

THE RATE OF RISE OF P_{aCO_2} IN THE APNEIC ANESTHETIZED PATIENT

E. I. EGER, M.D., AND J. W. SEVERINGHAUS, M.D.

AMONG the commonly cited causes of prolonged apnea is over-ventilation¹⁻⁴ with the assumption that there may be a delayed recovery of the arterial P_{CO_2} to a level that will initiate respiration. This delay has been estimated to be ". . . as long as 3 minutes"⁸ although it also has been noted that there is considerable variation in the response to over-ventilation.²

Studies in man and animals may be used to estimate the rate at which arterial and alveolar P_{CO_2} will rise during apnea. The volume of CO_2 stored in the body with rising P_{CO_2} was found by Shaw⁵ to be as high as 16 ml./mm. Hg/kg. in cats, but he subsequently reported a value of 1.78 ml./mm. Hg/kg.⁶ Farhi and Rahn⁷ gave a value of 1.5 ml./mm. Hg/kg. for the dog, and Freiman and Fenn⁸ reported 11.6 ml./mm. Hg/kg. in rats. In man, Vance and Fowler⁹ reported the capacity to be 1.30 to 2.05 ml./mm. Hg/kg. If the last figures apply during apnea, then in a 70 kg. man with a CO_2 production of 200 ml./minute, the rate of rise would be approximately 2.2 to 1.5 mm. Hg/minute. However, a major portion of the body mass is poorly perfused and slowly metabolizing. We should anticipate that most of the CO_2 production and storage occurs in less than half the body mass which would double the expected rate of rise.

Brocklehurst and Henderson¹⁰ in conscious subjects rebreathing in a bag filled with 95 per cent O_2 and 5 per cent CO_2 found a rate of rise of between 5 and 6 mm. Hg/minute. This figure for end tidal samples was obtained between $\frac{1}{2}$ and $1\frac{1}{2}$ minutes of rebreathing. Frumin, Epstein, and Cohen¹¹ during a study of apneic oxygenation in man observed an average rate of rise of about 3.2 mm. Hg/minute. In dogs during diffusion respiration, Roth *et al.* recorded figures of 0.8 per cent per minute¹² and Draper *et al.* 1.08 per cent per

minute.¹³ In Denver, where they worked, this is a range of 4.5–6.0 mm. Hg/minute. Holmdahl,¹⁴ in a six-minute period of apneic oxygenation in nine men, found a rate of rise of alveolar P_{CO_2} of about 5 mm. Hg per minute. The rise was fairly linear with a tendency toward a decreasing rate of rise as time of study increased.

The application of the above figures to the case of prolonged apnea after anesthesia (and/or hyperventilation) may be suspect on several grounds. The figures of Brocklehurst and Henderson¹⁰ were obtained from awake subjects who were hyperventilating. The figures obtained during apneic oxygenation^{11, 12, 13} are averages obtained over a fairly long period of time and over a wide range of CO_2 change. To use these average figures implies that the rate of rise of CO_2 is linear whereas it has been shown that this probably is not the case.^{8, 9, 15} In addition, none of the above studies gives information on the rate of rise after prolonged hyperventilation.

The following study was performed to obtain data on the rate of rise of P_{CO_2} in the alveoli during anesthesia in apneic man. Specifically, we attempted to determine the rate of rise from a relatively normal alveolar P_{CO_2} and then from a lowered alveolar P_{CO_2} which had been produced by prolonged hyperventilation.

METHODS

Five healthy adults who were to undergo various operative procedures were selected for study. Each was premedicated with scopolamine 0.4–0.6 mg. and morphine 10–15 mg. or merperidine 100 mg. Anesthesia was induced and maintained with thiopental and merperidine. Succinylcholine was injected intravenously and a cuffed endotracheal tube inserted into the trachea. Succinylcholine was continued as an intravenous drip or in intermittent doses sufficient to eliminate spontaneous respiration. The endotracheal tube was connected to a rubber sampling tube about

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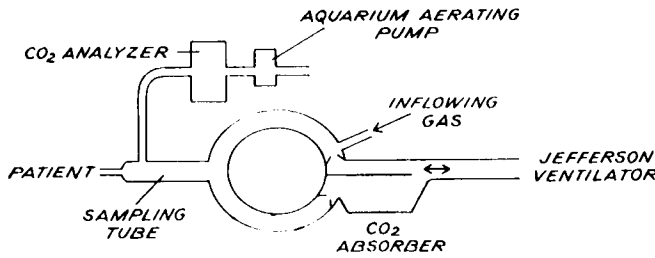


Fig. 1 A

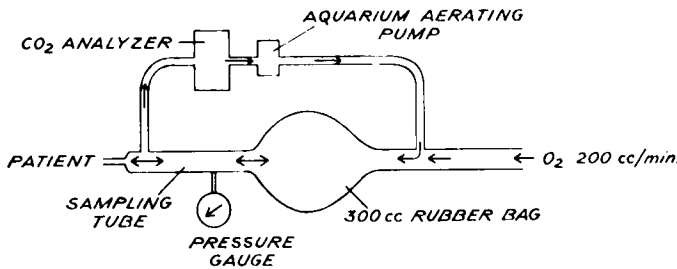


Fig. 1 B

FIG. 1. A. Arrangement of apparatus prior to period of apnea.
B. Arrangement of apparatus used during apnea.

20 cm. long with an internal volume of about 25 ml. This in turn was connected to a conventional carbon dioxide absorbing circle system (fig. 1-A). Pulmonary ventilation was effected with a Jefferson self-cycled ventilator at a rate and volume which maintained an end tidal P_{CO_2} of about 30 mm. Hg. The CO_2 in the endotracheal tube was continuously monitored with an infrared analyzer. Denitrogenation was achieved with 10 liters per minute

or greater flows of oxygen for a minimum of 10 minutes. The sampling tube was then disconnected from the circle filter system and connected to the 300 ml. (maximum capacity) rebreathing bag (fig. 1-B). Oxygen was rapidly admitted to the system until the rebreathing bag was filled without appreciable tension. This state of fullness was maintained by introducing a constant inflow of oxygen of about 200 ml./minute. The end-expiratory

TABLE 1
PATTERN OF RISE OF PCO_2 IN APNEIC ANESTHETIZED PATIENTS

	Pre-hyperventilation Subject					Average	Post-hyperventilation Subject					Average
	1	2	3	4	5		1	2	3	4	5	
Initial PCO_2	26.6	31.9	30.8	29.4	28.7	29.5	13.3	16.5	14.3	14.7	11.2	14.0
Mm. Hg PCO_2 change in first minute	13.3	15.0	15.8	11.2	11.6	13.4	8.1	8.0	11.2	10.9	9.8	9.6
Mm. Hg PCO_2 change per minute from end of first minute to last minute	3.03	3.72	2.71	2.45	3.14	3.01	2.19	3.38	2.12	2.66	1.64	2.40
Average mm. Hg PCO_2 change per minute	4.06	5.60	4.02	3.32	3.99	4.20	2.48	4.83	2.63	3.25	2.08	3.05
Minutes duration of apnea	10	6	10	12	10	9.6	20	10	18	14	20	16.4
Minutes to a PCO_2 of 40 mm. Hg	1	0.5	0.5	0.75	1	0.75	10	3.5	7	5	13	7.7

pressure in the system was approximately 5 cm. water. Pressures were observed on the aneroid pressure gauge noted in figure 1-B. End-tidal samples were drawn through the infrared sample cuvette using an aquarium aerating pump and returned to the system at the tail of the rebreathing bag. The rebreathing bag was intermittently compressed during this "apneic" period in order to obtain an alveolar gas sample. The alveolar P_{CO₂} was allowed to rise in this system to between 60 and 70 mm. Hg. Then the sampling tube was disconnected from the rebreathing bag and reconnected to the circle filter system. One hour of artificial hyperventilation followed, using the ventilator and flows of 6 liters per minute nitrous oxide and 2 liters per minute oxygen. The end-tidal CO₂ decreased to a fairly stable level in 15 minutes. This level was then maintained (if necessary by adjustment of the pressure and frequency settings on the ventilator) until the next period of apnea. During this period of hyperventilation meperidine 100-250 mg. was administered intravenously in divided doses. Ten minutes before the second period of apnea 100-300 mg. of thiopental were administered intravenously and the inflowing gas mixture changed to 8-10 liters per minute of pure oxygen. At the end of this period, the sampling tube was disconnected from the circle system and reconnected to the apparatus drawn in figure 1-B. The procedure following this was identical to the previous period of rebreathing except that

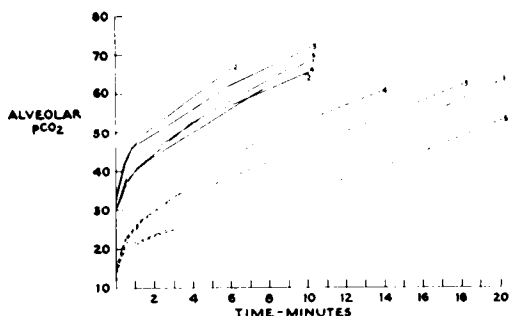


FIG. 2. These graphs illustrate the rates of rise of P_{CO₂} in relation to time in the 5 subjects studied. The unbroken lines represent the rises before hyperventilation, the broken lines represent those following. Subject numbers are given with each graph.

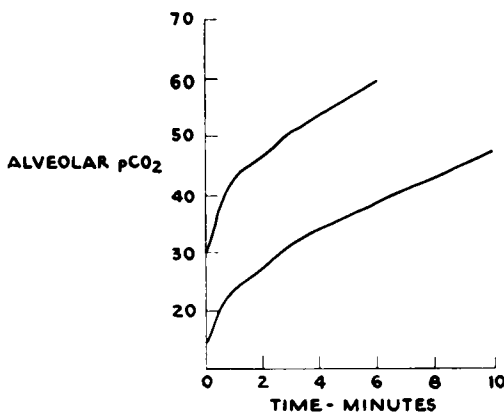


FIG. 3. Average rates of rise of P_{CO₂} before (upper graph) and after (lower graph) hyperventilation. The length of each graph is determined by the number of minutes during which points are present from all 5 subjects.

readings were obtained for a longer period of time.

A single patient was similarly studied before and after hypothermia rather than hyperventilation. In this patient, hyperventilation was obtained both before and after hypothermia.

RESULTS

The results from individual patients are given in table 1 and are diagrammatically represented in figure 2. Both before and after hyperventilation the rate of rise of alveolar P_{CO₂} during rebreathing follows a common pattern. A rapid rise occurs in the first minute and is followed by a slower and nearly linear rise thereafter. The over-all rate of rise before hyperventilation was 4.20 and after hyperventilation 3.05 mm. Hg/minute. These rates of rise are comparable to the value of 3.2 given by Frumin. If only the first six minutes are considered, then an average of about 4 to 5 mm. Hg/minute rise was recorded in this work which is close to the value of 5 mm. Hg/minute found by Holmdahl¹⁴ in the same time interval.

The rate of rise of P_{CO₂} in the first minute of rebreathing was significantly less ($P < 0.05$) following hyperventilation (9.6 compared to 13.4 mm. Hg). The rate of rise after the first minute was also less following hyperventila-

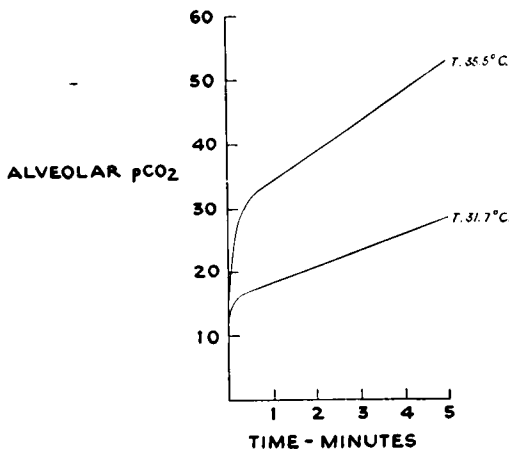


FIG. 4. Rate of rise of P_{CO_2} before (upper graph) and after (lower graph) reduction of esophageal temperature from 35.5 C to 31.7 C. Mild relative hyperventilation is noted to be present during hypothermia by the lowered initial P_{CO_2} .

tion (2.40 compared to 3.01 mm. Hg/minute) but this was not statistically significant.

The average rates of rise are plotted for both circumstances in figure 3.

Figure 4 illustrates the effect of hypothermia on the rate of rise of P_{CO_2} . The esophageal temperature was reduced from 35.5 C to 31.7 C between the two groups of readings. Both the initial rate of rise and the subsequent rate of rise were markedly decreased under hypothermia. In the first minute, the values were 17.5 versus 6.3 mm. Hg, respectively. In the succeeding minutes, the rate of rise was 4.7 mm. Hg/minute before hypothermia and 2.6 mm. Hg/minute following.

DISCUSSION

Sources of Error. The rebreathing system described above introduced a small error by adding to the gas volume about 400 ml. more than would be present in apnea. With the observed rates of rise, about 2 ml. of CO_2 per minute were accumulating in the bag instead of in the patient, an error of about 1 per cent of the CO_2 production.

A second error was introduced by the 5 cm. H_2O positive pressure maintained within the rebreathing apparatus. This pressure presumably increased the volume of gas within the patients' lungs by 300 ml. adding another 1

per cent error similar to that noted above. This pressure may have also decreased the cardiac output. However, as Suskind and Rahn¹⁶ have pointed out, alteration of the cardiac output has little effect on end-tidal P_{CO_2} unless the alteration is extreme. The effect of a reduction in perfusion of storage tissue would be to increase the rate of rise of P_{CO_2} . Reduction in flow in actively metabolizing organs would have an opposite but only transient effect. The magnitude of these errors cannot be estimated except to note that arterial pressure remained remarkably constant during the entire procedure.

Significance of the Non-linear Rise of P_{CO_2} . The graphs of rise of alveolar P_{CO_2} versus time may be divided into two sections. The rise during the first 15 to 45 seconds was quite rapid and represented the equilibration of alveolar P_{CO_2} with venous blood.¹⁷ In essence then, if recirculation has not occurred, this rise represented the arterio-venous difference in P_{CO_2} which was about 6–10 mm. Hg. This rapid rise was then succeeded by a slower and near linear rate of rise of about 3 mm. Hg/minute. This represented the balance of the metabolic production of carbon dioxide and the available CO_2 storage capacity of the body. The latter did not represent the total storage capacity⁹ but rather those areas of the body that were well perfused and thus available to accept CO_2 . Physical solution of CO_2 in body water could account for about 0.5 ml. CO_2 /mm. Hg/kg. of body weight. Any additional CO_2 stored must have been combined with buffers as bicarbonate, carbonate or carbamino groups.

Effects of Hyperventilation. The shape of the graphs before and after hyperventilation remained the same. There were, however, quantitative differences between them. During the first minute of apnea, the P_{CO_2} rose an average of 13.4 mm. Hg, but after hyperventilation, this rise was only 9.6 mm. Hg. This difference may relate to the shape of the CO_2 dissociation curve which would allow for the greater retention of CO_2 for a given rise of P_{CO_2} at a lower starting P_{CO_2} . A second cause of this difference may be the presence of alveolar dead space, producing a "gradient" between alveolar (end-tidal) and arterial P_{CO_2} .

This gradient decreases in proportion to the fall in arterial P_{CO₂} so would be less of an error during hyperventilation. A reasonable estimate of this gradient during controlled ventilation might be 4 mm.^{18, 19} During re-breathing, this gradient, as well as the A-V difference, disappears. During hyperventilation it might be reduced below 2 mm. A decreased arteriovenous P_{CO₂} difference after hyperventilation could also be caused by an increased cardiac output or decreased metabolic activity, although neither of these appear likely.

Although there was a difference before and after hyperventilation in the rate of rise of P_{CO₂} after the first minute of apnea (3.01 mm. Hg/minute versus 2.40 mm. Hg/minute) this is not statistically significant. This, of course, does not rule out the possibility of such a difference. Possible reasons for such might include (1) a difference in the starting point on the CO₂ dissociation curve as noted above, (2) an increase in blood flow to tissues such as resting muscle which can act to store CO₂, (3) a decrease in metabolism, although the work of Benzinger²⁰ who found the converse would make this unlikely.

Of what significance are these findings to the anesthesiologist? First, if alveolar may be equated to arterial P_{CO₂} then the data may be used to predict in the average case how long it will take to reach a certain arterial P_{CO₂} during apnea. During the first minute the P_{CO₂} will rise about 10 mm. Hg and in the succeeding minutes will rise at a rate of about 2.5 to 3 mm. Hg/minute. Under these circumstances, it would take about 8 minutes to rise from an initial P_{CO₂} of 15 to a "normal" of 40 mm. Hg (fig. 3) in the average patient. It must be remembered that any particular patient may not be an average patient. Examination of figure 2 shows that a rise in alveolar P_{CO₂} from about 15 to 40 mm. Hg may occur in anything from 3 to 13 minutes. Any factor which would alter the available CO₂ storage capacity or metabolic production of CO₂ would alter the rate of rise. An example of this is found in a change in body temperature. Body temperature reduction increases the solubility of carbon dioxide and reduces the metabolic rate. This is illustrated in figure 4 where the

patient was prepared in a manner similar to those described earlier except that in this case hypothermia was induced along with very mild hyperventilation. A similar result might be expected during profound anesthesia since anesthesia is associated with a fall in metabolic rate.²¹⁻²⁴

This brings us to the original question which prompted the present study: how long must a patient remain apneic after hyperventilation before his arterial P_{CO₂} will have risen to a level that will cause the initiation of respiration? The answer depends not only on the rate of rise of P_{CO₂} as described, but on the arterial P_{CO₂} at which respiration will be stimulated to begin again. Studies in awake subjects show that in a limited number of cases respiration does not cease despite a markedly lowered P_{CO₂}.²⁵ However, in the majority of anesthetized subjects, apnea is produced by over-ventilation. Ether anesthesia is probably an exception. The factors that determine the P_{CO₂} at which respiration will be initiated are the nature of and depth of anesthesia, and the coexistence of other stimulating or depressing factors. The apneic threshold with light halothane in other experiments we have conducted has been as low as 30 mm. Hg, and with 20 per cent cyclopropane has been as high as 60 mm. Hg without narcotics.²⁶ The carotid body response to hypoxia which is very weak at low P_{CO₂} becomes stronger as P_{CO₂} rises.^{27, 28} Conversely, the action of hyperventilation itself may be to decrease this threshold.^{29, 30, 31}

It might also be noted that this study shows there is little danger of high P_{CO₂} levels during the course of tracheal intubation assuming a normal starting P_{CO₂}.

SUMMARY

The rate of rise of alveolar P_{CO₂} in 5 apneic anesthetized subjects has been determined by artificial re-breathing in a 400 ml. system. Determinations were made before and after prolonged (average 69 minutes) hyperventilation.

Alveolar P_{CO₂} showed an initial rise of 13.4 mm. Hg P_{CO₂} (range 8-16) in the first minute and a subsequent fairly linear rise of about 3.0 mm. Hg (range 2-4) per minute. The initial

rapid rise was caused by the equilibration of the gas with mixed-venous P_{CO_2} while the succeeding rise was due to the metabolic production of CO_2 divided by the available storage capacity of the body for CO_2 . A reduction in the rate of rise of P_{CO_2} occurred after one hour of hyperventilation. During the first minute, the mean rise was 9.6 mm. Hg (range 8.0 to 11.2) and the subsequent rise was 2.4 mm. Hg/minute (range 1.6 to 3.4). In one patient at normal temperature after hyperventilation, 13 minutes of apnea elapsed before the P_{CO_2} had risen to 40 mm. Hg. Body hypothermia may reduce this rate as may any factor which decreases metabolism or increases the available storage capacity of the body for CO_2 .

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AZEOTROPIC MIXTURE In an effort to reduce the flammability limits and the expense of production, an azeotropic mixture of trifluoroethyl vinyl ether (Fluormar) and trifluoro-trichloroethane (Genetron 113) has been prepared. This mixture has been administered to three monkeys and one man. The mixture exhibited desirable anesthetic properties in the animals. In the one human being, induction was smooth and rapid, respiration and blood pressure essentially unaffected, and abdominal relaxation good. Anesthesia was maintained for thirty minutes. Recovery was uneventful and rapid. (*Krantz, J. C., Ling, J. S. L., and Kozler, V. F.: Anesthesia; Anesthetic Properties of the Azeotropic Mixture of Trifluoroethyl Ether (Fluoromar) and 1,1,2-Trifluoro-2,2,1-Trichloroethane (Genetron 113), J. Pharmacol. Exp. Ther.* 130: 492 (Dec.) 1960.)

HYPOTHERMIA Muscular relaxation produced by succinylcholine or tubocurarine increases the cooling time. Alcohol or chloro-

promazine do not change the cooling rate. Data show that oxygen consumption and heat production play a minor role in hypothermic anesthesia and that the heat exchange on the body shell is the important factor. (*Mellinger, T. J.: Muscle Relaxants and Cooling Rate in Hypothermic Anesthesia, Ann. Surg.,* 152: 1078 (Dec.) 1960.)

HYPOTHERMIA Vagal stimulation was effective in producing slowing of the heart at all temperatures down to 12 C. in the rat although greater intensity and slower frequency of stimulation were required as the animals were cooled. Atropine was equally effective in blocking the effects of vagal stimulation on the heart during hypothermia or euthermia. The effect of vagal stimulation on cardiac rate disappeared approximately 2 degrees centigrade above the temperature at which the spontaneous heart beat disappeared. (*Adolph, E., and Nail, R.: Vagal Inhibition of Heart in Deep Hypothermia, J. Appl. Physiol.* 15: 911 (Sept.) 1960.)