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Institutional review – Cardiopulmonary bypass

Study in three different types of cardiopulmonary bypass on arterial ketone body ratio: its prognostic implication and participation of body temperature

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Abstract

The aim of this study was to investigate the change of hepatic metabolic activity presented by the ketone body ratio (AKBR) during and after cardiopulmonary bypass (CPB) and to evaluate the prognostic value. AKBR were measured in 20 cases of coronary aortic bypass grafting using moderate hypothermic CPB (group M), ten cases of aortic arch surgery using deep hypothermia with selective cerebral perfusion (DHSCP) with an open technique (group D) and 15 cases of descending thoracic aortic replacement using partial CPB (group N). AKBR decreased significantly in all groups 5 min after CPB compared with the value before CPB. There was a significant difference in AKBR 1 h after CPB among the three groups and AKBR returned to the prebypass value in group N (group M, 0.32 ± 0.16; group D, 0.14 ± 0.04; group N, 0.48 ± 0.14; $P < 0.0001$). AKBR rose significantly after the discontinuation of CPB compared with the value during CPB and returned to the prebypass value in groups M and D. The patients who underwent DHSCP with an open technique had a value of AKBR below 0.2, but liver function still recovered normally. The value of AKBR correlated with temperature significantly and a very low level of AKBR below 0.2 was observed during core cooling to 20 °C without negative prognostic implications. AKBR decreased 5 min after CPB in group N which suggested decreased hepatic perfusion at an early stage of partial CPB. The prognostic implication of AKBR during CPB is whether low level AKBR recovers or not.

Keywords: Arterial ketone body ratio; Hepatic metabolism; Cardiopulmonary bypass; Deep hypothermia

1. Introduction

Hepatic dysfunction after cardiovascular surgery with cardiopulmonary bypass (CPB) has frequently been experienced and its dysfunction is often transitional and mild. The incidence of post-CPB hyperbilirubinemia has been as high as 20% in large series [1], however, the metabolic effects of CPB on the liver have not been extensively studied because of difficulties in measurement. In hepatic mitochondria, acetoacetic acid undergoes reduction to β-hydroxybutyric acid by β-hydroxybutyric acid dehydrogenase and the ratio of acetoacetic acid to β-hydroxybutyric acid (arterial ketone body ratio, AKBR) reflects the redox potential (NAD + / NADH) [2,3] and positively correlates with the hepatic energy charge [(ATP + 1/2ADP)/(ATP + ADP + AMP)] [4]. Decreasing AKBR is associated with hepatic energy deficit and closely related to postoperative organ failure [5]. In the present prospective study we employed three types of CPB for cardiovascular surgery and measured AKBR in 45 patients before, during and after CPB. The aim of this study was to investigate the change of hepatic metabolic activity presented by AKBR during CPB and its participation in postoperative progress.

2. Patients

The AKBR was measured in 45 patients who underwent aortocoronary bypass surgery, total aortic arch replacement and descending thoracic aortic replacement. They were divided into three groups according to the type of CPB; group M consisted of 20 patients who had undergone aortocoronary bypass surgery using moderate hypothermic CPB, group D consisted of ten patients who had undergone replacement of aortic arch using deep hypothermia with selective cerebral perfusion (DHSCP) with an open technique, and group N consisted of 15 patients who had undergone replacement of descending thoracic aorta using normothermic partial CPB. All patients had normal liver function preoperatively as evaluated by a standard liver function test

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Table 1
Patient characteristics

	DHSCP with an open technique ($n = 10$)	Moderate hypothermic CPB ($n = 20$)	Normothermic partial CPB ($n = 15$)
Age (years)	70 ± 5	68 ± 6	65 ± 11
Sex (male/female)	7/3	12/8	9/6
CPB time (min)	215 ± 30	182 ± 57	90 ± 23*,§
Cardiac ischemic time (min)	99 ± 26	90 ± 30	85 ± 29
Lower body ischemic time (min)	59 ± 20	0*	0*

* $P < 0.0001$ versus DHSCP with an open technique.
§ $P < 0.0001$ versus moderate hypothermic CPB.

(AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase).

3. Method

CPB was conducted with membrane oxygenation and non-pulsatile flow by roller pump in all groups. In group M, the perfusion rate was 2.4 l/min per m^2 and the rectal temperature was 28 °C during CPB. In group D, cooling was continued until 20 °C of rectal temperature using CPB and then the circulation was arrested and antegrade selective cerebral perfusion was established at 800–1200 ml/min. Distal aortic anastomosis was then performed with an open technique. A hypothermia blanket was placed on the operating table and activated once the patient was anesthetized in groups M and D. In group N, CPB was performed to maintain a mean arterial pressure over 60 mmHg and rectal temperature was maintained above 34 °C. All patients were supplied with sufficient glucose and oxygen during CPB.

Blood samples were taken from an arterial line or CPB circuit at four time-points: immediately before CPB (point A); 5 min after the initiation of CPB (point B); 1 h after the institution of CPB (point C); and 5 min after the end of CPB (point D). AKBRs were calculated semiautomatically by measuring total ketone body (Total Ketone Body, Kainos, Kainos Laboratories, Inc., Tokyo, Japan) and 3-hydroxybutyric acid (3-HB, Kainos, Kainos Laboratories, Inc., Tokyo, Japan). Moreover, the peak values of AST, ALT, and LDH levels during 7 days after the operation were analyzed to check postoperative liver function. Results were expressed as means ± standard deviation and the paired Student's *t*-test was used to compare the values before, during and after CPB. The ANOVA for repeated measures was used to compare the values of the three groups. A P value less than 0.05 was considered to be significant.

4. Results

There was no significant difference in the average age. The CPB time of group N was significantly shorter than the other two groups ($P < 0.001$). The aortic cross-clamping time was 90 ± 30 min in group M and 99 ± 26 min in group D. An average lower body ischemic time was 59 ± 20 min in group D (Table 1).

As for the temperature, there was a significant difference at points A, B and C among the three groups (Table 2). The difference at point A was due to the use of a hypothermia blanket in groups M and D. Within each group, there were significant differences among the four points in groups M and D, but there was no change in group N (Fig. 1).

With respect to AKBR, there was a significant difference among the three groups at point A (group M, 0.42 ± 0.18; group D, 0.35 ± 0.24; group N, 0.63 ± 0.33; $P = 0.02$) and point C (group M, 0.32 ± 0.16; group D, 0.14 ± 0.04; group N, 0.48 ± 0.14) (Table 3). The value of AKBR fell quickly after the start of CPB and there was a significant difference between the value of point A and the value of point B in all three groups. The value of AKBR gradually increased in group N, was unchanged in group M and significantly decreased in group D ($P < 0.001$) during CPB (point C). After the discontinuation of CPB (point D), the value of AKBR rose significantly in group M ($P < 0.05$) and group D ($P < 0.001$). There was no significant difference

Table 2
Changes in the blood temperature before, during and after CPB

	Just before CPB	5 min after CPB	60 min after CPB	5 min after weaning
DHSCP with an open technique ($n = 10$)	34.1 ± 0.9*	33.4 ± 1.0*	18.9 ± 1.3*,§	34.9 ± 0.7
Moderate hypothermic CPB ($n = 20$)	34.2 ± 0.6*	34.0 ± 0.6*	26.8 ± 1.0	34.4 ± 0.7
Normothermic partial CPB ($n = 15$)	35.4 ± 0.9	35.3 ± 0.8	35.1 ± 0.9	34.9 ± 0.9

* $P < 0.0001$ versus moderate hypothermic CPB.
§ $P < 0.0001$ versus normothermic CPB.

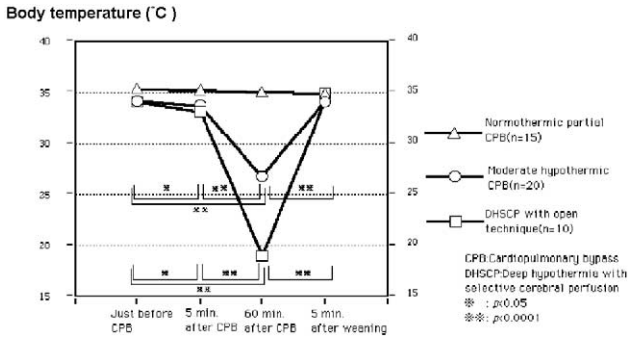

Fig. 1. Time-course of the blood temperature before, during and after CPB.

with respect to AKBR between points A and D in all groups (Fig. 2).

Correlation and liner regression statistics indicated a liner association between AKBR and blood temperature at points A ($r = 0.353$, $P < 0.05$), B ($r = 0.419$, $P < 0.01$) and C ($r = 0.766$, $P < 0.0001$).

There was no significant difference with respect to the peak value of AST, ALT and LDH after the operation among the three groups (Table 4). All patients had no hepatic failure and were discharged uneventfully.

5. Discussion

This is the first study that describes the hepatic mitochondrial redox state represented by AKBR during three types of CPB: moderate hypothermic CPB, DHSCP with an open technique and normothermic partial CPB. AKBR is in equilibrium with the ratio between oxidized and reduced forms of free nicotinamide-adenine dinucleotides (NAD + / NADH) in the mitochondria [2] which is closely related to oxidative phosphorylation [3,5]. Tanaka et al. [4] revealed that a change in the hepatic energy charge [(ATP + 1/2ADP)/(ATP + ADP + AMP)] was positively correlated with AKBR in rabbits subjected to ligation of the common bile duct and both AKBR and energy charge were restored to normal levels after biliary decompression. Yamamoto et al. [6] showed that when AKBR below 0.4 was prolonged for more than 5 days, there was a high incidence of multiple organ failure and a 100% mortality rate and AKBR in the critical zone (between 0.40 and 0.25) must be returned to normal values within 2 days to obtain a good prognosis.

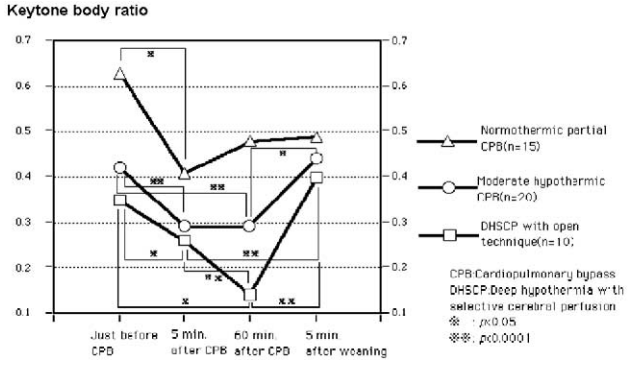

Fig. 2. Time-course of the ketone body ratio before, during and after CPB.

In spite of the technical and mechanical refinement of CPB, the basic disadvantage in the use of non-physiological perfusion still remains and patients undergoing CPB have decreased organ function during CPB or in the postoperative period. In this study, we examined the influence of CPB on hepatic metabolism using AKBR in patients undergoing three types of CPB and speculated that AKBR would drop to a critical level during DHSCP with an open technique because of no hepatic flow and would return to the normal level if managed properly during CPB. Furthermore, we predicted that AKBR would be maintained at a normal level during partial normothermic CPB. However, the level of AKBR showed a significant decrease 5 min after the beginning of CPB in all groups.

Hepatic dysfunction after CPB is widely recognized and hypoperfusion of the liver during CPB is thought to be the primary cause. Concerning the alteration of hepatic blood flow during CPB there are conflicting results in the literature. Hampton et al. [7] measured hepatic blood flow using a galactose clearance technique and observed a mean decrease in blood flow of 19% during hypothermic non-pulsatile CPB at a perfusion rate of 2.1–2.8 l/min per m^2. Yamada et al. [8] measured portal venous flow by color Doppler ultrasonography and reported that portal venous blood flow was maintained during non-pulsatile hypothermic CPB at a flow rate of 2.4 l/min per m^2. Mathie et al. [9] measured the hepatic blood flow by indocyanine green (ICG) and they showed that it is well maintained during normothermic CPB at 2.4 l/min per m^2 and decreases in liver blood flow during hypothermic perfusion with the pulsatile rather than with the non-pulsatile technique. They concluded that high flow and normal temperature is the best way to reserve the hepatic function during CPB, and if the hypothermia was used during CPB non-pulsatile flow during hypothermia would be better. Autschbach et al. [10] calculated hepatic blood flow using an ICG infusion extraction technique and they showed an insignificant increase in hepatic blood flow during mild hypothermic CPB. In a recent animal study, Koizumi et al. [11] showed that hepatic blood flow measured by electromagnetic flowmeter did not change during normothermic CPB, but it decreased significantly during hypothermic CPB. According to the change in AKBR we are convinced that there was a possibility of decreased hepatic flow during hypothermic CPB.

There were some reports concerning AKBR or hepatic metabolism in patients requiring CPB. Nomoto et al. [12] first investigated alternation in hepatic function during and after CPB by measuring AKBR, and they revealed that it decreased to a critical level (below 0.4) during CPB and remained dangerously low throughout CPB. They suggested that ischemia and hypoxia of the liver occurred under

Table 3
Changes of the ketone ratio before, during and after CPB

	Just before CPB	5 min after CPB	60 min after CPB	5 min after weaning
DHSCP with an open technique ($n = 10$)	0.37 ± 0.23*	0.24 ± 0.06	0.14 ± 0.04*,§	0.40 ± 0.15
Moderate hypothermic CPB ($n = 20$)	0.43 ± 0.16*	0.28 ± 0.09	0.28 ± 0.11*,**	0.44 ± 0.28
Normothermic partial CPB ($n = 15$)	0.63 ± 0.33	0.41 ± 0.14	0.48 ± 0.04§,#	0.40 ± 0.15

# $P < 0.01$ versus moderate hypothermic CPB.
* $P < 0.001$ versus normothermic CPB.
§ $P < 0.01$ versus moderate hypothermic CPB.
** $P < 0.01$ versus DHSCP with an open technique.

controlled shock by CPB and they provided no data relating to body temperature. Liu et al. [13] found the same results on hepatic energy metabolism in patients with cardiac operations and they revealed that changes in AKBR were significantly associated with those in blood pressure and body temperature. Liu et al. [13] supposed that the reason for the decrease in AKBR was the acute suppression of aerobic respiration in the liver occurring with ischemia and hypoxia, and hypothermia possibly protected hepatic energy metabolism because of immediate recovery of AKBR on termination of CPB. Autschbach et al. [10] found a reduction of hepatic metabolic activity during mild hypothermic CPB of up to 30% of prebypass activity as described by the monoethylglycinexylide formation kinetics given in the arterial and hepatic vein serum concentration/time curves. We also revealed decreased hepatic metabolism presented by AKBR in three types of CPB and the liner association between AKBR and blood temperature. Many essential enzymes have been found to be temperature-sensitive and decreased AKBR is in part due to a decrease in the activity of enzymes involved in AKBR by hypothermia.

Body temperature was maintained in patients who underwent partial CPB but the level of AKBR still decreased during partial CPB. This fact testifies to decreased hepatic flow in partial CPB. In patients with descending thoracic aneurysm, partial CPB is begun by starting the arterial pump at a flow rate of 0.5 l/m^2 per min, and then slowly opening the venous line. After venous drainage is satisfactory, the flow rate is increased. During this procedure we clamped a descending aorta to prevent cerebral embolism caused by atheroma which may be scattered by the pump flow through the femoral artery, so the hepatic flow decreased at an early stage of partial CPB.

There are few reports concerning hepatic function or metabolism during deep hypothermic circulatory arrest, and AKBR was not studied in DHSCP with an open technique. Hypothermia is an effective method for decreasing the metabolism, and it is used together with CPB as a supplementary means in cardiovascular surgery. Deep hypothermia is an essential method during cardiac surgical procedures requiring total circulatory arrest because the metabolism of the whole body and the amount of oxygen consumption decreased and the tolerance to ischemia increased in the state of hypothermia. The value of AKBR was 0.2 or less in all cases during DHSCP with an open technique and there was no complication including hepatic failure in association with prompt recovery of AKBR after the cessation of CPB in our study. Hoshino et al. [14] evaluated the possibility of successful liver transplantation from hypotensive non-heart-beating donors and they measured energy charge (EC) in the liver. They found that EC levels were below 0.2 during the period of core cooling of 15 °C after hypotensive warm ischemia, and EC recovered sufficiently after the transplantation. Their results and the change in EC during the procedure were almost the same as our results and the change in AKBR during DHSCP with an open technique.

6. Conclusion

In three kinds of CPB, the metabolic state of the liver was researched by measuring AKBR during and after CPB. The value of AKBR correlated with temperature significantly and a very low level of AKBR below 0.2 can be observed during core cooling to 20 °C without negative prognostic implications. The value of AKBR decreased 5 min after normothermic partial CPB and it suggested decreased hepatic perfusion

Table 4
Peak value of AST, ALT and LDH levels after the operation

	DHSCP with an open technique ($n = 10$)	Moderate hypothermic CPB ($n = 20$)	Normothermic partial CPB ($n = 15$)	P value
AST (IU/l)	198 ± 229	78 ± 47	64 ± 44	0.18
ALT (IU/l)	151 ± 234	25 ± 13	27 ± 10	0.14
LDH (IU/l)	1159 ± 368	1128 ± 610	836 ± 370	0.14

at an early stage of partial CPB. AKBR decreased significantly during CPB and returned to the prebypass value after CPB. The prognostic implication of AKBR during CPB is whether low level AKBR recovers or not.

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