The Changes in Arterial Keton Bodies during Upper Abdominal Surgery

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The relationship between the arterial keton body ratio (AKBR: acetoacetate/β-hydroxybutyrate) and the plasma hormone activities were studied under a general anesthesia using enflurane group (group G) and a GO + Epidural group (group E) with continuous glucose loading ($10g \cdot hr^{-1}$) during partial gastrectomy. In both groups, the AKBR increased significantly during the operation. The plasma insulin activity was significantly positively correlated with the AKBR and it was negatively correlated with log (β-hydroxybutyrate) in both groups. We could not find any significant difference of the AKBR between group G and group E. Our results indicate that the plasma insulin activity affects the arterial keton body ratio and that the AKBR must be evaluated considering the plasma hormone activity, especially insulin activity during the operation. (Key words: arterial keton body ratio, insulin, β-hydroxybutyrate, upper abdominal surgery)

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Since it was reported that the keton body ratio (acetoacetate/β-hydroxybutyrate) in arterial blood reflects the oxide-reduction state of free NAD in liver mitochondria, the arterial keton body ratio (AKBR) was commonly used as a useful index of a redox state in liver mitochondria[1–3].

But do any other factors which influence the concentration of the plasma keton bodies act on the value of the AKBR?

Harano[4] showed that the concentration of the β-hydroxybutyrate in blood changed inversely proportional to the plasma level of insulin. Other studies have reported that glucagon: insulin ratio was more important than the absolute concentration of either hormone in the keton metabolism[5,6].

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I wonder whether the plasma hormone activity or the anesthetic method influence the AKBR during an operation. However, a few reports[7] have published on the analysis of the changes of keton bodies and AKBR during the upper abdominal surgery.

The present study was designed to examine whether the plasma hormone activity or the anesthetic method affect the AKBR and to evaluate the role of keton bodies as a metabolic signal in glucose and fat metabolism during an operation.

Method

After obtaining approval from our committee on Human Research and consent from each patient, 14 patients, ASA physical status I and II, who were scheduled for elective partial gastrectomy starting at 9:00 AM were included in this study. None of them had metabolic disturbance and had received drugs known to affect blood glucose and IRI values. All patients had a normal preoperative dietary intake, and were

Table 1. Comparison of the two groups (each group: 7 patients)

	GO + Epidural	GOE
Age (years)	52.3 ± 3.7	58 ± 3.1
Weight (kg)	57.6 ± 2.3	54.3 ± 3.7
Fluid (ml/kg/min)	9.3 ± 0.8	9.1 ± 0.8
Blood loss (g)	376 ± 99	414 ± 129
Surgical duration (hr)	3.4 ± 0.30	3.9 ± 0.26

(mean ± S.E.)

premedicated diazepam 10 mg orally 2 hr before surgery, but they recieved no calories from 12 hr before arriving at the operating room. Each patient was administered glucose continuously via the peripheral vein at the rate of $10 g \cdot hr^{-1}$ from the first blood sampling during the preanesthetic period to the last measurement. The patients were divided into two groups of seven. One group was anesthetized with nitrous oxide, oxygen and enflurane (group G). The other received epidural anesthesia with nitrous oxide and oxygen (group E).

In group E, the patients were placed in a lateral position and epidural catheter was inserted at Th8/9. Mepivacaine, 2% plain, was injected and pin-prick anesthesia from T4 to L1 was confirmed before a general anesthesia was induced. Regular additional doses of 2% mepivacaine plain were administrated every 40 mins through the epidural catheter during surgery.

The patients were given 1 mg of pancuronium bromide before endotracheal intubation to minimize fasciculation with succinylcholine (S.C.C.). General anesthesia was induced by using thiopentone $4 mg \cdot kg^{-1}$, the orotracheal tube was intubated with S.C.C. $1.5 mg \cdot kg^{-1}$ and the lungs were ventilated with 60% nitrous oxide in oxygen. In group G. the patients were intubated as in group E. Anesthesia was maintained with 1.5–2.5% enflurane and 60% nitrous oxide in oxygen. Blood pressure was adjusted primarily by the administration of a lactated Ringer solution although persistent hypotention was corrected by intermittent administration of vasopressor drugs.

The blood samples were drawn through

Table 2. Plasma insulin, blood sugar, glucagon, FFA, keton body concentration during partial gastrectomy with continuous glucose loading $10 g \cdot hr^{-1}$.

		after induction	30 min after incision	90 min	150 min	after extubation
Insulin ($\mu u \cdot ml$)	GOE	5.3 ± 1.0	6.9 ± 1.6	12.4 ± 3.4	14.6 ± 3.6*	20.3 ± 4.4*
	Epi	4.9 ± 0.6	8.4 ± 1.4*	15 ± 4.4*	18.7 ± 4.2*	22.6 ± 4.5*
Glucagon (pg·ml)	GOE	103 ± 5.1	102 ± 98	96 ± 10	86 ± 7.6	85 ± 11.7
	Epi	89 ± 7.7	98 ± 10.4	89 ± 15	81 ± 12.2	89 ± 17.9
Blood sugar (mmol·l)	GOE	5.7 ± 0.5	8.6 ± 0.8**	11.4 ± 0.7**	12.1 ± 0.8**	± 0.9**
	Epi	6.5 ± 0.8	7.7 ± 0.8*	9.7 ± 0.8**	10.5 ± 0.9**	11.6 ± 0.8**
Free Fatty Acid (mEq·l)	GOE	0.84 ± 0.11	0.75 ± 0.12	0.63 ± 0.09**	0.52 ± 0.09**	0.45 ± 0.09**
	Epi	0.67 ± 0.08	0.39 ± 0.06**	0.43 ± 0.07**	0.44 ± 0.09**	0.39 ± 0.09**
Total keton body (μmol·l)	GOE	134 ± 32.4	119 ± 34.4	96.3 ± 33.3	73 ± 24.4*	56.7 ± 17.4*
	Epi	149 ± 41.5	110 ± 36.2*	53.4 ± 7.5*	45.1 ± 6.4*	40.4 ± 6.9*
Acetoacetate (μmol·l)	GOE	64.4 ± 7.5	53 ± 8.7	44.7 ± 4.8	39 ± 3.3	36 ± 3.9*
	Epi	57.4 ± 11	47.7 ± 8.3	83.4 ± 4.5	33 ± 3.0	30 ± 3.7*
β-hydroxy butyrate (μmol·l)	GOE	98.3 ± 24.9	66.4 ± 26	51.6 ± 28.7	34.7 ± 21*	22 ± 13.4*
	Epi	86 ± 29	42 ± 22*	17.6 ± 6.2*	13 ± 4.3*	11 ± 4.1*

*$P < 0.05$, **$P < 0.01$ compared with control (after induction). No significant difference was found between the two groups.

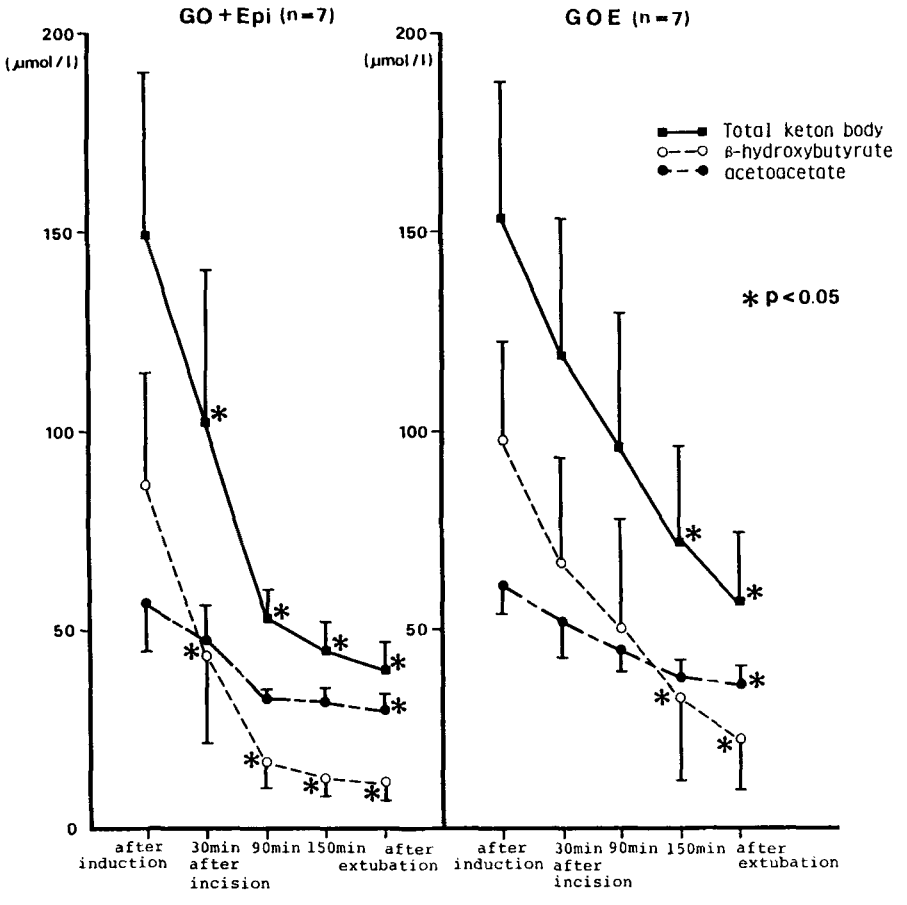

Fig. 1. The plasma total keton body, β-hydroxybutyrate, and acetoacetate concentration during partial gastrectomy with continuous glucose loading 10 g·hr^{-1}. (■——■) total keton body, (○– –○) β-hydroxybutyrate, (●– –●) acetoacetate

*$P < 0.05$ compared with the control. No significant difference was found between the two groups. The values are mean ± S.E.

the cathether placed in the radial artery at the following periods; immediately after the induction of anesthesia, 30, 90, 150 mins after skin incision and the end of anesthesia. Insulin and glucagon, blood sugar, free fatty acid, ε keton bodies were measured by RIA[8], t! glucose oxidase method, the colorimetry[9] and enzymatic method[10] respectively. S tistic analyses were performed using the paired and unpaired student t-test and correlation coefficients were calculated using linear regression analysis. A probability value of less than 0.05 was regarded as statistically significant.

Results

The details of the patients are shown in table 1. No significant difference was found between the two groups.

The level of blood sugar increased significantly in both groups during surgery. No significant difference was found between the two groups. Plasma IRI increased significantly in both groups during surgery as blood sugar became elevated. Plasma glucagon in both groups remained unchanged during surgery. The plasma FFA in both groups decreased significantly during the operation. No signif-

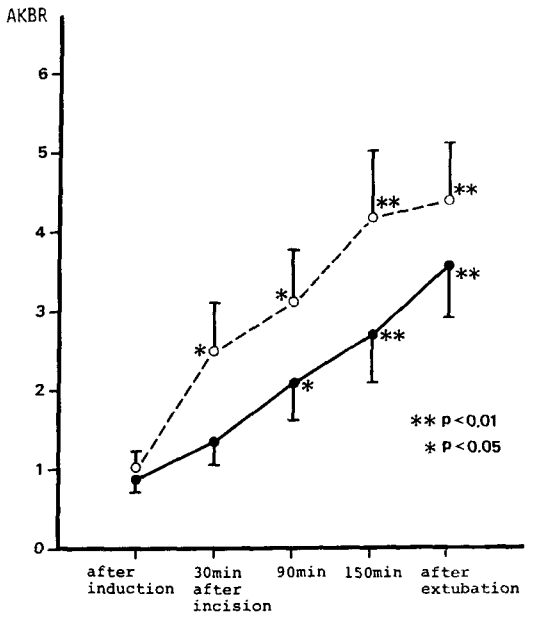

Fig. 2. The AKBR during partial gastrectomy with continuous glucose loading ($10g \cdot hr^{-1}$). (○−−○) GO + Epidural (●−−●) GOE $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control. No significant difference was found between the two groups. The values are mean ± S.E.

icant difference was found between the two groups (table 2).

Arterial keton bodies decreased significantly in both groups. In the keton body fraction, the value of β-hydroxybutyrate decreased more rapidly than those of acetoacetate, and β-hydroxybutyrate contributed to much of the decrease in total keton bodies in both groups. No significant difference was found between the two groups (fig. 1). AKBR increased significantly during surgery in both groups (fig. 2).

Figure 3 shows the relation between the plasma IRI and AKBR. In both groups, the changed in AKBR was positively correlated with the plasma insulin activity. The plasma insulin activity was significantly negatively correlated with log (β-hydroxybutyrate) concentration. However, no correlation was found between the plasma insulin activity and acetoacetate, blood glucose or free fatty acid (fig. 4).

Discussion

The results of our study suggest that the

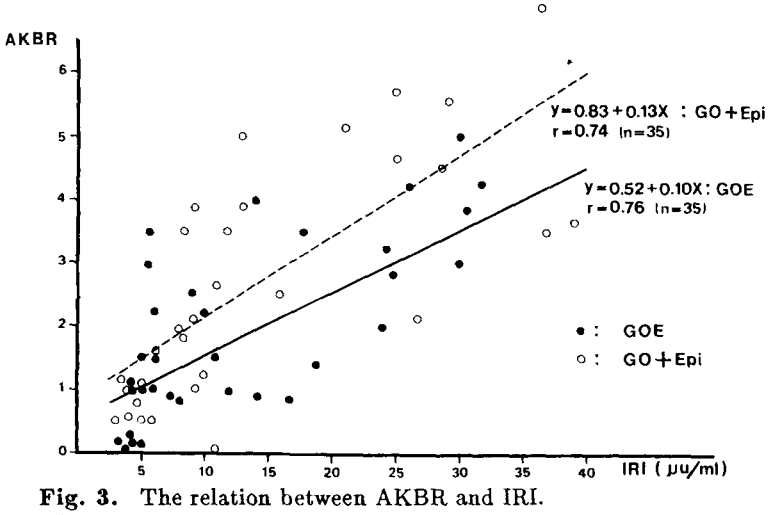

Fig. 3. The relation between AKBR and IRI.
(○) indicates the GO + Epidural group (35 determinations).
(●) indicates the general anesthesia with enflurane group (35 determinations).
The dashed line represents the regression line of GO + Epidural group ($r = 0.74$ $P < 0.01$ $Y = 0.83 + 0.13X$)
The solid line represents the regression line of general anesthesia with enflurane group ($r = 0.76$ $P < 0.01$ $Y = 0.02 + 0.10X$).

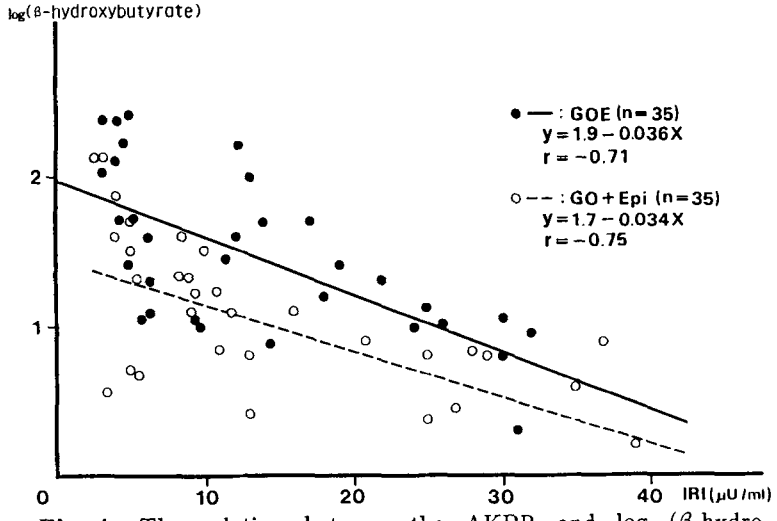

Fig. 4. The relation between the AKBR and log (β-hydroxybutyrate).

(○) indicates the GO + Epidural group.

(●) indicates the general anesthesia with enflurane group.

The solid line represents the regression line of GOE group ($r = -0.71$ $P < 0.01$ $Y = 1.9 - 0.036X$).

The dashed line represents the regression line of GO + Epidural group ($r = -0.75$ $P < 0.01$ $Y = 1.7 - 0.34X$).

plasma insulin activity affects the arterial keton body ratio during partial gastrectomy in both GOE and GO + Epidural groups.

It was reported that the keton body ratio (acetoacetate/β-hydroxybutyrate) in arterial blood reflects the energy level of the liver[1,2], since this ratio is on an equilibrium with the hepatic mitochondrial free nicotinamide adenine dinucleotide (NAD) dehydrogenase (NADH) ratio as shown in the following formula. Acetoacetate + NADH + H $\rightleftharpoons$ β-hydroxybutyrate + NAD

$$\text{Thus } \frac{\text{free NAD}}{\text{free NADH}} = \frac{1}{k} \frac{\text{acetoacetate}}{\beta\text{-hydroxybutyrate}}$$

where k is the equilibrium constant of β-hydroxybutyrate dehydrogenase, which is high activity in liver mitochondria[11]. It is well-known that these keton bodies pass readily through the cell membrane into the blood stream and reach the peripheral tissues. Asano[12] et al suggested that the blood keton body ratio is high, with an increase of NAD, associated with glucose oxidation in liver mitochondria when a normal subject takes sufficient glucose, but they did not measure the changes in the hormones.

Our results demonstrated that the AKBR increased significantly in both groups during surgery with continuous $10g \cdot hr^{-1}$ glucose loading during surgery and the plasma insulin activity was positively correlated with the changes in the arterial keton body ratio in both groups. These results suggest two things; First, $10g \cdot hr^{-1}$ glucose loading after 12 hr starvation produces glucose oxidation via the TCA cycle with an increase in NAD. Second; the insulin activity affects the arterial keton body ratio in both groups.

The keton production in the liver is influenced not only by glucose but also by the other substrates and hormones. When malonyl-CoA concentration is high, carnitinacyl transferase I activity will be inhibited and consequently the rate of fatty acid oxidation and ketogenesis will be low[6]. Other reports suggest that the availability of FFA plays a major role as determi-

nant of keton body production rate[13]. Insulin deficiency is known to increase the rates of lipolysis and to provide increased free fatty acid for ketogenesis[6]. A number of studies[12,13] indicate that glucagon has an important ketogenic effect on the liver. Other studies reported that (glucagon); (insulin) ratio is more important than the absolute concentration of either hormone in the keton production[5,6]. Our result showed plasma glucagon remained unchanged during surgery, which is consistant with the results of Brandt et al[14,15]. Our findings suggest that the plasma insulin plays a major role in controlling the concentration of keton bodies in arterial blood than the plasma glucagon during surgery.

In spite of many reports on the keton production, there are a few data regarding the keton utilization in peripheral tissues[16,17]. Ballase et al reported that utilization of ketons in extrahepatic tissue is influenced by insulin[17]. In our study, the decrease of the keton bodies in arterial blood may reflect by not only the decrease of the keton body production in the liver but also the increase of keton utilization in peripheral tissues.

From our results, we suggest that the AKBR must be estimated during surgery by considering the many factors which influence the keton production and the keton utilization, because our results indicate that the plasma insulin activity affects the AKBR.

As concernes the effects of the anesthetic method on the AKBR, we could not find any significant difference between the general anesthesia with enflurane and the general anesthesia with epidural block.

It was supposed that this result might attribute to the plasma insulin activity, which showed no significantly difference between the two groups during an operation.

Stanley[18] advocated the glucose-fatty acid-keton body cycle. It has been shown that high concentration of β-hydroxybutyrate stimulate the secretion of the antilypolytic hormone insulin and directly inhibit the rate of mobilization of fatty acids from adipose tissues as well as increasing the sensitivity of the adipose tissues to the effect of insulin. The keton body concentration in the blood can vary over a 20 fold range during starvation. Such changes in concentration are not found in the case of other blood metabolites such as glucose and fatty acid. In our present study the values of β-hydroxybutyrate decreased more rapidly than those of acetoacetate. Plasma insulin activity was significantly negatively correlated with log (β-hydroxybutyrate). But we could not find any correlation between plasma insulin activity and acetoacetate, blood glucose, or free fatty acid. We could not prove the relation of the glucose-fatty acid-keton body cycle in this study but our results revealed that β-hydroxybutyrate is useful as a metabolic signal to evaluate glucose and fat metabolism, because the level of β-hydroxybutyrate more sensitively responds to the plasma insulin activity than acetoacetate, blood glucose and free fatty acid.

In conclusion, 1) the plasma insulin activity affects the arterial keton body. 2) There is no significant difference of the AKBR between the general anesthesia with enflurane and general anesthesia with epidural block. 3) β-hydroxybutyrate is useful as a metabolic signal to evaluate glucose and fat metabolism. These conclusions suggest that AKBR must be evaluated during surgery with considering the many factors which influence the keton production in liver and keton utilization in the peripheral tissues.

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