

Respiratory Responses During Induced Malignant Hyperthermia with 2,4-Dinitrophenol in Dogs

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The following experiment was carried out to obtain pathophysiological information at abnormally high body temperatures in malignant hyperthermia during anesthesia.

Anesthesia was induced with pentobarbital in 17 adult mongrel dogs and 8 mg/kg of 2,4-dinitrophenol was administered intravenously under spontaneous respiration. These animals were observed for change in body temperature elevation, occurrence of muscle rigidity and change in respiratory condition, and oxygen uptake was determined. The results were as follows:

- 1) Body temperature rose to 41°C or above within 1–2 hours in every animal and, in 90% of them, body temperature rose to 42°C or above.
- 2) Muscle rigidity or convulsion didn't occur in any animal from the early to late stages of body temperature elevation, which seemed attributable to the effect of pentobarbital.
- 3) Respiratory rate and minute volume increased rapidly with body temperature elevation and reached their maximum values at about 42°C, followed by gradual decrease.
- 4) Oxygen uptake also increased rapidly and reached its maximum value at 42°C.
- 5) These changes in minute volume, respiratory rate and oxygen uptake suggest that the upper limit of body temperature regulation lies around 42°C in dogs.

INTRODUCTION

It has been known that malignant hyperthermia as one of complications during general anesthesia can be divided into rigid type with muscle rigidity and non-rigid type without it on the basis of clinical features. The former has been investigated by many authors and similar symptoms have been noted in a certain kind of pigs. In this type, abnormal findings have been noted especially in caffeine contracture test by muscle

biopsy and it has been considered that malignant hyperthermia is due to an inability to control calcium concentrations within the muscle fiber. On the other hand, in the non-rigid type abnormal findings have not been noted in muscle biopsy and it has not been elucidated fully with respect to etiology, though Britt & Kalow¹⁾ and Strobel & Bianchi¹²⁾ have suggested that anesthetic agents may act as uncouplers on oxidative phosphorylation in mitochondria.

Accordingly, the authors have made this experiment using 2, 4-dinitrophenol (DNP), a representative uncoupler considered as a contributory factor of the non-rigid type, in order to know physiological changes at high body temperature.

MATERIALS AND METHODS

Seventeen adult mongrel dogs were used for this experiment. After intravenous injection of 25 mg/kg of pentobarbital and cannulation, the animals were maintained under spontaneous respiration. Infiltration anesthesia was induced with 2 % lidocaine and then incision was made for cannulation in the right and left femoral artery and vein. Arterial pressure and central venous pressure were measured and recorded together with ECG.

Respiratory rate and minute volume were measured at varying body temperatures and oxygen uptake was determined by Benedict-Roth type spirometer.

Body temperature was measured by fixing a probe PD-1 of thermometer: Core Temp (Terumo, Co. Ltd.) on the skin surface of the upper part of the abdomen.

In addition, blood samples were obtained at varying times for the measurement of blood gas, serum electrolytes and serum enzymes.

Body temperature elevation was induced by 2, 4-dinitrophenol as described above. It was administered in the average dose of 8.0 mg/kg.

RESULTS

1) Change in body temperature (Fig. 1)

When DNP was administered intravenously, body temperature began to rise within several minutes. All of the animals died with 1-2 hours because of hyperthermia at 41°C or above. No animals showed muscle rigidity or convulsion during such body temperature elevation. The maximum temperatures attained were as shown in Table 1. Namely, 90% of the animals showed a maximum temperature of 40°C or above and 60 % of them died from hyperthermia at 44°C or above.

2) Change in respiratory rate and minute volume

Change in respiratory condition was examined by using a respirometer (Right, Co., Ltd.). As shown in Fig. 2, respiratory rate increased rapidly and reached the maximum value at 42°C, followed by rapid decrease to arrest. These changes showed significant difference from the values at 39°C.

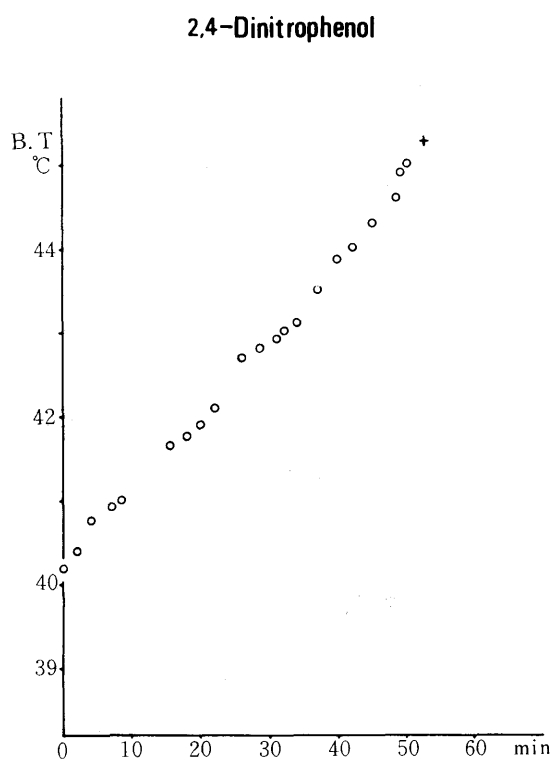


Fig. 1, Body temperature responses on 2,4-Dinitrophenol induced hyperthermia.
+ : Cardiac arrest occurred at this point

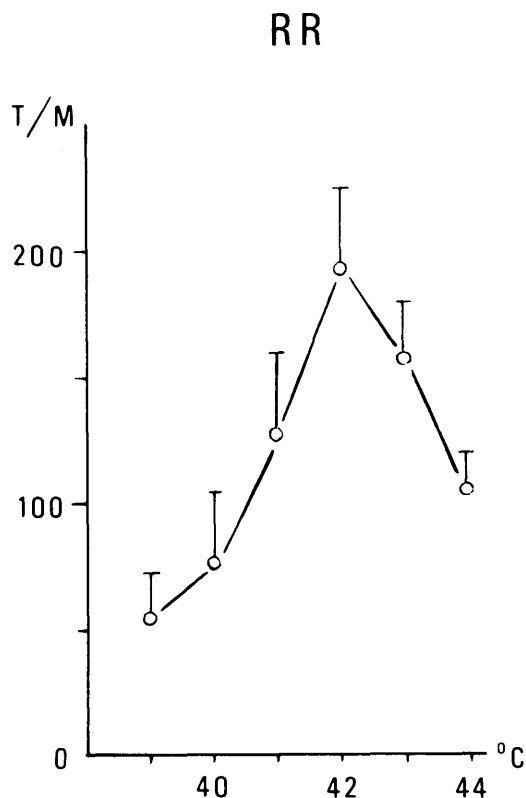


Fig. 2, Average respiratory rate at body temperature elevation in dogs.
Vertical bars on each mean value indicate standard deviations. The values at 41°C or above showed significant difference from the values at 39°C. ($p=0.01$)

Table 1. Maximum body temperature and number of dogs.

Maximum Body Temp.	Number of dogs
41.0 ~ 42 °C	2
42.0 ~ 43	3
43.0 ~ 44	2
44.0 ~	10
Total	17

Table 2. Oxygen uptake at body temperature elevation.

Body Temperature	O ₂ uptake (cc/min/kg)
38 °C	11.5 ± 2.9
39	15.1 ± 7.8
40	24.4 ± 8.1
41	26.4 ± 4.5
42	32.5 ± 9.0
43	28.0 ± 4.3
44	28.3 ± 4.8

Significant difference was noted between 38°C and 40°C ($p=0.02$) or above ($p=0.01$)

Miunte volume showed the same pattern. Namely, the maximum value was reached at 42°C and significant difference was between 39°C and 41°C or above (Fig. 3).

3) Oxygen uptake

As shown in Table 2, oxygen uptake increased rapidly with body temperature elevation and attained the maximum value at 42°C, followed by slight decrease, but significant difference was noted between 38°C and 40°C or above.

Such an increase in oxygen uptake is clearly represented in Fig. 4. In this case, oxygen uptake increased rapidly, as compared with the control, at 40°C or above.

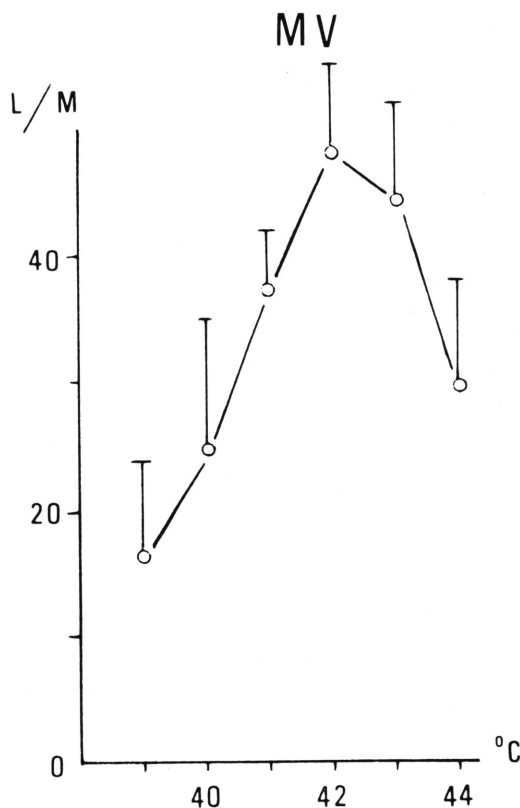


Fig. 3, Average minute volume at body temperature elevation in dogs.
Explanation of this figure is same as Fig. 2.

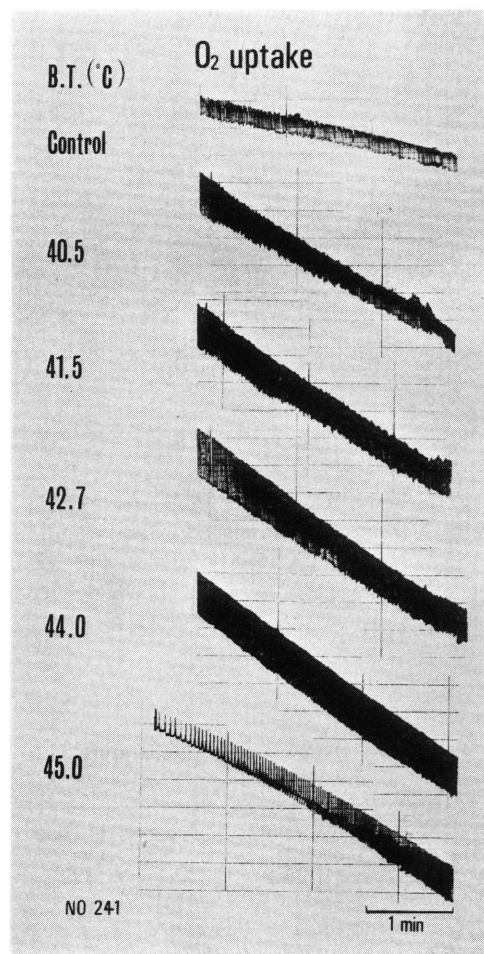


Fig. 4, Typical hyperthermic response of oxygen uptake.

Spirogram at 40.5°C or above showed rapid elevation as compared with the control.

(Time course was shown from right side to left side)

DISCUSSION

As described above, malignant hyperthermia can be classified into two type. Only a few study reports have been presented on non-rigid type hyperthermia and the mechanism involved in its appearance has never been elucidated fully, though it has been suggested that anesthetics may act as uncouplers. There have been some reports using DNP as an uncoupler, but they aimed at the examination of the degree of body temperature elevation and physiological changes were not discussed in detail.

Wilson et al.¹⁰⁾ noted that body temperaure elevation was larger when DNP was combined with Halothane than when it was combined with pentobarbital in dogs and suggested later that malignant hyperthermia might be induced by uncoupling of oxidative phosphorylation¹¹⁾. Hull et al.⁹⁾ made a similar experiment and reported that pentobarbital had a protecting effect against hyperthermia induced by DNP or Halothane. Gatz & Johnes³⁾ administered DNP to rats and noted that Haloperidol antagonized hyperthermia induced by DNP. They⁴⁾ studied anesthetics and described that the effect of Halothane was similar to that of DNP. Gatz⁵⁾ also reported that Halothane and Chlorpromazin acted as uncouplers in vitro and enhanced hyperthermia in vivo, while Droperidol, Haloperidol and pentobarbital exerted the reverse effects. Honda et al.⁷⁾ described that Thiamylal had a protecting effect against hyperthermia induced by DNP and Halothane accerelated body temperature elevation.

Following these findings, it is clear that Halothane enhances the effect of DNP, but it remains to be elucidated in malignant hyperthermia whether Halothane acts as an uncoupler from its early stage or some other predisposing factors are involved.

Concerning muscle rigidity, Hoch & Hogan⁶⁾ described that it developed when rats treated with DNP died from rapid increase in rectal temperature. Honda et al.⁸⁾ administered DNP to dogs and noted appearance of muscle rigidity before death. They considered that this rigidity was not peripheral but central and was different from rigor mortis, because it did not appear or disappeared when pnetobarbital was used during induction or Halothane, muscle relaxants or pentobarbital was administered during body temperature elevation.

Rigidity was not noted in the present experiment, probably because pentobarbital was used during induction. However, body temperature showed a rapid increase, which seemed attributable to that the authors administered 8 mg/kg of DNP instead of 5 mg/kg by Wilson et al. and Hull et al.

Only blood gas, serum electrolytes and metabolic rate have been examined for the evaluation of physiological changes during body temperature elevation. Since tissue metabolism is enhanced rapidly at such abnormal hyperthermia, respiratory conditions should vary to a large extent. However, it has been described only by Honda et al.⁸⁾

In the present study, respiratory rate and minute volume showed almost the same pattern of fluctuation and reached the maximum values at about 42°C. It was interesting that oxygen uptake also reached the maximum value at 42°C. In this case, tidal volume

had been expected to increase, but it showed no evident change. All of respiratory rate, minute volume and oxygen uptake reached the maximum values at 42°C as described above, which seemed closely related to tissue metabolism and also to the limit of physiological function of living bodies.

There may be species differences between men and animals, but it is generally accepted in men that the upper limit of body temperature regulation lies around 41°C and the survival time is limited at 41.5°C or above. Supporting this hypothesis, it has been said that the survival rate in malignant hyperthermia is 61% when the highest body temperature is 41.5°C or below, but 18 % and 17 % when it is 41.5-44°C and 44°C or above, respectively²⁾. Accordingly, in the present study, it seemed that the maximum values of respiratory rate and minute volume were reached at about 42°C in relation to the upper limit of body temperature regulation and hypoxia occurred rapidly in the animals with body temperatures of 42°C or above, resulting in death.

This study was presented at the 7th World Congress of Anesthesiologists (Hamburg, F. R. G.).

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