ORIGINAL

Experimental study of the evaluation of liver function on the opposite side during portacaval anastomosis and ligation of the left portal branch

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Abstract : *Background*. Hepatocellular carcinoma is likely to accompany liver cirrhosis in which the portal pressure increases with portasystemic shunt. When portal tumor thrombus is present in the primary bifurcation, blood flow differs between the thrombolic lobe and the non-thrombolic lobe. In those cases, it is difficult to evaluate exactly residual liver function by conventional test. Therefore, the following studies were performed.

***Materials and Methods*. Adult mongrel dogs are divided into a control group (C group), group undergoing ligation of the left portal branch (PL group), group undergoing portacaval anastomosis (PCS group) and group undergoing both ligation of the left portal branch and portacaval anastomosis (PL+PCSgroup)(n=5). ICG-R_{15} and MEGX15 in peripheral venous blood and right hepatic venous blood were determined. Mitchondrial metabolic capacity (adenosine triphosphate level, energy charge) was measured by high-performance liquid chromatography using liver biopsied specimens.**

***Results*. The MEGX ratio (right hepatic venous blood MEGX15/peripheral venous blood MEGX 15) positively correlated with energy charge in the right hepatic lobe.**

***Conclusions*. In evaluating liver function of the right hepatic lobe during portacaval shunt and the left portal branch ligation, the MEGX ratio may sensitively reflect the mitochondrial function. J. Med. Invest. 51 : 84-95, February, 2004**

Keywords **:** *portacaval shunt, hepatic functional reserve, hepatic venous blood sampling, MEGX, ICG*

INTRODUCTION

In most cases, hepatocellular carcinoma is associated with portasystemic shunt resulting from liver cirrhosis. Furthermore, the progression of cancer causes portal tumor thrombus, further increasing blood flow in the shunt. At the same time, blood flows unevenly in the thrombolic and non-thrombolic lobes when portal tumor thrombus is present in the primary branch of the portal vein. In this case, it is difficult to evaluate residual liver function (Fig.1). When residual liver function is evaluated only by effective blood flow in the entire liver, surgery may be indicated for a smaller number of cases than needed. Recently in our department, major hepatectomy was performed in 3 patients with hepatocellular carcinoma in portal vascular invasion, although they showed a poor mean value for ICG-R_{15} in the peripheral venous blood (22.8±4.6%).

Abbreviations : ICG-R_{15}, the retention rate 15 minutes after injection of indocyanine green ; ICG-Bmax, the maximal rate of ICG excretion in bile ; MEGX15, monoethylglycinexylidide concentration in serum 15 minutes after lidocaine injection ; HPLC, high-performance liquid chromatography ; AMP, adenosine monophosphate ; ADP, adenosine diphosphate ; ATP, adenosine triphosphate ; EC, energy charge

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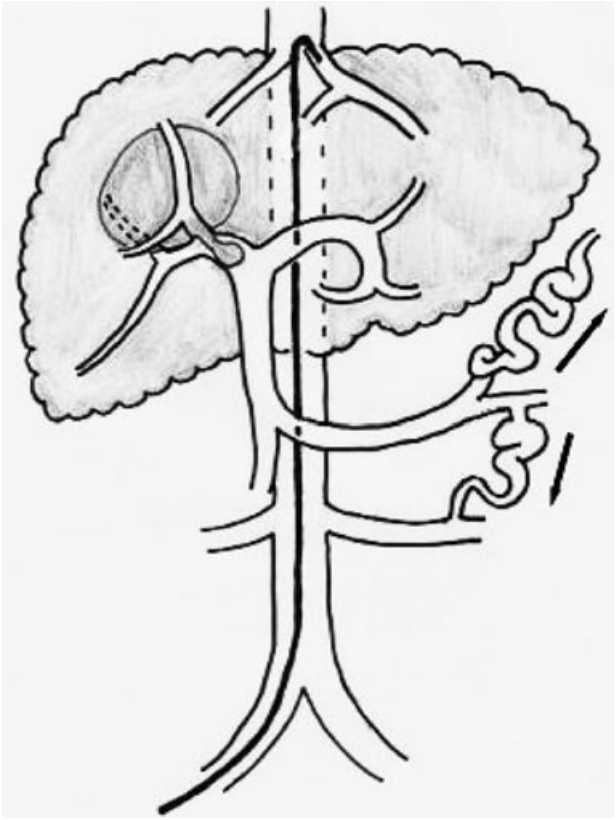

Fig. 1. Hemodynamics in patients with hepatocellular carcinoma accompanied with portal vascular invasion.
The progression of cancer causes portal tumor thrombus and increasing blood flow in the portasystemic shunt. At the same time, blood flows unevenly in the thrombolic and non-thrombolic lobes when portal tumor thrombus is present in the primary branch of the portal vein.

Previously, such patients with 20-29% of ICG-R_{15} were treated by hepatic segmentectomy alone (1-14). However, extended lobectomy was successfully performed in these 3 patients because they showed a favorable mean value for ICG-R_{15} in the hepatic venous blood (12.7±6.5%)(15, 16) and a high mean value for the MEGX ratio (4.47±0.23)(Table 1). From these findings, we studied the retention rate 15 minutes after injection of indocyanine green (ICG-R_{15}), monoethylglycinexylidide concentration in serum 15 minutes after lidocaine injection (MEGX15) in the right hepatic venous blood and the ICG excretion rate into bile in the area of the right hepatic lobe during portacaval shunt and the left portal branch ligation.

MATERIALS AND METHODS

This study was approved by the Animal Investigation Committee of Tokushima University and followed the guidelines of the American Physiological Society for the human use of animals in Research.

Adult mongrel dogs weighing from 12 kg to 18 kg, were used. Animals were starved for 12 hours before an operation and ad lib with feedstuff and water immediately after the operation. The abdomen was dissected with median incision of the epigastric region under general anesthesia with enflurane and nitrous oxide. A catheter was placed in the portal venous trunk through the mesenteric vein by cut down method for pressure measurement. Other two catheters were transpapillarily placed in the common bile duct and right hepatic duct through an incision in the duodenum to collect bile. Under fluoroscopy another catheter was placed in the right hepatic vein through the right jugular vein by cut down method for blood collection. Dogs were divided into four groups. Control group (n=5) underwent sham operation. PL group (n=5) underwent ligation of the left portal branch. PCS group (n=5) underwent portacaval anastomosis. PL+PCS group (n=5) underwent both ligation of the left portal branch and portacaval anastomosis (Fig.2).

Subsequently, hepatic arterial blood flow and portal blood flow were measured by pulse Doppler ultrasonography immediately after surgery. Blood flow in the liver tissue was measured by the laser Doppler method immediately and 14 days after surgery. Simultaneously, portal venous pressure were measured. ICG-R_{15} and MEGX15 in peripheral venous blood and right hepatic venous blood as well as the maximal rate of ICG excretion in bile collected from the common bile duct and right hepatic duct (ICG-Bmax) were deter-

Table 1. Resected cases of hepatocellular carcinoma (Vp4)(3 cases)

case	site of tumor thrombus	ICG-R_{15}	MEGX ratio (>2.60)	operation	operative death
1	left to trunk as far as right	17.7	4.76	Hr 3+(LMCa)	no
2	right to trunk as far as left	24.0	4.28	Hr 3+(APCm)	no
3	right to trunk	26.7	4.41	Hr 2(AP)	no

Hr 3+(LMCa) : Extended left hepatic lobectomy with combined resection of the caudate lobe
Hr 3+(APCm) : Extended right hepatic lobectomy with combined resection of the caudate lobe
Hr 2(AP) : Right hepatic lobectomy

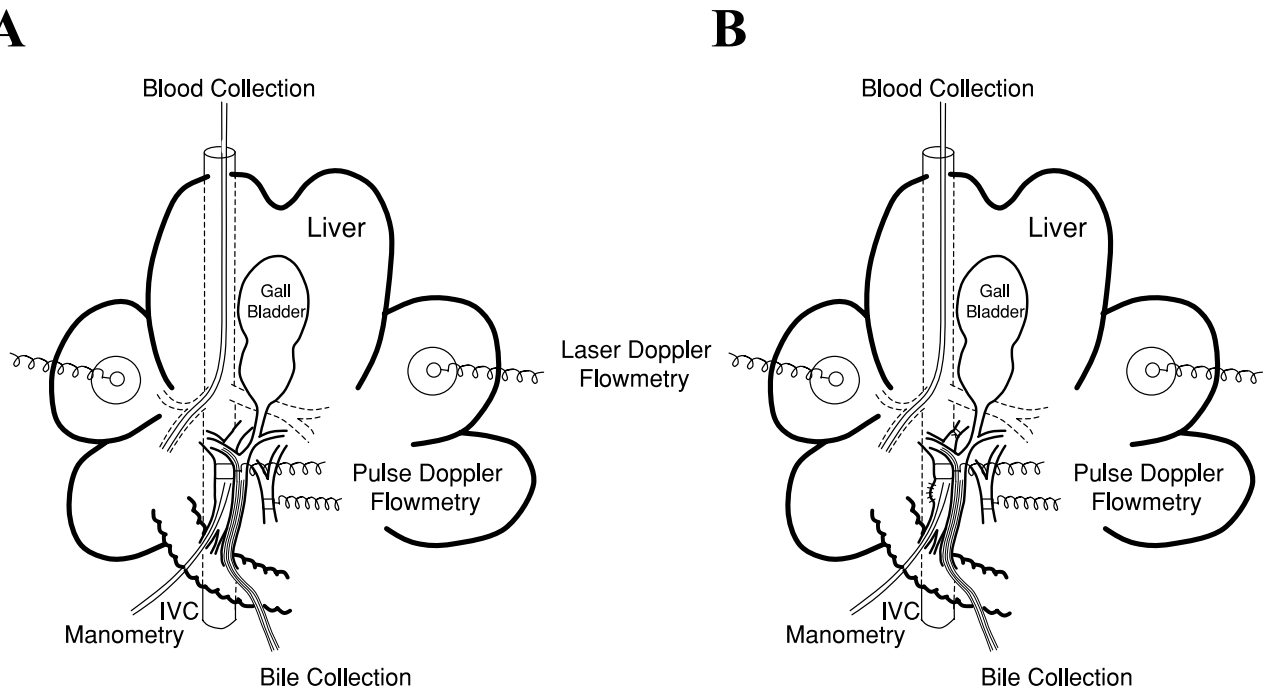

Fig. 2. Schema of experimental model for C group(A) and PL+PCS group(B). PL+PCS group (B) underwent both ligation of the left portal branch and portacaval anastomosis.

mined. As an index of hepatic mitochondrial metabolic capacity, liver tissue energy charge (EC) was measured by high-performance liquid chromatography (HPLC) using biopsied specimens. After animals were sacrificed, liver weight was measured, and liver histopathological study was examined significantly.

ICG retension rate (ICG-R_{15} ;%), the maximal rate of ICG excretion in bile (ICG-Bmax)

Indocyanine green (Diagnogreen®, Daiichi) was injected i.v. 0.5 mg/kg over thirty seconds and 3 ml of peripheral venous blood was collected before and 15 minutes after the administration. One ml of bile from the common bile duct and right hepatic duct were collected before and every fifteen minutes after administration. Each sample was submitted for determination of ICG concentration. Absorbance at 805nm on a spectrophotometer was measured and ICG concentration was determined with a calibration curve. Then ICG-R_{15} was determined of an actual measurement of the former. After actual measurements of the latter were plotted, biliary maximum ICG concentration (C) and the time reaching the maximum concentration(t) were determined. Then ICG-Bmax=$\log_e$ {$\log_e$ (10× C)/t } was calculated.

MEGX15

Lidocaine (2% Xylocaine®, Fujisawa) was injected i.v. 1mg/kg over one minute and 3 ml of peripheral venous blood was collected and centrifuged, before and 15 minutes after the administration. Then the sera were frozen (-20 deg.C) and submitted for measuring MEGX concentration. MEGX concentration was measured by fluorescence polarization immunoassay (Abbot Laboratories, Chicago, Illinois, USA) using the TDx fluorescence immunoassay system.

Right hepatic venous blood ICG-R_{15}

Right hepatic venous blood is collected through an indwelling catheter. ICG-R_{15} is determined similarly to peripheral venous blood.

Right hepatic venous blood MEGX15

Right hepatic venous blood is collected with the same method as for right hepatic venous blood ICG-R_{15}. MEGX15 is determined similarly to peripheral venous blood.

MEGX ratio

MEGX ratio=(MEGX15 in right hepatic venous blood)/(MEGX15 in peripheral venous blood) was calculated.

Hepatic arterial, portal venous blood flow and liver tissue blood flow

Blood flow in the proper hepatic artery and the portal venous trunk was measured by ultrasonic pulse doppler method using Transit time blood flowmeter (T101

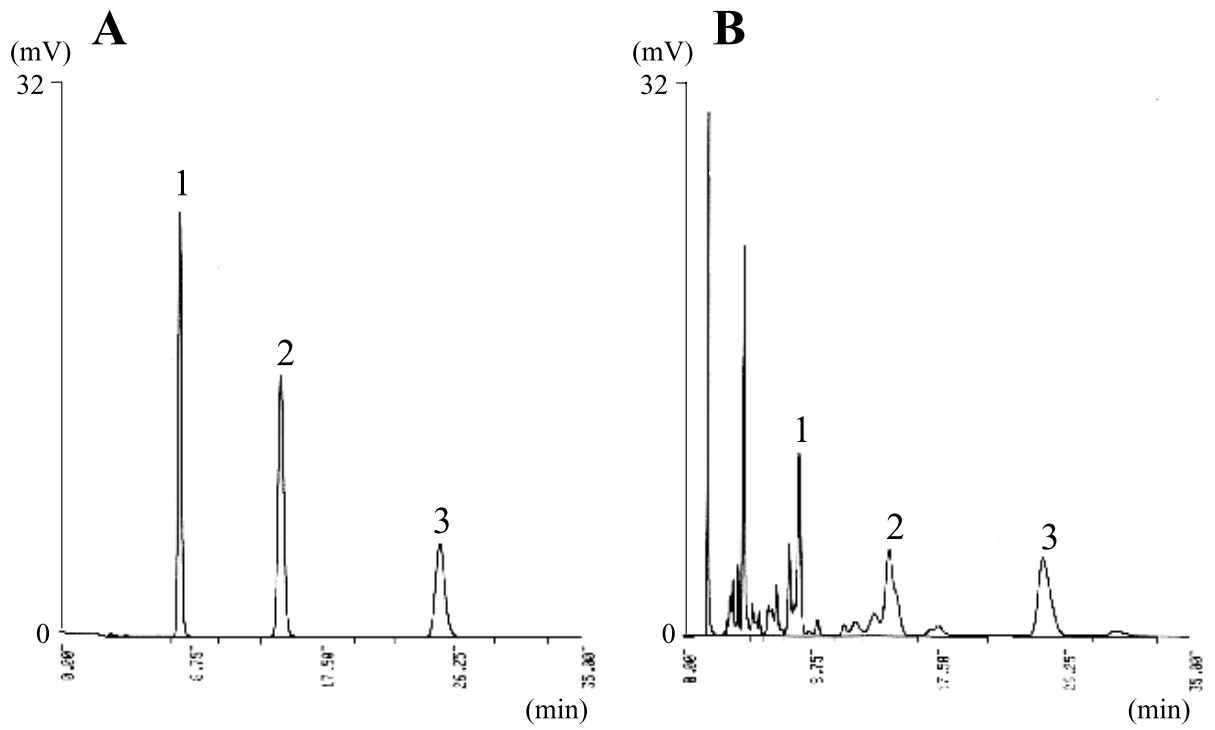

Fig. 3. Chromatograms of standard sample(A) and extracts from liver biopsied specimen (B).
Peaks were detected using optical detector which had been calibrated against known qualities (100 μM) of stardard nucleotides (A). Peak 1 shows adenosine monophosphate (AMP) level, 2 shows adenosine diphosphate (ADP) and 3 shows adenosine triphosphate (ATP), respectively. As for the liver biopsied specimen (B), the concentration of AMP was 66.5 μM, ADP was 126.2 μM and ATP was 131.5 μM. Therefore, EC=(ATP+1/2 ADP)/(ATP+ADP+AMP) was calculated as 0.60.

Transonic Systems, Japan).

Liver tissue blood flow in bilateral hepatic lobes was measured by laser doppler method using laser doppler tissue blood flowmeter (LaserMed® ALF-21D, Advance, USA).

Liver tissue EC

The biopsied liver tissue (0.5-1.0g) was immediately frozen in liquid nitrogen and preserved in a deep freezer (-80 degree C). The frozen liver tissue was pulverized in a liquid nitrogen-cooled mortar and 0.2 to 0.7g of powder were extracted in 3ml/g of 0.6 M perchloric acid. Extracts were centrifuged to remove precipitated protein and then neutralized with 2ml/3ml supernatant of 1N $KHCO_3$ after centrifugation to remove potassium perchlorate, aliquots of these extracts (50 μl) were analysed by anion exchange chromatography. A Varian Model UV-8020 (Toyo Soda Manufacturing Co., Ltd, Japan) high-performance liquid chromatography, fitted with TSK-gel DEAE-2SW column (0.46×25cm)(Toyo Soda Manufacturing Co., Ltd, Japan) was used, and buffer conditions were described by Lui *et al* (17). Peaks were detected using optical detector at 260 nm and electronically integrated using a Varian Model SIC-12 (Toyo Soda Manufacturing Co., Ltd, Japan) which had been calibrated against known qualities of stardard nucleotides (Fig.3). Then EC=(ATP+1/2ADP)/(ATP+ADP+AMP) was calculated (18).

Statistical analysis

All results were expressed as means±SD. Statistical analysis was performed by paired or unpaired Student-t test. p Values less than 0.05 were regarded as significant.

RESULTS

Hepatic arterial blood flow, portal venous blood flow and portal venous pressure (Table 2)

Portal venous pressure and portal venous blood flow in the PCS group were 154.2±16.1 mmH_2O and 37.6±55.3 ml/min, significantly lower than those in the C group, 184.6±7.9 mmH_2O and 104.0±21.9 ml/min, respectively ($p<0.01$, $p<0.05$). Portal venous pressure in the PL group was 195.4±51.9 mmH_2O, significantly higher than that in the C group ($p<0.01$). Portal blood flow in the PL+PCS group was 22.0±11.0 ml/min, significantly lower than that in the C group ($p<0.01$). There were no significant changes in hepatic arterial blood flow among any groups. Shunt rates in the PCS group and the PL+PCS group were 73.2±40.4% and 84.7±6.9%, respectively.

Table 2. Hepatic blood flow and portal venous pressure after the operation

Group	Blood flow (ml/min)			Portal venous pressure (mmH_2O)
	PHA	PV		
C (5)	31.1±16.8	104.0±21.9		184.6±7.9
PL (5)	32.8±17.8	107.8±27.7		195.4±51.9**
PCS (5)	22.5±13.4	37.6±55.3*	((73.2±40.4))	154.2±16.1**
PL+PCS (5)	32.6±16.5	22.0±11.0**	((84.7±6.9))	163.4±42.0*

Means±SD. Numbers of animals are given in parentheses. Shunt rates (%) are given in double parentheses.
*p<0.05, ** p<0.01, compared with the corresponding C group.

Blood flow in the liver tissue (Table 3)

Blood flow in the left hepatic lobe of the PL+PCS group immediately after and 14 days later were 9.69± 2.52 ml/min/100g and 9.35±3.18 ml/min/100g, significantly lower than those of the C group, 14.46± 3.94 ml/min/100g and 19.15±6.74 ml/min/100g, respectively (p<0.05, p<0.05). Blood flows in bilateral hepatic lobes of the PCS group immediately after and 14 days later were 11.11±5.83 ml/min/100g and 9.04±0.65 ml/min/100g in the right hepatic lobe, 10.64±2.65 ml/min/100g and 8.70±1.91 ml/min/100g in the left hepatic lobe, significantly lower than those of the C group, respectively (p<0.05 and p<0.01, p<0.05 and p<0.05). In the PL group, the PL+PCS group, blood flow in the right hepatic lobe immediately after and 14 days later were 22.96±5.52 ml/min/100g and 20.72±6.49 ml/min/100g, 15.13±2.26 ml/min/100g and 15.26±4.51 ml/min/100g, significantly higher than those in the left hepatic lobe, 11.69±3.63 ml/min/100g and 12.17±4.43 ml/min/100g, 9.69±2.52 ml/min/100g and 9.35±3.18 ml/min/100g, respectively (p<0.01 and p<0.01, p<0.05 and p<0.05). No time course changes were shown in any lobes of each group.

Liver tissue energy charge (Table 4)

In the PL+PCS group, the EC levels in the right lobe immediately after and 14 days later were 0.53±0.11 and 0.52±0.01, significantly higher than those in the left lobe, 0.43±0.08 and 0.46±0.11, respectively (p< 0.01, p<0.05). However, there were no significant differences in EC levels betweeen the right and left lobes among other groups. No time course changes were shown in any lobes of each group, significantly.

Peripheral venous blood ICG-R_{15}, hepatic venous blood ICG-R_{15} and ICG-Bmax (Table 5)

In the PCS group and the PL+PCS group, peripheral venous blood ICG-R_{15} 14 days later were 40.2±10.7%, 38.2±7.0%, significantly higher than those in the C group and the PL group, 26.0±3.8% and 27.2±4.8%, respectively (p<0.05 and p<0.05, p<0.05 and p<0.01). However, there were no significant differences in hepatic venous blood ICG-R_{15} among groups. In the C group, the PL group and the PCS group, peripheral venous blood ICG-R_{15} did not significantly differ from hepatic venous blood ICG-R_{15}. In the PL+PCS group, hepatic venous blood ICG-R_{15} immediately after and 14 days later were 29.4±10.1% and 30.8±4.1%, sig-

Table 3. Liver tissue blood flow after the operation

Days after operation	Group	Liver tissue blood flow (ml/min/100g)	
		RHL	LHL
immediate	C(5)	14.37±4.51	14.46±3.94
	PL(5)	22.96±5.52****	11.69±3.63
	PCS(5)	11.11±5.83*	10.64±2.65*
	PL+PCS(5)	15.13±2.26***	9.69±2.52*
14 days	C(5)	21.04±6.76	19.15±6.74
	PL(5)	20.72±6.49****	12.17±4.43
	PCS(5)	9.04±0.65**	8.70±1.91*
	PL+PCS(5)	15.26±4.51***	9.35±3.18*

Means±SD. Numbers of animals are given in parentheses.
*p<0.05, **p<0.01, compared with the corresponding C group on the same day.
***p<0.05, ****p<0.01, compared with LHL on the same day.

Table 4. Liver tissue energy charge after the operation

Days after operation	Group	Liver tissue energy charge	
		RHL	LHL
immediate	C (5)	0.54±0.14	0.56±0.06
	PL (5)	0.45±0.09	0.44±0.14
	PCS (5)	0.47±0.17	0.47±0.14
	PL+PCS (5)	0.53±0.11**	0.43±0.08
14 days	C (5)	0.48±0.15	0.45±0.12
	PL (5)	0.45±0.12	0.42±0.13
	PCS (5)	0.42±0.03	0.43±0.04
	PL+PCS (5)	0.52±0.01*	0.46±0.11

Means±SD. Numbers of animals are given in parentheses.
*p<0.05, **p<0.01, compared with LHL on the same day.

Table 5. ICG-R_{15}, ICG Bmax after the operation

Days after operation	Group	ICG-R_{15} (%)		ICG-Bmax	
		Peripheral	Rt. hepatic vein	Common bile duct	Rt. hepatic duct
Immediate	C (5)	32.6±4.0	28.8±4.5	1.40±0.23	1.43±0.35
	PL (5)	32.8±8.6	29.8±10.5	1.29±0.19	1.40±0.21
	PCS (5)	39.8±33.1	33.4±25.9	1.01±0.12	1.17±0.34
	PL+PCS (5)	39.4±9.3	29.4±10.1***	1.13±0.19	1.46±0.27*****
14 days	C (5)	26.0±3.8	23.8±4.1	1.17±0.58	1.21±0.47
	PL (5)	27.2±4.8	25.4±5.3	1.12±0.22	1.42±0.19
	PCS (5)	40.2±10.7*	36.8±9.5	1.04±0.15	1.14±0.38
	PL+PCS (5)	38.2±7.0**	30.8±4.1***	0.85±0.15	1.14±0.16****

Means±SD. Numbers of animals are given in parentheses.
*p<0.05, **p<0.01, compared with the corresponding C group on the same day.
***p<0.01, compared with ICG-R_{15} of the peripheral venous blood.
****p<0.05, *****p<0.01, compared with ICG Bmax of the common bile duct bile.

nificantly lower than peripheral venous blood ICG-R_{15}, 39.4±9.3% and 38.2±7.0%, respectively (p<0.01, p<0.01). In the PL+PCS group, ICG-Bmax for the right hepatic duct immediately after and 14 days later were 1.46±0.27 and 1.14±0.16, significantly higher than those for the common bile duct, 1.13±0.19 and 0.85±0.15, respectively (p<0.01, p<0.05). No time course changes were shown in ICG-R_{15} and ICG-Bmax of each group, significantly.

Peripheral venous blood MEGX15 and hepatic venous blood MEGX15 (Table 6)

In all groups, hepatic venous blood MEGX15 was significantly higher than peripheral venous blood MEGX15 immediately after and 14 days later. Furthermore, peripheral venous blood MEGX15 in the PL+PCS group was significantly lower than those in the C group, the PL group and the PCS group immediately after surgery (p<0.01, p<0.01, p<0.01). However, there were no significant differences in hepatic venous blood MEGX15 among groups. In both the PCS group and the PL+PCS group, the right hepatic venous blood MEGX15 14 days after were 404.4±47.6 ng/ml and 377.5±91.5 ng/ml, significantly higher than those immediately after 272.6±70.0 ng/ml and 201.0±91.8 ng/ml, respectively (p<0.05, p<0.01). The MEGX ratio, relative ratio of hepatic venous blood MEGX15 to peripheral venous blood MEGX15 in both groups 14 days after were 3.65±1.24 and 4.26±1.86, also significantly higher than those immediately after, 2.73±1.49 and 3.40±0.90, respectively (p<0.05, p<0.01).

The MEGX ratio positively correlated with EC in the right hepatic lobe both immediately after (r=0.562, p=0.0124) and 14 days later (r=0.521, p=0.0185), also (Fig. 4, 5).

Liver weight and cellular square 14 days after the operation (Table 7)

In the PL and PL+PCS groups, the weight of the right lobe were 194.6±39.2g and 182.4±48.3g, signifi-

cantly higher than that in the C group, 121.2±31.3g ($p<0.05$, $p<0.05$). In both groups, the weight of the left lobe were 230.8±37.0g and 281.6±41.4g, significantly lower than that in the C group, 345.2±50.5g, respectively ($p<0.01$, $p<0.05$). Furthermore in the PL and PL+PCS group, the square of a hepatocyte of left hepatic lobe were $(2.39\pm0.60)\times10^{-3}mm^2$ and $(2.05\pm0.35)\times10^{-3}mm^2$, significantly lower than that in the C group, $(3.71\pm0.56)\times10^{-3}mm^2$, respectively ($p<0.01$, $p<0.05$). In both groups, the squares of a hepatocyte of left hepatic lobe were significantly lower than those of right hepatic lobe, $(4.02\pm0.94)\times10^{-3}mm^2$ and $(3.38\pm1.19)\times$

Table 6. MEGX15, MEGX ratio after the operation

Days after operation	Group	MEGX15 (ng/ml)		MEGX ratio (Rt.hepatic vein / Peripheral)
		Peripheral	Rt.hepatic vein	
Immediate	C (5)	120.9±18.6	266.6±45.8***	2.24±0.45
	PL (5)	118.7±41.3	282.6±95.8***	2.43±0.75
	PCS (5)	117.6±48.5	272.6±70.0**	2.73±1.49
	PL+PCS (5)	61.3±24.4*	201.0±91.8**	3.40±0.90
14days	C (5)	120.7±38.4	343.5±79.6***	3.26±1.71
	PL (5)	144.8±63.8	305.7±134.9**	2.13±0.70
	PCS (5)	120.0±37.5	404.4±47.6***	3.65±1.24****
	PL+PCS (5)	98.2±35.5	377.5±91.5***	4.26±1.86*****

Means±SD. Numbers of animals are given in parentheses.
*p<0.01, compared with the corresponding C group on the same day.
**p<0.05, ***p<0.01,compared with MEGX15 of the peripheral venous blood.
****p<0.05, *****p<0.01,compared with MEGX ratio immediately after the operation

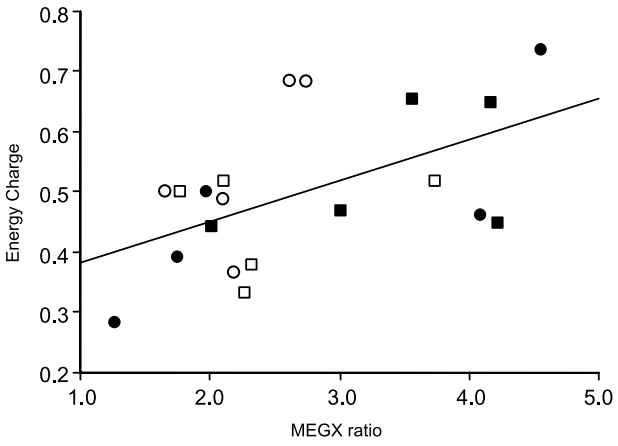

Fig. 4. Relationship between MEGX ratio and Energy Charge immediately after the operation.
A positive correlation (r=0.562, p=0.0124) was found in C group (*open circles*), PL group (*open boxes*), PCS group (*closed circles*) and PL+PCS group (*solid boxes*).

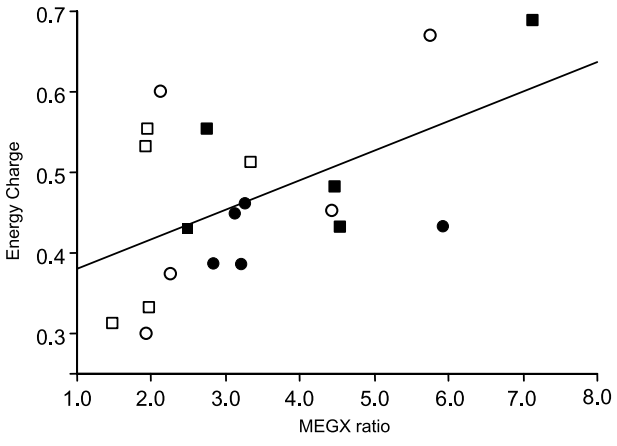

Fig. 5. Relationship between MEGX ratio and Energy Charge 14 days after the operation.
A positive correlation (r=0.521, p=0.0185) was found in C group (*open circles*), PL group (*open boxes*), PCS group (*closed circles*) and PL+PCS group (*solid boxes*).

Table 7. Liver weight and cellular square 14 days after the operation

Group	Liver weight (g)		Cellular square ($\times10^{-3}mm^2$)	
	RHL	LHL	RHL	LHL
C (5)	121.2±31.3	345.2±50.5	3.63±0.64	3.71±0.56
PL (5)	194.6±39.2*	230.8±37.0**	4.02±0.94	2.39±0.60**
PCS (5)	115.8±50.7	278.2±66.7	3.10±0.79	3.32±0.72
PL+PCS (5)	182.4±48.3*	281.6±41.4*	3.38±1.19	2.05±0.35**

Means±SD. Numbers of animals are given in parentheses.
*p<0.05, **p<0.01, compared with the corresponding C group.

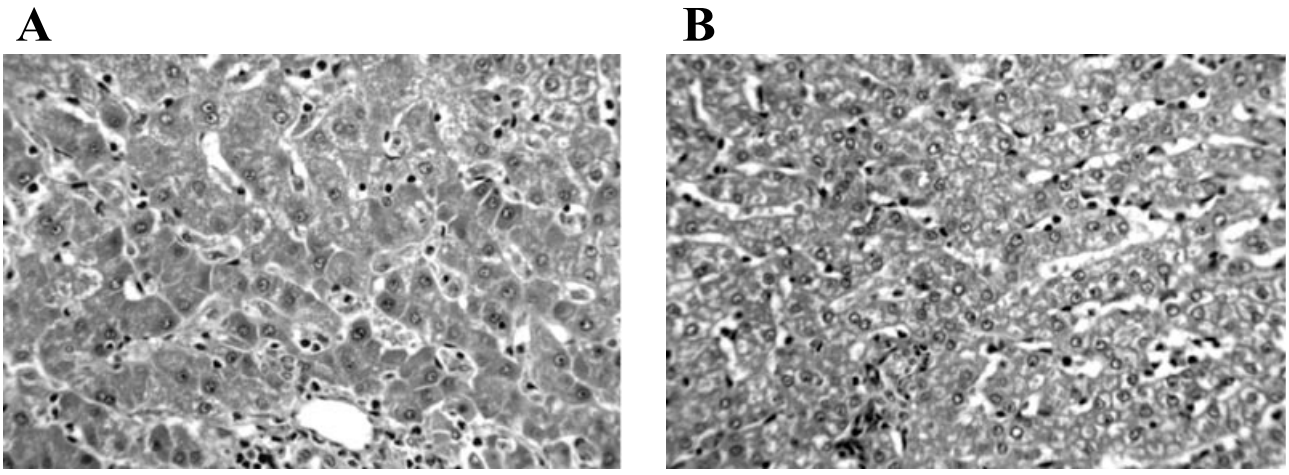

Fig. 6. Photomicrographs (original magnification×400) of liver biopsied specimen from right hepatic lobe (A) and from left hepatic lobe (B) of the PL+PCS group, HE stain.
In the PL+PCS group, the square of a hepatocyte of left hepatic lobe (B) was $(2.05\pm0.35)\times10^{-3}mm^2$, lower than that of right hepatic lobe(A), $(3.38\pm1.19)\times10^{-3}mm$. ($p<0.05$).

$10^{-3}mm^2$, respectively ($p<0.01$, $p<0.05$)(Fig.6).

DISCUSSION

Elements to decide propriety or range of hepatectomy are a developmental range of lesions and hepatic functional reserve (19). The latter includes protein synthetic ability and hepatospecific metabolic ability (20). Especially, the peripheral venous ICG loading test is believed to reflect the hepatic efficacious blood flow volume directly associated with the postoperative course, including hepatic regeneration, and has been used widely (1-14). However, this is premised on the assumption that there is no shunt and that intrahepatic blood flow is even, and is not sufficiently reliable in obstructive jaundiced liver. However, in Japan, hepatocellular carcinoma is likely to accompany liver cirrhosis in which the portal venous pressure increases with portasystemic shunt (21, 22). When a portal obstruction occurs accordance with the advance of cancer, the shunt blood flow is expected to further increase and ICG-R_{15} in peripheral venous blood shows worse than that of true value (23, 24).When an obstruction is present hepatoproximal to the primary bifurcation, local hepatic blood flow volume in the same liver becomes uneven. In this case, in evaluating residual hepatic function, the peripheral venous blood ICG loading test may reduce surgical indication unnecessarily. From the above viewpoints, to clarify residual hepatic function in case of portal obstruction, ICG-R_{15}(15, 16), MEGX15 which is thought to reflect the total number of functional hepatic cells and protein synthetic ability even in the liver with jaundice (25, 26), in hepatic venous blood of the residual hepatic lobe and ICG loading test in bile (ICG-Bmax) (27-29) were examined in dogs .

It has been supposed that ICG bound with albumin is transported to the liver, dissociated by Na^+-K^+ ATPase in the cell membranes of hepatic cells within the liver sinusoid to release albumin, and taken in through

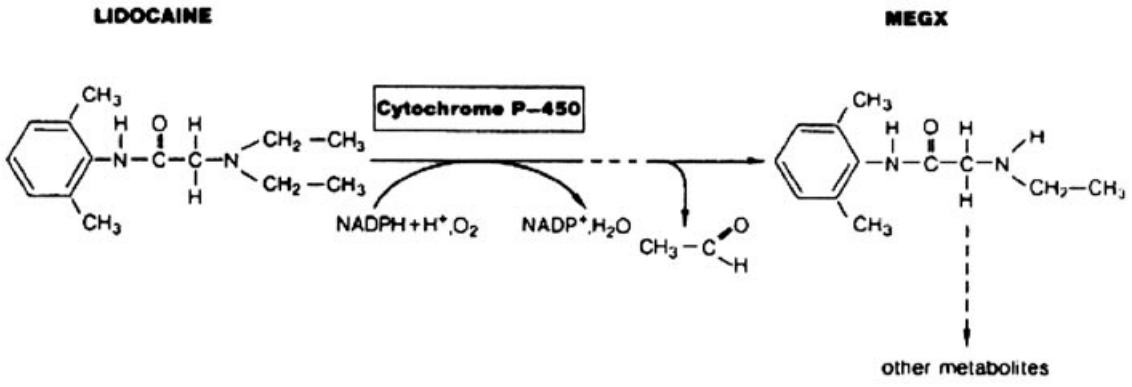

Fig. 7. Metabolic pathway of lidocaine
Lidocaine is metabolized to MEGX after oxidative deethylation by mitochondrial cytochrome P450.

the cell membrane, and excreted into the bile without passing through intracellular organelles. That is, the ICG loading test does not reflect the functioning of hepatic cells, but the blood flow through the liver, only. On the other hand, monoethylglycinexylidide (MEGX) (30-37) is intermediate metabolite of lidocaine. Lidocaine taken into the hepatic cells in the liver sinusoid in the same way as ICG undergoes oxidative de-ethylation by cytochrome p450 in microsomes of mitochondria, one of intracellular organelles, to be metabolized into MEGX and excreted into hepatic veins via the central veins (Fig 7). It may be conceived, therefore, that the concentration of MEGX in the lidocaine loading test reflects the blood flow through the liver and the contents of microsomes, and hence, the hepatic mitochondrial function. According to Oellerich *et al*., the results of the ICG loading test and the lidocaine loading test reflect the survival probability of patients with liver cirrhosis, and may be applied to the assessment of donor liver for the liver grafting. If MEGX15 is 90ng/ml or more, the graft shows good viability and high probability of survival (38).

In the present experiment, the portal blood flow in PCS and PL+PCS groups was lower than that in C group, and the portal blood pressure increased in PL group, and decreased in PCS group. On comparing between the PL group and PL+PCS group, both portal blood flow and portal venous pressure were significantly higher in the PL group. However, there was no significant difference between the portal blood flow of the PL+PCS group and that in the right lobe of the C group, as calculated from the proportion of liver weight. That is, while in the PL group, the entire portal blood flow is led to the right lobe to raise the portal blood pressure, in the PL+PCS group, the portal blood pressure is lowered by the portacaval shunt despite the portal blood flow is kept intact in the right lobe. There was no significant difference between both liver tissue blood flow and EC of the right hepatic lobe in the PL group and those in the PL+PCS group. On the basis of these facts, it may be surmised that the lower portal pressure supresses a rise of pressure in the liver sinusoid and keeps the hepatic mitochondrial function in fine conditions, so long as the blood flow through the liver tissue is kept intact.

In the PL group and PL+PCS group, hypertrophy of the right hepatic lobe and atrophy of the left hepatic lobe were noted. As for the liver weight, in the PL and PL+PCS groups, the weight of the right lobe increased and that of the left lobe decreased in comparison to those in the C group. The histopathological examination proved that the square of a hepatocyte of left hepatic lobe decreased and that of the right hepatic lobe made no significant changes in the PL and PL+PCS groups in comparison to that in the C group. On the basis of these results, it might be concluded that in the PL and PL+PCS groups, the right hepatic lobe hypertrophied because of increased number of cells, while the left hepatic lobe in the PL and PL+PCS groups atrophied principally through shrinking hepatic cells.

In the PL+PCS group, there was a significant difference in ICG-R_{15} between the peripheral venous blood and the hepatic venous blood. On the other hand, there was no significant difference in the PCS group. This difference may be attributed to an increase of the level in the peripheral venous blood caused by an increase in shunt blood flow and to a decrease of the level in the right hepatic venous blood caused by an increase of blood flow through the tissue of right lobe. Similar hemodynamic aspects may be expected in patients with portasystemic shunt caused by hepatocellular carcinoma combined with portal tumor thrombus. If the effective hepatic blood flow is estimated on the basis of the level in peripheral venous blood alone, the indication for surgery may be restricted more than necessary. In the PL+PCS group, the level of ICG-Bmax was higher in the right hepatic duct than that in the common bile duct. This difference may be attributed to the similar reason with that of ICG-R_{15}.

The MEGX15 level presented a significant difference between the peripheral venous blood and the right hepatic venous blood in all groups. On the other hand, ICG-R_{15} showed a significant difference only in the PL+PCS group. The hemodynamic difference may be attributed to the slow release of MEGX, an intermediate metabolite of lidocaine, produced in the liver and transferred from the hepatic vein to the systemic circulation, while ICG diffuses into the systemic circulation and then releases from the liver into bile rather quickly. Similar to the ICG-R_{15}, the level of MEGX15 in the peripheral venous blood was lower in the PL+PCS group than that in C group immediately after surgery, and there was no significant difference in the level of MEGX15 in the hepatic venous blood among the groups.

In this way, it has been studied whether or not the relative proportion of the level in the hepatic venous blood derived from the right hepatic lobe to the level in the peripheral venous blood flowing into the right hepatic lobe, is useful as a parameter for the functional efficiency of the right hepatic lobe, when a discrepancy was recognized in levels between the peripheral venous blood and the right hepatic venous blood.

In all those groups where a significant difference

was recognized in the MEGX15 level between the peripheral venous blood and the right hepatic venous blood, the relation of MEGX ratio [=(MEGX15 in right hepatic venous blood)/(MEGX15 in peripheral venous blood)] to the right hepatic lobe tissue EC was examined. A positive correlation was found (r=0.562, p=0.0122) immediately after surgery, (r=0.521, p=0.0185) 14 days after surgery, respectively. This suggested that MEGX ratio may be at least a parameter for the mitochondrial function of right hepatic lobe. Furthermore, no correlation of the level of MEGX15 in the right hepatic venous blood to the right hepatic lobe tissue EC was found, but the correlation of the MEGX ratio was. Based on the fact, it may be surmised that the level of MEGX ratio reflects the proper function of mitochondria in the hepatic cells which is not related to hepatic blood flow, that is, functional compliance, while the right hepatic venous MEGX15 reflects the function of mitochondria at the actual blood flow.

As described above, it was speculated that ICG-R_{15} reflects only hepatic blood flow and MEGX15 primarily reflects the hepatic mitochondrial function. In addition, ICG-R_{15} was recognized to have a discrepancy in levels between the peripheral venous blood and the right hepatic venous blood only in the PL+PCS group, while MEGX15 was recognized to have the discrepancy in levels between the peripheral venous blood and the right hepatic venous blood in all the groups. Thus, it was conceived that MEGX ratio is useful for evaluating the function of right hepatic lobe.

CONCLUSION

The present study supposed that the ICG-R_{15} and MEGX15 of the right hepatic venous blood and the maximum rate of ICG excretion into the right hepatic duct bile (ICG-Bmax) can be a set of means for evaluating the function of separated liver on the occasion of evaluating the function of the right hepatic lobe under portacaval shunt and ligation of the left branch of portal vein. In particular, MEGXratio may be at least a parameter for the functional efficiency of the right hepatic lobe, suggesting that it may reflect the mitochondrial function of right hepatic lobe.

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