Effects of Hyperthermia (by Surface Warming Method) on the Circulatory System and Others

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The body temperature used for hyperthermotherapy is that close to the limit of thermoregulation, which causes an exceptionally high metabolism. Therefore, in this treatment it is very important that the respiratory and circulatory systems supplying required oxygen are in a stable condition. The present experiment was carried out to study possible changes in hemodynamic conditions under hyperthermia.

Fourteen adult mongrel dogs were used in the experiment and injected with thiamylal. Arterial pressure, central venous pressure, and electrocardiograms were recorded in spontaneous respiratory conditions, and at the same time possible changes in respiratory conditions and in blood gas were observed. Hyperthermia was induced by a surface warming method with the animal dipped in warm water. The results obtained were as follows:

1. In the electrocardiogram tachycardia appeared with body temperature elevation. A depression in ST. became gradually more distinct in some dogs. On cardiac arrest, cardiac standstill appeared more frequently than ventricular fibrillation.

2. Systolic pressure tended to increase with a rise in body temperature, but showing no marked changes, expressed as average arterial pressure. It showed a tendency to decrease rapidly at a body temperature above 41°C.

3. Heart rate presented no significant changes so long as the body temperature was 41°C or below, but began to increase rapidly at a temperature above 42°C.

These changes were presumably accompanied with an increase in cardiac output. An increase of catecholamine in the blood seemed to be responsible for such increase. In a temperature above 42°C, presumably, respiration rate, minute volume and blood pressure decrease rapidly and hypoxia is exacerbated abruptly.
INTRODUCTION

Clinical hyperthermia has once been used as an approach to the treatment of syphilis and arthritis. Recently, it began to be applied to the treatment of malignant tumor. The body temperature used for this treatment is that over 41°C which is presumed the limit of thermoregulation of the living body. It is too high to occur in ordinary clinical cases, and is readily considered to be dangerous for the body.

In general, hyperthermia is accompanied with hypermetabolism. As already reported, it induced an increase in oxygen consumption and changes in the respiratory system. If the respiratory or circulatory system is disturbed in such hyperthermia, tissue will rapidly suffer from hypoxia. Then, it is assumed that the least changes in these systems under hyperthermia may possibly have serious influences. The present investigation was carried out to study possible responses of the circulatory system at a temperature high enough to be applied to the hyperthermic treatment or over the limit of thermoregulation. The results obtained are reported.

MATERIALS AND METHODS

Fourteen adult mongrel dogs weighing 4-12 kg were used in the experiment, which were administered with 50 mg/kg of thiamylal and equipped with an endotracheal tube under spontaneous respiration.

After the intubation, the inguinal regions in the dogs were anesthetized by infiltration with 2% lidocain. By a femoral arterial and venous cannulation, arterial and central venous pressures were measured, and the same time electrocardiograms were recorded at lead II by using a polygraph system manufactured by the Nippon Koden Co., Ltd. Amplifiers, F-M25 and RM150 were used in the record of both pressures and in electrocardiogram. With an increase in body temperature, respiration rate, minute volume, oxygen uptake, and blood gas were determined simultaneously.

To produce hyperthermia, the animal was wrapped with vinyl sheet and dipped in warm water 39-40°C. The temperature of water was elevated up to 45-46°C.

Body temperature was measured by using a probe PD-1 of thermometer manufactured by the Thermo Co., Ltd. and the probe fixed on the skin of epigastric region.

RESULTS

With the start of surface warming, body temperature rose up in parallel with the increase in water temperature, reaching its maximum in about 2-3 hours after the start of heating, when the animal died.

During that period the electrocardiogram tended to show a tachycardia with the increase in body temperature until the animal died. It presented sinus rhythm all the time in some dogs or premature beat on the body temperature elevation in some other
Fig. 1, Changes in Electrocardiogram (ECG II), Central venous pressure (CVP) and Arterial pressure (AP) during Hyperthermia in Case No. 307. CVP didn’t show remarkable change but AP tended to increase as shown in record.

Fig. 2, Changes in Electrocardiogram (ECG II), Arterial pressure (AP) and Central venous pressure (CVP) during Hyperthermia in Case No. 310.
dogs or gradual depression in ST segment in some other dogs. Consequently, it hardly showed any definite tendency. Upon cardiac arrest, the electrocardiogram presented cardiac standstill in many dogs and ventricular fibrillation in a few dogs.

Arterial pressure showed a rise and fall, as shown in the records. When the body temperature began to rise, both systolic and diastolic pressures tended to increase. This tendency persisted until the temperature reached 40–41°C. Each pressure tended to decrease when the temperature exceeded 41°C, and at the same time pulse pressure was reduced gradually. (Fig. 1, 2)

Mean arterial pressure examined during the same period as mentioned above, revealed no marked changes until the body temperature surpassed 41°C, without changes in systolic and diastolic blood pressures. When the temperature exceeded 42°C, it tended obviously to decrease, as shown in the records of arterial pressure. There was

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**MAP**

![MAP Diagram](image)

**HR**

![HR Diagram](image)

Fig. 3, Average mean arterial pressure at body temperature elevation in dogs. Vertical bars on each mean value indicated standard deviations. The value at 43°C or above showed significant difference from the value at 38°C.

Fig. 4, Average mean heart rate at body temperature elevation in dogs. Explanation of this figure is same as Fig. 3.
Fig. 5, Hyperthermic responses of respiratory rate (RR), Mean arterial pressure (MAP) and Heart rate (HR) in Case No. 303.

Fig. 6, Hyperthermic responses of pH and Oxygen saturation (O₂ sat). 
A: Arterial blood. V: Central venous blood.
a significant difference (P=0.01) between mean arterial pressure measured at 38°C of body temperature and that measured at any temperature higher than 43°C. (Fig. 3)

Heart rate had no marked changes until the body temperature reached 41°C, beginning to increase rapidly when the temperature exceeded 42°C. There was a significant difference (P=0.01) between the rate estimated at 38°C and that estimated at a temperature over 42°C. (Fig. 4)

Comparison with other items of measurement: Fig. 5 and 6 give the results of experiment on a group of items of measurement, in which the respiratory rate reached a maximum when the body temperature was about 41°C. It revealed a rapid decrease when the temperature exceeded 41°C. In this case mean arterial pressure decreased gradually until the temperature reached 41°C. Thereafter, it showed a rapid decrease. Heart rate increased until the body temperature reached 42°C. Thereafter, it decreased suddenly until cardiac standstill occurred. Oxygen saturation examined in the course of experiment mentioned above, decreased slowly in arterial blood, but rapidly in venous blood when the body temperature exceeded 41°C. In other words, the difference in oxygen saturation between arterial and venous bloods began to be enhanced suddenly when the body temperature exceeded 41°C. It is of interest to note that pH began to decrease rapidly when the body temperature exceeded 42°C.

**DISCUSSION**

Many papers have been published to report studies on possible physiological changes in the body treated by the surface warming method or placed in a high-temperature environment to produce a hyperthermic condition. It was one of the purposes of these studies to clarify the pathophysiology of an heatstroke. Attention should be paid to a series of papers published by Frankel et al. in the field of hyperthermia, who carried out an experiment with dogs, in which the heart rate was increased remarkably when the body temperature was within a range of 40.0 to 42°C. Average arterial pressure began to decrease outstandingly when the body temperature exceeded 41.5°C. The respiratory rate reached a maximum when the body temperature was within a range of 40.8 to 42.7°C. It should be noted that respiratory rate reached its maximum almost at the same time when the heart rate and mean arterial pressure presented conspicuous changes. NEMOTO et al. also obtained essentially similar results from their observations on changes in the circulatory system. Besides, WAKIM, K.G. pointed out a decrease in R–R interval in the electrocardiogram as a hyperthermic effect, and mentioned that various changes were generally induced by hyperthermia, which also caused increases in heart rate and cardiac output but found no definite changes in blood pressure. In the present investigation the electrocardiogram presented no definite tendency. As far as the depression in ST is concerned, however, seeing that ST-segment depression and T wave changes as well as supraventricular tachycardia were observed in the case of the heatstroke by CLOWES, H.A., and O’DONNELL,
T.F., it does not seem to be changes independent of hyperthermia. The body during hyperthermotherapy is not always in the same condition as that affected with heatstroke, since premedication and anesthesia are carried out in that treatment. On the other hand, PETTIGREW, R.T., et al. noticed increases in heart rate, blood pressure, and central venous pressure when the body temperature was raised from 36.0 to 41.8°C, and found, however, that blood pressure and central venous pressure returned gradually to their initial levels while the body temperature was maintained at 41.8°C, and especially on blood pressure observed little change in diastolic pressure while systolic pressure increased by 20–50 mmHg. BYNUM, G.D., et al. raising up the body temperature in healthy and diseased adult human beings, found similar tendency in blood pressure and heart and respiratory rates in the former, but no changes in blood pressure in the latter. It should be noted, that these patients were administeted with ketamin and diazepam.

It short, blood pressure and heart and respiratory rates seem to increase until the body temperature reaches 41–42°C. In the present investigation almost similar tendency was shown in the results obtained.

On the other hand, KOROXENIDIS, G. T., et al. noticing increase in heart rate and cardiac output in accordance with a rise in body temperature, reported that the increase in cardiac output was induced by that in heart rate because there was no change in stroke volume. DAMATO, A.N., et al. found increases in heart rate and cardiac output when the environmental temperature was raised from 25°C to 51°C, and mentioned nothing about the body temperature, which seemed to have been raised to a considerable extent at such environmental tempeartuer. In hyperthermotherapy BULL, J.M., et al. observed that heart rate and cardiac index were higher and mean arterial pressure was lower when the body temperature was 41.8°C than when it was 37.0°C. Moreover, the authors, using droperidol as an α-blocker to obtain similar results, reported no change in stroke volume.

The results mentioned above make quite sure that an increase in cardiac output accompanies that in heart rate. Referring to the report of KIM, Y. D., et al., an increase in catecholamine, especially norepinephine, in blood plasma was presumably responsible for these changes in the circulatory system. These changes were probably induced with the liberation of catecholamine urged by hypermetabolism due to hyperthermia. Similar interpretation may be applied to malignant hyperpyrexia, one of the complications of anesthesia, and some other types of hyperpyrexia. Besides, an increase in catecholamine may further stimulate hyperthermia. It is assumed that when the body temperature exceed 42°C, oxygen supply may be reduced by a decrease in respiratory rate, and that hypoxia may progress so rapidly that the results mentioned above may be obtained.
REFERENCE