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Allowable Exposure Limits for Carbon Dioxide During Extravehicular Activity

Andrew J. Seter, M.D., Ames Research Center, Moffett Field, California

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Ames Research Center
Moffett Field, California 94035-1000



Table of Contents

| | Page |
|---|-------------|
| Nomenclature | v |
| Summary | 1 |
| Introduction | 1 |
| Purpose | 1 |
| Extravehicular Activity Considerations | 1 |
| Carbon Dioxide | 2 |
| Acid-Base Chemistry | 2 |
| Normal Respiratory Parameters | 3 |
| Respiratory | 4 |
| Acute Exposures to CO ₂ | 4 |
| Ventilation | 4 |
| Acid-base changes | 5 |
| Symptoms | 7 |
| Variability | 7 |
| Chronic Exposures to CO ₂ | 8 |
| Introduction | 8 |
| Physiologic responses | 9 |
| Intermittent Exposures to CO ₂ | 10 |
| Pathology | 11 |
| Dead space | 11 |
| Histology | 12 |
| Submarine studies | 12 |
| Summary | 13 |
| Renal | 14 |
| Introduction | 14 |
| Acid-Base Status | 14 |
| Bone | 15 |
| Calcium | 15 |
| Histology | 15 |
| Electrolytes | 16 |

| | |
|--|----|
| Pathology | 17 |
| Histology | 17 |
| Submarine studies | 17 |
| Summary | 17 |
| Neurologic | 18 |
| Performance | 18 |
| Blood Flow | 19 |
| Neurotransmission | 19 |
| Summary | 20 |
| Cardiovascular | 20 |
| Basic Responses | 20 |
| Coronary (Myocardial) Blood Flow | 21 |
| Sympathoadrenal Function | 22 |
| Exercise | 22 |
| Summary | 24 |
| Gastronintestinal | 25 |
| Basic Function | 25 |
| Summary | 25 |
| Extravehicular Activity | 25 |
| Exposure | 25 |
| Zero and Partial Gravity | 26 |
| Exercise | 26 |
| Bone | 26 |
| Oxygen | 27 |
| Summary | 27 |
| Recommendations | 28 |
| Organ System Review | 28 |
| Respiratory | 28 |
| Renal | 28 |
| Neurologic | 28 |
| Cardiovascular | 29 |
| Gastrointestinal | 29 |

| | |
|-------------------------|----|
| Discussion..... | 29 |
| Recommendations..... | 30 |
| References | 30 |

Nomenclature

| | | | |
|--------------------------------|-------------------------|-----------------------------|------------------------------------|
| α | solubility coefficient | LiOH | lithium hydroxide |
| atm | atmospheres | L/min | liters per minute |
| CBF | cerebral blood flow | MBF | myocardial blood flow |
| Cl | chloride | meq/L | milliequivalents per liter |
| CO ₂ | carbon dioxide | min | minute |
| CSF | cerebrospinal fluid | ml | milliliter |
| ECG | electrocardiogram | ml/min | milliliters per minute |
| EEG | electroencephalogram | mmHg | millimeters mercury |
| EST | electroshock therapy | N ₂ | nitrogen |
| EVA | extravehicular activity | Na | sodium |
| GI | gastrointestinal | NMR | nuclear magnetic resonance |
| GU | genitourinary | O ₂ | oxygen |
| H ⁺ | hydrogen ion | P _{CO₂} | partial pressure of carbon dioxide |
| HCO ₃ ⁻ | bicarbonate | pH | -log[H ⁺] |
| H ₂ CO ₃ | carbonic acid | pK | dissociation constant |
| H ₂ O | water | psi | pounds per square inch |
| K | potassium | psia | pounds per square inch absolute |
| kcal/hr | kilocalories per hour | 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 (CO₂) and to recommend allowable exposure limits for extravehicular activity (EVA). Respiratory, renal, and gastrointestinal systems may be adversely affected by chronic low dose CO₂ exposure. Ventilation was increased 15% with 1% CO₂ and 50% with 2% CO₂. Chronic exposure to <2% CO₂ 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% CO₂. No changes were seen with exposure to 0.5% CO₂. Cycling of bone calcium stores with associated changes in blood and urinary calcium levels occurs with long term CO₂ exposure. Histologic changes in bone have been noted in guinea pigs exposed to 1% CO₂. Renal calcification has been noted in guinea pigs with exposure to as low as 0.5% CO₂. An increase in gastric acidity was noted in subjects with long term exposure to 1% CO₂. 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 CO₂ from 1.2% to 0.8-0.9%. Oxygen (O₂) and CO₂ stimulate respiration independently and cumulatively. The addition of CO₂ to high dose O₂ led to the faster onset of seizure activity in mice. Experiments evaluating the physiologic responses to intermittent, repetitive exposures to low dose CO₂ and 100% O₂ mixtures should be performed. A reduction in the current NASA standard for CO₂ 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 (CO₂) 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 CO₂ from the space suit is unnecessary, however, from a physiologic viewpoint. Humans can breathe small quantities of CO₂ for prolonged periods without any apparent

long term ill effects. The allowable limit of residual CO₂ 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 CO₂ levels in the space suit of 7.6 mmHg under nominal operation and 15.2 mmHg for periods of heavy exertion. Currently, CO₂ is removed from the suit with a lithium hydroxide (LiOH) absorbent. Relaxation of the current CO₂ 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 CO₂ limits may also allow the consideration of technologies which are superior to LiOH absorbents but which cannot achieve the current CO₂ standard.

The effect of carbon dioxide on the body is protean. The maintenance of CO₂ 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 CO₂, however, compensation is time dependent and not complete. Each organ system is effected differently by variations in CO₂. An understanding of each organ system and its inherent response to altered CO₂ levels is necessary in order to recommend exposure limits.

This paper will address the effects of high levels of CO₂ on physiologic performance of the various organ systems of the body. Attention will be paid to the specific level of CO₂ which causes physiologic decrement in each organ system. The highest level of CO₂ 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 CO₂ exposures for portable life support will be made.

Extravehicular Activity Considerations

An awareness of the extravehicular and terrestrial environments is important when addressing CO₂ exposure limits. Terrestrial exposure to CO₂ 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% CO₂, therefore, represents an increment of 7.6 mmHg. Ambient CO₂ comprises only 0.03% (0.228 mmHg) of atmospheric gases. Exposure to 1%

CO₂ during EVA represents 7.6 mmHg CO₂ 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 CO₂ in the body is dependent on the partial pressure of CO₂ only (P_{CO₂}). Therefore, the operating pressure of the suit will not affect the CO₂ 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 (O₂). 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 O₂ and CO₂ concentrations above terrestrial norms, this produces a concurrent hyperoxic and hypercarbic (high CO₂) EVA environment. Both O₂ and CO₂ 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 CO₂ 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, CO₂ would accumulate to harmful levels quickly. An appreciation of the physiologic significance of CO₂ is required in order to set exposure limits.

Changes in CO₂ concentration directly influence the acid-base status by a mechanism which will be discussed shortly. An excessive accumulation or elimination of CO₂ is physiologically detrimental, largely due to the resultant change in acidity. In order to control acidity, an elaborate control mechanism for CO₂ has developed in the body.

Acute and chronic changes in CO₂ are compensated for in different fashions. An acute accumulation of CO₂ 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 CO₂ 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 CO₂ 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 CO₂ will be vented between excursions. If breathing air for 16 h is not sufficient to eliminate 8 h of accumulated CO₂, repetitive EVAs may lead to the establishment of chronic compensatory mechanisms. If accumulated CO₂ 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 CO₂. These responses will be discussed within the context of each organ system.

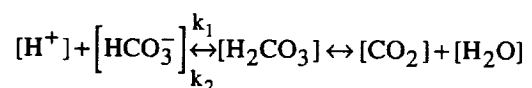
Acid-Base Chemistry

A review of acid-base chemistry reveals the significant role of CO₂ in maintaining acidity (ref. 3). Acidity is defined as the negative logarithm of the concentration of hydrogen ions:

$$\text{pH} = -\log[\text{H}^+]$$

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, H₂CO₃, and bicarbonate, HCO₃⁻:



The constants k₁ and k₂ 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 $37^\circ C$, 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

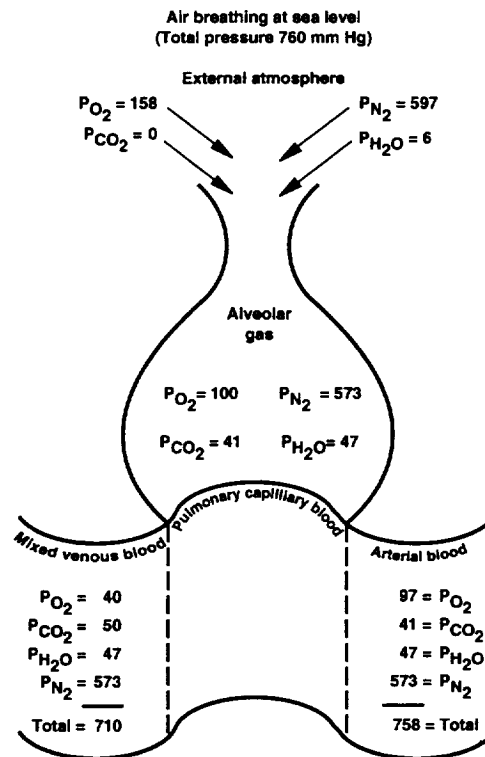


Figure 1. Breathing air at sea level. The partial pressures of each of the major gaseous constituents of the normal external atmosphere are shown as different from the tensions of the same gases in the pulmonary alveoli (from Lambertsen (ref. 4)).

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 CO₂ 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 CO₂ diffuses into the blood. Venous blood returning to the lung has a P_{O₂} of 40 mmHg and a P_{CO₂} of 50 mmHg. Within the lung, CO₂ 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 CO₂

Ventilation—Respiratory stimulation is noted with acute exposure to elevated CO₂. Respiratory minute volume (RMV) increases steadily with increased concentrations of

CO₂ (ref. 5) (fig. 3). RMV increases gradually with CO₂ below 2%, but rises more sharply thereafter (ref. 6). A curvilinear relationship appears to apply with exposures below 5% CO₂. Above 5% CO₂, RMV increases in a more linear fashion (ref. 7). A plateau effect is noted above 10% CO₂ as respiratory responses become taxed. At 25% CO₂, RMV is pushed to its physiologic limit and further increases in CO₂ do not elicit an additional increase in RMV (ref. 5).

Resting RMV is about 7.5 L/min. At 1% CO₂, RMV is increased 15% to 8.5 L/min (ref. 7). Conscious awareness of increased respiration begins at 2% CO₂ as RMV rises 50% to 11 L/min. At 3% CO₂, RMV is doubled and the onset of uncomfortable breathing (dyspnea) is noted. Above 5% CO₂, RMV continues to rise and individuals become increasingly symptomatic.

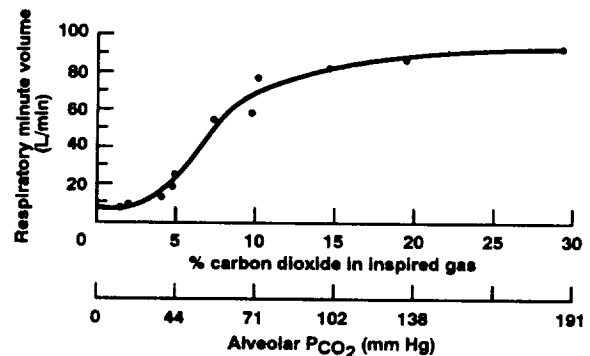


Figure 3. Relationships between respiratory minute volume and inspired CO₂ concentration in man. Points indicate averages of peak values. Solid circles indicate measurements in normal men; open circles are measurements in psychoneurotic patients (from Lambertsen (ref. 5)).

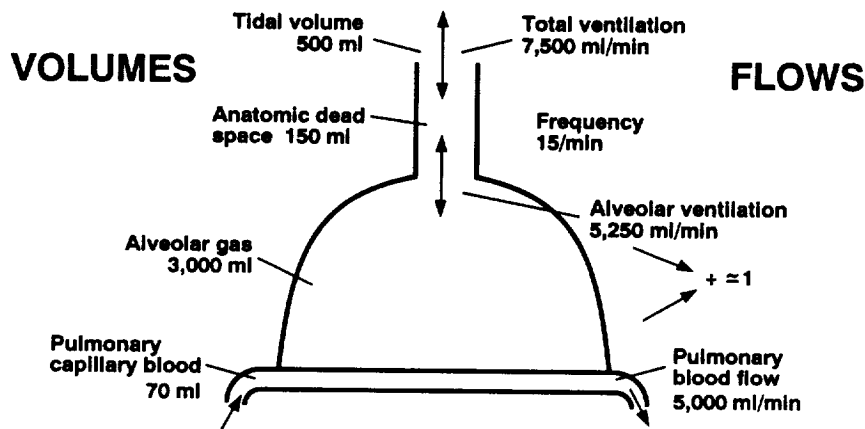


Figure 2. Diagram of a lung showing typical volumes and flows. There is considerable variation around these values. Modified from JB West. *Ventilation/Blood Flow and Gas Exchange*. Oxford, Blackwell, 1977, p. 3 (from West (ref. 1)).

The increase in RMV below 3% CO₂ is primarily due to an increase in tidal volume. At 2% CO₂, 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% CO₂, a rise in both tidal volume and respiratory rate are noted (ref. 9).

With acute exposure to CO₂ below 5%, respiratory responses stabilize within 15 min (ref. 9). Higher concentrations of CO₂ require longer time periods for stabilization.

The nature of the respiratory response with CO₂ 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_{CO₂} (Pa_{CO₂}) rises. The rise in arterial P_{CO₂} indicates that respiratory responses are insufficient to eliminate the additional CO₂. As arterial P_{CO₂} rises, carbon dioxide begins to accumulate in the body above normal levels.

Arterial P_{CO₂} rises steadily with increased CO₂ exposure in a curvilinear fashion (ref. 14) (fig. 4). Arterial P_{CO₂} rises even with CO₂ exposures of 1% (ref. 15). Whether increased RMV is sufficient to keep arterial P_{CO₂} at normal levels even with very small increases in CO₂ is a matter of debate.

The stimulus for the increase in respiration with CO₂ exposure is also open to debate (refs. 11 and 16). Whether it is CO₂ itself or the subsequent acid-base changes caused by CO₂ 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 CO₂ exposure (ref. 17). Contractility and the time to onset of fatigue were reduced by CO₂ exposure (refs. 18 and 19). The influence of such an effect on ventilatory function is undetermined.

Acid-base changes— Initial exposure to elevated CO₂ leads to the development of an acute respiratory acidosis. As CO₂ levels rise in the body, pH falls. As the diaphragm attempts to return the pH to normal, increased ventilation ensues. As CO₂ is eliminated, the pH begins to return toward normal. Since the primary cause of the

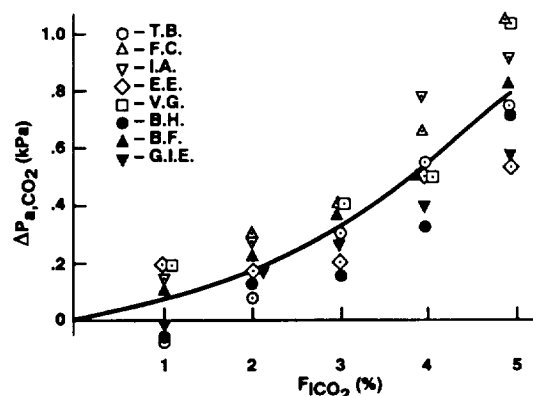


Figure 4. The change in arterial P_{CO₂} ($\Delta P_{a,CO_2}$) at five different levels of inspired CO₂ (F_{i,CO_2}) in eight healthy subjects. Each subject is designated with one symbol. The curve is of the form $(aF_{i,CO_2} + b(F_{i,CO_2})^2)$. H_j , where a and b are common to all individuals, while 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 CO₂ are seen quickly. Exposure to 1-2% CO₂ for only 6 min led to a decrease in pH (ref. 15). Progressive exposure to increasing levels of CO₂ (P_{I,CO₂}) in 30-min increments showed a steady decrease in pH (ref. 12) (fig. 5). During the fifth minute at P_{I,CO₂} of 42 Torr, Pa_{CO₂} was lower and PH was higher ($P < 0.05$) than during the remainder of the period. During the fourth control period, pH and HCO₃⁻ 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_{CO₂} between room air breathing (P_{I,CO₂} < 0.4 Torr) and inhalation of gas mixtures with a P_{I,CO₂} of 7 and 14 Torr. Generally, acute CO₂ 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% CO₂ 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_{CO₂} and pH (refs. 20 and 11). Others have reported sharp increases in pH with P_{CO₂} above 2.2% (ref. 6).

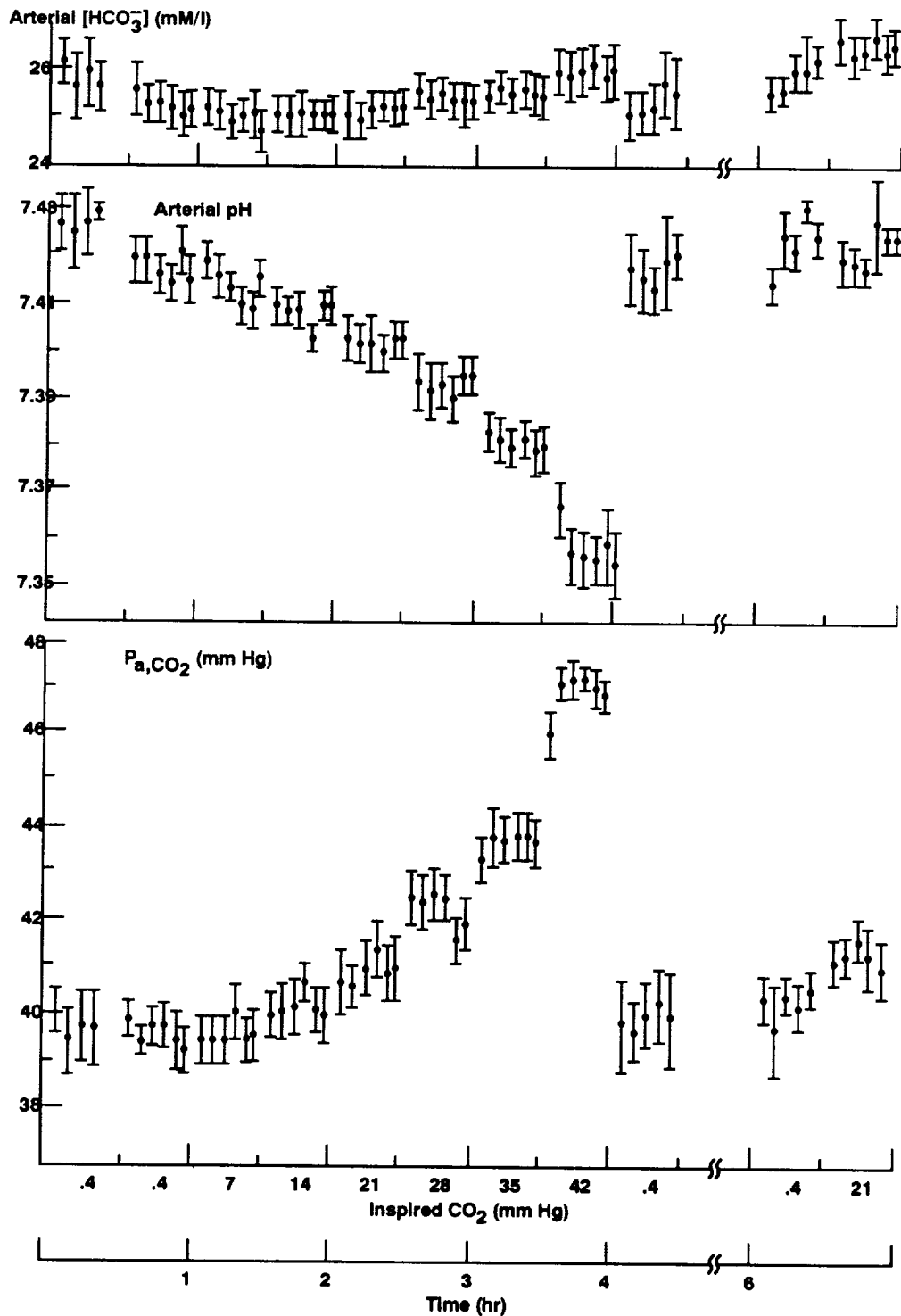


Figure 5. Mean (\pm SE) arterial PCO_2 , pH, and HCO_3^- of 10 subjects over 7 h during which chamber PO_2 was 147 Torr, while chamber PCO_2 was altered as indicated (study 2) (from Forster (ref. 12)).

Significance bands relating PCO_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 CO₂ 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 CO₂ 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 CO₂ (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 CO₂.

Acute exposures to CO₂ of less than 2% produce few symptoms. Dyspnea on exertion and conscious awareness of increased respiration begins near 2% CO₂. The onset of dyspnea at rest is noted with breathing 3% CO₂. After termination of exposure to 3% CO₂, respiratory symptoms quickly abate but headaches occasionally occur.

Inhalation of 4-5% CO₂ for 30 min causes dyspnea, sweating, dizziness, and headaches. Breathing 6% CO₂ 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% CO₂ led to marked symptomology within minutes (ref. 7). Further increases in CO₂ lead to convulsions and loss of consciousness in minutes.

Variability— The respiratory response to increased CO₂ displays marked individual variability (refs. 25, 11, 5, and 26). Subjects exposed to varying concentrations of CO₂ 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_{CO₂}. These individuals may have an inherently decreased sensitivity to CO₂. Individuals in the high ventilation group have a higher resting RMV and a lower arterial P_{CO₂}.

On exposure to elevated CO₂, 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 CO₂ may account for these observations (ref. 27).

Exposure to low levels of CO₂ tends to exaggerate the differences between the ventilation groups. A progressive rise in CO₂ tends to diminish the difference so that at 7.5% CO₂, no difference is noted (ref. 26). It is likely that

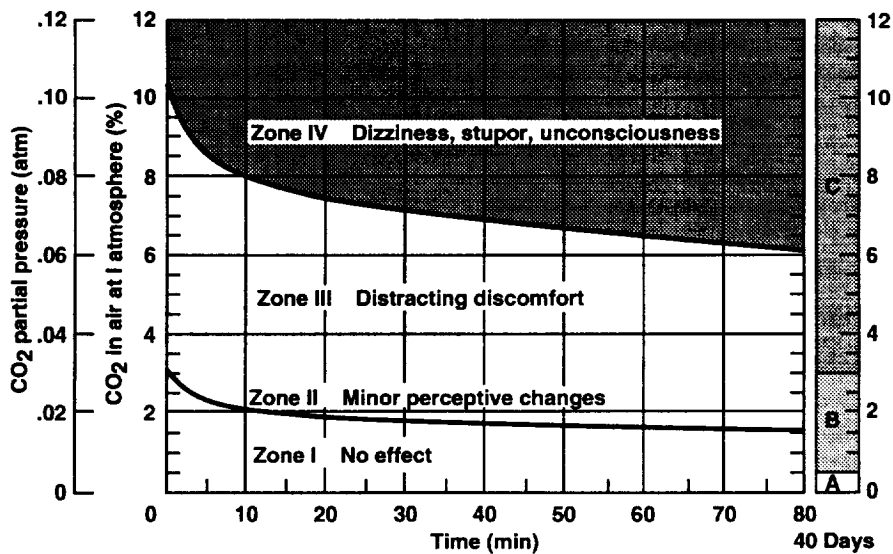


Figure 6. Relation of physiological effects to carbon dioxide concentration and exposure period (from U. S. Navy Diving Gas Manual (ref. 23)).

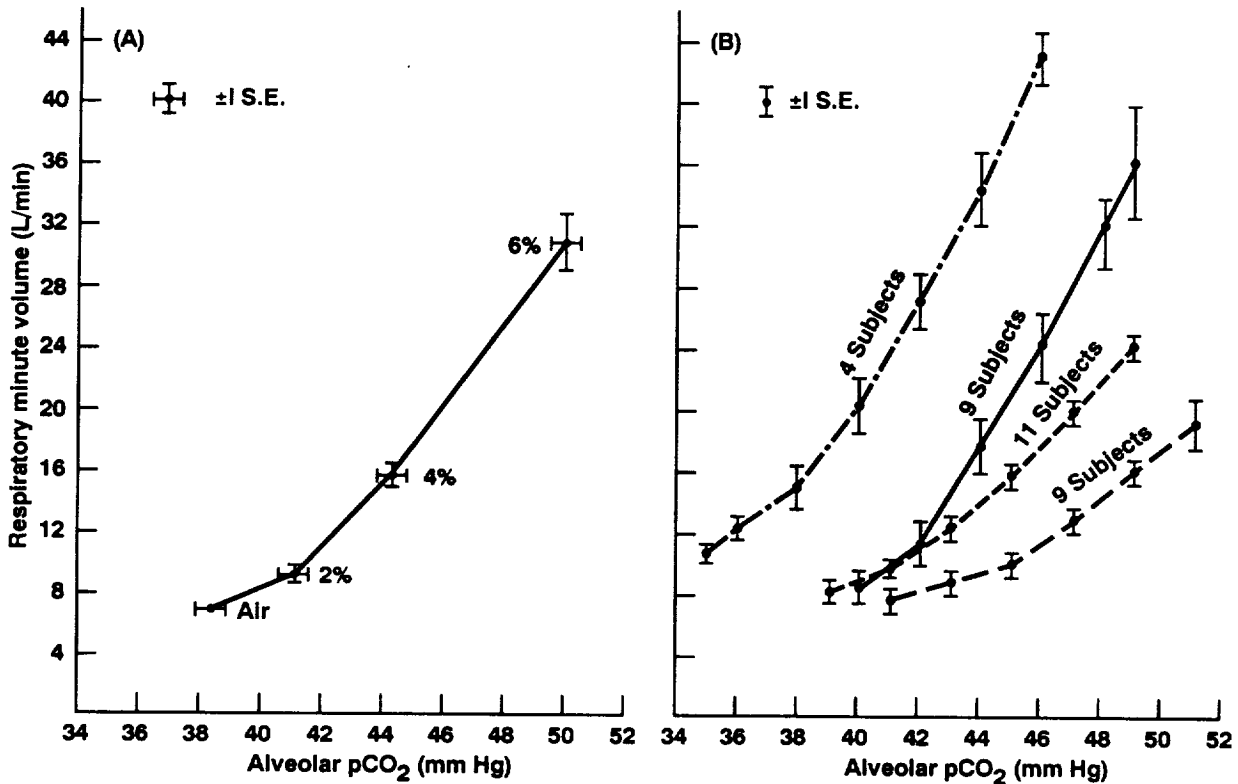


Figure 7. Variability of the respiratory response of normal subjects to low concentrations of inspired carbon dioxide. In A, the responses to approximately 2, 4, and 6% CO₂ in 21% O₂ in N₂ are averaged. For B, the individual CO₂ "Response" curves were appraised to obtain interpolated values of respiratory minute volume at selected levels of P_{CO₂} (from Lambertsen (ref. 11)).

the intense respiratory stimulation noted at such an elevation of CO₂ 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 CO₂ in the past are likely to do so again on repeated exposure. Women and the elderly are also less tolerant of the effects of CO₂. 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 CO₂

Introduction— The differentiation between acute and chronic CO₂ exposure is somewhat arbitrary. Generally, with acute elevations in CO₂, the respiratory system predominates in limiting adverse effects to the exposure. With chronic CO₂ exposures, other systems contribute to this process.

The renal system is of importance in compensating for the effects of inhaling high CO₂ concentrations for long peri-

ods 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 CO₂ exposures of low concentration. Even without a renal response, other biologic systems are active in limiting the effects of CO₂. Since biologic responses outside the respiratory tract contribute to compensating for the effects of CO₂, any exposure greater than 24 h in duration will be considered to be chronic in nature.

The time course and degree of adaptation to CO₂ exposure is dependent on the concentration of CO₂ (ref. 28) (fig. 8). The discussion of chronicity is not appropriate with 6-10% CO₂ since exposure is time limited by symptoms. Exposures to CO₂ of 3-5% have occurred for days and even weeks. Renal responses are elicited and adaptation occurs within days. Exposure to CO₂ 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 CO₂ will be discussed later in this paper.

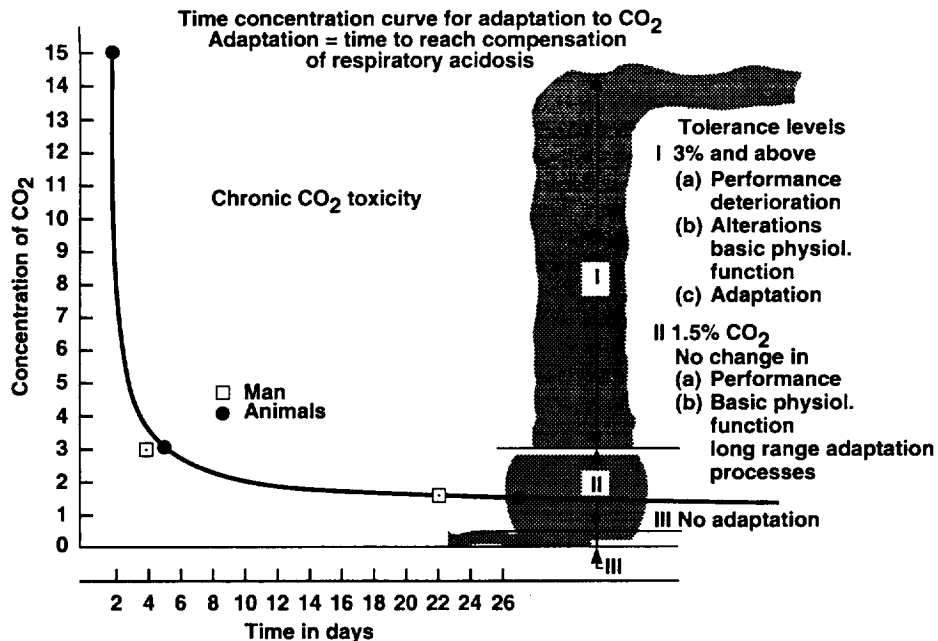


Figure 8. Time concentration relationship in adaptation to increase carbon dioxide concentration based on experiments in human and animal and tolerance limits for chronic carbon dioxide toxicity based on three different levels of activity (from Schaefer (ref. 28)).

Physiologic responses—

Laboratory studies: A biphasic biologic response occurred during a 42 day exposure of 21 subjects to 1.5% CO₂ in a sealed compartment (ref. 29) (fig. 9). During the first 23 days of exposure, a period of uncompensated respiratory acidosis occurred. Alveolar P_{CO₂} 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 CO₂ excretion. Alveolar P_{CO₂}, 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, CO₂ excretion increased to a level higher than during exposure (ref. 28). Pulmonary CO₂ excretion peaked on the day post-exposure followed by a higher peak on days 8 and 9. Urinary CO₂ peaked at day 2 post-exposure and recovered by day 9. The three separate and distinct periods of CO₂ elimination are postulated to reflect three different reservoirs for CO₂ 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

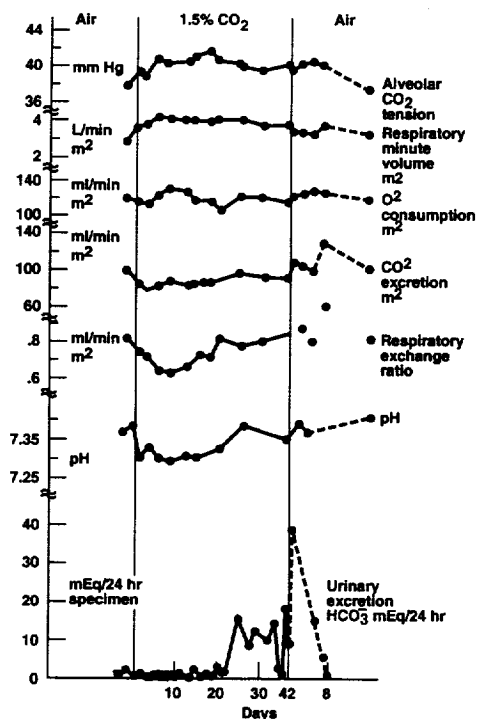
alveolar P_{CO₂} rose. All parameters had returned to normal by 4 weeks of recovery. No symptomology was noted throughout the experiment.

Exposure of 6 men to 2% CO₂ for 30 days revealed different results (ref. 30). Alveolar P_{CO₂} 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.

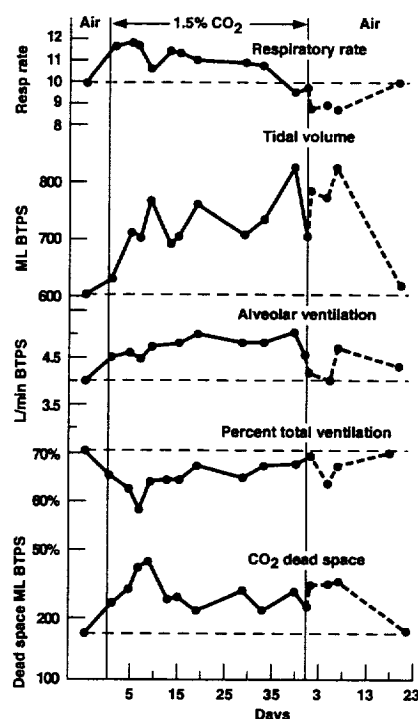
Acid-base changes followed a different time course than with exposure to 1.5% CO₂. A mild respiratory acidosis with a drop in pH from 7.380 to 7.377 was noted at 24 h. Acidity dropped again at day 3 to a pH of 7.371 but was fully compensated by day 15. Bicarbonate levels increased slightly during the 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% CO₂ for 5 days produced a rise in arterial P_{CO₂} 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



(a)



(b)

Figure 9. (a) Effect of prolonged exposure to 1.5% CO₂ on alveolar CO₂ tension, respiratory minute volume, oxygen consumption, carbon dioxide excretion, respiratory exchange ratio, urinary HCO₃⁻ excretion, and venous blood pH. (b) Effect of prolonged exposure to 1.5% CO₂ on respiratory rate, tidal volume, alveolar ventilation, and anatomical dead space. Alveolar ventilation ($V_T - V_{D \text{ anat.}}$) \times respiratory rate is also expressed in per cent total ventilation, which shows a marked decrease during exposure to 1.5% CO₂ (from Schaefer (ref. 29)).

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

Submarine patrol studies: Physiologic responses to elevated CO₂ in 13 Polaris submarine patrols have been reported (ref. 32). Average CO₂ 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_{CO₂} and HCO₃⁻ occurred during the first 20 days. The next 20 days were characterized by an increase in pH and a fall in P_{CO₂} and HCO₃⁻. 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 CO₂

Very few studies have been conducted on intermittent exposure to CO₂. Progressive, intermittent increases in CO₂ were studied in 1 subject over 6 days (ref. 33). The subject was exposed to elevated CO₂ for 15 h followed by 9 h on room air. The level of CO₂ 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, CO₂ accumulated in the body. On room air, alveolar CO₂ rose on days 4 and 5 indicating that the 9 h period of air breathing was not sufficient to

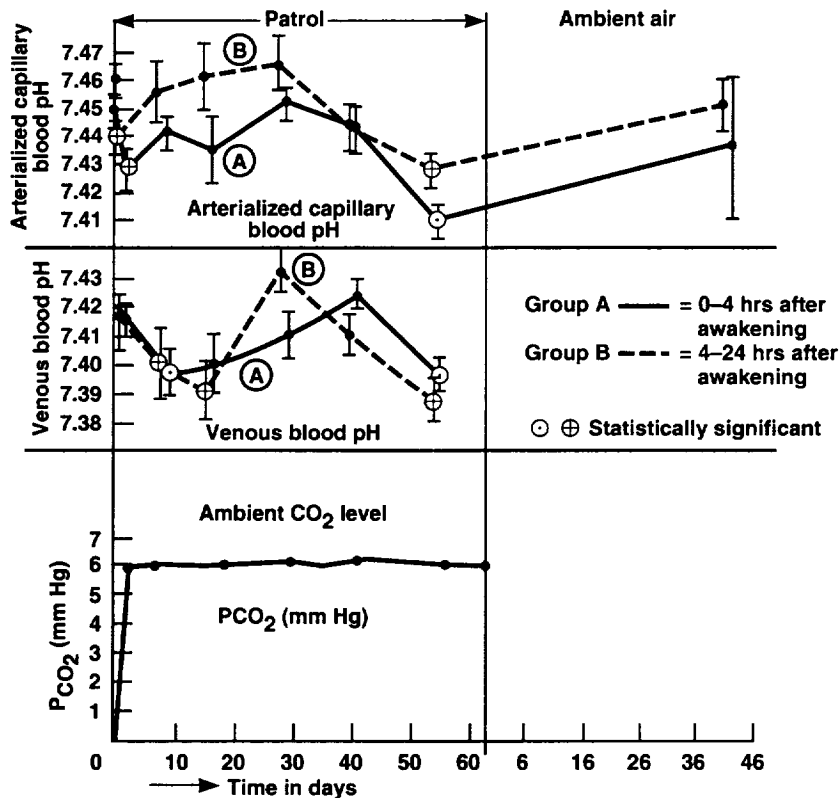


Figure 10. Time course of pH in arterialized capillary and venous blood during patrol. Average ambient PCO_2 level 6 mmHg (Peck 1971: 15 subjects, two groups: group A: sample taken 0-4 h after awakening; B: samples taken 4-24 h after awakening) (from Schaefer (ref. 32)).

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 O₂ carrying capacity of the blood. Arterial O₂ content decreased only slightly at the end of the 42 day exposure.

Exposures of 0.8-0.9% CO₂ 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% CO₂ 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 CO₂.

Histology—Chronic inhalation of low dose CO₂ produces histologic changes in the architecture of guinea pig lungs. The changes noted are dependent on the degree and duration of CO₂ exposure.

Exposure of guinea pigs to 1% CO₂ showed ultrastructural changes in the lung four and six weeks after expo-

sure (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% CO₂ 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 CO₂ 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 CO₂ levels between 0.5 and 1% CO₂. Although the changes noted after 8 weeks of exposure with 1% CO₂ appear to be reversible, it is not known if the same is true for higher concentrations of CO₂ or for longer exposures. Additionally, it is unknown if CO₂ 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).

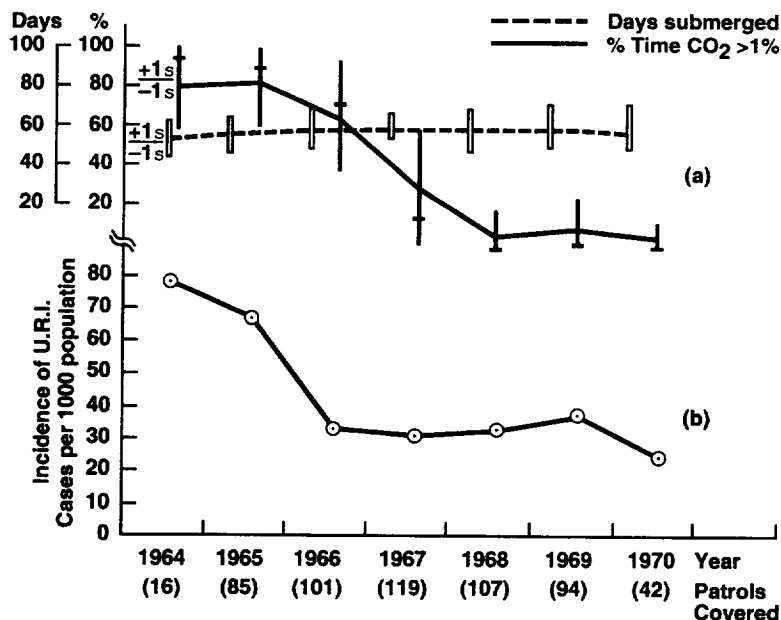


Figure 11. (a) Summary of average ambient CO₂ levels on 546 Fleet Ballistic Missiles (FBM) submarine patrols between 1964 and 1970. (b) Incidence of upper respiratory infection cases per 1000 population observed on 546 Fleet Ballistic Missile (FBM) submarine patrols between 1964 and 1970. ○ = Incidence 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 CO₂ scrubbers were installed, leading to a 33% reduction in environmental CO₂ 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 CO₂, was the primary contributor to the decrease in respiratory illness.

Summary

Physiologic responses to elevated CO₂ levels are dependent on the degree and duration of exposure. Exposure to CO₂ 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 CO₂ levels of 2-3% can be tolerated for weeks to months. Concentrations of CO₂ below 2% can be tolerated indefinitely.

During long term exposure to 1.5% CO₂, 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_{CO₂} and ventilation. A period of compensated respiratory acidosis lasting about 20 days follows. Compensation is characterized by an increase in urinary excretion of CO₂ and a rise in pH towards normal. A second period of uncompensated respiratory acidosis follows the period of compensation. Alveolar P_{CO₂} 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 CO₂ 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 CO₂ exposure may occur. Intermittent, repetitive exposures to CO₂ have not been studied sufficiently to denote which time periods are required to vent all accumulated CO₂ between exposures.

Dead space increases with low dose CO₂ exposure. The primary change in dead space is likely due to the bronchodilatory effects of CO₂. 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 CO₂ exposure is unknown.

Reversible, histopathologic changes in the lung, characterized by a proliferation of Type II pneumocytes, occurs with chronic exposure to 1% CO₂ in guinea pigs. No change is seen with chronic exposure to 0.5% CO₂. 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 CO₂ 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 NH₄⁺, H₂PO₄⁻, 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 CO₂ balance (ref. 3). Along the inner layer of the nephron is a protein called carbonic anhydrase. Carbonic anhydrase catalyzes the reaction converting CO₂ (an acid) and H₂O into HCO₃⁻ (a base) and H⁺ (an acid). Through the selective retention or excretion of HCO₃⁻ 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 CO₂ in the bloodstream is converted into HCO₃⁻ and H⁺ in the nephron. The HCO₃⁻ 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 CO₂ are limited. Exposure of 7 subjects to CO₂ of 7-10% for a maximum of 90 min produced a large change in pH with only a minimal rise in HCO₃⁻ (ref. 20). Sources other than the kidney exist for HCO₃⁻ generation. With high-dose, acute CO₂ exposures, renal generation of HCO₃⁻ was not apparent.

Acid-base changes with chronic respiratory acidosis are dependent on time of exposure and concentration of CO₂ (ref. 28). Exposures greater than 3% CO₂ led to earlier compensation of pH. At 3% CO₂, compensation occurred in 5 days.

With chronic exposures to less than 3% CO₂, acid-base responses are much different. Compensatory responses are not elicited as quickly with lower levels of CO₂. As discussed in the section on respiration, a 20-day period of uncompensated respiratory acidosis occurred with exposure to 1.5% CO₂ 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 CO₂ and fall in pH, plasma HCO₃⁻ 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 HCO₃⁻ levels rose. Urinary pH also rose subsequent to an increase in the excretion of urinary HCO₃⁻ (ref. 43). During this phase, total HCO₃⁻ levels were increased. The kidney may have played a role in generating some of the additional HCO₃⁻ but the degree of this response is uncertain.

Submarine patrol studies with 1% CO₂ for long durations reveals a similar cycling of pH and HCO₃⁻ (ref. 32). Apparently renal responses were not elicited under these circumstances. Comparison of laboratory and submarine patrols have shown similar results.

Exposure to 2% CO₂ for 30 days elicited the start of compensation in 3 to 8 days with the process completed in 15 days (ref. 30). Plasma HCO₃⁻ rose slightly. Urinary excretion of HCO₃⁻ 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% CO₂ may be caused by several factors. Renal responses were initiated with 2% CO₂ but took several days to reach full activity. Exposure to 1.5% CO₂ may simply fall below the threshold limit of inducing a renal response. Above 3% CO₂, renal responses are initiated quickly and compensation persists throughout the exposure.

Bone

Calcium— Bone serves as a storage site for CO₂ (ref. 44). The CO₂ 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 CO₂ levels (ref. 29). The long time periods required in establishing bone stores for CO₂ may explain the 20-day periods of time required to initiate compensation with chronic low dose CO₂ exposure.

Exposure of 20 subjects to 1.5% CO₂ 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 CO₂ 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 CO₂ (ref. 45). Urinary excretion of CO₂ 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 CO₂ excretion. The release of the CO₂ from storage in bone was probably responsible for this response.

Plasma calcium changes in association with pH changes were also seen with 1% CO₂ during submarine patrol studies (ref. 32). Calcium changes were not seen with a 30-day exposure to 2% CO₂ (ref. 30).

Histology— Bone has about 80% of the body's storage capacity for CO₂ (refs. 46 and 32). Bone carbonate (heat stable bone) exists in the lattice of bony crystals and comprises about 70% of bone CO₂. Bone bicarbonate (heat labile bone) exists in the hydration shell of the hydroxyapatitic crystals and comprises the remaining 30% of bone CO₂.

Changes in bone CO₂ content were measured in guinea pigs exposed to 1% CO₂ for 8 weeks (ref. 46) (fig. 12). A continuous rise in bone CO₂ 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 CO₂ exposure, the release of bone bicarbonate during the compensatory phase of chronic respiratory acidosis accounts for the rise in HCO₃⁻ seen (ref. 32).

Exposure of guinea pigs to 0.5% CO₂ 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 CO₂ have been inconclusive (refs. 39, 45, and 47).

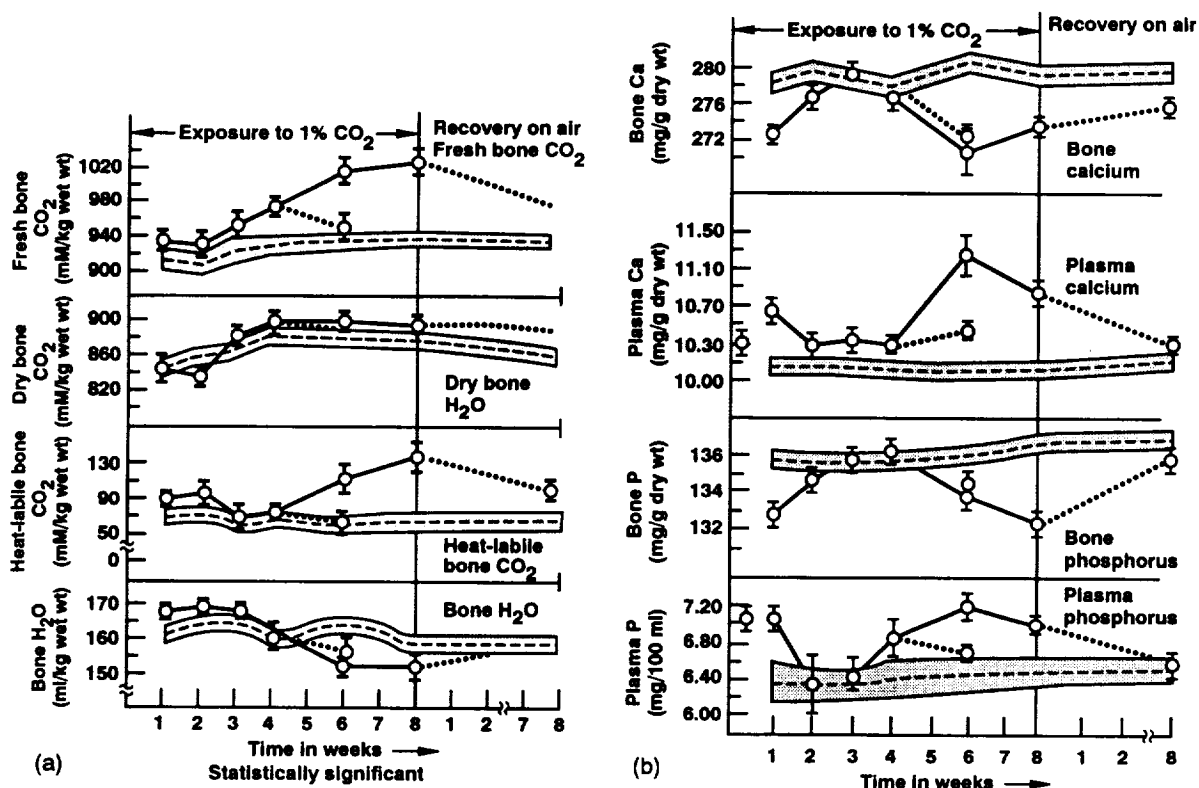


Figure 12. (a) Effect of prolonged exposure to 1% CO₂ on total bone CO₂ content of fresh bone, dry bone, difference between fresh bone and dry bone CO₂ content (heat-labile CO₂) and bone H₂O content. Data represent means and SE in mmol/kg wet wt. Exposed animals — control animals ----- recovery following 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% CO₂ 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 CO₂ exposure on bone strength is unknown. The threshold level below which CO₂ exposure does not lead to changes in bone has also not been determined.

Electrolytes

Blood and urine levels of calcium, HCO₃⁻, CO₂, and pH are related to CO₂ exposure by the degree of compensation present in the system. The mechanism of compensation to elevated CO₂ involves associated changes in each of these parameters. These responses have been discussed in earlier sections of this paper.

Exposure to elevated CO₂ has been associated with changes in other blood and urine electrolytes. Exposure to

7-10% CO₂ 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% CO₂ 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% CO₂ 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 H₂O 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% CO₂ (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% CO₂ 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% CO₂ 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% CO₂.

Throughout the range and duration of CO₂ 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 CO₂. Calcification was seen in the kidneys of guinea pigs during long term exposure to 15% CO₂ (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% CO₂ 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% CO₂ 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% CO₂ 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 CO₂ 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 CO₂ 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 CO₂ which produce irreversible kidney calcification have not been determined. Further, a threshold limit below which CO₂ 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 CO₂ scrubbers were installed in submarines leading to a 33% reduction in environmental CO₂ 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 CO₂ exposure. A direct association between increased CO₂, increased deposition of calcium in the kidney, and increased incidence of renal stones is likely.

Summary

Exposure to CO₂ 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% CO₂ is characterized by a prolonged phase of uncompensated respiratory acidosis. Renal compensation is limited. Compensation occurs after 20 days marked by rises in pH, HCO₃⁻, and plasma calcium. It is postulated that CO₂ complexes with calcium in bone where it is deposited. Compensation is thought to occur when HCO₃⁻ and calcium are liberated from the bone.

Guinea pigs exposed to 1.5% CO₂ for 8 weeks revealed changes in bone content of CO₂. Total bone CO₂ stores increased throughout the length of exposure. The effect of changes of bone CO₂ and calcium on bone strength are unknown. A threshold limit below which CO₂ 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 CO₂ exposure. Kidney calcification has been noted with 8 week exposures to CO₂ as low as 0.3 to 0.5%. The physiologic significance of these histologic findings is unknown. A threshold limit below which CO₂ 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 CO₂ levels is unknown.

Neurologic

Performance

Impairment of performance from CO₂ exposure is related to length and concentration of exposure. Loss of consciousness occurs when 15-20% CO₂ is breathed for only several minutes. Additional increases to 20-30% CO₂ quickly lead to convulsions. Concentrations of CO₂ 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 CO₂ 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 CO₂. Reasoning skills were significantly slowed at exposures at and above 5.5% CO₂ (fig. 13).

Exposure of 21 subjects to 6.5% CO₂ 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 CO₂ inhalation but still remained below control values.

Subjects exposed to 6% CO₂ for 16 min displayed a slight slowing in performing a card sorting task (ref. 24). No

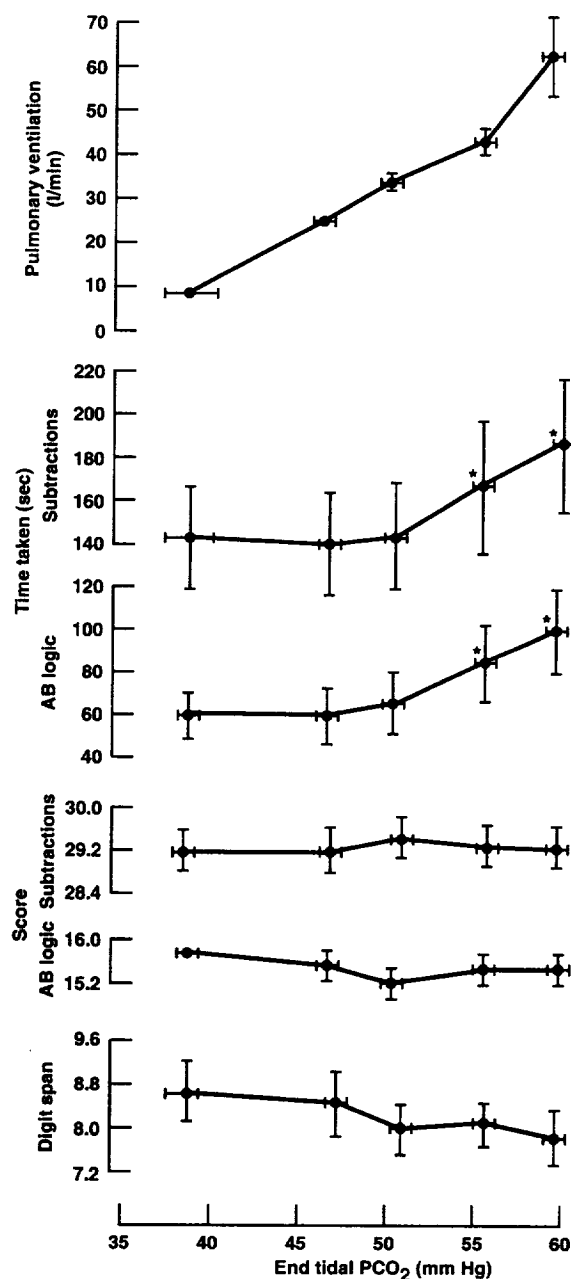


Figure 13. Effects on pulmonary ventilation and reasoning of breathing (from left to right) 0, 4.5, 5.5, 6.5, and 7.5% CO₂ for 5 minutes. Points, means; brackets ±SE. * Differs significantly (P < 0.01) from data with 0, 4.5, and 5.5% CO₂ (from Sayers (ref. 51)).

appreciable change in the number of errors was noted in comparison to a control group.

Submarine patrol studies revealed a significant impairment of performance when subjects were exposed to 3% CO₂ for 6 days (ref. 43). Performance did not improve with length of exposure.

Exposure of 6 men to 2% CO₂ 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% CO₂ 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% CO₂ produced sensations similar to panic attacks (refs. 52 and 53). The immediate respiratory acidosis induced by the elevated CO₂ is followed by a period of lowered alveolar P_{CO₂} and hypocapnic respiratory alkalosis lasting approximately 60 sec. Panic symptoms correlated with the period of lowered alveolar P_{CO₂} but not to the acid-base status of the body.

Subjects exposed to 5-7.5% CO₂ for 15 min displayed dose related increases in anxiety and panic symptoms (ref. 54). Individuals with preexistent panic disorders exhibited panic symptoms at lower CO₂ levels than normal subjects.

A correlation between respiratory sensitivity to CO₂ and neurotic personality traits has been noted for women but not for men. The use of the ventilatory response to CO₂ 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 CO₂ scrubbers were installed in submarines leading to a 33% reduction in environmental CO₂ 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 CO₂ 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 CO₂ removal from the brain and subsequently control the acidity of the cerebrospinal fluid (CSF). Changes in pH alone without alterations in CO₂ lead to comparatively weak changes in cerebrovascular tone.

The response of the cerebrovascular system to changes in CO₂ appears to be prompt. Any delays noted in reaching

steady state likely reflects the time required for alveolar and arterial P_{CO₂} to reach equilibrium.

Studies have indicated that the cerebrovascular response to CO₂ may have a threshold effect (ref. 56). Exposure to CO₂ levels below 2.5% apparently has little effect on CBF. Exposures to 3.5 and 5% CO₂ increased CBF about 10 and 50%, respectively. With 7% CO₂, 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% CO₂ 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 CO₂ tension.

Cerebral blood flow was measured for 6 h in anesthetized dogs exposed to approximately 12% CO₂ (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 CO₂ revealed that CBF increased linearly with rising CO₂ 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 CO₂ and CBF.

Neurotransmission

The effects of CO₂ 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 CO₂ inhalation (fig. 14) (ref. 61). Phase 1 occurs with less than 10% CO₂ 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 CO₂. Phase 2 occurs with 10-20% CO₂ and is characterized by an increase in seizure activity. This response probably

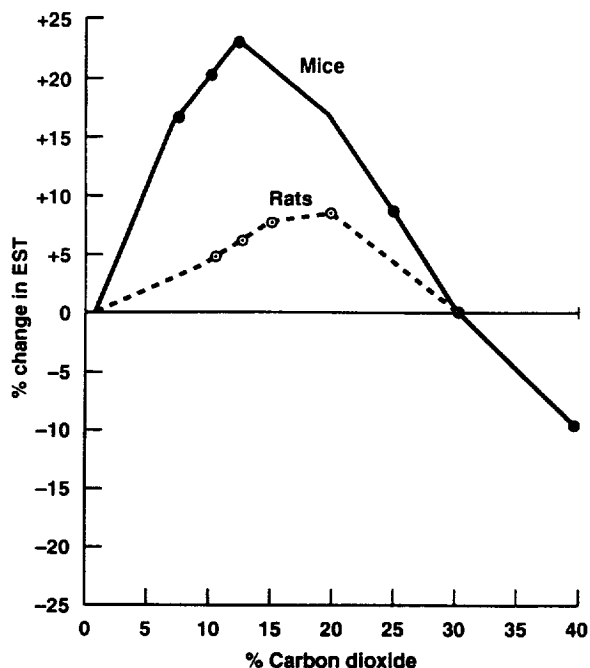


Figure 14. Effect of inhalation of various concentrations of CO₂ on electroshock seizure threshold (EST) of mice and rats (from Woodbury (ref. 61)). Ordinate is percentage change in EST referred to control values. Abscissa is inhaled CO₂ concentration in percent

reflects increased cortical activity due to activation of subcortical centers by CO₂. The third phase occurs at CO₂ levels above 30% and is characterized by an anaesthetic phase with marked cortical depression.

The effects of CO₂ on the electroencephalogram (EEG) reflect the triphasic excitability response noted above. Low level CO₂ 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 CO₂ usually causes flattening of the EEG in man and animals.

The production and breakdown of acetylcholine has been shown to be dependent on CO₂ levels (ref. 62). Acetylcholine is an important neurotransmitter that directly influences neurologic function. Adrenal stimulation by CO₂ 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 CO₂ exposure is related to length and concentration of exposure. Performance

decrement occurs within minutes with exposure to 10% CO₂. Exposure to 5-7% CO₂ leads to a decrease in performance in minutes to hours. Slowing of reasoning skills has been noted with exposure to 3% CO₂ for several days. Long term exposure to 1.5-2% CO₂ has been tolerated without any performance decrement.

Anxiety symptoms can be produced with short exposures to high dose CO₂. Individuals predisposed to panic attacks are at increased risk. The use of the ventilatory response to CO₂ 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 CO₂ may have a threshold effect. Exposures to CO₂ below 2.5% apparently have little effect on CBF. With 7% CO₂, CBF was approximately doubled. Whether further increases in CBF occur in humans with higher CO₂ levels is unknown.

Animal studies show progressive increases in CBF with elevated CO₂ 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 CO₂. 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 CO₂, were the likely causative factors.

Cardiovascular

Basic Responses

The cardiovascular system plays an important role in the elimination of CO₂. Vascular perfusion helps to determine local CO₂, O₂, and pH values as well as serving to control metabolism. It is not surprising then, that many cardiovascular responses are influenced by CO₂ 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 CO₂ and subsequently control the pH of the local environment.

Each circulatory bed has different inherent responses to CO₂ (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 CO₂ in the blood. Carbon dioxide diffuses very quickly

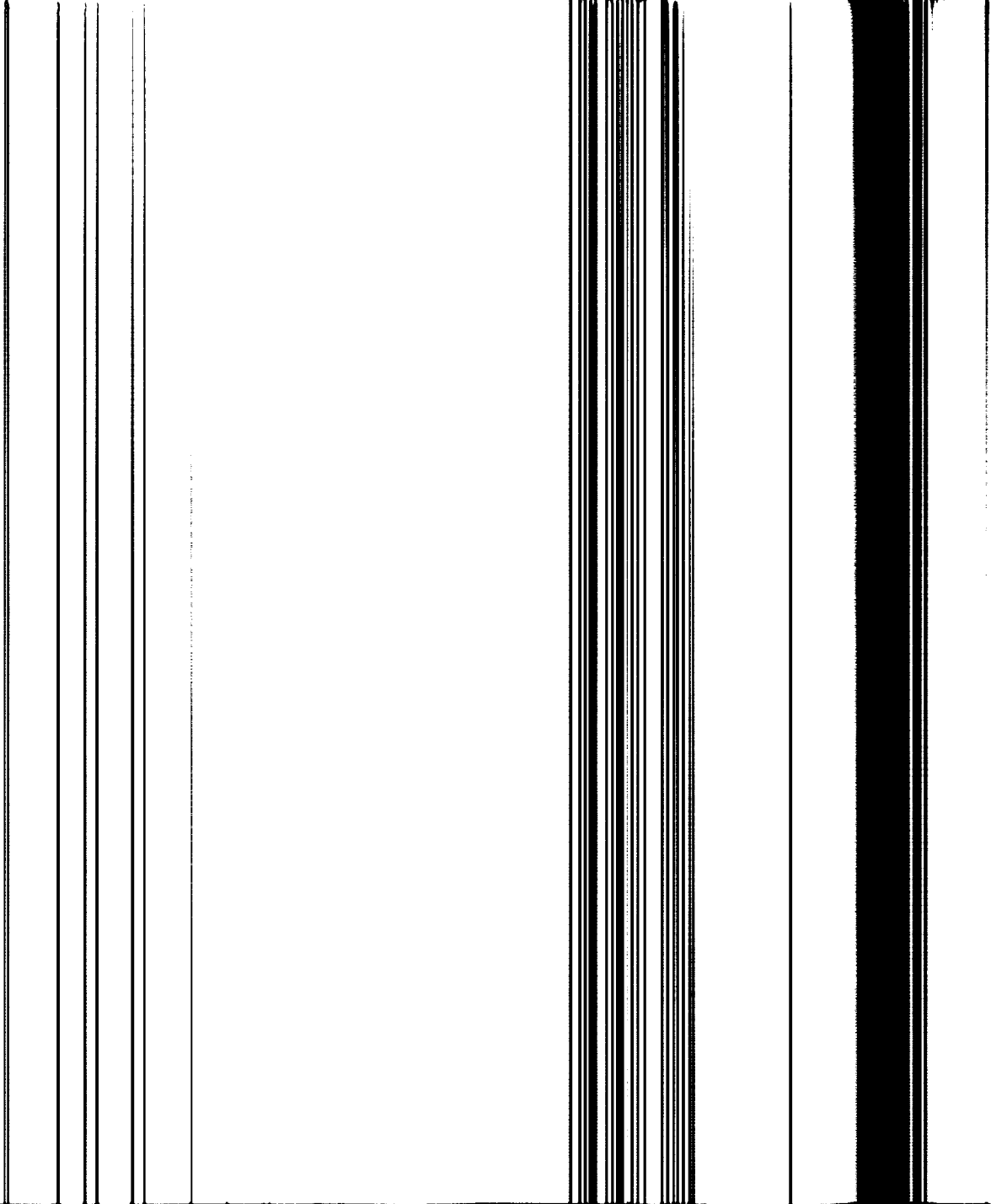
unchanged (ref. 43). Diastolic pressure showed a slight increase. Length of exposure did not appreciably affect any of the cardiac parameters under observation.

At very high levels of CO₂

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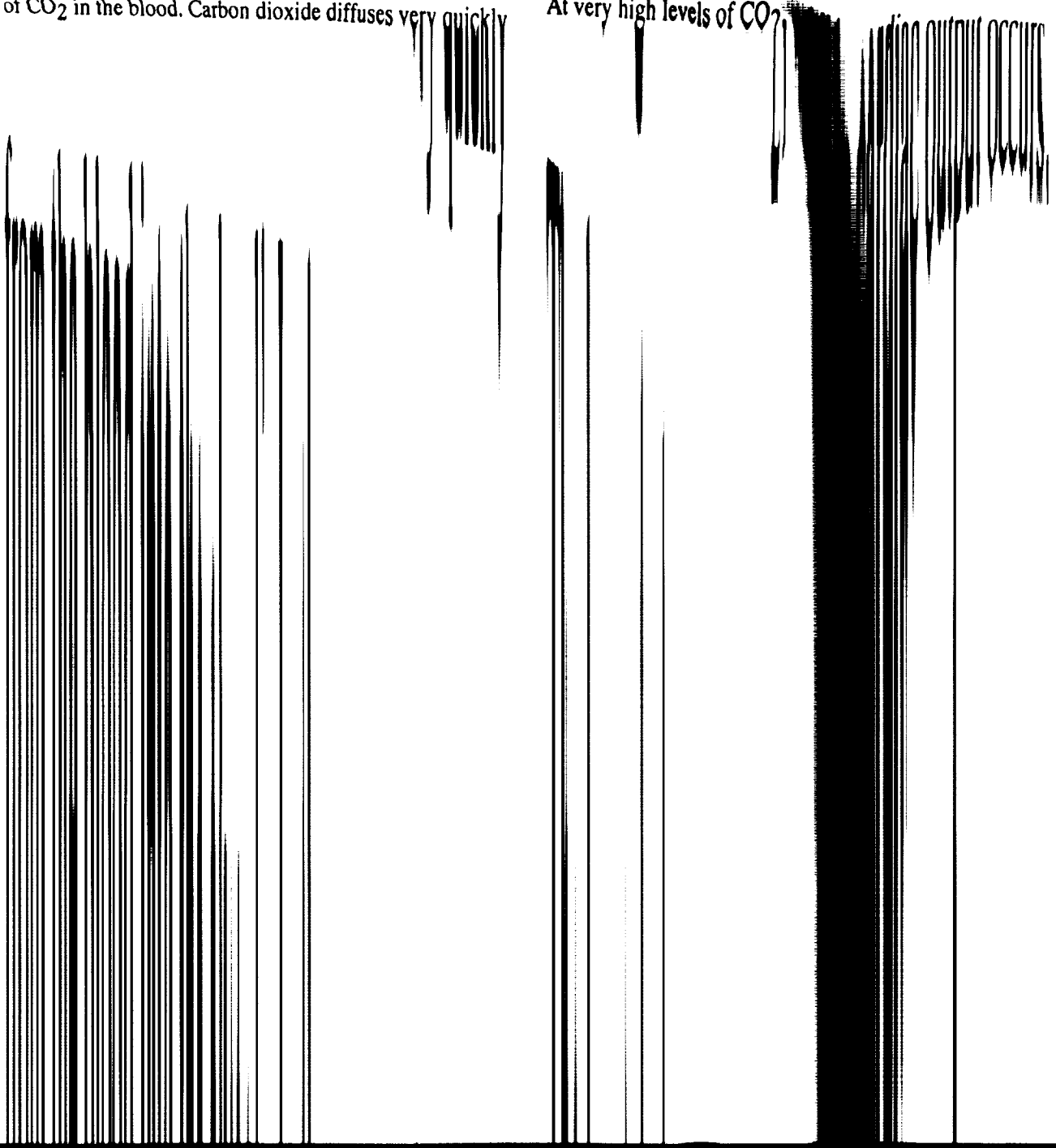
At very high levels of CO₂, cardiac output occurs.



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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 CO₂ 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 CO₂ 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 CO₂, 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 CO₂ levels (ref. 5) (table 2). Systolic pressure rises faster than diastolic pressure although both are increased.

Twelve subjects exposed to 7-14% CO₂ 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 CO₂, hypotension was minimal and no arrhythmias were observed.

Exposure of 44 subjects to 7.6-10.4% CO₂ 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% CO₂ for 30 days revealed no changes in heart rate, systolic, or diastolic blood pressure (ref. 30). No ECG changes or arrhythmias were noted.

Exposure of 23 subjects to 1.5% CO₂ 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 CO₂, a fall in cardiac output occurs. The heart, being very active metabolically, is strongly influenced by local pH and CO₂ 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% CO₂ for approximately 30 sec revealed a variety of ECG changes (ref. 66). Atrial arrhythmias 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% CO₂ for 4 h developed life threatening cardiac arrhythmias 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 CO₂ on blood flow to the heart itself is also characterized by vasodilation. Anesthetized dogs exposed to 12% CO₂ 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% CO₂ (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 _{CO₂} (min. Ilg) | 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 CO₂ did not affect MBF. Removal of nervous system innervation of the heart diminished the increase in MBF seen with CO₂ exposure. CO₂ probably acts as a direct mediator of coronary vasodilation whose action is supplemented by nervous system activity.

Anesthetized dogs exposed to 0-40% CO₂ revealed progressive increases in myocardial blood flow (ref. 70). Increases in myocardial oxygen demand could not account for the degree of vasodilation seen. CO₂ may have a direct effect on coronary vasodilation.

The full mechanism by which CO₂ 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 CO₂ 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% CO₂ in air and O₂ for 1 h were evaluated for adrenal activity (ref. 73). It was noted that high levels of CO₂ in air stimulated the adrenal cortex. This effect was not seen with high dose CO₂ in O₂, however.

Twelve subjects exposed to 7-14% CO₂ 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% CO₂ 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 CO₂ is unknown.

Exposure of 60 subjects to 1.5% CO₂ 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 CO₂ 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 CO₂ 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 CO₂ (ref. 77). The increase in ventilation was noted to be blunted at high workloads in combination with increased CO₂ (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% CO₂ 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 CO₂ exposure.

Six subjects exposed to 0-6% CO₂ were exercised for 30 min (ref. 78). Ventilation increased directly with inspired CO₂. With 6% CO₂ and heavy exercise, pH fell from 7.37 to 7.23.

Ventilatory responses were measured in 9 men exposed to 2-4% CO₂ and compared to ventilatory changes induced by exercise (ref. 8). With low dose CO₂ 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 CO₂ were exercised at various speeds on a treadmill (ref. 79). At moderate workloads with CO₂ below 4%, the effects of

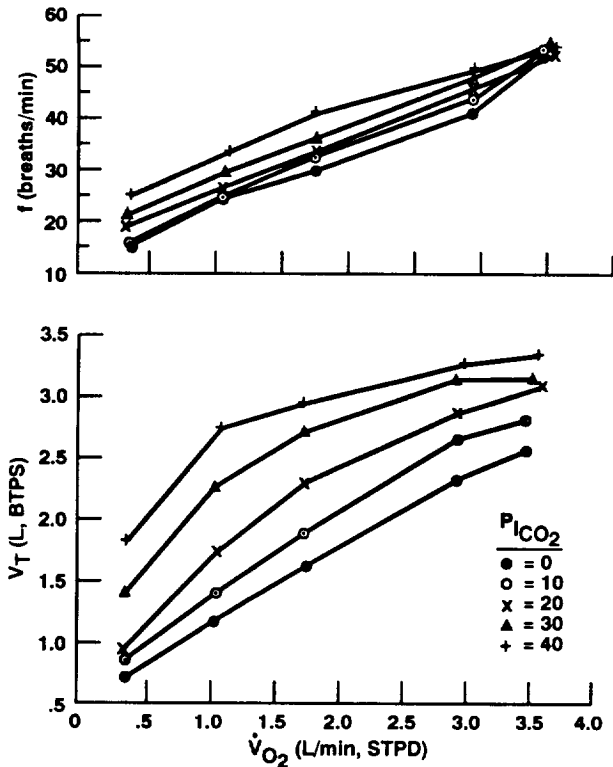


Figure 15. Relationships of respiratory rate (f) and tidal volume (V_T) to oxygen uptake (\dot{V}_{O_2}) during exercise at different levels of inspired CO_2 tension (P_{iCO_2}) (from Clark (ref. 77)).

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.

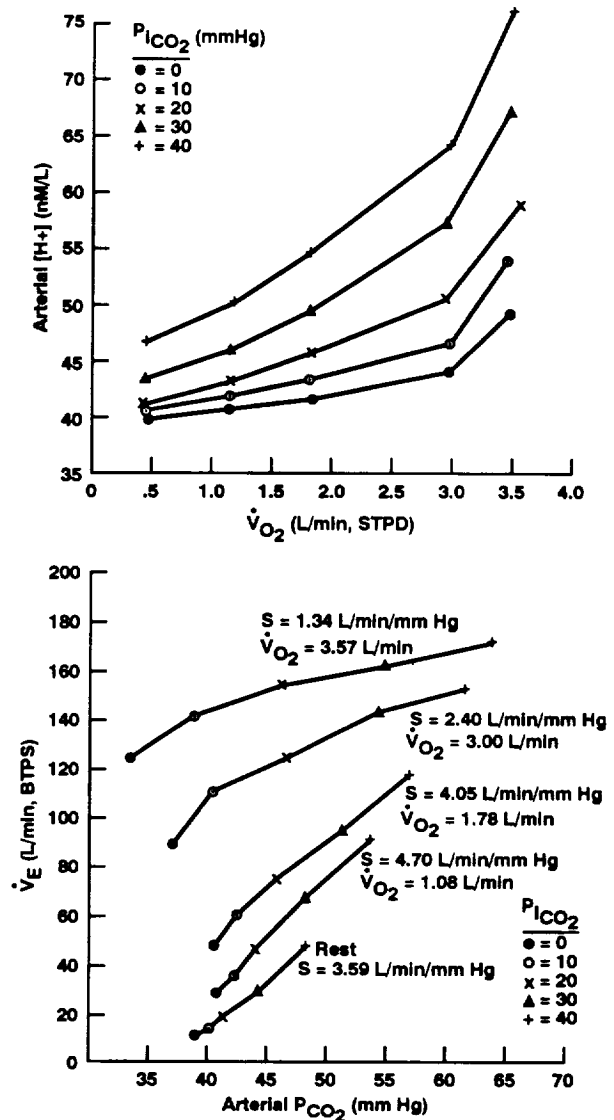


Figure 16. Relationships of ventilation (\dot{V}_E) to arterial P_{CO_2} at different work loads during combined exercise and hypercapnia. Average slopes of the \dot{V}_E - P_{aCO_2} relationships at rest and at four levels of exercise are shown. Corresponding average values of O_2 uptake (\dot{V}_{O_2}) 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

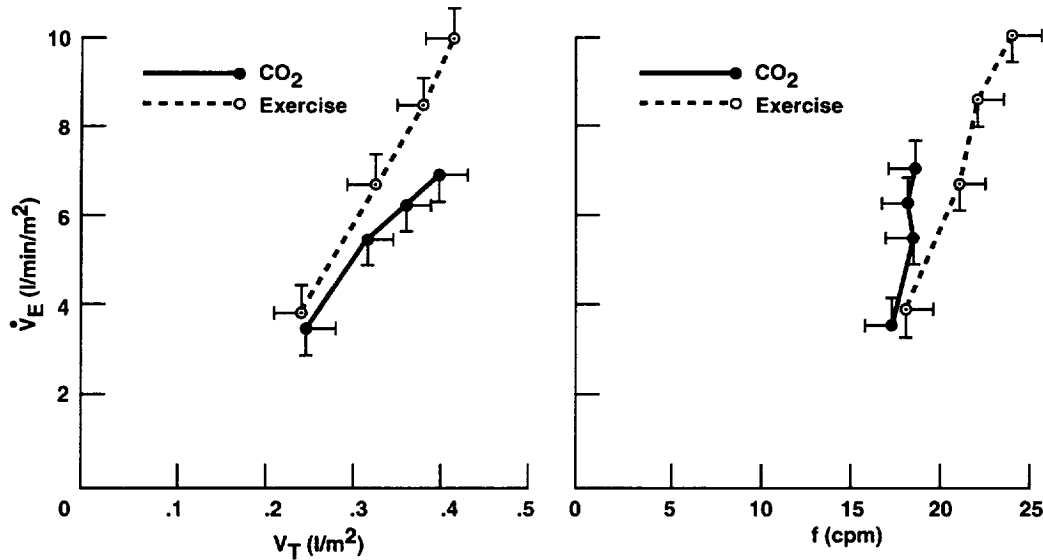


Figure 17. Minute ventilation (V_E) is plotted vs V_T (left) and f (right). Mean values \pm SD for all 9 subjects are shown (from Askanazi (ref. 8)).

circulatory reserve which may prove significant at higher workloads.

The effects of CO₂ on metabolic processes are undetermined. An apparent decrease in lactate production or release occurs in accordance with increased CO₂ (refs. 78 and 82). The breakdown of glycogen was not affected by elevations in CO₂ (ref. 83).

Summary

Carbon dioxide leads to vasodilation in practically all vascular beds. Stimulation of the sympathoadrenal system with CO₂ leads to a compensatory vasoconstriction and an increase in heart rate. At low levels of CO₂, the overall vascular response leads to an increase in blood pressure and cardiac output. No significant ECG changes are noted. Exposures to CO₂ below 2% revealed essentially no change in cardiac function.

At high concentrations of CO₂, 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 CO₂ environment.

Myocardial blood flow increases with exposure to CO₂. 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 CO₂ 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 CO₂ below 4%, the effects of CO₂ and exercise act independently and cumulatively to increase respiration. At higher levels of CO₂ and exercise, ventilatory responses become taxed and further increases in respiration become limited.

Exercise tolerance is adversely affected by exposure to CO₂ above 2%. No exercise difficulty was noted at high workloads for 30 min with 2% CO₂. Exposure to 2% CO₂ for 30 days revealed adaptation to exercise to be slightly impaired. Exposure to 1.5% CO₂ 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 CO₂ exposure to gastrointestinal (GI) function note an increase in gastric acidity with elevated CO₂ levels. Five subjects exposed to 1% CO₂ 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 HCO₃⁻. 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 CO₂

scrubbers were installed in submarines leading to a 33% reduction in environmental CO₂ 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.

Summary

An increase in gastric acidity has been noted with long term exposure to 1% CO₂. 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 CO₂ exposure. Acute and chronic exposures to CO₂ lead to different physiologic responses. The duration and frequency of CO₂ 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 CO₂ 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.

Table 3. Effect of prolonged exposure to 1% CO₂ 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.

Given that daily, 8-h exposures to elevated CO₂ 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 CO₂ exposure. The concentration of CO₂, the duration of exposure, the frequency of exposure, and the time period between exposures will likely all be important in separating acute from chronic CO₂ responses.

Very few studies have been performed concerning repetitive acute CO₂ exposure. Given that bone apparently acts to sequester CO₂ and that long time constants are involved in bone CO₂ transfer, implies that acute repetitive CO₂ exposures can lead to chronic physiologic responses. Studies evaluating repetitive 8-h CO₂ exposures are not known to this author. Additional experiments addressing the physiologic responses to repetitive CO₂ exposure are needed.

An option in setting exposure limits is to assume that repetitive 8-h CO₂ exposures produce chronic physiologic responses. The establishment of CO₂ exposure limits under this assumption would serve to promote safety. Assuming chronic exposure would necessitate setting a lower space suit CO₂ level. The periods of non-exposure would allow for off-gassing of accumulated CO₂ 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 CO₂ 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% CO₂ in terrestrial settings. Subjects could perform heavy exercise for 30 min breathing 2% CO₂. 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% CO₂ under nominal conditions. Given that exercise tolerance was essentially normal with 2% CO₂ 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% CO₂ most likely reflects a decrease in cardiac reserve. Any cumulative effect of CO₂ 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 CO₂. Chronic exposure to low dose CO₂ is characterized by cycling of bone stores of calcium and CO₂. Given the loss of bone calcium induced by zero gravity, any additional losses induced by CO₂ exposure are obviously of concern. The significance and contribution of bone changes induced by low dose CO₂ exposure deserves further evaluation. The threshold below which CO₂ 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 CO₂ leads to increases in

urinary calcium and renal calcification. The combination of calcium excretion from zero G and CO₂ 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 CO₂ 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% CO₂ for the occurrence of renal calcification. The existence and level of such a threshold in humans is unknown. Establishing a threshold limit for CO₂ induced kidney calcification would help to set exposure limits for chronic CO₂ 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 O₂ above normal limits. Exposure to high concentrations of O₂ can produce convulsions and death. A full discussion of O₂ exposure is beyond the scope of this paper.

It is important to realize that O₂ is a physiologically active gas. Both O₂ and CO₂ 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 counterbalancing effects may prove of concern. Setting exposure limits for CO₂ must be considered with concurrent O₂ exposure in mind.

Oxygen causes vasoconstriction thereby decreasing blood flow. Exposure of 33 men to 100% O₂ at 1 and 3.5 atmospheres (atm) revealed decreased cerebral perfusion and a slight rise in cerebral CO₂ levels (ref. 89). Neither change is thought to be the inherent cause of O₂ toxicity. The toxicity observed from high dose O₂ may result from its direct toxic effect on cerebral function.

Exposure of 4 subjects to 100% O₂ at 3 atm revealed marked increases in cerebral venous O₂ on the addition of 2% CO₂ (ref. 90). It was postulated that the vasodilating

effect of CO₂ would increase cerebral blood flow thereby increasing cerebral venous O₂. This effect would serve to increase the risk of oxygen induced convulsions.

Mice exposed to high dose O₂ and CO₂ concurrently were evaluated for induction of convulsions (ref. 91). Exposure to 100% O₂ was convulsigenic at 3 atm and fatal at 4 atm. The addition of CO₂ at high atmospheric pressure shortened the time to convulsion and death. Carbon dioxide in 100% O₂ 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 CO₂ 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% O₂ was not reversed by the addition of 5% CO₂ (ref. 92). In addition, 5% CO₂ in air did not produce substantial retinal vasodilation.

Exposure to O₂ leads to changes in ventilation. Upon the administration of high dose O₂, 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 O₂ interferes with central CO₂ transport producing a rise in cerebral acidity. Hyperventilation ensues in an attempt to limit this effect.

Exposure to CO₂ in O₂ stimulates respiration to a greater extent than exposure to CO₂ in air (ref. 94). The increase in ventilation from 1% CO₂ in O₂ was similar to that of breathing 2% CO₂ 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% CO₂ in air or in 60% O₂ (ref. 85). Ventilation was lower and arterial P_{CO₂} was higher with 0% CO₂ in 60% O₂ than in air. Ventilation and arterial P_{CO₂} progressively rose for each increase in CO₂ for both air and 60% O₂ conditions. Acidity was higher with 60% O₂ vs. air and with increasing CO₂ in both conditions.

Summary

The number and duration of EVAs is important in establishing CO₂ 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 CO₂ exposures. Assuming that daily 8-h exposures to CO₂ would produce chronic physiologic responses would necessitate setting a lower limit for CO₂ and would serve to promote safety. Additional experiments that establish the physiologic responses to daily 8-h exposures to low dose CO₂ 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 CO₂ in zero and partial G environments on exercise tolerance is speculative. Exercise tolerance is essentially normal with CO₂ exposures <2% in terrestrial settings.

Zero gravity exposure leads to a loss of bone calcium similar to disuse osteoporosis. Chronic exposure to low dose CO₂ leads to cycling of bone calcium and CO₂.

Exposure to CO₂ leads to increases in urinary calcium excretion and renal calcification. The combination of calcium excretion from zero G and CO₂ exposure may place an astronaut at high risk of kidney stone formation. Studies of guinea pigs reveal a threshold of 0.5% CO₂ 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 O₂ and CO₂ may play an important role in establishing exposure limits for each gas. High dose O₂ can cause convulsions. The addition of CO₂ lowers the time to convulsion with concurrent O₂.

Exposure to O₂ stimulates respiration. The combination of O₂ and CO₂ stimulates ventilation in a cumulative fashion as follows. Ventilation, arterial P_{CO₂} and acidity all increased progressively with increases of CO₂ in O₂.

Recommendations

Organ System Review

Respiratory—Respiration is stimulated by CO₂ exposure. Ventilation is increased 15% with 1% CO₂ and 50% with 2% CO₂. Conscious awareness of ventilation and dyspnea on exertion is noted at 2% CO₂. Exposure to 100% O₂ and 1% CO₂ concurrently stimulates respiration to a level similar to that induced by 2% CO₂ in air.

Chronic exposure to <2% CO₂ leads to 20 day cycles of uncompensated and compensated respiratory acidosis. Acid-base changes are small. Intermittent exposures to CO₂ have not been adequately evaluated.

Histopathologic changes in guinea pig lungs have been noted with exposure to 1% CO₂. No changes were seen with exposure to 0.5% CO₂. Increases in V/Q mismatching and dead space volumes were observed in human studies with chronic exposure to 1% CO₂.

A decrease in the incidence of respiratory disease was noted in submariners coincident with a decrease in CO₂ 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% CO₂ exposure. Excluding calcium, electrolyte changes of the blood and urine are small.

Bone serves as a storage site for CO₂. Cycling of bone calcium stores occurs with long term CO₂ exposure. Histologic changes in bone have been noted in guinea pigs exposed to 1% CO₂. 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 CO₂ exposure on bone strength is unknown.

Increases in urinary and blood calcium levels occur with low dose CO₂ exposure. Renal calcification has been noted in guinea pigs with exposure to as low as 0.5% CO₂.

A decrease in the incidence of GU disease was noted in submariners coincident with a decrease from 1.2% to 0.8-0.9% CO₂. The main factor was due to a fall in the incidence of kidney stones. With 0.8-0.9% CO₂, 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 CO₂ may place astronauts at high risk of kidney stone formation.

Neurologic—Performance was impaired in subjects exposed to 3% CO₂ for 6 days. No change in speed or accuracy of performance was noted during long term exposures to 2% and 1.5% CO₂. EEG, psychomotor, and biorhythm testing was all normal.

Carbon dioxide is a potent cerebrovascular dilating agent. Exposure of humans to CO₂ below 2.5% apparently has little effect on cerebral blood flow. Animal studies show progressive increases in cerebral blood flow with elevated CO₂ levels.

High levels of O₂ can cause seizures. The addition of CO₂ to high dose O₂ lead to the faster onset of seizure activity in mice. It was postulated that cerebrovascular dilation from CO₂ allows for greater O₂ delivery to the brain and faster onset of O₂ toxicity.

Neurotransmitter production and function is affected by elevated CO₂. An increase in the incidence of neuropsychiatric disorders was seen in submariners coincident with a decrease in CO₂ 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 CO₂ 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 arrhythmias occur. Subjects exposed to 1.5-2% CO₂ 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 O₂ supply.

Ventilatory responses are stimulated by a dual combination of metabolic and respiratory acidosis. The effects of CO₂ and exercise act independently and cumulatively to increase respiration.

Exercise tolerance is adversely affected by exposure to CO₂ above 2%. Exposure to 1.5-2% CO₂ revealed adaptation to exercise to be slightly impaired but performance was normal. CO₂ exposure may cause a reduction in cardiac reserve. Zero G leads to a diuresis and cardiac deconditioning. The cumulative effects of CO₂ 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% CO₂. 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 CO₂ 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 CO₂ exposure limits based on this estimate is appropriate.

The physiologic responses to repetitive 8-h CO₂ 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% CO₂ in 100% O₂. The respiratory stimulation of breathing 1% CO₂ in 100% O₂ is similar to that of breathing 2% CO₂ in air. Conscious awareness of ventilation and dyspnea on exertion occur at the level of respiratory stimulation produced by 2% CO₂ in air.

Exercise is an additional, independent stimulus to respiration. The combination of increased CO₂, exercise, and high level O₂ on ventilation may cause significant respiratory changes. Until this is determined, CO₂ exposure should remain at or below 1% CO₂.

Cycling of bone calcium stores occurs with long term CO₂ exposure. Histologic changes in bone have been noted in guinea pigs exposed to 1% CO₂. Since bone loss in zero G is a problem, any additional loss in bone or bone strength due to CO₂ exposure should be studied. The determination of a threshold limit below which CO₂ exposure does not produce bone changes would help to set exposure limits.

Neurologic changes due to low dose CO₂ do not appear to be significant. Performance is not affected with chronic 2% CO₂ exposure. Little if any change occurs in cerebral blood flow. The addition of CO₂ to 100% O₂ may be significant in that the time to onset of seizures is decreased. With higher operating pressures for future spacesuits, O₂ toxicity may become more of a concern. The influence of CO₂ exposure on O₂ toxicity deserves further attention.

Cardiovascular responses are basically normal with exposure to CO₂ below 2%. A slowing in the adaptation to exercise with CO₂ 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 CO₂ is of potential concern. The physiologic significance of the observed histologic changes is unknown. A threshold of 0.5% CO₂ apparently exists for the occurrence of histologic changes in guinea pig lungs. The existence of histologic changes in human lungs from CO₂ exposure is unknown.

An improvement in environmental control in association with the reduction of CO₂ 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% CO₂, the incidence of respiratory disease was similar between submariners and surface personnel. These observations support the reduction of CO₂ exposure during EVA to at least 0.8%.

The findings of histopathologic changes in the kidneys of guinea pigs exposed to low dose CO₂ is also of potential concern. A threshold limit for CO₂ below which changes do not occur in guinea pig kidneys has not been established. Exposures as low as 0.3% CO₂ have caused renal calcification.

A decrease in the incidence of kidney stones was observed in submariners in association with a reduction in CO₂ 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 CO₂ exposure. A similar response is likely if repetitive CO₂ exposures induce chronic physiologic changes. The additional calcium excretion induced by zero gravity will contribute to the calcium excretion caused by low dose CO₂ 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 CO₂ to 0.5% may be appropriate.

A decrease in the incidence of GI symptoms in submariners was noted in association with lowering CO₂ 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% CO₂. These observations support lowering CO₂ exposure limits during EVA to at least 0.8%.

Drawing conclusions from a variety of disparate studies in order to set CO₂ 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 CO₂ exposure limits for EVA. Monitoring physiologic and histologic changes to repetitive, daily 8 h exposures to low dose CO₂ and 100% O₂ 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 CO₂ and 100% O₂ mixtures should be performed. Based on the results presented in this paper, a lowering of the current NASA standard for CO₂ exposure during EVA should be considered. A reduction in the current NASA standard for CO₂ 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.

References

1. West, J. B.: Respiratory Physiology – The Essentials, 3rd edition. Williams and Wilkins, Baltimore, Maryland, 1985.
2. Fisher, W. F.; and Price, C. R.: Space Station Freedom External Maintenance Task Team Final Report. NASA Johnson Space Center, Houston, TX, July 1990.
3. Schrier, R. N.: Renal and Electrolyte Disorders, 3rd ed. Little, Brown, and Co., Boston, MA, 1986.
4. Lambertsen, C. J.: The Philosophy of Extremes for the Gaseous Environment of Closed, Ecological Systems. Aerospace Medicine, vol. 34, no. 4, 1963, pp. 291-9.
5. Lambertsen, C. J.: Carbon Dioxide Tolerance and Toxicity. Institute for Environmental Medicine, Univ. of Pennsylvania Medical Center, 1971.
6. Lambertsen, C. J.; Kough, R. H.; Cooper, D. Y.; Emmel, G. L.; Loeschcke, H. H.; and Schmidt, C. F.: Comparison of Relationship of Respiratory Minute Volume to P_{CO₂} and pH of Arterial and Internal Jugular Blood by Low Concentrations of CO₂ at 1 Atmosphere and by O₂ at 3.0 Atmospheres. J. Appl Physiol., vol. 5, June 1953, pp. 803-13.
7. Dripps, R. D.; and Comroe, J. H.: The Respiratory and Circulatory Response of Normal Man to Inhalation of 7.6 and 10.4 Per Cent CO₂ with a Comparison of the Maximal Ventilation Produced by Severe Muscular Exercise, Inhalation of CO₂ and Maximal Voluntary Hyperventilation. Am. J. Physiol., vol. 149, 1947, pp. 43-51.

8. Askanazi, J.; Milic-Emili, J.; Broell, J. R.; Hyman, A. I.; and Kinney, J. M.: Influence of Exercise and CO₂ on Breathing Pattern of Normal Man. *J. Appl. Physiol.*, vol. 47, no. 1, 1979, pp. 192-6.
9. Reynolds, W. J.; Milhorn, H. T., Jr.: and Holloman, G. H., Jr.: Transient Ventilatory Response to Graded Hypercapnia in Man. *J. Appl. Physiol.*, vol. 33, no. 1, 1972, pp. 47-54.
10. Anthonisen, N. R.; and Dhingra, S.: Ventilatory Response to Low Levels of CO₂. *Resp. Physiol.*, vol. 32, 1978, pp. 335-44.
11. Lambertsen, C. J.: Carbon Dioxide and Respiration in Acid-Base Homeostasis. *Anesthesiology*, vol. 21, no. 6, Nov.-Dec. 1960, pp. 642-51.
12. Forster, H. V.; Klein, J. R.; Hamilton, L. H.; and Kampine, J. P.: Regulation of PaCO₂ and Ventilation in Humans Inspiring Low Levels of CO₂. *J. Appl. Phys.*, vol. 52, no. 2, 1982, pp. 287-94.
13. Dejours, P.; Puccinelli, R.; Armand, J.; and Dicharry, M.: Concept and Measurement of Ventilatory Sensitivity to Carbon Dioxide. *J. Appl. Physiol.*, vol. 20, no. 5, 1965, pp. 890-7.
14. Ellingsen, I.; Liestöl, K.; Sydnes, G.; Hauge, A.; and Nicolaysen, G.: Arterial P_{CO₂} and Lung Ventilation in Man Exposed to 1-5% CO₂ in the Inspired Gas. *Acta Physiol. Scand.*, vol. 129, 1987, pp. 269-276.
15. Ellingsen, I.; Sydnes, G.; Hauge, A.; Zwart, J-A; Liestol, K.; and Nicolaysen, G.: CO₂ Sensitivity in Humans Breathing 1 or 2% CO₂ in air. *Acta Physiol. Scandinavia*, vol. 129, 1987, pp. 195-202.
16. Schuitmaker, J. J.; Berkenbosch, A.; De Goede, J.; and Oliebier, C. N.: Effects of CO₂ and H⁺ on the Ventilatory Response to Peripheral Chemoreceptor Stimulation. *Respiration Physiology*, vol. 64, 1986, pp. 69-79.
17. Gustavo, J.; Calverley, P.; Talamo, C.; Schnader, J.; and Roussos, C.: Effect of Carbon Dioxide on Diaphragmatic Function in Human Beings. *N.E. J. M.*, vol. 310, no. 14, 1984, pp. 874-9.
18. Schnader, J. Y.; Gustavo, J.; Howell, S.; Fitzgerald, R.; and Roussos, C.: Arterial CO₂ Partial Pressure Affects Diaphragmatic Function. *J. Appl. Physiol.*, vol. 58, no. 3, 1985, pp. 823-9.
19. Schnader, J. Y.; Howell, S.; Fitzgerald, R. S.; and Roussos, C.: Interaction of Fatigue and Hypercapnia in the Canine Diaphragm. *J. Appl. Phys.*, vol. 64, no. 4, 1988, pp. 1636-43.
20. Brackett, N. C., Jr.; Cohen, J. J.; and Schwartz, W. B.: Carbon Dioxide Titration Curve of Normal Man. *New England J. Med.*, vol. 272, no. 1, 1965, pp. 6-12.
21. Bercovici, M.; Chen, C. B.; Goldstein, M. B.; Steinbaugh, B. J.; and Halperin, M. L.: Effect of Acute Changes in the PaCO₂ on Acid-Base Parameters in Normal Dogs and Dogs with Metabolic Acidosis or Alkalosis. *Can. J. Physiol. Pharmacol.*, vol. 61, 1983, pp. 166-73.
22. King, B. G.: High Concentration-Short Time Exposures and Toxicity. *J. Ind. Hyg. and Toxicol.*, vol. 31, no. 6, 1949, pp. 365-75.
23. U.S. Navy Diving Gas Manual Second Edition. NAVSHIPS 0994-003-7010, 1971.
24. White, C. S.; Humm, J.; Armstrong, E., and Lundgren, N., P.V.: Human Tolerance to Acute Exposure to Carbon Dioxide Report No. 1: Six Percent Carbon Dioxide in Air and in Oxygen. *Aviation Medicine*, vol. 23, 1952, pp. 439-55.
25. Irsigler, G. B.: Carbon Dioxide Response Lines in Young Adults: The Limits of the Normal Response. *Am. Rev. of Resp. Dis.*, vol. 114, 1976, pp. 529-36.
26. Schaefer, K. E.: Respiratory Pattern and Respiratory Response to CO₂. *J. Appl. Physiol.*, vol. 13, no. 1, 1958, pp. 1-14.
27. Kellogg, R. H.: Acclimitization to Carbon Dioxide. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 634-41.
28. Schaefer, K. E.: Environmental Physiology of Submarines and Spacecraft. *Arch. of Env. Med.*, vol. 9, 1964, pp. 320-32.

29. Schaefer, K. E.; Hastings, B. J.; Carey, C. R.; and Nichols, G., Jr.: Respiratory Acclimitization to Carbon Dioxide. *J. Appl. Phys.*, vol. 18, no. 6, 1963, pp. 1071-8.
30. Guillermin, R.; and Radziszewski, E.: Effects on Man of 30-Day Exposure to a PI_{CO_2} of 14 Torr (2%): Application to Exposure Limits. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S91-S114.
31. Glatte, H.; and Motsay, G. J.: Normal Man and Chronic Hypercapnia: Metabolic Aspects. *The Physiologist*, vol. 9, 1966, p. 188.
32. Schaefer, K. E.: Physiological Stresses Related to Hypercapnia During Patrols on Submarines. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S15-S47.
33. Schaefer, K. E.; Carey, C. R.; Dougherty, J. H., Jr.; Morgan, C.; and Messier, A. A.: Effect of Intermittent Exposure to 3% CO_2 on Respiration, Acid-Base Balance, and Calcium-Phosphorus Metabolism. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S115-34.
34. Schaefer, K. E.: Experiences with Submarine Atmospheres. *Aviation Medicine*, vol. 30, 1959, pp. 350-9.
35. Douglas, W. H.; Schaeffer, K. E.; Messier, A. A.; and Pasquale, S. M.: Proliferation of Pneumocyte II Cells in Prolonged Exposure to 1% CO_2 . *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S135-S142.
36. Schaefer, K. E.; Douglas, W. H.; Messier, A. A.; Shea, M. L.; and Gohman, P. A.: Effect of Prolonged Exposure to 0.5% CO_2 on Kidney Calcification and Ultrastructure of Lungs. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S155-S161.
37. Tansey, W. A.; Wilson, J. M.; and Schaefer, K. E.: Analysis of Health Data from 10 Years of Polaris Submarine Patrols. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S217-S246.
38. Harrison's Principles of Internal Medicine, 11th Edition. McGraw-Hill Book Co., New York, 1987.
39. Kennedy, Thomas J., Jr.: The Effect of Carbon Dioxide on the Kidney. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 704-16.
40. Chinard, F. P.; Nolan, M. P.; and Enns, T.: Renal Handling of Exogenous and Metabolic Carbon Dioxide. *Am. J. Physiol.*, vol. 206, no. 2, 1964, pp. 362-8.
41. Madias, N. E.; Wolf, C. J.; and Cohen, J. J.: Regulation of Acid-Base Equilibrium in Chronic Hypercapnia. *Kidney International*, vol. 27, 1985, pp. 538-43.
42. Schaefer, K. E.; Nichols, G., Jr.; and Carey, C. R.: Acid-Base Balance and Blood and Urine Electrolytes of Man During Acclimitization to CO_2 . *J. Appl. Physiol.*, vol. 19, no. 1, 1964, pp. 48-58.
43. Schaefer, K. E.: A Concept of Triple Tolerance Limits Based on Chronic Carbon Dioxide Toxicity Studies. *Aerospace Medicine*, vol. 32, 1961, pp. 197-204.
44. Farhi, L. E.; and Rahn, H.: Dynamics of Changes in Carbon Dioxide Stores. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 604-14.
45. Schaefer, K. E.; Nichols, G., Jr.; and Carey, C. R.: Calcium Phosphorus Metabolism in Man During Acclimatization to Carbon Dioxide. *J. Appl. Physiol.*, vol. 18, no. 6, 1963, pp. 1079-84.
46. Schaefer, K. E.: Effects of Increased Ambient CO_2 Levels on Human and Animal Health. *Experientia*, vol. 38, 1982, pp. 1163-8.
47. Schaefer, K. E.; Hasson, M.; and Niemoeller, H.: Effect of Prolonged Exposure to 15% CO_2 on Calcium and Phosphorus Metabolism. *Proc. Soc. Exp. Biol. Med.*, vol. 107, 1961, pp. 355-9.
48. Bidani, A.; and Crandall, E. D.: Analysis of the Effects of Hemotocrit on Pulmonary CO_2 Transfer. *J. Appl. Phys.*, vol. 53, no. 2, 1982, pp. 413-8.
49. Kwant, G.; Oeseburt, B.; Zwart, A.; and Zijlstra, W. G.: Human Whole-Blood O_2 Affinity: Effect of CO_2 . *J. Appl. Physiol.*, vol. 64, no. 6, 1988, pp. 2400-9.
50. Schaefer, K. E.; Pasquale, S. M.; Messier, A. A.; and Niemoeller, H.: CO_2 -Induced Kidney Calcification. *Undersea Biomed. Res. Sub. Suppl.*, 1979, pp. S143-S153.

51. Sayers, J. A.; Smith, R. E. A.; Holland, R. L.; and Keatinge, W. R.: Effects of Carbon Dioxide on Mental Performance. *J. Appl. Physiol.*, vol. 63, no. 1, 1987, pp. 25-30.
52. Van den Hout, M. A.; and Griez, E.: Peripheral Panic Symptoms Occur During Changes in Alveolar Carbon Dioxide. *Comp. Psych.*, vol. 26, no. 4, 1985, pp. 381-7.
53. Van den Hout, M. A.; and Griez, E.: Panic Symptoms After Inhalation of Carbon Dioxide. *Br. J. Psych.*, vol. 144, 1984, pp. 503-7.
54. Woods, S. W.; Charney, D. S.; Goodman, W. K.; and Heninger, G. R.: Carbon Dioxide-Induced Anxiety. *Arch. Gen. Psych.*, vol. 45, 1988, pp. 43-52.
55. Singh, B. S.: Ventilatory Response to CO₂. I. A Psychobiologic Marker of the Respiratory System. *Psychosom. Med.*, vol. 46, no. 4, 1984, pp. 333-45.
56. Sokoloff, L.: The Effects of Carbon Dioxide on the Cerebral Circulation. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 664-73.
57. Wilson, D. A.; Traystman, R. J.; and Rapela, C. E.: Transient Analysis of the Canine Cerebrovascular Response to Carbon Dioxide. *Circ. Res.*, vol. 56, 1985, pp. 596-605.
58. Warner, D. S.; Turner, D. M.; and Kassell, N. F.: Time-Dependent Effects of Prolonged Hypercapnia on Cerebrovascular Parameters in Dogs: Acid-Base Chemistry. *Stroke*, vol. 18, 1987, pp. 142-9.
59. Bryan, R. M., Jr.; Myers, C. L.; and Page, R. B.: Regional Neurohypophysial and Hypothalamic Blood Flow in Rats During Hypercapnia. *Am. J. Physiol.*, vol. 255, 1988, pp. R295-R302.
60. Petroff, O. A.; Prichard, J. W.; Behan, K. L.; Rothman, D. L.; Alger, J. R.; and Shulman, R. G.: Cerebral Metabolism in Hyper- and Hypocarbica: 31P and 1H Nuclear Magnetic Resonance Studies. *Neurology*, vol. 35, 1985, pp. 1681-8.
61. Woodbury, D. M.; and Karler, R.: The Role of Carbon Dioxide in the Nervous System. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 686-703.
62. Tenney, S. M.: The Effect of Carbon Dioxide on Neurohumoral and Endocrine Mechanisms. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 674-85.
63. Gesell, R.; Brassfield, C. R.; and Hamilton, M. A.: An Acid-Neurohumoral Mechanism of Nerve Cell Activation. *Am. J. Physiol.*, vol. 136, 1942, pp. 604-8.
64. Price, H. L.: Effects of Carbon Dioxide on the Cardiovascular System. *Anesthesiology*, vol. 21, no. 6, 1960, pp. 652-63.
65. Sechzer, P. H.; Egbert, L. D.; Linde, H. W.; Cooper, D. Y.; Dripps, R. D.; and Price, H. L.: Effect of CO₂ Inhalation on Arterial Pressure, ECG and Plasma Catecholamines and 17-OH Corticosteroids in Normal Man. *J. Appl. Physiol.*, vol. 15, no. 3, 1960, pp. 454-8.
66. Macdonald, F. M.; and Simonson, E.: Human Electrocardiogram During and After Inhalation of Thirty Per Cent Carbon Dioxide. *J. Appl. Physiol.*, vol. 6, 1953, pp. 304-10.
67. Brown, E. B.; and Miller, F.: Ventricular Fibrillation Following a Rapid Fall in Alveolar Carbon Dioxide Concentration. *Am. J. Physiol.*, vol. 169, 1952, pp. 56-60.
68. Wexels, J. C.: Myocardial Oxygen Supply During Hypocapnia and Hypercapnia in the Dog. *Can. J. Physiol. Pharmacol.*, vol. 64, 1986, pp. 1376-80.
69. Eliades, D.; and Weiss, H. R.: Effect of Hypercapnia on Coronary Circulation. *Cardiovascular Res.*, vol. 20, 1986, pp. 127-33.
70. Powers, E. R.; Bannerman, K. S.; Fitz-James, I.; and Cannon, P. J.: Effect of Elevation of Coronary Artery Partial Pressure of Carbon Dioxide (P_{CO₂}) on Coronary Blood Flow. *J. Am. Coll. Cardiol.*, vol. 8, no. 5, 1986, pp. 1175-81.
71. Burget, G. E.; and Visscher, M. B.: Variations of the pH of the Blood and the Response of the Vascular System to Adrenalin. *Am. J. Physiol.*, vol. 81, 1927, pp. 113-23.
72. Tenney, S. M.: Sympatho-Adrenal Stimulation by Carbon Dioxide and the Inhibitory Effect of Carbonic Acid on Epinephrine Response. *Am. J. Physiol.*, vol. 187, 1956, pp. 341-6.

73. Schaefer, K. E.; King, C. T. G.; Mego, J. L.; and Williams, E. E.: Effect of Narcotic Level of CO₂ on Adrenal Cortical Activity and Carbohydrate Metabolism. *Am. J. Physiol.*, vol. 183, 1955, pp. 53-62.
74. Cha, E. J.; Sedlock, D.; and Yamashiro, S. M.: Changes in Lung Volume and Breathing Pattern During Exercise and CO₂ Inhalation in Humans. *J. Appl. Physiol.*, vol. 62, no. 4, 1987, pp. 1544-50.
75. Gallagher, C. G.; Brown, E.; and Younes, M.: Breathing Pattern During Maximal Exercise and During Submaximal Exercise with Hypercapnia. *J. Appl. Physiol.*, vol. 63, no. 1, 1978, pp. 238-44.
76. Flenley, D. C.; and Warren, P. M.: Ventilatory Response to O₂ and CO₂ During Exercise. *Ann. Rev. Physiol.*, vol. 45, 1983, pp. 415-26.
77. Clark, J. M.; Sinclair, R. D.; and Lenox, J. B.: Chemical and Nonchemical Componentis of Ventilation During Hypercapnic Exercise in Man. *J. Appl. Physiol.*, vol. 48, no. 6, 1980, pp. 1065-76.
78. Graham, T. E.; Wilson, B. A.; Sample, M.; Van Kijk, J.; and Goslin, B.: The Effects of Hypercapnia on the Metabolic Response to Steady State Exercise. *Med. Sci. Sports Exerc.*, vol. 14, no. 4, 1982, pp. 286-91.
79. Craig, F. N.: Pulmonary Ventilation During Exercise and Inhalation of Carbon Dioxide. *J. Appl. Physiol.*, vol. 7, no. 5, 1955, pp. 467-71.
80. Jacobi, M. S.; Iyawe, V. I.; Patil, C. P.; Cumin, A. R.; and Saunders, K. B.: Ventilatory Responses to Inhaled Carbon Dioxide at Rest and During Exercise in Man. *Clinical Science*, vol. 73, 1987, pp. 177-82.
81. Menn, S. J.; Sinclair, R. D.; and Welch, B. E.: Effect of Inspired P_{CO₂} up to 30 mmHg on Response of Normal Man to Exercise. *J. Appl. Physiol.*, vol. 28, no. 5, 1970, pp. 663-71.
82. Graham, T. E. and Wilson, B. A.: Effects of Hypercapnia and Hyperoxia on Metabolism During Exercise. *Med. Sci. Sports Exerc.*, vol. 15, no. 6, 1983, pp. 514-9.
83. Graham, T. E.; Barclay, J. K.; and Wilson, B. A.: Skeletal Muscle Lactate Release and Glycolytic Intermediates During Hypercapnia. *J. Appl. Physiol.*, vol. 60, no. 2, 1986, pp. 568-75.
84. Waligora, J. M.; and Horrigan, D. J., Jr.: Metabolic Cost of Extravehicular Activities, in *Biomedical Results from Skylab*, Johnston, R. S.; Dietlein, L. F., eds., NASA-SP-377, 1977, pp. 395-399.
85. Waligora, J. M.; and Horrigan, D. J., Jr.: Metabolic Cost of Extravehicular Activities, in the *Proceedings of the Skylab Life Sciences Symposium*, vol. 2, Johnston, R. S.; Dietlein, L. F., eds., NASA-TM-X-58154, vol. 2, 1975, pp. 775-84.
86. Waligora, J. M.; and Horrigan, D. J., Jr.: Metabolism and Heat Dissipation During Apollo EVA Periods, in *Biomedical Results of Apollo*, Johnston, R. S.; Dietlein, L. F.; Berry, C.A., eds., NASA-SP-368, 1976, pp. 115-128.
87. Horrigan, D. J., Jr.; Waligora, J. M.; Stanford, J.; and Edwards, B. F.: Overview of Crew Member Energy Expenditure During Shuttle Flight 61-B Ease/ACCESS Task Performance. *Space Construction Conference, LaRC*, Hampton, VA, Aug. 6-7, 1986, NASA CP-2490, pp. 228-35.
88. Cutler, R. G.; Robertson, W. G.; Herlocher, J. E.; McKenzie, R. E.; Ulvedal, F.; Hargreaves, J. J.; and Welch, B. E.: Human Response to Carbon Dioxide in the Low-Pressure, Oxygen-Rich Atmosphere. *Aerospace Medicine*, vol. 35, no. 4, 1964, pp. 317-23.
89. Lambertsen, C. J.; Kough, R. H.; Cooper, D. Y.; Emmel, G. L.; Loeschcke, H. H.; and Schmidt, C. F.: Oxygen Toxicity. Effects in Man of Oxygen Inhalation at 1 and 3.5 Atmospheres upon Blood Gas Transport, Cerebral Circulation and Cerebral Metabolism. *J. Appl. Physiol.*, vol. 5, no. 9, 1953, pp. 471-86.
90. Lambertsen, C. J.; Ewing, J. H.; Kough, R. H.; Gould, R.; and Stroud, M. W. III: Oxygen Toxicity. Arterial and Internal Jugular Blood Gas Composition in Man During Inhalation of Air, 100% O₂ and 2% CO₂ in O₂ at 3.5 Atmospheres Ambient Pressure. *J. Appl. Physiol.*, vol. 8, 1955, pp. 255-63.
91. Marshall, J. R.; and Lambertsen, C. J.: Interactions of Increased P_{O₂} and P_{CO₂} Effects in Producing Convulsions and Death in Mice. *J. Appl. Physiol.*, vol. 16, no. 1, 1961, pp. 1-7.

92. Deutsch, T. A.; Read, J. S.; Ernest, J. T.; and Goldstick, T. K.: Effects of Oxygen and Carbon Dioxide on the Retinal Vasculature in Humans. *Arch. Ophthalmol.*, vol. 101, 1983, pp. 1278-80.
93. Downes, J. J.; and Lambertsen, C. J.: Dynamic Characteristics of Ventilatory Depression in Man on Abrupt Administration of O₂. *J. Appl. Physiol.*, vol. 21, no. 2, 1966, pp. 447-53.
94. Shock, N. W.; and Soley, M. H.: Effect of Oxygen Tension of Inspired Air on the Respiratory Response of Normal Subjects to Carbon Dioxide. *Am. J. Physiol.*, vol. 130, 1940, pp. 777-83.

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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 to 1% 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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