Response of Hepatic Mitochondrial Redox State to Oral Glucose Load

Redox Tolerance Test as a New Predictor of Surgical Risk in Hepatectomy

KEIICHIRO MORI, M.D., KAZUE OZAWA, M.D., YUZO YAMAMOTO, M.D., ATSUHIKO MAKI, M.D., YASUYUKI SHIMAHARA, M.D., NOBUAKI KOBAYASHI, M.D., YOSHIO YAMAOKA, M.D. and KAORU KUMADA, M.D.

The redox tolerance test introduced in this article attempts to quantify the deterioration of hepatic mitochondrial energy metabolism by measuring the changes in arterial ketone body ratio in response to 75-g oral glucose loading, and is discussed in relation to its predictive value for assessing surgical risk in hepatectomy. The indicator, called redox tolerance index (RTI), represents a 100-fold cumulative enhancement of ketone body ratio relative to glucose level (100 × △KBR/△ glucose). The redox telerance index was significantly different between 31 liver cirrhotics and 10 normal volunteers ($p < 0.001$). Subjects were divided into three classes (I: RTI ≧ 1.0, II: 0.5 ≦ RTI < 1.0, III: RTI < 0.5). Postoperative mortality was significantly different among the three classes in 127 hepatic resections ($x^2 = 9.843$, $p < 0.01$). Of 97 hepatocellular carcinoma cases, major hepatic resections in class III showed significantly higher postoperative morbidity and mortality rates ($p < 0.05$ and $p < 0.05$, respectively). The present findings indicate that RTI based on redox theory is of potential value in predicting posthepatectomy outcome.

THE ABSOLUTE CURE for liver cancer requires the complete resection of the tumor along with sufficient surrounding liver tissue. An underlying cirrhosis, however, as in the case of hepatocellular carcinoma (HCC), often delimits the operation because of the high risk of hepatic failure followed by multiple organ failure. To reduce this risk requires the accurate preoperative assessment of hepatic functional reserve, which is a matter of great concern not only in the field of liver surgery[1,2] but also in general surgery.[3-5] A number of methods of assessing hepatic functional reserve have been proposed.[5-13]

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Address reprint requests to Keiichiro Mori, M.D., Second Department of Surgery, Faculty of Medicine, Kyoto University, 54-Kawaracho, Shogoin, Sakyoku, Kyoto, 606, Japan.

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From the Second Department of Surgery, Faculty of Medicine, Kyoto University, Kyoto, Japan

Because hepatocytes consume an enormous amount of energy, namely ATP, to carry out their cellular functions they must produce energy constantly. Our laboratory has proposed that the essential hepatic function is the energy production carried out in the hepatic mitochondria, and that the energy-producing capacity of mitochondria may be said to represent the hepatic functional reserve. Previous experimental studies from our laboratory have shown that the energy metabolism in the hepatic mitochondria is closely related to glucose tolerance pattern, and that the changes in hepatic energy charge [(ATP + 0.5ADP)/(ATP + ADP + AMP)] after an oral glucose load are positively correlated with those in blood glucose levels and immunoreactive insulin levels in normal rats.[14] Glucose intolerance, which is observed in icteric rats and rabbits,[15] as well as in human and other mammals after massive liver resection,[16] has been found to be closely related to the decrease in hepatic energy charge and the derangement of mitochondrial function.[17-20] In clinical application the assessment of hepatic functional reserve has shown that oral glucose tolerance test provides a predictive postoperative prognosis in hepatectomized[9] and pancreatectomized[21] patients. Another report from our laboratory has shown that the redox state of liver mitochondria (NAD^+/NADH), reflected by hepatic ketone body ratio (acetoacetate/β-hydroxybutyrate), changes in proportion to the blood glucose levels after an oral glucose load, concomitant with changes in the hepatic energy charge level.[22] In other studies, the hepatic mitochondrial redox state, which is reflected in the ketone body ratio (KBR) of arterial blood, was positively correlated with the hepatic energy charge level in jaundiced,[23] hepatectomized,[24,25] and shocked animals,[26,27] and the changes in

arterial KBR were positively correlated with those of hepatic venous blood after hepatic artery embolization in cirrhotic patients with hepatocellular carcinoma.[28]

It has been observed that the arterial KBR is often highly decreased in the postoperative course after hepatic resection,[24] and that morbidity and mortality rates increase in accordance with the extent of decrease in arterial KBR.[29] Generally the decrease in arterial KBR is accompanied by massive systemic metabolic derangements that eventually result in multiple-organ failure. Because this metabolic regulation is based on the hepatic mitochondrial redox state, we have called our proposal the redox theory.[30,31] This theory has gained wider support among researchers in surgery and critical medicine in recent years,[32-34] and a recent paper reports on arterial KBR as a useful and beneficial indicator to diagnose the primary nonfunction of the graft after liver transplantation and to determine the necessity of retransplantation.[35]

The present study focuses on the response of the arterial KBR during oral glucose tolerance test (O-GTT) and introduces a new redox tolerance test as part of a larger plan to establish a method of evaluating hepatic functional reserve based on the redox theory.

Subjects and Methods

Comparison of Responses of the Arterial Ketone Body Ratio During Oral Glucose Tolerance Test Between Normal Subjects and Liver Cirrhotics

Thirty-one cirrhotic patients admitted to Kyoto University Hospital were examined and their liver cirrhoses were confirmed histologically. The clinical status of these patients was stratified into class A (4), class B (19), and class C (8) according to Child's classification. Patients with overt diabetes mellitus were excluded, hence those who were formerly diagnosed and treated for diabetes or showed high fasting glucose levels of 120 mg/dL or more were eliminated from this study. The patients were 24 men and 7 women who ranged in age from 42 to 76 years, with a mean age of 57 years. Ten healthy volunteers, seven men and three women aged from 20 to 62 years old, were the normal controls. None of those subjects had been administered any drug or hormone which would affect carbohydrate metabolism.

Under informed consent, the subjects underwent oral glucose tolerance test (O-GTT) followed by measurement of arterial KBR, which was performed as follows. After an overnight fast lasting at least 12 hours, each subject ingested 75 g of glucose in the morning. A 8-mL blood sample was collected either through a fine teflon catheter inserted into the radial artery or by individual puncture of the femoral artery, the choice of which was left to each subject, just before taking glucose and subsequently at 30, 60, 90, and 120 minutes. To determine KBR, acetoacetate and β-hydroxybutyrate were measured enzymatically by the methods reported previously.[36] Blood glucose level was determined by the o-toluidine method[37] and immunoreactive insulin (IRI) by radioimmunoassay.[38] Serum-free fatty acids were measured by a standard colorimetric method.[39]

Calculations. To quantify the response of arterial KBR to O-GTT, because both blood glucose level and KBR increased above fasting value until 120 minutes after glucose loading, the cumulative enhancement of A (ΔA), in which A indicates blood glucose level or KBR, was calculated as a value estimated from the shaded area consisting of one triangle and three trapezoids, as shown in Figure 1, using the following formula:

$$\Delta A = \frac{a_1 - a_0}{2} \times K + \frac{(a_1 - a_0) + (a_2 - a_0)}{2} \times K + \frac{(a_2 - a_0) + (a_3 - a_0)}{2} \times K + \frac{(a_3 - a_0) + (a_4 - a_0)}{2} \times K = \frac{K}{2}(2a_1 + 2a_2 + 2a_3 + a_4 - 7a_0)$$

when K is substituted by 1,

$$\Delta A = \frac{1}{2}(2a_1 + 2a_2 + 2a_3 + a_4 - 7a_0) = (a_1 + a_2 + a_3) + \frac{a_4 - 7a_0}{2}$$

where a_0, a_1, a_2, a_3, and a_4 represent each value of glucose level and KBR at 0, 30, 60, 90, and 120 minutes in O-GTT, respectively.

The changes of arterial ketone body ratio in response to O-GTT will hereafter be referred to as the 'redox tolerance test.'

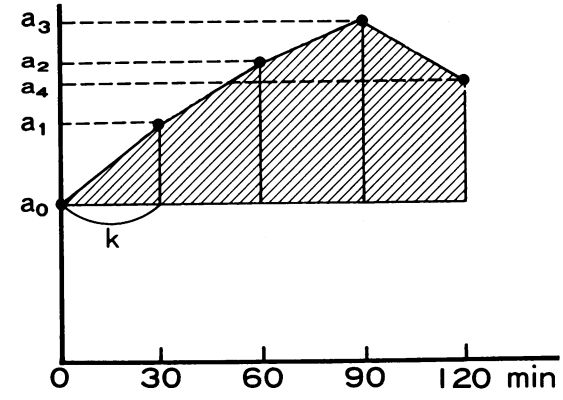


FIG. 1. Schematic pattern of blood ketone body ratio and glucose level for the calculation in redox tolerance test. Cumulative enhancement of each can be estimated as the shaded area.

Redox Tolerance Test in Hepatectomy Cases

Cases. Of 182 patients who underwent hepatic resections from January 1987 to December 1988 in the Second Department of Surgery, Kyoto University Hospital, the redox tolerance test was performed in 155 patients (85%) before operation. Patients with overt diabetes mellitus showing high fasting glucose levels of more than 120 mg/dL, patients with obstructive jaundice, and patients who underwent hepatectomy with hepatic vasculature reconstruction were eliminated from this study. Predictive values of redox tolerance test were eventually studied in 127 patients who underwent simple hepatecomy for solid hepatic tumor (82% of redox tolerance tests examined). Histologic diagnoses were done by clinical pathologists at Kyoto University Hospital. Esophageal varices were diagnosed by endoscopic findings of F_2-rosary or F_3-nodular form according to the Rules and Nomenclature determined by the Japan Portal Hypertension Research Association.[40] Details of these cases are summarized in Table 1.

Hepatectomy. In hepatic anatomy, the Glisson pedicle, which consists of the portal vein, hepatic artery, and bile duct, is divided into three branches: posterior segment (VI and VII of Couinaud's segment),[41] anterior segment (V and VIII), and left lobe (lateral and medial segments), each of which terminates in almost equal volume of hepatic parenchyma. Therefore all patients were classified according to the mode of hepatectomy into one of two groups: major hepatic resection, which included posterior segmentectomy, anterior segmentectomy, right lobectomy, left lobectomy, or trisegmentectomy; or minor hepatic resection, which meant subsegmentectomy (resection of one Couinaud's segment) or unanatomical enucleation of tumor. Excluded from this classification were five patients who underwent partial hepatic resection with distal splenorenal shunt (PH + DSRS) for impending rupture of esophageal varices.

Redox tolerance test and laboratory data. Preoperative redox tolerance tests were all performed approximately 1 week before the surgery. Liver function tests, namely serum GOT, GPT, bilirubin, albumin and choline esterase levels, prothrombin time, and platelet counts were determined at the clinical laboratory division of our hospital. Indocyanine green test was also examined before operation and K-value (K-ICG: disappearance constant) was determined. All tests were performed on or around the day the redox tolerance test was performed.

Postoperative morbidity and mortality. Postoperative morbidity was defined in this study as follows: hyperbilirubinemia more than 8 mg/dL, elevated BUN more than 50 mg/dL, and/or serum creatinine more than 2 mg/dL with or without hemodialysis, respiratory failure necessitating assistance by mechanical ventilator, hemorrhagic tendency necessitating blood transfusion, hypotension necessitating infusion of inotropic drug such as dopamine, and encephalopathy with the patient being restless, excited, or at a worse stage of deterioration.

Postoperative deaths were classified as operative mortality if they occurred within the 30th postoperative day, regardless of cause. Hospital mortality was defined as death during hospitalization on the 31st postoperative day or thereafter.

Statistical analyses. All results were expressed as mean ± standard error. Student's t test and chi square test were used for statistical analysis and p values less than 0.05 were regarded as significant.

Results

Differences of Redox Tolerance Test Between Liver Cirrhotics and Normal Subjects

This study was performed in 31 tumor-free cirrhotic patients whose diagnoses were confirmed histologically and in 10 normal volunteers who served as controls. Re-

TABLE 1. *Summary of 127 Hepatectomized Patients Examined by Redox Tolerance Test*

Disease (n)	Age	Sex (male/female)	Comments
HCC (97)	60.1 ± 0.9	73/24	Underlying liver disease (histologically diagnosed)
			Liver cirrhosis 69
			Chronic hepatitis 22
			None (normal liver) 6
Metastatic tumor (13)	56.1 ± 10.5	6/7	Original tumor
			Colorectal cancer 9
			Breast cancer 3
			Leiomyosarcoma 1
Biliary tumor (12)	59.8 ± 10.4	4/8	Disease without obstructive jaundice
			Cholangiocellular carcinoma 8
			Gall bladder cancer 4
Hemangioma (5)	57.8 ± 10.0	2/3	All were huge liver hemangioma measuring more than 20 cm in diameter

HCC, hepatocellular carcinoma.

sponses of blood glucose level and arterial KBR during 75-g O-GTT are shown in Table 2 and Figure 2. At fasting state, blood glucose levels were not different between the liver cirrhotic group (LC group) and the normal control group (N group), although IRI concentrations in the LC group were higher and the arterial KBRs in the LC group were lower than those in the N group ($p < 0.05$). After the oral glucose load, the LC group showed a gradual increase in blood glucose level, while the N group showed the typical return toward normal after a peak at 30 minutes. The blood glucose level in the LC group was significantly higher than that in the N group at 60, 90, and 120 minutes. Increase of the arterial KBR in the LC group was significantly lower than that in the N group throughout the 120-minute period tested.

Cumulative enhancement of blood glucose level and arterial KBR, here referred to as integrated glucose response (Δglucose) and integrated KRB response (ΔKBR), respectively, are compared between the two groups in Table 2. ΔGlucose in the LC group was significantly greater than in the N group ($p < 0.001$), and ΔKBR in the LC group was significantly smaller than in the N group ($p < 0.001$). Accordingly the ΔKBR-to-ΔGlucose ratio (ΔKBR/ΔGlucose), which means the response of arterial KBR to glucose loading, showed a marked difference between the two groups ($p < 0.001$). These findings suggest that the ratio ΔKBR to Δglucose in the redox tolerance test is indicative of the responsiveness of hepatic mitochondrial redox state to glucose loading. In this paper, for convenience, a redox tolerance index (RTI), which is a 100-fold ratio of ΔKBR to Δglucose (RTI = 100 × ΔKBR/Δglucose), is used as an indicator for the redox tolerance test.

TABLE 2. *Comparison Between Normal Subjects and Liver Cirrhotics in Redox Tolerance Test*

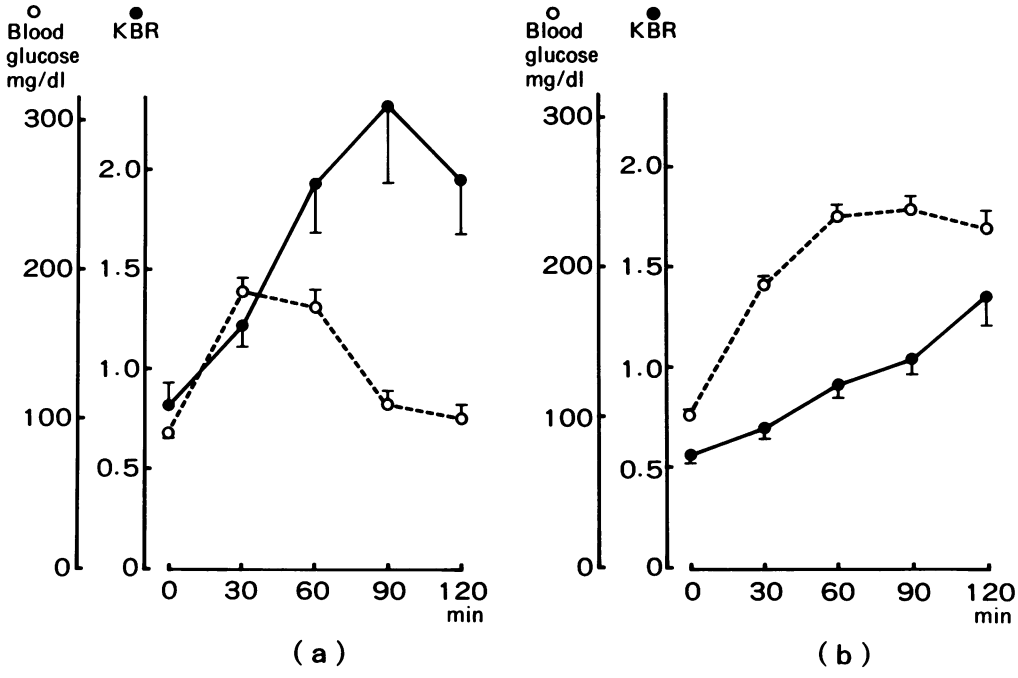
Subjects (n)	Fasting State					Redox Tolerance Test		
	Blood Glucose (mg/dL)	IRI (μU/mL)	FFA (μ*Eq/L)	Ketone Body Concentration (μmol/mL)	Ketone Body Ratio	ΔGlucose	ΔKBR	ΔKBR/ΔGlucose ($\times 10^{-2}$)
N (10)	90.6 ± 3.1	7.8 ± 0.6	796 ± 95	0.078 ± 0.023	0.82 ± 0.11	204 ± 16	3.60 ± 0.70	1.84 ± 0.36
LC (31)	100.3 ± 2.7	12.9 ± 0.8*	1049 ± 67	0.157 ± 0.028	0.55 ± 0.04†	426 ± 20‡	1.37 ± 0.17‡	0.36 ± 0.05‡

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

Predictive Value of Redox Tolerance Test in Hepatectomy

As shown in Figure 3, RTI in 127 hepatectomized patients was plotted in comparison to 10 normal controls. Table 3 shows RTI and postoperative mortality rate in these patients. Redox tolerance index in hepatocellular carcinoma cases was significantly lower than those in metastatic liver tumor, biliary tumor, or liver hemangioma cases ($p < 0.01$, $p < 0.001$, and $p < 0.01$, respectively). The 11 patients who died in hospital after operation were all HCC cases. These results indicate that patients showing lower RTI before operation make poor candidates for hepatic resection.

To study the further relationship between RTI and surgical risk, the patients were placed in one of three classes according to RTI (class I: RTI ≧ 1.0; class II: 0.5 ≦ RTI < 1.0; and class III: RTI < 0.5) and their postoperative mortality rates were compared. The classification system was established by the following method. The 127 patients were divided into a chronic liver disease group (69 liver



FIGS. 2A and B. Changes in blood ketone body ratio and glucose levels in redox tolerance test. (A) 10 normal subjects, (B) 31 liver cirrhotics. ● —— ● ketone body ratio, O - - - O blood glucose level.

cirrhosis and 22 chronic hepatitis in HCC cases), and a normal liver group (6 patients with HCC and all 30 patients with metastatic tumors, biliary tumors, and hemangiomas) according to the histologic appearance of their tumor-free hepatic parenchyma. Redox tolerance index was obtained from each patient. Redox tolerance index of the chronic liver disease group was 0.56 ± 0.45 (mean ± SD, n = 91) and that of the normal liver group was 1.37 ± 0.86 (mean ± SD, n = 36). Statistically, because 83% of all values were included within the range of mean ±1 SD, an RTI of more than 1.0 (0.56 + 0.45 = 1.01, mean + 1 SD in the chronic liver disease group) was regarded as normal, while an RTI of less than 0.5 (1.37 − 0.86 = 0.51, mean-1 SD in the normal liver group) was regarded as abnormally low. Hence class I, the normal class, was defined as RTI more than 1.0; class II, the intermediate class, as RTI between 1.0 and 0.5; and class III as RTI less than 0.5. As shown in Table 4 the postoperative mortality rate in the 127 hepatectomy cases correlated significantly with the preoperative RTI (x^2 = 9.843, and $p < 0.01$).

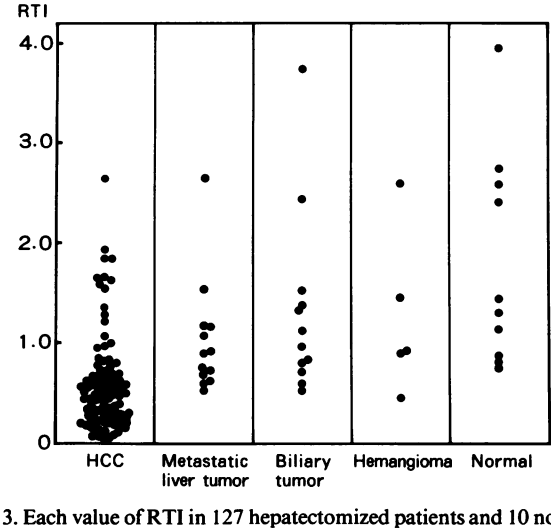


FIG. 3. Each value of RTI in 127 hepatectomized patients and 10 normal subjects.

We then investigated the relationship of the redox tolerance test to the postoperative courses of the 97 HCC cases because postoperative deaths had occurred only in HCC cases in this study and because the preoperative evaluation of hepatic functional reserve is crucial in hepatic resection for liver tumor with chronic liver damage.

Redox tolereance index in normal parenchyma cases was significantly higher than that in liver cirrhosis (LC) or in chronic hepatitis (CH) cases ($p < 0.001$ and $p < 0.01$, respectively), while no difference was observed between

TABLE 3. *Redox Tolerance Index and Postoperative Mortality in 127 Hepatectomized Patients*

Disease (n)	RTI	Operative Mortality % (n)	Hospital Mortality % (n)	Total Mortality % (n)
HCC (97)	0.61 ± 0.05	4.1 (4)	7.2 (7)	11.3 (11)
Metastatic (13)	1.03 ± 0.16*	—	—	—
Biliary (12)	1.35 ± 0.28†	—	—	—
Hemangioma (5)	1.28 ± 0.41*	—	—	—
Total (127)		3.1 (4)	5.5 (7)	8.7 (11)

* $p < 0.01$; † $p < 0.001$ *vs.* HCC.

TABLE 4. *Classification of Redox Tolerance Index and Postoperative Mortality*

Class	Survived	Dead	Total	Postoperative Mortality
I (RTI ≧ 1.0)	27	0	27	0%
II (0.5 ≦ RTI < 1.0)	49	2	51	3.9%
III (RTI < 0.5)	40	9	49	18.4%
Total	116	11	127	

$x^2 = 9.843$; $p < 0.01$.

LC and CH cases (Fig. 4). Among 69 liver cirrhosis cases, 20 cases with esophageal varices showed significantly lower RTI than 49 cirrhotics without varices ($p < 0.05$) (Fig. 5). Eighteen HB-antigen positive patients showed no difference in RTI compared to 77 HB-antigen negative patients. Table 5 shows the relationship between RTI and other conventional laboratory data for liver function. Redox tolerance index did not show any statistical correlation between serum GOT, GPT, total bilirubin, albumin, choline esterase level, prothrombin time, platelet count, or K-ICG.

There were 11 postoperative deaths (4 operative and 7 hospital deaths), 2 of which were in class II and 9 in class III. While both class II cases manifested symptoms of hepatic failure after an initial episode of sudden bleeding from cut surface of liver or renal failure, all but one class

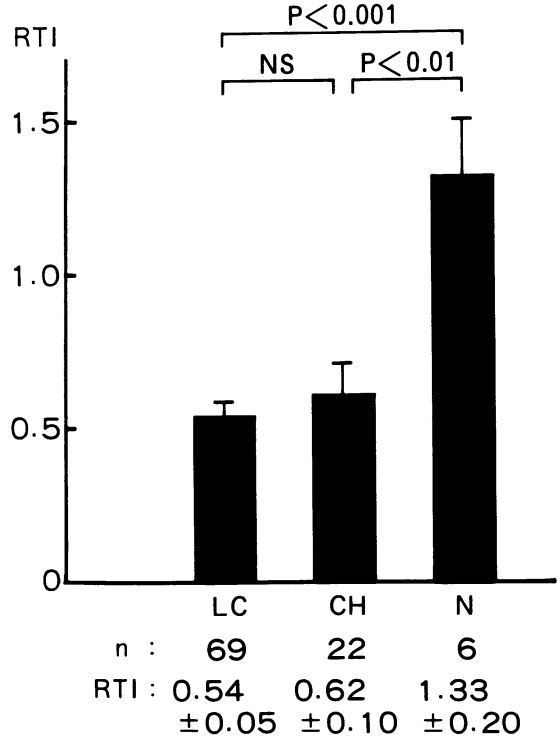


FIG. 4. Comparison of RTI among histologic findings of hepatic parenchyma in 97 HCC cases. LC, liver cirrhosis; CH, chronic hepatitis.

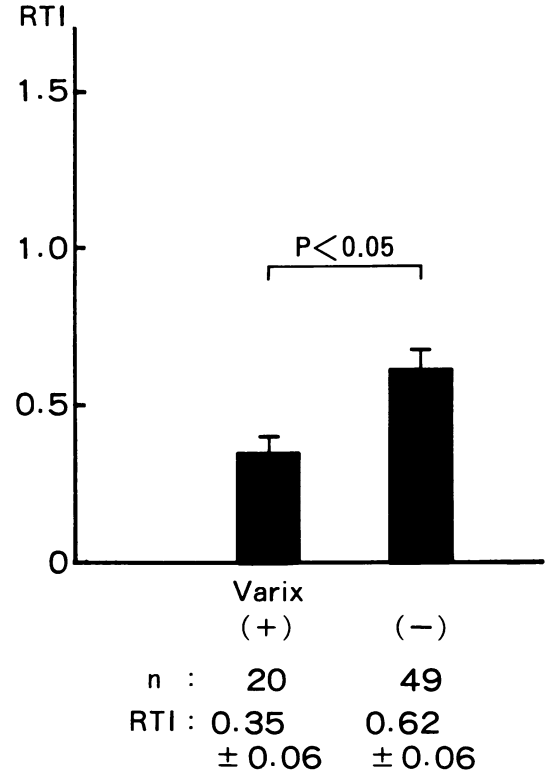


FIG. 5. Comparison of RTI between liver cirrhotics with esophageal varices and without varices.

III case showed gradual aggravation of liver function without any specific and particular episode, followed by multiple organ failure. The operations performed in these 11 patients were 7 major hepatic resections, 2 minor resections, and 2 partial hepatic resections with DSRS.

The contribution of this RTI classification to surgical risk was examined based on morbidity and mortality (Table 6). First the morbidity and mortality of class I patients were compared with those of class II and III patients together to raise statistical confidence because the number of patients in each class was so small. Chi square test, however, revealed no significant difference in morbidity and mortality rates in class I patients compared with those in the others. The morbidity and mortality rates of class III patients were then compared with those of class I and II patients together. Class III patients had higher morbidity or mortality rates than the class I and II patients. Of the total number of cases, the postoperative mortality of class III was significantly higher than that in class I and II ($x^2 = 5.189$, $p < 0.05$). In the major hepatic resection group, both the morbidity and mortality rates of class III were higher than class I and II ($x^2 = 6.617$, $p < 0.05$ and $x^2 = 3.948$, $p < 0.05$, respectively). In addition class III patients showed significantly different degrees of deterioration in serum bilirubin, platelet count, and K-ICG as compared to class I and II patients ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively).

TABLE 5. *Relationship Between Redox Tolerance Index and Laboratory Data in 97 HCC Cases*

	RTI	GOT (IU/L)	GPT (IU/L)	Bilirubin (mg/dL)	Albumin (g/dL)	Ch E ($\times 10^3$IU/L)	Prothrombin Time (seconds)	Platelet ($\times 10^4/\mu$L)	Kp-ICG
Preoperative values	0.61 ± 0.05	75.5 ± 4.4	70.4 ± 5.0	0.99 ± 0.04	3.84 ± 0.05	2.08 ± 0.09	12.6 ± 0.1	13.2 ± 0.9	0.112 ± 0.005
Correlation coefficient		−0.19	−0.15	−0.11	−0.02	0.04	−0.11	0.20	0.36
Significance		NS	NS	NS	NS	NS	NS	NS	NS

NS, not significant.

Discussion

In the perioperative period, when the hepatic function undergoes massive metabolic changes, excessive surgical stress can precipitate postoperative hepatic failure, even when a normal preoperative liver assessment has been made. In contrast patients with highly deteriorated hepatic function are known to tolerate surgical intervention well, as long as the intraoperative stress is minimal, *i.e.*, if the resected volume of hepatic parenchyma and other hepatodepressant factors, such as operation time, massive bleeding, blood transfusion, ischemic time, and anesthesia and drug damage are minimized. In the perioperative treatment, therefore, hepatic function or hepatic functional reserve should be evaluated on the basis of a theoretically consistent method. Previously we have suggested that the most important consideration in postoperative care is to keep the arterial KBR greater than the critical point of 0.4 because hepatectomized patients with markedly decreased arterial KBR have a high risk of hepatic failure and multiple-organ failure.[29–31] The redox tolerance test introduced in this article attempts to quantify the deterioration of hepatic mitochondrial energy metabolism by analyzing the changes in arterial KBR in response to oral glucose loading.

Although the precise mechanism governing the reduction of the mitochondrial redox potential in fasting state has yet to be clarified, one likely and highly persuasive argument for the regulation of glucose and fatty acid metabolism in hepatocytes at starvation is that once the glucose supply is interrupted, the subsequent inhibition of glycolysis provokes β-oxidation of fatty acids, resulting in a reduced mitochondrial redox state that inhibits the oxidizing process of acetyl CoA through the TCA cycle, and in an enhanced ketone body formation.[42–46] Direct spectrophotometric measurement has also revealed a decrease in the ratio of NAD^+ to NADH, *i.e.*, the redox state, in the suspensions of fatty acid oxidizing mitochondria.[47,48] Oral glucose loading at starvation, which induces the sufficient supply of glucose and insulin for hepatic cells, then enhances the ADP-phosphorylating reaction by mitochondria, resulting in the shift of mitochondrial redox potential from a reduced to an oxidated state,[49–51] which is possibly reflected as an increase in the arterial KBR. This response of hepatic mitochondrial redox state may be said to reflect the degree of deterioration in the hepatic energy metabolism. Indeed, as shown in the present study, the changes in arterial KBR in response to oral glucose tolerance test (ΔKBR/Δglucose or $100 \times \Delta$KBR/Δglucose referred to as RTI) were significantly decreased in liver cirrhotics than in normal subjects (Table 2). Liver cirrhotics with esophageal varices also showed significantly lower RTI, compared to those without varices, which seems to indicate the potentiality of RTI to distinguish the extent of liver damage in liver cirrhosis (Fig. 5). However chronic hepatitis could not be differentiated from liver cirrhosis by RTI (Fig. 4). These results are consistent with the fact that histologic diagnosis in chronic liver disease is not always correlated with actual hepatic function.

Conventional parameters of hepatic function, especially

TABLE 6. *Postoperative Morbidity and Mortality Classified in Relation to Redox Tolerance Index in 97 HCC Cases*

				Operation Procedures								
	Total Cases			Major Resection			Minor Resection			PH + DSRS		
Class	n	C	D^+	n	C^{++}	D^{+++}	n	C	D	n	C	D
I	14	2	0	12	2	0	2	0	0	—	—	—
II	35	8	2	26	5	1	8	2	1	1	1	0
III	48	17	9	22	11	6	22	3	1	4	3	2
Total	97	27	11	60	18	7	32	5	2	5	4	2

C, postoperative complication case; D, death; +, ++, +++. The numer in class III is significantly larger than that of class I + class II, $x^2 = 5.189$, $x^2 = 6.617$, $x^2 = 3.948$, respectively, and $p < 0.05$.

serum bilirubin level, platelet count, and K-ICG also showed significantly abnormal values in patients with markedly decreased RTI of class III, although there was no direct correlation between routine liver function test results and the corresponding RTI. Because the hepatic cells perform many functions, the derangement of which would vary depending on the pathologic state, the individual hepatic function tests would not necessarily correlate directly with each other. Furthermore, as these results suggest, the fact that the routine tests become abnormal is probably due to the acute energy deficit that occurs once the mitochondrial function becomes markedly deteriorated.

Our findings strongly indicate that the RTI is of potential value in predicting surgical outcome, regardless of the form of intraoperative stress, apart from the volume of resected liver. The statistical analyses of the postoperative morbidity and mortality rates in hepatectomized patients showed that class III patients are of high risk for major hepatic resection. That there was no statistical difference in morbidity and mortality rates in HCC cases between class I patients and the rest may be attributed to the relatively few class I patients in our hospital because the results of hepatectomy including noncirrhotic patients are generally satisfactory, as shown in Table 4. Accordingly the lower the preoperative RTI, the higher the surgical risk, especially in the case of major hepatic resection for hepatocellular carcinoma. Class I patients, with normal liver function, can tolerate virtually any type of hepatic resection. Those in class II, the intermediates, are candidates for major hepatic resection pursuing surgical curability, providing that they receive intensive perioperative care to prevent postoperative hepatic failure. In class III patients, major hepatic resection is risky despite intensive postoperative care, although one day this may become feasible with the reduction of surgical stress.

The present study showed that the redox tolerance test may be a useful and reliable indicator of preoperative hepatic functional reserve. Further studies are being conducted to assess the extent of intraoperative hepatodepressant factors by measuring arterial KBR to establish a program of intensive metabolic care based on redox theory throughout the entire perioperative period.

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