CIRCUMVENTION OF ANOXIA DURING ARREST OF CEREBRAL CIRCULATION FOR INTRACRANIAL SURGERY

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Comparison of Shunts and of Local and Systemic Hypothermia. Effect of Hypothermia on Cerebral Metabolic Rate and Cerebral Tolerance to Anoxia. Vascular lesions of the brain could be treated more adequately if the blood supply to the affected area were occluded or at least diminished. This necessitates supplying the brain distal to the lesion with arterial blood or protecting it from anoxia. In searching for a method to facilitate the neurosurgical approach to these lesions of the brain, we first tried in dogs various kinds of polyethylene shunts and perfusion pumps to deliver arterial blood to the brain distal to points of occlusion of its trunk arteries. The disadvantages proved so great that we moved to a study in dogs of hypothermia, which we now consider the method of choice.

Since Bigelow2-4 first suggested the use of hypothermia for cardiac surgery there has been an ever increasing interest in this field. Bigelow, Lewis and Taufic17 and Swan et al.18 have demonstrated conclusively the protection it affords both the heart and the brain during circulatory arrest.

POLYETHYLENE SHUNTS AND PERFUSION PUMPS

Polyethylene shunts varying from 0.5 to 2.0 mm. in diameter were used. In order to test them easily, the superficial femoral artery was occluded by a bulldog clamp and the artery was cannulated above and below the point of occlusion with this polyethylene tubing. The occurrence of thrombosis in all preparations was the prime factor in the failure of these shunts. The time interval before thrombosis occurred usually varied between 5 and 10 min.; only an occasional shunt lasted longer. Unless a flow meter is available for continuous observation of blood flow, the occurrence and site of thrombosis in the shunt are not detectable and represent a great danger and inconvenience. It was proposed to use these shunts for lesions of the middle cerebral artery. The external carotid artery was cannulated with polyethylene tubing and the shunt was then carried externally around the head and inserted into one of the branches of the middle cerebral artery. We found, however, that it was impossible to cannulate the cerebral vessels with a mere tip of polyethylene, and so mounted a #22 needle, which had been especially ground on its outside diameter, on the end of the polyethylene shunt. The needle on this end even though siliconed acts as a nidus for thrombosis. These small shunts deliver only a small amount of blood, and they are very difficult to maintain in place.

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CIRCUMVENTION OF CEREBRAL ANOXIA

It was decided to increase the pressure of the blood in order to increase the rate of circulation. A simple perfusion pump was built to do this. It consisted of two 500 cc. bottles arranged in such a way that the arterial blood could flow into one bottle (from a cannula in the carotid) while arterial blood previously collected could be forced into the cerebral artery by oxygen pressure delivered to the bottle that was perfusing the blood (Fig. 2). The cannula receiving the blood from the animal had a double barrel, so that citrate could be mixed with the blood as it entered the pump.

By this method we were able to perfuse the area of brain that had its blood supply isolated, but it was very difficult to insert a cannula in the small branches of the middle cerebral artery and even harder to maintain it in place, for the slightest movement resulted in tearing of the small branch out of its bed. We, therefore, concluded that the above methods present three disadvantages, in that:

1) The use of anticoagulants is contraindicated during neurosurgical procedures.

2) The preparation of the extracorporeal circulation becomes an operation in itself before a lengthy neurosurgical operation is embarked upon.

3) The large blood vessels of the brain do not have sufficient collateral circulation to allow them to be sacrificed for cannulation. Therefore, it is necessary to cannulate a small cerebral artery. This reduces the quantity of blood that can be perfused through the isolated portion of the brain. These small vessels are very delicate and it is difficult to maintain the cannula in place. For the above reasons we have given up these approaches for the simpler and more feasible one of hypothermia.

HYPOTHERMIA

Prior to a discussion of the advantages of hypothermia, it is essential to be aware of its dangers and disadvantages. The primary dangers of hypothermia are ventricular fibrillation and cardiac failure. As a part of this investigation, studies of the cardiac output, mean femoral and pulmonary arterial pressures, and mean right and left auricular pressures were done, from which calculations of the total pulmonary and peripheral resistance and the right and left ventricular stroke works were made. The electrocardiogram was recorded at sampling intervals. These findings will be reported separately. It is sufficient to state here that ventricular fibrillation did not occur in this series of dogs at temperatures above 25°C. (excluding local hypothermia). Below 25°C. there were 3 dogs out of 15 that died from fibrillation. Our findings agree with those of Clark8 and Starling et al.18, 21, 22

The latter said:

"... the minimum temperature at which the mammalian heart can beat against what may be called an average resistance varies between 23° and 26°C. As the heart is gradually cooled, when the critical temperature is reached, it suddenly dilates, the output diminishes rapidly, and unless the arterial resistance is relaxed and the blood warmed quickly, the heart ceases to beat, often going into fibrillary
contraction. . . In the case of a heart embarrassed by a cardiometer, the critical
temperature was 26°C. In other cases, it was as low as 23°C. When the arterial
pressure is relaxed as the heart is cooled, it may go on beating more and more slowly
and fully until a lower temperature is reached . . . flow through the coronary vessels
varied very little with alteration in the temperature, being somewhat greater at a
low temperature (below 28°C). In view of the extreme susceptibility of the coronary
vessels to locally produced metabolites, it seems possible that this dilatation at
low temperatures may be due to a slowing of the process of oxidation. Partially
oxidized metabolites may escape the cells and exert a dilating influence on the
coronary vessels.

It is thus realized from Starling’s observations that ventricular fibrillation
may signify a terminal event in cardiac failure occurring at tempera-
tures below 25°C. Ventricular fibrillation at this low temperature occurs at a
time when the contractility of the ventricle is diminished, and after de-
fibrillatory procedures, ventricular contractions may not resume.

In addition to the above-mentioned mechanism, ventricular fibrillation
has been reported to occur during cooling or rewarming at temperatures
higher than those required to limit effective ventricular contractility. The
factors responsible have not been clarified. Hegnauer et al. have shown
that fatal ventricular arrhythmias from intraventricular catheters occur in
80 to 85 per cent of cooled animals. Hoff and Stansfield reported that cool-
ing of one portion of the ventricle makes the heart susceptible to fibrillation
by a single shock applied anywhere in the non-cooled portion of the ventricle.
Swan et al. as well as Brown, Miller et al. have indicated that sudden
changes in pH and carbon-dioxide tension with changes in the serum potas-
sium may precipitate ventricular fibrillation. Wégria et al. have dem-
strated that slowing of the heart rate per se with consequent increase in
the relative refractory period will render the heart more susceptible to
arrhythmias from ectopic ventricular foci. Patterson, Piper and Starling emphasized
that the rate of the beat of the isolated mammalian heart is
directly proportional to the temperature. Clark has shown that vagal
stimulation in the frog results in more prolonged asystole at 18°C. than at
28 to 35°C. The effects of vagal stimulation may be potentiated and pro-
longed by a decrease in the blood pH, as demonstrated by Campbell et al., and have been attributed to a decrease in cholinesterase activity at low
blood pH. Cholinesterase activity decreases in vitro with lowering of the
temperature. Specific information is not available in the intact cooled animal
to quantitate the possible role that acetylcholine may play in the slowing of
the heart rate or in occurrence of ventricular arrhythmias.

Although the mechanism or mechanisms of ventricular fibrillation during
hypothermia are not clearly defined, it is believed at present that reduction
in the body temperature should ideally not exceed 25°C., a temperature that
allows the maximum reduction in the cerebral metabolic rate with minimum
reduction in the ventricular contractile force.

Fibrillation presents more of a problem to the cardiac surgeon than to the
neurosurgeon because the cold heart is more susceptible than a warm one to the stimulation that must occur during cardiac surgery. It seemed reasonable that two methods of approach to hypothermia were available: (1) Local hypothermia of the brain or (2) systemic hypothermia. It was reasoned that local hypothermia would eliminate the problem of fibrillation.

**LOCAL HYPOTHERMIA**

*Method* (Figs. 1 and 2). Dogs weighing 11–17 kg. were anaesthetized with pentobarbital sodium (30 mg./kg.). Through a thyroid incision the blood supply to the head was isolated, except for the anterior spinal arteries. The external carotid arteries were ligated. A perfusion pump was then connected with the proximal and distal segments of one carotid artery. The pump consists of two 500 cc. bottles arranged in such a way that the arterial blood can flow into one bottle (from the cannula in the carotid) while arterial blood previously collected (in the second bottle) may be forced out into the cephalad cannula by oxygen pressure. The blood leaving the pump was passed through an ice-water bath and cooled to between 12 and 9°C. prior to entering the carotid artery. When the pump was started, the blood supply, save for the anterior spinal arteries, was then occluded. By this method the brain temperature could be lowered in 15 to 20 min. to 20°C. and in one animal it was lowered to 15°C. The brain temperature was measured by a thermocouple, which was inserted into the cerebral hemisphere contralateral to the side of the perfusion. Thermocouples were inserted in the inflow and outflow of the pump and in the rectum.
This experiment was carried out on 6 dogs and all of the animals except 1 died of ventricular fibrillation. In 2 of these dogs the probable explanation for fibrillation was air embolism. The rate of flow through the pump and brain averaged 66 cc./min. This rate was not rapid enough in 15 min. to lower the animal's total body temperature as in Delorme's work; however, the blood returning to the pump from the body was usually 7 to 10° lower than the body temperature. During the 15 to 20 min. that was required to lower the brain temperature to 20°C, the body temperature of the animal was lowered from 39 to approximately 35°C. The blood returning to the external pump had come from the left heart; its temperature measured at the pump was usually 7 to 10° lower than the body temperature. One might, therefore, conclude that the heart was receiving very cold blood from the brain so that we were not only cooling the brain, but also lowering the temperature of the myocardium. Perhaps the cold stream of venous blood returning from the brain to the heart may have set up a myocardial temperature differential. This might be comparable then to the experiments of Hoff and Stansfield vide supra, and therefore explain the fibrillation. The actual temperature of the myocardium (assuming that it were the same as the temperature of the blood leaving the left ventricle) was never below 32 to 33°C. This temperature is much higher than the temperature at which

![Diagram](image-url)
fibrillation is usually seen when systemic hypothermia is practised and, therefore, we assume that special susceptibility to fibrillation of non-cooled portions of the irregularly cooled ventricles occurred here. During these experiments cerebral arterial and venous oxygen\(^{26}\) determinations, and those of serum lactate,\(^1\) pyruvate,\(^{13}\) hemoglobin\(^{19}\) and sugar \(^{20}\) were performed at various temperatures; these will be discussed together with samples taken under systemic hypothermia. Regional hypothermia has been given up until we discover the factors initiating the fibrillation in this perfusion system. Since this work was done Jensen and Parkins\(^{16}\) have reported lowering the dog’s brain to 20\(^\circ\)C. by a similar technique, the while provoking a “low incidence of spontaneous cardiac arrhythmias.” From their brief report we are uncertain as to the reason for our discrepant results on this score.

SYSTEMIC HYPOTHERMIA

Method. Systemic hypothermia is more practical than the above techniques because of the simplicity of the procedure. Mongrel dogs were anaesthetized either with pentobarbital sodium or with thiopental sodium. Pentobarbital was given intravenously in amounts equivalent to 30 mg./kg. body weight and thiopental sodium in amounts varying from 500 to 800 mg./animal. The femoral artery was cannulated and a trephine opening was made over the posterior aspect of the sagittal sinus. This sinus was also cannulated, electroencephalographic electrodes were placed on the dura mater, and a thermocouple was buried in the cerebral hemisphere (Fig. 1). The body temperature was recorded by thermocouples in muscle and rectum. A centigrade thermometer was placed in the rectum. An electrocardiogram was taken. As in the animals with local cerebral hypothermia we carried out determinations of arterial and venous oxygen content, and of serum lactate, pyruvate, and glucose. On some of the animals the total body oxygen consumption, cardiac output, total serum CO\(_2\),\(^{36}\) pH, hematocrit, sodium, potassium, and amino acid nitrogen\(^4\) were also measured. The animal was rendered anoxic at normal body temperature for 2–3 min. by clamping his airway or by ventilation with nitrogen, and blood samples were again taken. The animal was then placed in the ice-water bath and cooled. Similar data were collected at various temperatures. At 25\(^\circ\)C. the animals were again rendered anoxic.

TOLERANCE TO ANOXIA

The above method was designed in an attempt to measure the animals’ tolerance to anoxia during hypothermia at 25\(^\circ\)C. It was felt that if one could calculate the percentage reduction of the cerebral metabolic rate at 25\(^\circ\)C., then one might predict the length of time that anoxia could be tolerated. Having once made this prediction, it could be tested by biochemical changes, survival studies, electroencephalographic recordings, and pathological sections.

1) Biochemical Changes. (a) A-V Oxygen Difference. The figures for differences between arterial and venous oxygen content, whether obtained under regional hypothermia (with controlled blood flow) or under systemic hypothermia, tended to parallel each other (Table 1). The differences were less during hypothermia but those during local hypothermia tended to be
more striking because the blood flow was kept constant and did not decrease with the temperature. The reduction in cerebral oxygen consumption (Fig. 3) either represents a reduction in the cerebral metabolic rate or, because of a leftward shift of the oxygen dissociation curve in the direction of a lower partial pressure of oxygen, an inability of the brain to extract oxygen from the blood at lowered temperatures. If the latter were true, then evidences of anoxia should be observed in the electroencephalogram, electrocardiogram,

![Graph](image-url)

**Fig. 3. A-V O₂ difference during hypothermia shows the progressive reduction in O₂ uptake with increasing depth of hypothermia.**
CIRCUMVENTION OF CEREBRAL ANOXIA

other biochemical tests, pathological sections and an increased oxygen uptake on rewarming. It will be shown later that all the above-mentioned tests support each other in indicating that no cerebral anoxia existed. Furthermore Penrod's demonstration of normal coronary A-V oxygen differences in dogs at 20°C is additional evidence that the leftward shift of the hemoglobin dissociation curve in the cold produces no cardiac hypoxia.

The total body oxygen consumptions were also measured and these show a progressive fall as the temperature is reduced. They tend to parallel the reduction in cerebral oxygen consumption and the cerebral metabolic rate, providing there is no shivering. Fig. 4 shows representative samples. Shivering will cause the total body oxygen consumption to rise but will not affect the cerebral oxygen consumption. Therefore, if there is no shivering, the total body oxygen consumption curve is a fair index of the cerebral metabolic rate (Fig. 5).

b) Cerebral Metabolic Rate. From the A-V oxygen differences the cerebral metabolic rate was calculated (Fig. 5). The metabolic rate was expressed as the number of cc. of oxygen extracted by the brain per min. The A-V oxygen difference in volume per cent represents the number of cc. extracted by the brain per 100 cc. of blood. Therefore, the oxygen utilized from 1 cc. of blood is equal to this A-V oxygen difference divided by 100. If the cerebral blood flow at this time was Y cc. per min., then the cerebral metabolic rate would be $Y \times \text{A-V oxygen difference divided by 100.}$ Since the rate of blood flow was known for all the A-V oxygen differences, the cerebral metabolic rate could be calculated for various temperatures. The blood flow at 25°C. was usually a few cc. slower than that at 39°C., so that the reduction in cerebral metabolic rate was usually slightly more striking than that of the A-V oxygen differences. From Fig. 5 it will be seen that at 25°C. there is a reduction in cerebral metabolic rate which lies somewhere between 35 and 23 per cent of normal.
Elliott\textsuperscript{11} stated that the temperature coefficient for each 10°C change in temperature, Q\textsubscript{10}, for rat brain respiration between 10\textdegree{} and 40\textdegree{}C. is 2.13. Since this Q\textsubscript{10} is a normal value for chemical reactions in general it seems appropriate to use it to calculate the expected reduction in cerebral metabolic rate in these dogs. The reduction from 38 to 25\textdegree{}C. equals a drop of 13°C. and would be equivalent to a reduction in the cerebral metabolic rate to 1/2.77 or 36 per cent of the level at 38\textdegree{}C. It is interesting that this theoretically derived reduction in cerebral metabolic rate correlates fairly well with the reduction actually measured in the above dogs.

2) \textit{Survival Studies.} According to our determinations the cerebral metabolic rate at 25\textdegree{}C. is reduced to about 25 per cent of normal. This should mean that the hypothermic animal at 25\textdegree{}C. would withstand anoxia for about four times as long as the normothermic animal. To test this hypothesis 8 animals when hypothermic at 25\textdegree{}C. were ventilated with 100 per cent nitrogen for 15 to 30 min. and the time required for electrocardiographic and electroencephalographic changes indicative of anoxia was noted.

In order to judge the length of such ventilation the animal would safely withstand, we observed the electrocardiogram and when marked changes indicative of anoxia and impending myocardial failure developed, the experiment was terminated by allowing the animal to breathe room air (Fig. 6).

The changes that usually occurred were lengthening of the PR and QT interval, elevation of the ST segment and high T-waves. As these changes progressed they were usually accompanied by an increasing bradycardia.

\textbf{Fig. 5.} As the temperature decreases, the cerebral metabolic rate is reduced. At 25\textdegree{} the cerebral metabolic rate varied between 35 and 33 per cent of normal values.
The changes appeared anywhere between 5 and 10 min. but did not become severe nor was there any fall in blood pressure, indicating myocardial failure, until at least 15 min. had elapsed. Some animals went as long as 30 min. If this anoxia was prolonged beyond the tolerance, death occurred as a result of cardiac arrest or ventricular fibrillation. When ventricular fibrillation occurred, it was a terminal phenomenon which usually commenced after normal ventricular contractions had ceased. The electrocardiographic changes which occurred at 5 min. in the hypothermic animals appeared within 1 min. in the normothermic animal. Of the 8 animals undergoing this test only 1 showed signs of clinical neurological deficit but this animal had sustained a severe loss of blood (over half of his blood volume) which may have prejudiced his recovery (Table 2).

**TABLE 2**

*Survival*

<table>
<thead>
<tr>
<th>Dog</th>
<th>Temp.</th>
<th>Trachea Clamped</th>
<th>100% Nitrogen</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>30'</td>
<td>25'</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>23.6</td>
<td>40'</td>
<td>not done</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>—</td>
<td>22'</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>23.6</td>
<td>—</td>
<td>16'</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>—</td>
<td>17'</td>
<td>Yes</td>
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<td>6</td>
<td>24</td>
<td>—</td>
<td>17'</td>
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</tr>
<tr>
<td>7</td>
<td>24.5</td>
<td>—</td>
<td>17'</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>—</td>
<td>16'</td>
<td>Yes</td>
</tr>
</tbody>
</table>
3) *Electroencephalogram.* Scott *et al.* and Chatfield *et al.* have shown the depressant effect of hypothermia on the brain waves. Scott showed that in monkeys electrical silence occurred at 22°C. The brain waves of the dog at 25°C are much reduced in amplitude and slow waves become more prominent. Since the brain waves are a sensitive test of cerebral dysfunction, it was felt that they would be a reliable and early indicator of cerebral anoxia. The electroencephalographic changes with anoxia are increase in number of slow waves and reduction in amplitude which, if carried further, approach electrical silence (Fig. 7). These changes appeared much later than the electrocardiographic changes and usually not until the latter were becoming severe. It was the heart, therefore, that limited the experiment and not the brain. It is possible that hypothermia results in a much greater reduction in cerebral oxygen requirement than that of the dynamically contracting myocardium. Had it not been for fear of myocardial failure, perhaps some of the animals could have remained anoxic for even longer without evidence of cerebral damage. The neurosurgeon does not need to render the heart anoxic, so perhaps the length of time the brain may be excluded from circulation can be increased. The animal who developed a neurological deficit had gross electroencephalographic changes and was the only animal showing any evidence of pathological changes of anoxia. The electroencephalogram, therefore, may be used to preclude carrying the period of anoxia too far.
4) **Pathology.** The brains of 5 of these animals were sectioned 6 months later and there was no specific evidence of anoxia in these specimens. In one brain, in the lateral thalamic area, there was a small region of decreased number of nerve cells with microglial and astrocytic reaction. In another brain, sections of the cortex showed an occasional patchy area of cellular loss with increased number of microglial cells. These changes were subtle and were not definitely abnormal. One could not be certain of the significance of these findings but there certainly were no typical findings of anoxia. This tends to support further the hypothesis that the cerebral tissues are protected by hypothermia from the adverse effects of anoxia.

5) **Further Data Indicating Little If Any Cerebral Hypoxia Or Anoxia Occurred.** It seems necessary to prove that the reductions in A-V oxygen differences were not caused by a shift in the oxygen dissociation curve but by a reduction in the oxygen requirement by the brain. It might be argued that this shift would prevent the cerebral tissue from taking up the oxygen it required and so render it hypoxic. The following facts support the theory that there was no hypoxia present:

a) Clinical and pathological evidence of cerebral damage did not occur from hypothermia alone.

b) Electroencephalographic changes were not severe and recovered on rewarming.

c) There was no increase in the A-V oxygen difference or total body oxygen consumption during rewarming.

d) The lactate:pyruvate ratio is an important indication of tissue anoxia. When tissues become anoxic, the lactate rises but the pyruvate stays constant or falls. Table 3 shows no significant rise during hypothermia and

<table>
<thead>
<tr>
<th>Temp.</th>
<th>Case 28</th>
<th>LP Ratio 33</th>
<th>Case 30</th>
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<tr>
<td></td>
<td>AL</td>
<td>AP</td>
<td>Ratio</td>
</tr>
<tr>
<td>39°C.</td>
<td>6.0</td>
<td>1.6</td>
<td>3.8</td>
</tr>
<tr>
<td>36°C.</td>
<td>4.4</td>
<td>1.1</td>
<td>4.0</td>
</tr>
<tr>
<td>25°C.</td>
<td>8.5</td>
<td>1.6</td>
<td>5.3</td>
</tr>
<tr>
<td>25°C. and anoxia 25 min.</td>
<td>42.2</td>
<td>2.1</td>
<td>20.0</td>
</tr>
<tr>
<td>25°C. and anoxia 26 min.</td>
<td>51.0</td>
<td>1.1</td>
<td>46.3</td>
</tr>
<tr>
<td>Post anoxia</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AL = arterial serum lactate.
AP = arterial serum pyruvate.
hence the brain must be able to extract oxygen during hypothermia. However, at the end of 25 min. in an atmosphere of 100 per cent nitrogen the cerebral tissues become anoxic and by 26 min. the change in the lactate: pyruvate ratio is marked (Table 3). It, therefore, appears that the hypothermic brain is metabolizing oxygen and that the reduction in A-V oxygen differences during hypothermia is not caused by the change in the oxygen dissociation curve but rather by a decreased metabolic demand on the part of the brain.

SUMMARY

1) Preliminary studies of various types of extracorporeal circulation are presented. These procedures proved to be too time-consuming and technically too difficult to be of practical use.

2) All animals, except one, in which local cerebral hypothermia was tried, died of ventricular fibrillation, which appeared to have been precipitated by the creation of a myocardial temperature differential in the right heart.

3) An experimental method is presented for studying the metabolism of the cold brain.

4) The cerebral metabolic rate in hypothermia (25°C.) varied from 23 to 35 per cent of control values.

5) Total body oxygen consumptions were reduced and paralleled the reduction in the cerebral metabolic rate in the absence of gross clinical shivering.

6) Of 15 dogs cooled to 25°C. or lower, none developed ventricular fibrillation above 25°C. Below 25°C. 3 died of fibrillation.

7) Preliminary studies indicate that the percentage reduction in cerebral metabolic rate is a reliable index which can be used to calculate the time that the blood supply may be safely arrested. The brain waves and the cardiogram are also reliable guides in predicting the tolerance to anoxia.

8) Eight dogs at 23.6°C to 25°C. survived 15 minutes of anoxia (ventilated with 100 per cent nitrogen) and only 1 showed neurological deficit.

9) Pathological examination of those surviving without clinical deficit revealed no signs of anoxia.

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CIRCUMVENTION OF CEREBRAL ANOXIA 239
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