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

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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.¹ Therefore, under these situations, it is conceivable that the investigation of the change of myocardial metabolism presents one of the criteria to evaluate hypothermia for open-heart surgery. This study was performed to investigate the myocardial metabolism of carbohydrate and lipid during hypothermia, measuring coronary arteriovenous difference of glucose, lactate, pyruvate, total fatty acid and NEFA, and pyruvate dehydrogenase. Moreover, the influence of high dose administration of corticosteroid and ATP upon the myocardial 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, promethazine and 0.01 mg/kg of atropine. Anesthesia was induced with pentobarbital and maintained 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 transfusion was made with 5 ml/kg of low molecular weight dextran or hydroxyethyl starch and 5 ml/kg of xylitol in the cooling phase.² 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,³ plasma total fatty acid and composition of total fatty acid by gas chromatography,⁴ plasma NEFA,⁵ pyruvate dehydrogenase⁶ and coronary blood flow by electromagnetic flowmeter were measured before cooling and as low as 23°C. Myocardial oxygen consumption (ml/100 g/min.) was represented as coronary blood flow (ml) × coronary arteriovenous oxygen difference × 1/100. Myocardial metabolism was evaluated by A-V difference ratio, indicating an uptake or a release of substance.

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:

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Fig. 1. Acid-base balance of arterial blood in hypothermia in each group.

Fig. 2. Coronary blood flow and myocardial oxygen consumption in hypothermia in group I.

Blood base excess also decreased significantly from -5.2 ± 3.6 mEq/l at 37°C to -13.5 ± 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 ± 3.7 ml/min. at 37°C was reduced to approximately half of the precooling level as 17.6 ± 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 ± 9 mg/dl to 182 ± 15 at 23°C in the group I, from 130 ± 18 to 174 ± 5 in the group II, from 180 ± 10 to 210 ± 15 in the group III. Namely, blood glucose showed a significant increase ($p < 0.05$) at 23°C in each group. Coronary arteriovenous glucose

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.

Fig.6. Pyruvate dehydrogenase of the cardiac muscle in hypothermia in group I.

Fig.7. Plasma total fatty acid (left) and coronary A-V difference ratio of total fatty acid (right) in hypothermia in group I.

difference ($136 \pm 9 - 136 \pm 7$ 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 ($182 \pm 15 - 180 \pm 20$) 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

Fig. 8. Fatty acid of the dog liver in hypothermia in group I.

Fig. 9. Composition of plasma total fatty acid in hypothermia in group I.

A-V pyruvate difference ratio showed the same value to that of precooling. This result suggests that pyruvate plays an important role as energy source in cardiac muscle during hypothermia. As for the influence of corticosteroid and ATP upon myocardial pyruvate metabolism, there were no special differences between each group (Fig. 5).

6. Pyruvate dehydrogenase

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 precooling 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 precooling and as 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

Fig.10. Plasma NEFA (left) and coronary A-V difference ratio of NEFA (right) in hypothermia in each group.

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 acid metabolites in the condition of anaerobic glycolysis and the disability to metabolize the acid metabolites in the liver¹. 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^{7,8}. In this study, coronary A-V oxygen difference was unchanged as low as 23°C because of hyper-

ventilation of FiO_2 100%. 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^{9,10,11}. 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^{12,13}. 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 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 corticosteroid¹⁴ and ATP^{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 lactic acidemia 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.

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