HYPOTHERMIA: FURTHER OBSERVATIONS ON SURFACE COOLING*

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IN A PREVIOUS communication the authors described some of the physiological changes and the limitations attending the reduction of the body temperature of dogs by surface cooling.[4] Briefly, the conclusions drawn from that study were three in number. First, the method of producing hypothermia is not of great importance, but surface cooling is the simplest method available. Secondly, the risk of irreversible ventricular fibrillation is the greatest limitation of reducing the body temperature below 25 deg.C. Thirdly the younger the animal, the greater is the margin of safety. These conclusions were drawn from the consideration of animals with presumably healthy myocardiums. Since the widest application of hypothermia may be as an adjunct to the surgical correction of cardiac abnormalities, congenital and acquired, in which the myocardium is weakened, it is possible that the above limitation may become a problem at much higher body temperatures than 25 deg.C.

The purpose of hypothermia is to reduce the metabolic processes of the body to a sufficiently low level that exclusion of the heart and brain, in particular, from a functional circulation for long periods may be tolerated without detriment to their recovery. It may be that a mild degree of hypothermia will achieve this end. However, if the required reduction in metabolism can be obtained only by deep hypothermia then it is necessary to be able to correct, or preferably prevent the development of, ventricular fibrillation. Since the oxygen consumptions obtained in the previous study were unreliable the aims of the present investigation were to relate, as accurately as possible, the changes in oxygen consumption to the reduction of body temperature during deep hypothermia and to record some attempts to prevent and to correct cardiac arrhythmias at low body temperatures.

Methods

Thirty-two unselected mongrels weighing from 8 to 17 kg. were used. Body temperature was measured by a rectal thermocouple checked

* This work was done at the Buckston Browne Research Farm by kind permission of the President and Council of the Royal College of Surgeons of England.

against a standardized centigrade thermometer and the blood pressure was measured from a mercury manometer connected to a cannula in the femoral artery. The electrocardiogram, Lead 2, was displayed continuously on an oscilloscope and representative tracings photographed at periods during the reduction of body temperature. The method of cooling was that previously reported with the variations described below. Two series of dogs were studied.

Series I—(12 dogs). Each animal was premedicated with 0·4 mgm. of atropine and then anaesthetized with intravenous thiopentone sodium, 30 to 60 mgm. per kg. body weight, given in divided doses as required until a state of cold narcosis was reached. The trachea was intubated with a cuffed tube. All respiratory activity was paralysed with succinylcholine chloride and the animals were connected to an automatic positive-negative pressure respirator running at 24 cycles per minute at a pressure of +15 to −3 mm. of Hg. A closed circuit carbon dioxide absorption system was used and fresh supplies of oxygen admitted through a one-way valve leading from a Benedict-Roth spirometer filled with 100 per cent. oxygen. They were then transferred to the water bath the temperature of which was adjusted to approximately 32 deg.C. Once oxygen consumptions were obtained at normal body temperature the water in the bath was replaced with that from the cold water tap (10 deg.C.) and finally crushed ice was added to lower the water temperature to about 2 to 3 deg.C. Special care was taken to keep the water level in the bath constant throughout each study. Oxygen consumption measurements were obtained over five to 10 minute periods for every 2 deg. drop in body temperature. Measurements were continued until there was electrocardiographic evidence of death after which the respirator was left running for an hour connected to the dog so that any possible leaks in the system could be estimated and accounted for in the final calculation of the oxygen consumption.

Series II—(20 dogs). Each animal was premedicated with 0·4 mgm. of atropine and then anaesthetized by intravenous thiopentone sodium, 0·015 gm. per kg. of body weight. Succinylcholine chloride, 5 mgm. per kg. of body weight, was administered to facilitate endotracheal intubation with a cuffed tube. Anaesthesia was maintained with oxygen and ether in a closed-circuit apparatus with carbon dioxide absorption. With certain exceptions (infra) spontaneous respiration was permitted. The animals were transferred to the water bath at a water temperature of 18 to 20 deg.C., crushed ice was added and the bath temperature maintained at 2 to 3 deg.C. Cooling was continued until the body temperature was below 22 deg.C. or until death.

The following procedures were carried out to see if ventricular fibrillation could be prevented, or corrected once it had developed.

Autonomic Blockade—(6 dogs). The role of the cardiac division of the autonomic nervous system on cardiac arrhythmias during cooling was studied by dividing the vagus nerves in the neck in three dogs and, in one

of these and in the remaining three administering large doses of ganglionic blocking agents (hexamethonium chloride and pendiomide). In the vagotomized animals attempts were made to induce ventricular fibrillation by electrical stimulation of the cardiac end of the vagus nerve.

Graded Anoxia—(3 dogs). The same procedure was used as in Series I except that, instead of 100 per cent. oxygen being used, 10 per cent. oxygen was used throughout to determine whether the effects of positive-negative pressure respiration were due to the 100 per cent. oxygen or the artificial respiration.

Increased Carbon Dioxide Tension—(3 dogs). An attempt was made to increase the oxygen content of the plasma by lowering the pH of the blood by administering an excess of carbon dioxide (5—20 per cent.) in the inspired air.

Maintained Blood Pressure—(2 dogs). Attempts were made to maintain the systemic blood pressure at a mean level of 80 mm. of Hg. throughout cooling, by means of a noradrenaline intravenous drip.

In six dogs attempts were made to correct spontaneous or induced (by manipulation of the heart) ventricular fibrillation by electrical defibrillation[5] as well as by the use of potassium chloride and calcium chloride injections combined with cardiac massage[9].

Results

Series I—No dog in this group was permitted to survive, but the cooling was continued until death resulted from cardiac standstill in six dogs and from ventricular fibrillation in six dogs. The oxygen consumption calculated in ccs. per kg. of body weight per minute, fell in a linear fashion from an average of 8·26 ccs. at a body temperature of 38 deg.C. to an average of 0·62 ccs. when the average body temperature of the five surviving dogs was 14 deg.C. (Figs. 1 and 2). Correction for the increased solubility of oxygen in body water at low temperatures does not significantly affect the oxygen consumption figures. For comparison, the oxygen consumption of the animals previously studied with spontaneous respiration are illustrated on the same graph (Fig. 1). In both groups the reduction in oxygen consumption is linear although this is more clearly seen when controlled respiration is used since the scatter at a particular body temperature is much less. All of the animals in this group survived a body temperature of 20 deg.C., and at 16 deg.C. eight were still alive. Five were alive at body temperatures between 13·5 and 14·5 deg.C. and one dog did not die until its body temperature reached 11 deg.C. The mean blood pressures and pulse rates are compared to those of the original series[4] in Fig. 3. The striking difference between the two series is that the mean blood pressure was maintained at a higher level at low body temperatures when controlled positive-negative respiration was used. None of the dogs in the present series died of cardiac arrhythmias until the body temperature was below 20 deg.C. whereas in the original study three dogs died at body temperatures of 22 to 22·5 deg.C.

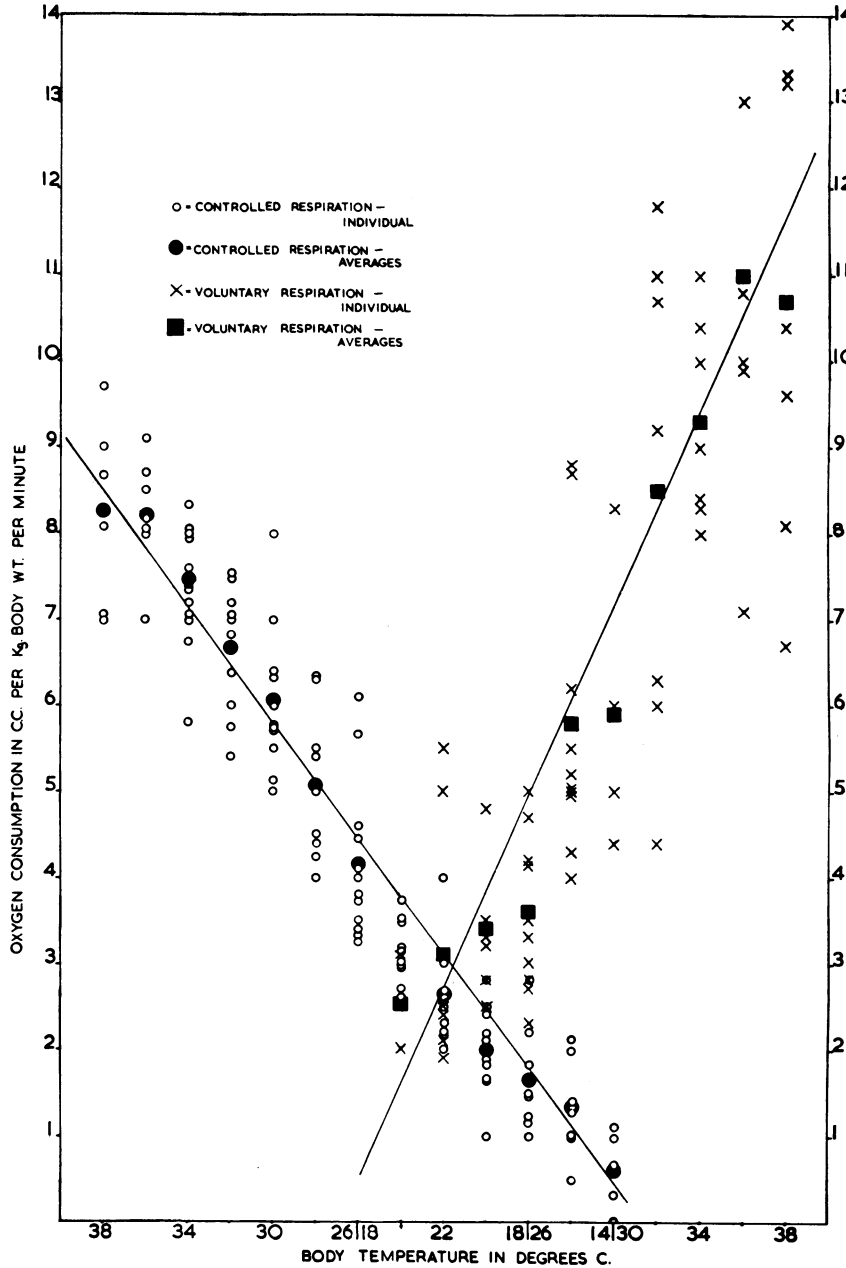

Fig. 1. The change in oxygen consumption during hypothermia. The values on the left are for controlled respiration down to 14°C. and those on the right for spontaneous respiration down to 20°C. The solid lines indicate averages.

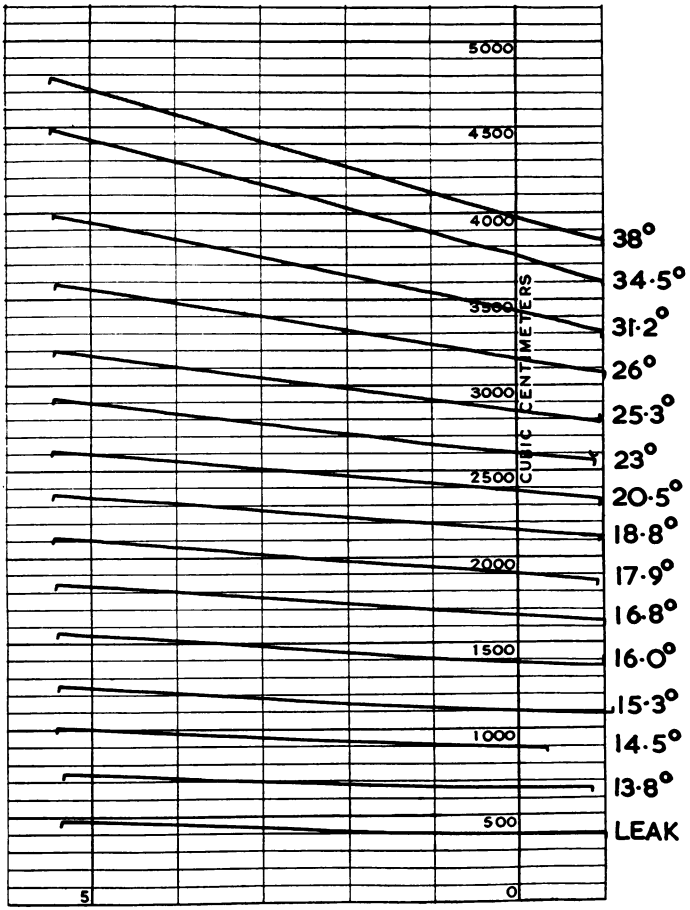

Fig. 2. A record of the oxygen consumption during surface cooling taken during an actual experiment.

Series II—The findings in this group of dogs need little amplification. Briefly, none of the attempted methods prevented the eventual development of ventricular fibrillation or standstill. Ganglionic blocking agents afforded no protection. In one vagotomized animal the body temperature was reduced to 10 deg.C. and then the dog was rewarmed to 38 deg.C. with restoration of blood pressure and voluntary respirations before it was sacrificed. However, similar recovery has been our experience in isolated non-vagotomized dogs, particularly if young. Ventricular fibrillation could not be induced by electrical stimulation of the cardiac end of a vagus nerve.

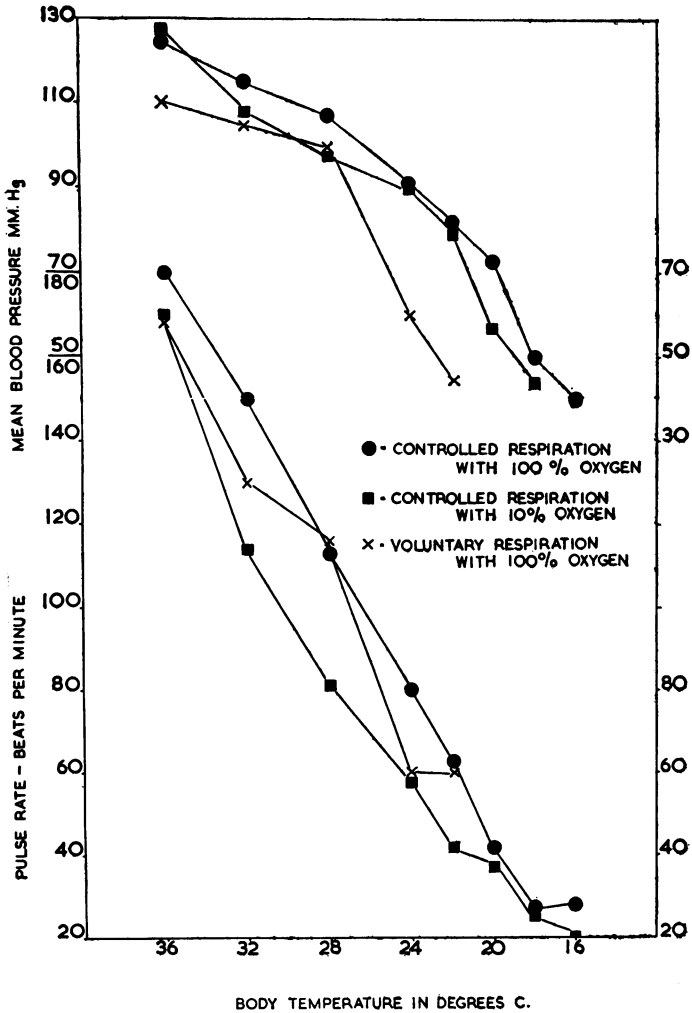

Fig. 3. The reduction of pulse rate and blood pressure during hypothermia.

The addition of carbon dioxide to the respired air caused death with gross cardiac irregularities at a body temperature of 22 deg.C. and the use of a noradrenaline drip to maintain the blood pressure precipitated death at a similar temperature.

In no case was electrical defibrillation successful in restoring the normal rhythm to a fibrillating ventricle below a body temperature of 22 deg.C. With the intra-aortic injection of KCl and $CaCl_2$ and cardiac massage, a normal rhythm was restored in three of six dogs in which it was tried. In none of these was recovery sustained but ventricular fibrillation recurred and became irreversible.

The most interesting results were obtained in the animals rendered hypothermic whilst breathing 10 per cent. oxygen with controlled respiration. Each of these dogs was alive at body temperatures of 16 deg.C. and one survived to 14 deg.C. The mean blood pressure in these animals remained higher than would be expected with voluntary respiration (Figure 3).

Discussion

The oxygen consumption obtained in this study verifies that there is a linear reduction in metabolic demands by the organism as a whole during reduction of the body temperature from 38 deg. to 14 deg.C. It would appear therefore that the lower the body temperature the greater the metabolic benefit to be obtained from hypothermia. It has been suggested that a moderate reduction of body temperature, i.e., 30 deg.C., is all that is necessary but from our data it will be seen that at that temperature there has been only a 27 per cent. reduction in oxygen consumption. The reduction of oxygen consumption by anaesthesia alone in humans undergoing surgery is in the region of 20 per cent.[6] Taking the figures in the literature for unanaesthetized dogs as being from 12 to 14 ccs. per kg. body weight per minute[7] it will be seen that in this series the anaesthetic was responsible for about a 35 per cent. reduction in oxygen consumption. This high reduction of oxygen consumption may have been the result of the respiratory paralysis accompanying the anaesthesia in this series and it is probable that the oxygen consumption in a conscious dog can never be basal so that a more accurate figure for the effect of the usual anaesthetic alone is more in the region of 20 per cent. as reported for humans. Thus anaesthesia plus hypothermia to 28 deg. to 30 deg.C. may reduce the total oxygen consumption by close to 50 per cent. if anaesthesia is complete and shivering is prevented. However, it has been reported that with such a degree of hypothermia the period of complete cessation of the circulation may not exceed 15 minutes [8, 9]. So it would seem that mild hypothermia will not permit a period of cessation of the general circulation such as may be required for unhurried intracardiac manipulations unless it can be clearly demonstrated that there is a disproportionate reduction of metabolic requirements by individual vital organs during body cooling. In view of this and the data in this report it seems probable that for hypothermia to be of the greatest value a body temperature of between 10–15 deg.C. should be aimed at, since, by extrapolation, the oxygen consumption will be approximately zero at 10 deg.C. Since eight of the 12 dogs studied with controlled respiration were alive at 16 deg.C. this possibility is not necessarily so remote in the absence of cardiac manipulation.

Unfortunately the greater the reduction of body temperature the greater are the risks of spontaneous ventricular fibrillation and cardiac standstill. These risks are exaggerated and occur at a higher body temperature when cardiac manipulations are imposed. It may well be that when cardiotomy is imposed upon a myocardium already weakened from the

effects of congenital or acquired heart disease cardiac arrhythmias will become exceedingly common. No method that we have attempted has produced permanent restoration of normal cardiac rhythm when the body temperature has fallen below 22 deg.C. Attempts to prevent the onset of cardiac irregularities were not generally successful. The administration of a high carbon dioxide content in the inspired air in an attempt to make available to the heart more oxygen by lowering the pH of the blood were not beneficial. Attempts to isolate the heart from central nervous influences by vagotomy and ganglionic blockade did not produce a useful extension of hypothermia. The maintenance of the blood pressure at normal levels by a noradrenaline drip was disastrous. The only method which was less associated with cardiac arrhythmias than any other and which allowed a body temperature of below 20 deg.C. to be reached in every instance without death was controlled respiration as used to study the oxygen consumption. Why should controlled respiration be of benefit ?

The only significant difference in data so far obtained from animals maintained on controlled respiration and those permitted to breath voluntarily is that in the former the blood pressure is maintained at a higher level throughout the period of cooling. At a body temperature of 22 deg.C., when at least 15 per cent. of dogs not on controlled respiration will be dead but all of those being artificially respired will be alive, the blood pressure in the latter group is approximately twice that of the former (Fig. 3). That this effect is not a result of the 100 per cent. oxygen is shown by the fact that controlled respiration with 10 per cent. oxygen produces a similar extension of hypothermia. It may be that acapnia attending controlled respiration with carbon dioxide absorption is the responsible factor, although we have as yet no evidence to support this. The beneficial effects of controlled positive-negative pressure respiration may be the ability of the method to maintain the blood pressure and so, in all probability, the coronary circulation, and it has been reported that controlled positive-negative respiration will maintain the cardiac output.[2] Other authors too have reported the beneficial effects of artificial respiration during reduction of the body temperature[1, 9].

During hypothermia the myocardium maintains a high level of work and, because of the shift in the oxygen dissociation curve to the left at low temperature[3], a reduction of the coronary blood flow may result in myocardial anoxia. It may be that during deep hypothermia the oxygen requirements of the heart are satisfied more by the oxygen dissolved in the plasma than by that in the red cells, and even though these requirements are probably reduced by a low body temperature they may be supplied only by the coronary blood flow being maintained at a relatively high level. Cardiac standstill and ventricular fibrillation are the usual manifestations of myocardial anoxia and since they are the modes of death in deep hypothermia and are irreversible by present methods it seems a reasonable hypothesis that the coronary circulation is the real limiting factor in deep hypothermia.

When prolonged or total cessation of the general circulation is not required it is probable that a mild reduction of body temperature will suffice but for unhurried intracardiac manipulations to be properly performed mild hypothermia provides a narrow margin of safety. But because of the enhanced dangers accompanying deep hypothermia it must be considered an experimental method not yet applicable to man.

Summary

(1) Surface cooling has been used to lower the body temperature of dogs to death whilst oxygen consumption was estimated and attempts to prevent and to treat ventricular fibrillation were applied.

(2) The oxygen consumption falls in a linear fashion down to 14 deg.C. and should, by extrapolation, be zero at about 10 deg.C.

(3) No method was found to prevent ventricular fibrillation or cardiac standstill. Once these had developed they were permanently irreversible at body temperatures below 22 deg.C.

(4) The best method of delaying the onset of cardiac irregularities and death was the use of controlled respiration.

(5) In the light of our present knowledge deep hypothermia must be considered as not yet applicable to man.

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SIR FRANK COLYER, K.B.E., F.R.C.S., F.D.S.

The Council have learned with deep regret of the death on 30th March of Sir Frank Colyer, Honorary Curator of the Odontological Collection. An appreciation will appear in the next issue of the Annals.