HYPERVENTILATION WITH OXYGEN—A POSSIBLE CAUSE OF CEREBRAL HYPOXIA

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The demonstration by Kety and Schmidt that active or passive hyperventilation resulted in decreased cerebral blood flow suggested to us the intriguing possibility that this decreased blood flow might result in cerebral hypoxia even in the presence of increased arterial oxygen saturation. To explore this area we needed a method to measure the actual brain tissue oxygen tension and for this we turned to the oxygen electrode, a brief history and description of which follows.

In 1897 Dammel electrolyzed oxygen in aqueous solution by applying electrical force to platinum electrodes. Cottrell, Grassi, Salomon, and Nernst established the validity of basic laws of electrolysis involved in polarography. However, the first true polarographic instrument was developed by Heyrovsky and Shikata in 1925. This employed the dropping mercury electrode and although this type of instrument is no longer widely used, the basic principle of polarography utilized by this device still applies to the modern oxygen electrode. This principle is that if an anode and cathode are placed in a conductive aqueous solution and a constant voltage is applied, the rate of reduction of a reducible substance dissolved in that solution is directly proportional to the amount of current that flows between the electrodes. Since the rate of reduction is in turn dependent upon the concentration of the substance in question, it then follows that a measure of current would be a measure of the concentration of the substance in solution. Because oxygen is readily and constantly reduced at a voltage of .3 to .8 volts, an electrode system operating in this voltage range would show a current flow proportional to the concentration of oxygen near the electrode. This is illustrated in figure 1. This phenomenon is attributed to the reaction $\text{O}_2 + 2\text{H}_2\text{O} + 2e \rightarrow \text{H}_2\text{O}_2 + 2\text{OH}^-$ (alkaline solution)—Kolthoff and Miller, Kolthoff and Lingane, and Clark.

Baumberger and his co-workers using the dropping mercury electrode did much of the pioneer work in determining polarographically the oxygen tension of whole blood. This work was complicated by the fact that erythrocytes interfered with the diffusion of oxygen to the electrode and the presence of hemoglobin with its oxygen binding properties caused linearity in polarographic determinations, Markus. In spite of these difficulties they were able to obtain good quantitative measurements of oxygen tension in whole blood.

In 1931 Glasstone and Reynolds demonstrated the practicability of the use of platinum wire as a substitute for the mercury cathode in the polarograph and a new era of polarography was born.
Kolthoff further advanced the use of platinum in the polarograph by introducing the rotating platinum electrode. Until the introduction of the bare platinum electrode, it had been possible to do only in vitro oxygen determinations with the bulky dropping mercury electrode but the small platinum electrode made it possible for the first time to obtain in vivo measurements of relative oxygen tension. In 1942 Davies implanted platinum electrodes in cat’s brains and recorded changes in oxygen tension in the mammalian brain for the first time. Later investigators used bare, recessed, coated, and rotating platinum electrodes for measuring blood and tissue oxygen tensions but even after elaborate calibration techniques these electrodes could at best give only semi-quantitative values of oxygen tension for short periods of time. Absolute quantitative measurements of oxygen tension alone were extremely difficult using the electrodes described previously by virtue of the fact that since the electrode was bare, its electrical properties were influenced by other constituents of the tissue being analyzed. As mentioned previously, erythrocytes caused nonlinearity in current flow and in addition it was found that pH, temperature, and electrolyte composition caused variations in recording the oxygen tensions.

In 1953 Clark described a modification of the platinum electrode that was to pave the way for truly quantitative measurement of oxygen tension. This modification was the enclosure of a platinum cathode and a silver anode in various membranes that were impervious to liquids, but which allowed diffusion of gases. By placing a known constant conductive solution such as potassium chloride within the envelope formed by the membrane, it was possible to insulate the electrode from the variables mentioned in the previous paragraph. The variable that could not be ruled out with this instrument was temperature. Fortunately, changes in this modality resulted in linear deviation in the current flow so that absolute measurement could be obtained by calculating the percentage of change caused by variations in temperature. The Clark electrode, as this instrument was called, was used by many workers for analyzing the oxygen tension of various tissues and was modified to some extent by other workers. An excellent review of the types of electrodes with their advantages and disadvantages was given by Connelly in 1957.

The original Clark electrode could be used only in vitro because of its large size. In 1958 Liston of the Beckman Instrument Company succeeded in miniaturizing the electrode to the size of a 20 gauge needle which could be inserted into tissue. A schematic section of this needle can be seen in figure 2. The amplifier for the electrode—the Beckman/Spinco Model 160 contains a thyatron circuit which delivers .6 volts at a rate of 8 pulses per second to the electrode as the polarizing voltage. The current changes due to different concentrations of oxygen are then amplified in an AC amplifier circuit to a level which will operate a direct writing oscillograph. The response time of this instrument is 30–60 seconds.

**METHODS**

Calibration was performed by equilibrating in a tonometer, samples of blood with known
concentrations of oxygen whose tensions had been determined by a Beckman-Pauling oxygen analyzer. The electrode was then inserted into the gas and then into the blood in the tonometer. Little if any variation between the two phases was noted in terms of oxygen tension. Samples of blood in the tonometer were then analyzed for oxygen concentration by the method of Peters and Van Slyke and these values were plotted against those obtained by the electrode. The correlation between the polarograph and the oxygen analyzer was excellent and variations in readings between the two instruments were under 3 mm. for various oxygen concentrations. With due allowances for mathematical errors, the correlation with the Van Slyke values were within 5 mm. oxygen tension.

Homogenized samples of dog brain were inactivated by formalin and equilibrated with oxygen tensions of 80 mm., 150 mm., and 752 mm. Variations between the gas, supernatant liquid and semi-liquid brain tissue phases were found to be in the order of 1/2 to 1 per cent. In all of these calibrations allowances were made for temperature changes. In view of the minor variations between the gas, liquid, and semi-solid phases, it was decided to use only known gas concentrations as the calibrating medium in the experiments that followed.

Dogs were lightly anesthetized with pentobarbital 30 mg. per kilogram, their tracheas intubated, and a femoral artery cannulated with plastic tubing which was then connected to a Statham pressure transducer. Three-fourth inch burr holes were made in the skull overlying a temporal lobe and the dura was carefully excised from the exposed area. Avoiding as much as possible any area with visible blood vessels, a small nick was made in the pia and the electrode was inserted into the cerebral cortex for a length of approximately ½ inch. Since the gray matter of dog brain is approximately 1/8 inch thick, the electrode was inserted parallel to the brain surface to avoid entering the relatively avascular white matter. The electrode could be seen bulging just under the brain surface and it was fairly easy to position the tip so that it was not close to a visible blood vessel. Caution was exercised so that there was minimal blood loss during the operative procedure. The electrode was firmly clamped in place and its output recorded on one channel of a direct writing oscillograph (Offner-Model RMS). Other channels recorded arterial pressures as measured by the Statham strain gauge and the alveolar carbon dioxide concentration as measured by a Liston-Becker Model 16 carbon dioxide analyzer using microcatheter sampling from the endotracheal tube. Hyperventilation at approximately 15 liters per minute was obtained by the use of a piston type pump or the Stephenson Controlled Respiration Unit with a non-rebreathing (Ruben) valve.

Base line recordings were taken of cerebral \( P_{O_2} \), alveolar \( CO_2 \) and arterial pressure in the anesthetized dog spontaneously breathing room air. Oxygen was then given through a non-rebreathing valve and changes in all modalities were recorded. Breathing of room air was then resumed. The dogs hungs were then hyperventilated with room air, then room air with approximately 10 per cent \( CO_2 \), then room air only. After discontinuing hyperventilation the animal was allowed to resume spontaneous respiration. The above pattern of hyperventilation was repeated using 100 per cent oxygen, then a 90 per cent oxygen–10 per cent \( CO_2 \) mixture, followed by 100 per cent oxygen again. After this the animal resumed

![Fig. 3. A three section photograph of recordings taken during hyperventilation with room air and 5 per cent carbon dioxide.](image-url)
spontaneous respiration on room air. Continuous recordings of the three above mentioned modalities were obtained during this time. These procedures were performed on 8 animals. In one animal, recordings were made of hyperventilation with approximately 5 per cent \( \text{CO}_2 \) in room air immediately following base line recordings during spontaneous respiration.

**RESULTS**

The animal last mentioned whose lungs were hyperventilated with 5 per cent \( \text{CO}_2 \) and room air following spontaneous breathing on room air showed a gradual but marked increase in cerebral \( P_{O_2} \) from 20 mm. to 45 mm. of mercury (fig. 3). The return to normal was prolonged although due allowance must be made for the lag time which is in the order of 30 to 60 seconds in the oxygen electrode system. Figure 4 illustrates the 90 per cent rise in cerebral \( P_{O_2} \) (10 mm. to 18 mm. Hg) when oxygen was given to the spontaneously breathing animal.

The return to base line values when the oxygen is removed is quite apparent.

When the experimental animals' lungs were hyperventilated on room air alone, the cerebral oxygen tension dropped (fig. 5). The magnitude of this drop was usually in the neighborhood of 50 per cent (8 mm. to 3 mm. Hg) and this low value persisted so long as hyperventilation was continued for 5-10 minutes. The addition of approximately 10 per cent carbon dioxide to the inspired air resulted in a marked rise in oxygen tension (3 mm. to 50 mm. Hg) (fig. 5). Discontinuing the carbon dioxide while maintaining hyperventilation with room air resulted in a drop to 3 mm. \( P_{O_2} \). When the dog was allowed to resume spontaneous respiration on room air, the oxygen tension returned to baseline values within a few minutes. The results of hyperventilation with 100 per cent oxygen following spontaneous respiration on room air can be seen in figure 6. Following an occasional initial rise, the drop in cerebral \( P_{O_2} \) (8 mm. to 3 mm. Hg) was certainly as marked

**Fig. 4.** An illustration of the rise that occurs in cerebral oxygen tension when the spontaneously breathing animal is allowed to breathe 100 per cent oxygen.

**Fig. 5.** The results of hyperventilation of the animal with room air and the changes that occur when 10 per cent carbon dioxide is added to the room air.
as the drop which occurred when ambient air was used for hyperventilation. However, it can be seen that the use of a 10 per cent carbon dioxide–90 per cent oxygen mixture in the inspired gases (fig. 6) resulted in a dramatic rise of cerebral oxygen tension to 100 mm. of mercury in spite of continuing hyperventilation. Again discontinuing carbon dioxide and returning to 100 per cent oxygen in inspired air resulted in a drop of cerebral \( P_{O_2} \) to its previous low level while hyperventilation was continued. In the experiments where 100 per cent oxygen was used, the dogs remained apneic for a much more prolonged period after the pump had been turned off than in cases where room air was used. In both types of experiments however, we noted that even with apnea the cerebral oxygen tension rose to fairly normal levels after hyperventilation had been discontinued and before spontaneous respirations were resumed.

The changes seen in alveolar carbon dioxide levels in figures 3, 5, and 6 are self explanatory. There is good correlation between drop in alveolar \( CO_2 \) and brain \( P_{O_2} \) in these recordings.

Changes in blood pressure did not correlate with changes in cerebral oxygen except at the start of hyperventilation where there was usually a transitory drop in blood pressure probably due to the positive pressure exerted by the pump. However, with hyperventilation using room air or oxygen only, the cerebral oxygen continues to drop or stays at a low level while the blood pressure usually returns close to its normal level.

**Discussion**

Perhaps the first question that arises in discussing the results of these experiments is whether the \( P_{O_2} \) measurements are absolute indicators of the exact oxygen tension of cerebral tissue. The multitude of factors that enter into the determination of tissue oxygen tension, some of which were outlined by Kety, makes this a difficult question to answer precisely. We have observed an abrupt rise in oxygen tension with the electrode placed near a vein or artery and the proximity of the tip to a hidden vessel when it is inserted into the cortex is a matter of conjecture. In these studies, if the electrode was placed so that the basal \( P_{O_2} \) reading was 30–50 mm., and hyperventilation with air or oxygen showed a rise in \( P_{O_2} \), this indicated that the \( P_{O_2} \) of the blood rather than tissue was being measured. Accordingly the criterion for proper electrode placement was the finding of an initial \( P_{O_2} \) of 8 to 20 mm. and a decrease in this value in response to hyperventilation. Bronk also observed the importance of the proximity of a vessel to the electrode in determining the oxygen tension of the cerebral cortex.

In view of the known importance of the diffusion factor of oxygen through tissue, it might be asked if diffusion was great enough to insure accurate tissue measurement. The
answer to this lies perhaps in the fact that, first, the oxygen consumption and current flow \((3 \times 10^{-10} \text{ amperes})\) of a microelectrode such as we used is much less than that of a larger electrode \((2 \times 10^{-7} \text{ amperes})\). Secondly if the electrode is inserted and the animal is undisturbed there is no decline in \(P_{O_2}\) readings over a period of 10 to 15 minutes. These reasons support the belief that whatever oxygen is consumed by the electrode is replaced by sufficient diffusion to insure a steady state.

The values of cerebral \(P_{O_2}\) found by us are supported by the findings of Davies \(^{38}\) who used recessed platinum electrodes in mammalian brain.

Cerebral blood flow, measured by the method of Kety and Schmidt \(^{39}\) diminishes with active or passive hyperventilation. This has been demonstrated by the above authors.\(^1\) \(^{10}\) Whether this diminution in blood flow is great enough to cause cerebral hypoxia has been questioned previously by Mallette \(^{41}\) \(^{42}\) who seems to believe that a great deal of the possible hypoxia is caused by the Bohr effect \(^{43}\) with its shift of the oxygen dissociation curve to the left. Although Clark \(^{44}\) observed that hyperventilation caused a drop in \(P_{O_2}\) and both he and Furlong \(^{45}\) observed a rise in \(P_{O_2}\) with the addition of 5 to 15 per cent \(CO_2\) to the inspired air, the values noted were not quantitative.

The measurements we obtained were, we believe, close to absolute values, and as such indicate that cerebral hypoxia is indeed induced probably as a result of diminished blood flow due to cerebral vasoconstriction caused by the hypocapnia that results from hyperventilation. That this cerebral vaso-constriction is a result of diminished carbon dioxide due to hyperventilation and not the action of increased oxygen tension has been demonstrated by Lamberty and associates.\(^{16}\) In addition to causing cerebral vaso-constriction it has been demonstrated that hyperventilation and hypocapnia can also cause changes in plasma cations,\(^{47}\) diminished cardiac output and mental deterioration,\(^{48}\) electrocardiographic changes \(^{49}\) \(^{50}\) and change the activation threshold of human nerves.\(^{51}\) Hyperventilation is also said to cause changes in central venous pressure with a rise in catechol amines.\(^{52}\) Change the blood flow of extremities \(^{53}\) and decrease urea clearance with possible harmful effects to the kidneys.\(^{54}\) Electroencephalographic changes consisting mainly of the appearance of slow delta waves with hyperventilation have been noted.\(^{55}\) \(^{56}\) \(^{57}\) Morrice \(^{58}\) showed that these electroencephalographic changes could be reversed by the addition of \(CO_2\) to the inspired air. Darrow \(^{59}\) observed photometrically through a cranial window in a cat’s skull, the blanching of pial vessels indicating vasoconstriction when the animal was hyperventilated and flushing of the vessels indicating vasodilation when carbon dioxide was given. Direct observation of the diminution of pial vessel size with hyperventilation and dilatation with the addition of \(CO_2\) to the inspired air has been noted.\(^{60}\) \(^{61}\)

Dundee \(^{62}\) has showed that lower concentrations of anesthetic agents could be used when hyperventilation was used. Explanations for this phenomenon range from the action of carbon dioxide on the reticular activating system \(^{63}\) \(^{64}\) to diminution of the respiratory center activity by the low \(P_{CO_2}\) \(^{62}\) to cerebral hypoxia.\(^{65}\) Whether the above effects of hypoxacapnia and our findings that the cortical \(P_{O_2}\) drops about 50 per cent with hyperventilation with 100 per cent oxygen can cause transient or permanent damage to the brain and other organ systems is a question that cannot be readily answered. However, if the human brain shows changes similar to those found in the dog, perhaps a re-evaluation of the use of hyperventilation with normal or high oxygen content gases in anesthesia and resuscitation is warranted.

**Summary**

The question is raised whether hyperventilation can cause cerebral hypoxia as a result of diminished cerebral blood flow which is in turn caused by hypoxacapnia. A brief history of the development of and the description of the oxygen electrode used to measure cerebral oxygen tension is given. The method used was a direct quantitative measurement of cerebral \(P_{O_2}\) in the anesthetized dog during spontaneous respiration and during hyperventilation. The results are as follow: (1) A 90 per cent rise in cerebral \(P_{O_2}\) with the inspiration of
pure oxygen by the spontaneously breathing dog. (2) A marked drop in cerebral oxygen tension from a normal of 8–15 mm. to 3–5 mm. of mercury as a result of hyperventilation, whether with room air or 100 per cent oxygen. (3) An excellent correlation between low alveolar carbon dioxide and a low cerebral P\textsubscript{O\textsubscript{2}}. (4) A dramatic rise in cerebral oxygen tension content when CO\textsubscript{2} is added to the inspired gases during hyperventilation and the prompt fall to low levels when the CO\textsubscript{2} is removed.

The effects of hyperventilation on the brain, heart and other organ systems are discussed. The conclusion is drawn that cerebral hypoxia may be caused by hyperventilation in the dog and that if this is true in the human, perhaps the use of hyperventilation in anesthesia and resuscitation may be harmful.

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REFERENCES


ANESTHETICS AND HYPOTHERMIA
The mean lethal temperature for anesthetized dogs subjected to cold-water immersion is influenced by the specific preinduction anesthetic, the degree of respiratory assistance during the course of cooling and the anesthetic agent. Pentobarbital is associated with a higher LT50 than thiopental or ether. Hypercapnea increased the frequency of ventricular fibrillation. Fragmentary reports in man suggest that the LT50 of unanesthetized man is 27 C. (Hegnauer, A. H.: Lethal Hypothermic Temperatures for Dog and Man, Ann. New York Acad. Sc. 80: 315 (Sept. 14) 1959.)

VENTRICULAR FIBRILLATION A large series of unrelated pharmacologic agents were tested as to their ability to protect the dog heart from ventricular fibrillation during hypothermia. Drugs included antiarrhythmics (quinidine and procaine amide), antihistaminics, antimalarials, local anesthetics, and miscellaneous drugs. Quinidine was found to effectively protect against hypothermic ventricular fibrillation whereas procaine amide did not. The majority of the effective compounds were antihistaminics. (Angelakos, E. T., and Hegnauer, A. H.: Pharmacological Agents for Control of Spontaneous Ventricular Fibrillation under Progressive Hypothermia. J. Pharmacol. & Exper. Therap. 127: 137 (Oct.) 1959.)

HYPOTHERMIA Of 18 children admitted with decerebrate rigidity due to head injury and subjected to hypothermia to 30 to 32 C., ten survived. A follow-up of from twenty-two to six months showed one patient with gross intellectual impairment (an intelligence quotient of sixty five), 4 completely recovered, and others showed varying motor involvement. There were no vegetative or institutional care patients among the survivors. (Heedrick, E. B.: Use of Hypothermia in Severe Head Injuries in Childhood. A. M. A. Arch. Surg. 79: 362 (Sept.) 1959.)

VENTRICULAR FIBRILLATION The effects of hypothermia and hyperthermia upon ventricular fibrillation threshold have been likewise tested in dogs and monkeys. The effect of coronary occlusion on the threshold was likewise tested. The heart was exposed, the electrocardiograph recorded on one oscilloscope and a second oscilloscope recorded the magnitude in milliamperes of the stimulating current delivered. The fibrillation test shown for any given animal was remarkably constant. Coronary occlusion decreased the threshold in the area of the infarct. Hyperthermia (40 C.) markedly elevated the fibrillation threshold. Rapidity of cooling seemed to have no influence. (Phibbs, C. M., Levy, L. M., and MacLean, L. D.: Influence of Temperature and Coronary Occlusion on Ventricular Fibrillation Threshold, Surg. Gynec. & Obst. 109: 216 (Aug.) 1959.)