1149

0041-1337/91/5101-0164$03.00/0
TRANSPLANTATION

Vol. 51, 164-171, No. 1, January 1991
Printed in U.S.A.

THE CLINICAL SIGNIFICANCE OF THE ARTERIAL KETONE BODY RATIO AS AN EARLY INDICATOR OF GRAFT VIABILITY IN HUMAN LIVER TRANSPLANTATION[1,2]

K. ASONUMA,[3] S. TAKAYA,[4] R. SELBY,[4] R. OKAMOTO,[3] Y. YAMAMOTO,[3] T. YOKOYAMA,[3] S. TODO,[4] K. OZAWA,[3,5] AND T.E. STARZL[4]

The Second Department of Surgery, Faculty of Medicine, Kyoto University, Shogoin, Sakyo-ku, Kyoto, Japan; and The Department of Surgery, University Health Center of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania

Arterial ketone body ratio (AKBR) was measured sequentially in 84 liver transplantations (OLTx). These transplantation procedures were classified into 3 groups with respect to graft survival and patient condition at the end of the first month (Group A, the grafts survived longer than 1 month with satisfactory patient condition; Group B, the grafts survived longer than 1 month but the patients were ICU-bound; Group C, the grafts were lost and the patients died or underwent re-OLTx). In Group A, the AKBR was elevated to above 1.0 by the second postoperative day. In Group B, the AKBR was elevated to above 0.7 but stayed below 1.0 during this period. In Group C, the AKBR remained below 0.7 longer than 2 days after operation. Although conventional liver function tests showed significant increases in Groups B and C as compared with Group A, they were less specific in predicting ultimate graft survival.

Several parameters have been proposed for the prediction of liver graft failure, such as the levels of hepatic enzymes, serum bilirubin, plasma amino acids, and biopsy findings (*1, 2*), but none can forecast graft recovery until the patient's condition becomes critical. As a step toward this objective, an interinstitutional study was undertaken between Kyoto University and the University of Pittsburgh. The Kyoto team has quantified derangements of hepatic energy metabolism after cirrhotic liver resection, liver transplantation, and other disease states (*3–5*). The redox potential (reduction-oxidation potential) of hepatic mitochondria is one of the fundamental regulatory factors of the liver metabolism, and can be assessed by measuring the ketone body ratio in the arterial blood (AKBR)* of patients (3). The AKBR is closely correlated with the energy charge level of the liver in jaundice, massive hemorrhage, experimental liver transplantation, and after hepatic resection (*6–8*).

After liver transplantation, patients with well-functioning grafts usually recover from the stress of the operation quickly and uneventfully, and can be discharged within one or 2 days from the intensive care unit (ICU). In contrast, there is extreme morbidity and mortality in patients whose new livers do not resume function promptly, whose grafts fail secondarily because of rejection or technical accidents, and whose grafts are secondarily damaged after renal or cardiopulmonary complications (*9*). Accurate prediction of the fate of these hepatic grafts is an important objective.

The Hannover liver group proposed the metabolic assessment of transplanted liver allografts with AKBR as a parameter (*10, 11*). They showed that an AKBR below 0.7 at 24 hr after organ recirculation was an early predictor of graft failure, but did not provide information beyond the first day. In the present study, the redox potential of the liver allografts was monitored with AKBR during the operation and daily until the patient was discharged from the ICU, died, or underwent retransplantation. A close relationship between the ultimate graft function and the changes in the AKBR within 2 postoperative days could be documented. This information should be helpful in making early decisions in future cases about the need for retransplantation.

MATERIALS AND METHODS

Between September 9, 1989 and December 13, 1989, 81 adult patients were studied after 87 orthotopic liver transplantations (OLTx). Two patients who died of strokes in the immediate postoperative period and one who died of cytomegalovirus pneumonia on the 29th postoperative day were excluded from the analysis. This left 84 OLTx in 78 patients for analysis. There were 42 males and 36 females, with ages ranging between 16 and 66 years (mean±SEM: 45.7±1.4). Their diverse original diseases are summarized in Table 1. The degree of illness of each patient was defined prospectively by the criteria for urgency used by the 6-tier United Network for Organ Sharing (UNOS) distribution system (*12*).

Seven of the 78 patients had a diagnosis of diabetes mellitus before operation. Four were insulin-dependent and another 3 were on oral hypoglycemic agents for control of blood sugar. An additional 5 patients also required insulin during the immediate postoperative period, and in the data stratification these were classified as diabetic.

Transplant procedures. All donor procurements were with in situ infusion techniques (*13*). The livers were preserved for 12.9±0.68 (mean ± SEM) hr with University of Wisconsin solution. HLA typing and cytotoxic antibody crossmatch was performed but did not influence case selection since the results were not known until later. The anhepatic phase was defined as the interval between the interruption of the recipient's hepatic circulation and the restoration of portal or arterial circulation to the graft. Throughout the operation, including the an-

* Abbreviations: AKBR, arterial ketone body ratio; T-BIL, total bilirubin (mg/dl); PNC, postnecrotic cirrhosis; ICU, intensive care unit.

[1] Presented at the 16th Annual Meeting of the American Society of Transplant Surgeons, May 30–June 1, 1990, Chicago, IL.

[2] This work was supported by Research Grants from the Veterans Administration, by Project Grant DK 29961 from the National Institutes of Health, Bethesda, MD, and by the Scientific Research Fund of the Ministry of Education, Japan.

[3] Kyoto University.

[4] University Health Center of Pittsburgh and the Veterans Administration Medical Center.

[5] Address correspondence to: Kazue Ozawa, M.D., Second Department of Surgery, Kyoto University Faculty of Medicine, 54-Kawaracho, Shogoin, Sakyo-ku, Kyoto, Japan 606.

TABLE 1. Indications for orthotopic liver transplantation

Category	Diagnosis	Number of grafts used	Number of grafts that failed within the first month
Parenchymal Liver disease	Cirrhosis, idiopathic	26	4
	Cirrhosis, hepatitis	12	2
	Cirrhosis, autoimmune	4	1
Cholestatic	Primary biliary cirrhosis	7	1
	Secondary biliary cirrhosis	2	0
	Sclerosing cholangitis	7	0
	Carolis disease	1	0
	Alagille's syndrome	1	0
	Biliary atresia	1	0
Graft failure[a]	Rejection	6	2
	Hepatitis	3	0
	Hepatic artery stenosis	2	0
	Undetermined	4	3
Others	Fulminant hepatitis	1	0
	Malignant tumor	3	0
	Budd-Chiari syndrome	2	0
	Wilson's disease	1	0
	Hemochromatosis	1	0

[a] Six of these transplantations were after primary transplantation that failed during the time of study. The other 9 were for graft failure following transplantation in an earlier year in patients whose primary course was not studied.

hepatic phase, serum lactate, blood glucose, and blood gases were measured at frequent intervals.

Immunosuppression and rejection. Sixty-eight of the 84 grafts (including retransplantations) were under treatment with FK506, to which a rapidly tapering course of prednisone was added, usually starting with 200 mg on the first day, and ending with 20 mg on the sixth day. The other 16 transplantations were done with similar management but with cyclosporine instead of FK506, and azathioprine in addition if there was a peripheral WBC >4000/mm^3. In 2 patients, a course of OKT3 was started within the first 7 days because of suspicion of accelerated rejection, and in 9 patients whose grafts failed to function promptly one or more treatments with hemodialysis or continuous venovenous hemofiltration were given in the hope that antibodies or some other undetected harmful substance could be removed.

The AKBR was measured within 40 min by the enzymatic method using a Ketorex kit (Sanwa Chemical Company, LTD, Nagoya, Japan) and a KETO-340 semiautomatic spectrophotometer (Ihara-denshi Company, LTD, Kasugai, Japan) (*14, 15*). Four milliliters of arterial blood was withdrawn before the portal vein was unclamped, at 6, 12, and 24 hr after organ reperfusion, and once a day thereafter until the patient was discharged from the ICU, or died. No hypoglycemia was encountered at the time of the AKBR measurement. The management of the patients in the ICU was performed independently of the AKBR measurement.

Statistical analyses. Statistical analyses were based on analysis of variance and the *t* test. A *P* value less than 0.05 was regarded as significant. Values are expressed as the mean ± SEM. Receiver operating characteristic curve analyses were applied to comparison of various clinical parameters and AKBR.

RESULTS

Of the 78 patients, 70 (89.7%) are alive. Survival was markedly influenced by the original diagnosis, with the poorest results being in patients with cirrhosis and in those undergoing retransplantation after the first graft had been lost for unexplained reasons (Table 1). These latter patients have been called "liver-eaters." The following analyses are of graft survival.

Overall graft survival. In 66 (78.6%) of the 84 transplantations, the patients were discharged from the ICU in satisfactory condition within one month. These procedures were designated group A (successful graft). After 5 (6.0%) transplantations, the patients were still on the ICU at the end of the first month. Their procedures were consigned to group B (compromised graft). Another 13 (15.4%) operations constituted group C (failed graft). Five of these recipients underwent retransplantation.

Table 2 shows the clinical features in the 5 compromised graft cases of group B. Patient 1 was undergoing retransplantation because of primary graft nonfunction 2 days after the first OLTx. All of the patients were classified as classes 4–6 by the United Network for Organ Sharing. Class 5 patients are ICU-bound and class 6 patients are life support–dependent. All 5 required hemodialysis and/or mechanical respiratory assist postoperatively and all but one (case 2) had progressive increases in bilirubin levels. Patient 3 survived the study period but ultimately underwent retransplantation on the 46th postoperative day.

In group C, graft death occurred, with a mean interval of 11.4±2.9 days (Table 3). Specimens of eleven grafts were examined by a pathologist during either the re-OLTx or at autopsy. In the other cases in which an autopsy was denied, the final diagnosis of the graft was made based on the clinical events, premortem hepatic biopsies, and infectious disease data. The majority of the failed grafts had necrosis or severe ischemic injury. Five were lost from death or retransplantation after 1–4 days. Ischemic injury with the supervention of sepsis led more slowly to the same result in the other 7 after 12 days. Sepsis was thought to have caused delayed hepatic failure in 4 of these patients. Humoral or cellular rejection was the primary diagnosis in patients who became septic secondarily.

Graft viability and AKBR. The AKBR was significantly suppressed in groups B and C as compared with group A, suggesting a close correlation between the redox state of the mitochondria of the transplanted graft in the early postoperative days and graft survival ($P<0.01$) (Fig. 1). Because the ATP synthesizing ability of the liver mitochondria is closely related to the insulin level (*16*), the changes in the AKBR after OLTx were measured in diabetic and nondiabetic patients. In 12 diabetic patients in group A the AKBR was significantly suppressed as compared with that in the 54 nondiabetic patients up to the third postoperative day (Fig. 2). Afterwards the AKBR increased as insulin need decreased or with stabilization of insulin requirements.

Among the 54 nondiabetic cases in group A, 24 were successfully discharged from the ICU within 2 days. The AKBRs in the morning of the day of discharge from the ICU are shown in Figure 3. All were above 1.05.

AKBR in nondiabetics. Because of the confounding factor of insulin therapy, a separate analysis was performed of AKBR after culling 12 diabetic patients in group A and one diabetic patient in group C. For this analysis, the following stratification was used: state I, AKBR≧1.0; state II, 0.7–1.0; state III, AKBR<0.7.

Group A: In 52 (96.3%) of 54 nondiabetic patients, the AKBR was elevated in state I by 2 days, and in 11 of these state I had already been reached within 24 hr. In the 2 exceptional cases (3.7%) the ratio was restored to state I by the 5th postoperative day.

Group B: In all 5 cases, the AKBR remained in state II

TABLE 2. Clinical profiles of 5 cases with compromised grafts (group B)

No. (age/sex)	Disease	Preoperative class*	Postoperative course
1 (63/F)	PNC-C[b]	Class 6 Re-OLTx 2 days after the 1st OLTx, renal failure	CVVH (5 POD→) Cardioversion (5 POD) Biopsy (17 POD): mild acute rejection Bilirubin[c]
2 (37/F)	PNC-E	Class 4 Encephalopathy	Mechanical ventilation (OP → 10 POD) Biopsy (10 POD): necrosis Biopsy (27 POD): moderate rejection
3 (35/F)	PNC-C	Class 4 Encephalopathy	Renal failure, hemodialysis (5 POD→) Respiratory failure Bilirubin,[c] Re-OLTx (46 POD)
4 (32/M)	Wilson's disease	Class 5 Respiratory failure, encephalopathy	Renal failure, hemodialysis (2 POD→) Mechanical ventilation (OP→) Bilirubin[c]
5 (56/F)	PNC-B	Class 5 Pulmonary edema encephalopathy	Mechanical ventilation (OP → 5 POD, 7 POD→) Renal failure (3 POD→), Laparotomy for bleeding (13 POD) Bilirubin[c]

* The criteria for urgency using for the UNOS distribution system: Class 4, hospital-bound, not in intensive care unit (ICU); Class 5, ICU-bound, not ventilator-dependent; Class 6, in ICU, on ventilator, and often unconscious.

[b] PNC: postnecrotic cirrhosis: PNC-C: cryptogenic; PNC-E: ethanol; PNC-B: hepatitis B; CVVH: continuous venovenous hemofiltration.

[c] Total bilirubin level increased progressively more than 10 mg/dl or the pre-OLTx level.

TABLE 3. Clinical profiles of 13 failed grafts

Diagnosis	Graft No.	Survival	Outcome	AKBR state
Graft necrosis (PNF*)	3	2, 3, 4	ReOLTx, ReOLTx, ReOLTx	III, III, II
Rejection (plus sepsis)	2	16, 30	Died, died	II, II
Ischemia (plus rejection)	1	7	ReOLTx	I (→II)
Ischemia (plus sepsis)	1	12	Died	III
Sepsis (plus secondary liver failure)	4	17, 21, 22, 20	Died, died, died, died	II, II, II, II
Cardiopulmonary failure (plus secondary liver congestion)	1	2	ReOLTx	II
Intraperitoneal bleeding	1	1	Died	III

* Primary nonfunctioning graft.

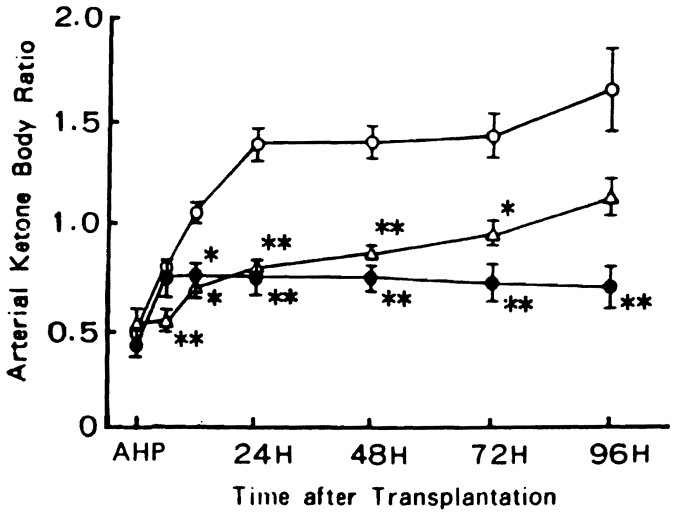

FIGURE 1. Changes in the AKBR immediately after OLTx in relation to graft outcome. Values are presented as means ± SEM. (*) and (**): $P<0.05$ and $P<0.01$, respectively. (O) successful graft (group A); (Δ) compromised graft (group B); (●) failed graft (group C). (AHP) anhepatic period.

during the first 2 days. Figure 4 shows the eventual changes in the AKBR of these 5 patients. Their AKBR fluctuated with a relatively high amplitude during their stay in the ICU, but never maintained normal levels (state I).

Group C: In 7 of 12 cases the AKBR remained in state II for the first two postoperative days and gradually decreased to state III (Fig. 5). Five of the 7 cases died and two underwent re-OLTx. In one patient, the AKBR was in state I after one day but declined to state II (0.71) by the second postoperative day (Fig. 5). This patient underwent re-OLTx with the diagnosis of accelerated acute rejection made from surgical specimen. In another 4 patients, the AKBR remained in state III without fluctuation (Fig. 6). All patients were in critical condition. Two of the 4 patients underwent re-OLTx and the other 2 patients died.

Figure 7 shows a schematic representation of the above results in nondiabetic patients, correlated with the outcome of OLTx. When the AKBR was restored to above 1.0 within 2 days after OLTx, all grafts resumed satisfactory initial function. When the AKBR was suppressed below 0.7 (state III) for longer than 24 hr after OLTx, no grafts survived. When the AKBR was between 0.7 and 1.0 (state II) for two days after

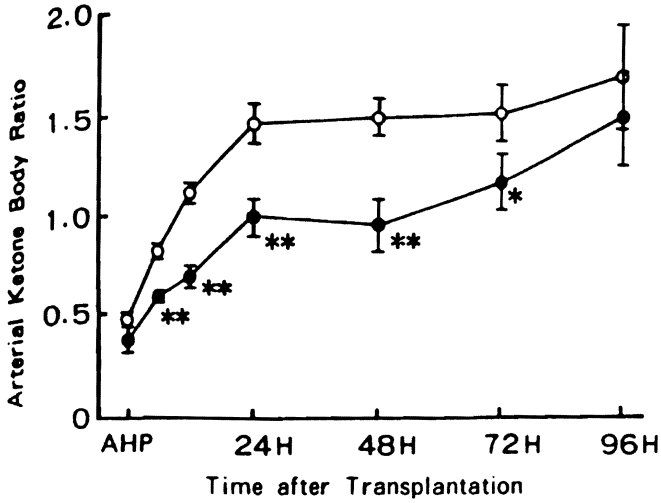

FIGURE 2. Comparison of the changes in the AKBR immediately after OLTx between diabetic (DM) and nondiabetic (non-DM) patients with successful grafts. Values are presented as means ± SEM. (○) non-DM; (●) DM. (*) and (**): $P<0.05$ and $P<0.01$, respectively. (AHP) anhepatic period.

OLTx, 50% of the grafts failed and 36% of the grafts were compromised (i.e., succeeded, although with a prolonged recovery).

In 2 exceptional patients in group A the AKBR decreased rapidly after it first rose to state I on the first day. The cause of the rapid decrease could have been acute rejection, an unrecognized technical error, or inappropriate postoperative care. Figure 8 shows how acute rejection can effect AKBR at a later time. A 51-year-old woman suffering from hemocromatosis had an AKBR of 1.5 on the first and second postoperative days but it decreased below 1.0 as the bilirubin began to rise on the third postoperative day. Therapy with cyclosporine was replaced with FK506 5 days after transplantation. The AKBR increased to 1.5 of normal levels, concomitant with normalization of the bilirubin level.

Various clinical parameters and AKBR. Table 4 shows the changes in the levels of lactate, total bilirubin, GOT, GPT, and PT in each group. The levels of total bilirubin on the first and second postoperative days were significantly increased in groups B and C as compared with those in group A ($P<0.005$). The levels of GOT and GPT on the first and second postoperative days were significantly increased in group C as compared with those in groups A and B. The levels of lactate at the end of operation and PT on the first operative day were significantly increased in group C as compared with those in group A. These conventional liver function tests were shown to be inaccurate in discriminating between group A and group C, however, when compared with AKBR by receiver operating characteristic curve analysis (Figs. 9 and 10).

AKBR in primary and retransplant cases. Of the 84 grafts whose function was studied here, 69 were primary and the other 15 were retransplantations. In 6 of 15 retransplantations, both the primary and secondary graftings were followed with AKBR testing. In the other 9 cases, the primary grafting had been done before this study, and only the second liver could be studied. The first grafts were lost later for a variety of reasons, and after retransplantation the AKBR had decreased more

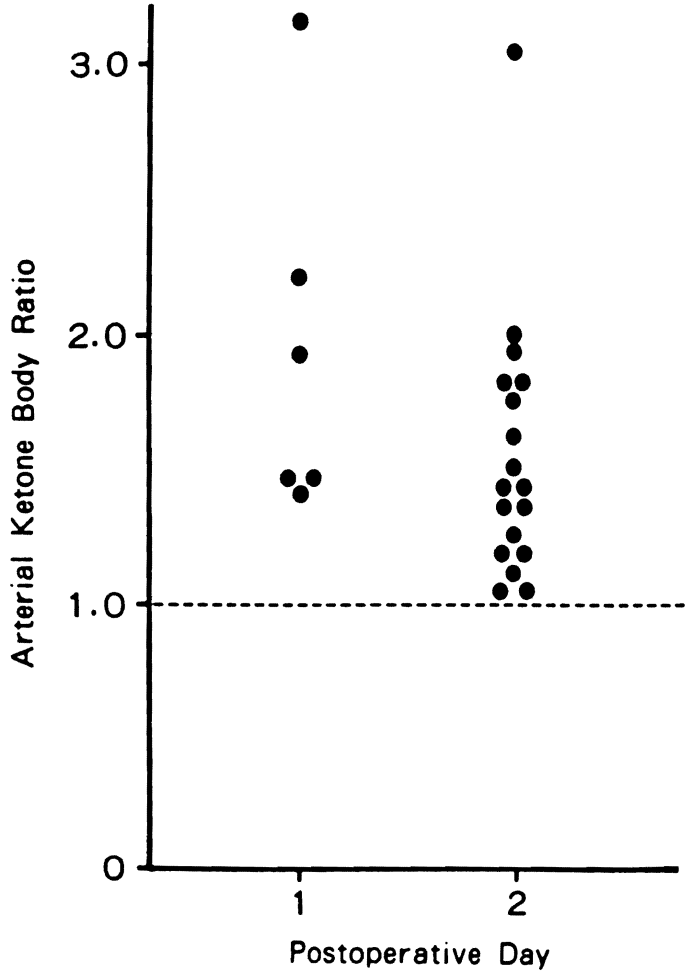

FIGURE 3. The AKBRs of 24 patients at discharge from the ICU by the second postoperative day.

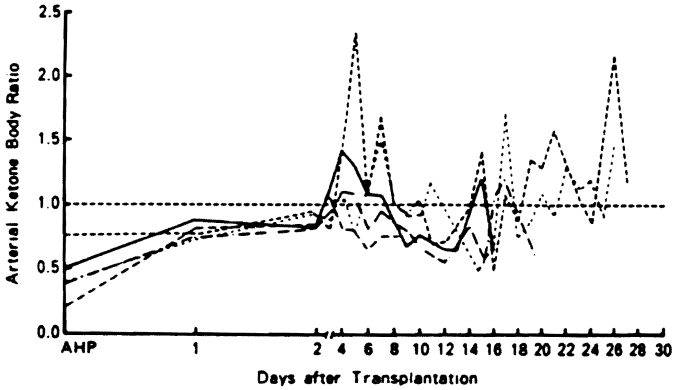

FIGURE 4. Changes in the AKBR after OLTx of the 5 cases with compromised grafts. (AHP) anhepatic period.

than with primary grafting (Fig. 11). This observation emphasized the greater risk of graft failure born by patients undergoing retransplantation after the failure of a first graft.

DISCUSSION

It is documented that a reduced redox state of hepatic mitochondria indicating the accumulated intramitochondrial

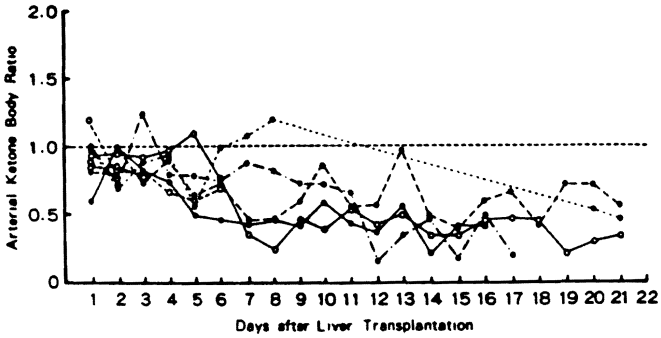

FIGURE 5. Changes in the AKBR after OLTx of the 7 cases with failed grafts in state II and one case with failed graft in state I→II.

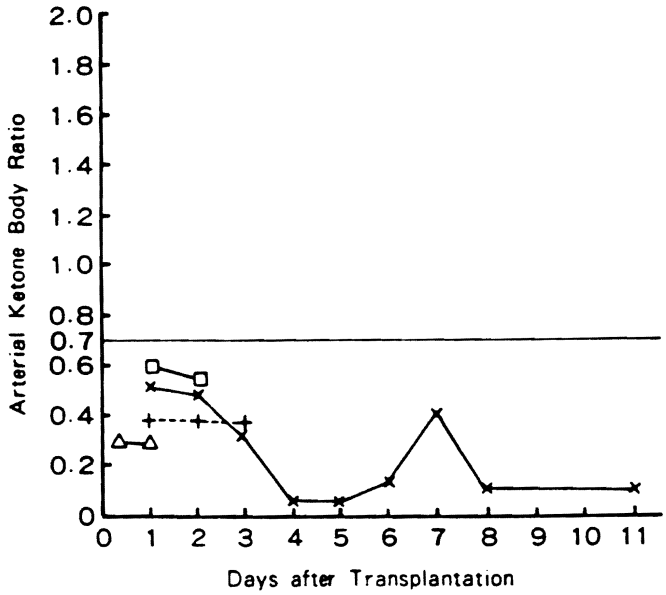

FIGURE 6. Changes in the AKBR after OLTx of the 4 cases with failed grafts in state III.

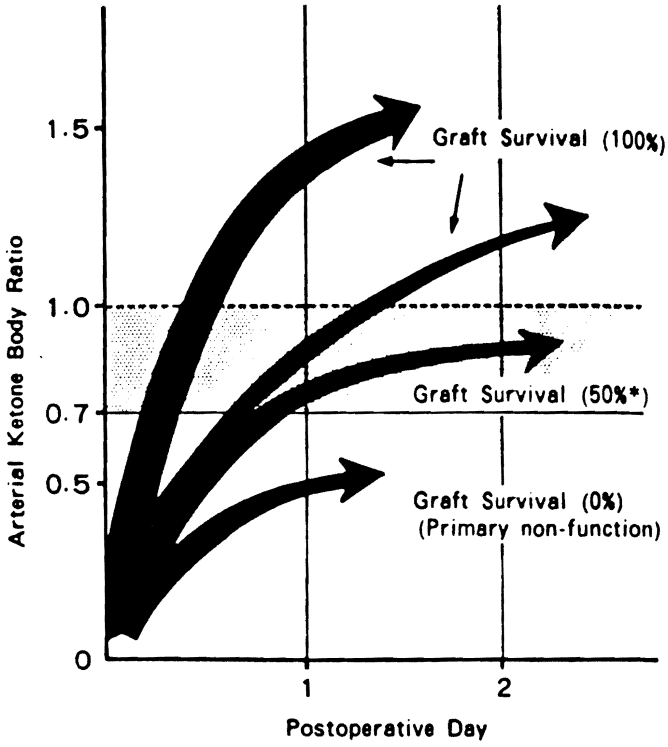

FIGURE 7. Relationship between the increase pattern of the AKBR by the second postoperative day and graft outcome. (*) 50% includes 5 compromised cases that succeeded, although with prolonged recovery.

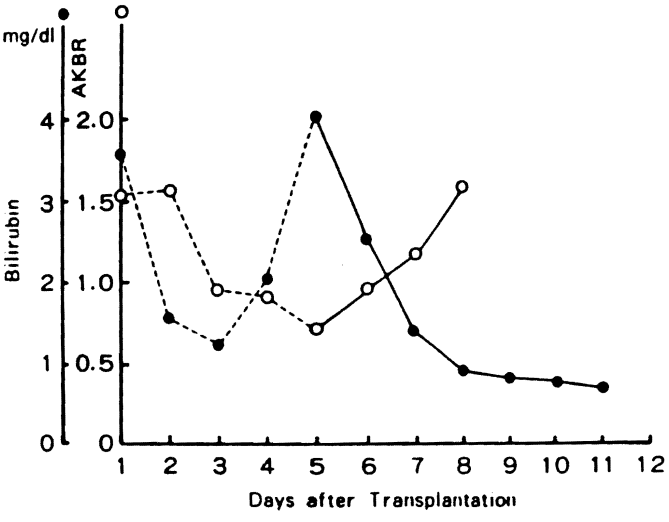

FIGURE 8. A typical case in which the recovery of the AKBR was obtained by FK506. (○) AKBR; (●) bilirubin.

NADH, inhibits the activity of citrate synthase, which controls the turnover rate of the Krebs cycle, and the activity of pyruvate dehydrogenase, which controls the reaction from pyruvate to acetyl CoA. These result in a fall in the ATP-synthesizing ability of the liver mitochondria. With the depletion of ATP, many biological reactions cease in the hepatocytes, and biological membranes start to malfunction. There is considerable evidence to show that the AKBR is correlated closely with hepatic functions, not only in the case of primary hepatic disease but also in hemorrhagic shock, hypoxia, hemodilution, and multiple organ failure. As a result, the redox theory is gradually receiving wider acceptance among investigators, and the assessment of hepatic function according to AKBR has begun to be adopted in the medical field.

Because it has been suggested that the mitochondrial function is a powerful predictor of the outcome of hepatic surgery (*3, 4*), it was natural to apply the AKBR testing in liver transplantation. In the present study a close correlation of the redox state of the graft mitochondria with graft survival was clearly demonstrated. During the anhepatic state, a rapid decrease in the AKBR occurred that was promptly returned toward normal by a well-functioning graft. This restoration did not occur if the liver had been damaged by events in the donor death, poor procurement or preservation, or performance of a flawed recipient operation. Even with a good liver, the AKBR could secondarily fail as early as 2 days after an initial increase. This may be due to accelerated rejection or other unidentified recipient factors.

The AKBR test is discriminating of liver quality, but it does not determine the etiology of the dysfunction. Taki et al. (*10, 11*) reported that the cut-off below which recovery could not be expected after liver transplantation was 0.7 when the determination was made after 24 hr. After liver transplantation, the restoration and maintenance of a high AKBR depends upon

TABLE 4. Comparison of various parameters among groups A, B, and C

	Lactate[a] (mmol/L)	T-BIL (mg/dl)		GOT (IU/ml)		GPT (IU/ml)		PT (second)	
		1 POD	2 POD	1 POD	2 POD	1 POD	2 POD	1 POD	2 POD
Group A	5.6±0.4	5.2±0.4	3.7±0.4	906.6±96.4	598.9±93.1	771.0±88.5	823.9±133.6	16.4±0.5	16.4±1.9
Group B	6.0±2.3	12.6±2.2[b]	10.3±2.5[b]	956.8±226.8	458.2±110.6	547.6±110.3	685.6±175.6	16.9±0.8	16.3±1.4
Group C	9.2±2.0[c]	9.8±1.6[d]	11.2±1.9[d]	2816.1±644.9[d,f]	3107.4±891.0[d,f]	2139.0±530.9[d,f]	2480.6±813.2[d,e]	21.0±1.7[d]	18.4±1.2

[a] Values at the end of the operation.
[b] Group A versus group B, $P < 0.005$.
[c] Group A versus group C, $P < 0.01$.
[d] Group A versus group C, $P < 0.005$.
[e] Group B versus group C, $P < 0.05$.
[f] Group B versus C, $P < 0.005$.

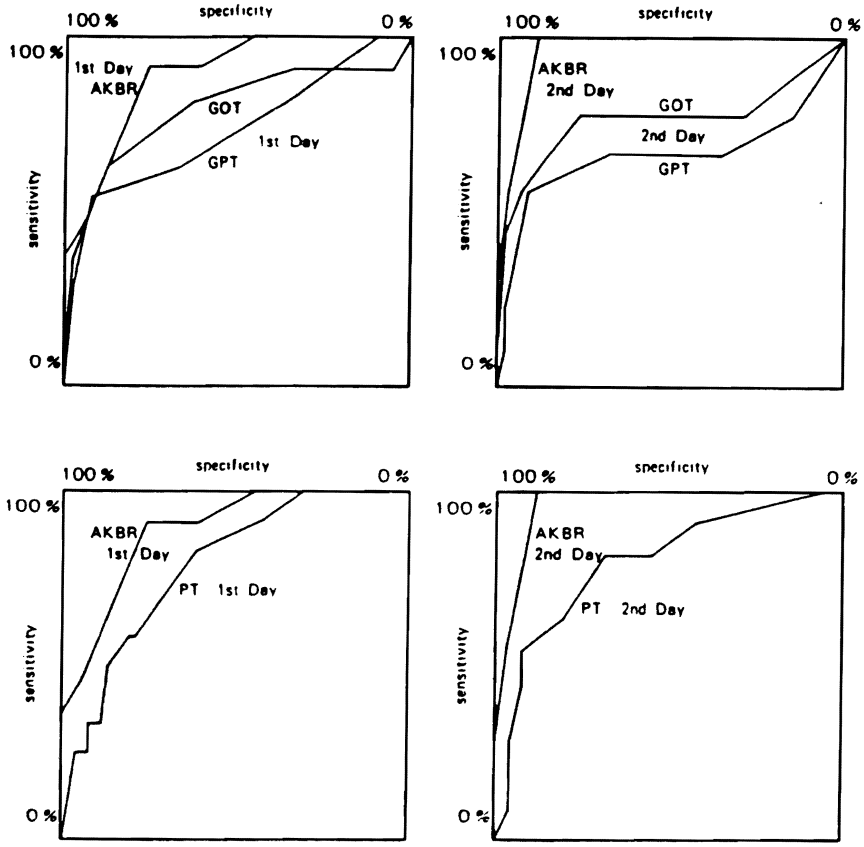

FIGURE 9. Receiver operating characteristic curve for the analysis of accuracy in discriminating between the successful and the failed graft groups. (upper left) Comparison between GOT and GPT with AKBR on the 1st postoperative day; (upper right) Comparison between GOT and GPT with AKBR on the 2nd postoperative day; (lower left) Comparison between PT and AKBR on the 1st postoperative day; (lower right) Comparison between PT and AKBR on the 2nd postoperative day.

several factors: (1) recipient condition, (2) the viability of the donor liver, (3) the degree of intraoperative stress caused by anesthesia, transfusions, and transplantation techniques, (4) proper general postoperative care, and (5) harmful immune events including rejection. If the AKBR decreases, the cause is probably the failure to adequately meet one or more of these requirements. Which one(s) may be difficult to identify, but a signal can be obtained within 24 to 48 hr that retransplantation will be necessary. If the AKBR is less than 0.7 in a nondiabetic patient, the graft is hopeless. Even with AKBR levels of 0.7 to 1.0 in nondiabetic patients, the option of retransplantation should be considered seriously. Conversely, the achievement of an AKBR of 1.0 or better should discourage a decision for retransplantation in spite of anxiety for other reasons about graft viability.

Unfortunately, the road map is not so clear in patients who are temporarily or chronically diabetic, and in whom a reduced AKBR does not have the same prognostic significance. In this population, most of the AKBR levels were suboptimal, but this was not a uniformly ominous finding.

It is known that the mitochondrial response to hepatectomy is suppressed in diabetic rats and that insulin is regarded as the primary factor governing the changes in the mitochondrial metabolism (*16–18*). It also has been shown the liver mitochondria are oxidized (the AKBR is increased) concomitant with a rise in serum insulin levels (*19*). Finally, apart from a

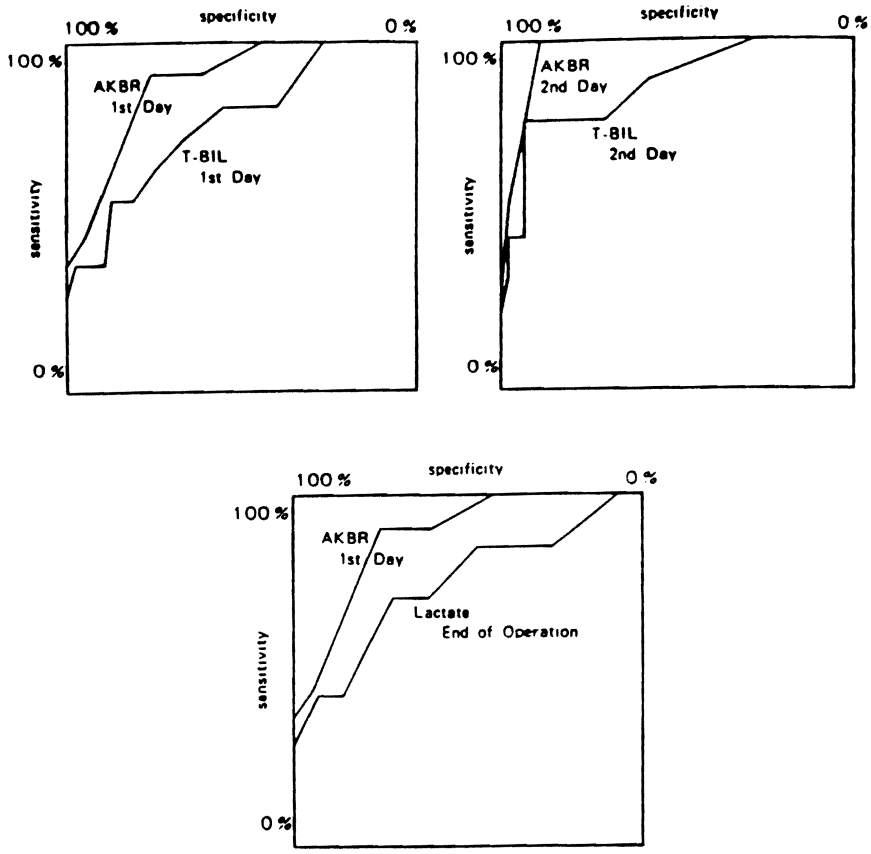

FIGURE 10. Receiver operating characteristic curve for the analysis of accuracy in discriminating between the successful and the failed graft groups. (upper left) Comparison between T-BIL and AKBR on the 1st postoperative day; (upper right) Comparison between T-BIL and AKBR on the 2nd postoperative day; (lower) Comparison between lactate at the end of operation and AKBR on the 1st postoperative day.

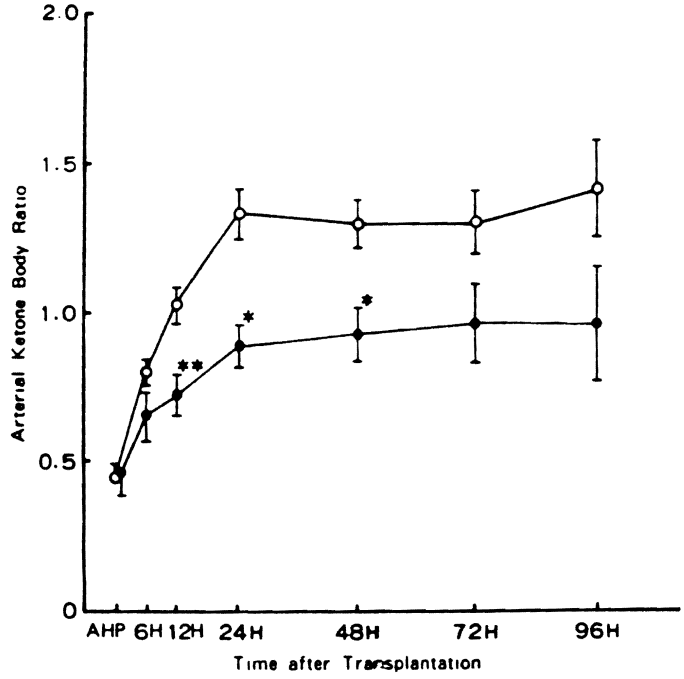

FIGURE 11. Changes in the AKBR after primary and secondary grafting. Values are presented as means ± SEM. (○) primary; (●) secondary. (*) and (**): $P<0.05$ and $P<0.01$, respectively. (AHP) anhepatic period.

specific effect on the mitochondria, insulin has a proven influence on other measures of hepatocyte structure, function, and the capacity for regeneration and repair (*20, 21*). These effects have been termed "hepatotrophic." Although further investigations are needed, it is already clear that insulin administration via an adequate route in "diabetic" patients could be of the utmost importance in postoperative management. Other supportive care should include parenteral nutrition, including provision of suitable energy substitutes.

After the immediate postoperative period, acute rejection has been shown in rats to decrease the redox potential of hepatic mitochondria (*22*). The same thing was seen dramatically in one of our recipients whose rejecting liver was rescued with FK506. The patient who was unconscious with rapidly developing hyperbilirubinemia and declining AKBR had reversal of all these parameters within a short time after substituting FK506 for cyclosporine.

Recent studies in Pittsburgh have demonstrated a correlation of high endotoxin levels pre- and postoperatively and during the anhepatic period with graft failure and a high mortality (*23, 24*). Related studies in Kyoto have shown that severe endotoxemia typically occurs after the decrease in the AKBR in patients undergoing partial hepatectomy (*25*). A decrease in the AKBR may be the basic cause leading to multiple organ failure (*3, 4*). A marked decreased in the AKBR could be a case of endotoxemia and graft failure, or alternatively could be the consequence of endotoxemia. The interaction of these factors will be important to clarify in future research.

ORAL DISCUSSION

DR. BUSUTTIL (Los Angeles, California): As you know, we are looking at KBR at UCLA, and our results with adults are very similar to what you have shown. However, in a group of children which we have studied, we found that they are much more forgiving. They can have a lower KBR for a longer period of time and still show evidence of very nice graft function. Do you have an explanation for that?

DR. ASONUMA: I have no data for the children, so I can't say anything, but there might be some difference between the children and adults. In adults we think the State 3 KBR at 24 hr or at 48 hr is very critical.

DR. GORDON (Pittsburgh, Pennsylvania): Have you studied at all patients who are taking FK with the KBR? FK has interesting effects on the liver that far exceed those of cyclosporine, such as the hepatotrophic effect. Is there any difference in these ratios in patients taking FK versus cyclosporine?

DR. ASONUMA: Both of these patients are FK patients and you can see the results. The graft failure is less than the previous reports of the cyclosporine. We tried to compare the cyclosporine patients and the FK patients in the changes of the AKBR, but we cannot find that here in this study.

DR. BOLLINGER (Duke University): Can I ask, Dr. Asonuma, how you are using this indicator at Pittsburgh right now?

DR. ASONUMA: We're trying to do a preliminary study to the routine examination, but the system is not yet established.

REFERENCES

1. Fath JJ, Ascher NL, Konstantinides FN, et al. Metabolism during hepatic transplantation: indicator of allograft function. Surgery 1984; 96: 664.
2. Ray RA, Lewin KJ, Colonna J, et al. The role of liver biopsy in evaluating acute allograft dysfunction following liver transplantation. Hum Pathol 1988; 19: 835.
3. Ozawa K. Biological significance of mitochondrial redox potential in shock and multiple organ failure: redox theory. In: Lefer AM, Schumer W, eds. Molecular and cellular aspects of shock and trauma. New York: Liss, 1983: 39.
4. Ozawa K, Aoyama H, Yasuda K, et al. Metabolic abnormalities associated with postoperative organ failure: a redox theory. Arch Surg 1983; 118: 1245.
5. Ketone body ratio: an index of multiple organ failure [Editorial]? Lancet 1984; 1: 25.
6. Tanaka J, Ozawa K, Tobe T. Significance of blood ketone ratio as an indicator of hepatic cellular energy status in jaundiced rabbits. Gastroenterology 1979; 76: 691.
7. Yamamoto M, Kono Y, Ukikusa M, et al. Significance of acetoacetate/β-hydroxybutyrate ratio in arterial blood as an indicator of the severity of hemorrhagic shock. J Surg Res 1980; 28: 124.
8. Taki Y, Ukikusa M, Morimoto T, et al. Short-term changes in blood ketone body ratio in the phase immediately after liver transplantation. Transplantation 1987; 43: 350.
9. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982; 2: 614.
10. Gubernatis G, Bornscheuer A, Taki Y, et al. Total oxygen consumption, ketone body ratio and a special score as early indicators of irreversible liver allograft dysfunction. Transplant Proc 1989; 21: 2279.
11. Taki Y, Gubernatis G, Yamaoka Y, et al. Significance of arterial ketone body ratio measurement in human liver transplantation. Transplantation 1990; 49: 535.
12. Starzl TE, Gordon RD, Tzakis A, et al. Transplant Proc 1988; 20: 131.
13. Starzl TE, Miller C, Broznick B, Makowka L. An improved technique for multiple organ harvesting. Surg Gynecol Obstet 1987; 165: 343.
14. Mellanby J, Williamson DH. Acetoacetate. In: Bergmeyer HU, ed. Methods of enzymatic analysis. New York: Academic, 1974: 1840.
15. Williamson DH, Mellanby J. D-(-)-3-hydroxybutyrate. In: Bergmeyer HU, ed. Methods of enzymatic analysis. New York: Academic, 1974: 1836.
16. Ozawa K, Yamada T, Honjo I. Role of insulin as a portal factor in maintaining the viability of liver. Ann Surg 1974; 180: 716.
17. Ozawa K, Yamada T, Yamamoto M, et al. Suppression of mitochondrial response to hepatectomy in diabetic rats. Life Sci 1976; 19: 1865.
18. Yamada T, Yamamoto M, Ozawa K, et al. Insulin requirement for hepatic regeneration following hepatectomy. Ann Surg 1977; 185: 35.
19. Kimura K, Ukikusa M, Ozawa K, et al. Changes in mitochondrial redox state following an oral glucose load. Acta Diabetol Lat 1978; 15: 253.
20. Starzl TE, Watanabe K, Porter KA, Putnam CW. Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. Lancet 1976; 1: 821.
21. Starzl TE, Porter K, Francavilla A. The Eck fistula in animals and humans. Curr Probl Surg 1983; 29: 687.
22. Asonuma K, Tanaka K, Uemoto S, et al. Blood ketone body ratio with reference to graft viability after liver transplantation in rats. Transplant Int 1989; 2: 133.
23. Miyata T, Todo S, Imventarza O, et al. Endogenous endotoxemia during orthotopic liver transplantation in dogs. Transplant Proc 1989; 21: 3861.
24. Miyata T, Yokoyama I, Todo S, et al. Endotoxemia, pulmonary complications and thrombocytopenia with clinical liver transplantation. Lancet 1989; 2: 189.
25. Ozawa K. Hepatic functional reserve and liver resection. J Hepatol Gastroenterol (in press).

Received 18 June 1990.
Accepted 5 September 1990.