Energy Metabolic Changes during Induced Hyperthermia

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Abstract: The influence of induced hyperthermia on energy metabolism was investigated by elevating body temperature up to 43℃ with warm water in anesthetized 8 mongrel dogs. This study showed that both the oxygen consumption and carbon dioxide production increased 8-10% for a body temperature rise of one centigrade degree, and also increased about 50% and 40%, respectively at 43℃ although non-protein respiratory quotient was kept constant. Blood glucose level has been kept more than 100 g/dl during experiment. On the other hand, both arterial acetoacetate and β-hydroxybutyrate levels increased significantly about 60% and 100%, respectively at 43℃. These results may show that both carbohydrate and fat utilization for energy expenditure tends to be higher during hyperthermia.

Key words: Energy metabolic changes, Blood glucose, Arterial acetoacetate, β-hydroxybutyrate

INTRODUCTION

Malignant hyperthermia is one of the most common cause of death in anesthetized patients, although mortality has decreased over the last 20 years from 80% to less than 10% (Kaplan, 1991). Previous experiments have shown that the hyperthermia is associated with an increase in oxygen consumption and carbon dioxide production (Honda *et al.,* 1980).

It was uncertain however whehter this hypermetabolic state could effect on energy requirements. The present study examines the influence of induced hyperthermia by surface warming on fuel utilization in mongrel dogs which were hypermetabolic.

SUBJECTS AND METHODS

The study was approved by the Institutional Committee for Animal Use and Care of the Oita Medical University.

The experiments were carried out in eight mongrel dogs of male and weighing 13.6±0.9 kg (mean±SE). Anesthesia was induced with pentobarbital (25 mg/kg) and pancuronium bromide (0.2 mg/kg); the trachea was intubated; and ventilation volume was con-

trolled at 12-15 ml/kg using an Aika Respirator for Animals. The frequency of respiration was adjusted so as to maintain endtidal carbon dioxide pressure between 33 mmHg and 38 mmHg. Anesthesia was maintained with nitrous oxide in oxygen and by a continuous infusion of pentobarbital (1 mg/kg). Pnacuronium bromide was given incrementally for muscle relaxattion to prevent increasing the oxygen cost of panting. Ventilation and fractional oxygen concentration were adjusted to maintain normoxia and normocapnia.

External juglar or femoral vein canulation was performed for the infusion of IV fluid, central venous pressure monitoring, and the measurement of blood temperature (Nihonkoden Co, Ltd., M 631 thermal unit). A femoral arterial catheter was used for blood sampling and blood pressure monitoring (Nihonkoden Co, Ltd., P200 pressure transducer).

A left thoracotomy at the fifth intercostal space was performed; An electomagnetic flowmeter probe (Nihonkoden Co, Ltd., MOT1200 flowmeter) were placed at the origin of the aorta. After midline abdominal incision, hepatic arterial blood flow was measured continuously using electromagnetic flow probe. On the other hand, portal venous blood flow was measured simultaneously utilizing an ultrasonic transit-time volume flowmeter (Adbance Co, Ltd., T101 flowmeter). Total hepatic blood flow (THBF) was caliculated as hepatic arterial blood flow plus portal venous blood flow. Saline was administered at 20 ml/kg/hr during the surgical procedure by drip infusion and at 30-40 ml/kg/hr during the temperature elevation to maintain central venous pressure at level 3-5 mmHg. Glucose was also administered at 0.6 g/kg/hr. Oxygen consumption and carbon dioxide production were measured with indirect calorimetry (breath by breath method) using Medical Gas Analyzer MG360 and Respiromonitor RM300 (Minato Co, Ltd.).

The respiratory quotient (RQ; in this case, nonprotein RQ) means the ratio of the volume of carbon dioxide production to the volume of oxygen consumption. Arterial blood concentration of acetoacetate and β-hydroxybutyrate were measered by enzymic determination of Williamson method with spectrophotometer Keto340 (Iharadenshi Co, Ltd.). The temperature was raised by wrapping the dogs with vinyl sheet and immersing them in hot water as high as 45°C in 2 to 3 hr. Water temperature was regulated with the Heater (Taiyou Co, Ltd., Thermal Unit 302) to keep the temperature difference between water and body within 10°C.

The measurement of following paramenters and blood sampling were done 6 times, at 38°C as a control, and 39, 40, 41, 42 and 43°C.; cardiac index, hepatic arterial blood flow, portal venous blood flow, oxygen consumption, carbon dioxide production, blood glucose, arterial blood concentration of acetoacetate and β-hydroxybutylate.

Data were analyzed using analysis of variance and Student's t test. Statistical significance was set at $P < 0.05$. Data are presented as the mean±SE.

Results

1) Changes in energy metabolism (Table 1)

As shown Table 1 the control oxygen consumption ($\dot{V}O_2$ was 122 ml/min. $\dot{V}O_2$ increased 8-10% for a body temperature elevation of one centigrade degree, and also increased 52% at 43℃. The control carbon dioxide production ($\dot{V}CO_2$) was 100 ml/min. $\dot{V}CO_2$ also increased about 10% for a body temprature elevation of one centigrade degree, and 56% at 43℃. Both $\dot{V}O_2$ and $\dot{V}CO_2$ increased similarly according to body temperature elevation. So the respiratory quotient was kept constant (from 0.81 to 0.84) during hyperthermia.

2) Acetoacetate, β-hydroxybutyrate and blood glucose (Table 1)

Arterial acetoacetate concentration increased significantly at more than 42%, and 134% at 43℃. Changes in arterial β-hydroxybutyrate concentration show similar tendency to the blood concentration of acetoacetate. Arterial β-hydroxybutyrate increased 67% at 43℃. Blood glucose concentration decreased significantly at 43℃, but we could not find out hypoglycemia during hyperthermia.

3) Cardiac index and total hepatic blood flow (THBF) (Fig. 1)

Cardiac index increased significantly 35% at 42℃, showing the parallel increase with the oxygen consumption, but cardiac index decreased at 43℃, not in parallel with an increase in $\dot{V}O_2$. THBF was well maintained at the control level. And there were also no significant differences in hepatic arterial and portal venous blood flow at different hyperthermic body temperature.

Table 1. O_2 consumption, CO_2 production, respirratory quotient (R), acetoacetate, β-hydoxybutyrate and blood glucoses

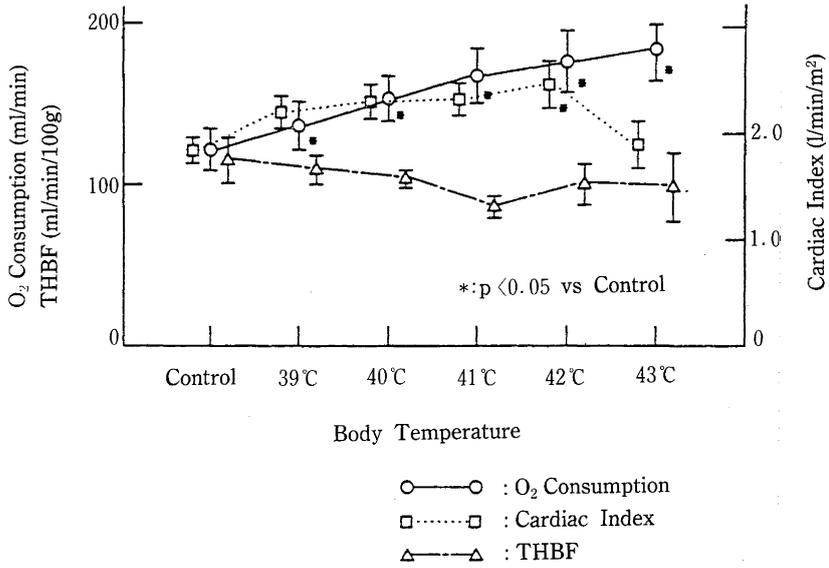|	Control	39℃	40℃	41℃	42℃	43℃
$\dot{V}O_2$ (ml/min)	122±13	137±15*	154±14*	168±17*	177±19*	185±20*
$\dot{V}CO_2$ (ml/min)	100±12	112±13*	123±13*	137±12*	143±15*	156±16*
R	0.82±0.03	0.82±0.02	0.81±0.01	0.82±0.02	0.81±0.03	0.84±0.02
Acetoacetate	35.0±6.0	35.8±5.9	36.0±2.5	54.1±5.6	73.2±8.5*	81.9±6.7*
β-hydoxybutyrate	32.2±3.7	30.2±2.8	37.4±5.7	38.7±5.2	48.4±6.5*	53.8±2.2*
Blood glucose	185±25	182±24	187±20	162±11	156±14	118±13*

(M±SE)
*P<0.05 vs Control

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Fig. 1. Changes in O_2 consumption, cardiac index and total hepatic blood flow (THBF).
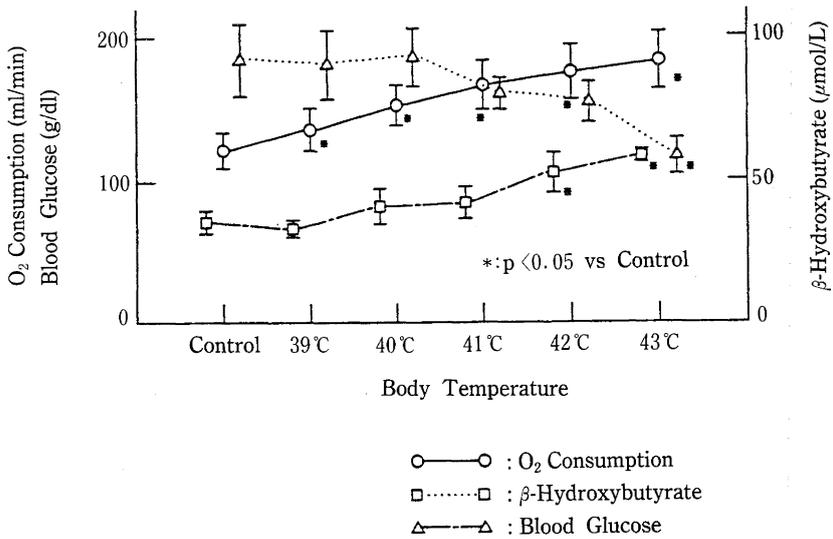Values are means±SE.

Fig. 2. Changes in O_2 consumption, β-hydroxybutyrate and blood glucose. Values are
mean±SE.

DISCUSSION

Although the complex metabolic reactions to hyperthermia are not actually understood, it is well known that oxygen consumption will increase with increasing body temperature according to van't Hoff's rule. The effect of increasing body temperature on metabolic rate is related to acceleration of the rates of biochemical reactions. In biochemical reactions, the expected Q_{10} may be between 2 and 3. In our study muscle relaxants were given sufficiently to prevent panting. So it seems quite resonable to neglect that the increase in work of breathing participates in producing the increased $\dot{V}O_2$ (Usinger, 1968). Our data show $\dot{V}O_2$ increase 8-10% rise for a body temperature rise of one centigrade degree, and 52% at 43%. Since metabolic rate is correlated with $\dot{V}O_2$, we could estimate that a body temperature of 43℃ may also increase metabolic rate by about 50%. This result may well correlate with earlier studies. Du Bois (1954) summarized his studies of the influence of body temperature on metabolic rate, stating that metabolic rate increased 13% per degree Celsius (Du Bois, 1954). The respiratory quotient is a helpful part of indirect calorimetry determination, since it establishes the caloric equivalent of oxygen. Our data show unequivocally an increase in $\dot{V}CO_2$ during hyperthermia associated with an increase in $\dot{V}O_2$. Since an increase in $\dot{V}CO_2$ showed parallel increase with $\dot{V}O_2$, nonprotein respiratory quotients were well preserved at control value. Although metabolic rate increased by 50%, this constant RQ in our study is considered to represent the oxidation of carbohydrate and fat as a fuel is increased equally with progressive rise of body temperature. In other words, there was continued utilization of both endogenous fat and carbohydrate for energy, even though the hypermetabolic state was induced by the progressive hyperthermia. Because a general value for RQ is 0.84 resulting from the arithmetic mean of the RQ of the foodstuffs: 1 for carbohydrate, 0.89 for protein, and 0.707 for fat (Burszttein, 1989). The proportions of nonprotein energy derived from either fat or carbohydrate oxidation, represented by the nonprotein RQ. In our study, we did not measure nitrogen excretion, but we think this factor may be neglectable. This is because protein represents only about 15% of the total calories in the fuel mixture of the average daily diet and has an RQ in mid-range between fat and carbohydrate.

Carpentier *et al.* (1979) reported that fat oxidation tends to be higher in hypermetabolic patients than in normal subjects or than in malnourished patients (Carpentier, 1979). Increased fat oxidation will be confirmed to measure the concentration of acetoacetate or β-hydroxybutyrate (the "ketone" bodies) which are oxidized products of fatty acids. In our study, both acetoacetate and β-hydroxybutyrate increased significantly at more than 42℃ of body temperature, but the increase of acetoacetate is about twice higher than that of β-hydroxybutyrate at 43℃. The reduction of acetoacetate is effected by β-hydroxybutyrate dehydrogenase and yields β-hydroxybutyrate. Although this reaction is reversible, it is said that when liver glycogen is abundant, the formation of β-hydroxybutyrate is favored; when liver glycogen is relatively low, acetoacetate predominates (White, 1978). Therefore we think liver glycogen is relatively low at 43℃ when metabolic rate seems to be 50% higher than control value. This finding is coincident with a decrease in blood glucose at 43℃, although

hypoglycemia did not occur. In our progressive hyperthermic study, we speculate the following adaptaions will occur owing to increased metabolic rate. In hyperthermic state, terminal glucose combustion mainly occur in the brain and the remainder organism-heart, kidney, skeletal muscle and so forth-uses either fatty acids released directly into the circulation or fatty acids oxidized to acetoacetate or β-hydroxybutyrate by liver (Sherwood, 1970).

Although liver is at the center of the adaptive mechanism, Collins et al. (1980) reported that hepatic metabolic and biosynthetic functions are impaired at higher temperatures, as are many other metabolic functions (Collins, 1980). Our data show cardiac index increased at body temperatures of up to 42°C, showing the parallel increase with the metabolic rate and deareased at 43°C. But total hepatic blood flow was well maintained at control value even though at 43°C. According to hepatic blood flow, hepatic circulation may be well maintained in our induced hyperthermia.

We have discussed energy metabolic changes in induced hyperthermia in dogs. Our preliminary results suggest that hypermetabolic state induced by hyperthermia uses both glucose and fat as a fuel for increased energy demand. But our induced hyperthermic time course is short (3 to 4 hr), so we need further analysis about muscle protein brakdown, fuel sources and its utilization.

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