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REPORT NUMBER 791

EFFECT OF CHRONIC HYPERCAPNIA ON BODY TEMPERATURE REGULATION

by

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and G. T. Baker, III

Bureau of Medicine and Surgery, Navy Department
Research Work Unit MR041.01.01-0125.03

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SUMMARY PAGE

THE PROBLEM

Increased blood CO₂ levels have a measurable effect on thermoregulation and presumably can be a serious hazard in a cold environment. There is a need for a better understanding of the mechanisms of CO₂ action in temperature regulation.

FINDINGS

Guinea pigs and rats were exposed for prolonged periods to 3% and to 15% concentrations of CO₂. At 15% CO₂, the pH and body temperature fell maximally after six hours of exposure, with a subsequent rise in pH and body temperature in most animals. Some of the guinea pigs had no rise in pH or body temperature and did not compensate the CO₂ induced respiratory acidosis by the three-day exposure point. Body temperature variation appeared to be the best indicator of the acid-base status and adaptive potential of the animals to CO₂. The mechanisms underlying the effect of CO₂ on temperature regulation were found to involve: (1) decreased oxygen consumption up to 30%, with decreased heat production; (2) heat loss by cutaneous vasodilation; (3) adrenal function involvement with an increased catecholamine release with an inhibition of the action of catecholamines, and (4) biphasic changes in the neurochemical transmitters controlling thermoregulation. Changes in the norepinephrine content of the hypothalamus with opposite changes in the serotonin content were found to be associated with the decrease and subsequent increase in body temperature.

Exposure to lower levels of CO₂ (3%) stimulated the metabolism and led to a transient rise in body temperature. The multiple and complex effects of CO₂ on physiological functions participating in thermoregulation underscore the hazard of CO₂ retention in a cold environment.

APPLICATION

The results of this study are of interest to Submarine and Diving Medical Officers and investigators of thermoregulation.

ADMINISTRATIVE INFORMATION

This investigation was conducted as part of Bureau of Medicine and Surgery Research Work Unit MR041.01.01-0125. The present report is Number Three on this Work Unit. The manuscript was submitted for review on 14 June 1974, approved for publication on 1 August 1974, designated NavSubMedRschLab Report Number 791.

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ABSTRACT

In an effort to add to our knowledge of the role of increased blood CO_2 levels in thermoregulation, guinea pigs and rats were exposed to 15% carbon dioxide for seven days. Results showed a parallel time course of changes in pH and in body temperature. After six hours of exposure, the maximal drop in extracellular pH occurred in the guinea pigs, simultaneously with the maximal fall in body temperature. During the subsequent period, both pH and body temperature rose again. After three days of exposure, body temperature had reached initial levels, while pH remained markedly below control levels, although it was steadily rising. The body temperature of those animals showing no partial compensation to respiratory acidosis during the three days exposure also failed to return to normal in this time. The behavior of the body temperature was found to be the best indicator of the acid-base status and adaptive potential of the animals to hypercapnia.

Similar results were obtained in rats. Thermoregulatory processes in the hypothalamus were affected during exposure to 15% CO_2 . Both guinea pigs and rats showed a decrease in norepinephrine content of the hypothalamus during the first part of exposure, reaching a maximal fall at the end of 24 hours. The serotonin content increased slightly during this period. When using 3% CO_2 for prolonged exposures, the body temperature of these animals showed a transient rise and \dot{V}_{O_2} was slightly elevated.

EFFECT OF CHRONIC HYPERCAPNIA ON BODY TEMPERATURE REGULATION

INTRODUCTION

The acute effects of exposure to CO₂ on body temperature regulation have been studied extensively in different animal species. It has been demonstrated that acute exposure to concentrations above 8% CO₂ causes a fall in body temperature in rats at ambient room temperatures of 24 - 28° C. Similar effects have been demonstrated in cats, mice, dogs and rabbits^{6,7,13,15}.

The fall in body temperature is usually associated with a fall in oxygen consumption^{1,5,31}. Exposure to lower concentrations of CO₂ causes a rise in body temperature. The difference between the acute effects of lower and higher concentration of CO₂ is according to Stupfel³² based on stimulatory and depressive effects on metabolism.

There are no reports in the literature on chronic effects of CO₂ on temperature regulation.

This report deals with studies of guinea pigs and rats exposed for prolonged periods to 15% CO₂ and 3% CO₂.

METHODS

Male guinea pigs of the Hartley strain weighing between 400-600 grams and Sprague-Dawley rats weighing between 200-300 grams were exposed to 15% CO₂ and 3% CO₂ in 21% O₂, with the balance of the gas mixture being

nitrogen, for prolonged periods of time in environmental chambers with temperature and humidity control (Sherer-Gillette). The environmental temperature was kept at 78° F \pm 2° F and the humidity between 65-75%. The gas mixtures were prepared by mixing proportional amounts of CO₂ to air; oxygen was added from a high pressure cylinder. The carbon dioxide concentration in the chamber was continuously monitored with a Beckman Infrared CO₂ Analyzer and the oxygen content was sampled intermittently with a Beckman O₂ Analyzer. The CO₂ concentrations were kept at 15% within limits of \pm .5% and 3% \pm .2% and the oxygen concentrations at 21% \pm .5%. Ammonia vapor was absorbed by boric acid placed in the chamber. The chamber was opened each morning for a period of 3-5 minutes to fill the water and food containers and to remove the urine and faeces.

Prior to blood sampling, the animals received 40 mg pentobarbital per kilogram of body weight subcutaneously and were returned to the CO₂ exposure chamber. The body temperature was measured using a thermistor probe placed 7 cm deep into the colon. The anesthesia was usually effective after approximately 5 min, at which time the animals were taken out of the exposure chamber and immediately placed under a mask through which they breathed the same CO₂ gas mixture to which they had been exposed. Blood samples were drawn from the abdominal aorta. Blood pH was determined with an Instrumentation-Laboratory

blood gas and pH analyzing system.

The animals were decapitated and the brain removed as rapidly as possible, dissected and stored at -10°C until time of assay.

Measurements of serotonin and norepinephrine of hypothalamic and cortical areas of the brain were carried out, using the method of Maikel, et al¹⁶.

Oxygen consumption of guinea pigs exposed to 15% CO_2 for 7 days was measured in 10 individual animals throughout control and exposure periods using a Beckman I_3 -paramagnetic oxygen analyzer with a span of 20-21% O_2 and an all glass metabolic chamber which was submerged in a water bath at 25°C .

Included in this report are the results of a separate series of studies on blood distribution in the skin during 7 days exposure to 15% CO_2 . The blood volume of the skin and other organs was measured by a modification of the technique of Dewey⁹. The animals were injected intravenously via the jugular vein with reconstituted blood tagged with CR-51 and I-125 as previously described by Baker and Schaefer². Whole blood samples were taken after 15 minutes and assayed as previously described. All tissue samples were taken as soon as the blood sampling was completed. The skin was obtained from the abdominal region. Care was taken to remove all adhering muscle and adipose tissue. The skin tissue was then blotted with surgical gauze and placed

in pre-weighed glass test tubes. Tissue samples were weighed in pre-weighed test-tubes with a-Torbal top loading balance to ± 2 mg. Tissue samples were digested for 24 hours with an equal volume by weight of KOH (38 percent) as described by Martin, et al.¹⁷. The tissue samples were then counted three times for a minimum of 15 minutes of 10,000 counts with a Picker Spectroscaler II for CR-51 and I-125.

Calculations:

$$(a) \text{ Red cell wt. per gm of tissue} = \frac{\text{cpm CR-51 per gm RBC (circulating)}}{\text{cpm CR-51 per gm tissue}}$$

$$(b) \text{ Plasma wt per gm of tissue} = \frac{\text{cpm I-125 per gm plasma (circulating)}}{\text{cpm I-125 per gm tissue}}$$

$$(c) \text{ Blood volume per gm of tissue} = (\text{Plasma volume per gram tissue} + \text{red cell volume per gm tissue}) \times \text{total weight of the tissue}$$

$$(d) \text{ Tissue hematocrit} = \frac{\text{red cell volume per gm tissue}}{\text{red cell} + \text{plasma volume per gm tissue}} \times 100$$

The weight of one ml of whole blood as determined in duplicate on 12 guinea pigs to be $1.0271 \pm .004$ grams, was used to convert the weight values to volume. Since the net amount of blood removed by sampling was less than five percent of the initial blood volume no correction was made for this loss in determination

of the tissue blood volumes, Gibson, et al¹². All blood tissue sampling was done at the same time of day (between 11 AM and 12 noon) to avoid any possible errors due to circadian oscillations in the parameters studied.

RESULTS

As shown in Figure 1 exposure of guinea pigs to 15% CO₂ causes initially a fall in body temperature; but with adaptation to CO₂, the body temperature

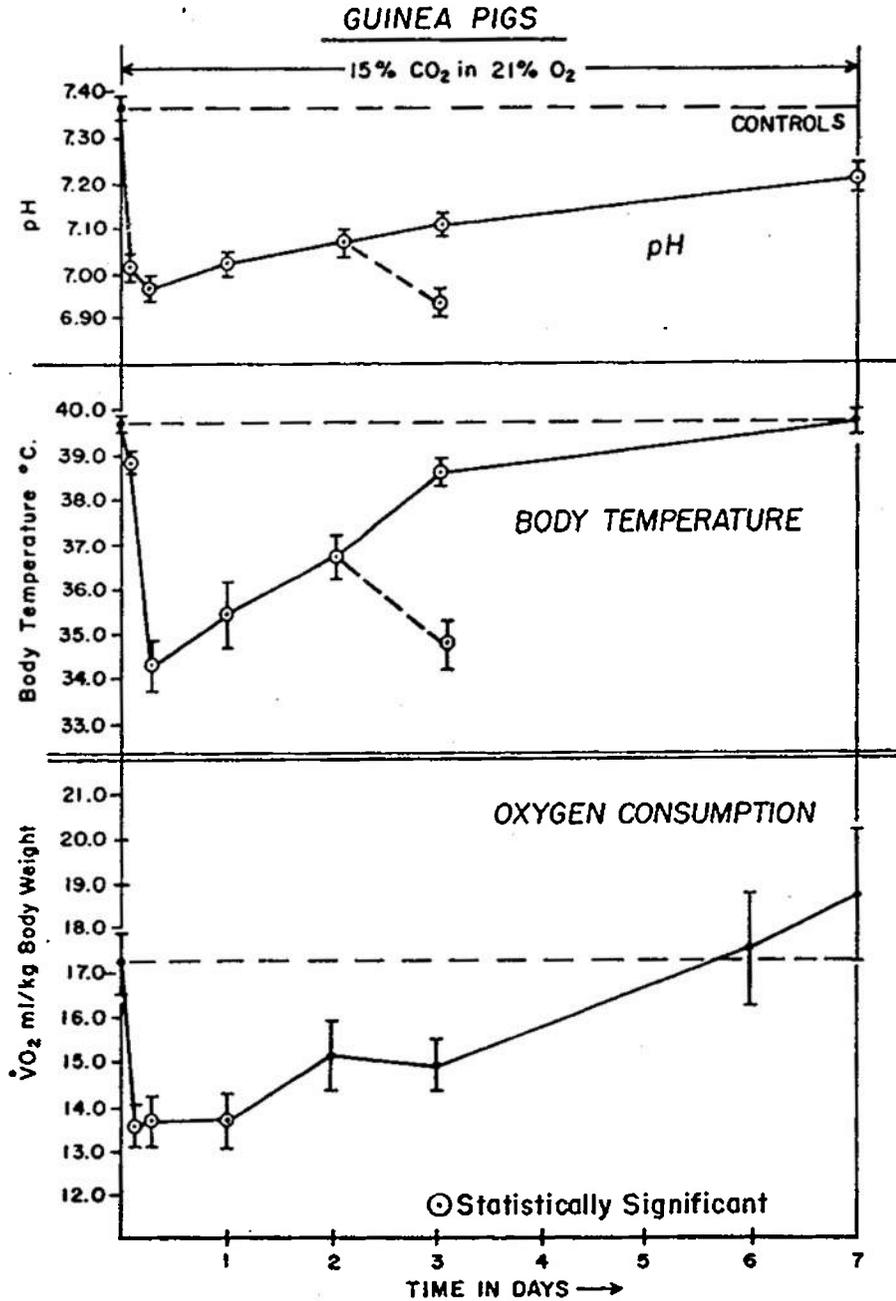


Fig. 1. Effect of Prolonged Exposure of Guinea Pigs to 15% CO₂ in 21% O₂ on pH, Body Temperature, and Oxygen Consumption. (Number of Controls - 20; Experimental group 14-21)

returns to control levels after 3 days. The time courses of body temperature and pH parallel each other. Guinea pigs have about 30 to 50% mortality under 15% CO₂. It was observed that animals which are unable to adapt to CO₂ by achieving a partial compensation of the acidosis and rise of the pH after 3 days will die. It was also noted that their body temperature failed to rise.

Body temperature and pH data from such a group of animals were obtained at the third day of exposure (broken line) and were found to be significantly lower, as compared with those animals which had adapted to chronic hypercapnia at the third day of exposure. In these experiments, body temperature proved to be the best indicator of the acid-base status of the animal. Oxygen consumption followed the pH changes, decreasing significantly during the first day and slowly rising during the subsequent days, during which adaptation developed.

Rats are much more resistant to CO₂ and do not exhibit any mortality during exposure to 15% CO₂. This is apparently related to their higher buffer capacity²⁸. The time courses of pH and body temperature of rats exposed to 15% CO₂ (Figure 2) shows the same pattern as that observed in guinea pigs. A transitory fall of body temperature was found during the acute state of acidosis and a return to control values

by three days after a partial compensation has been reached.

Figure 3 shows the changes in red cell volume (CR-51), hematocrit, and total blood volume of the skin during prolonged exposure to 15% CO₂ in 21% O₂. A significant increase of both red cell volume and plasma volume and of the skin was found after 1 hour exposure. The calculated total blood volume rose nearly 60 percent, for the first six hours but subsequently dropped 20% by the third day and a total of 40% below control levels by seven days. Both red cell and plasma volume decreased, with the overall volumetric change. Since both red cell volume and plasma volume exhibited these biphasic changes, the hematocrit remained practically unchanged.

Measurements of norepinephrine and serotonin content of the hypothalamus of guinea pigs exposed to 15% CO₂ for prolonged periods are exhibited in Figure 4. The norepinephrine concentration showed a pH dependent fall and rise while the serotonin levels did not change significantly but exhibited a tendency to increase. Similar findings were obtained in rats as shown in Figure 5.

During exposure to 3% CO₂ guinea pigs did not show a fall in body temperature; as a matter of fact there is a small but significant rise of body temperature after 1 hour amounting to 0.7°C (Figure 6). Oxygen consumption is slightly elevated.

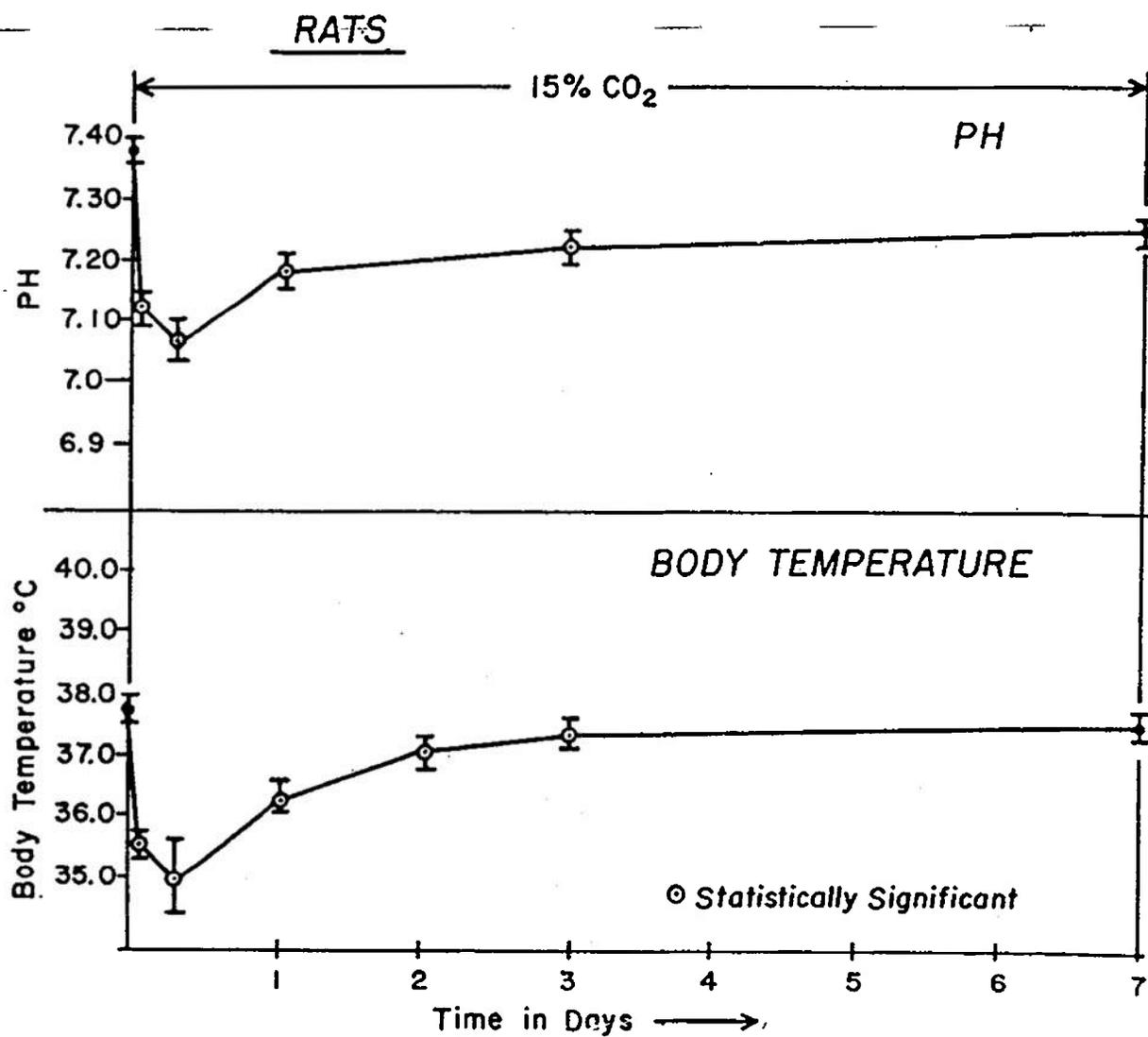


Fig. 2. Effect of Exposure of Rats to 15% CO₂ in 21% O₂ on pH and Body Temperature. (Number of Controls - 10; Experimental subjects 10-12)

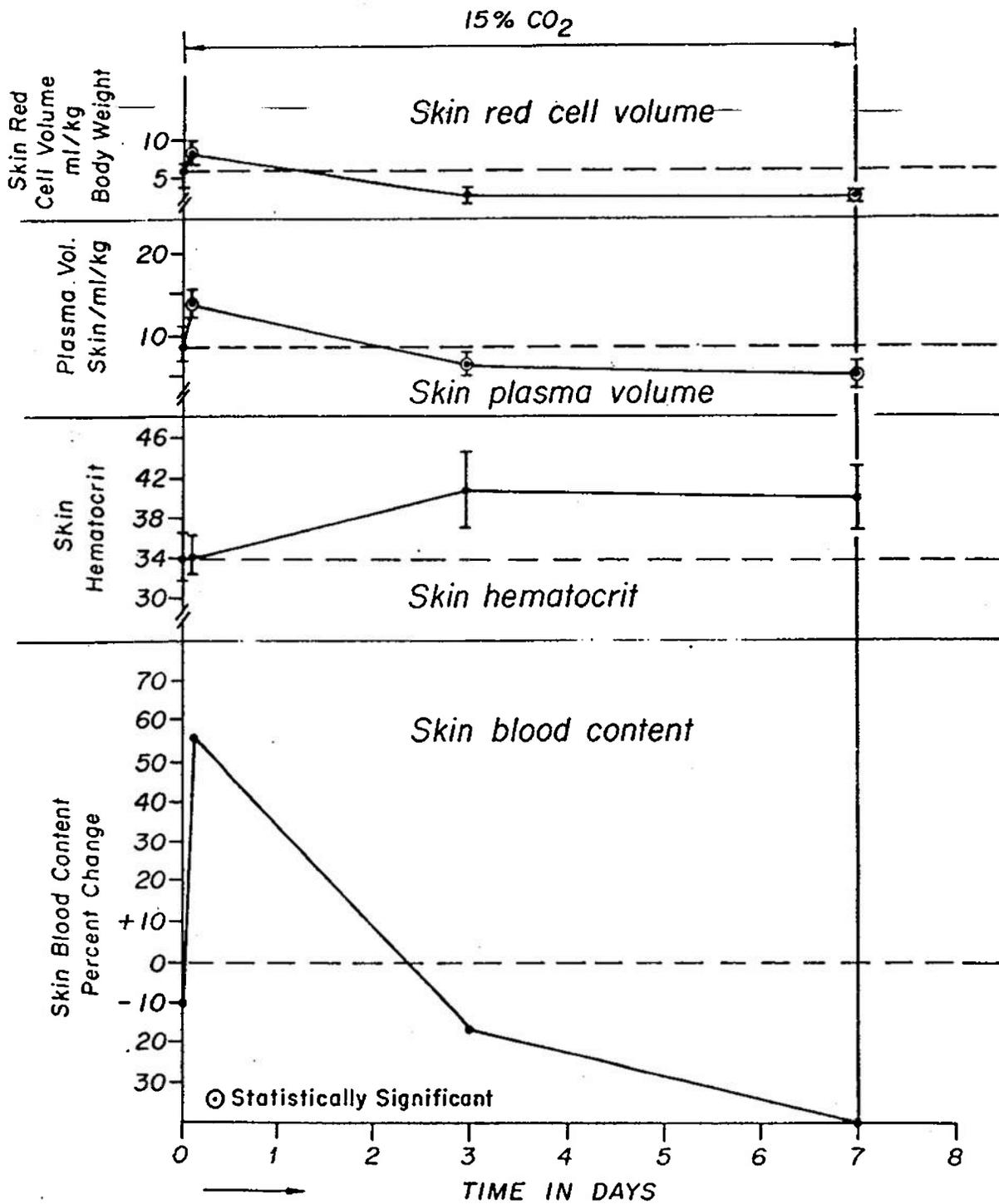


Fig. 3. Effect of Prolonged Exposure to 15% CO₂ in 21% O₂ on Red Cell Volume, (CR-51), Plasma Volume (I-125), Hematocrit, and Total Blood Volume of the Skin of Guinea Pigs. (Number of Controls - 13; Experimental Group 4-8)

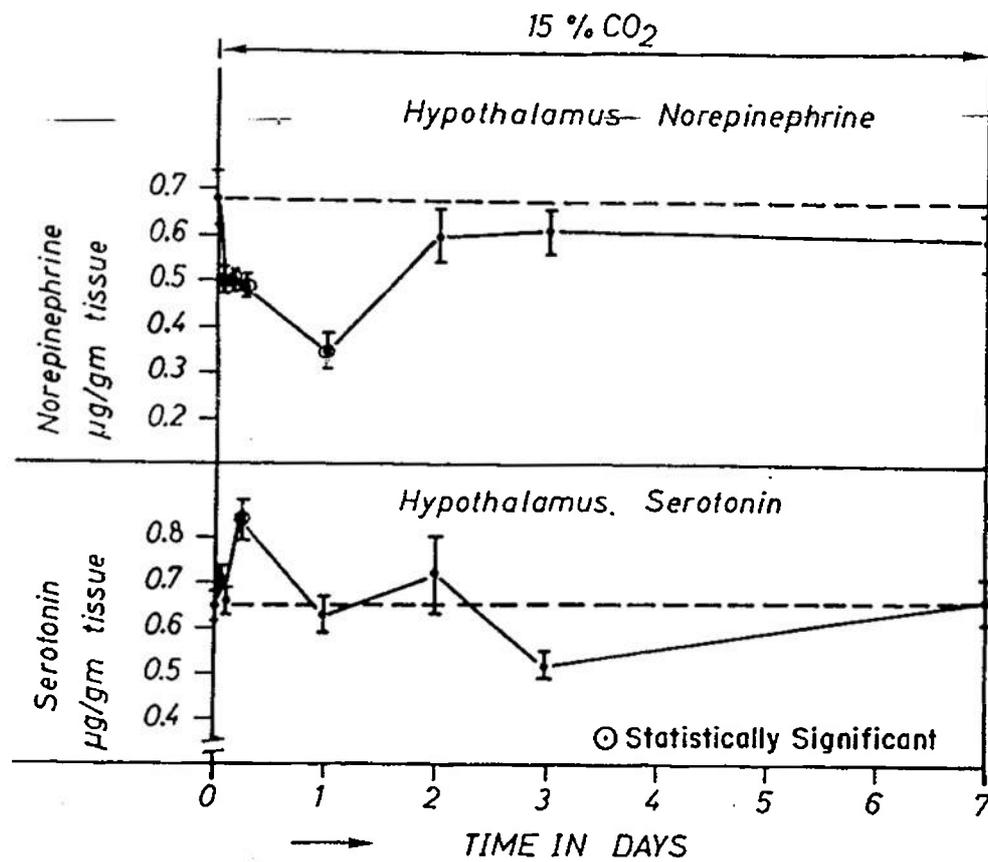


Fig. 4. Effect of Prolonged Exposure to 15% CO₂ in 21% O₂ on Norepinephrine and Serotonin Content of the Hypothalamus in Guinea Pigs. (Number of Controls - 10; Experimental Group 11-20)

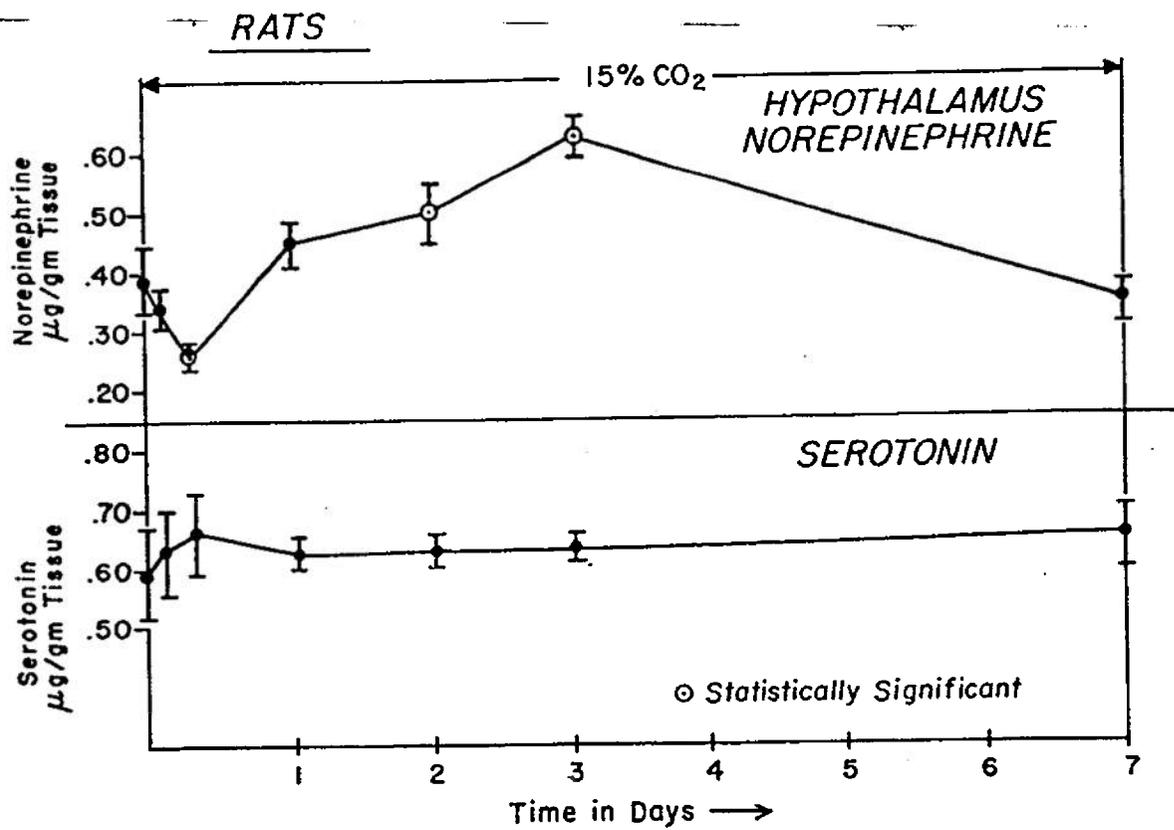


Fig. 5. Effect of Prolonged Exposure of 15% CO₂ in 21% O₂ on Norepinephrine and Serotonin Content of the Hypothalamus in Rats. (Number of Controls - 10; Experimental Group 6-9).

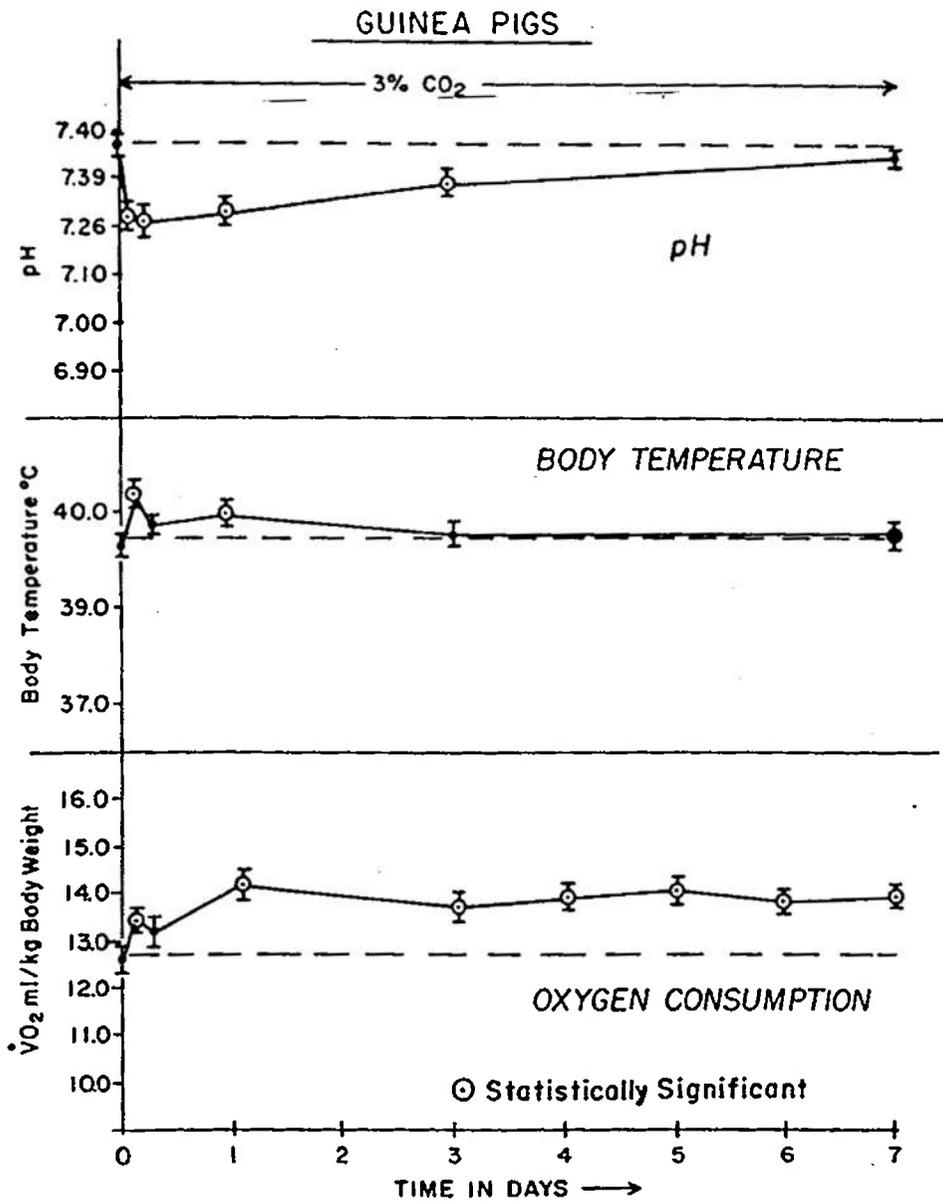


Fig. 6. Effect of Prolonged Exposure to 3% CO₂ in 21% O₂ on pH, Body Temperature, and Oxygen Consumption of Guinea Pigs. (Number of Controls - 38; Experimental Group 12-39).

DISCUSSION

In chronic hypercapnia induced by prolonged exposure to 15% CO₂, guinea pigs and rats show changes in body temperature which clearly depend on the acid-base status of the animals.

The maximal fall in extracellular pH in guinea pigs exposed to 15% CO₂ occurs at 6 hours of exposure simultaneously with the maximal fall in body temperature. During the subsequent period, both pH and body temperature rise again. Similar results were obtained in rats.

Guinea pigs have a lower resistance to CO₂ than rats due to their lower buffer capacity and develop, in contrast to rats during exposure to 15% CO₂, a super-imposed metabolic acidosis for 3 days as indicated in the fall of standard bicarbonate²⁸. As a consequence, guinea pigs exhibit a 30-50% mortality during prolonged exposure to 15% CO₂, while rats have no mortality under these experimental conditions.

The guinea pigs which did not survive were unable to compensate the respiratory acidosis by the three-day point or to elevate the pH above the low level attained at six hours. It was also noted that their body temperature failed to rise following its initial fall of 6 - 7° C.

The behavior of the body temperature turned out to be the best indicator of the acid-base status of the animals and their potential for adapting to chronic CO₂ exposure. These findings clearly prove the dependence of body temperature on pH in chronic respiratory acidosis.

Because of the many sided effects of CO₂ on physiological functions, it is difficult to identify the exact mechanism of action of CO₂ in regard to body temperature regulation. However, the results of these studies shed light on some of the effects of CO₂ involved in body temperature regulation. Metabolic heat production is inhibited in guinea pigs during the first three days of exposure to 15% CO₂, as indicated in a 30% fall of O₂ consumption below basal metabolic rate. Simultaneously the blood volume of the skin is increased by nearly 60%, a condition which must

result in an increased heat loss. During the subsequent period in which pH and body temperature increase, oxygen consumption returns to control levels after three days and the blood volume of the skin falls significantly below initial values. Heat production returns to normal with a partial compensation of the acidosis, while vasodilation of blood vessels of the skin results in an increased heat loss during the acute phase of respiratory acidosis. Subsequently, vasodilation changes into a vasoconstriction with a consequent reduction of heat loss.

In this connection, it would be interesting to know whether an inhibitory action of CO₂ inhalation on the cold thermoreceptors, as suggested by the experiments of Dodt¹⁰, and Bowman, Hensel, and Witt³, persists throughout the period of chronic hypercapnia, or whether it changes in association with the biphasic alterations of skin blood volume.

The biphasic changes in the skin blood content are most likely produced by the opening and closing of the extensive artero-venous anastomoses, since the hematocrit did not change significantly during the large variations of blood volume associated with the two phases of respiratory acidosis. The opening of the arterio-venous anastomoses has been found to be associated with excessive blood flow resulting in heat dissipation¹⁸. During the first two days of exposure to 15% CO₂, guinea pigs in particular hyperventilate strongly accompanied by a high degree of panting, which must result in an increased heat loss via the respiratory system and increased water loss.

Stupfel measured increased water loss in rats exposed to 10% CO₂³².

The concentration of 15% CO₂ was chosen, for these studies, because it is below the level of narcotic effects, and it is high enough during the acute phase to cause a fall in pH (7.4 to 7.0) sufficiently large to affect pH-dependent enzymes. During the subsequent adaptation to respiratory acidosis, the pH rises again above the level at which most of the pH-dependent enzymes are inhibited²⁹. Under these conditions, a direct action of CO₂ or pH on metabolism must be considered as a factor in impairing glucose and fat utilization and thereby heat production.

Other studies demonstrated that during exposure to 15% CO₂, a transient pH-dependent inhibition and subsequent recovery of glucose utilization occurs, as indicated in the elevation of blood sugar and decline of lactate and pyruvate during the acute phase of respiratory acidosis¹⁴. Adenosine, mono, di, and triphosphate levels of the blood were not significantly changed by exposure to 15% CO₂.

Phosphofructokinase activity which regulates glycolysis was found to be reduced 55% during maximal extracellular acidosis and showed a partial recovery during the later phase of exposure to 15% CO₂ without returning to control values¹⁵.

These findings indicate that glucose energy sources cannot be sufficiently utilized for heat production during the acute phase of respiratory acidosis induced by exposure to 15% CO₂.

Acidosis also inhibits lipolysis and impairs fat utilization as demonstrated by Nahas and Poyart²⁰. They observed that adrenalin-induced lipolysis and calorogenesis is inhibited in dogs when breathing a mixture of 10% CO₂ and 25% O₂ in N₂ which results in an average pH of 7.0 similar to the conditions in our experiments.

In subsequent in vitro experiments using rat epididymal tissue, Triner and Nahas³³ demonstrated that acidosis in the medium inhibited the lipolytic activity induced by noradrenaline and ACTH, which suggests an inhibiting effect of H⁺ on cyclic 3'5' AMP formation.

We obtained more evidence of inhibition of lipolytic activity during exposure of guinea pigs to 15% CO₂. No significant increase in free glycerol and triglycerides were observed, although there was a marked stress response during the first two days of exposure as indicated in an increase in blood corticosterone, decrease in adrenal catecholamines and increase in free fatty acids²⁶.

Moreover, the fat content of organs such as liver, muscle and heart increased markedly during the first three days of exposure to 15% CO₂ in guinea pigs, which gives further support for the existence of an inhibition of lipolysis²⁸.

Changes in fat metabolism seem to be of particular significance in chronic hypercapnia and require a more detailed investigation to elucidate the mechanisms involved.

In the endocrine control of heat production, the adrenal medulla plays a major role by releasing epinephrine and norepinephrine and increasing metabolism. Evidence has been cited above showing an inhibitory effect of acidosis on the metabolic activity of catecholamines. On the other hand, numerous studies in guinea pigs²⁵, and rats²¹ and man²⁴ have demonstrated that acidosis produced by CO₂ inhalation causes a marked elevation of blood epinephrine and norepinephrine levels. In addition to the increased release of catecholamines, an increase synthesis of catecholamines was demonstrated in rats exposed to 20% CO₂²¹. We are dealing, therefore, with a dissociation of normally correlated functions. Acidosis stimulates enzymes that control catecholamine synthesis and inhibits enzymes that regulate intermediary metabolism and are activated by catecholamines.

The pH-dependent fall in body temperature found in guinea pigs and rats could also have been caused by pH-dependent changes in the neurochemical transmitters of the hypothalamus affecting thermoregulation.

Epinephrine injections in the hypothalamic areas of guinea pigs and rats have been found to cause a rise in body temperature. According to Feldberg and Myers¹¹, norepinephrine and serotonin levels in the hypothalamus affect thermoregulation by stimulation or inhibition of the heat production and heat-loss pathways and influence the setpoint serving as a reference for the thermoregulatory system.

The monoamine theory of thermoregulation advanced by Feldberg and Myers¹¹ has found further support by Cranston, et al⁸ providing evidence concerning the effects of endogenous noradrenaline changes upon body temperature in cats and dogs. The findings reported here give additional support showing that the pH-dependent alterations in body temperature produced in chronic hypercapnia in guinea pigs are related to the changes in the concentrations of the endogenous epinephrine and serotonin in the hypothalamus.

Myers¹⁹ introduced more recently a second chemical factor in his chemical model of temperature regulation according to which changes in the Na-Ca ratio in the posterior hypothalamus (ionic thermostat) control the "set point" temperature of the body. The earlier version of the chemical model was limited to the "aminergic" thermostat in the anterior hypothalamus which responds to peripheral and internal stimuli of temperature regulation. The transmitter substance acetylcholine is thought to transmit the activity of the center in the anterior hypothalamus to the center of the posterior hypothalamus.

There is some evidence that the set point of body temperature regulation is changed by different internal stimuli and in particular by acidosis.

Injections of norepinephrine in the anterior hypothalamus of unanaesthetized guinea pigs increased O₂ uptake and body temperature and led to an upward shift of the threshold temperature for the onset of shivering³⁴.

In a separate study carried out jointly with Dr. Wuennenberg at the J. B. Pierce Foundation, Yale University, New Haven, Conn., the response of hypercapnic guinea pigs exposed for various time periods to 15% CO₂ in a cold environment (1 hour at 15°C) was investigated (unpublished observations). During control conditions, oxygen consumption and electrical activity increased upon exposure to cold, but were suppressed following one hour exposure to 15% CO₂. In animals which had reached partial compensation of the acidosis after three days of exposure to 15% CO₂, both energy production and muscle activity were restored to normal in response to cold. These findings demonstrate that during the acute respiratory acidosis induced by exposure to 15% CO₂ the threshold response to shivering is shifted to lower temperatures, but returns to control levels following adaptation to CO₂.

Moreover, the hypothalamic set point for shivering in conscious dogs breathing 5% CO₂ was found to be decreased by more than two degrees C.²³

The increase in oxygen consumption and the transient rise in body temperature found in guinea pigs during exposure to 3% CO₂ is in line with findings of Stupfel³² who established that in most mammals O₂ consumption is increased during exposure to CO₂ concentration between 3 and 10% CO₂.

The increased oxygen consumption under these conditions is most likely caused by the CO₂ induced hyperventilation and the increased amount of respiratory work.

It would appear in a recapitulation of this study that the findings are quite definitive and the conclusion that the body temperature depends on the pH values in chronic respiratory acidosis is valid. It is, however, difficult to identify the exact mechanism of action of CO₂ in respect to body temperature regulation because of the many effects of CO₂ on physiological functions.

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