Temporary whole-body hypothermia in theory offers an ideal way of greatly reducing metabolism, and seems to hold great promise in clinical surgery. Yet, although the reptile or the hibernating mammal can withstand very low body temperatures without distress, body temperatures much below 28°C produce severe and often fatal physiological stress in the non-hibernating mammal.

In the course of a series of studies of the physiology of experimental hypothermia in the dog, we have observed profound changes in the auto-regulation of respiration and of blood pH. These changes appear to be important components of the stress effect of low body temperatures in higher mammals. Prevention or control of these changes appears to greatly increase the ability of the dog to survive extremely low body temperatures.

MATERIALS AND METHODS

Dogs weighing between 8 and 15 kg were anesthetized with intravenous Nembutal and cooled by immersion in a water-bath maintained at a temperature between 9°C and 10°C. Rewarming was carried out by raising the bath temperature to 40°C. Heparin was administered intravenously, 3 mg/kg body weight, to prevent clotting in the pH electrode chambers. Body temperatures were measured with a recording thermometer by rectum on the basis of Bigelow's (1) finding that rectal and cardiac temperatures usually differ by less than 1 degree. Arterial pH was continuously recorded by a Cambridge pH recorder using shielded glass and calomel electrodes in a small chamber through which blood was passed from the femoral artery to the femoral vein. Arterial blood pressure was recorded on a kymograph, using a mercury manometer connected to the opposite femoral artery. In the first series of animals, changes in apparent respiratory volume were estimated on an arbitrary scale as the product of chest excursion (recorded from a Manning Pneumograph) and respiratory rate. In subsequent animals respiratory volume was measured directly in several ways, eventually by passage through a recording dry-type gas-meter. The expired air was collected, and in earlier dogs was passed continuously through a modified Marriott bicarbonate buffer solution (2) with indicator dye to provide an estimation of CO₂ concentration. In later experiments, CO₂ concentration of expired air was measured by thermal conductivity in an appropriate pair of cells and gas-train (3). Positive pressure respiration in controllable amount was administered when necessary by means of a Starling pump through a balloon tracheal catheter. Samples of the blood serum were analyzed for CO₂ content and electrolytes by standard clinical laboratory procedures.

Hypothermia Under Moderate Anesthesia. Fremont-Smith (4) has drawn attention to the hyperventilation which coincides with the onset of hypothermia, but it has not been studied intensively. However, large variations in respiratory exchange and in blood pH have recently been related by several investigators to anesthetic shock (5–7). These studies led us to look for similar disturbances during hypothermia.

In an initial series of experiments, arterial pH and relative respiratory minute volume (product of chest excursion and respiratory rate) were followed in four dogs during cooling. These animals received enough intravenous Nembutal to provide adequate surgical relaxation, but not enough to completely prevent shivering. They reacted to cooling quite uniformly as follows.

A linear fall in rectal temperature began almost as soon as the animal was placed in the cooling tank. Shivering began shortly afterwards, and generally continued until a body temperature of about 27°C was reached. At about the time of an onset of shivering, all animals began to increase the depth and usually the rate of respiratory movements. Coinciding with this apparent increase in pulmonary ventilation there occurred a gradual rise in arterial pH to 7.6 or higher, which continued until the rectal temperature dropped...
under about 31°C. Thereafter respiratory volume began to diminish, and arterial pH began to fall again. With decreasing temperatures under 36°C, respirations slowly diminished until they ceased at rectal temperatures near 24°C. During this time, arterial pH fell rapidly, usually reaching 7.2 or 7.1 when the rectal temperature reached 23°C. This acidosis in most instances was not accompanied by visible cyanosis. The record of one shivering during the initial stages of cooling, and would at the same time prevent the initial respiratory alkalosis. The consequent respiratory depression, of course, tended to hasten the respiratory acidosis during later stages of cooling.

The classical limits of blood pH compatible with life have been given (8) as 6.8–7.8. These limits may be over conservative, but there is evidence that rapid changes in pH may be as traumatic as extremes of acidosis or alkalosis (6).

Every one of our animals subjected to hypothermia as described, without mechanical control of the respiration, showed major shifts in arterial pH, the typical reaction of animals under light anesthesia being an early rise in pH of over two-tenths of a unit, followed by a severe drop often more than 0.6 pH units. Death due to ventricular fibrillation usually occurred in these animals soon after the temperature fell under 23°C.

Effect of Artificial Respiration. As the shifts in arterial pH during hypothermia described above appeared to be directly caused by CO₂ elimination or retention, in our next series of experiments we studied quantitatively the effect of artificial respiration. It has been emphasized by other workers that artificial respiration is necessary for successful experimental hypothermia (1). In order to obtain more detailed data on its effect, we attempted to control the arterial pH by varying the pulmonary ventilation. We planned to initiate cooling without artificial respiration while observing the arterial pH. A balloon catheter was placed in the trachea, and a Starling pump made ready for tight connection as soon as there should be a substantial change in arterial pH. We expected that it would be a simple matter to maintain a constant arterial pH by maintaining a relatively constant minute volume of respiration with the Starling pump.

This did not entirely turn out to be the case. A rise in arterial pH often still occurred during the initial cooling period, in spite of constant artificial respiration. This may have been due to some leakage past the balloon tracheal-catheter during the strong respiratory efforts of the animal. And at temperatures below 30°C acidosis usually appeared and increased

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**Fig. 1.** Hypothermia under light anesthesia (11 kg dog); no artificial respiration.

*Product of respiratory rate and chest expansion.

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of these animals is presented as figure 1, group A of table I gives selected data during two such experiments.

Serum electrolytes and serum CO₂ content were measured at intervals during cooling. In general, there was a gradual fall in serum sodium and chloride concentrations and in CO₂ content. However these ionic changes were not sufficient to account for the changes in pH. The pH changes seem therefore to be due to changes in arterial pCO₂, associated with the changing respiratory minute volume.

In several animals, it was found that a large increase in the dose of Nembutal would abolish
as in previous dogs, in spite of a constant or moderately increased pulmonary ventilation rate. Figure 2 presents data on one of four such experiments. All were essentially similar in showing steady increase in acidosis at temperatures below 30°C in spite of artificial respiration, which maintained a respiratory minute volume equal to or above that of the warm, anesthetized dog. *Group B, table 1, gives selected data during three such experiments.

CO₂ concentration in the expired air of these animals was estimated by visual comparison of the color of an indicator (phenol red) with standards, in a series of NaHCO₃ buffer tubes through which the air was bubbled (2). This method is adequate for the qualitative estimation of large changes in CO₂ concentration, but is subject to considerable absolute error. Subject to these qualifications, the findings appear worth recording and appear in column 5 of table 1. From initial levels of about 5% CO₂ in the expired air, the concentration of CO₂ put out by the animals slowly diminished during initial cooling, reaching about 4% at rectal temperatures near 30°C. However, in most animals, as rectal temperatures fell past 27°C, the concentration of CO₂ in the expired air dropped sharply, usually reaching levels at or below 1% at rectal temperatures near 24°C. This drop in concentration of exhaled CO₂ coincided with the most rapid development of respiratory acidosis.

Bigelow (9) has shown that oxygen consumption decreases in an almost linear fashion with cooling as far down as about 20°C. It would seem reasonable that cellular CO₂ production might decrease in the same regular and linear way. Yet the sudden decrease in concentration of expired CO₂ which we observed appears to be out of proportion to previous measurements of decrease in oxygen consumption. This decrease occurred in spite of artificial respiration at a constant or increased minute volume, and was associated with a rapid fall in blood pH and increase in arterial pCO₂, indicating a rather sudden partial block in elimination of CO₂ from the blood.

This block in elimination of carbon dioxide in theory might be either chemical (due to change with temperature in the chemical
reactions involved in CO₂ transport) or physical, due either to changes in actual alveolar ventilation or wall-thickness, or to changes in the blood supply to the alveolus. We have had the opportunity to establish an extracorporeal circulation including an artificial lung in several hypothermic animals. Carbon dioxide elimination appeared to proceed freely in the artificial lung at temperatures where it is partially blocked in the animal's own lung. This is evidence against a chemical block (such as for instance a disturbance in activity of carbonic anhydrase). We have no clear evidence to distinguish whether there may be a decrease in alveolar ventilation due perhaps to bronchiolar constriction at low temperatures, or whether elimination of CO₂ is slowed mainly by progressive slowing of the pulmonary circulation. However, from inspection of our individual records, we have the distinct impression that elimination of CO₂ proceeds much more effectively in those animals in whom the blood pressure is well maintained and in whom there is no major alteration in hematocrit than in animals exhibiting evident failure of the circulation

hyperventilation. At the same time, we planned to prevent the initial alkalosis of early hypothermia by decreasing the respiratory volume at that time to any extent necessary.

Therefore in our next series of animals, arterial pH was continuously observed, and the minute volume of artificial respiration was constantly adjusted in the attempt to maintain a constant arterial pH. In several animals it was possible to prevent alkalosis and acidosis, provided considerable adjustment was made in the respiratory volume. In particular, prevention of the acidosis of late hypothermia
sometimes required extremely large respiratory volumes. Figure 3 presents records of one such experiment. Data on individual animals are presented in group C of table I. In the animal of figure 3, it was necessary to increase pulmonary ventilation by a factor of 300% above the normal (warm) requirement to prevent acidosis at body temperatures below 23°C. There was considerable variation in the amount of ventilation necessary in different animals to prevent acidosis. For instance, the second animal of group B (table I) developed acidosis in spite of an increase in pulmonary ventilation of an amount which prevented acidosis in two animals in group C. We have no adequate explanation for this variation.

Since completion of these experiments, Swan (10) has independently reported data emphasizing the importance of hyperventilation in the prevention of acidosis and ventricular fibrillation during hypothermia.

**Rewarming and Survival.** In animals who survived cooling to under 20°C, rewarming was carried out by raising the temperature of the water-bath to 40°C. Figures 2 and 3 include some data during warming. Detailed data will not be presented here, but in general we observed changes in blood pH and CO₂ elimination which appeared to be mirror-images of the changes during cooling. Acidosis persisted (except in the presence of extreme hyperventilation) during warming usually until body temperatures near 25°C were reached, while concentration of CO₂ in the expired air remained at 1% or below. Then rather suddenly, usually near a rectal temperature of 26°C, we observed a rapid rise in expired CO₂ concentration together with a rapid rise in arterial pH. At temperatures near 38°C

![Fig. 3. Hypothermia and beginning of rewarming, with controlled artificial respiration; pH maintained constant by hyperventilation, followed by extreme hyperventilation.](http://ajplegacy.physiology.org/)

..This figure shows the changes in rectal temperature, respiratory minute volume, arterial CO₂ tension, arterial pH and estimated CO₂ in expired air during cooling and rewarming.

At this point we were able to review our data in relation to survival. We found a close relation between major pH changes during cooling and immediate mortality (usually due to ventricular fibrillation). For example one group of 12 animals had the body temperatures lowered to under 20°C. Of these, seven showed an early alkaline shift of pH, followed later by acidosis. All these seven died just before or during rewarming, of ventricular fibrillation. Of the other five animals, none showed the early pH rise (in most cases it was prevented by artificial
control of respiratory volume) and only one showed an acidosis during later cooling of over 0.3 pH units. All of these animals survived rewarming to normal body temperature, and were thereafter able for a time to maintain their own circulation and respiration.

The difference in immediate mortality between these two groups of animals is statistically significant at the 1% level according to Mainland’s tables (11).

No animal who showed an early alkaline shift to a pH of over 7.6 survived to the beginning of rewarming, but several animals with a late acidosis did not die until during rewarming. Hence prevention of the alkalosis associated with the first stages of cooling appeared to be perhaps even more important than prevention of acidosis during deep hypothermia.

However, up to this point long-term survival was not achieved. Even those animals who apparently were recovering successfully from hypothermia for a few hours, died within 24 hours in shock. Similar shock after hypothermia has been reported by Bigelow (1) and others and has been a major hazard in hypothermia second only to cardiac arrest or fibrillation. Two other factors implicit in our experimental method contributed to the mortality in our animals. First, the operation of cannulating the femoral vessels and diverting a considerable quantity of blood through the pH electrode chamber was traumatic in itself, and under our conditions of tank immersion, the operative field could not be kept sterile.

Secondly, to maintain uniform conditions, body temperature in all animals was lowered to well under 20°C, regardless of the animal’s condition, unless ventricular fibrillation occurred earlier.

**Serum Bicarbonate in Relation to Fibrillation.** Changes in serum electrolytes were studied in many of our animals. In general, serum sodium and chloride concentrations fell during hypothermia, and also (in contrast to the findings of Bigelow (1)) serum potassium concentration. While the concentrations of these extracellular ions fell, the hematocrit usually rose, often as much as ten per cent. The extent of these changes was quite variable in different animals, and no clear correlation was found between them and cardiac abnormalities.

However review of our data on serum bicarbonate (as measured by serum CO₂ content corrected for pH by the Henderson-Hasselbalch equation) presented a close association between low serum bicarbonate and the onset of severe ECG changes or ventricular fibrillation. Table 2 presents determinations of serum bicarbonate in several different experiments. Each value represents a different animal, sample being taken during cooling when the body temperature was below 25°C. The animals are divided into three groups: a) those animals who subsequently went into ventricular fibrillation, b) those animals who did not fibrillate but who showed severe ECG changes of the ‘current of injury’ type (see section on ECG below) and c) those animals who neither fibrillated or showed major ECG alterations and who were subsequently temporarily revived after rewarming. Without exception those animals who were rewarmed without major ECG changes retained relatively high concentrations of serum bicarbonate while cold. In individual animals, serial determinations of serum bicarbonate during cooling showed a sharp drop in bicarbonate concentration during and after the alkalosis of early cooling, but in dogs in whom the pH was maintained constant and alkalosis prevented, the serum bicarbonate changed very little during cooling.

Thus preservation of a high serum bicarbonate appeared closely linked to successful recovery from cooling. A logical next step

### Table 2: Serum bicarbonate, at body temperature under 25°C, in relation to later ventricular fibrillation

<table>
<thead>
<tr>
<th>Serum HCO₃⁻, mEq/l</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Animals which subsequently fibrillated</td>
</tr>
<tr>
<td>17</td>
<td></td>
</tr>
<tr>
<td>16.7</td>
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</tr>
<tr>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Animals which did not fibrillate, but who showed severe current of injury in ECG</td>
</tr>
<tr>
<td>19</td>
<td></td>
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<tr>
<td>23</td>
<td></td>
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<tr>
<td>17</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Animals which did not fibrillate, and in whom current of injury in ECG was minimal</td>
</tr>
<tr>
<td>26</td>
<td></td>
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<tr>
<td>27</td>
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was to try to raise the serum bicarbonate of the subject before beginning cooling. A convenient way to achieve this is to induce respiratory acidosis and maintain it long enough to allow chemical compensation by the animal. Accordingly, in a small series of animals we intubated the trachea and administered respiration at a controlled minute volume by means of the Starling pump, using air containing between 5% and 10% CO₂. Respiratory minute volume was maintained high enough to prevent cyanosis, and this respiration with elevated CO₂ was maintained for at least an hour. The animal was then dropped in the cooling bath, and the concentration of CO₂ was gradually reduced during cooling, added CO₂ being entirely eliminated when the body temperature reached about 25°C.

Six animals were cooled to rectal temperatures under 19°C following this procedure. In each animal, at the lowest temperature reached, artificial respiration was stopped and the tracheal catheter clamped for 15 minutes to determine the tolerance for anoxia at the low temperature. Two of these animals recovered completely following rewarming. These represent the first completely successful recoveries from body temperatures below 19°C in our experiments. Two more survived over 36 hours, and can be presumed to have survived the ‘late shock’ of hypothermia. Death in one appeared to be due to secondary infection associated with the operative procedure of cannulating the femoral vessels. Death of the second was associated with severe pulmonary symptoms. One of the six animals died within 24 hours of warming, in shock indistinguishable from that of previous animals. The last animal spontaneously fibrillated during the period of tracheal clamp-off. This was an animal who was anesthetized only after a prolonged and vigorous struggle. Following this excessive muscular exertion, he continued to eliminate CO₂ in relatively large amounts; at a rectal temperature of 20°C the CO₂ concentration of his expired air was double that of previous dogs at the same temperature.

Serial determinations of serum bicarbonate were carried out during several of these experiments. As expected, the bicarbonate concentration rose during the period of induced hypothermia (lead 2 throughout). Standardization 1 mv = 1 cm. A. Hypothermic dog 7 min. before onset of ventricular fibrillation. Animal showed early alkalosis followed by acidosis. Rectal temp. 23°C, pulse 50. B. Diagram of ECG shown in A, identifying current of injury. C. Hypothermic dog in which arterial pH was controlled during cooling. Animal did not fibrillate. Rectal temp. 20°C, pulse 35. D. Dog cooled after 1 hr. of induced respiratory acidosis. Recording made while still inhaling 3% CO₂. Note small current of injury. Rectal temp. 22.5°C, pulse 20. E. Same dog as D, 13 min. after elimination of CO₂ from inspired air, but at same respiratory minute-volume. Current of injury has now virtually disappeared. Temp. 21.5°C, pulse 15.
respiratory acidosis before cooling, and thereafter remained relatively constant. For example, a typical animal showed a serum bicarbonate of 24 mEq/l when first anesthetized. This rose to 27.5 mEq/l after 1 hour of induced respiratory acidosis. He was then cooled, and at a body temperature of 24°C, the bicarbonate fell to 25.9 mEq/l. At a temperature of 18.5°C it was 25.5 mEq/l, and during rewarming at a temperature of 20°C was 25.2 mEq/l.

Electrocardiographic Changes. A particular form of ECG has come to be thought of as associated with profound hypothermia. Its form is particularly well seen in lead II, and examples have been published by Bigelow et al. (12) and by Juvenelle et al. (13). It has been described (12) as characterized by a doubling of the QRS interval, and lengthening of the QT interval by three to four times. The T-wave is long and irregular, and usually inverted. A very constant finding in our animals, and in the examples shown by the previously mentioned authors has been a secondary wave closely following the S-wave, so closely that it appears to be part of the QRS complex. Evidence from leads VI and V6 indicates that this abnormal wave following S represents a current of injury, rather than a widening of the ventricular complex due to a conduction defect. This wave, which we interpret as a current of injury, is so closely associated with the QRS complex as to prevent accurate measurement of the actual duration of the QRS wave. A typical example of the current of injury is shown in figure 4, A and B. We have found this current of injury with only one exception in every animal who later fibrillated. It usually begins to show up to 3 hours before fibrillation, usually at a rectal temperature under 25°C and gradually increases until the usual termination of fibrillation. We have come to look upon it as a very bad prognostic sign.

However this current of injury has been minimal or absent in animals in whom we have maintained the arterial pH constant by manipulation of the respiration (see fig. 4, C). It has only occurred once in the presence of a serum bicarbonate concentration of over 25.5 mEq/l except while the animal was breathing air with increased CO₂ concentration. When it has appeared in animals receiving increased inspiratory CO₂, we have repeatedly been able to cause the current of injury to decline or disappear by decreasing the concentration of CO₂ in the inspired air, or by increasing the respiratory minute volume (see fig. 4, D and E). We regard this as evidence that the ECG changes associated with hypothermia, particularly of the 'current of injury' type may not be associated with the low temperature directly, but rather may be more closely associated with faulty elimination of CO₂ under hypothermic conditions.

DISCUSSION
We have presented evidence that the dog subjected to hypothermia normally shows considerable changes in arterial pH. An initial alkalosis associated with hyperventilation is followed by an acidosis apparently due to carbon dioxide retention. This retention of carbon dioxide is not entirely respiratory, as it is not prevented by artificial respiration at normal minute volumes. We are not clear as to its cause, but believe that it is largely due to inadequate pulmonary circulation.

We have also shown evidence that cardiac abnormalities and eventually ventricular fibrillation usually occur in the hypothermic dog under conditions of a low arterial pH (presumably due to the carbon dioxide retention) being most severe when the serum bicarbonate is low. We have also shown that the alkalosis of initial cooling normally causes a compensatory lowering of serum bicarbonate. The low serum bicarbonate thus achieved renders the dog particularly susceptible to the later stage of respiratory acidosis which will follow at lower temperatures.

The only complete recoveries from deep hypothermia under 19°C which we have achieved have been in animals subjected to a period of respiratory acidosis long enough to allow some chemical compensation in the serum, before cooling was begun. During the induced acidosis these animals have been able to increase the concentration of their serum bicarbonate, and apparently have been better able to withstand the acidosis of deep hypothermia.

The mechanism of adjustment of the extracellular fluid to respiratory acidosis has been well documented by Gamble (14). Essentially it consists in an expansion of avail-
able base and of serum bicarbonate concentration. From the Henderson-Hasselbalch equation, increase of serum bicarbonate will allow an increased concentration of $\text{H}_2\text{CO}_3$ and therefore a rise in $\text{pCO}_2$ without depression of the $\text{pH}$. This in turn allows a greater gradient between arterial $\text{pCO}_2$ and alveolar $\text{pCO}_2$, increasing the efficiency of $\text{CO}_2$ elimination. An adjustment of this type would appear to be beneficial during the conditions of deep hypothermia. But such an extensive adjustment of the chemistry of the body fluids requires a considerable time, and probably takes place too slowly under the shock-like conditions of hypothermia, to be protective. It is therefore reasonable to allow this chemical compensation for respiratory acidosis to take place in the intact, warm animal, before cooling. He will then be chemically in a position to maintain a high arterial $\text{pCO}_2$ without a destructively low $\text{pH}$, with a consequent increase in the volume of $\text{CO}_2$ eliminated from the lung for every unit of ventilated pulmonary blood.

Also, the chemical compensation of the cells themselves in the presence of respiratory acidosis may be of considerable importance. Valuable attempts have been made to study intracellular changes in response to acid-base changes of the serum (15, 16), but techniques are difficult and not wholly satisfactory. Yet it is reasonable to assume that given time for adjustment, the cell can so alter its buffer systems as to give itself considerable protection in the presence of a rising serum $\text{pCO}_2$. In this connection, in our animals who have exhibited large changes in arterial $\text{pH}$, we have sometimes observed changes in electrolyte concentrations which would indicate considerable movement of fluid and ions across the cell membrane. Similar changes have appeared minimal in animals in whom the $\text{pH}$ was maintained almost constant.

There has been a rather wide range in the mortality rates following experimental hypothermia as reported by different workers (1, 14, 17, 18). Data presented by Haterius and Maison (19) indicate much of this variation in mortality may be due to differences in anesthetic techniques. Our results lead us to speculate that a reason for this may be that different anesthetic techniques may cause an increase or a moderation in the shifts of arterial $\text{pH}$ which in our data have been so closely associated with mortality.

While we have reported what we believe to be interesting and important relations between respiratory physiology and cardiac abnormalities during hypothermia, we do not by any means feel that they represent a full explanation of the problem of arrhythmias and fibrillation at low body temperatures. To mention only two factors which we have not had an opportunity to explore, myocardial anoxia and vagal stimulation have both been shown to play important roles in the production of ventricular fibrillation in the human surgical patient (20). There may well be a relative myocardial anoxia in the hypothermic animal, due to the shift of the dissociation curve of hemoglobin with temperature, and we have noted extreme sensitivity of the heart to vagal stimulation at low temperatures. Yet in spite of the many other factors undoubtedly involved in the abnormal physiology of hypothermia, it appears to us evident that the stabilization of the ‘milieu interieur’ in regard to the basic factors of $\text{pH}$ and of carbon dioxide tension is of primary importance.

**SUMMARY**

Arterial $\text{pH}$ and some elements of respiratory exchange have been followed during deep hypothermia in dogs. The normal response to hypothermia consists of an initial rise in arterial $\text{pH}$ due to hyperventilation, followed (when the body temperature drops below about 29°C) by a prolonged fall in $\text{pH}$, apparently due to $\text{CO}_2$ retention.

This apparent respiratory acidosis may persist and increase in spite of artificial respiration at a constant minute volume. The reason for the $\text{CO}_2$ retention is not clear. By mechanical control of respiratory rate the initial rise in arterial $\text{pH}$ can be prevented, but prevention of the fall in $\text{pH}$ at temperatures below 29°C is more difficult and uncertain and may require extreme mechanical hyperventilation.

In our animals, major changes in arterial $\text{pH}$ during hypothermia have been significantly associated with high mortality. Animals surviving rewarming for over two hours have been those in whom the arterial $\text{pH}$ was main-
tained relatively constant by mechanical control of the respiratory minute-volume.

In a small series of animals, induction of respiratory acidosis for an hour before cooling appeared to have protective effect. The only animals in our experience who achieved long term survival after body temperatures under 19°C were in this group.

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