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Oxygen Tension of the Brain and its Modification with Hypothermia*

An Experimental Study

By

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With 8 Figures in the Text

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Although considerable attention has been directed towards the elucidation of the patho-physiologic factors observed when the body temperature is lowered, there has been a relative paucity of investigation in the area of tissue oxygen tension. The lack of such information is understandable, in view of the difficulties imposed by a direct approach, and the inherent inaccuracies of an indirect approach.

Previous investigations in our laboratory on animals and humans have indicated that continuous quantitative oxygen tension measurements of the cisternal or ventricular cerebrospinal fluid could be easily accomplished using a platinum microelectrode. Furthermore, it was observed that the oxygen tension of the cerebrospinal fluid quickly reflected changes in arterial pO_2, cerebral blood flow, and cerebral metabolism[1]. Since the cerebrospinal fluid appeared to be in dynamic equilibrium with the brain and its circulation, it was thought that some advance in the knowledge of the oxygen tension changes of the central nervous system, during hypothermia, might accrue from the application of this technique.

Methods

Experiments were performed on 31 mongrel dogs, weighing an average of 13.8 kg. A total perfusion pump oxygenator technique was used to minimize the variable of cardiac output so that temperatures down to 10° C could be more easily explored. To decrease the effects of anesthesia on cerebral metabolism and normal vasomotor activity, the animals were intubated under light thiamylal sodium (Surital) anesthesia. During the period of preparation, the animals were immobilized with intramuscular succinyl choline and mechanically respirated.

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Using local anesthesia, the right thorax was opened through the fourth interspace and a 40 plastic catheter was inserted into the right atrium. The main pulmonary artery was encircled with a ligature to institute complete cardiopulmonary by-pass. The left atrium was decompressed with a catheter, which was drained by gravity into the venous reservoir. The Clowes membrane oxygenator[4] was used for the majority of these experiments and the temperature of the blood was controlled with a Brown-Emmons heat exchanger[2] interposed in the arterial line.

The sagittal sinus, internal carotid and femoral arteries were cannulated. The following parameters were measured continuously: quantitative cerebrospinal fluid oxygen tension via cisternal puncture with a Beckman platinum microelectrode, blood pressure, central venous pressure, esophageal temperature, brain temperature, EKG, and EEG. Arterial and sagittal sinus pO_2's were for the most part obtained by sampling. The sample oxygen tension determinations were made in an electrode-cuvette system which was thermostated to the animal's temperature within 0.2 of a degree centigrade. The oxygen electrodes were calibrated at the appropriate temperatures. Total cerebral blood flow determinations were made utilizing the Stewart principal[6,7]. Indocyanine green dye, 0.5 mgs, was injected into the internal carotid artery, and sagittal sinus concentration curves were obtained with a Water's densitometer by withdrawing blood at a constant rate. Observations were made on the effects of perfusion rates and total circulatory arrest at temperatures ranging from 37° to 10° C. Sufficient time was allowed at each temperature level so that no temperature gradient existed between brain and esophagus.

Results

The relationship of parameters studied to decreasing temperatures (Fig. 1): The data from 82 observations, when expressed as percent change from control value, revealed that all parameters, except the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and the arterial oxygen content, shift with decreasing temperature in such a direction that one might anticipate a lowering of the ambient partial pressure of oxygen in the brain. The arterial oxygen content remained essentially unchanged from 37° C to 10° C and averaged 18.6 Vol-%. The blood pressure fell to 68% of the control value. The sagittal sinus oxygen tension fell from 37.7 mm Hg to 17.3 mm Hg or to 46% of its initial value. A fall from 4.38 cm_3/min to 0.472 cm_3/min at 10° C was seen in the total cerebral oxygen consumption ($CMRO_2$), or to approximately 10% of its 37° C control value.

Relationship of sagittal sinus oxygen content (SSO_2) and sagittal sinus pO_2 ($SSpO_2$) to decreasing temperature (Fig. 2): The average of 111 observations of the SSO_2 content rose progressively—as the temperature decreased—from 8.6 Vol-% at 37° C to 18.5 Vol-% at 10° C, an increase of 186%. Concomitantly the cerebral venous oxygen tension fell from 37.7 mm Hg to 17 mm Hg, a fall of 54%. The pO_2 values at each temperature agree rather closely with the shift to the left of the oxygen dissociation curve of dogs' blood reported by Brown and Hill[3].

Effect of hypothermia on cerebral blood flow (CBF) regulatory mechanisms (Fig. 3): Sixteen observations were made on the effect of

decreasing the total perfusion. When the perfusion rate was decreased by 50% at normal body temperatures, the CBF fell to 62% of the control value. However, when the body temperature was lowered to below 20° C,

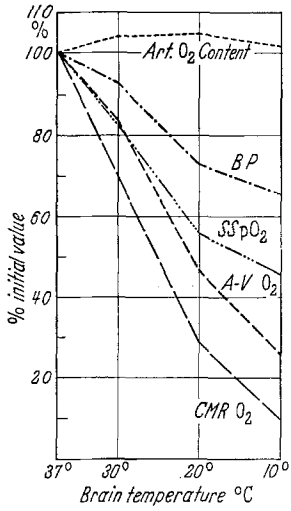

Fig. 1

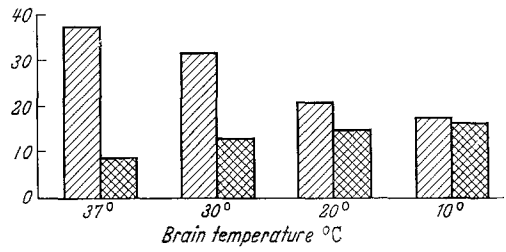

Fig. 2

Fig. 1. The data from 82 observations are expressed in percent change from control values with decreasing temperature. The arterial oxygen content remained essentially unchanged. The mean arterial pressure fell to 68% of the control value. At 10° C the sagittal sinus oxygen tension fell to 46% of its initial value, and the arterial-sagittal sinus difference fell to 26%. The oxygen uptake ($CMRO_2$) of the brain fell to approximately 10% of its 37° C value

Fig. 2. As the temperature decreases the cerebral venous oxygen content increases, but the pO_2 falls in accordance with the leftward shift of the oxyhemoglobin dissociation curve. ▨ Sagittal sinus pO_2 (mm Hg); ▩ Sagittal sinus content (Vol-%)

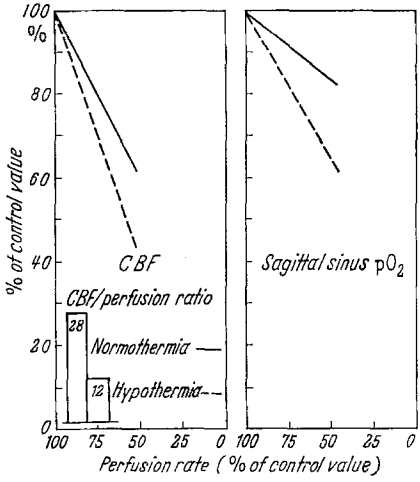

Fig. 3

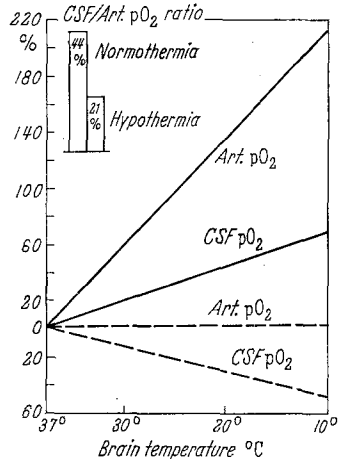

Fig. 4

Fig. 3. The percent fall in CBF and $SSpO_2$ is shown when the perfusion rate was decreased 50% during normothermia (solid line) and hypothermia (broken line). The effect is significantly greater ($P < 0.1$) in the hyperthermic state, and the CBF/perfusion ratio decreases, indicating abrogation of the regulatory mechanisms controlling CBF

Fig. 4. When the arterial pO_2 rises consequent to reduced oxygen consumption in the cold state, a concomitant rise is noted in the CSF pO_2. When the arterial pO_2 is held constant, a progressive fall in CSF pO_2 is seen as the temperature is lowered. The decrease in CSF/arterial pO_2 ratio from 44% at 37° C to 21% at 10° C further indicates the decreased transfer of oxygen from the blood to the brain during hypothermia

the cerebral blood flow fell significantly to 43% of the control value ($P< 5\%$). A similar disparity was observed in the SSpO_2 fall between the normothermic and hypothermic preparation when the perfusion rate

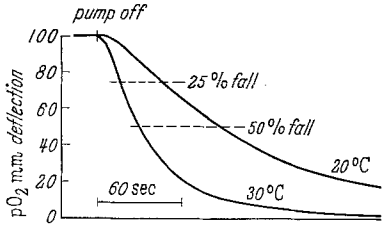

Fig. 5. Typical curve at 30° C and 20° C observed when the CSF pO_2 is continuously monitored during circulatory arrest. The rate of pO_2 fall (oxygen consumption) is directly related to the temperature

Fig. 6. The time for a 25% fall in CSF pO_2 during circulatory arrest plotted against temperature demonstrates an exponential relationship. The oxygen consumption is decreased sevenfold between 37° C and 10° C

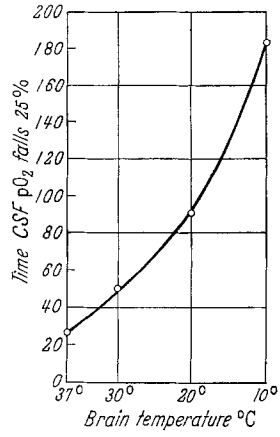

Fig. 6

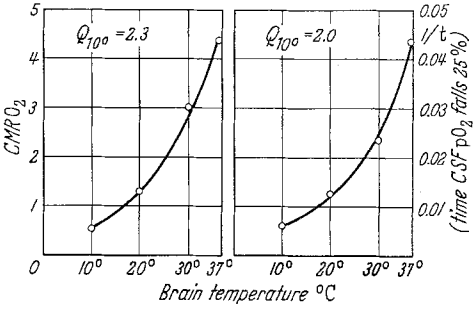

Fig. 7

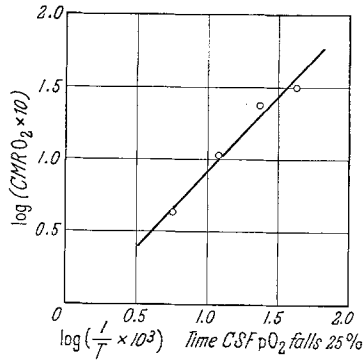

Fig. 8

Fig. 7. A comparison of temperature effect on $CMRO_2$ and oxygen consumption as measured by rate of fall of CSF pO_2 during circulatory arrest, yields similar curves (see text)

Fig. 8. The logs of the $CMRO_2$ at each temperature are plotted against the logs of the CSF pO_2 25% fall time. The resultant straight line indicates a direct relationship. (F value = 87.42, $P < 0.05$

was halved. At 37° C the sagittal sinus pO_2 fell to 82% of the control value (18% decrease); at temperatures below 20° C, the average fall was to 60% (40% decrease). When the CBF/perfusion ratio was considered, again a striking difference was seen. An average of 28% of the perfused blood was diverted to the brain in the normothermic animal; at hypothermic levels the ratio fell to 12%. These data indicate abrogation of the regulatory mechanisms controlling CBF by reduced temperatures.

Effect of hypothermia on cisternal cerebrospinal fluid (CSF) oxygen tension (Fig. 4): In the normal course of the experiments the arterial pO_2 rose approximately 220% as the total oxygen uptake of the animals fell consequent to cooling. The concomitant rise in the CSF pO_2 was 70%. However, when the arterial pO_2 was held relatively constant, the oxygen tension of the CSF fell 46% at hypothermic levels. The CSF/arterial pO_2 ratio fell from a control value of 44% at 37° C to 21% at 10° C, indicating a decreased oxygen transfer from the blood to the CSF.

Effect of temperature on CSF pO_2 during circulatory arrest: Following circulatory arrest the rate fall or utilization was found to be related to the temperature. It may be noted in Fig. 5 that at a temperature of 30° C the cisternal oxygen tension fell 25% in 17 sec and 50% in 31 sec. This is to be compared with the 20° C curve where it took 46 sec to fall 25% and 88 sec to fall 50%. In this instance a 10° decrease in brain temperature increased the time for an equivalent pO_2 fall by 280%. The 25% pO_2 fall time (41 observations) when plotted against temperature (Fig. 6) revealed that as the temperature decreased, the time for equal decrements in oxygen tension increased in an exponential fashion. Conversely, the consumption or disappearance rate of oxygen is decreased approximately sevenfold between 37° C and 10° C.

Comparison of temperature effect on $CMRO_2$ and CSF pO_2: The total cerebral metabolic rate of oxygen consumption, calculated from 74 observations of the total CBF and A-V oxygen difference, fell exponentially as the brain temperature was decreased (Fig. 7). When the reciprocal of the 25% fall time of the cisternal pO_2, during circulatory arrest, was plotted as a function of the temperature, a similar curve resulted (Fig. 7). When the logs of these data were graphed as a function of centigrade temperature, linear plots were produced and from these the slopes of the curves were calculated. The value of the van't Hoff coefficient Q_{10}, is given by the slope over a 10° interval. The Q_{10} for the $CMRO_2$ was 2.3 and that for the rate of fall of CSF oxygen consumption was 2.0. These are in close agreement with the Q_{10} value of approximately 2.13 found in excised mammalian brain reported by FIELD et al.[5]

If one postulates that the CSF pO_2 is in equilibrium with the brain, then one would anticipate that the rate of disappearance of oxygen from the CSF, during circulatory arrest, would vary directly with the reduction of the cerebral metabolic rate. A straight line results when the log of the $CMRO_2$ at each temperature is plotted against the log of the reciprocal of the time it takes the CSF pO_2 to fall 25% during circulatory arrest; this demonstrates that a direct relationship between the $CMRO_2$ and the CSF pO_2 does exist (Fig. 8).

Summary and conclusions

1. At 10° C the cerebral A-V oxygen difference fell to 26% of its control value, and the cerebral metabolic rate fell to 10%. The sagittal sinus pO_2 fell to 46%, an amount which correlates well with the leftward shift of the oxygen dissociation curve. The cisternal cerebrospinal fluid pO_2 fell 46% when the arterial oxygen tension was constant, and the CSF/arterial pO_2 ratio fell an average of 52% at 10° C.

2. When the perfusion rate was decreased 50% at both normothermic and hypothermic levels the cerebral blood flow and sagittal sinus pO_2 both fell significantly more in the cold state. This would indicate an abrogation of the regulatory mechanisms by hypothermia.

3. All factors studied, except the cerebral metabolic rate, shift in such a direction that one would anticipate a lowering of the ambient partial pressure of oxygen in the brain.

4. Oxygen consumption of the brain, as measured by the decrement in the cerebrospinal fluid pO_2 during circulatory arrest, appears to be clearly related to the cerebral metabolic rate. This is interpreted as indicating that the CSF oxygen tension is in equilibrium with the brain, and that its measurement may prove useful in determining the time that circulatory arrest may be safely employed.

Zusammenfassung

In Versuchen an Hunden mit künstlicher Durchblutung wurden die Veränderungen der Kreislaufgrößen und des partiellen Sauerstoffdrucks (pO_2) im arteriellen und venösen Blut sowie im zisternalen Liquor bei verschiedenen Perfusionsraten und Körpertemperaturen zwischen 37° und 10° C gemessen. Zur Messung des zisternalen O_2-Gehalts wurde eine kleine Beckmannsche Platin-Mikroelektrode verwendet, die auf die verschiedenen angewandten Temperaturen geeicht war.

Folgende Veränderungen wurden festgestellt:

1. Bei 10° C fiel die cerebrale A.-V.-Sauerstoffdifferenz auf 26% und die cerebrale Stoffwechselrate auf 10% ihrer Kontrollwerte. Der Sauerstoffdruck im Sinus sagittalis fiel auf 46%. Dieser Wert korreliert gut mit der Linksverschiebung der Sauerstoffdissoziationskurve. Das pO_2 im zisternalen Liquor fiel auf 46%, während der arterielle Sauerstoffdruck konstant war, und der pO_2-Quotient von Liquor und arteriellem Blut fiel bei 10° C im Durchschnitt auf 52%.

2. Wenn die Perfusionsrate um 50% vermindert wurde, sanken sowohl die cerebrale Durchblutung als auch das pO_2 im Sinus sagittalis signifikant stärker bei hypothermem als bei normothermem Zustand. Dies spricht für ein Versagen der Regulationsmechanismen bei Hypothermie.

3. Alle untersuchten Größen, außer der cerebralen Stoffwechselrate, wurden in einer Richtung verändert, die eine Verminderung des ambienten Partialsauerstoffdruckes im Gehirn annehmen läßt.

4. Der cerebrale Sauerstoffverbrauch steht, gemessen an der Abnahme des pO_2 im Liquor bei Unterbrechung des Kreislaufs in direkter Beziehung zur cerebralen Stoffwechselrate. Es wird gefolgert, daß der Sauerstoffdruck des Liquors im Gleichgewicht mit dem Hirngewebe steht und daß die Messung des pO_2 im Liquor geeignet ist, die Zeitspanne zu bestimmen, während der eine Unterbrechung des Kreislaufs ohne Schaden vorgenommen werden kann.

Bibliography

[1] BLOOR, B. M., J. FRICKER, F. R. HELLINGER, H. NISHIOKA and J. J. MCCUTCHEN: A study of cerebrospinal fluid oxygen tension. Arch. Neurol. (Chic.) **4**, 37—46 (1961).

[2] BROWN, I. W., jr., W. W. SMITH, W. G. YOUNG jr. and W. C. SEALY: Experimental and clinical studies of controlled hypothermia rapidly produced and corrected by a blood heat exchanger during extracorporeal circulation. J. thorac. Surg. **36**, 497—505 (1958).

[3] BROWN, W. E. L., and A. V. HILL: The oxygen-dissociation curve of blood and its thermodynamical basis. Proc. roy. Soc. B **94**, 297—334 (1922/23).

[4] CLOWES, G. H. A., jr., and W. E. NEVILLE: The membrane oxygenator, in extra-corporeal circulation, p. 81. Springfield, Ill.: Ch. C. Thomas 1958.

[5] FIELD, J., F. A. FUHRMAN and A. W. MARTIN: Effect of temperature on the oxygen consumption of brain tissue. J. Neurophysiol. **7**, 117—126 (1944).

[6] FOX, I. J., and E. H. WOOD: Medical Physics, Vol. 3, p. 155—178. Yearbook 1960. Ed. Glasser, O.

[7] MEIER, P., and K. L. ZIERLER: On the theory of the indicator-dilution method for measurement of blood flow and volume. J. appl. Physiol. **6**, 731—744 (1954).

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