EXPERIMENTAL STUDIES ON MYOCARDIAL METABOLISM
OF CARBOHYDRATE AND LIPID
IN SURFACE INDUCED DEEP HYPOTERMIA

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In the open-heart surgery undergoing surface-
induced deep hypothermia, especially in
cooling period, metabolic acidosis resulting from
lactacidemia is ordinarily observed. Moreover,
it is supposed that the lactacidemia results from
the anaerobic glycolysis due to the tissue
hypoxia, and the disability to metabolize an
acidic metabolite in the liver. Therefore, under
these situations, it is conceivable that the
investigation of the change of myocardial metabolism
presents one of the criteria to evaluate hypo-
thermia for open-heart surgery. This study was
performed to investigate the myocardial metabo-
lism of carbohydrate and lipid during hypo-
thermia, measuring coronary arteriovenous dif-
ference of glucose, lactate, pyruvate, total fatty
acid and NEFA, and pyruvate dehydrogenase.
Moreover, the influence of high dose administra-
tion of corticosterone and ATP upon the myo-
cardial metabolism during hypothermia was also
observed.

MATERIALS AND METHODS

Mongrel adult dogs were divided into 3 groups
with 5 to 7 dogs in each group. In the first group,
no drug was administered during hypothermia.
In the second group, 2 mg/kg of dexamethason
phosphate was administered intravenously, and
in the third group, 10 mg/kg of ATP-Na₂ was
administered. The dogs were premedicated with
1 mg/kg of triflupromazine, pethidine, pro-
methazine and 0.01 mg/kg of atropine. Anes-
thesia was induced with pentobarbital and main-
tained with ether 2.0–2.5 ml/kg and 100%
oxygen in a closed system. After deep anesthesia
was induced with ether, the dog was placed in an
ice water bath to approximately 23°C in an
average in esophageal temperature. The transfu-
sion was made with 5 ml/kg of low molecular
weight dextran or hydroxyethyl starch and
5 ml/kg of xylitol in the cooling phase. Arterial
blood was taken from the ascending aorta and
coronary venous blood was taken from coronary
sinus by cannulation or direct puncture. Blood
gas by Astrup's method, blood glucose by OTB
method, blood lactate and pyruvate by enzymatic
determination, plasma total fatty acid and
composition of total fatty acid by gas chromato-
graphy, plasma NEFA, pyruvate dehydro-
genase and coronary blood flow by electro-
magnetic flowmeter were measured before cool-
ing and as low as 23°C. Myocardial oxygen con-
sumption (ml/100 g/min.) was represented as
coronary blood flow (ml) x coronary arterio-
venous oxygen difference x 1/100. Myocardial
metabolism was evaluated by A-V difference
ratio, indicating an uptake or a relase of sub-
stance.

RESULTS

1. Acid Base Balance.

Blood pH decreased significantly from 7.49 at
37°C to 7.23 ± 0.21 at 23°C in the group I
(p < 0.05) and showed the same fashion to that
of the group I in the group II and III.

Key Words:
Carbohydrate metabolism
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Blood base excess also decreased significantly from $-5.2 \pm 3.6$ mEq/l at 37°C to $-13.5 \pm 4.1$ at 23°C in the group I ($p < 0.01$), showing the same change in the group II and III. Namely, metabolic acidosis developed during hypothermia in each group. On the other hand, no significant change was observed in PaCO$_2$. In hypothermic anesthesia, FiO$_2$ was 100% and ventilation was made in the fashion of hyperventilation (Fig. 1).

2. Coronary blood flow and myocardial oxygen consumption.

Coronary blood flow of $34.1 \pm 3.7$ ml/min. at 37°C was reduced to approximately half of the precooling level as $17.6 \pm 3.1$ ml/min. at the lowest temperature, showing a significant decrease ($p < 0.05$). Myocardial oxygen consumption ($87.3$ ml/100 g/min. in an average) which was calculated by coronary blood flow and coronary arteriovenous oxygen difference also showed a significant decrease (38.6 in an average) at 23°C ($p < 0.05$), showing a reduction of approximately half of the precooling level. However, as mentioned above, in hypothermic ether anesthesia in a closed system, the PaO$_2$ level was extremely high. Therefore, to obtain an absolute value of myocardial oxygen consumption, further investigations are necessary (Fig. 2).

3. Myocardial glucose metabolism

Blood glucose increased from $136 \pm 9$ mg/dl to $182 \pm 15$ at 23°C in the group I, from $130 \pm 18$ to $174 \pm 5$ in the group II, from $180 \pm 10$ to $210 \pm 15$ in the group III. Namely, blood glucose showed a significant increase ($p < 0.05$) at 23°C in each group. Coronary arteriovenous glucose
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Fig. 3. Blood glucose (left) and coronary arteriovenous (A-V) difference ratio of glucose (right) in hypothermia in each group.

Fig. 4. Blood lactate (left) and coronary A-V difference ratio of lactate (right) in hypothermia in each group.

Fig. 5. Blood pyruvate (left) and coronary A-V difference ratio of pyruvate (right) in hypothermia in each group.

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difference (136 ± 9 - 136 ± 7 mg/dl) was extremely low even at 37°C, suggesting a very slight uptake in the cardiac muscle. As low as 23°C, no significant change (182 ± 15 - 180 ± 20) was observed. In the group II and III, the same findings were observed. There were no special differences between them. (Fig. 3).

4. Blood lactate

Blood lactate increased from 3.9 ± 1.9 mM at precooling to 7.3 ± 2.7 at 23°C in the group I, from 3.9 ± 1.5 to 7.2 ± 2.8 in the group II, from 4.6 ± 2.2 to 8.8 ± 3.2 in the group III. Namely, a significant increase of blood lactate was observed at 23°C in each group (p < 0.05). While, coronary A-V lactate difference ratio was approximately 20% at the precooling, showing a definite utilization in the cardiac muscle. At 23°C, the ratio decreased approximately half of the precooling level, however, it still showed a definite uptake in the cardiac muscle. In group II and III, the same findings were observed. Therefore, it seems that high dose exogenous corticosteroid and ATP do not influence on myocardial lactate metabolism (Fig. 4).

5. Blood pyruvate

Blood pyruvate increased from 0.22 ± 0.16 mM at precooling to 0.34 ± 0.20 at 23°C in the group I, from 0.27 ± 0.15 to 0.35 ± 0.05 in the group II, from 0.23 ± 0.18 to 0.35 ± 0.15 in the group III. Namely blood pyruvate showed a significant increase (p < 0.02) at 23°C in each group as well as the change of lactate. From the aspect of myocardial pyruvate metabolism, coronary A-V pyruvate difference ratio was more than 20% at the precooling, showing a definite utilization of pyruvate. As low as 23°C, coronary
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Fig. 8. Fatty acid of the dog liver in hypothermia in group I.

The active form of pyruvate dehydrogenase (PDH) in the cardiac muscle was 754 ± 492 mU/g tissue at 37°C and 542 ± 227 at 23°C in the group I. The total activity was 1099 ± 514 at 37°C and 985 ± 408 at 23°C. Namely, the active form PDH in the cardiac muscle showed a trend of decrease as low as 23°C, and the total activity also showed the same finding as that of the active form. However, there was no statistical difference between them (Fig. 6).

7. Total fatty acid

Plasma total fatty acid showed a significant decrease (p < 0.02) at 23°C, changing 183 ± 28 mg/dl at precooking to 149 ± 28 at 23°C in the group I (Fig. 7, left). As for the mechanism of decrease of plasma total fatty acid, as shown in Fig. 8, total fatty acid in the liver significantly increased as well as other fatty acid (p < 0.05). Therefore, it seemed that the accumulation of fatty acid in the liver during hypothermia played an important role. On the other hand, in the aspect of myocardial metabolism of total fatty acid, coronary A-V difference ratio showed less than 10% uptake at the precooking and at low as 23°C, indicating no significant change (Fig. 7, right).

8. Composition of total fatty acid

Compared with the composition of total fatty acid of coronary arterial blood and coronary sinus blood at 37°C, there was no significant difference between them. While, as low as 23°C, there was also no significant difference between that of coronary arterial blood and coronary sinus blood. Moreover, compared with the composition of total fatty acid in both coronary arterial blood and coronary sinus blood at 37°C
and that at 23°C, there was no definite difference (Fig. 9).

9. Plasma NEFA

Plasma NEFA was 0.34 ± 0.17 mEq/l at 37°C and 0.36 ± 0.18 at 23°C in the group I, 0.29 ± 0.07 at 37°C and 0.29 ± 0.07 at 23°C in the group II, 0.30 ± 0.13 at 37°C and 0.31 ± 0.11 at 23°C in the group III respectively. Namely, plasma NEFA showed no significant change as low as 23°C in the condition without heparin in each group. As for myocardial metabolism of NEFA, coronary A-V difference ratio of NEFA showed approximately 15% uptake at the precooling in each group. While, coronary A-V difference ratio of NEFA except the steroid group still maintained more than 10% uptake at 23°C (Fig. 10).

DISCUSSION

As for the characteristic change associated with open-heart surgery undergoing surface-induced deep hypothermia, metabolic acidosis due to lactacidemia has been generally observed. Moreover, it has been assumed that the mechanism of lactacidemia results from the increase of acetylmetabolites in the condition of anaerobic glycolysis and the disability to metabolize the acetylmetabolites in the liver. While, as for the change of coronary blood flow and myocardial oxygen consumption associated with hypothermia, it is reported that oxygen uptake by the myocardium is reduced as temperature falls, however, the rate of reduction in coronary flow is less than that for the entire body, indicating the greater need of oxygen by the heart. In this study, coronary A-V oxygen difference was unchanged as low as 23°C because of hyper-ventilation of FiO₂ 100%. Coronary blood flow was reduced 46% of normal and oxygen uptake by the myocardium was reduced 44% of normal at 23°C.

In general, the heart normally used many substances other than oxygen such as glucose, lactate, pyruvate and fatty acids for energy fuels. From the standpoint of the coronary A-V difference of lactate and pyruvate, lactate and pyruvate uptake by the myocardium as low as 23°C was approximately more than 50% of normal, though myocardial oxygen consumption was reduced 44% of normal. Moreover, pyruvate dehydrogenase showed no reduction at 23°C, suggesting the stimulation of ATP production mediated by TCA cycle from lactate and pyruvate as energy fuels in the cardiac muscle. Therefore, it seems that lactate and pyruvate play an important metabolic role in the hypothermic heart.

As for lipid metabolism in the cardiac muscle, fatty acid, especially NEFA supposedly plays an important role. In this study, plasma NEFA showed a trend of slight increase as low as 23°C, indicating the decrease of peripheral utilization of NEFA. While, the hypothermic heart still used NEFA as energy fuel in the aspect of coronary A-V difference of NEFA at 23°C.

In starvation, it is reported that blood glucose decreases, while a compensatory increase of NEFA is observed, indicating a reverse correlation between blood glucose and plasma NEFA. There is also the reverse correlation between glucose and NEFA in the aspect of myocardial metabolism. On the other hand, in hypothermia, blood glucose showed a significant increase, suggesting a decrease of utilization of glucose.
glucose in the peripheral tissue and a suppression of insulin secretion. However, in the myocardial metabolism of glucose, coronary A-V difference ratio of glucose was 1 to 6% before the cooling and 0 to 2% as low as 23°C. Namely, in this study, glucose uptake by the myocardium was decreased as low as 23°C.

From the standpoint that hypothermia regarded as a controlled shock, the influence of high dose of corticosteroid\textsuperscript{14} and ATP\textsuperscript{15,16} which are supposed to have antishock effects, upon the carbohydrate and lipid metabolism of cardiac muscle was investigated. In this study, no definite effect of the administration of corticosteroid and ATP on myocardial metabolism of carbohydrate and lipid was observed.

**SUMMARY**

In surface-induced deep hypothermia, metabolic acidosis resulting from lactacidaemia was observed. In the aspect of myocardial metabolism, the rate of reduction in coronary A-V difference ratio of lactate, pyruvate and NEFA was less than that of coronary flow and myocardial oxygen consumption in the hypothermic heart. Namely, it seems that lactate, pyruvate and NEFA play an important role as energy fuel in the hypothermic heart. On the other hand, myocardial metabolism of glucose was reduced in the hypothermic heart. Moreover, it seems that exogenous corticosteroid and ATP do not influence on the myocardial metabolism of carbohydrate and lipid in the hypothermic heart.

**REFERENCES**