

Oxygen and Carbon Dioxide Tensions as Factors in Respiration after Apnea from Hyperventilation

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CONTROLLED breathing during anesthesia almost invariably results in hyperventilation. This raises the interesting question of what factors are involved in the resumption of spontaneous respiration following the apnea after such hyperventilation in the nonparalyzed subject.

The following is an investigation of the possible roles played by carbon dioxide and oxygen tensions in effecting the return of respiration after the apnea described above.

Methods

For continuous analysis of the oxygen and carbon dioxide tensions of arterial blood, a technique used by us for many years was utilized. This technique involves the creation of a small artificial arterio-venous shunt by cannulating the aorta, via the femoral artery of the experimental animal, with small-diameter polyethylene tubing (.034 inch, inside diameter) and conducting the blood to the cuvettes containing O_2 and CO_2 electrodes. The blood is returned from the cuvettes to the animal by a large polyethylene catheter (.066 inch, inside diameter) inserted into the ipsilateral femoral vein. By using a small, hence low-flow, arterial catheter and a large venous catheter, any flow or pressure artifacts that might occur would be minimized. This technique is illustrated in figure 1.

Both the P_{O_2} and P_{CO_2} electrodes used have been described in previous articles,^{1, 2} but some modifications were made for the sake of decreased response time. In the case of the P_{CO_2}

electrode, instead of using .01N $NaHCO_3$ -0.1N KCl electrolyte with the .001-inch Teflon membrane, .001N $NaHCO_3$ -0.1N KCl electrolyte was used with a .0005-inch Teflon membrane. As a result of these modifications, there was some decrease in stability of the electrode; but since stability was required for only short periods of time (15 minutes), we believed this would not seriously affect our data, especially since calibrations with known gases were performed before and after each individual experiment. With the above modifications, we found that the response time of the electrode upward from 10 to 60 mm. of mercury P_{CO_2} was about twenty seconds for 99 per cent of that range in contrast to the 60 seconds response time of this electrode without the modifications. The oxygen electrode tip was

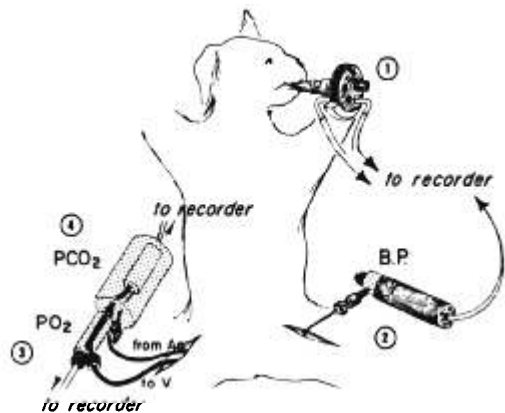


FIG. 1. An illustration of the instruments and technique used in these experiments: (1) pneumotachograph attached to endotracheal tube, (2) strain gauge for the direct measurement of intra-arterial blood pressure, (3) cuvette containing O_2 electrode, and (4) cuvette containing CO_2 electrode. Blood flow is from femoral artery through small diameter plastic tubing into the cuvettes and back into the femoral vein through large diameter plastic tubing.

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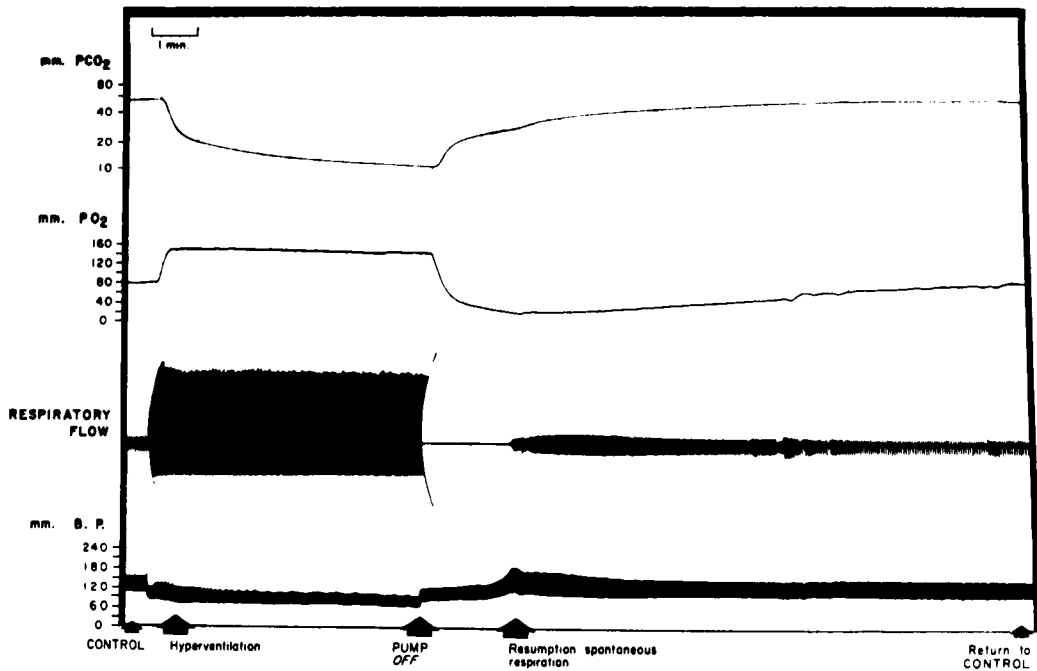


FIG. 2. Recording of an experiment using pentobarbital anesthesia. Note P_{CO_2} and P_{O_2} levels before, during, and after hyperventilation using room air as the inspired gas mixture. Respirations begin 110 seconds from the time respiratory pump is off. Return to control values ten minutes after this point.

modified by the manufacturer* to permit improved application of the polyethylene membrane which resulted in a response time of fifteen seconds for 99 per cent of the range from 20 to 160 mm. of mercury P_{O_2} for the electrode. In these ranges, the response of the CO_2 electrode was about five seconds slower than the response of the O_2 electrode; and where P_{O_2} and P_{CO_2} are compared temporally on the recordings, the difference in time must be taken into account.

The contralateral femoral artery was utilized to record arterial blood pressure by means of a strain gage pressure transducer. The outputs of the P_{CO_2} and P_{O_2} electrodes, a pneumotachograph, and the blood pressure strain gage were recorded on a multichannel oscillograph.

Dogs were lightly anesthetized either with pentobarbital (20 mg./kg.) or open drop ether, and their tracheas were intubated with a cuffed endotracheal tube. The pneumo-

tachograph sensing unit was attached to the endotracheal tube to record respiratory flow rate. With pentobarbital anesthesia, the animals breathed room air throughout the experiment, but those anesthetized with ether were maintained in a light plane of anesthesia (wink reflex intact) by means of ether delivered through a nonbreathing valve from a Copper Kettle vaporizer in a 25 per cent oxygen-75 per cent nitrous oxide mixture. These percentages of oxygen and nitrous oxide were chosen in order to simulate a commonly-used anesthetic mixture. During hyperventilation with this gas mixture, the ether concentration was decreased by about one-half to prevent possible "deepening" of anesthesia.

After the induction of anesthesia, cutdowns were performed in both inguinal regions and heparin 50 mg./kg. was given intravenously. All animals used were in apparently good condition.

The animals were allowed to breathe spontaneously until a control steady state recording of blood pressure, respiration, arterial P_{O_2} and P_{CO_2} were obtained. They were then hyper-

* Beckman Instrument Company, Fullerton, California.

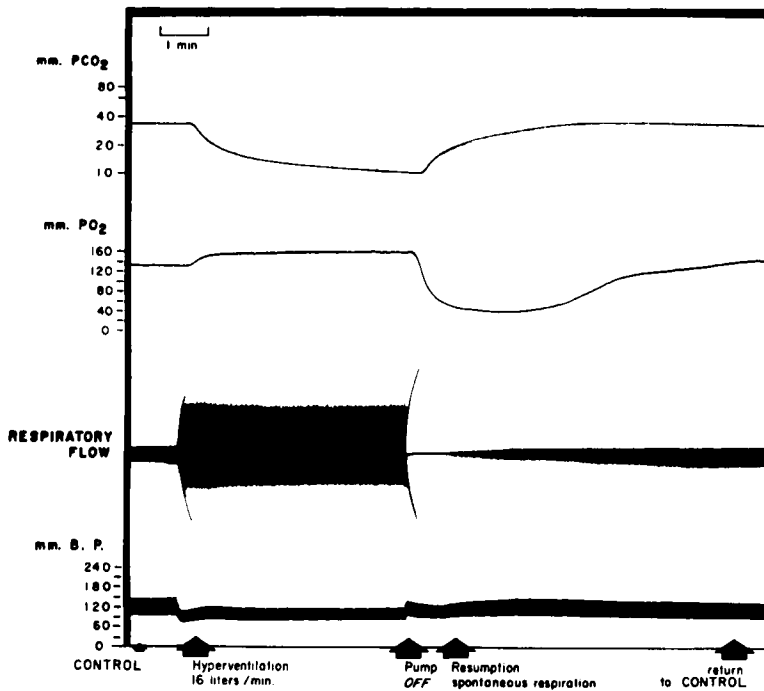


FIG. 3. Recording of an experiment using ether anesthesia. Note P_{O_2} and P_{CO_2} levels before, during, and after hyperventilation using 25 per cent oxygen-75 per cent nitrous oxide and ether as the inspired gas mixture. Respirations begin 50 seconds from the time respiratory pump is off. Return to control values six minutes after this point.

ventilated by a piston-type pump at about sixteen liters per minute (400 ml. forty times per minute) until the P_{CO_2} dropped to a steady low level (10-15 mm. of mercury) over a period of three to six minutes, at which time the pump was turned off and the time required for the resumption of spontaneous respiration was noted. The above routine was repeated when the recordings returned to control values and remained steady for at least fifteen minutes.

Ten blood samples were drawn at random times before, during, and after hyperventilation, and the various blood levels of CO_2 that were indicated by our instruments were compared with the values obtained from analysis with the Van Slyke-Neill apparatus for total CO_2 and P_{CO_2} calculated from the Henderson-Hasselbalch equation. The values obtained by this method were found to be within 2 mm. of mercury of those recorded by the CO_2 electrode.

Results

The results of an experiment using pentobarbital anesthesia with room air as the respired gas are shown in figure 2 and are

representative of the data obtained from fifteen experiments on seven dogs with pentobarbital as the anesthetic agent. In this experiment, the arterial P_{O_2} rapidly increased from 80 mm. of mercury during spontaneous respiration to 145 mm. of mercury and remained at that level with hyperventilation, while the arterial P_{CO_2} decreased from 55 mm. of mercury to a plateau of 11 mm. of mercury after five and one-half minutes of hyperventilation. The blood pressure and pulse pressure decreased rapidly, probably as a result of the positive pressure exerted by the pump, but returned to normal at the end of hyperventilation. The recording of the respiratory flow shows a slow rate and low amplitude of respiration during the control period with marked increase during hyperventilation followed by a period of apnea lasting 110 seconds when the respiratory pump was turned off. During this apneic period there was a rise in P_{CO_2} to a level of 28 mm. of mercury and a drop in P_{O_2} to 20 mm. of mercury at which time spontaneous respiratory movement occurred. Over a period of ten minutes there was a return to control values of O_2 , CO_2 , blood pressure and respiratory flow.

Figure 3 is a photograph of a record made during an experiment using 25 per cent oxygen and 75 per cent nitrous oxide with "light ether" as the respired gas. This gas mixture was used in nine experiments on three dogs. With ether anesthesia there was less depression of respiration than with pentobarbital anesthesia. This is not unexpected. Probably as a result of a near normal respiratory pattern, the control arterial P_{CO_2} in this experiment was 37 mm. of mercury. The rather high control level of P_{O_2} (130 mm. of mercury) can be explained by the higher oxygen concentration of the inspired gas (25 per cent) and lack of respiratory depression. With hyperventilation, a rapid and sustained rise in P_{O_2} to 160 mm. of mercury and a gradual fall in P_{CO_2} to 11 mm. of mercury over a period of five minutes is shown in this illustration. Spontaneous respiration in this case resumed after an apnea of 50 seconds, at which time a P_{CO_2} level of 20 mm. of mercury and a P_{O_2} level of 40 mm. of mercury can be seen to exist. The return to control values occurred more rapidly with ether anesthesia than with pentobarbital anesthesia, approximately six minutes being required for a return to control.

The results of the experiments are summarized in table 1, with the averages of all the data obtained. In comparing pentobarbital anesthesia with ether anesthesia, several points are apparent. Among them are the higher arterial P_{O_2} and lower P_{CO_2} in the control levels of dogs anesthetized with ether compared to those anesthetized with pentobarbital. The fall in blood pressure during hyperventilation is less with ether than with pentobarbital, and the duration of apnea is shorter with the former than the latter anesthetic agent. Although the arterial P_{CO_2} at the resumption of respiration did not differ greatly in the two forms of anesthesia, the arterial P_{O_2} , when spontaneous respiration occurred, was higher in the dogs with ether anesthesia than with pentobarbital anesthesia. The average duration of apnea with pentobarbital anesthesia exceeded by forty seconds the apnea produced with ether anesthesia. It should be emphasized that with both forms of anesthesia, resumption of respiration occurred at a very low average P_{O_2} level and at an average P_{CO_2} level much lower than that

TABLE 1. Averages of Values Obtained from Experiments Using Pentobarbital or Ether Anesthesia

Data	Pentobarbital (7 dogs-15 experiments)	Ether (3 dogs 9 experiments)
Control P_{CO_2}	Averages 46 mm. Hg	Averages 33 mm. Hg
P_{O_2}	70 mm. Hg	128 mm. Hg
Percentage drop in blood pressure during hyperventilation	23%	17%
P_{CO_2} at end of hyper- ventilation	14 mm. Hg	11 mm. Hg
P_{O_2} at end of hyper- ventilation	120 mm. Hg	151 mm. Hg
Duration of apnea	140 seconds	72 seconds
P_{CO_2} at resumption of respiration	28 mm. Hg	20 mm. Hg
P_{O_2} at resumption of respiration	21 mm. Hg	53 mm. Hg

found during the control period just before hyperventilation.

Discussion

The resumption of spontaneous respiration after the apnea following pronounced overbreathing has been largely attributed to a rise in carbon dioxide tension from the hypocarbic levels which exist during hyperventilation to a "threshold" concentration in the respiratory center.^{3, 4} The hypoxia which often occurs during this period of apnea has been suggested as a factor, along with the rise in CO_2 , in stimulating the return of respiration.⁵⁻⁷ However, with the exception of work by Hall,⁸ the possible role played by low oxygen tensions in the carotid and aortic chemoreceptors in activating a hypoxic drive to initiate respiration after the apnea of hyperventilation has not been widely investigated.

Meyer-Wegener⁹ hyperventilated human volunteers and concluded that factors other than a rising CO_2 concentration affected the duration of apnea. Horvath¹⁰ found that humans did not become apneic after breathing 4 to 6 per cent oxygen for three minutes and hyperventilating up to 30 liters per minute with oxygen saturations of 40 per cent (approximately 25 mm. P_{O_2}) and a P_{CO_2} of 23 mm. of mercury. Nielsen and Smith,¹¹ Lloyd, Jukes and Cunningham,¹² and Cormack, Cun-

ningham, and Gee,¹³ using both humans and experimental animals, demonstrated that below a threshold level of 30–31 mm. P_{CO_2} , varying the CO_2 tension had no effect on respiration while the subjects were breathing hypoxic O_2 concentrations. Bartels and Witzleb¹⁴ recorded electroneurograms of the nerves leading from the carotid chemoreceptor and were able to show that action potentials became evident only at about 30 mm. P_{CO_2} and linearly increased in frequency as CO_2 concentration was raised.

Based on the studies described above, it would seem that P_{CO_2} values below 30 mm. of mercury would have little effect on respiration either by affecting the chemoreceptors or the respiratory center. However, Heymans and Neil¹⁵ state that although the chemoreceptors are not essential to the respiratory response to changes in CO_2 levels, normally carbon dioxide probably does influence the action of the chemoreceptors. Lambertsen¹⁶ believes that although there is agreement that the effects of carbon dioxide are greater on the respiratory center than on the chemoreceptors, there is no general agreement as to contribution of carbon dioxide stimulus to the chemoreflexes.

In our experiments, the average P_{CO_2} at the start of respiration in dogs anesthetized with pentobarbital or ether was below 30 mm. of mercury. Therefore, it seemed that some other stimulus to initiate respiration in these apneic dogs should be present. Painful stimuli or passive exercise of the hind limbs did not seem to affect the duration of apnea. Infusion of acidic solutions was not done.

In view of the above findings it seemed reasonable to us that the hypoxic drive was probably responsible for the initiation of respiration that terminated the apnea after hyperventilation.

Heymans and Bouckaert¹⁷ were the first to demonstrate conclusively that the primary respiratory response to hypoxia was mediated by the carotid and aortic chemoreceptors. The P_{O_2} level at which this chemoreflex is activated has been the subject of investigation by many workers. Von Euler¹⁸ recorded potentials from the chemoreceptors and concluded that the threshold for hypoxic stimulus was about 85 mm. of mercury. Bernthal¹⁹ placed it at about 100 mm. of mercury. However, Lam-

bertsen²⁰ cites evidence to show that even with a normal P_{O_2} there is tonic chemoreceptor discharge in the nerves leading from these receptors and that the frequency of impulses increases progressively as the arterial P_{O_2} falls. Schmidt²¹ and Dripps and Comroe²² found that the ventilatory response in man to hypoxia was small until the P_{O_2} level dropped to 40–50 mm. of mercury. Our figures show that at the start of respiration following apnea, the average P_{O_2} in dogs anesthetized with pentobarbital was 21 mm. of mercury. Although the average P_{O_2} at this point for dogs anesthetized with ether and 25 per cent oxygen–75 per cent nitrous oxide was 53 mm. of mercury, it should be pointed out that in these animals the control average P_{O_2} of 128 mm. of mercury was quite high. Furthermore, analysis of individual records shows that the P_{O_2} at the start of respiration in dogs anesthetized with ether was below 40 mm. of mercury in six of nine experiments.

It might be argued that the values of P_{CO_2} of 10–15 mm. of mercury are unrealistic and uncommon. However, Klocke²³ found end-tidal alveolar CO_2 values ranging down to 14 mm. of mercury P_{CO_2} after voluntary hyperventilation by normal human subjects. Our observations on anesthetized patients under controlled respiration show frequently end-tidal alveolar CO_2 concentrations of 2 per cent (infrared analysis). The increase in arterial oxygen tension that followed the onset of hyperventilation is similar to the finding by Houston²⁴ that there is a marked rise in blood oxygen saturation during voluntary hyperventilation by human subjects.

Although other factors such as the influence of anesthetic agents on the response to carbon dioxide were undoubtedly present,^{25, 26} on the basis of our experiments it would seem that hypoxia was the main stimulus to respiration after the apnea of hyperventilation. This conclusion is based upon our finding that the initiation of respiration under the previously mentioned conditions took place when the P_{CO_2} was below 30 mm. of mercury in every case and when the P_{O_2} was below 40 mm. of mercury in the great majority of experiments.

Whether similar changes will occur in humans subjected to the same experimental meth-

ods as the above is a question that is now being studied at our institution.

It is interesting to speculate on the significance of this investigation on the mechanism of accidents in swimmers who hyperventilate with air at the edge of the pool before attempting prolonged underwater swimming. This practice is in contrast to that of breathing oxygen prior to long and inactive underwater submersion. In these accidents swimmers have lost consciousness while under water and apparently unaware of any pressing desire to breathe. It is possible that these swimmers have become hypoxic to the point of euphoria, disorientation, or unconsciousness without ever experiencing the overwhelming respiratory stimulus of a carbon dioxide excess which would have brought them to the surface.^{27, 28}

Summary and Conclusions

This study was undertaken to determine, if possible, the respective roles of hypoxia and carbon dioxide excess in terminating the apnea that results after hyperventilation under light anesthesia, using ether or pentobarbital as the anesthetic agent. In order to record continuously changes in arterial carbon dioxide and oxygen tensions, an artificial A-V shunt was created which bypassed arterial blood through cuvettes containing modified P_{CO_2} and P_{O_2} electrodes. The outputs of these electrodes as well as blood pressure and respiratory flows were recorded on an oscillograph.

Fifteen experiments using seven dogs were performed with pentobarbital as the anesthetic agent and room air as the respired gas. A similar series consisting of nine experiments on three dogs were studied using ether anesthesia with a 25 per cent oxygen-75 per cent nitrous oxide gas mixture. A brief history and discussion of the respiratory physiology possibly involved in these experiments has been presented.

Based on this series of experiments which consisted of continuously recording P_{O_2} , P_{CO_2} , blood pressure, and respiratory flow before, during, and after hyperventilation under anesthesia, the following conclusions are made:

(1) Hyperventilation results in increased arterial oxygen tension which remains consistently high while arterial carbon dioxide ten-

sion falls to very low levels (10 to 15 mm. of mercury).

(2) The resumption of respiration following the apnea of hyperventilation occurs when the P_{O_2} drops to low levels and at low P_{CO_2} and seems to be independent of the carbon dioxide tension at that time. The initiation of respiration after this form of apnea is possibly a function of the hypoxic drive from the aortic and carotid body chemoreceptors rather than an effect of carbon dioxide on the respiratory center.

(3) There are quantitative differences in the creation and termination of apnea following hyperventilation under pentobarbital anesthesia and under ether anesthesia.

(4) Dangerous levels of hypoxia may occur during apnea after hyperventilation with gas mixtures containing 20-25 per cent oxygen if respiratory assistance is not given in the interval between the onset of apnea and the resumption of respiration from whatever stimulus initiates breathing at this time.

(5) These findings suggest a relationship of hypoxia without carbon dioxide excess to unexplained accidents in swimmers attempting prolonged underwater swimming following pool-side hyperventilation with air.

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