Cooling responses in shivering and non-shivering dogs during induced hypothermia

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Summary

1. Hypothermia to a temperature of 30°C was induced in both shivering and non-shivering groups of dogs.
2. There was a sustained increase in oxygen consumption in the dogs allowed to shiver and this was up to 300% greater than the oxygen consumption in the relaxed dogs.
3. The increased tissue requirement for oxygen was met both by increased cardiac output and increased oxygen extraction from haemoglobin.
4. Oxygen utilization remained adequate in hypothermia, as shown by the absence of hypoxic acidosis.
5. Heart rate fell during cooling and stroke volume increased to meet the increased oxygen demands associated with shivering during the induction of hypothermia.

Key words: heart, hypothermia, metabolic acidosis, oxygen utilization, shivering.

Introduction

Considerable research has been undertaken on controlled hypothermia as an aid to cardiac and neurosurgery, and Bigelow, Lindsay, Harrison, Gordon & Greenwood (1950) demonstrated that dogs cooled to 30°C were able to withstand total circulatory arrest for as long as 30 min with safety and that the reduction in tissue oxygen uptake bore a linear relationship to the fall in deep body temperature. This depended upon effective muscle relaxation to abolish shivering together with controlled ventilation. Accidental hypothermia is, however, usually associated with a period of marked shivering, which may continue through the cooling phase and result in an increase in oxygen consumption of up to five times the resting value (Horvath & Howell, 1964).

Although metabolic acidosis may occur in induced hypothermia as a complicating factor after prolonged circulatory arrest, transfusion of blood-citrate/citric acid/glucose solution, and assisted ventilation (Brewin, Gould, Nashat & Neil, 1955; Henneman, Bunker & Brewster, 1958; Burton, 1964; Ledingham & Norman, 1965), it is generally accepted that it is of negligible significance as long as shivering is prevented (Rosenfeld, 1963). In accidental hypothermia, however, the extra oxygen requirements may not be met because of cardiorespiratory depression, in association with inability of haemoglobin to give up its oxygen despite low tissue oxygen tensions after the shift to the left of the oxyhaemoglobin-dissociation curve (Nisbet, 1964). A marked metabolic acidosis may thus develop from increased lactate production during shivering thermogenesis (Henneman et al., 1958; Rosenfeld, 1963; Michenfelder, Uhlein, Daw & Theye, 1965), which is not efficiently metabolized by the liver. Under such circumstances the heart is at considerable risk (Ledingham & Norman, 1962).

It seems likely that the pathophysiology of accidental hypothermia is different from induced surgical hypothermia and the purpose of this
experimental study was to compare physiological and biochemical effects in an animal model of accidental hypothermia with those in a group of cooled animals relaxed and ventilated as in induced, surgical hypothermia.

Methods
Twenty-five adult mongrel dogs were anaesthetized with sodium pentobarbitone (25 mg/kg) and intubated. They were divided into two groups (A and B). Dogs in group A \((n = 15)\) breathed room air spontaneously and shivered freely during cooling; the animals in group B \((n = 10)\) were given pancuronium bromide (100 \(\mu\)g/kg), which caused effective muscle relaxation and abolished shivering. Group B animals were ventilated with a Manley ventilator so as to maintain the same arterial \(P_{\text{CO}_2}\) as that in the dogs of group A.

Cu/CuNi thermocouples enclosed in soft plastic cannulae attached to a Comarck electronic thermometer were used to monitor midoesophageal and rectal temperatures. Cannulation of the femoral vessels and the pulmonary artery, by means of a Swan-Ganz catheter introduced through the external jugular vein, allowed measurement of mean aortic, central venous and pulmonary arterial pressures and sampling of arterial and mixed venous blood. It also allowed the measurement of cardiac output, by the dye-dilution technique, indocyanine green, a Guildford pump and a Waters Densitometer Cuvette being used. The electrocardiograph was recorded by subcutaneous needle electrodes and a Gould-Brush recorder throughout the experiment. This allowed detection of arrhythmias and the measurement of heart rate. Stroke volume was subsequently calculated from simultaneous cardiac output and heart-rate measurements.

The oxygen content of arterial and mixed venous blood was measured with a Lex-O\(_2\)-Con analyser and values for total body oxygen consumption were then calculated from the arteriovenous difference in oxygen content and the cardiac output. Acid–base status was monitored with the ABL1 acid–base analyser (Radiometer, Copenhagen). \(\text{pH, } P_{\text{CO}_2}\text{, and } P_{\text{O}_2}\) were measured at 37°C and the values obtained adjusted to the body temperature of the dog by applying the correction factors of Burnett & Noonan (1974).

The correction factors used were subsequently verified in our laboratory with a IL237 (Instrumentation Laboratories) tonometer. Arterial lactate estimations were made by an enzymatic method by using the biochemico-test combination.

When a steady, resting state had been achieved the animals were all cooled by immersion in ice/water until the midoesophageal temperature fell to 29°C. The average duration of cooling was 3 h, although this tended to be somewhat shorter in those animals in which shivering was prevented. The various parameters were measured at half-hourly intervals throughout the experiment.

Results
In Fig. 1 may be seen the measurements of total oxygen consumption (mean ± SEM) made in both groups of dogs during cooling. The group in which shivering was prevented (group B) showed the expected decline in oxygen consumption as core temperature fell and the value obtained at 30°C approached 50% of the resting value. The dogs of group A showed a marked and sustained increase in oxygen consumption during cooling and shivering; thermogenesis was still evident at 30°C when the oxygen consumption was 300% greater than that found in the relaxed dogs of group B.

Measurements of cardiac output and oxygen extraction are shown in Fig. 2 for both groups of dogs. Increased demand for oxygen by shivering tissues of group A dogs was reflected by a sharp increase in cardiac output as cooling commenced \((P < 0.001)\), suggesting that the cooling tissues were able to extract increased quantities of oxygen from the haemoglobin when demands were increased despite the shift to the left of the oxyhaemoglobin-dissociation curve, which occurs at reduced body temperature. The cardiac output in the relaxed dogs (group B) fell in phase with the reduced oxygen extraction during cooling and cardiac output thus declined in proportion to the fall in oxygen consumption.

![Fig. 1. Measurements of total oxygen consumption (means ± SEM) made during cooling to 30°C in shivering (●) and relaxed (△) dogs.](image-url)
The increased affinity of haemoglobin for oxygen at low temperatures has been said to be partly counterbalanced by the increased solubility of oxygen in plasma as temperature falls. The responses of oxyhaemoglobin to the increased oxygen needs of shivering at low temperatures is set out in Fig. 3, which shows the relationship between oxygen tension, saturation and content in arterial and mixed venous blood taken from the shivering dogs of group A before and at the end of cooling. The position in vitro of the oxyhaemoglobin dissociation curve is shown at 38°C and 30°C at pH 7.4. The measured mean values are shown in association with the respective dissociation curves and the simultaneous measurements of oxygen content are shown above (Fig. 3). It seems clear that at 30°C desaturation of haemoglobin provides a considerable proportion of the increased oxygen needs of the tissues, and the close proximity of the measured values to the standard dissociation curve suggests that the changes shown in Fig. 4(a) in pH and Pco₂ during the experiments were minimal. Of particular importance is the striking ability of shivering muscles to extract oxygen from haemoglobin at low temperature. This is shown in the arteriovenous oxygen difference.

Fig. 4(b) shows the measurements (mean ± SEM) of the metabolic component of acid–base balance in both groups of dogs, and the measurements of serum lactate are tabulated above the Figure. This shows that the arterial values obtained from both groups are similar and that a mild metabolic acidosis develops in the presence or absence of shivering, but it is of similar magnitude in both groups and is partially reversed on rewarming. The nature of this acidosis is unclear, but it is not attributable to lactic acid accumulation and is not worsened by shivering thermogenesis. The absence of increased accumulation of fixed acids in the shivering group suggests adequate utilization of oxygen in that group to meet the increased oxygen demands associated with shivering.

The cardiac response to cold is shown in Fig. 5. The fall in heart rate paralleled body temperature and was uninfluenced by the increased tissue oxygen requirements of the shivering group. In the relaxed group, stroke volume values varied in sympathy with reduced rate and oxygen needs, but
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Fig. 4. Acid–base measurements (means ± SEM) made during cooling to 30°C and rewarming in both shivering (●) and relaxed (△) groups of dogs. (a) pH and PCO₂ values corrected for temperature. (b) Lactate, standard bicarbonate and base deficit. Serum lactate concentrations (mmol/l) are shown at the arrows at the top of the Figure.

Fig. 5. Measurements of heart rate and stroke volume (means ± SEM) made during cooling to 30°C in both shivering, (●) and relaxed (△) groups of dogs.

the stroke-volume values in the shivering group rose progressively and strikingly to that at 31–29°C (P < 0.01). The increased cardiac output required to provide for the increased oxygen needs of shivering in the face of falling heart rate was thus largely obtained by a progressive increase in stroke volume in the shivering group. This stress on the myocardium in the shivering group did not produce an increased incidence of arrhythmias (6% group A, 10% group B) and no deaths were recorded during the experiments.

Statistical analysis was carried out with Student's t-test.

Discussion

There has been considerable debate over the years as to whether tissue oxygen requirements are met at low body temperature (Table 1). Unless suppressed by alcohol, narcotics or other sedative drugs, shivering normally occurs during cold exposure and there have been few experimental studies on the sequelae of shivering thermogenesis in either normothermic or hypothermic conditions. It has been shown, for example, by Halkald,
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Koivikko & Lansimies (1972) that oxygen consumption and cardiac output both increase in shivering dogs during cooling. The effects of shivering on carbohydrate metabolism in dogs exposed to the cold, but at normothermia, has also been studied (Pernod, Vincent-Falquet, Jomain & Minaire, 1961; Minaire, Pernod, Vincent-Falquet & Mottaz, 1973) and it was shown that a well-oxygenated metabolism was maintained with low concentrations of plasma lactate. Despite these studies it is widely held that this metabolic state will not hold true in hypothermia on account of its association with tissue hypoxia, lactic acidosis, depressed hepatic metabolism and those other factors outlined in Table 1. This belief is based more on theoretical considerations than experimental proof, for it has been shown that hepatic metabolism is only significantly depressed at liver temperatures well below 30°C (Ballinger, Vollweider, Templeton & Pierrucci, 1961) and at such temperatures shivering may become greatly depressed. When the temperature falls below 33°C in humans shivering may also then be significantly depressed (Editorial, 1964). In this present study, lactic acid concentrations remained low in both groups of dogs and recent metabolic studies reviewed by Nesbakken (1973) have shown that serious inhibition of carbohydrate metabolism occurs during hypothermia with preferential utilization of lipid. It seems likely that metabolic acidosis during hypothermia has been attributed to lactic acidosis on the basis of early work involving circulatory arrest, transfusion of blood-citrate/citric acid/glucose solution and assisted ventilation with relative hypocapnia.

Attention has also been focused on the response of oxyhaemoglobin to cooling and several workers believe that tissue hypoxia may occur at low temperatures because of the shift to the left of the oxyhaemoglobin-dissociation curve, resulting in failure of dissociation of oxyhaemoglobin (Fairley, 1961; Nisbet, 1964; McNicol, 1967). Astrup, Engel & Severinghaus (1965) investigated the influence of temperature on the dissociation curve and this is reproduced in Fig. 3. In the present study, the arteriovenous oxygen difference was well maintained during cooling in the absence of shivering and greatly increased in response to the increased demands of shivering; the availability of oxygen to the tissues was largely due to desaturation of oxyhaemoglobin at low tissue oxygen tensions. This finding is in accordance with that of Nicolas, Nicolas, Heurtel, Baron, Rodineau & de Lajartre (1974), who noted that lactic acidemia was an inconsistent finding in a series of hypothermic patients despite low arterial oxygen tensions and contrary to the belief that the hypothermic patient will compensate poorly for any extra oxygen demand (McNicol & Smith, 1964; Jones & McLaren, 1965).

Interpretation of blood-gas data in hypothermia causes much argument and errors may occur in relating corrected values to normal values at normothermia. It is generally agreed where measurements are made at electrode temperatures higher than body temperature that corrections should be made to reflect the acid–base status in vivo. This also applies to oxygen tension, since change in temperature of a sealed blood specimen affects the solubility of oxygen in plasma and also the equilibrium between oxyhaemoglobin and dissolved oxygen (Burnett & Noonan, 1974). Oxygen saturation and oxygen content values do not change during cooling in vitro and computed data of these factors should thus be made from pH, PCO₂ and PO₂ values relating to 37°C (Kelman & Nunn, 1966; Severinghaus, 1966). The mean value for arterial PO₂ at 30°C in the shivering group of the present study was 37 mmHg. It would be misleading to relate this value to the normal range for 37°C, as this would suggest hypoxia. Simultaneous measurements from the same specimen showed well-maintained oxygen saturation and content of arterial blood and a low concentration of lactic acid. Despite low oxygen tensions, aerobic metabolism and oxygen desaturation took place at this temperature (Figs. 3 and 4).

These results suggest that metabolic and pathophysiological events in accidental hypothermia are very different from those which take place in induced hypothermia, and the response of the heart to cooling is not only of fundamental importance in the consideration of oxygen availability but also in the consideration of the clinical consequences of accidental hypothermia. In induced hypothermia

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**Table 1. Shivering response during hypothermia**

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1. Extra oxygen demand may not be met: (a) Inadequate ventilation; (b) Inadequate circulation; (c) Shift of oxyhaemoglobin-dissociation curve

2. Metabolic acidosis: (a) Tissue hypoxia (due to 1); (b) Increased production of lactic acid; (c) Depressed hepatic metabolism

3. Arrhythmias: (a) Stress on cold myocardium; (b) Other factors (hypoxia, acidosis)
the fall in cardiac output is largely due to a fall in rate rather than stroke volume. Slowing of heart rate during hypothermia occurs in a linear fashion irrespective of tissue demands (Fig. 5), and during shivering thermogenesis the heart relies largely on the ability of the myocardium to maintain an increased stroke volume. This presented no apparent difficulties to the healthy dogs in this study but it points to the potential hazards of accidental hypothermia in the elderly and in those with pre-existing cardiac pathology. The greatest calls made on the myocardium are early in the process when shivering is maximal and it is perhaps fortunate that the very great demands of the tissues for oxygen during shivering thermogenesis are met partly by increasing cardiac output and partly by increasing oxygen extraction from haemoglobin.

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References


