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**FACTORS AFFECTING THE DURATION OF APNEA FOLLOWING
HYPERVENTILATION AT ALTITUDE**

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JUNE 1954

WRIGHT AIR DEVELOPMENT CENTER

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Aero Medical Laboratory
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RDO No. 696-77

Wright Air Development Center
Air Research and Development Command
United States Air Force
Wright-Fatteraon Air Force Base, Ohio

FOREWORD

This report by F. G. Hall et al. covers investigations conducted in the Aero Physiology Laboratory of the Department of Physiology and Pharmacology, Duke University School of Medicine, Durham, North Carolina. Research was performed under contract AF 33(616)377, RDO No. 696-77, "Explosive Decompression," with Contract Monitor, Captain Edwin G. Vail, USAF, Aero Medical Laboratory.

The valued technical assistance of K. D. Hall, M. D. and June Barker is recognized.

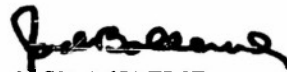
ABSTRACT

It is apparent that when an anaesthetized animal undergoes forced ventilation, the duration of subsequent apnea is influenced by the composition of the inspired air. The higher the oxygen concentration of the inspired air, the longer the period of apnea. A small concentration of carbon dioxide in this oxygen, however, will shorten the period of apnea. Likewise, experiments performed at simulated altitudes show a decreasing period of apnea following forced ventilation with ambient air at decreasing pressure altitudes. These results are discussed in the light of various theories proposed to explain the chemical regulation of breathing.

PUBLICATION REVIEW

This report has been reviewed and is approved.

FOR THE COMMANDER:



JACK EOLLERUD
Colonel, USAF (MC)
Chief, Aero Medical Laboratory
Directorate of Research

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INTRODUCTION

A worker in the field of respiratory regulation is confronted with many difficulties and one of these is that while various factors act independently to control breathing, any change in one of these factors may bring about changes in the others. Gray (1) has done much to define the role played by various factors in respiratory control, but not all investigators have accepted his multiple factor theory as an exclusive explanation for the regulation of pulmonary ventilation.

Apnea presents an interesting condition from the standpoint of respiratory regulation, for while it is caused primarily by lowering of carbon dioxide tensions, the two chief respiratory stimuli are both changing progressively during the apneic phase. Carbon dioxide tensions are rising and oxygen tensions falling. At some point one or the other or both of these stimuli must reach a threshold value for their respective receptors and then breathing resumes. This situation is also uncomplicated by alveolar exchange. Thus this experimental approach to the study of respiration is somewhat unlike that customarily employed.

No physiologist will question the advantages of having an animal in a steady state during experimental investigations of physiological processes, particularly those involving respiration. However, animals in their normal life probably only approach the steady state, so far as respiration is concerned, when they are asleep, or while they are under control of the experimenter. Perhaps something can be learned by studying respiratory processes during transitory states. The following study was attempted in order to make a different approach to the problem of control of breathing. The results are not very conclusive, but it is hoped that they will serve some useful purpose.

Douglas and Haldane in 1909 (2) in their discussion of the causes of periodic Cheyne-Stokes breathing report that they found higher than normal carbon dioxide tensions in subjects breathing high oxygen concentrations. Haldane (3), however, states that the duration of apnea following forced breathing was related only to the reduction carbon dioxide percentage of alveolar air. Gesell (4) states that "Hypoxia" has modifying effects upon eupneic breathing and seems to imply that hydrogen ion concentration is the principal driving force in the restoration of breathing from the apneic state. Rahn and Fenn's (5) "Oxygen-Carbon Dioxide Diagram" has been found very useful in plotting data.

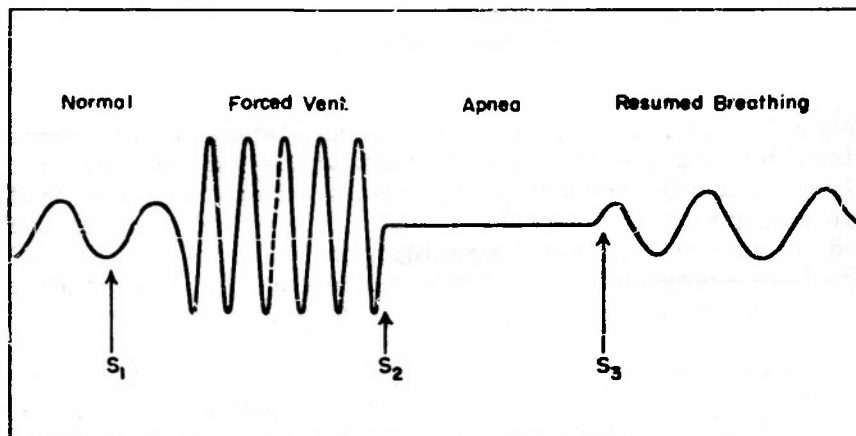


Figure 1. represents schematically the breathing pattern obtained during these studies. S_1 , S_2 , S_3 indicate the points where blood samples were taken. The period of time between S_2 and S_3 is called the duration of apnea.

PROCEDURE

Twenty-two mongrel dogs ranging in weight from 12 to 16 Kilograms were used in these investigations. Each dog was kept under observation for several days previous to experimentation, and every dog was considered to be in good condition. No postmortem examination indicated otherwise. These dogs were anaesthetized by intrape toneal injection of 55 mg of Dial in Urethane (Ciba) per Kilogram of body weight. A tracheal canula especially constructed to contain a wire cloth flow-meter capsule for recording respiratory flow patterns and intratracheal pressures was inserted in the trachea. A "T" shaped canula was inserted into the right common carotid artery. This canula permitted normal flow of blood to the head and made it possible to record blood pressure continuously. Blood samples were withdrawn from the side tube connected to the blood pressure transducers. An indwelling catheter was placed into the left jugular vein in such a manner as to allow unobstructed blood flow. The dead air of re-breathing space, while not especially important in this investigation, was kept small -- approximately 50 milliliters. Dogs were heparinized when surgery was completed. Blood pressures, intratracheal pressures and respiratory breathing patterns were recorded photographically on a Miller Oscillograph by use of Statham transducers and appropriate amplifiers.

Hyperventilation was accomplished by use of a Palmer variable stroke "Ideal" respiration pump. The stroke was adjusted to the size of the dog and ranged from 400 to 500 milliliters with a speed on 33 strokes per minute. Forced breathing for a period of six minutes was used and continuous oscillographic recordings were made throughout each experiment.

Blood samples were drawn simultaneously from the carotid and jugular vessels before and at the end of forced ventilation, and again at the resumption of breathing following the apneic period (Fig. 1). The type of oscillograph (Miller) used made it possible to observe visually the respiratory events and to know accurately the moment when apnea was over.

The operating table on which dogs were tied was placed inside an Air Force low pressure chamber. Observers wore A-13 oxygen masks during the simulated flights. Observations were made at ground level, 760 mm Hg; 10,000 feet, 523 mm Hg; 20,000 feet, 349 mm Hg; 25,000 feet, 282 mm Hg; and 30,000 feet, 226 mm Hg. Then the ground-level observations were repeated. In one-half of the experiments the tests were made in the above order and the other half in the reverse order.

Dogs breathed air mixed with oxygen during ascent and descent, but were hyperventilated with ambient air or known gas mixtures during actual observations. This procedure prevented chronic hypoxia. About fifteen minutes elapsed between each test. In these experiments each dog served as his own control. No anaesthetic was administered after tests began. The rectal temperature of each dog was kept at 38°C by appropriate warming devices. The arterial oxygen saturation was determined at the beginning

and end of each set of experiments as evidence of the satisfactory physiological state of the dog.

Blood samples were analysed in the following manner: Each sample was kept under mercury and analyses were made within a few minutes of blood withdrawal. The oxygen and carbon dioxide content of each sample was determined by use of the Van Slyke manometric gas analyser by well known procedures. Total hemoglobin was determined by converting hemoglobin to met-cyan hemoglobin and reading the concentration on an Evelyn photoelectric colorimeter. The factor of 1.36 was used to calculate total hemoglobin oxygen capacity. With appropriate correction for dissolved oxygen the percentage oxygen saturation of hemoglobin was determined. The pH of each sample was determined by use of a Cambridge Instrument Company research type glass electrode pH meter. Temperature corrections were made from Rosenthals (5) equation and the carbon dioxide pressure calculated. All gas compositions reported were determined by use of the standard Haldane gas analysers.

RESULTS

The results of these studies are summarized in Tables I and II and Figures 2-6. The first series of experiments on eight dogs was done at ground level and those of the second series of eight dogs were subjected to simulated altitudes. In addition to data shown in the illustrations and tables, a few tests were made at ground level in which carbon dioxide was added to gas mixtures used in forced ventilation. It was found that 3-4% of carbon dioxide in the inspired air prevented apnea from following forced breathing. A uniform time of six minutes hyperventilation was used in all tests. Time, blood pressure, and the breathing pattern were recorded, but since they fall within the normal range, results are not reported quantitatively. Blood analyses also showed that no significant hemoconcentration occurred. One dog found to be anemic was discarded before any tests were made, but all other animals had oxygen capacities within the normal range. In most of the illustrations mean or average values are plotted, although all data have been statistically analysed. No data have been discarded in plotting curves or interpreting results. It was noted that resumption of breathing always began in the inspiratory phase.

Results reported here must be viewed with certain qualifications. For example, it has been well established that respiration of the anaesthetized animal is influenced by the depressant action of barbiturates. Dial in Urethane is no exception, thus care was taken to produce as light anaesthesia as was compatible with the surgery involved. It was also suspected that there are accumulated effects of forced ventilation on acid-base, fluid, and electrolyte balance of the experimental animals. For this reason only a limited number of tests were made on each animal and the order in which each test was made varied according to a pattern so designed as to make results in experiments comparable with each other. Each animal served in a way as his own

Table I

Duration of apnea in eight anaesthetized dogs following six minutes of forced ventilation with various oxygen mixtures at ground level.

Oxygen mixtures (with nitrogen)	Duration of apnea in seconds		
	Mean	and	SD
10% O ₂	23	±	7
21% O ₂	55	±	14
100% O ₂	149	±	33

Table II

Showing the relative increase in carbon dioxide pressure between arterial and venous blood the percent oxyhemoglobin in carotid blood at the time of resumption of breathing following forced ventilation at various simulated altitudes.

Simulated altitudes	Arterial % HbO ₂	A-V pCO ₂ mm Hg
GL (100% O ₂)	96	7
GL (21% O ₂)	56	9
10,000 feet	56	11
20,000 feet	51	12
25,000 feet	38	12
30,000 feet	30	15

control. Continuous blood pressure records were made and also the degree of arterial oxygen saturation followed to determine the physiological condition of each animal. Both of these factors were within the normal range customarily considered normal for experimental work. Then too, there always exists the possibility that mongrel dogs may have pathological conditions which interfere with normal processes. Each of the dogs used in these studies was examined for gross pathology and none was observed that was considered to have affected the results recorded or otherwise worthy of mention.

In Table II the difference in carbon dioxide pressure between carotid and jugular blood is shown to vary some with the altitude at which ventilation occurred. The average of all carbon dioxide arterial-venous differences was found to be 11.2 mm Hg with a standard deviation of ± 4.6 mm Hg. The fact that greater differences were found at lower percent oxyhemoglobin levels and lesser differences at higher percent oxyhemoglobin levels would seem to indicate that a change in blood flow to the head occurred during the period of apnea. The higher rate of blood flow probably occurred when the percent oxyhemoglobin in arterial blood was high as a result of a concomitant high carbon dioxide pressure in arterial blood which built up during the longer period of apnea.

In Figure 4 it can be seen that the percentage oxygen saturation in carotid blood at the end of apnea bears a linear relationship to carbon dioxide pressure and that the values obtained for normal blood on the same animals before hyperpnea are approximately on the same line. It can also be seen that the standard deviation from the mean for percent oxyhemoglobin is greater at the low oxygen concentration, while the standard deviation is less for carbon dioxide pressure. The reverse is true for high oxygen concentrations. This seems to indicate that carbon dioxide exerts a more critical influence at high oxygen saturations.

In Figure 6 mean oxygen saturation values are plotted against their mean carbon dioxide pressure values for both carotid and jugular blood. Samples were taken at the end of apnea at the simulated altitudes previously described. It will be noted that except when 100% oxygen was used as the inspired gas during hyperpnea, the percentage oxygen saturation of carotid blood varies in a linear relationship with carbon dioxide pressure. This was not true with jugular blood, where at the upper part of the curve the carbon dioxide pressure values are influenced by a higher blood flow, while at the low oxygen saturations an uncompensated metabolic acidosis may have developed.

It may be of interest to note that when forced ventilation, using 100% oxygen as the inspired gas, was carried out at simulated altitudes of 25,000 feet, results were similar to those obtained in experiments performed at ground level.

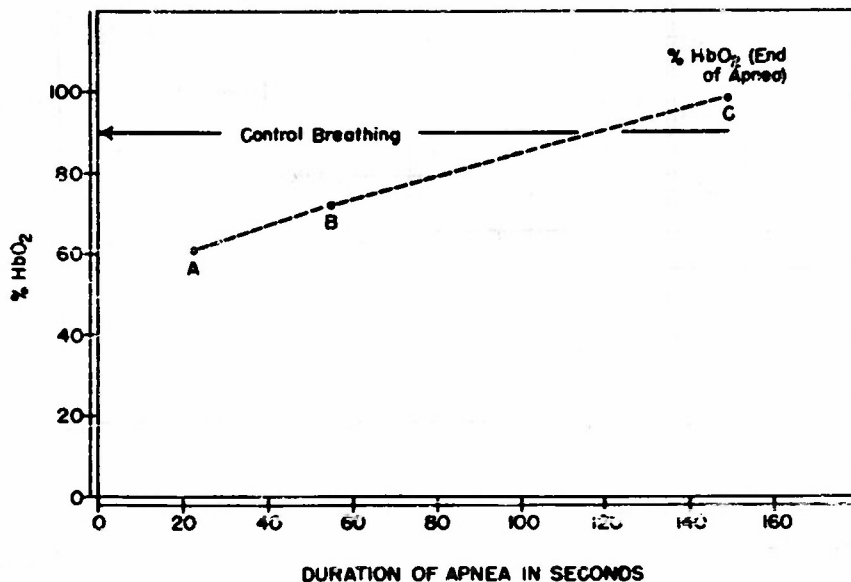


Figure 2.

Shows the oxygen saturation of carotid artery blood at the end of apnea following six minutes of forced ventilation at ground level with 10% oxygen, A; 21% oxygen, B; and 100% oxygen, C. These are average values for eight dogs. A "control breathing" line represents the average oxygen saturation of arterial blood taken at S_1 (Fig. 1).

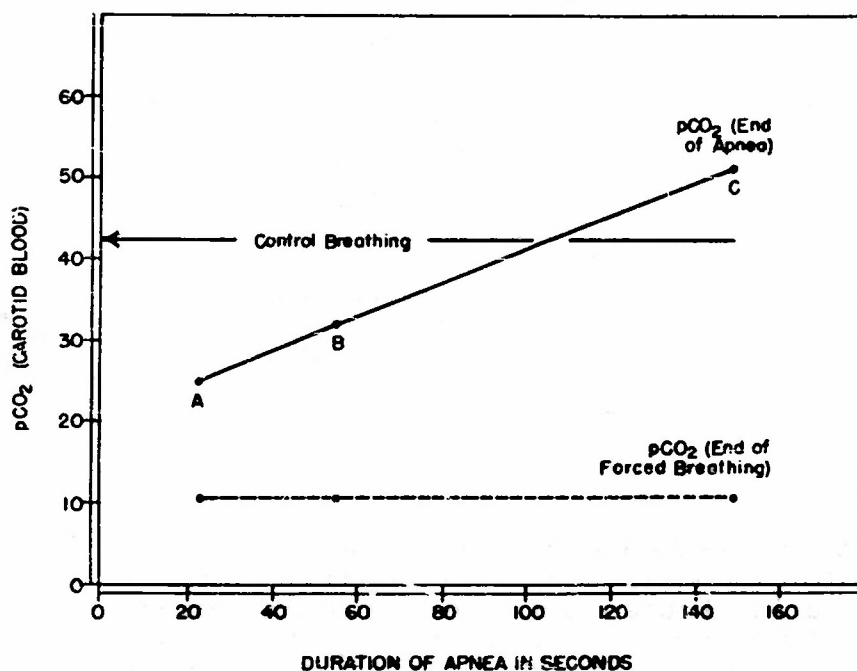


Figure 3.

Shows the carbon dioxide pressure of carotid artery blood of samples taken at S_1 "control breathing"; S_2 (end of forced breathing); and S_3 (end of apnea). Point A is average carbon dioxide pressure at the end of apnea following forced breathing with 10% oxygen; B, with 21% oxygen, C with 100% oxygen, respectively.

Figure 4.

Shows the relationship between the percent oxyhemoglobin and carbon dioxide pressure found in carotid blood at the end of apnea following forced ventilation with 10% oxygen; 21% oxygen and 100% oxygen at ground level. These are results with eight dogs and the mean values are at the intersections of standard deviation values for percent oxyhemoglobin and carbon dioxide pressure. The normal values of blood samples taken at S₁ (Fig. 1) are also shown.

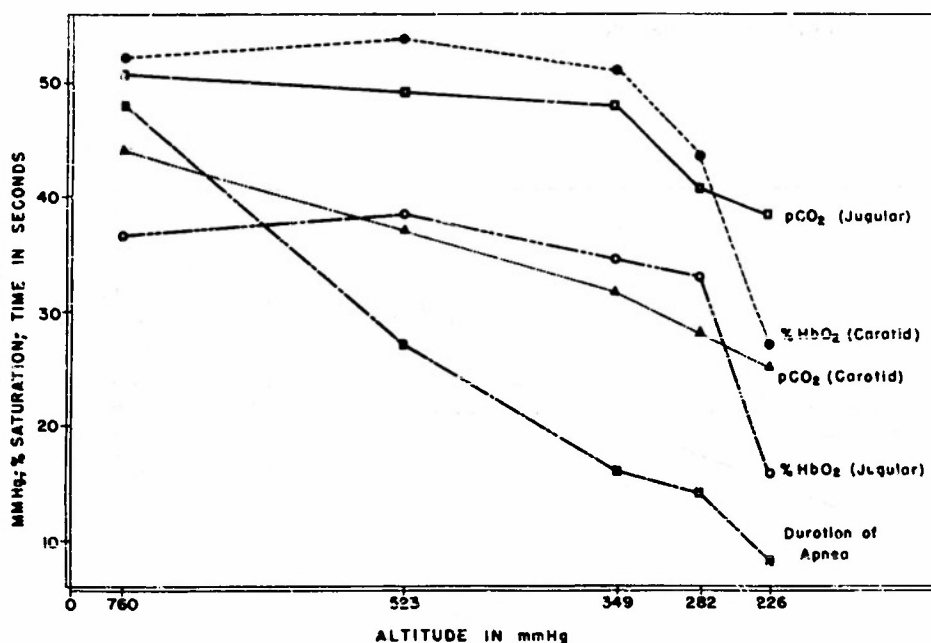
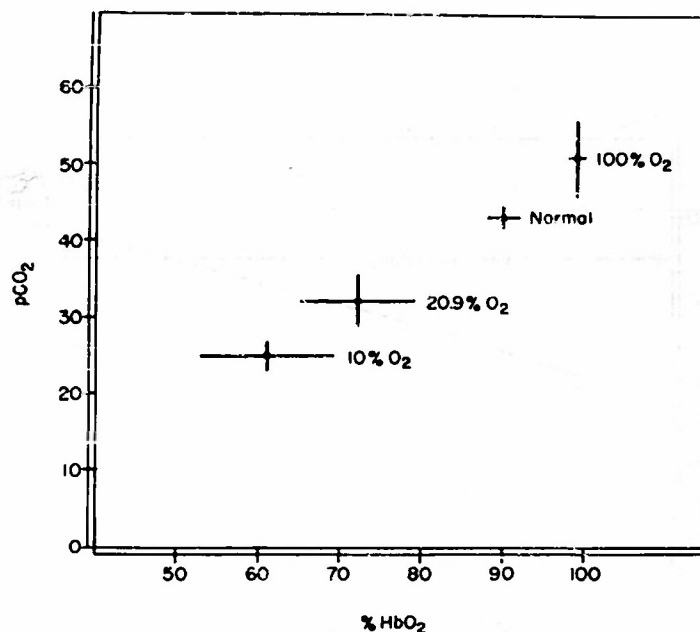


Figure 5. Shows results of experiments on eight dogs done at various simulated altitudes represented by the pressures. Blood samples were drawn simultaneously from carotid and jugular vessels at point S₃ (Fig. 1). Duration of apnea is shown in seconds, oxyhemoglobin in percent saturation, and carbon dioxide pressure in mm Hg.

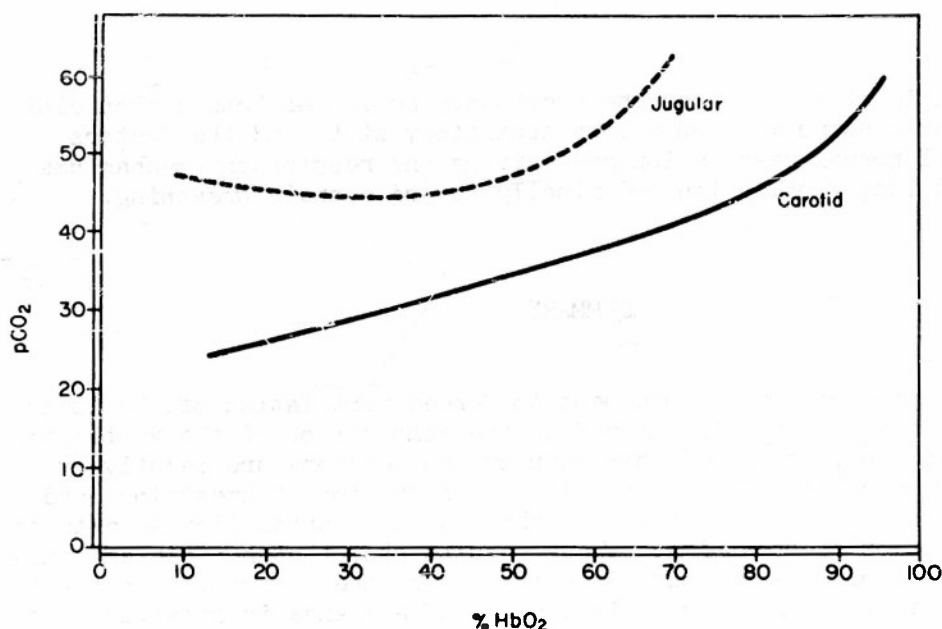


Figure 6. Shows the mean oxygen saturation values plotted against carbon dioxide pressure values for carotid and jugular blood. Samples were taken at the end of apnea. The highest oxygen saturation values were obtained following forced ventilation with 100% oxygen.

DISCUSSION

These experiments show that when forced ventilation is maintained in an anaesthetized animal for several minutes at a rate and depth of breathing greatly in excess of normal, a condition of apnea ensues. This pause will last for several seconds and its duration depends upon several factors. These results seem to show that while apnea is caused primarily by a lowering of carbon dioxide tension, its duration is modified by oxygen tension as well.

These results are probably applicable to some of the problems encountered in anaesthesiology and to methods employed in resuscitation. They also raise the question as to the concentration of oxygen which should be used in oxygen therapy.

Apnea is an interesting respiratory phenomenon. Breathing is somewhat analogous to the oscillations of a balance with changing weights on each pan. In apnea much of the weight from one side has been removed so oscillations stop and the balance is tipped far to one side. When the weight is slowly increased it reaches a point when the proper balance is regained, and if the weight on the other pan is likewise slowly removed as the weight on the first pan is increased, balance is regained sooner and finally a little later the original state is restored. The restoration of breathing

from the apneic state requires the excitatory action of both carbon dioxide and hypoxic stimuli. Apnea is a transitory state and the factors which control normal respiration are driving the respiratory mechanisms first toward lung ventilation and finally toward eupneic breathing.

SUMMARY

The duration of apnea subsequent to forced ventilation of the lungs in anaesthetized dogs was influenced by the composition of the ventilating gases. Blood analyses showed that when oxygen tensions are relatively lower, a low carbon dioxide existed at the resumption of breathing, and when oxygen tensions are relatively higher, a high carbon dioxide existed at the resumption of breathing. These results show that hypoxic and carbon dioxide stimuli are additive in establishing the threshold for the onset of breathing. There is some indication of a change in sensitivity to carbon dioxide at different oxygen tensions. There was a decrease in the duration of apnea in anaesthetized dogs subjected to forced ventilation at various simulated altitudes. This duration was directly related to the change in the pressure of ambient air.

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