BLOOD pH AND pCO₂ HOMEOSTASIS IN CHRONIC RESPIRATORY ACIDOSIS RELATED TO THE USE OF AMINE AND OTHER BUFFERS

by

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Bureau of Medicine and Surgery, Navy Department, Research Project MR005.14-3002-1.07
SUMMARY PAGE

THE PROBLEM

To present data and discuss the problem of control of carbon dioxide in the submarine atmosphere, especially concerning the use of amine buffers for the control of this problem.

FINDINGS

In World War II, when no adequate CO₂ removal equipment existed, concentrations of 3-5% had to be tolerated over extended periods. Attempts to remedy the situation by using alkaline buffers were made and found helpful only in alleviating symptoms related to the pH changes of the uncompensated phase of respiratory acidosis. Results of prolonged exposure to 1.5% CO₂ (for periods of 42 days as in Operation Hideout) demonstrated that the elevated pCO₂ persisting during the compensated phase of respiratory acidosis has significant effects on a number of physiological functions, independent of pH, and this condition is not amenable to treatment by amine buffers.

APPLICATION

The use of nuclear-powered submarines capable of greatly extended periods of submergence requires a solution to the carbon dioxide problem. The results of this study will contribute to effective control of this situation.

ADMINISTRATIVE INFORMATION

This investigation was undertaken as a part of Bureau of Medicine and Surgery Research Task MR005.14-3002-1, Physiological Mechanisms of CO₂ Toxicity. The present report is No. 7 on this Subtask. It was published in the Annals of the New York Academy of Medicine, Vol. 92, Art. 2, 401-413, June 1961.
BLOOD pH AND pCO₂ HOMEOSTASIS IN CHRONIC RESPIRATORY ACIDOSIS RELATED TO THE USE OF AMINE AND OTHER BUFFERS

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This report deals with the use of amine buffers in the CO₂ scrubber of submarines and the problems of chronic CO₂ toxicity as they relate to treatment with buffers. I propose to discuss the CO₂ control of the submarine atmosphere very briefly, since I can only provide some general information on this subject based on the work of engineers at the Naval Research Laboratory, Washington, D.C. I shall present data on the homeostasis of pH and pCO₂ obtained during the prolonged exposure of 23 subjects to 1.5 per cent CO₂ that indicate the effects of elevated pCO₂ independent of pH changes. Only the latter are subject to treatment with amine buffers. Moreover I shall mention earlier attempts to use alkalinizing agents, such as potassium salt, to increase the tolerance to hypercapnia.

Atmospheric Control with CO₂ Scrubbers Using Amines Buffers

Chronic CO₂ toxicity is known to have been a cardinal problem of submarine medicine for many years, simply because no technical advances were made to develop efficient self-regulating CO₂ removal equipment. With the advent of nuclear-powered submarines capable of greatly extended submergence times, it was necessary to find a solution. The introduction of a CO₂ scrubber using monoethanolamine represented the first satisfactory accomplishment to remove CO₂ with self-regenerating absorbent. Monoethanolamine (MEA) absorbs CO₂ at room temperature and releases it at higher temperature. A simplified diagram of the amine-type CO₂ removal equipment is presented in FIGURE 1. It consists of an absorber column, a CO₂ stripper, an amine pump, and a heat exchanger. The submarine air is pumped through a cool MEA solution in the absorber column and CO₂ is chemically absorbed. The MEA solution is recycled through the absorber column. Part of the MEA solution is piped to the CO₂ stripper, where it is heated under pressure to release the CO₂. The latter is further compressed and discharged overboard. The hot MEA is cooled and used again in the absorber. The CO₂ scrubbers presently in operation have a capacity to remove 10 lb. of CO₂/hour while operating at 170 c.f.m.

FIGURE 2 shows a comparison of a conventional lithium hydroxide (LiOH) scrubber used on battery-powered submarines with an MEA system in regard to weight, volume, and power requirements. It is obvious that the LiOH system has an advantage for short periods up to 10 days. For the longer periods, the MEA scrubber is of course the better choice.

According to Goodridge, it is believed that mono- and diethanolamines react with CO₂ by donating an electron of a hydrogen molecule from the amine linkage and formation of carbonates. Since the molecular weight of monoethanolamine is much smaller than that of diethanolamine and triethanolamine
THE CO₂ REMOVAL PLANT-AMINE TYPE
SIMPLIFIED FLOW DIAGRAM

Figure 1. Diagram of an amine-type CO₂ scrubber. (Reproduced by permission of The Macmillan Co., New York, N.Y.)

SYSTEM CHARACTERISTICS OF MEA SCRUBBER AND LiOH (based on 100 men)

Figure 2. Weight, volume, and power requirements of MEA and LiOH CO₂ scrubbers calculated for 100 men. (Reproduced by permission of The Macmillan Co., New York, N.Y.)
and only 1 mol. of amine is utilized per molecule of CO₂ reacted, the relative absorption capacity of CO₂ per pound is much greater for MEA (1.0:0.58:0.41). MEA leaves something to be desired as a regenerative carbon dioxide absorbent. It has a lack of resistance to oxidation that in time leads to a degradation of the MEA solution requiring replacement. Furthermore, MEA has a certain toxicity. The current maximal allowable concentration (MAC) established by the Bureau of Medicine and Surgery for the United States Navy is 1 ppm.*

**Blood pH and pCO₂ Homeostasis During Prolonged Exposure to Increased CO₂ Levels**

In World War II, when no adequate CO₂ removal equipment existed in submarines to allow prolonged submersions, CO₂ concentrations of 3 to 5 per cent had to be tolerated over extended periods. It was during this time that interest was developed in using alkali buffers to make men CO₂ resistant and, eventually, to raise the tolerance to CO₂ in submarine crews. These early attempts to treat respiratory acidosis with Na and K buffers will be discussed later. I shall concentrate first on the results of studies that produced evidence that the effects of increased pCO₂ independent of pH changes are significant. In emphasizing the aspects of pCO₂ homeostasis, which is not influenced by alkali or Tris buffer medication, it is hoped that a useful contribution may be made to define the limitations and indications for the use of Tris buffer in respiratory acidosis.

In a large experiment 23 subjects were confined in a submarine and exposed to 1.5 per cent CO₂ in 21 per cent O₂ over a period of 42 days, with a 9-day control period prior to and following exposure. The results showed no significant changes in performance* or in basic physiological parameters, such as blood pressure, pulse rate, weight, and body temperature (FIGURE 3). However, studies of respiration, acid-base balance, and electrolyte exchange* brought some unexpected findings. A slight uncompensated respiratory acidosis existed for a period of 23 days after which the pH returned to normal. During a 9-day recovery period following a 42-day exposure to 1.5 per cent CO₂ the alveolar pCO₂, blood pCO₂ remained elevated at the level reached during exposure. The existence of a phase of uncompensated respiratory acidosis for 23 days followed by a phase of compensated respiratory acidosis from the 24th to the 42nd day is indicated in FIGURE 4 in the changes of pH, of blood and urine, and CO₂ excretion in the urine. Moreover a significant depression of the respiratory response to 5 per cent CO₂, previously described as part of a respiratory adaptation to CO₂,* was found after 35 days of exposure to 1.5 per cent CO₂ (FIGURE 3). The central importance of the respiratory pattern in adaptation to CO₂ was demonstrated in a progressive increase in tidal volume throughout the 42 days of exposure and a decline of respiratory rate during the second phase subsequent to a transient increase during the first (uncompensated) phase of respiratory acidosis. This pattern of respiration is so strongly established at the end of a 42-day exposure to 1.5 per cent CO₂ that transition to air is not able to bring it back to normal. Contrary

*E. A. Ramskill, Naval Research Laboratory, Washington, D.C. Personal communication.
FIGURE 3. Effect of prolonged exposure to 1.5 per cent CO₂ over a period of 42 days on systolic and diastolic blood pressure, pulse rate, body weight, and oral temperature (mean values of 23 subjects). (Reproduced by permission of Aerospace Medicine.)

FIGURE 4. Effect of prolonged exposure to 1.5 per cent CO₂ over a period of 42 days on pH of blood and urine, CO₂ excretion in the urine, and ventilatory response to 5 per cent CO₂ (21 subjects). (Reproduced by permission of Aerospace Medicine.)
to expectation, a further drop in respiratory rate occurs, and the alveolar $\rho$CO$_2$
level is maintained at an elevated point for 9 days after return to air breathing
(Figure 6). We therefore have two periods: (1) the compensated phase of
respiratory acidosis from the 24th day to the 42nd day of exposure; and (2)
the 9-day recovery period on air following exposure to CO$_2$, in which the $\rho$H
is practically normal and the $\rho$CO$_2$ is elevated, while the blood $\rho$H changes
are limited to the first 23 days of exposure.

It therefore appears possible to delineate those functions that are particularly
influenced by the $\rho$H changes of the blood from those that seem to be affected

![Graph showing pH changes](image)

**Figure 5.** Effect of prolonged exposure to 1.5 per cent CO$_2$ over a period of 42 days on $\rho$H
of blood plasma, inorganic phosphorus, and plasma calcium.

predominately from $\rho$CO$_2$ changes. An example of $\rho$H-dependent variables
is seen in the changes of plasma calcium that mirror the alterations in blood
$\rho$H (Figure 5). The plasma inorganic phosphorus shows the opposite trend.

**Figure 6** shows some other physiological parameters that appear to be
independent of $\rho$H changes or that, still better, are not influenced by the return
of blood $\rho$H to normal. This is the pattern of respiration already mentioned
above. The elevated $\rho$CO$_2$ seems to be the dominant factor in the develop-
ment of a large tidal volume and a small respiratory rate, a pattern that in
turn maintains an elevated $\rho$CO$_2$ as seen in the recovery period.

The cardiovascular capacity was tested with the Harvard step-up test,
consisting of stepping 20 times within 30 sec. on an 18-inch high stool. Pulse
rate was counted immediately after the test, and 2 min. later. Cardiovascular score was computed as follows:

15 sec. to 20 sec. pulse rate plus
(1 min. 45 sec. to 2 min. 15 sec. pulse rate)

It can be noted that the cardiovascular score increases throughout the exposure to CO₂, indicating a reduction in cardiovascular capacity. The cardiovascular score continues to rise after the compensation of respiratory acidosis is reached.

![Diagram of pH, respiratory rate, tidal volume, cardiovascular score, and ketosteroid excretion over 42 days](image)

Figure 6. Effect of prolonged exposure to 1.5 per cent CO₂ over a period of 42 days on respiratory rate, tidal volume, cardiovascular score, and ketosteroid excretion (21 subjects).

and remains high in the recovery phase associated with the elevated pCO₂ level.

As a measure of the stress of CO₂ exposure, the ketosteroid excretion was measured and found higher in the compensated phase of respiratory acidosis. The eosinophils also began to fall during this second phase, reaching the lowest value during the 9-day recovery period. It could be argued that the factor of confinement might have caused these effects, rather than the elevated pCO₂ levels. However, the results of animal experiments carried out simultaneously under the same conditions of exposure to 1.5 per cent CO₂ on rats and guinea pigs showed similar findings, a significant increase in adrenal-cortical activity during the same two periods in which the pH was not different from control levels and the pCO₂ elevated.
Effects of Alkalinizing Agents in Chronic Respiratory Acidosis Induced by Prolonged Exposure to 2 to 3.5 per cent CO₂

These experiments were carried out by R. Pointner. Some of these data on individual subjects were summarized and statistically evaluated, and are reported here. The subjects were exposed for 4 days to 2 to 3.5 per cent carbon dioxide. There was a control period on air lasting for 2 to 3 days prior to exposure, and a 3-day recovery period on air following exposure. Measurements were made during these 3 periods of urinary pH and of excretion of CO₂ and ammonia; determinations were also made of intake and excretion of sodium, potassium, chloride, phosphorus, calcium, and water.

**Table 1** shows the effects of these alkalinizing agents on urinary pH, CO₂, and ammonia excretion prior, during, and after chronic respiratory acidosis.

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>CO₂ (total) gm.</th>
<th>Ammonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control period on air 2 to 3 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.36</td>
<td>6.25</td>
<td>6.30</td>
</tr>
<tr>
<td>SD</td>
<td>0.17</td>
<td>0.07</td>
<td>0.42</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Exposure to 2 to 3.5% CO₂ for 4 days**

| Mean | 6.14 | 6.81 | 6.90 | 7.7 | 38.7 | 40.7 | 79.0 | 741 | 443 | 461 |
| SD   | 1.14 | 0.09 | 0.00 | 0.03 | 0.64 | 0.73 | 1.56 | 1.56 | 14.9 |
| N    | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 |

**Recovery period on air following CO₂ exposure 3 days**

| Mean | 6.35 | 6.51 | 6.58 | 8.6 | 15.5 | 26.3 | 528 | 685 | 436 |
| SD   | 0.14 | 0.44 | 0.62 | 4.5 | 5.1 | 4.1 | 90 | 35.8 | 17.7 |
| N    | 4 | 2 | 2 | 4 | 2 | 2 | 4 | 2 | 2 |

*Adapted from Pointner.*

† Na salt (Sepdelen 7) and potassium salt.

‡ Values significantly different from control values at the 5 per cent level and better.

§ Values significantly different from control values at the 1 per cent level and better.

Combined with the results of an experiment in which no medication was used. **Table 2** gives some information about the retention of electrolytes based on the difference between intake and urinary excretion. Unfortunately no measurements of electrolytes in feces were made, consequently no complete balance could be established.*

The sodium salt Sepdelen 7 normally has diuretic effects that were not present under conditions of CO₂ exposure in which a water retention was found (Table 1). There was an increased chloride and potassium excretion under CO₂ exposure, but no significant change in sodium excretion. Alkalinizing effects of sodium salt medication were shown in an increase of pH and the CO₂ excretion of the urine and a decrease of the ammonia excretion. The results

*The potassium phosphorus salt consisted of two thirds potassium carbonate and one third potassium biphosphate; the sodium salt (Sepdelen 7) consisted of 22 per cent sodium citrate, 23 per cent sodium tartrate, 26 per cent sodium sulphate, 25 per cent secondary sodium phosphate, and 4 per cent sodium carbonate.
<table>
<thead>
<tr>
<th>Control period on air 2 to 3 days</th>
<th>H₂O</th>
<th>K</th>
<th>Na</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>322</td>
<td>270</td>
<td>680</td>
<td>3.01</td>
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<tr>
<td>SD</td>
<td>199</td>
<td>127</td>
<td>67</td>
<td>0.86</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Exposure to 2 to 3.5% CO₂ for 4 days</td>
<td>H₂O</td>
<td>K</td>
<td>Na</td>
<td>Cl</td>
</tr>
<tr>
<td>Mean</td>
<td>600</td>
<td>580</td>
<td>700</td>
<td>1.93</td>
</tr>
<tr>
<td>SD</td>
<td>183</td>
<td>169</td>
<td>149</td>
<td>1.04</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>2</td>
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<td>4</td>
</tr>
<tr>
<td>Recovery period on air following CO₂ exposure 4 days</td>
<td>H₂O</td>
<td>K</td>
<td>Na</td>
<td>Cl</td>
</tr>
<tr>
<td>Mean</td>
<td>555</td>
<td>200</td>
<td>1010</td>
<td>2.42</td>
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<tr>
<td>SD</td>
<td>136</td>
<td>297</td>
<td>113</td>
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</tr>
<tr>
<td>N</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Adapted from Pointner.†
† Na salt (Sepelen 7) and potassium salt.
‡ Values significantly different from control values at the 5 per cent level and better.
of potassium salt medication were somewhat similar to those of sodium salt treatment. The normally diuretic effect of potassium salt was not maintained during CO₂ exposure. Chloride excretion was reduced, and a slight increase in retention of potassium and sodium was noted. The alkalinizing effect was demonstrated in the increase of pH and CO₂ in the urine, as well as in the decrease of ammonia excretion.

The CO₂ dissociation curves of whole blood were taken under the same experimental conditions. Venous blood was equilibrated with 30, 40, and 50

![Effect of Na and K salt medication on CO₂ dissociation curves in chronic respiratory acidosis](image)

**FIGURE 7(a).** Effect of alkalinizing agents (Na salt and K salt) on CO₂ dissociation curves in chronic respiratory acidosis. Key: (1) control; (2) 4 days, 2 to 3.5 per cent CO₂, (2Na) as in 2, plus medication of Na salt, 10 gm. daily; (2K) as in 2, plus medication of K salt, 10 gm. daily.

**FIGURE 7(b).** Effect of alkalinizing agents (Na salt and K salt) on CO₂ dissociation curves in respiratory acidosis. Key: (1) control; (2) 4 days 2 to 3.5 per cent CO₂, (3) 2 hours, 5.5 to 6.0 per cent CO₂, following exposure to 2 to 3.5 per cent CO₂ for 4 days (1 to 3, 4 subjects); (3 Na) as in 3, plus medication of Na salt, 10 gm. daily; (3K) as in 3, plus medication of K salt, 10 gm. daily (3 Na and 3 K, 2 subjects). (Adapted from Pointner.11)

mm. Hg CO₂ tension in tonometers at 37° C. The results are shown in **FIGURES 7a and b.** The well-known increase in the buffer capacity of blood in chronic respiratory acidosis is demonstrated in the elevation of the CO₂ dissociation curves (No. 2, **FIGURES 7a and b**). Medication of Na salt or K salt did not produce a further rise in the CO₂ dissociation curves after 5 days of exposure to 2 to 3.5 per cent CO₂ (**FIGURE 7a**). However, the subjects who had received buffer salts appeared to be more resistant to a 2-hour exposure of 5.5 to 6.0 per cent CO₂, following prolonged exposure to 2 to 3.5 per cent CO₂ for 5 days. Under these conditions, a fall of the CO₂ dissociation curves occurs (No. 3, **FIGURE 7b**), that is completely prevented by K salt treatment and reduced by Na salt medication (No. 3 K and 3 Na, **FIGURE 7b**).

Furthermore beneficial effects, particularly of potassium buffer salts, were
noted in the alleviation of symptoms (such as headaches, restlessness, and flights of thought) that developed during the initial phase commensurate with the uncompensated respiratory acidosis. However, symptoms associated with the second phase (compensated respiratory acidosis), such as a general depression and apathy, did not seem to be relieved by potassium salt medication.

These findings, under conditions of a moderate chronic respiratory acidosis induced by a 4-day exposure to 2 to 3.5 per cent CO₂, indicate that oral medication of alkali salts does not raise the bicarbonate CO₂ level in the blood above a value reached by acid-base regulating mechanisms alone. Additional alkali, however, must be stored in tissues and made available during an acute exposure to a higher CO₂ concentration of 5.5 to 6 per cent CO₂ following chronic exposure to 2 to 3.5 per cent CO₂. This interpretation is in line with the findings of Swan et al., who demonstrated in nephrectomized dogs that 74 per cent of the infused bicarbonate was buffered from the tissues. The beneficial effects of these drugs in alleviating symptoms associated with the acute phase of respiratory acidosis are probably related to a more rapid restoration of the blood pH to normal. Compensation of the pH is accomplished without drugs within 3 days during exposure to 3 per cent CO₂. Symptoms persisting during the chronic compensated phase of respiratory acidosis due to increased pCO₂ are apparently not influenced by oral alkali medications.

**Discussion and Conclusions**

In the described experiment with 1.5 per cent CO₂ a combination of respiratory and metabolic processes occur. A plot of the obtained pH and bicarbonate data shows that the values lie above the normal buffer line, indicating a combination of respiratory acidosis with a metabolic alkalosis, the latter due to renal compensation.

The question also might be raised whether a potassium deficiency develops during the compensated phase of respiratory acidosis secondary to an increased HCO₃⁻ excretion. If this had been the case, a decrease in the plasma K level should have developed during the 18-day period of exposure in which the HCO₃⁻ excretion was markedly increased. However, the venous plasma potassium level showed no significant decrease.

Data on blood pH and pCO₂ homeostasis in chronic respiratory acidosis induced by prolonged exposure to 1.5 per cent CO₂ were shown to be related to specific changes in physiological functions. The significance of these established relationships depends to a certain extent on whether changes in blood pH produce corresponding changes in intracellular pH of tissues under these conditions, as is generally assumed, since no direct measurements on intracellular pH were obtained. There is evidence from studies on isolated tissues such as muscle that the intracellular pH is influenced very little by pH changes in the blood produced in acute experiments but is affected to a greater extent by changes in carbon dioxide tension of blood. These findings obtained with the DMO method are in agreement with others based on the CO₂ method of measuring intracellular pH. E. D. Robin (elsewhere in these pages), using the DMO method for the determination of whole body intracellular pH determination in acute experiments with dogs,
steroid excretion. An effect of increased $pCO_2$ tension hardly could be influenced by amine therapy unless THAM absorbs some metabolic products that do not affect the acidity of the blood but are produced by the increased CO$_2$ level.

The astonishingly long time periods required for acclimatization and deacclimatization to such low CO$_2$ concentrations as 1.5 per cent CO$_2$ expressed, for example, in the persisting change in respiratory pattern and altered calcium metabolism$^{17}$ suggest that some kind of pathophysiological state might develop under these conditions. The results of animal experiments that showed an increase in kidney calcification of guinea pigs exposed to 1.5 per cent CO$_2$ for periods of from 40 to 93 days seem to support this concept.$^{18}$ It seems doubtful, therefore, whether long continued adaptation to slightly increased $pCO_2$ levels can be accomplished without altering normal physiological processes. This consideration has led to the formulation of a triple tolerance concept for chronic CO$_2$ toxicity,$^{19}$ which is expressed in Figure 8 together with a time concentration curve for adaptation to CO$_2$. Time for adaptation is defined as the time to reach a compensation of the respiratory acidosis induced by carbon dioxide inhalation. Determinations of $pH$, CO$_2$, bicarbonate levels, and electrolytes in blood and urine were used for estimations of the two phases in respiratory acidosis. The three levels of acidosis used for tolerance limits are listed in Figure 8. The level at which no significant physiological, psychological, and adaptation changes probably occur is estimated to be 0.5 to 0.8 per cent carbon dioxide in the inspired air.

**Acknowledgment**

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