

FURTHER EXPERIENCES WITH HYPOTHERMIA FOR INTRACARDIAC SURGERY IN MONKEYS AND GROUNDHOGS*

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IT IS WELL KNOWN that human beings cannot exist without a functioning heart for much more than three minutes. For this reason, the interior of the heart has been a challenge to the surgeon. It would appear to be necessary to stop the flow of blood through the heart in order to carry out a definitive intracardiac procedure. Several experimental technics have been developed and described in the literature, in which the blood is diverted around the heart and the circulation maintained by an extracorporeal heart lung pump.

As an alternative method of obtaining a bloodless heart, a research team has been studying the use of hypothermia for the past five years. A state in which the body temperature is lowered and the oxygen requirements of tissues are reduced to a fraction of normal would conceivably allow exclusion of the heart from the circulation for prolonged periods without recourse to extracorporeal pumps.

Early studies showed that when the body temperature of an animal is lowered, its oxygen requirements are reduced. Following further investigation³ of the physiological and biochemical changes in hypothermia, our hypothesis regarding its possible use for intracardiac surgery was tested in a series of dogs.²

As previously reported, 39 unselected adult dogs were cooled to 20°C. In each case the venous return to the heart was obstructed for an arbitrary period of 15 minutes. This is three to five times as long as it is reasonably safe to exclude the heart at normal body temperature. In 23 of these animals the heart was opened and then re-sutured. Fifty-one per cent of them revived to normal body temperature with only 15 per cent late survivals.

The number of survivals was disappointing, but on analyzing the records it was found that in 85 per cent of these dogs the heart continued to beat during the period of exclusion. It was decided to extend this investigation to other mammals, including one capable of hibernation, where it was likely that the effects of still lower body temperatures could be observed and their unusual cold tolerance studied.

MONKEYS

Recognizing the possibility of a low species resistance to such a procedure in dogs, it was decided to repeat this experiment using an animal higher in the evolutionary scale and more akin to man. For this purpose, the *Macacus Rhesus* monkey was used.

Method: A minimal dose of Pentathol was injected to inhibit shivering and facilitate cooling. The trachea was intubated, under direct vision, and the tube was con-

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nected to a source of oxygen. The animal was clipped and German silver subcutaneous e.c.g. leads were inserted and connected to a continuous cathode ray electrocardiograph. The animal was then placed in special cooling blankets and the rectal temperature was recorded as the body temperature fell to 20°C.

At this temperature the monkey was removed from the blanket and the chest opened. The superior vena cava, inferior vena cava and the azygos vein were dissected free and clamped and the heart opened as a token operation. At the completion of this the incision, the heart was closed, clamps removed, chest closed and rewarming accomplished by immersion in water at 40°C. Three doses of Penicillin were given each monkey during their first postoperative week.

Observation: The results in this series have been encouraging. At body temperature of 16° to 19°C., interruption of the circulation was maintained for periods of 15 to 24 minutes in 13 experiments upon 12 monkeys. Only one death occurred at operation in this series. The heart was opened for the period of clamp off in all animals but one. The right auricle was widely incised in 11, and in one, the left ventricle was opened with survival.

The only death occurred in an animal upon whom cinephotographic records were being taken. Due to technical difficulties, the heart was exposed to the intense heat of the floodlights for an unduly long period, with resultant ventricular fibrillation. One other monkey developed ventricular fibrillation following removal of the clamps but normal heart action was restored with electrical defibrillation and massage. Unless the dose of anesthetic had been excessive, the animals would be alert and able to walk two hours after removal from the water bath. They were all quite active and well coordinated the day after exposure, and the procedure did not appear to alter their personality or responses in any way.

Six of the 12 survivors remained active and well until after the first week, when they showed signs of wound infection or pneumonia, and either died or were sacrificed. The other six monkeys were kept for several months under observation. Five of these were used later for other studies and the one whose left heart was opened was saved and now one and a half years later, acts as a mascot at a naval station. He appears normal in all respects.

The period of time required for cooling from 38°C. to 20°C. varied from one half to one hour. The respiratory rate fell from an average of 35 per minute at 38°C. to eight per minute at 20°C. In dogs, spontaneous respiration ordinarily ceased at 24°C. The cardiac rate decreased from about 180 per minute at 38°C. to 30 or 40 per minute at 20°C.

During the operation, there was very little bleeding due to the reduced blood pressure at low body temperatures. There was no evidence of serious bleeding after rewarming with the return of normal blood pressure. The rewarming period was one half to one hour.

THE GROUNDHOG

In order to learn more about the resistance to cold, we have recently turned to a study of hibernation. The groundhog is a classical hibernator. As fall approaches his activities become less and finally, as the cold weather appears, he rolls up in a ball and sleeps throughout the winter. During this period of hibernation he experiences a profound decrease in body temperature, frequently to as low as 2° or 3°C., depending on the environmental temperature. In extremely cold weather when his body temperature has fallen to 3°C., he is automatically stirred to activity. This appears to be a reflex which protects him from total freezing.

In this interesting state of torpor the heart rate, respiratory rate and the oxygen

consumption fall to a very low level. Under suitable conditions the groundhog will undergo apparently normal hibernation in captivity.

Besides being able to experience a seasonal fall in body temperature, it was found in a preliminary study that active groundhogs at normal body temperature, summer or winter, could be lightly anesthetized and cooled rapidly in cooling blankets by the same technic used upon dogs and monkeys. They were able consistently to survive a body temperature of 2° to 3°C. similar to their range of cooling in hibernation.

Since it is not possible to cool animals such as the dog or monkey much below 20°C. with safety, the groundhog appeared to offer an opportunity to further test our hypothesis and determine whether a greater reduction in body temperature would allow a longer period of exclusion of the heart from the circulation.

Methods: The method of cooling was similar to that used upon dogs and monkeys. Active groundhogs were very carefully and quickly grasped by the tail and suspended while 3 per cent sodium pentothal ($\frac{3}{4}$ cc. per kilo) was injected intraperitoneally. This was a minimum anesthetic to allow handling and cooling in the special blankets as described above. When the rectal temperature of the animal reached 7°C., an endotracheal tube was inserted and connected to a source of oxygen.

The subsequent technic was similar to that used upon the monkey. The groundhogs, however, were cooled to from 2.5°C. to 5°C. and, because of the presence of a right and left superior vena cava, a sternum splitting incision was used and the three caval veins and the azygos vein were clamped. The right auricle was opened in these animals and resutured before the clamps were removed.

After closure of the heart and chest, the groundhogs were rewarmed to 34°C. in a water bath of 38°C.

Observations: Six groundhogs were cooled to body temperature ranging from 2.5°C. to 5°C. Their circulation was interrupted and the heart opened in each animal for periods ranging from one to two hours. All six animals survived the procedure and were revived to normal body temperature with good cardiac function. One animal died from hemorrhage due to a faulty ligation shortly after resuscitation. The remaining groundhogs recovered normally from the operation and appeared as well coordinated as they were preoperatively.

Three animals died or were sacrificed because of wound infection three days to a week postoperatively, and one died two days later of bilateral pneumothorax. One animal survived several weeks in good health and was used for other studies.

DISCUSSION

The authors feel that the important feature of this work is the revival to normal activity of 12 of the 13 monkeys and five of the six groundhogs, after a prolonged exclusion of their hearts from the circulation at low body temperatures. The operative monkey death and the early groundhog death appeared to be due to technical errors. The late deaths were for the most part due to infection. It is conceivable that prolonged hypothermia may increase susceptibility to infection. However, our primary interest was to obtain revival to normal activity. It was felt that with more careful asepsis and more vigorous use of antibiotics, these infections could perhaps be controlled.

The groundhogs received no antibiotics postoperatively. No special housing facilities were used for the monkeys and they have proven susceptible to pneumonia and infection in this climate with a definite mortality rate while awaiting operation.

The results of these experiments tend to confirm the basic hypothesis that prolonged interruption of the circulation with exclu-

sion of the heart is possible at low body temperatures. The length of time that a heart can be excluded from the circulation is increased as the body temperature is reduced.

This technic for intracardiac surgery has not been used upon humans as yet. The body temperature should be near 25°C. to reduce the oxygen requirements sufficiently to allow adequate time for an intracardiac procedure. This does not leave a very great margin of safety from apparently lethal temperatures for adult humans. Judging from our previous references to acute hypothermia in humans, their tolerance to low body temperatures would probably be similar to that of monkeys.

Groundhogs, with their unusual tolerance to cold, differ very little anatomically from ordinary non-hibernating mammals. They possess a peculiar hibernating gland which enlarges before and during hibernation, and which has been the subject of a recent study to be published. They also demonstrate a more labile heat regulating center, and it is our impression that this is found in association with increased cold tolerance.

Adolph¹ has made an interesting study of the fact that "newborn mammals survive body temperatures that cannot be tolerated by adults of the same species" and we have found a similar increase in cold tolerance in young dogs. He found that the lethal temperature that could be endured increased with age; in the cat it rose from 7°C. as an infant to 18°C. as an adult; in the rat from 1°C. to 15°C.; while in the hamster, the increase was from 1°C. to 4°C. The hamster is a hibernating mammal and it would appear that they maintain their cold tolerance throughout life. The well-known inability of premature human infants to maintain normal body temperature indicates incomplete development of their heat regulating center, and is very likely associated with a greater tolerance to low body temperatures than

found in adult humans. This technic of hypothermia may be safe to apply to infants and children at the present time. Perhaps there is a relationship between the thymus and the hibernating gland. These facts at least lend encouragement to further study of hypothermia.

Our cooling technic has been made safer by the use of an electrical defibrillator for the heart, and the development of a method of supplying the heart with an electrical pacemaker for standstill.⁵ A radio-frequency method of rewarming has also been developed⁴ which is safe, efficient and more acceptable for clinical application than the hot water bath. One significant advantage of the hypothermia technic over that of an extracorporeal circulation is that in the former one does not have to contend with the coronary sinus inflow into the heart during the period of exclusion, since the aortic pressure approaches zero and one only encounters a slow ooze.

We have considered for some time, the possibility of combining hypothermia with an extracorporeal circulation. From the standpoint of clinical application, it would appear at present to be adding the risks of two dangerous procedures, although eventually it may prove necessary in order to obtain safe and prolonged exclusion of the heart from the circulation. It may be impossible to bestow the peculiar cold resistance of hibernating animals upon non-hibernating animals and man. Nerve conduction is more efficient in hibernating animals at low temperatures⁷ and we have evidence that whole blood of the groundhog releases oxygen more readily than whole blood of the dog at low temperatures.

The question is often asked whether cooling may cause injury to the brain. To answer this,⁶ formalized intelligence tests were performed upon ten monkeys, then they were cooled to 20°C. with constant electro-encephalographic recordings during cooling and rewarming. The E.E.C. waves

disappeared at 20°C., then reappeared with no evidence of cerebral anoxia. The post-cooling intelligence tests indicated no reduction in their intelligence level. These tests have not been repeated upon monkeys whose circulation has been obstructed at low body temperatures. However, following such a procedure, our monkeys were alert, well coordinated and their responses generally unaltered from the pre-operation normal.

Our study of hibernation is bringing out some interesting facts. It is rather remarkable that relatively little is known about this phenomenon which is so commonplace in cold climates. Living in the north, it appears that we have always accepted the annual hibernation of many of our animals without much question.

SUMMARY AND CONCLUSIONS

In monkeys at a body temperature of 16°C. to 19°C. it has been possible to exclude the heart from the circulation and open it for 15 to 24 minutes with survival in 12 of 13 experiments.

In groundhogs at a body temperature of 3°C. to 5°C., the heart has been excluded and opened for periods of one to two hours with survival in five of six experiments.

Prolonged interruption of the circulation and exclusion of the heart with survival is possible at low body temperatures. The length of time that a heart may be excluded from the circulation appears to be increased as the body temperature is reduced.

Age appears to be an important factor in cold tolerance. A greater knowledge of

hibernation may yield useful information on this problem.

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Author's Note: Since this article was written, Drs. Charles Bailey of Philadelphia and F. J. Lewis of Minneapolis, have reported the successful use of this technic of cooling upon 2 patients.

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