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Original article

Major liver resection reduces nonprotein respiratory quotient and increases nonesterified fatty acid at postoperative day 14 in patients with hepatocellular carcinoma

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SUMMARY

Background & aims: We reported decreased nonprotein respiratory quotient (npRQ) after liver resection in patients with hepatocellular carcinoma (HCC); however, whether liver resection volume affects energy metabolism in these patients is unclear. We aimed to examine the relationship between liver resection and energy metabolism indices.

Methods: NpRQ was measured in 53 patients with HCC and seven with at the pre- and postoperative days. Patients were classified into four groups: Minor-lowICG group (n = 17): minor (subsegment or less) resection and low indocyanine green retention rate at 15 min (ICGR15) (<15%); Minor-highICG group (n = 18): minor resection and high ICGR15 (≥15%) and Major-lowICG group (n = 18): major (lobe) resection and low ICGR15 (<15%). We investigated dietary intake and blood biochemistry at energy measurement. The difference in npRQ and nonesterified fatty acid (NEFA) pre- and post-hepatectomy was shown as ΔnpRQ and ΔNEFA, respectively.

Results: Compared with the preoperative values, npRQ significantly decreased in the Minor-highICG and Major-lowICG groups and NEFA significantly increased in the Major-lowICG group at postoperative day 14. In single regression analysis, ΔnpRQ significantly correlated with HCV infection and ΔNEFA with resection volume, HCV infection, and ICGR15. In multiple regression analysis, ΔNEFA significantly correlated with resection volume after adjusting for age, etiology, and ICGR15.

Conclusions: These results suggest that postoperative nutritional recovery is slower in major resection than in minor resection patients. Hence, nutritional care to prevent starvation is needed in major resection patients.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for 750,000 new cases and causing approximately 700,000 deaths each year [1,2]. Liver resection is the main treatment modality for liver cancer [3–5]. However, this treatment is invasive, it leads to deterioration of liver function easily. Hence perioperative nutritional therapy is crucial for these patients. Malnutrition leads to increased complications in liver disease patients [6], resulting in poor prognosis of liver disease [7,8]. Nutritional assessment is important for nutritional therapy, and the Harris–Benedict equation is the gold standard for estimating energy requirements [9]. It has been recommended for normal-weight patients with liver cirrhosis [10]. Perioperative nutritional treatment of a patient undergoing hepatectomy prevents malnutrition and affects postoperative complications [11]. The nonprotein respiratory quotient (npRQ), as an individual assessment index of nutritional condition, is extremely important

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in patients with liver disease. Due to metabolic disturbances, npRQ decreased after overnight fasting [12,13]. NPRQ has a negative correlation with nonesterified fatty acid (NEFA) [12]. Following liver resection, npRQ is influenced by decreased glycogen accumulation because of decreased liver volume and the worsening of the existing metabolic abnormalities. Therefore, severe patients cannot undergo a major liver resection. Additionally, npRQ decreases with the progression of liver disease, and patients with a low npRQ (<0.85) have poorer prognosis [14].

In our previous study, we reported that decreased npRQ and increased NEFA were observed at post-operative days in patients who underwent liver resection [15]. NPRQ decreases due to inadequate energy intake. In patients with insufficient oral intake, adequate nutritional support in the form of enteral nutrition or parenteral nutrition is required. Thus, identification of factors complicating nutritional status is very important while administering nutritional treatment to patients with liver disease. Richter et al. reported that patients undergoing major hepatectomy (e.g., lobectomy and extended lobectomy) predominately benefited from parenteral nutrition and that those undergoing minor hepatectomy (subsegmentectomy) benefited from enteral nutrition [16]. Moreover, Fan et al. reported that perioperative nutritional support can decrease complications after major hepatectomy in patients with HCC [17]. These studies suggest that nutritional management should be changed based on resection volume. Post-hepatectomy patients reached a state of starvation following surgery at a fasting state. Resection volume of liver would affect the level of starvation after operation, but there was little information about relationship between resection volume and postoperative nutritional state. Therefore, we investigated factors that affect energy metabolism in hepatectomy patients.

2. Methods

2.1. Participants

This study was conducted at the Tokushima University Hospital; 53 hospitalized patients with HCC who underwent liver resection were enrolled. These patients were classified into three groups depending on the resection volume: 1) minor resection (less segment or partial resection), indocyanine green retention rate at 15 min (ICGR15) <15% (Minor-lowICG group); 2) minor resection, ICGR15 ≥ 15% (Minor-highICG group); 3) major resection (resection ≥ one lobe), ICGR15 < 15% (Major-lowICG group). No applicant satisfied major resection (resection ≥ one lobe), ICGR15 ≥ 15% (Major-highICG group). In addition, we measured the nutritional index the day before the operation (Pre) and POD 14. The purpose of the study was explained in detail to all subjects, and informed consent was obtained. The study design was approved by the ethical committee of Tokushima University Hospital (No 810). The study conformed to the principles of the 1975 Helsinki Declaration.

2.2. Measurement of energy metabolism

Body weight and body mass index were measured using the DC-320 body composition meter (Tanita Corp., Tokyo, Japan) under fasting conditions.

Indirect calorimetric measurements were performed at Pre and POD 14. Patients were instructed to abstain from eating and drinking any fluids except noncaloric water or tea from 19:00 the day before indirect calorimetric measurements. Dietitians recorded the amount of intake of food (meals + snacks) and conducted food investigation on the day previous to the day of energy metabolism measurement. We calculated the energy intake on the basis of standard tables of food composition in Japan (fifth revised and enlarged edition). All patients were fed a standard daily hospital diet containing 30–35 kcal/kg (60% carbohydrate, <25% fat, and 15–20% protein) before operation and at POD 14. Patients with inadequate food intake who received supplemental enteral nutrients were excluded from the study. Additionally, 24-h urine samples were collected, and urinary urea nitrogen was measured. Energy metabolism was measured at 8:00 h after overnight fasting using the AE-300S respiratory gas analyzer (Minato Medical Science Corp., Ltd., Osaka, Japan). Following overnight fasting, patients were instructed to remain in bed for 30 min before indirect calorimetric measurement and to maintain a supine position throughout the measurement period. Oxygen consumption and carbon dioxide production rates were measured for 15 min, and the mean values for the final 10 min were used for analysis. Resting energy expenditure (REE) and npRQ for each patient were then calculated using measured oxygen consumption rates. Carbon dioxide was estimated according to the Harris–Benedict equation, and the ratio of REE to basal energy expenditure was expressed as % REE.

2.3. Blood biochemistry

Blood samples were collected when energy metabolism was measured and were analyzed to determine the following parameters: platelet count and levels of cholinesterase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), albumin (Alb), blood glucose, and NEFA (Tables 1 and 2).

2.4. Statistical analysis

All data were expressed as mean ± SEM. Statistical analyses were performed using SPSS for Windows, release 21.0 (SPSS Inc, Chicago, IL, USA). Clinical data on Pre and POD 14 were compared using Student's *t*-test, and npRQ and NEFA values were compared using one-way analysis of variance. The difference in npRQ and nonesterified fatty acid (NEFA) pre- and post-hepatectomy was shown as ΔnpRQ and ΔNEFA, respectively. Furthermore, predictive variables of ΔnpRQ and ΔNEFA in a single and multiple linear regression analysis were age, ICGR15, resection volume, and HBV and HCV infection in HCC. The significance threshold was $P < 0.05$.

Table 1
Clinical profiles of hepatectomy patients.

	Minor resection		Major resection
	HCC (ICGR15 < 15.0)	HCC (ICGR15 ≥ 15.0)	HCC (ICGR15 < 15.0)
	Minor-lowICG	Minor-highICG	Major-lowICG
	n = 17	n = 18	n = 18
Male/Female	14/3	14/4	13/5
Etiology			
HBV	4	5	8
HCV	8	6	3
HBV/HCV	0	1	0
Alcohol	0	1	3
Other	5	5	4
Child-Pugh			
A/B	17/0	14/3	18/0
ICGR15 (%)	8.6 ± 0.9	23.4 ± 1.6	9.5 ± 0.7
ChE (IU/L)	248 ± 17	180 ± 17	262 ± 17
Age (y)	66.6 ± 2.1	63.5 ± 2.2	65.1 ± 2
Hospital days (d)	14.7 ± 1.1	29.1 ± 6.3	20 ± 2.1

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, retention rate of indocyanine green in 15 min; ChE, cholinesterase.

Table 2
Biochemical profiles of hepatectomy patients.

	Minor resection				Major resection	
	Minor-lowICG (ICGR15 < 15.0)		Minor-highICG (ICGR15 ≥ 15.0)		Major-lowICG (ICGR15 < 15.0)	
	Pre	POD 14	Pre	POD 14	Pre	POD 14
BMI (kg/m^2)	21.8 ± 0.6	21.4 ± 0.6	22.7 ± 0.9	21.9 ± 0.9	23.4 ± 0.7	22.7 ± 0.7*
PLT (× 10^4/μL)	20.9 ± 1.3	27.9 ± 2.2*	11.8 ± 1.2	26 ± 3.1*	18.7 ± 1.1	30.5 ± 8.5
AST (IU/L)	36 ± 5	34 ± 4	40 ± 4	28 ± 2*	57 ± 9	38 ± 4
ALT (IU/L)	32 ± 4	52 ± 12	31 ± 4	25 ± 3*	60 ± 8	56 ± 7
T-Bil (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.3 ± 0.2*
Alb (g/dL)	3.8 ± 0.1	3.1 ± 0.1*	3.4 ± 0.1	2.9 ± 0.1*	3.8 ± 0.1	3 ± 0.1*
BG (mg/dL)	108 ± 5	104 ± 4	106 ± 5	111 ± 7	104 ± 6	114 ± 7
NEFA (μEq/L)	531 ± 61	578 ± 56	685 ± 53	696 ± 58	415 ± 49	666 ± 70*
npRQ	0.91 ± 0.01	0.88 ± 0.02	0.89 ± 0.01	0.84 ± 0.02*	0.91 ± 0.01	0.84 ± 0.01*
%REE (%)	99 ± 3.1	100 ± 2.5	91.6 ± 3.2	92.5 ± 3.7	97.5 ± 4	98.5 ± 3.6
Energy intake (kcal)	1893 ± 110	1753 ± 101*	1635 ± 116	1499 ± 134	1785 ± 106	1497 ± 95*
Protein intake (g)	71.2 ± 2.2	59.8 ± 3.7*	62.7 ± 4.6	56.9 ± 5.3	68.5 ± 3.6	56.4 ± 3.8*
N balance	5.3 ± 0.4	3.2 ± 0.6*	4 ± 1.1	2.5 ± 0.8	4.9 ± 1	3.9 ± 1

Values are expressed as mean ± standard error of mean.
* Significant difference from Pre ($P < 0.05$; paired t-test).
HCC, hepatocellular carcinoma; CC, cholangiocarcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, retention rate of indocyanine green in 15 min; BMI, body mass index; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; Alb, albumin; BG, blood glucose; NEFA, non-esterified fatty acid; npRQ, non-protein respirator.

3. Results

Clinical and laboratory data of the participants on Pre and POD 14 are shown in Table 1.

3.1. Blood biochemical testing

Changes in laboratory findings after the hepatectomy are presented in Tables 1 and 2. T-Bil levels significantly increased after the liver resection in the Major-lowICG group. Serum Alb levels were significantly decreased following surgery in all groups.

3.2. NpRQ and NEFA levels

NpRQ was significantly decreased in the Minor-highICG and Major-lowICG groups at POD 14 compared with Pre ($P = 0.010$, $P < 0.001$, and $P = 0.017$, respectively) (Fig. 1a). There was no significant difference in ΔnpRQ among three groups (Fig. 1b). The NEFA level of Minor-highICG group was higher than that of major-lowICG at Pre (Fig. 1c). NEFA was significantly elevated in the Major-lowICG group at POD 14 compared with that at Pre ($P = 0.003$). ΔNEFA was significantly higher in the Major-lowICG group than in the Minor-highICG group (Fig. 1d). In fact, despite the lower ICGR15, patients who underwent a major hepatectomy exhibited low RQ and high NEFA at Pre compared with those at POD 14.

3.3. Single regression analysis

We investigated the correlation between ΔnpRQ and the five parameters (age, resection volume, ICGR15, and HBV and HCV infection) by a single regression analysis in patients who underwent liver resection for HCC. ΔnpRQ was significantly correlated with HCV infection ($P = 0.018$) and was correlated with the resection volume but was not significant ($P = 0.068$; Table 3). ΔNEFA was significantly correlated with liver resection volume, HCV infection, and ICGR15, respectively ($P = 0.003$, $P = 0.028$, and $P = 0.042$; Table 4).

3.4. Multiple regression analysis

A multiple regression analysis was performed using ΔnpRQ and ΔNEFA as the dependent variable and age, resection volume, ICGR15, and HBV and HCV infection as independent variables in patients with HCC. As a result, ΔnpRQ showed a tendency for a correlation with HCV infection ($P = 0.056$), and ΔNEFA was significantly correlated with resection volume ($P = 0.045$; Table 5).

4. Discussion

Perioperative nutritional care is important to maintain preoperative and postoperative nutritional status. However, few reports have investigated energy metabolism after hepatectomy. In the healthy young living donors for liver transplantation group, npRQ was significantly decreased on POD 7, but it returned to near baseline value on POD 14. NpRQ was measured in liver resection patients with HCC, npRQ was significantly decreased on POD 7 and 14 compared with baseline [18]. However, the relationship among npRQ and resection volume, severity, and etiology is unclear. Therefore, we investigated the significant decrease in npRQ in the Minor-highICG and Major-lowICG groups at POD 14. Additionally, NEFA was significantly increased in the Major-lowICG group at POD 14 compared with prior to the hepatectomy (Fig. 1a and c). These data suggest that patients with mild liver disorder who underwent a minor resection did not have starvation. However, severe patients and major resection patients, exhibited starvation following surgery. In major resection patients, a small volume of residual liver led to a decrease in glycogen storage in the liver and increasing fat utilization decreased npRQ. These npRQ data suggest that major resection patients, even those with a mild or no disorder, require nutritional treatment after surgery.

Patients with liver cirrhosis show marked decreases in glucose oxidation after an overnight fast, with enhanced fat and protein catabolism similar to that observed in healthy controls after 2–3 days of starvation [18]. This starvation was improved by a late evening snack (LES) [19]. In particular, long-term oral nutritional support with branched chain amino acid (BCAA) after resection of HCC is beneficial for improving the clinical features and laboratory data, especially in patients with advanced cirrhosis or after a major

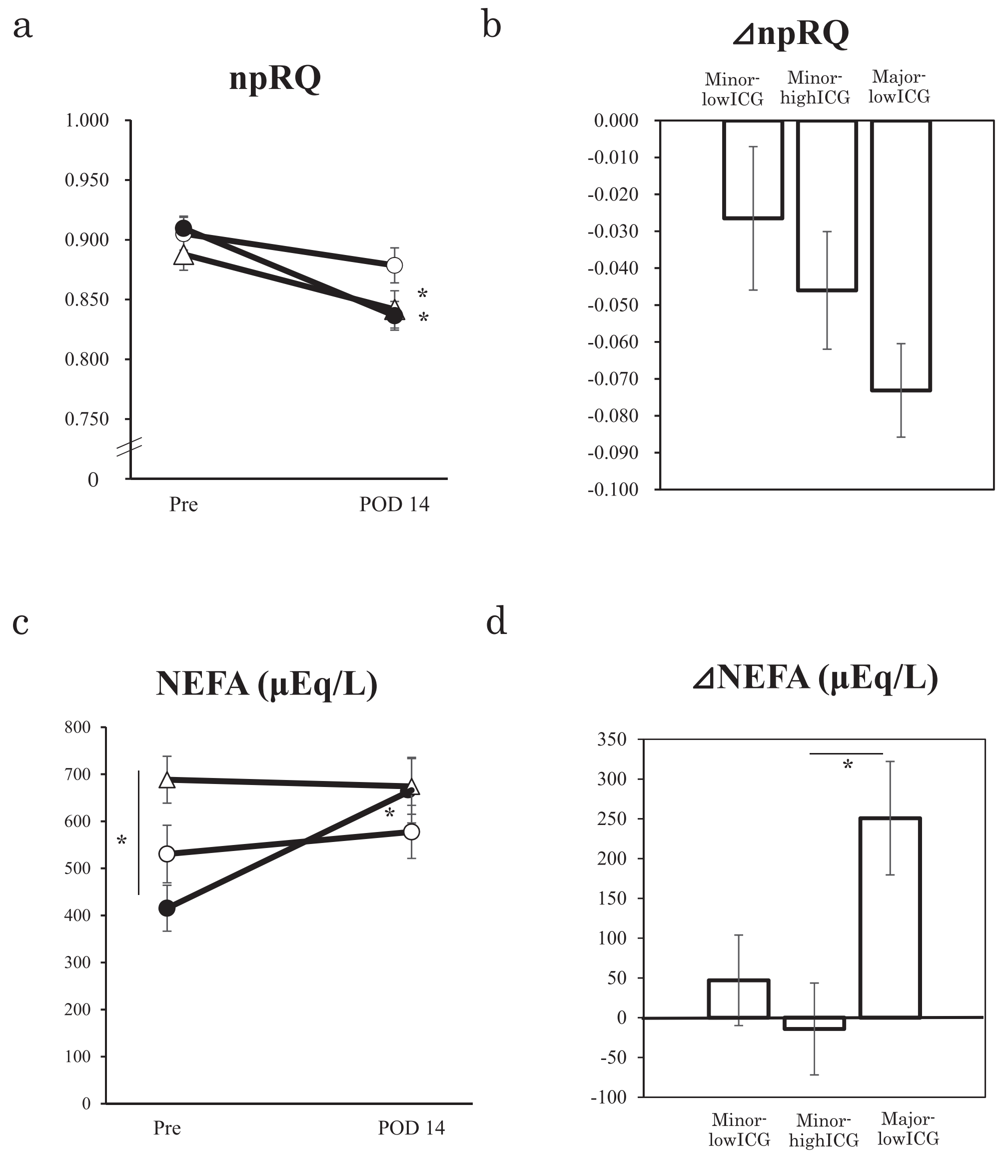

Fig. 1. a) NpRQ Pre and POD 14 in hepatectomy patients. b)ΔnpRQ in hepatectomy patients. c) NEFA at Pre and POD 14 in hepatectomy patients. d) ΔNEFA in hepatectomy patients. Values are expressed as mean ± standard error of mean., $^{*}P < 0.05$, ○:Minor-lowICG, △:Minor-highICG, ●:Major-lowICG, npRQ, nonprotein respiratory quotient; NEFA, nonesterified fatty acid; POD, postoperative day.

Table 3
Coefficient between serum biomarker and ΔnpRQ values.

Independent variable	Correlation coefficient	*p* Value
HCV	0.338	0.014
Resection volume	−0.253	0.068
HBV	−0.123	0.383
Age	0.047	0.738
ICGR15	0.029	0.838

Table 4
Coefficient between serum biomarker and ΔNEFA values.

Independent variable	Correlation coefficient	*p* Value
Resection volume	0.398	0.003
HCV	−0.305	0.028
ICGR15	−0.281	0.042
HBV	0.111	0.432
Age	0.057	0.687

hepatic resection [20]. Moreover, BCAA as LES improve serum Alb levels and npRQ in patients with cirrhosis [21]. Thus, major resection patients need LES with BCAA, and patients with a mild disease who had undergone minor resection may not require special nutritional care.

In our study, NEFA at Pre was high in the Minor-highICG group, which was maintained at POD 14 (Fig. 1c). These data suggest that severe patients with HCC were already in a state of starvation before the liver resection and continued in such a condition at POD 14. Therefore, severe patients should be administered perioperative nutritional treatment, such as LES or LES with BCAA. Additionally, NEFA was significantly increased at POD 14 compared with Pre in the Major-lowICG group (Fig. 1c), and the ΔNEFA was significantly increased in the Major-lowICG group compared with the Minor-highICG group (Fig. 1d). These data suggest that even though mild patients in the Major-lowICG group exhibited a favorable nutritional status at Pre, they were in a state of starvation following a major resection.

Table 5
Multiple regression analysis for eliminating confounding factors.

Dependent variable	Independent variable	Regression coefficient	Standardized regression coefficient	*p* Value
ΔnpRQ	(constant)	−0.059		
	Resection volume	−0.030	−0.206	0.182
	ICGR15	−0.001	−0.088	0.567
	HBV	0.009	0.065	0.687
	HCV	0.047	0.320	0.056
	Age	0.000	0.024	0.866
ΔNEFA	(constant)	82.663		
	Resection volume	177.580	0.301	0.045
	ICGR15	−5.014	−0.146	0.322
	HBV	−28.989	−0.048	0.753
	HCV	−116.583	−0.195	0.219
	Age	0.985	0.030	0.830

The liver has active regeneration ability; it can recover even if the liver cell mass and function has been decreased due to hepatectomy. However, chronic liver injury and malnutrition inhibit liver regeneration. In addition, major resection reduces the capacity to regenerate in the remnants of a cirrhotic liver [22,23]. Therefore, nutritional support for liver regeneration is extremely important, particularly in the case of a major liver resection, which has become the gold standard of treatment for a wide range of primary and secondary liver malignancies.

Previous our reports said, NEFA levels and HBV presence to be significantly related to the npRQ [15]. A large-scale controlled study found that HCV infection is associated with the onset of diabetes. In addition, the incidence of diabetes was shown to be higher in HCV patients than in the HBV patients [24]. Previous report said that the HCV core protein induces insulin resistance in transgenic mice without gain in body weight at young age [25]. These papers though to be indicate a direct involvement of HCV per se in the pathogenesis of diabetes and insulin resistance in patients with HCV infection.

In the single regression analysis, ΔnpRQ was significantly correlated with HCV infection, and ΔNEFA with resection volume, ICGR15, and HCV infection. In addition, in the multiple regression analysis, ΔNEFA was significantly correlated with the resection volume after adjusting for age, etiology, and ICGR15. These data suggest that starvation after surgery was correlated with resection volume, regardless of age, severity, and etiology. Blood biochemical data relating to liver function, such as AST and ALT levels, recovered to normal levels by POD 14 in all groups. Thus, these patients may need the divided meals for increasing dietary intake and LES for prevention of starvation.

This study suggests that postoperative nutritional recovery in major resection patients was slower than that in minor resection patients. Moreover, severe patients were in a state of starvation prior to surgery. Hence, nutritional care to prevent starvation would be needed for major resection patients before surgery.

Statement of authorship

The contributions of authors were as follows:

SW: wrote the manuscript; HY-O: contributed to the study design; SW and HY-O: collected the samples; WS and HY-O analyzed the data; TK, YM and MS: provided helpful comments about the study. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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