DIFFUSION RESPIRATION IN THE DOG ANESTHETIZED BY PENTOTHAL SODIUM *

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KROGH (1) divides the terrestrial lung-bearing animals into two physiologic groups, viz., those which respire by diffusion and those which employ mechanical respiration. By the term *diffusion* respiration, as used by Krogh, is meant gas-exchange between the atmosphere and lung alveoli in the absence of rhythmically recurring differences in the barometric pressures of these two areas, i.e., in the absence of respiratory movements of the chest. It does not, of course, include the gas exchange taking place between the blood and the alveolar gases, although this phase of respiration is also recognized as a diffusion process (2). On the other hand, in *mechanical* respiration the gas exchange is the result of differences recurring rhythmically between the barometric pressures of the intrapulmonary gases and the outside atmosphere. Mechanical respiration is by far the more efficient and is recognized as one of the conditions essential for the attainment by terrestrial vertebrates of a large or even medium size, combined with a high rate of metabolism. The evidence presented in this paper, however, shows that under certain artificial conditions, the anesthetized dog can obtain, for a limited period, sufficient oxygen for its metabolic requirements through diffusion alone.

We wish to emphasize at this point that diffusion respiration, in the sense that the term is used in this paper, does not involve the application of an external force with the object of producing a difference between the barometric pressures of the atmosphere and intrapulmonary gases. For this reason, it is fundamentally different from the mechanical type of respiration produced by the use of bellows (3), streams of air under pressure (4), and so forth. Diffusion respiration is distinguished from mere breath-holding by the fact that the latter does not involve gas exchange with the atmosphere.

Behnke and his associates (5, 6), during a study of the effect of four atmospheres of oxygen upon certain of the constituents of the blood, observed that the blood of one of their dogs in apnea remained well oxygenated for thirty-three minutes. The phenomenon was explained as

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due to diffusion respiration, but no evidence other than the maintenance of blood oxygenation was offered in proof. When, however, consideration is given to the fact that abnormal amounts of oxygen were present within the lungs at the time of respiratory arrest, that high pressures of oxygen (7) and toxic alveolar levels of carbon dioxide (8) substantially diminish the consumption of oxygen and also that, at four atmospheres of pressure, significant amounts of oxygen may have diffused into the blood through the mucous membranes, the maintenance of blood oxygenation during a thirty-three minute period of apnea cannot, of itself, be regarded as conclusively proving the existence of diffusion respiration. Nevertheless, in view of the favorable experimental conditions employed (see below), there is no doubt that diffusion respiration actually did take place during the experiment they describe.

Our attention was first directed to diffusion respiration when we observed, during the resuscitation of dogs from respiratory arrest produced by pentothal sodium,* that artificial respiration could be suspended for periods up to one-half hour without noticeable interference with oxygenation, provided there was a high concentration of oxygen in the respiratory tract and a mouth hook was in position delivering 10 liters of oxygen per minute. Under the proper conditions, this method of assuring oxygenation during respiratory arrest is quite effective. We have used it to the exclusion of artificial respiration in nearly 100 routine resuscitations from overdoses of pentothal sodium. The phenomenon seemed worthy of further investigation.

PROCEDURE

The experiments were conducted in Denver where the barometric pressure averages 630 mm. of mercury. Dogs were employed. Anesthesia was induced by an intravenous injection of 2.5 per cent pentothal sodium and the animal was made to breathe pure oxygen for a few minutes in order to replace the nitrogen in the respiratory tract with oxygen. A sensitive and *balanced* spirometer, filled with oxygen and fitted with a soda-lime chamber, was then connected to a cannula securely tied in the trachea, and the injection of the anesthetic was continued by means of a variable speed mechanical injector until the respiration ceased. In order to prevent the resumption of spontaneous breathing it was necessary to administer substantial amounts of the anesthetic continuously throughout the period of respiratory arrest.

EXPERIMENTAL RESULTS

Figure 1 is representative of 18 similar experiments. It records the oxygen uptake and blood pressure during two periods of respiratory arrest produced by overdosage of pentothal sodium. In the first period

* A generous supply of pentothal sodium was furnished through the courtesy of J. Bichn, M.D., of the Abbott Laboratories.

FIG. 1. Experiment 13. The space between each horizontal line of dots represents 35.1 cc. of oxygen at 760 mm. of mercury and 27 C. Spirometer bell filled with oxygen and fitted with a soda-lime chamber. Anesthesia, pentothal sodium 2.5 per cent. Anesthetic injected continuously throughout respiratory arrest. Time intervals, fifteen seconds. Lower tracing is the spirometer record. Upstroke, inspiration. The long downward strokes indicate the [illegible]

during the interval marked on the graph "surgical anesthesia," an average respiratory minute rate of 19 and minute volume of 3420 cc. was accompanied by the uptake of 145 cc. of oxygen per minute. During the next three and six-tenths minutes (x to a), the anesthesia was pushed through the toxic stage and a steady decline in the respiratory rate and volume resulted. Oxygen uptake, however, was well maintained and averaged 133 cc. per minute. Throughout the toxic stage and for the subsequent period of respiratory arrest, the color of the dog's tongue remained good until point "b" was reached when, as indicated, slight cyanosis appeared. During the eleven minutes of arrested respiration (a to b) the oxygen uptake averaged 108 cc. per minute. This is equivalent to 74.5 per cent of the uptake during surgical anesthesia and 81 per cent of that during toxic anesthesia. The blood pressure value which was maintained during surgical anesthesia at 125 mm. of mercury fell as the toxic stage developed and reached a level of 47 mm. of mercury during the period of respiratory arrest. The extent of this fall in blood pressure is probably a reflection of the deep level of anesthesia required to maintain respiratory arrest and of the accumulation of carbon dioxide to a toxic level. Coincident with the development of anoxemia, however, the blood pressure level rose, the heart slowed and the pulse pressure, as measured by a mercury manometer, was greatly increased.

Shortly after the appearance of cyanosis, breathing was spontaneously resumed in spite of the continued injection of anesthetic. Because, however, cyanosis still persisted, the injection of the anesthetic was stopped and the animal allowed to recover. After a delay of fourteen minutes to permit the relief of the anoxemia, the injection of anesthetic was resumed with the prompt reappearance of respiratory arrest. For the first five minutes of the second period of respiratory arrest the oxygen uptake continued much as it did during the first period, but later, presumably because the circulation was slowing, the uptake began to diminish and cyanosis reappeared.

At point "d" the circulation failed completely and there was an abrupt cessation of oxygen uptake. This portion of the graph is of particular interest because it depicts the gradual onset of circulatory failure and the final stasis through the resulting changes in oxygen uptake. The graph also illustrates two characteristics of pentothal sodium anesthesia which we have observed many times. During the first period of respiratory arrest (a to b) which lasted eleven minutes, a further 6.3 cc of 2.5 per cent pentothal sodium solution was injected into a 20 Kg. dog. In spite of this massive overdose and the resulting prolonged respiratory arrest, the circulation remained adequate for the survival of the animal. This indicates that pentothal sodium exhibits an impressive margin between the doses required to produce respiratory arrest and failure of the circulation provided oxygenation is good. On

the other hand, we have often observed that this margin may be much reduced in the presence of anoxemia. In barbiturate anesthesia, anoxemia is a particularly powerful stimulus to the respiratory center (9) and, as shown by the reappearance of respiration at point "b," it may result in spontaneous respiration in spite of gross overdosage. The unwary anesthetist, therefore, who relies too blindly upon respiration as an indication of the depth of anesthesia may be seriously misled.

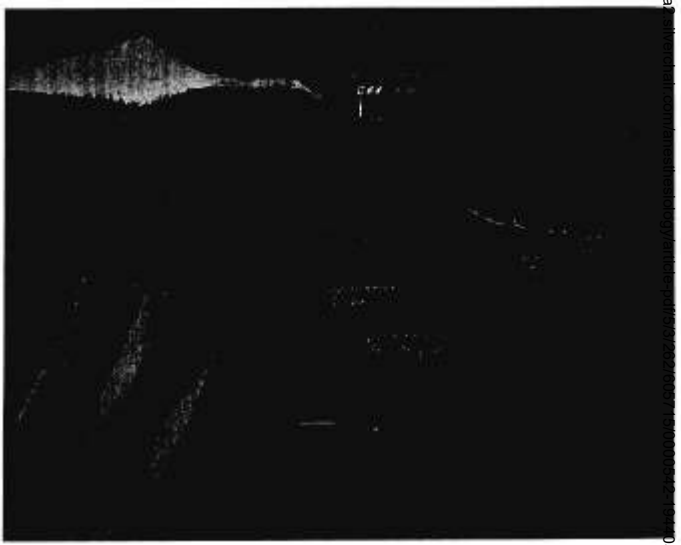

FIG. 2. Experiment 17. Dog, weight 15.25 Kg. Anesthesia, pentothal sodium 2.5 per cent. The space between each horizontal line of dots represents 35.1 cc. of oxygen at 760 mm. of mercury and 27 C. or 1.0 cm. of water pressure. Time intervals, fifteen seconds. Upper tracing made by a water manometer recording the pressure changes within the spirometer bell. Lower tracing is the spirometer record. Spirometer filled with oxygen and fitted with a soda-lime chamber. Upstroke, inspiration. The long downward strokes indicate refilling of the spirometer bell with oxygen.

In another series of experiments the spirometer bell was prevented from falling during respiratory arrest by a mechanical device, and the pressure changes which developed within the bell were measured with a water manometer. Figure 2, obtained from one of these experiments, shows that as soon as the bell is seized, the pressure within the spirometer (i.e., the intrapulmonary pressure) progressively falls. At first the fall is rapid, but later, with the onset of circulatory failure, it be-

comes slower. In this particular experiment the negative pressure reached a maximum of 10 cm. of water before the heart stopped. In other experiments, it was shown by means of appropriate apparatus that, with the development of negative intrapulmonary pressure, the chest becomes markedly contracted and the negative intrapleural pressure is greater. The development of a substantial degree of negative pressure within the respiratory tract during respiratory arrest is clear proof that the oxygen loss recorded by the spirometer in figure 1 is not caused by leaks or other faults of apparatus.

DISCUSSION

In figure 1 oxygen is shown to leave the spirometer and enter the lungs of a dog in respiratory arrest at a rate which is sufficient to maintain oxygenation of the blood. What force is responsible for this phenomenon? We offer the following explanation:

The oxygenation of reduced hemoglobin as it passes through the alveolar capillaries lowers the oxygen tension and total gas pressure within the alveolar cavity. This in turn results in diffusion of an equivalent amount of oxygen from the spirometer into the lungs. Simultaneously, the excreted carbon dioxide, under the influence of the fall in its tension gradient, diffuses outward along the respiratory passages toward the soda lime. Thus, the fall in the tension gradients of these two gases is in opposite directions and the effect is to ventilate the lungs. The primary force at work is the chemical affinity of oxygen for the reduced hemoglobin which is in transit through the alveolar capillaries. Slowing of the circulation proportionately reduces the rate of oxygen uptake, and, with stasis, uptake abruptly ceases.

In this series of experiments a spirometer and soda-lime chamber were used because we wished to obtain quantitative data on the uptake of oxygen. The tubing used to connect the tracheal cannula to the soda-lime chamber, however, constitutes an extension of the animal's trachea and substantially increases the distance the excreted carbon dioxide must diffuse before it is fixed. This has the effect of retarding the escape of carbon dioxide and may have been largely responsible for the fact that, in this type of experiment, we were not able to prolong diffusion respiration beyond fifteen minutes.

Conditions become more favorable for the escape of carbon dioxide when a mouth hook which permits 10 liters of oxygen to flow per minute is used to maintain a high concentration of oxygen at the glottis. Although we have obtained prolonged survival in numerous experiments of this type, the results are not presented as conclusive evidence for diffusion respiration because there is a possibility that the trachea may have been forcibly ventilated to some extent by the stream of oxygen entering the pharynx. The uptake of oxygen under these circumstances, however, must have been due, in large part, to diffusion (see

protocol Exper. 5) and experiments of this type are significant for the field of resuscitation. As mentioned, we now use this method routinely for resuscitation from overdoses of pentothal sodium.

In order to exclude the possibility of forcible ventilation of the trachea, experiments with diffusion respiration were conducted in an oxygen chamber in which the atmosphere remained practically still. The protocol of one of these experiments is presented below:

Exper. 4 (Series C). Dog, weight 6.8 Kg.
Anesthesia—pentothal sodium 2 per cent.

9:40 A.M. Anesthesia induced by the injection of 6.0 cc. of 2 per cent pentothal sodium. Tracheal cannula inserted in order to insure a patent airway. Injection cannula tied in vein and pneumograph adjusted to record respiration. A window permitted constant observation of the animal.

10:00 A.M. Dog placed in oxygen chamber. Twelve liters of oxygen per minute admitted into the chamber throughout the experiment. The animal was permitted to breathe for the ensuing thirteen minutes in order to replace the nitrogen in the respiratory tract with oxygen.

10:10 A.M. Anesthesia deepened.

10:13 A.M. Spontaneous respiration ceased and the first period of diffusion respiration begun. The color of the tongue was bright pink throughout this period and the pulse was slow and strong. A total of 5.0 cc. of anesthetic solution was injected at intervals during this period.

10:43 A.M. After thirty minutes of respiratory arrest, the animal was removed from the chamber in order to obtain a sample of alveolar air, but on compression of the chest, spontaneous respiration was reflexly produced and the sample was contaminated with atmospheric air. Analysis, however, showed $O_2 = 27.7$ per cent, $CO_2 = 8.8$ per cent. Apparatus readjusted and the animal returned to the chamber at 11:02 A.M. Spontaneous respiration allowed to continue for the next seven minutes. Anesthesia again deepened.

11:09 A.M. Spontaneous respiration ceased and the second period of diffusion respiration begun. Four and eight-tenths cc. anesthetic solution was injected during the ensuing fifteen minutes of respiratory arrest. Color remained good throughout this period.

11:24 A.M. Animal removed from the chamber and a sample of alveolar air obtained by compressing the chest. Analysis showed $O_2 = 58.3$ per cent, $CO_2 = 24.9$ per cent. The chest was then inflated three times with oxygen in order to remove the nitrogen which was inhaled when the pressure on the chest was released. Animal returned to the chamber.

11:26 A.M. Third period of diffusion respiration begun.

11:28 A.M. 0.5 cc. of anesthetic solution injected.

11:34 A.M. Pulse rate, 100. Color of tongue bright pink.

12:02 P.M. Pulse rate, 121. Color of tongue bright pink.

12:25 P.M. Pulse rate, 102. Tongue slightly cyanotic.
12:31 P.M. Pulse rate, 101. Cyanosis deeper.
12:40 P.M. Cardiac arrest.

In this experiment the one hundred forty-seven minutes separating the initial respiratory arrest from cardiac failure included twenty-seven minutes of spontaneous mechanical respiration and one hundred twenty minutes of diffusion respiration. It is evident from the very high alveolar content of carbon dioxide that the diffusion outward of carbon dioxide is much slower than the diffusion inward of oxygen. A similar finding is recorded by Behnke (6). In the course of time, this produces an alveolar gas containing a high tension of oxygen but a toxic or even fatal tension of carbon dioxide. The additive or potentiating action of high tensions of carbon dioxide on barbiturate narcosis (10) was probably responsible for the fact that no additional pentothal sodium was required to maintain respiratory arrest during the final seventy-two minutes of the third period of diffusion respiration. From the point of view of the anesthetist, this long interval between respiratory arrest and cardiac failure is an impressive demonstration of the low circulatory toxicity of pentothal sodium, even in the presence of toxic concentrations of carbon dioxide, as long as the alveolar oxygen tension is maintained at a high level.

We have referred to the necessity of replacing the nitrogen in the respiratory tract with oxygen. This is illustrated by the following experiment:

Exper. 5 (Series B). Dog, weight 16 Kg.
Anesthesia—2.5 per cent pentothal sodium administered as needed by means of a variable speed mechanical injector.

10:35 A.M. Anesthesia induced and oxygen administered.
10:45 A.M. Anesthesia gradually deepened in order to produce respiratory arrest.
10:49 A.M. Spontaneous respiration ceased and the first period of diffusion respiration begun with a mouth hook in position delivering 10 liters of oxygen per minute. Color of tongue excellent throughout this twenty-five minute period of respiratory arrest.
11:14 A.M. Spontaneous respiration reappeared due to lightening of the anesthesia. Oxygen administered and the anesthesia again deepened to respiratory arrest.
11:18 A.M. Spontaneous respiration ceased and the second period of diffusion respiration begun. The color of the tongue was bright pink throughout this thirty-three minute period of respiratory arrest.
11:51 A.M. Mouth hook removed and a sample of alveolar air obtained through the use of strong compression of the chest. Analysis showed the alveolar oxygen to be 60 per cent and the carbon dioxide 12 per cent. On the release of pressure on the chest, the animal took one inhalation of atmospheric air.

11:54 A.M. Color good. The mouth hook was replaced and diffusion respiration attempted in the presence of air in the respiratory tract.
11:55½ A.M. Color very cyanotic. Animal revived by artificial respiration and administration of oxygen.
11:59 A.M. Color good and the third period of diffusion respiration begun.
12:17 P.M. Tongue becoming cyanotic.
12:22 P.M. Cardiac arrest.

In this experiment an animal, which had remained well oxygenated as long as the respiratory tract was nearly free of nitrogen, became dangerously anoxemic very shortly after taking one inhalation of atmospheric air even though the original high concentration of oxygen at the glottis was still maintained. In three spirometer experiments, in which the spirometer bell and respiratory tract contained air, only a negligible uptake of oxygen was recorded after respiratory arrest, and the animals promptly died. *It is clear from the above that diffusion respiration does not take place until most of the nitrogen in the respiratory tract is replaced with oxygen.* This experiment also shows that the survival of the animal in the experiments mentioned, in which a mouth hook was employed, was not due primarily to forcible ventilation of the lungs.

What is responsible for the failure of diffusion respiration when the respiratory tract contains air? Possibly two factors are involved. In terrestrial vertebrates, because of the shape of the oxygen-hemoglobin equilibrium curve, only a small difference exists between the oxygen tension of their alveolar air and the minimum tension capable of supporting life. This fact, together with the high metabolic rate of these animals, renders them acutely vulnerable to interruptions in the replenishment of their alveolar oxygen. The negligible oxygen uptake during diffusion respiration in air, therefore, is the result, at least in part, of the fact that, in respiratory arrest, the alveolar oxygen is rapidly reduced to a level which cannot effectively oxygenate the reduced hemoglobin passing through the lungs. Another factor of great importance is the impeding effect of nitrogen upon the inward diffusion of oxygen. In air the progress of oxygen molecules along the respiratory passages toward the alveolar membrane is slowed by collisions with the more numerous nitrogen molecules. In this sense, therefore, the nitrogen of air may be regarded as a suffocating gas which acts to interfere with the ingress of oxygen during respiratory arrest. This concept is in harmony with the belief now held that adaptation to high altitudes is aided by the fact that a fall in barometric pressure, i.e., a reduction in the number of nitrogen molecules, is accompanied by an increase in the speed of oxygen diffusion *within the alveolar spaces.* (Haldane and Priestley, 11).

The evolution of lung-bearing terrestrial animals into higher forms having an increased metabolic rate has necessitated the development of

an apparatus for mechanically ventilating their lungs. Considering only the question of oxygen, the persistence of diffusion respiration in the mammal raises an interesting question in comparative physiology. Has mechanical ventilation of the lungs become necessary, in the course of evolution, because the tension of atmospheric oxygen is insufficient for respiration by diffusion or because the oxygen of air is diluted with nitrogen? Further investigation may show that both influences have been important.

Certain clinical applications for diffusion respiration may be noted. The anesthetist can take advantage of this phenomenon to reduce the hazard of anesthesia and to provide a more flexible anesthetic technic. We have shown that in the event of an overdose of pentothal sodium under circumstances favorable to diffusion respiration, the uptake of oxygen continues for a period of time after respiratory arrest. This has the effect of deferring cardiac arrest and of substantially improving the chances for resuscitation (12). The requisite essentials for diffusion respiration are present whenever a high percentage of oxygen is administered by the modern, closed-system, gas machine during the course of an anesthesia produced by a nonvolatile agent, provided, of course, the circulation is adequate and the airway patent. The question of whether respiration by diffusion can occur in the presence of the gaseous anesthetics has not been studied.

Occasionally, in such special situations as surgical procedures on the heart and lung, the anesthetist may employ diffusion respiration to facilitate brief periods of suspended respiration. The use of "controlled respiration," by which is meant the production of intervals of respiratory arrest through a combination of deep anesthesia, hyper-oxygenation and acapnia, has been recommended as a means of increasing the muscular relaxation obtained from a given depth of anesthesia (13). It is probable that considerable diffusion of oxygen from the breathing bag into the patient's lungs takes place during the respiratory pause and accounts, in part, for the success of the technic. Prolonged periods of diffusion respiration, however, may be inadvisable because of possible collapse of the lungs, of accumulation of carbon dioxide to a dangerous level, and because the aid normally given to the circulation by the respiratory movements is lost.

In a recent paper (12) dealing with resuscitation we said that "the most important thing in resuscitation is to begin artificial respiration." The fact that dogs can be resuscitated from an overdose of pentothal sodium by diffusion respiration does not invalidate this statement. On the contrary, to substitute diffusion respiration for artificial respiration in resuscitation would, in our opinion, be a misuse of one of nature's safety factors. A more logical application of this phenomenon would be as an *adjunct* to mechanical ventilation of the lungs. This is done automatically whenever the inhalation of oxygen is combined with arti-

ficial respiration through the use of such apparatus as the H. E. inhalator.

The possible direct application of diffusion respiration to aviation and oxygen therapy are not so immediately apparent, but an understanding of the phenomenon may shed some light upon the physiologic problems involved. For instance, it seems reasonable to assume, although it would be difficult to provide proof, that diffusion respiration supplements mechanical respiration whenever a very high concentration of oxygen is inhaled, and may be responsible, in part, for the benefit obtained from the administration of oxygen.

SUMMARY AND CONCLUSIONS

1. In the dog profoundly anesthetized by pentothal sodium, provided certain conditions are present, an uptake of oxygen sufficient for metabolic requirements continues for a considerable period after respiration has ceased.

2. The requisite conditions are the replacement of the nitrogen in the respiratory tract and surrounding atmosphere by oxygen, an adequate circulation, and a patent airway.

3. The diffusion of oxygen inward is caused by the lowering of its alveolar pressure produced when the reduced hemoglobin in transit through the alveolar capillaries is oxygenated.

4. The force exerted by diffusion respiration is considerable and can be easily measured if the ingress of oxygen into the lungs during respiratory arrest is prevented through seizure of the spirometer bell.

5. Although diffusion of carbon dioxide outward toward the atmosphere may be safely postulated in accordance with the laws governing the kinetics of gases, its escape is relatively slow, and considerable alveolar accumulation occurs.

6. A discussion of certain theoretical considerations and clinical applications of diffusion respiration is included.

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DELAYED MORPHINE POISONING

In recent reports from certain theaters of operations, attention has been directed to occasional cases of morphine poisoning or of dangerous respiratory depression and coma from the sudden absorption of large doses of morphine. This apparently has developed most frequently in wounded patients in shock or with a low blood pressure from other reasons who have been chilled from exposure, and to whom the one-half grain dose of morphine in the syrette has been administered subcutaneously on the battlefield.

Because of the markedly depressed circulatory state, the morphine is not absorbed and no clinical response is observed; consequently, a second dose of morphine frequently is given within a short time. Subsequently, when the patient recovers from shock or, having been taken to a hospital, becomes warm and more normal circulation is established, an excessive amount of morphine is suddenly absorbed, producing the clinical manifestations of overdosage or morphine poisoning and calling for immediate treatment. Prompt diagnosis and treatment are very important. A tourniquet should be placed proximal to the site of injection of the morphine to slow up its absorption. The tourniquet of course should be released from time to time.

The development of this serious and sometimes fatal condition can be avoided by administering the morphine to this type of patient intravenously rather than subcutaneously. The intravenous dose should be given slowly and should rarely exceed one-eighth grain (eight milligrams). The *Bulletin* of the U. S. Army Medical Department, No. 74, March, 1944, p. 5.