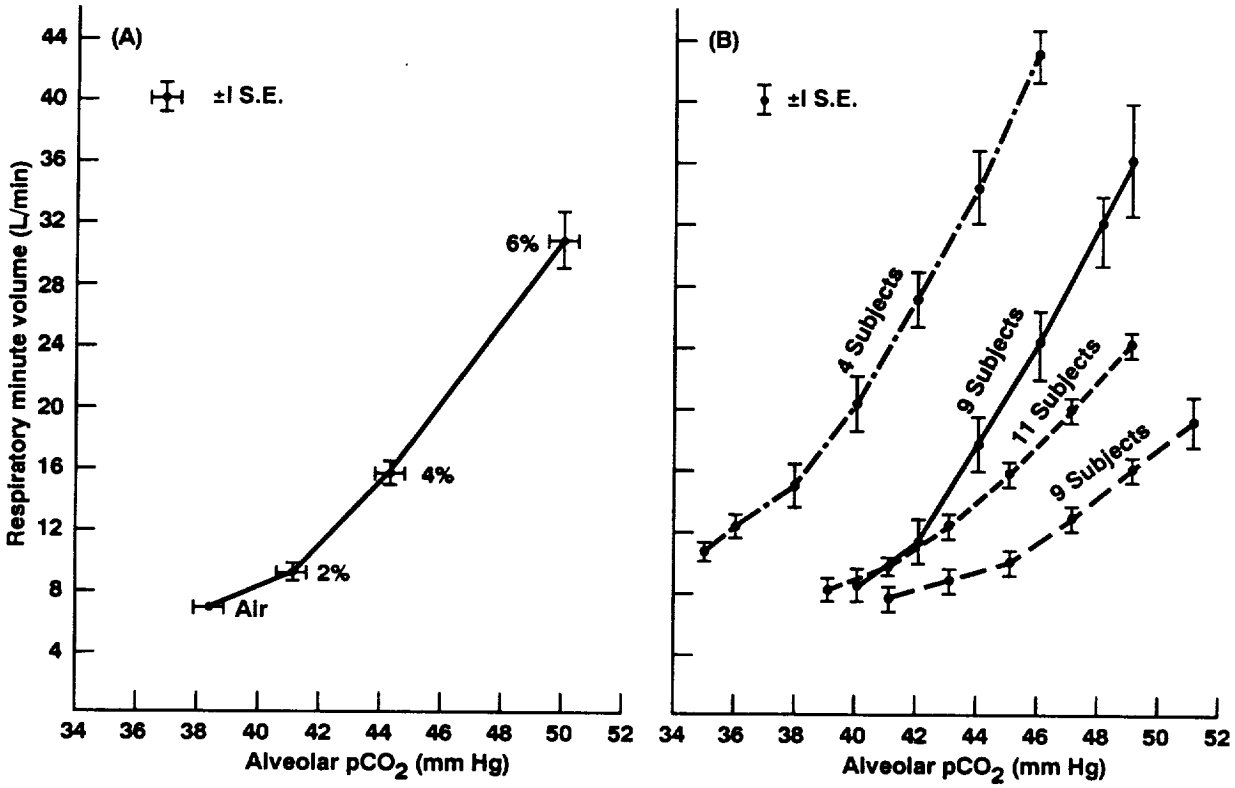


Figure 7. Variability of the respiratory response of normal subjects to low concentrations of inspired carbon dioxide. In A, the responses to approximately 2, 4, and 6% CO_2 in 21% O_2 in N_2 are averaged. For B, the individual CO_2 "Response" curves were appraised to obtain interpolated values of respiratory minute volume at selected levels of P_{CO_2} (from Lambertsen (ref. 11)).

the intense respiratory stimulation noted at such an elevation of CO_2 overpowers any effect of resting sensitivity.

Individuals tend to remain within their respective ventilation group over time (ref. 25). Those individuals who have displayed a marked sensitivity to CO_2 in the past are likely to do so again on repeated exposure. Women and the elderly are also less tolerant of the effects of CO_2. Whether such information can be used as a screening tool to determine which individuals may be better suited to work in a hypercarbic environment remains to be determined.

Chronic Exposures to CO_2

Introduction– The differentiation between acute and chronic CO_2 exposure is somewhat arbitrary. Generally, with acute elevations in CO_2, the respiratory system predominates in limiting adverse effects to the exposure. With chronic CO_2 exposures, other systems contribute to this process.

The renal system is of importance in compensating for the effects of inhaling high CO_2 concentrations for long periods of time. Generally, the onset of a renal response is not noted until after 12-24 h of exposure. Acid-base disorders of respiratory origin are considered chronic when renal compensation begins. However, as will be discussed later in this paper, renal responses are not elicited with long term CO_2 exposures of low concentration. Even without a renal response, other biologic systems are active in limiting the effects of CO_2. Since biologic responses outside the respiratory tract contribute to compensating for the effects of CO_2, any exposure greater than 24 h in duration will be considered to be chronic in nature.

The time course and degree of adaptation to CO_2 exposure is dependent on the concentration of CO_2 (ref. 28) (fig. 8). The discussion of chronicity is not appropriate with 6-10% CO_2 since exposure is time limited by symptoms. Exposures to CO_2 of 3-5% have occurred for days and even weeks. Renal responses are elicited and adaptation occurs within days. Exposure to CO_2 below 3% does not elicit an immediate renal response. In fact, cycling of respiratory and renal responses occurs over a protracted period of time. The nature of the renal response to low dose CO_2 will be discussed later in this paper.

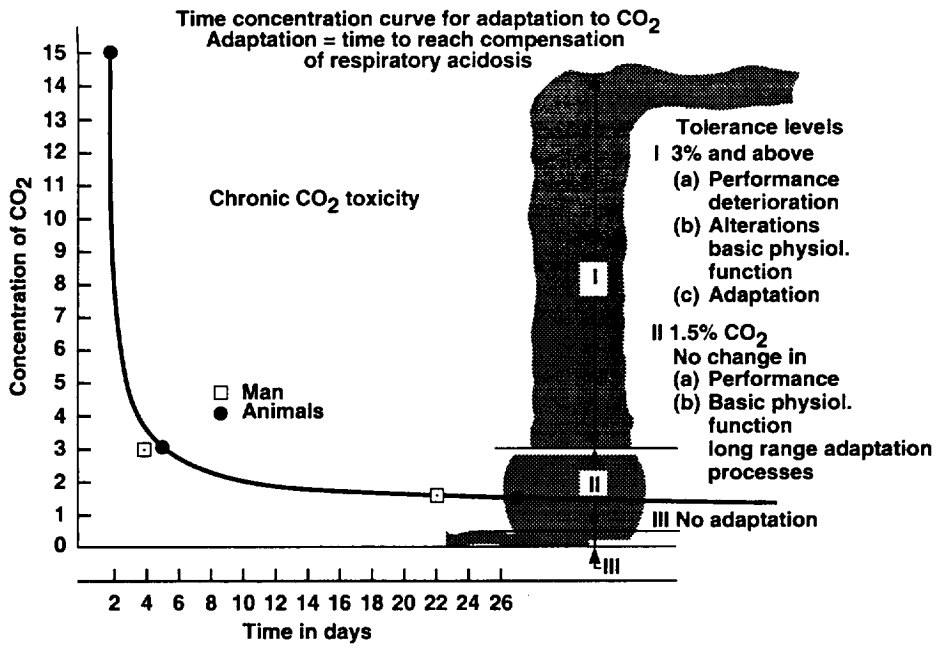


Figure 8. Time concentration relationship in adaptation to increase carbon dioxide concentration based on experiments in human and animal and tolerance limits for chronic carbon dioxide toxicity based on three different levels of activity (from Schaefer (ref. 28)).

Physiologic responses–

Laboratory studies: A biphasic biologic response occurred during a 42 day exposure of 21 subjects to 1.5% CO_2 in a sealed compartment (ref. 29) (fig. 9). During the first 23 days of exposure, a period of uncompensated respiratory acidosis occurred. Alveolar P_{CO_2} rose 2-3 mmHg. Acid-base changes were small with a venous pH change from 7.37 to 7.32. RMV increased 38% mostly due to increases in tidal volume. Respiratory rate increased slightly.

Days 24 to 42 were characterized by a phase of compensated respiratory acidosis. With compensation, the pH rose in conjunction with a rise in urinary CO_2 excretion. Alveolar P_{CO_2}, RMV, and respiratory rate all fell slightly but still remained above normal. Tidal volume remained elevated and rose during the latter phase of compensation.

On return to room air, CO_2 excretion increased to a level higher than during exposure (ref. 28). Pulmonary CO_2 excretion peaked on the day post-exposure followed by a higher peak on days 8 and 9. Urinary CO_2 peaked at day 2 post-exposure and recovered by day 9. The three separate and distinct periods of CO_2 elimination are postulated to reflect three different reservoirs for CO_2 each with different time periods of action.

During the first 9 days of recovery, respiratory rate decreased below normal. Tidal volume increased and remained elevated. RMV was slightly depressed and alveolar P_{CO_2} rose. All parameters had returned to normal by 4 weeks of recovery. No symptomology was noted throughout the experiment.

Exposure of 6 men to 2% CO_2 for 30 days revealed different results (ref. 30). Alveolar P_{CO_2} rose slightly and remained elevated throughout the exposure. RMV increased about 60% due primarily to changes in tidal volume. Respiratory rate was unchanged. Respiratory parameters stabilized between days 8-15 with no significant changes thereafter.

Acid-base changes followed a different time course than with exposure to 1.5% CO_2. A mild respiratory acidosis with a drop in pH from 7.380 to 7.377 was noted at 24 h. Acidity dropped again at day 3 to a pH of 7.371 but was fully compensated by day 15. Bicarbonate levels increased slightly during the first 20 days of exposure. No further changes in acidity were reported from days 15-30.

On return to ambient conditions, respiratory parameters returned to normal within 3 h. Bicarbonate levels returned to normal in 2 days. Acidity was normal at 3 h but a slight alkalosis was noted at day 2 which persisted to day 8 of recovery. No symptomology was noted.

Exposure of 7 subjects to 3% CO_2 for 5 days produced a rise in arterial P_{CO_2} of 3-4 mmHg (ref. 31). On the first day, arterial pH fell from 7.40 to 7.37. Compensation for acidity was complete by day 3. No renal response was noted. Symptoms included awareness of increased

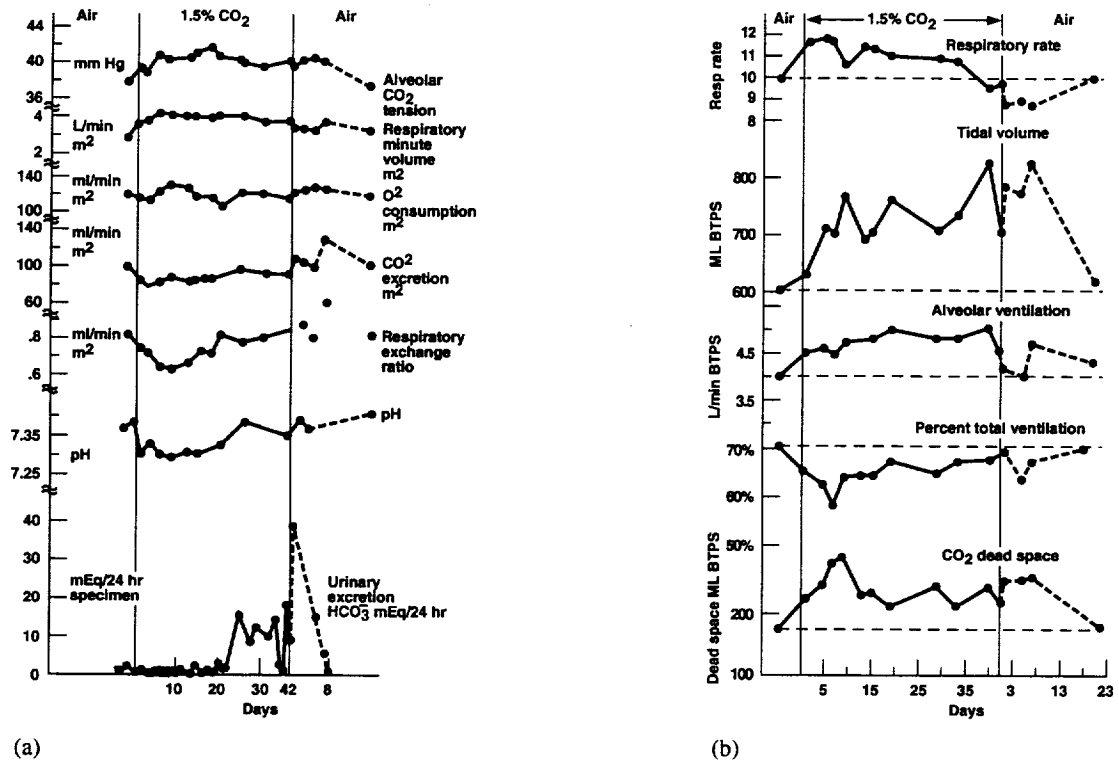


Figure 9. (a) Effect of prolonged exposure to 1.5% CO_2 on alveolar CO_2 tension, respiratory minute volume, oxygen consumption, carbon dioxide excretion, respiratory exchange ratio, urinary HCO_3^- excretion, and venous blood pH. (b) Effect of prolonged exposure to 1.5% CO_2 on respiratory rate, tidal volume, alveolar ventilation, and anatomical dead space. Alveolar ventilation ($V_T - V_D$ anat.) X respiratory rate is also expressed in per cent total ventilation, which shows a marked decrease during exposure to 1.5% CO_2 (from Schaefer (ref. 29)).

breathing and mild frontal headaches. Physiologic responses during recovery were not reported.

Submarine patrol studies: Physiologic responses to elevated CO_2 in 13 Polaris submarine patrols have been reported (ref. 32). Average CO_2 concentrations ranged from 0.7-1%. RMV rose steadily showing an increase of 40-63%. Respiratory rate was essentially unchanged. The total change in RMV was due almost entirely to an increase in tidal volume.

Acid-base changes appeared to cycle with an approximate 20 day period (ref. 32) (fig. 10). An initial fall in pH in association with a rise in both arterial P_{CO_2} and HCO_3^- occurred during the first 20 days. The next 20 days were characterized by an increase in pH and a fall in P_{CO_2} and HCO_3^-. A third period of acid-base change occurred after 40 days in a manner similar to the initial 20 day period. Studies extending to 90 days appear to show that cycling of acid-base parameters continues (ref. 32). The degree of pH change noted throughout the exposure was small.

Discrepancies between laboratory and patrol studies have been observed (ref. 32). Several explanations have been cited for the differences noted in these studies. The magnitude of change observed for several parameters was small enough to be affected by laboratory variability, making direct comparisons difficult. The submarine environment contains other gases of possible significance and the lack of sunlight may also be a factor.

Intermittent Exposures to CO_2

Very few studies have been conducted on intermittent exposure to CO_2. Progressive, intermittent increases in CO_2 were studied in 1 subject over 6 days (ref. 33). The subject was exposed to elevated CO_2 for 15 h followed by 9 h on room air. The level of CO_2 was gradually increased during the exposure until a maximum of 3% was reached at the end of the 15-h period.

Ventilation increased during exposure and returned to normal on room air. In spite of respiratory responses and intermittent exposure, CO_2 accumulated in the body. On room air, alveolar CO_2 rose on days 4 and 5 indicating that the 9 h period of air breathing was not sufficient to

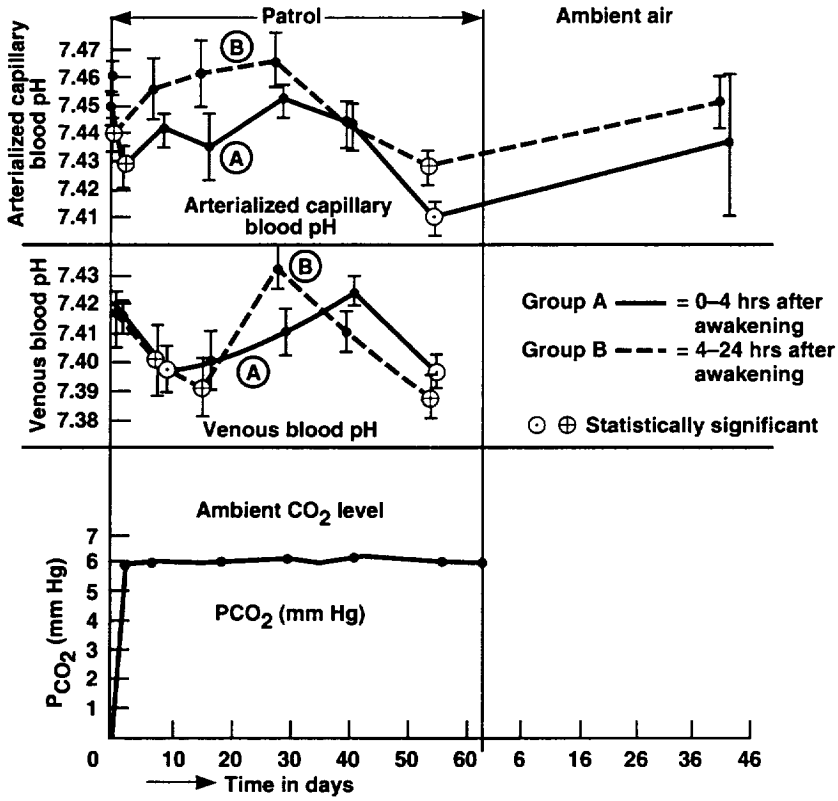


Figure 10. Time course of pH in arterialized capillary and venous blood during patrol. Average ambient P_{CO_2} level 6 mmHg (Peck 1971: 15 subjects, two groups: group A: sample taken 0-4 h after awakening; B: samples taken 4-24 h after awakening) (from Schaefer (ref. 32)).

eliminate previously accumulated CO_2. Renal responses were also noted on the 1st, 4th, and 5th days.

Subjects exposed to 3% CO_2 continuously for 6 days were switched to 8 h on CO_2 and 16 h on room air for an additional 9 days (ref. 34). On the 5th day of intermittent exposure, an increase in urinary excretion of CO_2 was noted. In addition, the symptomology which began during continuous exposure did not abate on intermittent exposure.

It is likely that the concentration of CO_2, the time of CO_2 exposure, and the time between exposures will influence the elimination of CO_2 accumulated during intermittent exposure. Further studies are required to address these questions.

Pathology

Dead space– An observation of potential concern with chronic low dose CO_2 exposure is an increase in pulmonary dead space. Dead space refers to the areas of the lung which receive air but do not participate in gas exchange with the blood. Dead space essentially lowers the functional efficiency of the lung.

Dead space is represented as three different but related entities. Anatomic dead space refers to those areas of the lung which are involved in the transfer of gas to the alveolus but do not involve the alveolus itself. Physiologic dead space refers to all areas of the lung which are not involved in gas transfer and includes the anatomic dead space plus all ventilated but non-perfused alveoli. Alveolar dead space refers only to ventilated and non-perfused alveoli. The dead spaces are related to each other by the equation: physiologic - anatomic = alveolar.

Exposure of 21 subjects to 1.5% CO_2 for 42 days led to an increase in physiologic, anatomic, and alveolar dead space (ref. 28). The increase in anatomic dead space is likely due to direct bronchodilation from CO_2. Dead space volumes had risen by about 62% at the end of exposure but returned to normal after 4 weeks recovery on room air.

Evidence suggests that ventilation/perfusion (V/Q) mismatching tripled with 1.5% CO_2 exposure for 42 days

(ref. 29). Ventilation/ perfusion (V/Q) mismatching refers to those areas of the lung in which either ventilation occurs without blood flow or blood flow occurs without ventilation. Blood from these areas is not oxygenated, thereby lowering the potential O_2 carrying capacity of the blood. Arterial O_2 content decreased only slightly at the end of the 42 day exposure.

Exposures of 0.8-0.9% CO_2 on Polaris submarine patrols for 20-21 days produced an increase in physiologic dead space of approximately 60% (ref. 32). Dead space values had returned to normal when measured after eight weeks recovery on room air.

Exposure of six subjects to 2% CO_2 for 30 days produced a rise in physiologic dead space of only 8% (ref. 30). No evidence of increased V/Q mismatching was noted. These results suggest only minimal changes in alveolar dead space or gas exchange occurred. The rise in dead space was postulated to reflect an isolated increase in anatomical dead space due to the bronchodilatory effects of CO_2.

Histology– Chronic inhalation of low dose CO_2 produces histologic changes in the architecture of guinea pig lungs. The changes noted are dependent on the degree and duration of CO_2 exposure.

Exposure of guinea pigs to 1% CO_2 showed ultrastructural changes in the lung four and six weeks after exposure (ref. 35). These increases were still present at two and, to a lesser extent, four weeks after recovery. Exposure of guinea pigs to 0.5% CO_2 revealed no significant changes in lung architecture at four, six, and eight weeks exposure (ref. 36).

Histopathologic changes in the lungs of guinea pigs primarily involved proliferation of Type II pneumocytes (ref. 35). These cells are involved in the production of pulmonary surfactant which acts to reduce surface tension within the alveolus thereby preventing the natural tendency of the alveolus to collapse. The changes noted in the Type II cells most likely reflect a compensatory reaction to an impairing effect of CO_2 on Type I alveolar lining cells.

The physiologic significance of the changes in lung architecture noted are unknown. The onset of histologic changes appears to occur with CO_2 levels between 0.5 and 1% CO_2. Although the changes noted after 8 weeks of exposure with 1% CO_2 appear to be reversible, it is not known if the same is true for higher concentrations of CO_2 or for longer exposures. Additionally, it is unknown if CO_2 exposure produces histologic changes in the lungs of humans.

Submarine studies– An analysis of health data from Polaris submarine patrols indicates a decrease in the incidence of respiratory disease after 1967 (ref. 37) (fig. 11).

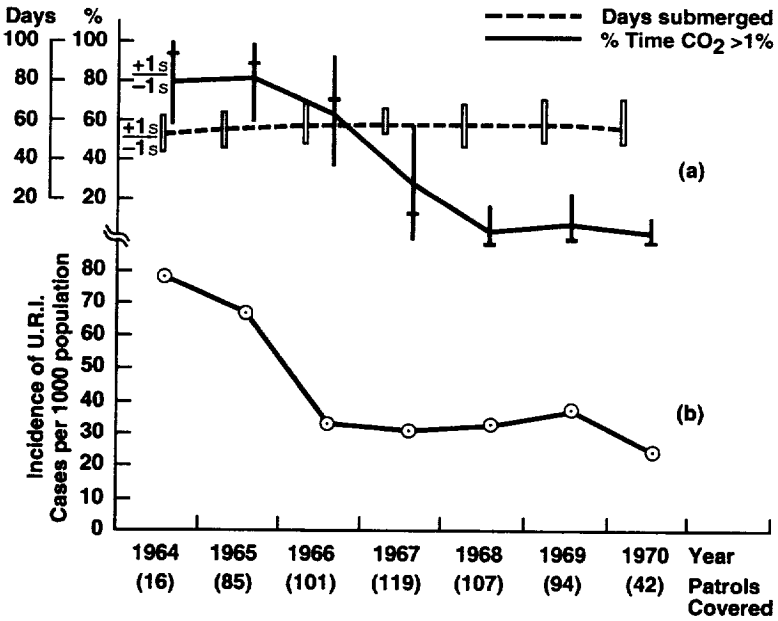


Figure 11. (a) Summary of average ambient CO_2 levels on 546 Fleet Ballistic Missiles (FBM) submarine patrols between 1964 and 1970. (b) Incidence of upper respiratory infection cases per 1000 population observed on 546 Fleet Ballistic Missile (FBM) submarine patrols between 1964 and 1970. ⊙ = Incidence significantly different from data obtained in 1964 (from Tansey (ref. 37)).

On average, each patrol was about 60 days in length. In 1967, larger and more efficient CO_2 scrubbers were installed, leading to a 33% reduction in environmental CO_2 from 1.2 to 0.8-0.9%.

The decreases in both total and respiratory illnesses from the periods encompassing 1963-1967 and 1968-1973 were significant. Both illness rates and days lost to respiratory illness were markedly decreased. The decrease in respiratory illness was the largest contributor to the decrease in total illness and total days lost between these two time periods (ref. 37) (table 1). The reduced incidence of respiratory disease was not seen in a comparison group of surface personnel. After improved environmental control, the incidence of respiratory disease was lower for submarine than for surface personnel.

Several reasons were postulated to explain these health findings. Although smoking rates also decreased during this time, the authors concluded that the improvement in environmental control, specifically the reduction in CO_2, was the primary contributor to the decrease in respiratory illness.

Summary

Physiologic responses to elevated CO_2 levels are dependent on the degree and duration of exposure. Exposure to CO_2 levels above 5% produces marked symptomology and cannot be tolerated for extended periods of time. Carbon dioxide levels between 3-5% produce symptoms of dyspnea, but individuals have tolerated these exposures for days to weeks. Exposure to CO_2 levels of 2-3% can be tolerated for weeks to months. Concentrations of CO_2 below 2% can be tolerated indefinitely.

During long term exposure to 1.5% CO_2, a period of uncompensated respiratory acidosis exists for approximately 20 days. This period is characterized by a fall in pH and increases in alveolar P_{CO_2} and ventilation. A period of compensated respiratory acidosis lasting about 20 days follows. Compensation is characterized by an increase in urinary excretion of CO_2 and a rise in pH towards normal. A second period of uncompensated respiratory acidosis follows the period of compensation. Alveolar P_{CO_2} and ventilation remain elevated throughout the entire exposure. Acid-base changes were small.

Table 1. Illness rate and rate of days lost in submarine service (from Tansey (ref. 37)). Total man-days 1963-1967 = 3,240,000: 1968-1973, 4,410,000

	1963-1967		1968-1973	
	Illness rate	Rate of days lost	Illness rate	Rate of days lost
Respiratory	0.07	0.23	0.03*	0.08*
Trauma	0.05	0.25	0.04	0.16
Gastrointestinal	0.05	0.22	0.03*	0.12*
Dermal	0.02	0.09	0.02	0.04*
Infection	0.02	0.05	0.01*	0.04
Genitourinary	0.02	0.09	0.01	0.05*
Systemic	0.01	0.11	0.01	0.06*
Cranial	0.02	0.05	0.01	0.04
Neuropsychiatric	0.004	0.03	0.01*	0.04*
Miscellaneous	0.003	0.01	0.0015	0.002*
Total	0.268	1.13	0.184*	0.63*
	National Center for Health Statistics			
	1963-1967		1968-1971	
Neuropsychiatric (from public outpatient psychiatric services, 25-34 year age group)	0.012		0.018*	

*Differences between two reporting periods within the submarine service and National Center for Health Statistics significant at the 5% level or better.

On return to ambient conditions, both pulmonary and urinary excretion of CO_2 remain elevated for the first several days post-exposure. All parameters returned to normal within four weeks.

The occurrence of a chronic physiologic response to repetitive CO_2 exposure may occur. Intermittent, repetitive exposures to CO_2 have not been studied sufficiently to denote which time periods are required to vent all accumulated CO_2 between exposures.

Dead space increases with low dose CO_2 exposure. The primary change in dead space is likely due to the bronchodilatory effects of CO_2. Any influence on V/Q mismatching has not been determined. The increase in dead space resolves with return to ambient conditions. The physiologic significance of an increase in dead space from CO_2 exposure is unknown.

Reversible, histopathologic changes in the lung, characterized by a proliferation of Type II pneumocytes, occurs with chronic exposure to 1% CO_2 in guinea pigs. No change is seen with chronic exposure to 0.5% CO_2. The physiologic significance of the observed histologic changes are unknown.

Polaris submarine patrol studies have shown a possible correlation between a decrease in the incidence of respiratory illness and improved environmental control. It is postulated that the reduction in CO_2 from 1.2 to 0.8-0.9% was the primary reason for a significant drop in the occurrence of respiratory illness.

Renal

Introduction

The kidneys act as a filter and serve to remove toxins from the body. Through selective absorption and excretion, plasma levels of various substances are established and maintained. Each kidney is composed of millions of individual structures called nephrons. The nephron is the functional unit of the kidney and each nephron essentially performs the overall function of the kidney on an individual basis.

Each nephron is in intimate contact with a capillary blood vessel. The nephron and the capillary blood vessel run closely paralleled to each other so that fluid is readily transferred between them. The kidneys receive a blood flow of nearly 1 L/min (ref. 38). Of this amount, almost 125 ml/min of the fluid portion of the blood is transferred into the early segment of the nephron. Substances are returned to the blood either by active processes requiring energy input or by passive diffusion. At the terminal portion of the nephron, nearly 99% of the initially transferred fluid has returned to the blood. The remaining fluid is comprised mostly of metabolic waste products and is eliminated as urine.

Urine contains a high proportion of breakdown products of metabolism (ref. 39). Most of these products are acidic in nature and are referred to as titratable acid. Titratable acids include NH_4^+, $H_2PO_4^-$, and others. By removing these substances from the circulation, the kidney controls the acid-base balance of the blood as a basic function.

The kidney is also intimately involved in CO_2 balance (ref. 3). Along the inner layer of the nephron is a protein called carbonic anhydrase. Carbonic anhydrase catalyzes the reaction converting CO_2 (an acid) and H_2O into HCO_3^- (a base) and H^+ (an acid). Through the selective retention or excretion of HCO_3^- and H^+, the kidney further serves to control the overall acidity of the body.

Compensation for chronic respiratory acidosis is characterized by a change in renal handling of both acid and base (refs. 40 and 41). Accumulated CO_2 in the bloodstream is converted into HCO_3^- and H^+ in the nephron. The HCO_3^- is selectively retained while the H^+ is excreted in the urine. In this manner, base is retained, as acid is eliminated, thereby helping to return the pH back towards normal. This process is known as renal compensation.

It is important to note that the lungs eliminate over 100 times as much total acid in a day as do the kidneys. For this reason, the kidneys act primarily to fine-tune the system's response to acid-base changes. Renal compensation rarely fully returns the acid-base status to normal.

Acid-Base Status

Renal responses to acute changes in CO_2 are limited. Exposure of 7 subjects to CO_2 of 7-10% for a maximum of 90 min produced a large change in pH with only a minimal rise in HCO_3^- (ref. 20). Sources other than the kidney exist for HCO_3^- generation. With high-dose, acute CO_2 exposures, renal generation of HCO_3^- was not apparent.

Acid-base changes with chronic respiratory acidosis are dependent on time of exposure and concentration of CO_2 (ref. 28). Exposures greater than 3% CO_2 led to earlier compensation of pH. At 3% CO_2, compensation occurred in 5 days.

With chronic exposures to less than 3% CO_2, acid-base responses are much different. Compensatory responses are not elicited as quickly with lower levels of CO_2. As discussed in the section on respiration, a 20-day period of uncompensated respiratory acidosis occurred with exposure to 1.5% CO_2 for 42 days (ref. 29). The pH was

partly compensated for by respiratory responses but was not returned to normal. In spite of the rise in alveolar CO_2 and fall in pH, plasma HCO_3^- increased only slightly (ref. 42).

After the initial 20 day period of uncompensated acidosis, a phase of pH compensation appeared. With compensation, arterial pH and HCO_3^- levels rose. Urinary pH also rose subsequent to an increase in the excretion of urinary HCO_3^- (ref. 43). During this phase, total HCO_3^- levels were increased. The kidney may have played a role in generating some of the additional HCO_3^- but the degree of this response is uncertain.

Submarine patrol studies with 1% CO_2 for long durations reveals a similar cycling of pH and HCO_3^- (ref. 32). Apparently renal responses were not elicited under these circumstances. Comparison of laboratory and submarine patrols have shown similar results.

Exposure to 2% CO_2 for 30 days elicited the start of compensation in 3 to 8 days with the process completed in 15 days (ref. 30). Plasma HCO_3^- rose slightly. Urinary excretion of HCO_3^- and titratable acid was elevated throughout the length of exposure. Cycling of compensatory phases was not seen.

The differences between the renal responses to 1.5 and 2% CO_2 may be caused by several factors. Renal responses were initiated with 2% CO_2 but took several days to reach full activity. Exposure to 1.5% CO_2 may simply fall below the threshhold limit of inducing a renal response. Above 3% CO_2, renal responses are initiated quickly and compensation persists throughout the exposure.

Bone

Calcium– Bone serves as a storage site for CO_2 (ref. 44). The CO_2 complexes with the calcium in bone where it is deposited. This is evidenced by the apparent cycling of calcium levels in close association with changes in pH and CO_2 levels (ref. 29). The long time periods required in establishing bone stores for CO_2 may explain the 20-day periods of time required to initiate compensation with chronic low dose CO_2 exposure.

Exposure of 20 subjects to 1.5% CO_2 for 42 days revealed that plasma calcium mirrored the change in pH (ref. 45). Plasma calcium levels fell during the first 23 days, returned to normal from days 24 to 42, and rose during recovery. Changes in plasma calcium also corresponded to pulmonary CO_2 excretion.

The highest plasma calcium value observed occurred on the first day of recovery on room air and was associated with a rise in pH and increased respiratory excretion of CO_2 (ref. 45). Urinary excretion of CO_2 peaked on day 2 of recovery. A second peak in both plasma and urine calcium was noted on day 8 of recovery in association with another rise in pulmonary CO_2 excretion. The release of the CO_2 from storage in bone was probably responsible for this response.

Plasma calcium changes in association with pH changes were also seen with 1% CO_2 during submarine patrol studies (ref. 32). Calcium changes were not seen with a 30-day exposure to 2% CO_2 (ref. 30).

Histology– Bone has about 80% of the body's storage capacity for CO_2 (refs. 46 and 32). Bone carbonate (heat stable bone) exists in the lattice of bony crystals and comprises about 70% of bone CO_2. Bone bicarbonate (heat labile bone) exists in the hydration shell of the hydroxyapetitic crystals and comprises the remaining 30% of bone CO_2.

Changes in bone CO_2 content were measured in guinea pigs exposed to 1% CO_2 for 8 weeks (ref. 46) (fig. 12). A continuous rise in bone CO_2 was observed throughout the 8 weeks of exposure. The rise was particularly marked during the 4 to 8 week period. An increase in bone bicarbonate associated with a decrease in bone carbonate occurred during the first two weeks of exposure. The following two weeks were characterized by a decrease in bone bicarbonate and an increase in bone carbonate levels. During the final four weeks, bone bicarbonate rose sharply while bone carbonate remained stable.

The phases of bone bicarbonate increase were associated with bone calcium and phosphorus loss while the phases of bone carbonate loss were associated with bone calcium and phosphorus gain. It has been postulated that with low dose CO_2 exposure, the release of bone bicarbonate during the compensatory phase of chronic respiratory acidosis accounts for the rise in HCO_3^- seen (ref. 32).

Exposure of guinea pigs to 0.5% CO_2 for 8 weeks revealed changes in bone calcium content (ref. 36). Bone calcium tended to decrease after 6 weeks of exposure concurrent with a rise in plasma calcium levels. All parameters had returned to normal by 8 weeks recovery on room air.

Parathyroid hormone (PTH) regulates calcium and phosphorus metabolism under normal physiologic conditions. PTH activity helps to control the uptake and liberation of calcium and phosphorus by bone. Attempts to quantify changes in PTH levels in association with calcium changes from elevated CO_2 have been inconclusive (refs. 39, 45, and 47).

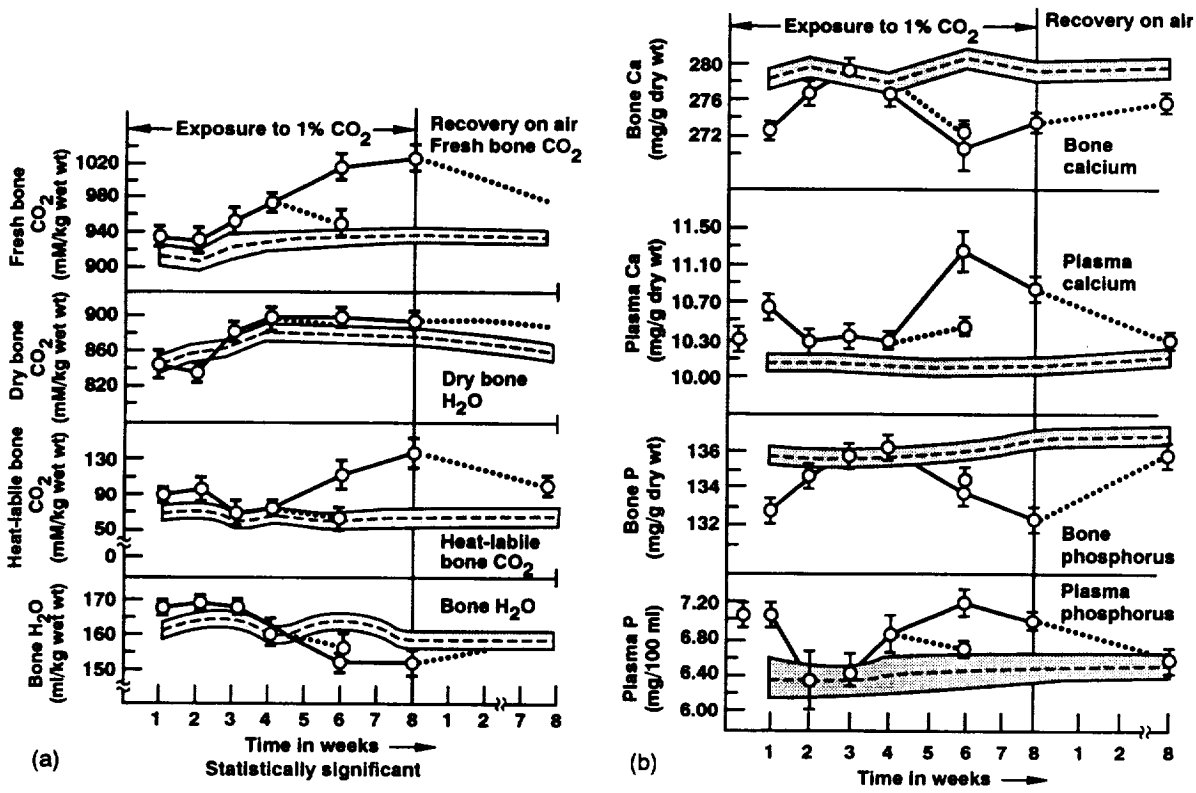


Figure 12. (a) Effect of prolonged exposure to 1% CO_2 on total bone CO_2 content of fresh bone, dry bone, difference between fresh bone and dry bone CO_2 content (heat-labile CO_2) and bone H_2O content. Data represent means and SE in mmol/kg wet wt. Exposed animals – control animals ------- recovery following exposure ····· Statistically significantly different from controls at 5% level and better. Each group of exposed animals consisted of 6 animals, each control group (littermates of the exposed guinea-pigs) of 3-4 animals. (b) Effect of prolonged exposure to 1% CO_2 on bone and blood calcium and bone and blood phosphorus. Data represent means and SE in mg/g dry wt. Exposed animals —; control animals -------; recovery following exposure ····· Statistically significantly different from controls at 5% level and better. Each group of exposed animals consisted of 6 animals each control group of 3-4 animals (from Schaefer (ref. 46)).

The effect of the histologic changes induced by CO_2 exposure on bone strength is unknown. The threshold level below which CO_2 exposure does not lead to changes in bone has also not been determined.

Electrolytes

Blood and urine levels of calcium, HCO_3^-, CO_2, and pH are related to CO_2 exposure by the degree of compensation present in the system. The mechanism of compensation to elevated CO_2 involves associated changes in each of these parameters. These responses have been discussed in earlier sections of this paper.

Exposure to elevated CO_2 has been associated with changes in other blood and urine electrolytes. Exposure to 7-10% CO_2 for 90 min revealed small increases in plasma sodium (Na) and potassium (K) (ref. 20). Plasma chloride was unaffected. The degree of change noted was of no physiologic significance.

Exposure to 2% CO_2 for 30 days revealed a rise in plasma Na during the first 15 days and a fall thereafter (ref. 30). Plasma K rose on the first day but remained below normal for the remainder of the exposure. The hematocrit, red blood cell count, and red blood cell volume were all slightly decreased. The degree of the changes noted were small. Urinary volume and Cl excretion were not affected.

With exposure to 1.5% CO_2 for 42 days, plasma levels of Na showed a transitory rise during the compensated phase of the resultant respiratory acidosis (ref. 42). Plasma levels of K, Cl and H_2O did not show any consistent

responses. The degree of the changes noted was of no physiologic significance.

Urinary excretion of Na, K, and Cl was diminished during the period of exposure to 1.5% CO_2 (ref. 42). The urinary levels of all 3 electrolytes remained lower than normal even after 4 weeks of recovery on room air. Total volume of urine decreased and remained so at 4 weeks recovery suggesting water retention.

Red blood cell Na and K fell with 1.5% CO_2 exposure (ref. 42). These findings are similar to changes seen with congestive heart failure, a condition characterized by an increase in total body fluid. Hematocrit, hemoglobin, and red blood cell count all fell slightly.

Exposure to 0.7-1.0% CO_2 during submarine patrols also revealed electrolyte changes (ref. 32). Plasma Na rose slightly as K fell. Both changes persisted throughout the exposure. Red blood cell Na and K levels decreased. Urinary volume was diminished. The degree of change was similar to that seen with exposure to 1.5% CO_2.

Throughout the range and duration of CO_2 exposures cited, plasma electrolyte changes were small. Red blood cell electrolyte changes were somewhat larger. Hematocrit and other red blood cell indices fell slightly (refs. 48 and 49).

Pathology

Histology– Histologic changes have been observed in the kidney after chronic exposure to elevated CO_2. Calcification was seen in the kidneys of guinea pigs during long term exposure to 15% CO_2 (ref. 47). An increase in renal calcium deposition occurred as early as 48 h into the exposure. The incidence of focal kidney calcification increased with length of exposure. Calcification was noted primarily in the tubules of the renal cortex.

Exposure to 1.5% CO_2 of guinea pigs for 42 days and rats for 90 days revealed progressive increases in kidney calcification over time (ref. 50). No focal calcification was noted during the first 2 weeks of exposure. At 42 days, 66% of the guinea pigs displayed renal calcification. At 90 days, all the rats had shown calcific changes. Medullary interstitial, intratubular, and tubular basement membrane calcification was observed.

Guinea pigs exposed to 1% CO_2 for 8 weeks revealed an increase in total kidney calcium content of 27% at 2 weeks (ref. 50). Kidney calcium content remained at this level and showed no further changes during the final 6 weeks of exposure. Plasma calcium levels fluctuated throughout the exposure. The findings suggested that once the process of kidney calcification had started, further mineralization was independent of plasma calcium levels.

Guinea pigs exposed to 0.5% CO_2 for 8 weeks also revealed kidney calcification (ref. 36). The extent of calcification was not significantly different from controls until 8 weeks of exposure. The changes noted had returned to normal by eight weeks recovery on room air.

The cause of kidney calcification from elevated CO_2 has been proposed to be a direct result of elevated plasma calcium levels from bone calcium mobilization. The effect may be mediated by increases in the level of parathyroid hormone.

Kidney calcification has been noted with CO_2 levels ranging from 0.3-15% (ref. 46). Most of the changes were noted to be reversible after long recovery periods on room air. The length of time and concentrations of CO_2 which produce irreversible kidney calcification have not been determined. Further, a threshhold limit below which CO_2 exposure does not produce renal calcification has not been determined.

Submarine studies– An analysis of health data from Polaris submarine patrols indicates a decrease in the incidence of genitourinary (GU) disease after 1967 (ref. 37) (table 1). On average, each patrol was about 60 days in length. A statistically significant decrease in the rate of days lost due to GU disease was noted. In 1967, larger and more efficient CO_2 scrubbers were installed in submarines leading to a 33% reduction in environmental CO_2 from 1.2 to 0.8-0.9%. After 1967, the incidence of overall GU disease was not statistically different between submariners and surface personnel.

The decrease in genitourinary illness was mostly due to a decrease in the occurrence of kidney stones. The majority of kidney stones are comprised of calcium. It is interesting to note the observation that increased urinary calcium excretion and increased calcium deposition within the kidney occurs with chronic CO_2 exposure. A direct association between increased CO_2, increased deposition of calcium in the kidney, and increased incidence of renal stones is likely.

Summary

Exposure to CO_2 above 3% leads to ready compensation of the induced respiratory acidosis. Renal compensation is elicited and cycling of compensatory phases is not seen.

Exposure to 1.5% CO_2 is characterized by a prolonged phase of uncompensated respiratory acidosis. Renal compensation is limited. Compensation occurs after 20 days marked by rises in pH, HCO_3^-, and plasma calcium. It is postulated that CO_2 complexes with calcium in bone where it is deposited. Compensation is thought to occur when HCO_3^- and calcium are liberated from the bone.

Guinea pigs exposed to 1.5% CO_2 for 8 weeks revealed changes in bone content of CO_2. Total bone CO_2 stores increased throughout the length of exposure. The effect of changes of bone CO_2 and calcium on bone strength are unknown. A threshold limit below which CO_2 does not induce changes in bone has not been determined.

Histologic changes in the kidney, characterized by deposition of calcium in the cortical tubules, occurs with chronic CO_2 exposure. Kidney calcification has been noted with 8 week exposures to CO_2 as low as 0.3 to 0.5%. The physiologic significance of these histologic findings is unknown. A threshold limit below which CO_2 does not produce kidney calcification has not been determined.

Polaris submarine patrol studies have shown a decrease in the incidence of genitourinary illness in association with improved environmental control. A fall in the occurrence of kidney stones was the greatest contributor to the decrease in GU disease. The direct correlation between decreased GU illness rates and lowered CO_2 levels is unknown.

Neurologic

Performance

Impairment of performance from CO_2 exposure is related to length and concentration of exposure. Loss of consciousness occurs when 15-20% CO_2 is breathed for only several minutes. Additional increases to 20-30% CO_2 quickly lead to convulsions. Concentrations of CO_2 from 7-10% produce marked symptomology but performance is largely unaffected for about 20 minutes. Longer exposures elicit progressive decreases in performance.

Ten subjects exposed for 20 min to varying levels of CO_2 ranging from 0-7.5% were evaluated for reasoning and short term memory skills (ref. 51). Accuracy of reasoning and short term memory were not significantly affected at all concentrations of CO_2. Reasoning skills were significantly slowed at exposures at and above 5.5% CO_2 (fig. 13).

Exposure of 21 subjects to 6.5% CO_2 for 80 min had no effect on the accuracy of reasoning or memory skills (ref. 51). A slowing of reasoning skills was noted. Speed of performance did improve after 40 min of CO_2 inhalation but still remained below control values.

Subjects exposed to 6% CO_2 for 16 min displayed a slight slowing in performing a card sorting task (ref. 24). No appreciable change in the number of errors was noted in comparison to a control group.

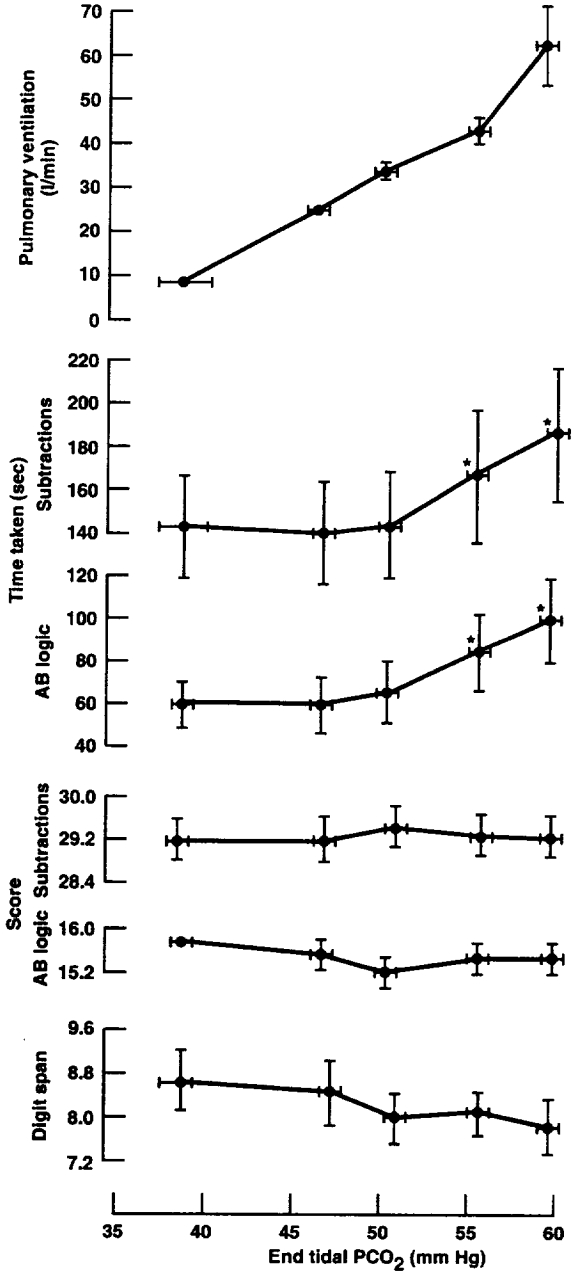


Figure 13. Effects on pulmonary ventilation and reasoning of breathing (from left to right) 0, 4.5, 5.5, 6.5, and 7.5% CO_2 for 5 minutes. Points, means: brackets ±SE. Differs significantly ($P < 0.01$) from data with 0, 4.5, and 5.5% CO_2 (from Sayers (ref. 51)).*

Submarine patrol studies revealed a significant impairment of performance when subjects were exposed to 3% CO_2 for 6 days (ref. 43). Performance did not improve with length of exposure.

Exposure of 6 men to 2% CO_2 for greater than 30 days revealed no changes in electrobiological (EEG), psychomotor, or biorhythm testing (ref. 30). Numerous psychomotor evaluations were made. Individuals exposed to 1.5% CO_2 for 42 days showed no impairment in memory, reasoning, or psychomotor efficiency (ref. 43). No change in the speed or accuracy of performance was noted during either experiment.

Single breath inhalation of 35% CO_2 produced sensations similar to panic attacks (refs. 52 and 53). The immediate respiratory acidosis induced by the elevated CO_2 is followed by a period of lowered alveolar P_{CO_2} and hypocapnic respiratory alkalosis lasting approximately 60 sec. Panic symptoms correlated with the period of lowered alveolar P_{CO_2} but not to the acid-base status of the body.

Subjects exposed to 5-7.5% CO_2 for 15 min displayed dose related increases in anxiety and panic symptoms (ref. 54). Individuals with preexistent panic disorders exhibited panic symptoms at lower CO_2 levels than normal subjects.

A correlation between respiratory sensitivity to CO_2 and neurotic personality traits has been noted for women but not for men. The use of the ventilatory response to CO_2 as a psychobiologic marker has been postulated (ref. 55).

An analysis of health data from Polaris submarine patrols indicates an increase in the incidence of neurologic and psychiatric diseases after 1967 (ref. 37) (table 1). On average, each patrol was about 60 days in length. In 1967, larger and more efficient CO_2 scrubbers were installed in submarines leading to a 33% reduction in environmental CO_2 from 1.2 to 0.8-0.9%.

An increase in the incidence of headaches accounted for the increase in neurologic problems. Although the decrease in CO_2 exposure should have caused a fall in the incidence of headaches, increased stress and longer periods of isolation may have caused in the increase in neuropsychiatric problems.

Blood Flow

Carbon dioxide is known to play an important role in the regulation of cerebral blood flow (CBF). Carbon dioxide greatly dilates the cerebral vasculature, producing decreased vascular resistance and increased blood flow to the brain. Vasodilation helps to enhance CO_2 removal from the brain and subsequently control the acidity of the cerebrospinal fluid (CSF). Changes in pH alone without alterations in CO_2 lead to comparatively weak changes in cerebrovascular tone.

The response of the cerebrovascular system to changes in CO_2 appears to be prompt. Any delays noted in reaching steady state likely reflects the time required for alveolar and arterial P_{CO_2} to reach equilibrium.

Studies have indicated that the cerebrovascular response to CO_2 may have a threshold effect (ref. 56). Exposure to CO_2 levels below 2.5% apparently has little effect on CBF. Exposures to 3.5 and 5% CO_2 increased CBF about 10 and 50%, respectively. With 7% CO_2, the highest level tested, CBF was approximately doubled. In spite of the vascular response, no significant change in cerebral metabolic rate has been observed.

Exposure of anesthetized dogs to 10% CO_2 led to an approximate threefold increase in CBF (ref. 57). A new steady state was achieved in about 5 minutes. Cerebral blood flow was closely related to cerebral venous and not arterial CO_2 tension.

Cerebral blood flow was measured for 6 h in anesthetized dogs exposed to approximately 12% CO_2 (ref. 58). A ninefold increase in CBF accompanied by a decrease in cerebral vascular resistance was noted during the first 3 h of exposure. An adaptive decrease in CBF with an associated increase in cerebral vascular resistance occurred during the following 3-h period. CBF was twice normal at the end of the 6-h exposure period. Regional variations in blood flow occurred. Total and regional CBF was noted to correlate with CSF pH.

Regional cerebral blood flow measured in rats exposed to elevated CO_2 revealed that CBF increased linearly with rising CO_2 levels (ref. 59). All areas of the brain were affected with the exception of the median eminence and the neural lobe where CBF remained normal.

High resolution nuclear magnetic resonance (NMR) was used to measure cerebral intracellular pH in paralyzed rats (ref. 60). Carbon dioxide levels were varied over a wide range. Exposures lasted 25 minutes. The brain exhibited twice the pH lowering capability as arterial blood. The ability of the brain to compensate for acid-base changes may help to limit any adverse effects imposed by changes in CO_2 and CBF.

Neurotransmission

The effects of CO_2 on the excitability of the brain has been measured in mice and rats. The threshold limit for seizure activity via electroshock therapy (EST) revealed a triphasic response to CO_2 inhalation (fig. 14) (ref. 61). Phase 1 occurs with less than 10% CO_2 and was characterized by an increase in the resistance to induced seizures. The decreased cortical excitability in phase 1 appears to be due to direct cortical depression from CO_2. Phase 2 occurs with 10-20% CO_2 and is characterized by an increase in seizure activity. This response probably

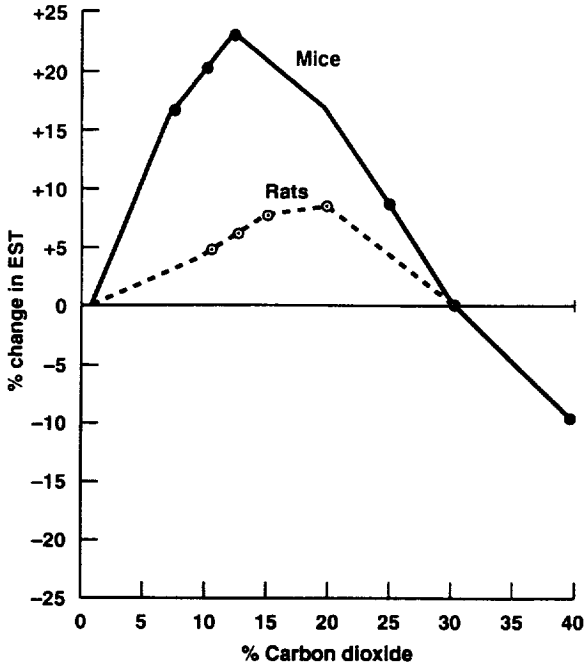


Figure 14. Effect of inhalation of various concentrations of CO_2 on electroshock seizure threshold (EST) of mice and rats (from Woodbury (ref. 61)). Ordinate is percentage change in EST referred to control values. Abscissa is inhaled CO_2 concentration in percent

reflects increased cortical activity due to activation of subcortical centers by CO_2. The third phase occurs at CO_2 levels above 30% and is characterized by an anaesthetic phase with marked cortical depression.

The effects of CO_2 on the electroencephalogram (EEG) reflect the triphasic excitability response noted above. Low level CO_2 exposures can interrupt overt clinical seizure activity. Such a response is consistent with the decreased cortical excitability noted in phase 1 above. Exposure to anaesthetic levels of CO_2 usually causes flattening of the EEG in man and animals.

The production and breakdown of acetylcholine has been shown to be dependent on CO_2 levels (ref. 62). Acetylcholine is an important neurotransmitter that directly influences neurologic function. Adrenal stimulation by CO_2 with resultant epinephrine release has also been shown to occur. More will be discussed on adrenal stimulation later in this paper. The combination of neurotransmitter, hormonal, and pH changes are likely to act in concert to influence neurologic function (ref. 63).

Summary

Impairment of performance from CO_2 exposure is related to length and concentration of exposure. Performance decrement occurs within minutes with exposure to 10% CO_2. Exposure to 5-7% CO_2 leads to a decrease in performance in minutes to hours. Slowing of reasoning skills has been noted with exposure to 3% CO_2 for several days. Long term exposure to 1.5-2% CO_2 has been tolerated without any performance decrement.

Anxiety symptoms can be produced with short exposures to high dose CO_2. Individuals predisposed to panic attacks are at increased risk. The use of the ventilatory response to CO_2 as a marker to identify those individuals prone to anxiety attacks is still under study.

Carbon dioxide is a potent cerebral vasodilator, however, the cerebrovascular response to CO_2 may have a threshold effect. Exposures to CO_2 below 2.5% apparently have little effect on CBF. With 7% CO_2, CBF was approximately doubled. Whether further increases in CBF occur in humans with higher CO_2 levels is unknown.

Animal studies show progressive increases in CBF with elevated CO_2 levels. As length of exposure increases, compensatory mechanisms begin to reduce the increase in CBF. Regional changes in CBF have been noted. The ability of the brain to compensate for acid-base changes is apparently greater than that seen in the general circulation.

Neurotransmitter production and function is affected by elevated CO_2. The significance of this observation is unknown.

An increase in neuropsychiatric disorders in submariners was noted to occur in concert with an improvement in environmental control. It was postulated that longer periods of isolation and increased stress, not the fall in CO_2, were the likely causative factors.

Cardiovascular

Basic Responses

The cardiovascular system plays an important role in the elimination of CO_2. Vascular perfusion helps to determine local CO_2, O_2, and pH values as well as serving to control metabolism. It is not surprising then, that many cardiovascular responses are influenced by CO_2 levels.

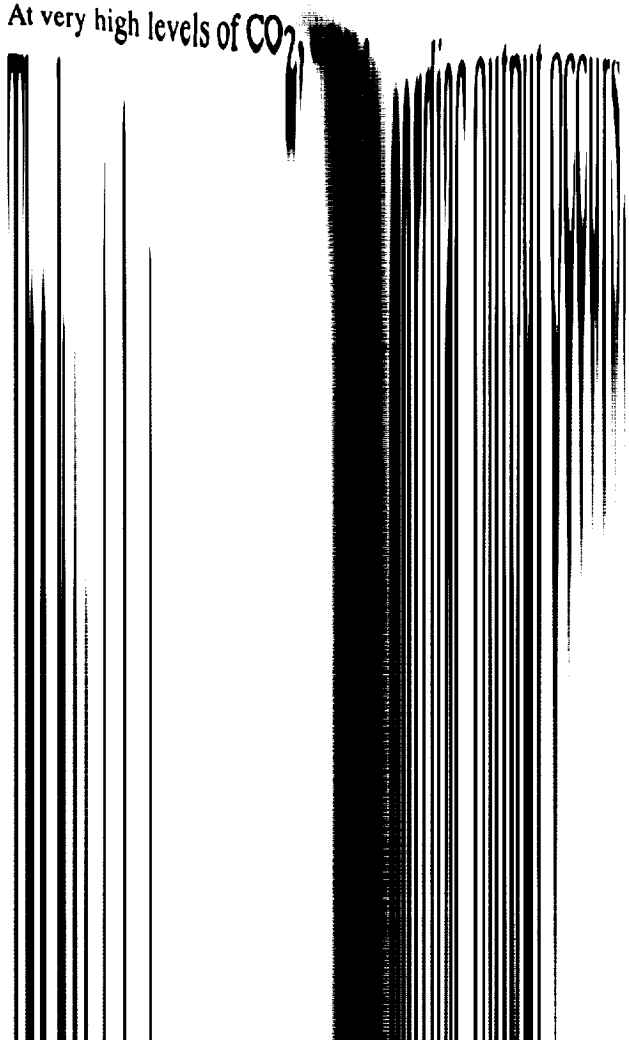
Carbon dioxide leads to vasodilation in nearly all vascular beds. Vasodilation decreases vascular resistance thereby allowing for increased blood flow. The increase in blood flow helps to remove CO_2 and subsequently control the pH of the local environment.

Each circulatory bed has different inherent responses to CO_2 (ref. 64). In cutaneous, muscular, renal, and splanchnic circulations, reflex actions may limit local

vasodilation acutely. With longer exposures, vascular resistance tends to diminish in these vascular beds. The pulmonary circulation may prove an exception by exhibiting vasoconstriction in response to elevated levels of CO_2 in the blood. Carbon dioxide diffuses very quickly

unchanged (ref. 43). Diastolic pressure showed a slight increase. Length of exposure did not appreciably affect any of the cardiac parameters under observation.

At very high levels of CO_2,



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At very high levels of CO_2 [redacted] cardiac output occurs. The heart [redacted]

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At very high levels of CO_2

vasodilation acutely. With longer exposures, vascular resistance tends to diminish in these vascular beds. The pulmonary circulation may prove an exception by exhibiting vasoconstriction in response to elevated levels of CO_2 in the blood. Carbon dioxide diffuses very quickly from the blood into the alveoli. In those areas of the pulmonary circulation where blood levels of CO_2 rise, ventilation is likely diminished. Localized vasoconstriction occurs in an attempt to shunt blood flow to areas of the lung which are better ventilated.

In spite of the vasodilatory effects of CO_2, arterial blood pressure increases with exposure (ref. 5). Carbon dioxide stimulates the sympathoadrenal system with a subsequent peripheral vasoconstriction and epinephrine release. The vasodilatory effect is muted but still predominates. Stimulation of the sympathoadrenal system leads to an increase in heart rate and cardiac output overcoming the effects of vasodilation and subsequently raising arterial blood pressure.

A continuous increase in blood pressure is noted in association with increasing CO_2 levels (ref. 5) (table 2). Systolic pressure rises faster than diastolic pressure although both are increased.

Twelve subjects exposed to 7-14% CO_2 for 20 min revealed increases in arterial pressure and heart rate (ref. 65). Systolic pressure was elevated more than diastolic pressure. No significant electrocardiogram (ECG) changes were noted. An occasional nodal or ventricular extrasystole was seen. On withdrawal from CO_2, hypotension was minimal and no arrythmias were observed.

Exposure of 44 subjects to 7.6-10.4% CO_2 for 3-10 min revealed increases in blood pressure and heart rate (ref. 7). Systolic and diastolic pressures rose 30 and 23 mmHg, respectively. Heart rate quickened by 16 beats per minute.

Exposure of 6 subjects to 2% CO_2 for 30 days revealed no changes in heart rate, systolic, or diastolic blood pressure (ref. 30). No ECG changes or arrythmias were noted.

Exposure of 23 subjects to 1.5% CO_2 for 42 days revealed that basic cardiovascular functions were largely unchanged (ref. 43). Diastolic pressure showed a slight increase. Length of exposure did not appreciably affect any of the cardiac parameters under observation.

At very high levels of CO_2, a fall in cardiac output occurs. The heart, being very active metabolically, is strongly influenced by local pH and CO_2 levels. Cellular function is closely tied to the pH of the local environment. The contractile force of the heart begins to decline as the pH becomes more acidic. Rhythm disturbances are also noted.

Exposure of 17 subjects to 30% CO_2 for approximately 30 sec revealed a variety of ECG changes (ref. 66). Atrial arrythmias including premature atrial contractions and atrial tachycardia predominated. Occasional ventricular extrasystoles were noted. None of the rhythm changes were felt to be clinically significant.

Anesthetized dogs exposed to 30-40% CO_2 for 4 h developed life threatening cardiac arrythmias on sudden return to room air (ref. 67). On gradual return to room air, no rhythm disturbances were seen.

An analysis of health data from Polaris submarine patrols revealed no change in the incidence of cardiovascular disease in association with an improvement in environmental control (ref. 37).

Coronary (Myocardial) Blood Flow

The effect of CO_2 on blood flow to the heart itself is also characterized by vasodilation. Anesthetized dogs exposed to 12% CO_2 were measured for myocardial blood flow (MBF) (ref. 68). An increase in MBF and myocardial oxygen delivery was noted; however, an increase in oxygen extraction in the coronary circulation was not seen. The authors concluded that hypercapnia results in myocardial overperfusion which is a luxury perfusion not essential in maintaining myocardial oxygen supply.

Anesthetized rabbits revealed a 62% increase in MBF on exposure to 7% CO_2 (ref. 69). Coronary vascular resistance decreased 42%. Changes in acidity without a change

Table 2. Blood pressure during carbon dioxide inhalation (from Lambertsen (ref. 5))

Alveolar P_{CO_2} (min. Hg)	Arterial pressures (mm. Hg)			Heart rate (beat/minute)	Number of observations
	Systolic	Diastolic	Pulse		
40	129	78	51	64	26
56	146	86	60	85	10
65	161	99	62	96	9
75	170	96	74	98	4
85	165	97	68	127	3

in CO_2 did not affect MBF. Removal of nervous system innervation of the heart diminished the increase in MBF seen with CO_2 exposure. CO_2 probably acts as a direct mediator of coronary vasodilation whose action is supplemented by nervous system activity.

Anesthetized dogs exposed to 0-40% CO_2 revealed progressive increases in myocardial blood flow (ref. 70). Increases in myocardial oxygen demand could not account for the degree of vasodilation seen. CO_2 may have a direct effect on coronary vasodilation.

The full mechanism by which CO_2 causes vasodilation has not been determined. It is likely that a combination of local chemical, hormonal, and neurologic factors contribute to the vascular response seen

Sympathoadrenal Function

Sympathoadrenal stimulation occurs throughout the range of CO_2 exposure. Adrenal stimulation can be mediated neurologically via the sympathetic tract, hormonally via cortisol, or directly. The adrenal glands secrete a variety of substances including epinephrine and norepinephrine. Collectively, these substances are referred to as catecholamines. The role of catecholamines is essentially to increase the cardiovascular capacity in preparation for sudden exertion.

In cats, the action of epinephrine was noted to change in conjunction with the pH of the blood (ref. 71). This action most likely reflects a pH-mediated change in the activity of the nervous system or a pH-mediated change in the inactivation of epinephrine. In other similar experiments, epinephrine release was felt to occur by a direct, non-pH-mediated mechanism (ref. 72).

Guinea pigs exposed to 30% CO_2 in air and O_2 for 1 h were evaluated for adrenal activity (ref. 73). It was noted that high levels of CO_2 in air stimulated the adrenal cortex. This effect was not seen with high dose CO_2 in O_2, however.

Twelve subjects exposed to 7-14% CO_2 for 20 min revealed evidence of adrenal stimulation (ref. 65). Both plasma catecholamine and steroid levels were increased, as well as heart rate and blood pressure. Adrenal stimulation may have contributed to the increase in heart rate and blood pressure noted.

Exposure of 6 subjects to 2% CO_2 for 30 days revealed no significant change in plasma cortisol levels (ref. 30). Heart rate and blood pressure remained stable and did not seem to be affected by hypercapnia. Whether cortisol levels truly reflect the state of adrenal activation by CO_2 is unknown.

Exposure of 30 subjects to 1.5% CO_2 for 42 days revealed an increase in adrenal activity (ref. 43). Urinary excretion of ketosteroids was elevated throughout the period of exposure. Ketosteroids are metabolites of adrenal secretion and reflect the degree of adrenal activation. Excretion of ketosteroids was slightly higher during the compensated phase of the respiratory acidosis.

Exercise

Exercise leads to an accumulation of metabolic acids. The rise in acidity causes a subsequent fall in pH and is called metabolic acidosis. Performing exercise while exposed to elevated CO_2 leads to a combination of metabolic and respiratory acidosis. Ventilation is increased in an attempt to limit the fall in pH (refs. 74 and 75).

The stimulation to respiration from combined exercise and CO_2 is thought to be multifactorial (ref. 76). It is postulated that direct stimulation of the central respiratory center via pH changes is the most important factor. Peripheral chemoreceptors are thought to play only a minor role.

Nine athletes performed treadmill exercise while exposed to varying levels of CO_2 (ref. 77). The increase in ventilation was noted to be blunted at high workloads in combination with increased CO_2 (fig. 15). Acidity rose as ventilatory responses were taxed (fig. 16). The cumulative stimulation to respiration was not felt to reflect a simple additive response to the combination of respiratory and metabolic acidosis.

The ventilatory response to a 10-min exposure to 7.6-10% CO_2 was compared to that induced by heavy muscular exercise (ref. 7). The stimulus to breathing was noted to be higher during heavy exercise. Both rate and depth of respiration increased with exercise whereas increased depth of respiration predominated with CO_2 exposure.

Six subjects exposed to 0-6% CO_2 were exercised for 30 min (ref. 78). Ventilation increased directly with inspired CO_2. With 6% CO_2 and heavy exercise, pH fell from 7.37 to 7.23.

Ventilatory responses were measured in 9 men exposed to 2-4% CO_2 and compared to ventilatory changes induced by exercise (ref. 8). With low dose CO_2 exposure, increased ventilation is largely due to an increase in tidal volume (fig. 17). Inspiratory time increases as expiratory time decreases. With exercise, increased ventilation is due to increases in both tidal volume and rate of breathing. Both inspiratory and expiratory time decrease.

Three subjects exposed to increasing levels of CO_2 were exercised at various speeds on a treadmill (ref. 79). At moderate workloads with CO_2 below 4%, the effects of

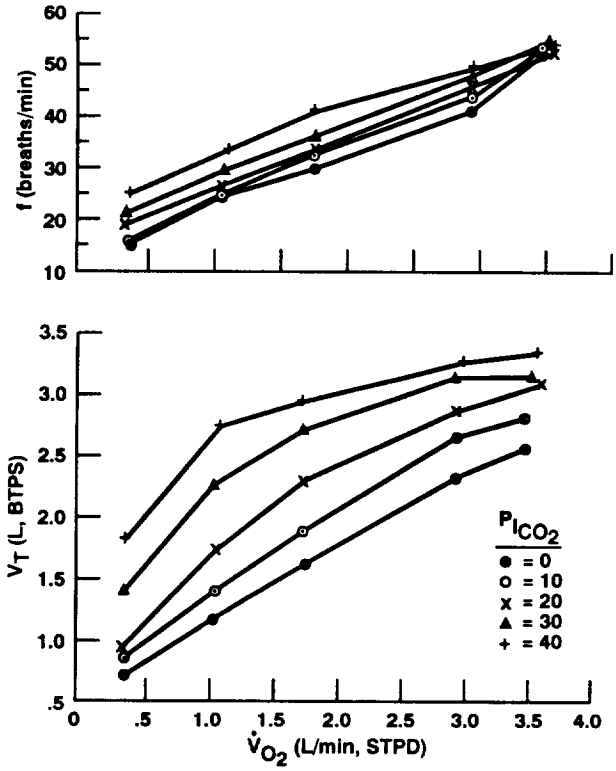

Figure 15. Relationships of respiratory rate (f) and tidal volume (V_T) to oxygen uptake ($\dot{V}_{O_2}$) during exercise at different levels of inspired CO_2 tension (P_{ICO_2}) (from Clark (ref. 77)).

CO_2 and exercise acted independently and cumulatively to increase ventilation. At higher levels of exercise and CO_2, ventilation was stimulated in a more logarithmic fashion.

Eleven subjects were exposed to 3-4% CO_2 while exercising on a stationary bicycle (ref. 80). At low workloads, increasing CO_2 led to increases in ventilation above that predicted by the additive effects of each stimulus alone. At higher workloads, however, increasing CO_2 eventually produced a plateau in ventilation.

Eight subjects were exposed to 0-4% CO_2 while exercising on a bicycle ergometer for 30 min (ref. 81). Arterial P_{CO_2} rose with increases in exercise and CO_2. Retention of CO_2 led to a combined respiratory and metabolic acidosis. Below 2% CO_2, no exercise difficulty was encountered even at high workloads. Higher CO_2 exposures lead to a decrease in exercise performance. With moderate levels of exercise, ventilation increased with increasing CO_2. Ventilation at maximum exercise level did not vary with increased CO_2, however.

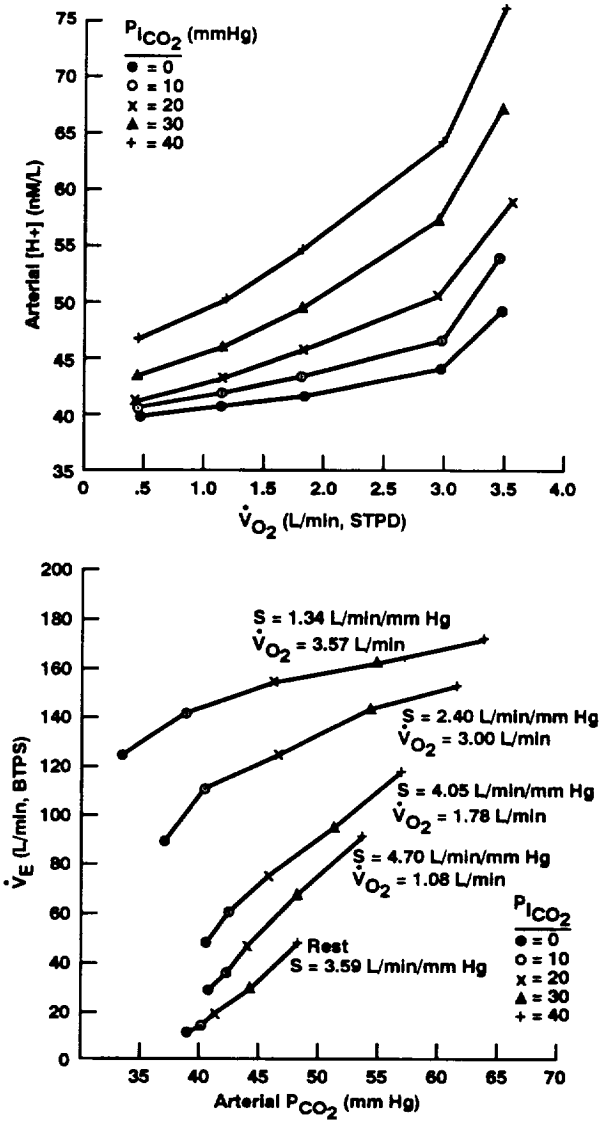

Figure 16. Relationships of ventilation ($\dot{V}_E$) to arterial P_{CO_2} at different work loads during combined exercise and hypercapnia. Average slopes of the $\dot{V}_E$ -Pa_{CO_2} relationships at rest and at four levels of exercise are shown. Corresponding average values of O_2 uptake ($\dot{V}_{O_2}$) are also indicated (from Clark (ref. 77)).

Exposure of 6 subjects to 2% CO_2 for 30 days revealed adaptation to exercise to be slightly impaired (ref. 30). Moderate levels of exercise were conducted for 10 min twice weekly. Increases in arterial P_{CO_2} during exercise were higher than expected.

Exposure of 23 subjects to 1.5% CO_2 for 42 days revealed an increase in pulse rate response to moderate exercise and a prolonged return to normal with rest (ref. 43). These observations were interpreted to reflect a reduction in

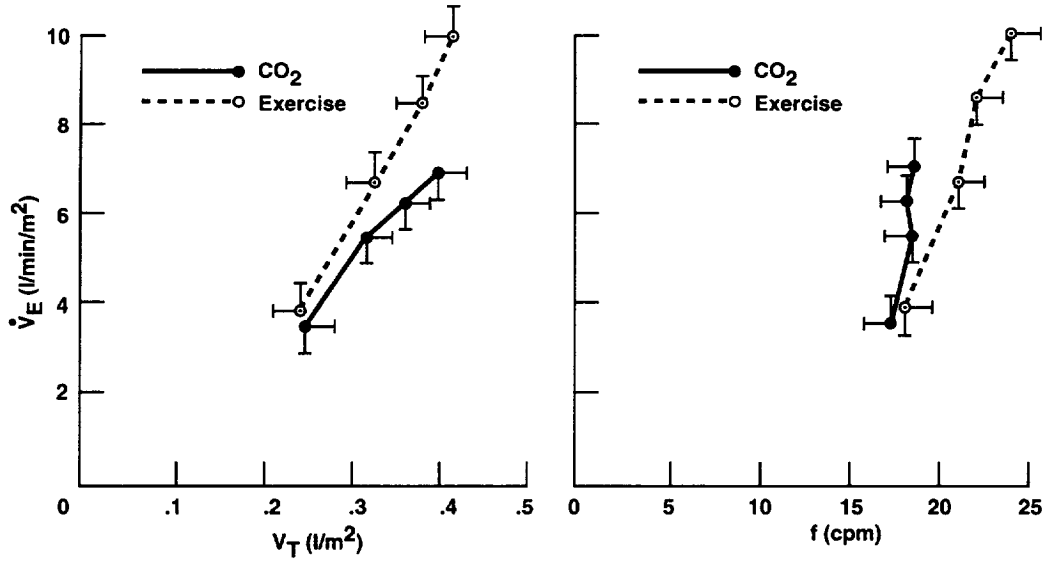

Figure 17. Minute ventilation (V_E) is platted vs V_T (left) and f (right). Mean values ±SD for all 9 subjects are shown (from Askanazi (ref. 8)).

circulatory reserve which may prove significant at higher workloads.

The effects of CO_2 on metabolic processes are undetermined. An apparent decrease in lactate production or release occurs in accordance with increased CO_2 (refs. 78 and 82). The breakdown of glycogen was not affected by elevations in CO_2 (ref. 83).

Summary

Carbon dioxide leads to vasodilation in practically all vascular beds. Stimulation of the sympathoadrenal system with CO_2 leads to a compensatory vasoconstriction and an increase in heart rate. At low levels of CO_2, the overall vascular response leads to an increase in blood pressure and cardiac output. No significant ECG changes are noted. Exposures to CO_2 below 2% revealed essentially no change in cardiac function.

At high concentrations of CO_2, acidosis adversely affects cellular function leading to a decrease in cardiac output. Electrocardiogram changes occur and can be significant, especially on sudden withdrawal from a high CO_2 environment.

Myocardial blood flow increases with exposure to CO_2. The increase in MBF is greater than required to compensate for any additional metabolic needs of the heart. The increase in MBF is thought to reflect an overperfusion not essential in maintaining myocardial oxygen supply.

The stimulation of the sympathoadrenal system is seen at all levels of CO_2 exposure. The exact mechanism of stimulation is not known.

Ventilatory responses are stimulated by a dual combination of metabolic and respiratory acidosis. At moderate workloads with CO_2 below 4%, the effects of CO_2 and exercise act independently and cumulatively to increase respiration. At higher levels of CO_2 and exercise, ventilatory responses become taxed and further increases in respiration become limited.

Exercise tolerance is adversely affected by exposure to CO_2 above 2%. No exercise difficulty was noted at high workloads for 30 min with 2% CO_2. Exposure to 2% CO_2 for 30 days revealed adaptation to exercise to be slightly impaired. Exposure to 1.5% CO_2 for 42 days revealed an increased pulse rate response with moderate exercise and a prolonged return to normal. This observation was interpreted to reflect a reduction in cardiac reserve which may prove significant at higher workloads.

An analysis of health data from Polaris submarine patrols reveals no change in the incidence of cardiovascular disease in association with an improvement in environmental control.

Gastrointestinal

Basic Function

The few studies that have been performed relating CO_2 exposure to gastrointestinal (GI) function note an increase in gastric acidity with elevated CO_2 levels. Five subjects exposed to 1% CO_2 during an extended submarine patrol were tested for gastric acidity (ref. 32) (table 3). All five subjects were noted to have increased gastric acidity throughout the patrol period. During submarine patrols, symptoms of pyrosis (heartburn) are second only to respiratory symptoms in frequency (ref. 46).

Increased acid in the stomach predisposes an individual to numerous GI problems (ref. 38). The stomach lining is protected from damage by the digestive acids by secreting an internal layer of mucus. Increased acidity serves to break down this protective layer and can lead to gastritis and stomach ulceration. As acids leave the stomach and enter the duodenum, they are neutralized by pancreatic enzymes and HCO_3^-. An overexcretion of acids can overwhelm the capacity for neutralization and cause duodenal ulceration.

A valve prevents regurgitation of stomach acids into the esophagus, thereby preventing heartburn and esophageal ulceration. Increased acid production can compromise the function of this valve, thereby causing heartburn and esophageal problems.

An analysis of health data from Polaris submarine patrols indicates a decrease in the incidence of GI disease after 1967 (ref. 37) (table 1). On average, each patrol was about 60 days in length. In 1967, larger and more efficient CO_2 scrubbers were installed in submarines leading to a 33% reduction in environmental CO_2 from 1.2 to 0.8-0.9%. Illness rates for GI disease were second only to respiratory disease in frequency of occurrence. The greatest contributor to the fall in GI illness was a decrease in the incidence of gastroenteritis. The reduced incidence of GI disease was not seen in a comparison group of surface personnel.

Table 3. Effect of prolonged exposure to 1% CO_2 on gastric secretion during patrol (from Schaefer (ref. 32))

Condition	Total acid, degrees
Control period on air	41.2 ± 3.3
On 1.0% CO_2 for	
8 Days	54.2 ± 6.4
23 Days	57.4 ± 11.7
54 Days	64.0 ± 13.4
Post-patrol	
4 Weeks recovery on air	32.2 ± 6.1

Values are means ± SEM: $n = 5$. Data derived from Foster 1969.

Summary

An increase in gastric acidity has been noted with long term exposure to 1% CO_2. Increased gastric acidity can cause a variety of GI problems including ulceration and heartburn. During submarine patrols, GI disease was second only to respiratory disease in incidence. With improved environmental control, the incidence of GI disease decreased.

Extravehicular Activity

Exposure

The number and duration of EVAs to be performed is important in establishing limits for CO_2 exposure. Acute and chronic exposures to CO_2 lead to different physiologic responses. The duration and frequency of CO_2 exposure which will elicit acute and chronic physiologic responses must be determined in establishing exposure limits.

The number of EVAs required to build, maintain, and repair Space Station Freedom is a matter of debate. Estimates range from as low as 100 to over 5000 h per year (ref. 2). Worst case scenarios estimate the need for EVAs to be performed almost daily. Each EVA has a maximum 8 h duration. It is feasible that daily EVAs over several weeks may be required to fulfill certain tasks.

If the physiological effects were the only consideration, it would be appropriate, given the uncertainties involved, to establish EVA requirements for Space Station Freedom as conservatively as possible. Daily EVAs of 8 h duration are within the capacity of planned spacesuits and life support systems. Exposure limits for CO_2 should be based on the estimate that daily, 8 h EVAs may need to be performed on Space Station Freedom.

Lunar and Martian scenarios call for extended stays in each environment. Lunar excursions may last 6 months. Daily EVAs of 8 h duration are certainly feasible and may be required. Carbon dioxide exposure limits for EVA in Lunar and Martian environments should also be based on the possible need for daily 8 h EVAs.

Given that daily, 8-h exposures to elevated CO_2 may occur with EVA, raises the question as to whether physiologic responses will exhibit chronic or repetitive acute characteristics. Different physiologic responses occur with acute and chronic CO_2 exposure. The concentration of CO_2, the duration of exposure, the frequency of exposure, and the time period between exposures will likely all be important in separating acute from chronic CO_2 responses.

Very few studies have been performed concerning repetitive acute CO_2 exposure. Given that bone apparently acts to sequester CO_2 and that long time constants are involved in bone CO_2 transfer, implies that acute repetitive CO_2 exposures can lead to chronic physiologic responses. Studies evaluating repetitive 8-h CO_2 exposures are not known to this author. Additional experiments addressing the physiologic responses to repetitive CO_2 exposure are needed.

An option in setting exposure limits is to assume that repetitive 8-h CO_2 exposures produce chronic physiologic responses. The establishment of CO_2 exposure limits under this assumption would serve to promote safety. Assuming chronic exposure would necessitate setting a lower space suit CO_2 level. The periods of non-exposure would allow for off-gassing of accumulated CO_2 thereby reducing the effects of the gas.

Zero and Partial Gravity

Exercise– The metabolic cost of performing EVA has been evaluated. During Gemini, EVAs were occasionally noted to be difficult and exhausting (ref. 84). Although metabolic rates were not measured, it was apparent that crewmen worked beyond the heat removal capacity of their life support systems. The need for proper training and restraint were recognized as the most important factors in task completion.

Metabolic rates for EVA performed during Apollo and Skylab ranged from 100 to 500 kcal/hr (refs. 85 and 86). Work at 500 kcal/hr could be tolerated without difficulty provided that life support capability was adequate. Average energy cost was 200-250 kcal/hr and was felt to largely reflect the crewman's voluntary pacing of activity. Apollo EVAs required less energy expenditure in zero G (150 kcal/hr) than during lunar (235 kcal/hr) excursions. Energy expenditure during Space Shuttle EVA was noted to average about 200 kcal/hr (ref. 87).

The effect of breathing CO_2 in zero and partial G environments on exercise tolerance is speculative. The metabolic costs of performing EVA are not excessive. Periods of high workload do occur but can be limited in duration. Exercise tolerance with EVA was mostly limited by heat removal capacity of the life support system.

Exercise tolerance was affected by exposure to >2% CO_2 in terrestrial settings. Subjects could perform heavy exercise for 30 min breathing 2% CO_2. Adaptation to exercise was slightly impaired with long term exposure to 1.5% although task performance was normal. Current EVA exposure is limited to 1% CO_2 under nominal conditions. Given that exercise tolerance was essentially normal with 2% CO_2 exposure, this result implies that lower limits of exposure should be even less of a factor.

Zero and partial gravity may prove to have their greatest effect on exercise with respect to cardiac deconditioning. Zero gravity exposure provides for fluid redistribution in the body. A loss of fluid (diuresis) ensues. Fluid losses can limit the ability of the cardiovascular system to respond to additional stresses.

The observation that adaptation to exercise was slightly impaired with long term exposure to 1.5% CO_2 most likely reflects a decrease in cardiac reserve. Any cumulative effect of CO_2 exposure and zero G cardiac deconditioning on exercise tolerance is also unknown.

Bone– Zero gravity exposure leads to a loss of bone calcium similar to disuse osteoporosis. The weight bearing bones of the lower body are particularly affected. Radiographic and photon absorptiometric measurements on Gemini and Apollo astronauts confirmed bone loss even after short duration space flights.

Urinary calcium loss in Skylab crewmembers reached a plateau after 30 days in flight whereas fecal calcium excretion increased throughout exposure. It has been estimated that 2% of the total body calcium stores were lost by each Skylab crewmember during an 84-day trip. Soviet researchers have reported upwards of 7% bone calcium loss from weight bearing bones after 6 months of spaceflight.

Bone also acts as a storage site for CO_2. Chronic exposure to low dose CO_2 is characterized by cycling of bone stores of calcium and CO_2. Given the loss of bone calcium induced by zero gravity, any additional losses induced by CO_2 exposure are obviously of concern. The significance and contribution of bone changes induced by low dose CO_2 exposure deserves further evaluation. The threshold below which CO_2 exposure does not cause bone changes needs to be determined.

Bone calcium loss due to zero G is also significant in that an increase in urinary calcium excretion occurs. Excretion of large amounts of urinary calcium increases the chances of kidney stone formation. Most kidney stones are composed of calcium. Exposure to CO_2 leads to increases in

urinary calcium and renal calcification. The combination of calcium excretion from zero G and CO_2 exposure may place an astronaut at high risk of kidney stone formation.

An analysis of health data from Polaris submarine patrols indicates a decrease in the incidence of genitourinary disease in association with an improvement in environmental control. Average CO_2 levels decreased from 1.2 to 0.8-0.9%. The decrease in genitourinary illness was mostly due to a fall in the occurrence of kidney stones.

Studies with guinea pigs reveal a threshold of 0.5% CO_2 for the occurrence of renal calcification. The existence and level of such a threshold in humans is unknown. Establishing a threshold limit for CO_2 induced kidney calcification would help to set exposure limits for chronic CO_2 exposure. Further evaluation of this problem is recommended.

Oxygen

EVA breathing gas is currently composed of 100% oxygen. The pressure of the space suit is planned to range anywhere from 4.3 to 8.4 psi. Regardless of the final operating pressure, astronauts will be exposed to concentrations of O_2 above normal limits. Exposure to high concentrations of O_2 can produce convulsions and death. A full discussion of O_2 exposure is beyond the scope of this paper.

It is important to realize that O_2 is a physiologically active gas. Both O_2 and CO_2 can be looked upon as medications. Both gases produce physiologic changes at varying concentrations of exposure. Concentrations of either gas that are too high or too low can cause damage to health and even death.

The issue of concurrent exposure to above normal concentrations of both gases is important (ref. 88). The interaction of the physiologic effects of each gas may play an important role in determining exposure limits. Drug-drug interactions can be significant in that additive or counter balancing effects may prove of concern. Setting exposure limits for CO_2 must be considered with concurrent O_2 exposure in mind.

Oxygen causes vasoconstriction thereby decreasing blood flow. Exposure of 33 men to 100% O_2 at 1 and 3.5 atmospheres (atm) revealed decreased cerebral perfusion and a slight rise in cerebral CO_2 levels (ref. 89). Neither change is thought to be the inherent cause of O_2 toxicity. The toxicity observed from high dose O_2 may result from its direct toxic effect on cerebral function.

Exposure of 4 subjects to 100% O_2 at 3 atm revealed marked increases in cerebral venous O_2 on the addition of 2% CO_2 (ref. 90). It was postulated that the vasodilating effect of CO_2 would increase cerebral blood flow thereby increasing cerebral venous O_2. This effect would serve to increase the risk of oxygen induced convulsions.

Mice exposed to high dose O_2 and CO_2 concurrently were evaluated for induction of convulsions (ref. 91). Exposure to 100% O_2 was convulsigenic at 3 atm and fatal at 4 atm. The addition of CO_2 at high atmospheric pressure shortened the time to convulsion and death. Carbon dioxide in 100% O_2 at 1 atm was fatal at very high levels but did not induce convulsions. These results may reflect concurrent effects on cerebral blood flow.

Oxygen and CO_2 mixtures are used in the treatment of central retinal artery obstruction in an attempt to improve retinal oxygenation. Oxygen causes vasoconstriction thereby decreasing blood flow. Carbon dioxide is added to the breathing gas in an attempt to counter this effect. The vasoconstriction noted in the retinas of 3 subjects exposed to 100% O_2 was not reversed by the addition of 5% CO_2 (ref. 92). In addition, 5% CO_2 in air did not produce substantial retinal vasodilation.

Exposure to O_2 leads to changes in ventilation. Upon the administration of high dose O_2, a transient phase of respiratory depression occurs (ref. 93). Maximal ventilation and respiratory rate are both decreased. The rapidity of the response suggests a direct chemo-reflexic action. A phase of mild hyperventilation then ensues (ref. 89). It is postulated that increased O_2 interferes with central CO_2 transport producing a rise in cerebral acidity. Hyperventilation ensues in an attempt to limit this effect.

Exposure to CO_2 in O_2 stimulates respiration to a greater extent than exposure to CO_2 in air (ref. 94). The increase in ventilation from 1% CO_2 in O_2 was similar to that of breathing 2% CO_2 in air. Each gas may stimulate respiration separately. Breathing a combination of the two gases leads to a cumulative response.

Five subjects were exercised for 30 min while exposed to gas mixtures of 0-6% CO_2 in air or in 60% O_2 (ref. 85). Ventilation was lower and arterial P_{CO_2} was higher with 0% CO_2 in 60% O_2 than in air. Ventilation and arterial P_{CO_2} progressively rose for each increase in CO_2 for both air and 60% O_2 conditions. Acidity was higher with 60% O_2 vs. air and with increasing CO_2 in both conditions.

Summary

The number and duration of EVAs is important in establishing CO_2 exposure limits. Estimates vary widely as to the number of EVAs which will need to be performed. Conservative estimates will serve to promote safety and flexibility. Exposure limits should be based on the estimate that daily EVAs of 8-h duration may be performed

on Space Station Freedom and during Lunar and Martian excursions.

Very few studies have been performed concerning repetitive, acute CO_2 exposures. Assuming that daily 8-h exposures to CO_2 would produce chronic physiologic responses would necessitate setting a lower limit for CO_2 and would serve to promote safety. Additional experiments that establish the physiologic responses to daily 8-h exposures to low dose CO_2 are needed.

The metabolic cost of performing EVA has been estimated to range from 100 to 500 kcal/hr. Average energy cost was 200-250 kcal/hr. Exercise tolerance during EVA was mostly limited by the heat removal capacity of the life support system.

The effect of breathing CO_2 in zero and partial G environments on exercise tolerance is speculative. Exercise tolerance is essentially normal with CO_2 exposures <2% in terrestrial settings.

Zero gravity exposure leads to a loss of bone calcium similar to disuse osteoporosis. Chronic exposure to low dose CO_2 leads to cycling of bone calcium and CO_2.

Exposure to CO_2 leads to increases in urinary calcium excretion and renal calcification. The combination of calcium excretion from zero G and CO_2 exposure may place an astronaut at high risk of kidney stone formation. Studies of guinea pigs reveal a threshold of 0.5% CO_2 for the occurrence of renal calcification. The existence and level of such a threshold in humans is unknown.

The interaction of breathing high concentrations of O_2 and CO_2 may play an important role in establishing exposure limits for each gas. High dose O_2 can cause convulsions. The addition of CO_2 lowers the time to convulsion with concurrent O_2.

Exposure to O_2 stimulates respiration. The combination of O_2 and CO_2 stimulates ventilation in a cumulative fashion as follows. Ventilation, arterial P_{CO_2} and acidity all increased progressively with increases of CO_2 in O_2.

Recommendations

Organ System Review

Respiratory– Respiration is stimulated by CO_2 exposure. Ventilation is increased 15% with 1% CO_2 and 50% with 2% CO_2. Conscious awareness of ventilation and dyspnea on exertion is noted at 2% CO_2. Exposure to 100% O_2 and 1% CO_2 concurrently stimulates respiration to a level similar to that induced by 2% CO_2 in air.

Chronic exposure to <2% CO_2 leads to 20 day cycles of uncompensated and compensated respiratory acidosis. Acid-base changes are small. Intermittent exposures to CO_2 have not been adequately evaluated.

Histopathologic changes in guinea pig lungs have been noted with exposure to 1% CO_2. No changes were seen with exposure to 0.5% CO_2. Increases in V/Q mismatching and dead space volumes were observed in human studies with chronic exposure to 1% CO_2.

A decrease in the incidence of respiratory disease was noted in submariners coincident with a decrease in CO_2 levels from 1.2% to 0.8-0.9%. The fall in the rate of respiratory disease was the greatest contributor to the improved health statistics observed with improved environmental control.

Renal– Renal responses are minimally stimulated with <3% CO_2 exposure. Excluding calcium, electrolyte changes of the blood and urine are small.

Bone serves as a storage site for CO_2. Cycling of bone calcium stores occurs with long term CO_2 exposure. Histologic changes in bone have been noted in guinea pigs exposed to 1% CO_2. The effect of these changes on bone strength is unknown. Zero G exposure induces bone loss similar to disuse osteoporosis. The combination of zero G and CO_2 exposure on bone strength is unknown.

Increases in urinary and blood calcium levels occur with low dose CO_2 exposure. Renal calcification has been noted in guinea pigs with exposure to as low as 0.5% CO_2.

A decrease in the incidence of GU disease was noted in submariners coincident with a decrease from 1.2% to 0.8-0.9% CO_2. The main factor was due to a fall in the incidence of kidney stones. With 0.8-0.9% CO_2, the incidence of GU disease was similar between submariners and surface personnel.

The combination of bone calcium loss from zero G and increased urinary calcium from CO_2 may place astronauts at high risk of kidney stone formation.

Neurologic– Performance was impaired in subjects exposed to 3% CO_2 for 6 days. No change in speed or accuracy of performance was noted during long term exposures to 2% and 1.5% CO_2. EEG, psychomotor, and biorhythm testing was all normal.

Carbon dioxide is a potent cerebrovascular dilating agent. Exposure of humans to CO_2 below 2.5% apparently has little effect on cerebral blood flow. Animal studies show progressive increases in cerebral blood flow with elevated CO_2 levels.

High levels of O_2 can cause seizures. The addition of CO_2 to high dose O_2 lead to the faster onset of seizure activity in mice. It was postulated that cerebrovascular dilation from CO_2 allows for greater O_2 delivery to the brain and faster onset of O_2 toxicity.

Neurotransmitter production and function is affected by elevated CO_2. An increase in the incidence of neuropsychiatric disorders was seen in submariners coincident with a decrease in CO_2 from 1.2% to 0.8-0.9%. It was postulated that increased stress and longer periods of isolation were the causative factors.

Cardiovascular– Chronic, low level exposures to CO_2 leads to simultaneous vasodilation and sympathoadrenal stimulation. The combination of effects causes a slight rise in blood pressure, heart rate, and cardiac output. No significant ECG changes or arrythmias occur. Subjects exposed to 1.5-2% CO_2 for long durations exhibited unchanged basic cardiovascular responses.

Exposure to carbon dioxide causes an increase in coronary blood flow above that required to maintain myocardial O_2 supply.

Ventilatory responses are stimulated by a dual combination of metabolic and respiratory acidosis. The effects of CO_2 and exercise act independently and cumulatively to increase respiration.

Exercise tolerance is adversely affected by exposure to CO_2 above 2%. Exposure to 1.5-2% CO_2 revealed adaptation to exercise to be slightly impaired but performance was normal. CO_2 exposure may cause a reduction in cardiac reserve. Zero G leads to a diuresis and cardiac deconditioning. The cumulative effects of CO_2 and zero G on exercise tolerance are unknown.

No change in the incidence of cardiovascular disease was noted in submariners in association with an improvement in environmental control.

Gastrointestinal– An increase in gastric acidity was noted in subjects on long term exposure to 1% CO_2. During submarine patrol, GI disease was second only to respiratory disease in incidence. With improved environmental control, the incidence of GI disease decreased.

Discussion

Current NASA standards call for EVA limits on CO_2 exposure to be set at 1% for nominal operation and 2% for short periods of very heavy workload. Based on evidence reported in this study, these standards should not be liberalized and may even need to be tightened.

On future space endeavors, daily 8 h EVAs may need to occur. Establishing CO_2 exposure limits based on this estimate is appropriate.

The physiologic responses to repetitive 8-h CO_2 exposure requires further study. Exposure limits based on the possibility that chronic physiologic changes will occur will be conservative estimates which will serve to promote safety.

Current NASA EVA breathing mixtures may reach a composition of 1% CO_2 in 100% O_2. The respiratory stimulation of breathing 1% CO_2 in 100% O_2 is similar to that of breathing 2% CO_2 in air. Conscious awareness of ventilation and dyspnea on exertion occur at the level of respiratory stimulation produced by 2% CO_2 in air.

Exercise is an additional, independent stimulus to respiration. The combination of increased CO_2, exercise, and high level O_2 on ventilation may cause significant respiratory changes. Until this is determined, CO_2 exposure should remain at or below 1% CO_2.

Cycling of bone calcium stores occurs with long term CO_2 exposure. Histologic changes in bone have been noted in guinea pigs exposed to 1% CO_2. Since bone loss in zero G is a problem, any additional loss in bone or bone strength due to CO_2 exposure should be studied. The determination of a threshold limit below which CO_2 exposure does not produce bone changes would help to set exposure limits.

Neurologic changes due to low dose CO_2 do not appear to be significant. Performance is not affected with chronic 2% CO_2 exposure. Little if any change occurs in cerebral blood flow. The addition of CO_2 to 100% O_2 may be significant in that the time to onset of seizures is decreased. With higher operating pressures for future spacesuits, O_2 toxicity may become more of a concern. The influence of CO_2 exposure on O_2 toxicity deserves further attention.

Cardiovascular responses are basically normal with exposure to CO_2 below 2%. A slowing in the adaptation to exercise with CO_2 has been postulated to reflect a decrease in cardiac reserve. The combination of this effect and the effect of cardiac deconditioning imposed by zero G on cardiac performance needs study.

The finding of histopathologic changes in the lungs of guinea pigs exposed to low dose CO_2 is of potential concern. The physiologic significance of the observed histologic changes is unknown. A threshold of 0.5% CO_2 apparently exists for the occurrence of histologic changes in guinea pig lungs. The existence of histologic changes in human lungs from CO_2 exposure is unknown.

An improvement in environmental control in association with the reduction of CO_2 from 1.2 to 0.8-0.9% led to a

significant decrease in the incidence of respiratory disease in submariners. The fall in the incidence of respiratory disease was the greatest contributor to improved health. With 0.8-0.9% CO_2, the incidence of respiratory disease was similar between submariners and surface personnel. These observations support the reduction of CO_2 exposure during EVA to at least 0.8%.

The findings of histopathologic changes in the kidneys of guinea pigs exposed to low dose CO_2 is also of potential concern. A threshold limit for CO_2 below which changes do not occur in guinea pig kidneys has not been established. Exposures as low as 0.3% CO_2 have caused renal calcification.

A decrease in the incidence of kidney stones was observed in submariners in association with a reduction in CO_2 from 1.2 to 0.8-0.9%. The majority of kidney stones are composed of calcium. Increased cycling of plasma and urinary calcium excretion occurs with low dose CO_2 exposure. A similar response is likely if repetitive CO_2 exposures induce chronic physiologic changes. The additional calcium excretion induced by zero gravity will contribute to the calcium excretion caused by low dose CO_2 exposure and will likely increase the incidence of kidney stone formation. In order to limit incidence of GU disorders, a reduction in the allowable EVA exposure limit for CO_2 to 0.5% may be appropriate.

A decrease in the incidence of GI symptoms in submariners was noted in association with lowering CO_2 levels from 1.2 to 0.8-0.9%. The incidence of GI symptoms was second only to respiratory problems in occurrence. Increased gastric acidity has been noted experimentally with exposure to 1% CO_2. These observations support lowering CO_2 exposure limits during EVA to at least 0.8%.

Drawing conclusions from a variety of disparate studies in order to set CO_2 exposure limits for EVA is difficult. Conditions between experiments and their application to EVA vary greatly. Any conclusions drawn from such experiments will necessarily be limited.

Experiments which simulate the gases and exposures likely to be confronted during EVA would be the most helpful in establishing CO_2 exposure limits for EVA. Monitoring physiologic and histologic changes to repetitive, daily 8 h exposures to low dose CO_2 and 100% O_2 in both humans and animals is recommended. The application of the information derived from such experiments to zero and partial gravity environments would need to be carefully evaluated.

Recommendations

Experiments evaluating the physiologic responses to intermittent, repetitive exposures to low dose CO_2 and 100% O_2 mixtures should be performed. Based on the results presented in this paper, a lowering of the current NASA standard for CO_2 exposure during EVA should be considered. A reduction in the current NASA standard for CO_2 exposure during EVA of 1% (7.6 mmHg) for nominal and 2% (15.2 mmHg) for heavy exertion to 0.5% (3.8 mmHg) for nominal and 1% (7.6 mmHg) for heavy exertion may be prudent. Only through further experimentation can this issue be settled. At a minimum, the current NASA standard should not be liberalized.

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13. ABSTRACT ***(Maximum 200 words)***

The intent of this paper was to review the research pertaining to human exposure to carbon dioxide (CO_2) and to recommend allowable exposure limits for extravehicular activity (EVA). Respiratory, renal, and gastrointestinal systems may be adversely affected by chronic low dose CO_2 exposure. Ventilation was increased 15% with 1% CO_2 and 50% with 2% CO_2. Chronic exposure to <2% CO_2 led to 20 day cycles of uncompensated and compensated respiratory acidosis. Acid-base changes were small. Histopathologic changes in guinea pig lungs have been noted with long term exposure to 1% CO_2. No changes were seen with exposure to 0.5% CO_2. Cycling of bone calcium stores with associated changes in blood and urinary calcium levels occurs with long term CO_2 exposure. Histologic changes in bone have been noted in guinea pigs exposed to1% CO_2. Renal calcification has been noted in guinea pigs with exposure to as low as 0.5% CO_2. An increase in gastric acidity was noted in subjects with long term exposure to 1% CO_2. Cardiovascular and neurologic function were largely unaffected. A decrease in the incidence of respiratory, renal, and gastrointestinal disease was noted in submariners coincident with a decrease in ambient CO_2 from 1.2% to 0.8-0.9%. Oxygen (O_2) and CO_2 stimulate respiration independently and cumulatively. The addition of CO_2 to high dose O_2 led to the faster onset of seizure activity in mice. Experiments evaluating the physiologic responses to intermittent, repetitive exposures to low dose CO_2 and 100% O_2 mixtures should be performed. A reduction in the current NASA standard for CO_2 exposure during EVA of 1% (7.6 mmHg) for nominal and 2% (15.2 mmHg) for heavy exertion to 0.5% (3.8 mmHg) for nominal and 1% (7.6 mmHg) for heavy exertion may be prudent. At a minimum, the current NASA standard should not be liberalized.

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