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Evaluation of the liver graft before procurement

Significance of arterial ketone body ratio in brain-dead patients

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Abstract. Hepatic energy metabolism was assessed by measuring the blood ketone body ratio (KBR), that is, the ratio of acetoacetate to β-hydroxybutyrate in the arterial blood, in 31 brain-dead patients in an intensive care unit (ICU) in Japan and in 25 donors just before procurement of the liver for transplantation in Germany. In the study in Japan, 7 of the 12 brain-dead patients treated with high-dose catecholamine showed significantly decreased KBRs, revealing the detrimental effect of catecholamine on liver metabolism. In contrast, 8 of the 9 untreated patients with blood pressure below 80 mm Hg showed almost normal KBRs. In the 25 donors in Germany, KBR was maintained within the normal range. Based upon conventional criteria, 21 livers were selected for use and the other 4 were discarded. Nineteen of the grafts were able to normalize KBR within 24 h after reperfusion, while 2 failed to function and required a second transplantation. It was suggested that a KBR in the normal range in donors is a prerequisite to immediate recovery of metabolic function of the liver graft after transplantation, and that hypotensive donors as a potential source of liver grafts may warrant further study.

Key words: Liver graft viability – Ketone body ratio, in brain-dead patients.

Since brain-dead patients are the only source of allografts for human liver transplantation, the assessment of organ function prior to harvesting is crucial if we are to obtain suitable organs for donation. Standard liver function tests are, however, known to be inadequate when it comes to the appraisal of metabolic function of the possible liver allograft, for they are neither sensitive nor specific enough to provide a picture of metabolic function of the organ [1, 8].

The redox state of liver mitochondria (free NAD^+/free NADH) is one of the fundamental parameters regulating energy production in the liver cell and is directly reflected by the ketone body ratio (KBR), i.e., the ratio of acetoacetate of β-hydroxybutyrate in the arterial blood. Because of this ability to reflect the energy-producing capability of liver mitochondria, KBR has received considerable attention as a potential indicator of liver metabolism and has been used to monitor critically ill patients suffering from shock of various etiologies and multiple organ failure [2, 13–15, 17, 19, 23]. In the liver transplantation field, we have demonstrated a clear relationship between the ability of the liver graft to elevate and maintain KBR after reperfusion and early transplant outcome. In cases with morbidity, KBR was persistently reduced to about 0.4, whereas it was elevated to above 0.7 within 24 h after reperfusion in cases who underwent liver transplantation uneventfully [5, 18].

Recently, Lin et al. reported that KBR also reflects hepatic energy metabolism in the hypotensive state in brain death in dogs, although the application of KBR as an index of hepatic energy metabolism had been precluded under decreased blood flow to the liver [6, 7]. This led us to hypothesize that metabolic abnormalities of the liver would also be reflected by KBR in human brain death. In the present study, hepatic energy metabolism was assessed by measuring KBR in prudently selected donors in Germany and in brain-dead patients receiving various kinds of treatment intended to stabilize hemodynamics and to prolong the heart-beating period in an intensive care unit (ICU) in Japan.

Patients and methods

Brain-dead patients in Japan

This study is a retrospective review of all 31 patients (13 males and 18 females) who became brain-dead in the ICU of Teikyo Medical School, Tokyo, from May 1988 until May 1989. The criteria of inclusion were no direct injury to the abdomen and KBR measurement at 6 h after confirmation of brain death [4]. Diabetic patients were excluded from this study since diabetes mellitus has a possible effect on ketone body metabolism by impairing cellular glucose uptake. The causes leading to brain death are summarized in Table 1.

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Table 1. Causes of brain death in Japan and Germany

	Japan	Germany
Head injury	9	18
Cerebrovascular disease	15	5
Asphyxia	7	2
Total	31	25

Brain-dead patients before procurement

In another study conducted at the medical school in Hannover from June 1988 to March 1989, arterial blood samples for the examination of KBR were obtained from 25 donors before procurement of the liver graft. The causes leading to brain death are summarized in Table 1. Diabetic patients were also excluded from this study. Of the 25 liver grafts, 21 were used for liver transplantation, and their postoperative courses were also followed by measuring KBR. The other 4 liver grafts were judged as unsuitable for liver transplantation after laparotomy because of either abnormal color or consistency [3].

Analysis of KBR

The concentrations of both ketone bodies were measured enzymatically using a Ketorex kit (Sanwa Chemical, Nagoya, Japan) and a KETO-340 semiautomatic spectrophotometer (Ihara Electric, Kasugai, Japan). Details of measurement are described elsewhere [9, 21, 22].

Results

Brain-dead patients in Japan

The patients were divided into two groups according to blood pressure: a normotensive group (systolic blood pressure above 80 mm Hg), consisting of 14 patients, and a hypotensive group (systolic blood pressure below 80 mm Hg), consisting of 17 patients.

Figure 1 shows the KBR in each group in relation to high-dose dopamine and/or dobutamine administration above 10 μg/kg per minute. In the normotensive group, 90% of the patients not receiving high-dose dopamine showed normal KBR above 0.7. In contrast, 75% of the patients who did receive it showed KBR levels below 0.7. Patients receiving high-dose catecholamine showed significantly lower KBR than those not receiving it (Fischer's direct probability 0.041). On the other hand, even when blood pressure was lower than 80 mm Hg, eight of the nine patients who were not on high-dose catecholamine showed almost normal KBR.

The total concentrations of ketone bodies in the normotensive and hypotensive groups were 101.1 ± 36.5 μmol/l and 75.3 ± 30.5 μmol/l, respectively. Although those were elevated in the normotensive group as compared to the hypotensive group, no statistical difference was obtained.

Case report (Fig. 2)

A 13-year-old female patient suffering from asthma developed apnea due to status asthmaticus, which was followed by deep coma in spite of intensive care. On the 3rd day after the attack, the pupils became completely dilated and spontaneous breathing was lost. EEG revealed total absence of electric activity. Blood pressure decreased rapidly and required catecholamine to sustain it. On the 4th day, the patient matched the criteria for brain death as defined by the Ministry of Health and Welfare of Japan [4]. KBR, which had been 1.05 despite hypotension of 80 mm Hg, decreased to 0.55 after catecholamine administration, although blood pressure was elevated to 120 mm Hg. On the 5th day, catecholamine administration was terminated after receiving consent of the patient's family. Blood pressure consequently decreased but stabilized at around 55 mm Hg, and KBR was restored to 1.20 despite hypotension.

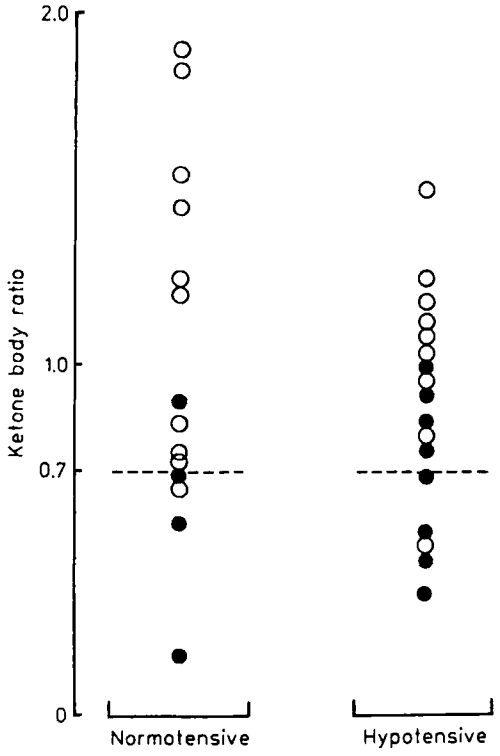

Fig. 1. Ketone body ratio *(KBR)* in the normotensive and hypotensive groups in relation to dopamine and/or dobutamine administration. ○, With low-dose dopamine and/or dobutamine administration (less than 10 μg/kg per minute); ●, with high-dose dopamine and/or dobutamine administration (more than 10 μg/kg per minute)

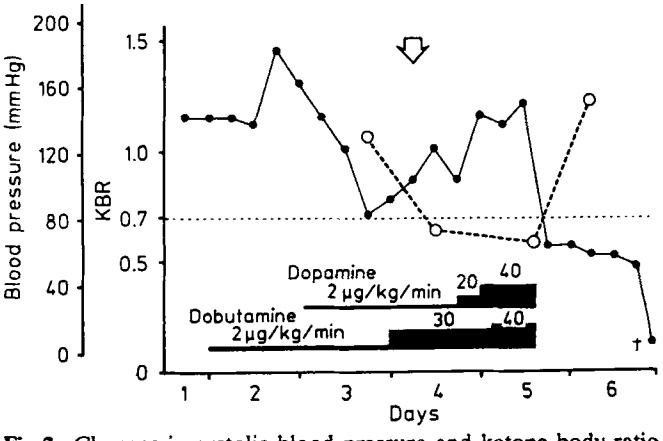

Fig. 2. Changes in systolic blood pressure and ketone body ratio *(KBR)* in the case report. ○, Changes in ketone body ratio; ●, changes in systolic blood pressure. ⇩, confirmation of brain death

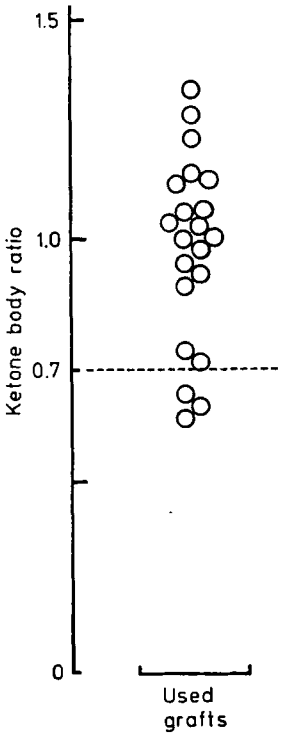

Fig. 3. Ketone body ratio *(KBR)* in patients just before procurement by transplantation team of the medical school in Hannover

Brain-dead patients in Germany

KBRs in the patients scheduled for liver donation are plotted in Fig. 3. Eighteen patients showed KBR above 0.70 just before procurement and the others above 0.60. Four of the 25 donor grafts inspected were judged as unsuitable for the following reasons: fatty liver ($n = 2$), pale liver after shock state ($n = 1$), and pancreas edema ($n = 1$).

KBRs in the recipients were also measured after transplantation. Nineteen grafts (90.5%) resumed normal KBRs within 24 h and the recipients were able to tolerate transplantation (Fig. 4a). Two grafts (9.5%) failed to increase KBR to above 0.7, and the recipients required a second transplantation (Fig. 4b).

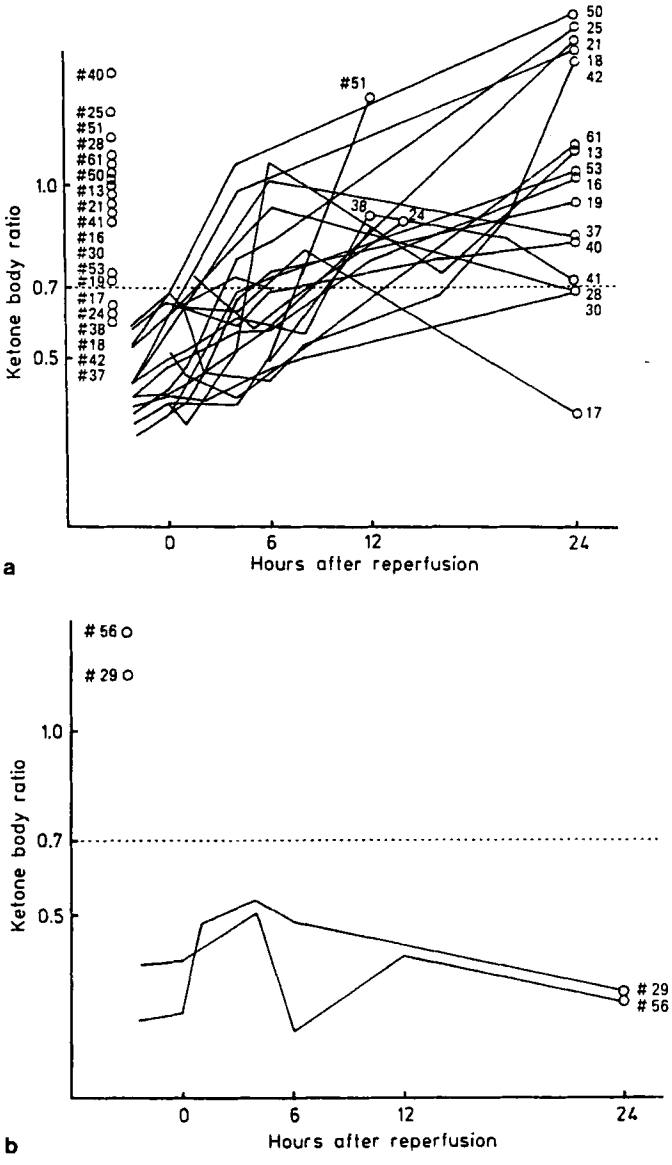

Fig. 4a, b. Ketone body ratio *(KBR)* in the 21 donors whose samples were obtained just before procurement (open circles on the left side) and changes in KBR in the recipients after transplantation. #, Consecutive donation number corresponding to each recipient; **a** *KBR* exceeded 0.7 within 24 h after hepatic reperfusion. Nineteen patients survived liver transplantation. One recipient (#17) had hepatic artery kinking necessary for laparotomy; **b** *KBR* never exceeded 0.7 following reperfusion. These two patients required a second transplantation

Discussion

Previous reports by various investigators on the assessment of potential liver donors may have been biased since their analyses were restricted to brain-dead patients selected on the basis of certain criteria [8, 10, 16]. Our primary criteria for exclusion of liver donors, for example, were intra-abdominal injury, hypotension, high-dose catecholamine administration, and ICU stay longer than 1 week [3]. In the donors thus selected, KBR was maintained within the normal range, indicating that aerobic energy production by hepatic mitochondria, a prerequisite to the maintenance of organ viability, was not curtailed in these donors. Although 4 of the 25 livers were judged as unsuitable for donation and later discarded, these decisions were made on nonmetabolic grounds. After transplantation, 2 of the 21 liver grafts, possibly with normal mitochondrial function, failed to resume previous metabolic activity. Since a number of factors would contribute to the critical status of the grafts, such as the conditions during harvesting, preservation, and transportation, as well as operative technique and preexisting metabolic abnormalities in the recipient [1, 3, 5, 8, 18], it is difficult to pinpoint which factor or factors exerted the most influence on the onset of graft failure. Our previous report suggested that an increased metabolic load predisposes the recipient to its occurrence [18]. In the present study, for instance, the recipients who developed graft failure had been comatose prior to transplantation.

The study conducted in Japan on brain-dead patients clearly demonstrated the detrimental effect of dopamine and dobutamine on hepatic energy metabolism. In addition, it was shown by the cases without high-dose cate-

cholamine administration that hepatic energy metabolism can be maintained regardless of blood pressure. In Japan, where brain death has yet to be accepted, brain-dead patients are subjected to various kinds of treatment up until the time respiratory support is terminated. This fact, on the other hand, contributed to the present analysis based on hepatic energy metabolism in more generalized brain-dead patients. Although the mechanism by which catecholamine compromises hepatic energy metabolism remains to be clarified, Okamoto et al. suggested a possible interaction of α-receptor stimulation by the drugs and the consequent reduction of tissue perfusion in the liver of brain-dead dogs [12]. At present, our recommendation is that a donor liver that is unable to sustain KBR within the normal range in the state of brain death should be discarded since it is most unlikely that such a liver would resume adequate metabolic function after transplantation.

In clinical liver transplantation, a donor who is hypotensive or normotensive and who is supported by catecholamine at high doses would probably be excluded, except in the most dire recipient circumstances [3, 10]. The deleterious effects of dopamine and dobutamine were clinically confirmed in the present study, although their effects are reversible to some extent, as shown in the case report. At the same time, it was suggested that even hypotensive donors and about one-fourth of the catecholamine-treated donors might be suitable candidates for liver donation. Given the increasing number of liver transplantations, the shortage of grafts is becoming more and more acute. This would appear to necessitate a reevaluation of conventional liver donor criteria in favor of less strict regulations. Our contention from a metabolic viewpoint is supported in part by the retrospective studies by Makowka et al. and Ohkohchi et al. that blood pressure of the donors does not affect the outcome of liver transplantation [8, 10].

It seems, therefore, reasonable to conclude that a normal KBR in donors is a prerequisite to immediate recovery of metabolic function of the liver graft after transplantation, and that the procurement of liver grafts from hypotensive donors may merit further study.

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