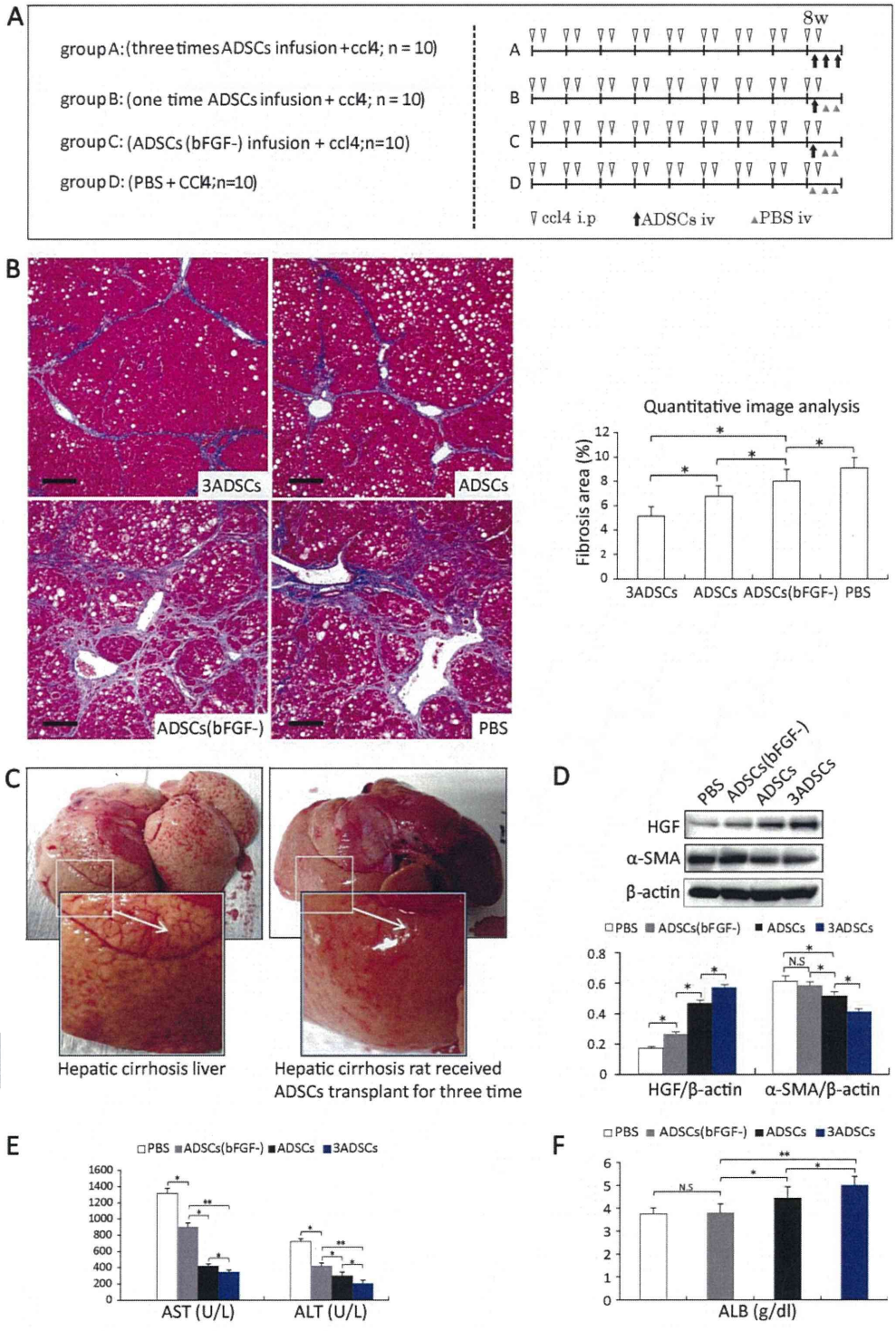

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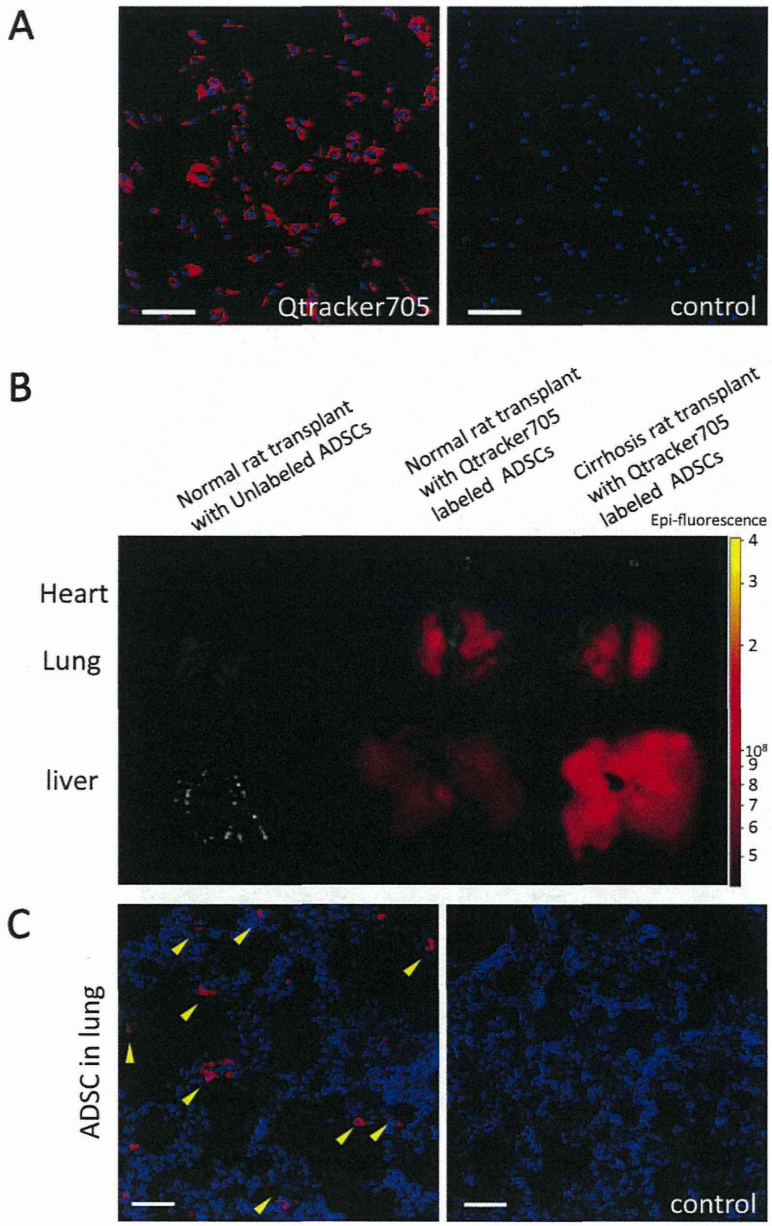

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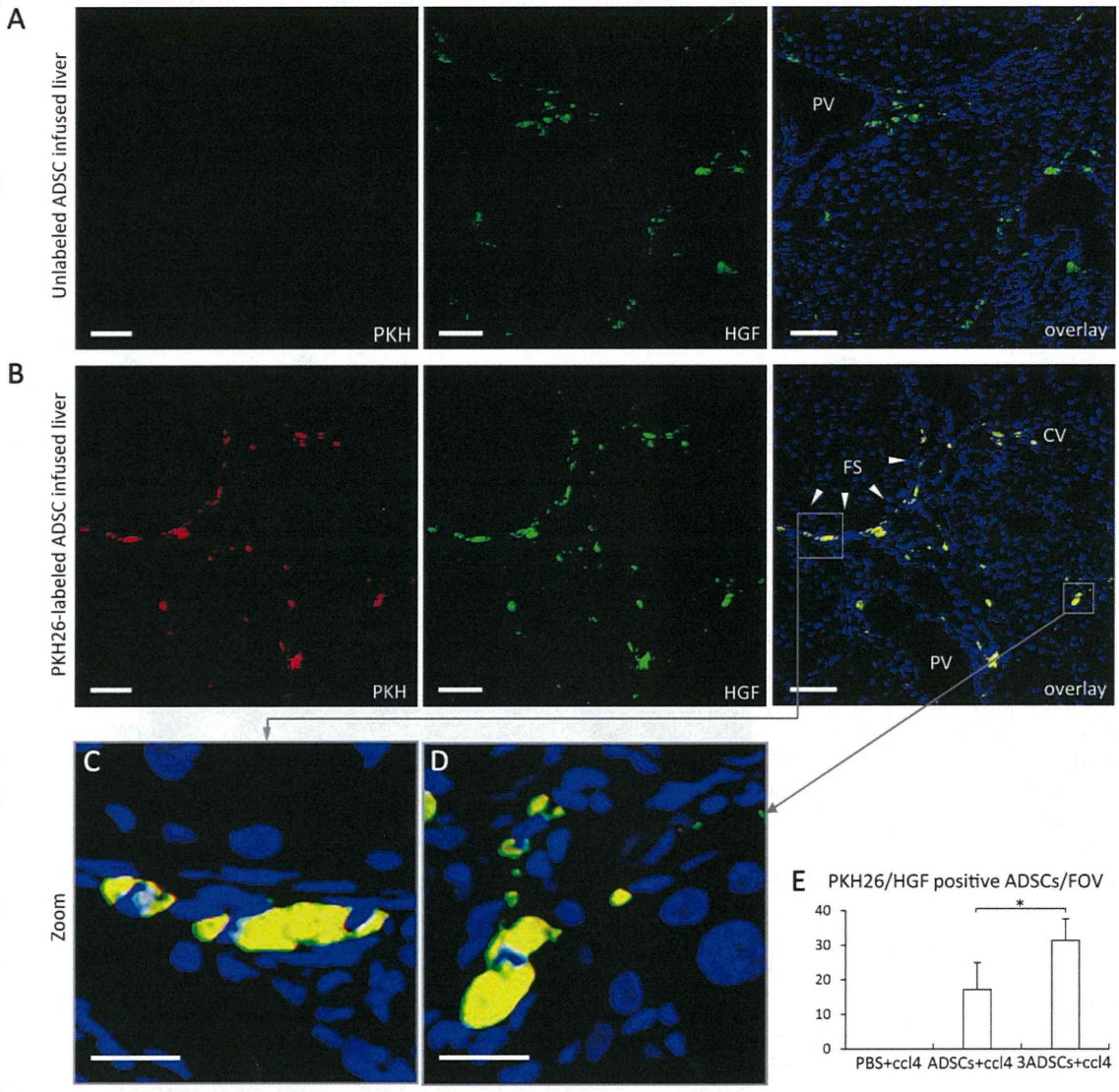

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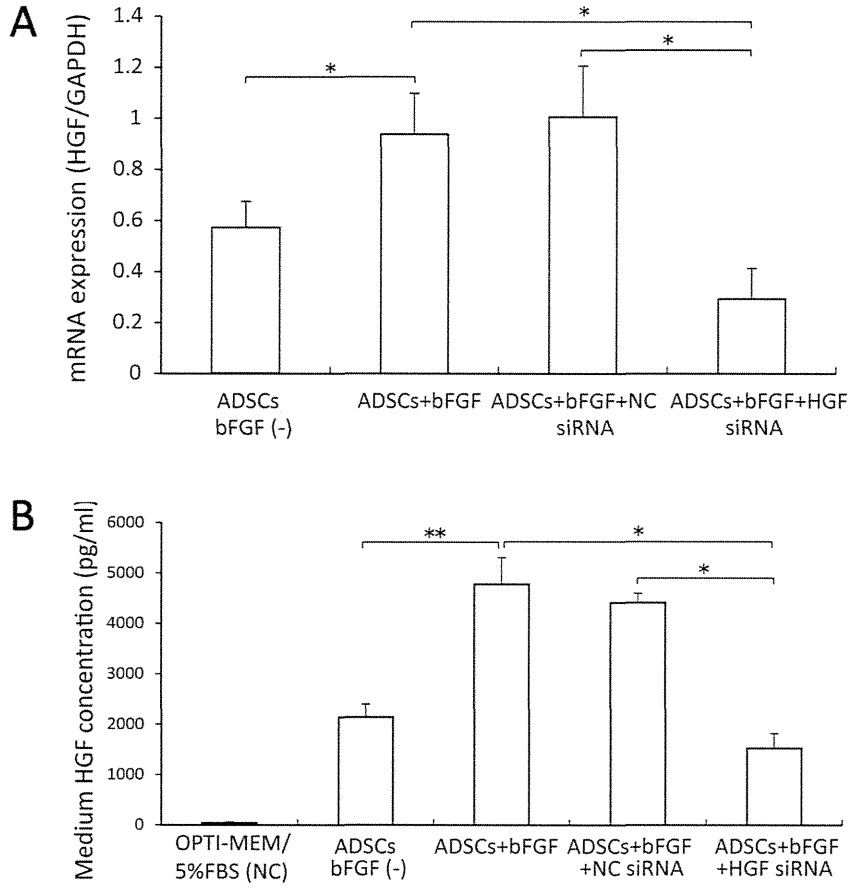

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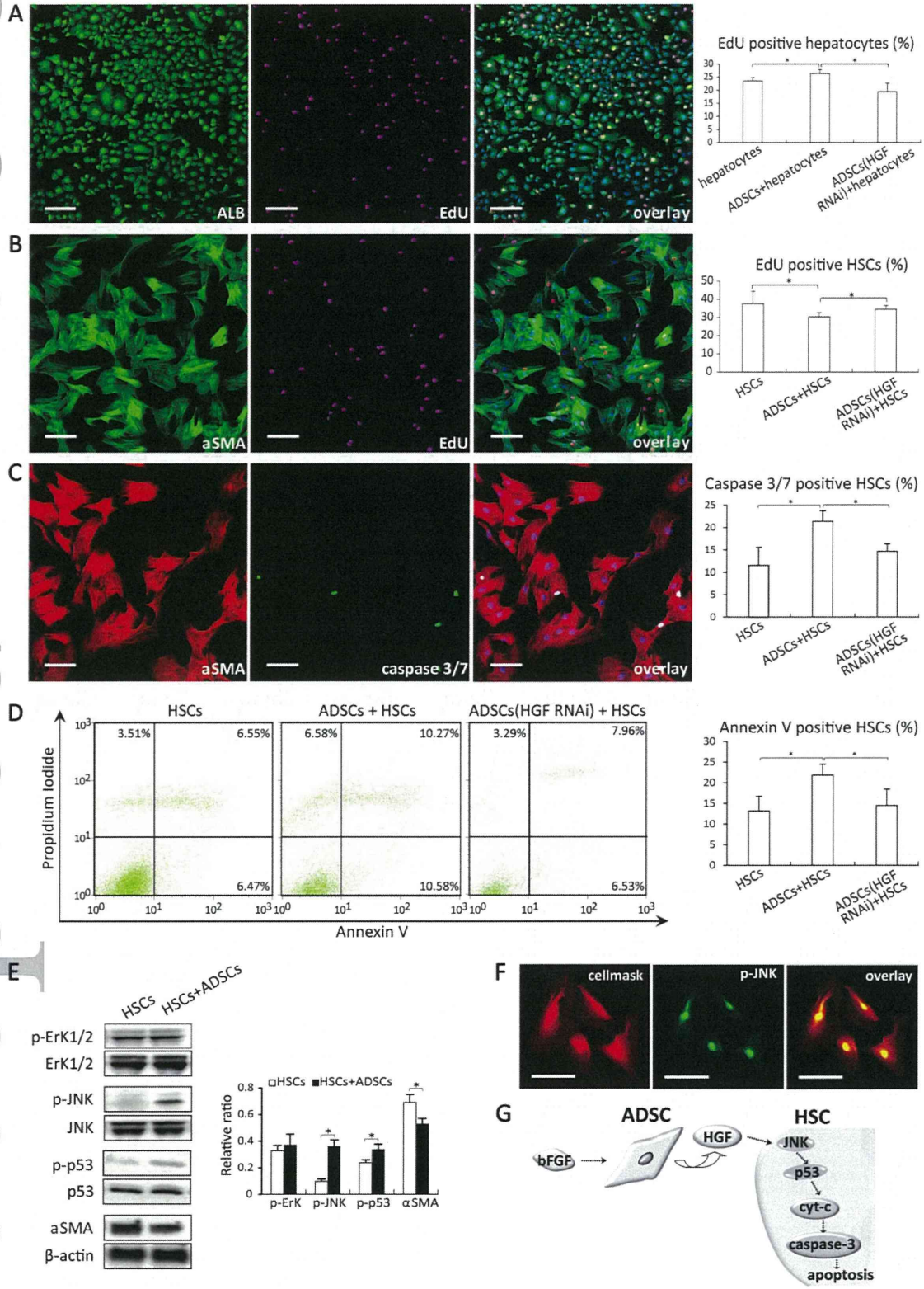

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55. JGH_12893_F6

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Evaluation of Esophagogastric Varices after Adult-to-Adult Living Donor Liver Transplantation Using a Left Lobe Graft

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Key Words
Esophageal varices · Gastric varices · Living donor liver transplantation · Velocity · Portal vein pressure · Transendoscopic microvascular Doppler sonography

Abstract
Background: There is little information on whether living donor liver transplantation (LDLT) reduces the supply of blood to esophagogastric varices. The aim of the present study was to assess the effects of LDLT on esophagogastric varices using both endoscopy and transendoscopic microvascular Doppler sonography (EMDS). ***Patients and Methods:*** 16 LDLT recipients were enrolled in the present study. Esophagogastric varices were assessed by endoscopy before and after LDLT. Direct measurement of variceal blood velocity was performed using EMDS in 12 of the 16 patients, and portal vein pressure before and after graft implantation was measured in 10 of them. ***Results:*** The median interval between LDLT and endoscopic examination was 129 days (range 20–624). Endoscopy demonstrated improvement of esophageal varices in 15 patients and of gastric varices in 4 of 5 patients assessed. The mean blood flow velocity in esophageal varices after LDLT was significantly lower than that before LDLT (8.8 ± 3.6 vs. 0.9 ± 1.2 cm/s, $p < 0.001$). The mean portal vein pressure did not decrease significantly after LDLT in comparison with that before LDLT (from 25.2 ± 5.2 to 23.1 ± 3.6 mm Hg, $p = 0.22$). ***Conclusion:*** Although portal vein pressure does not decrease immediately after left lobe LDLT, esophagogastric varices are ameliorated after a few months, and variceal blood flow velocity is reduced in almost all patients.

Liver transplantation not only cures the underlying liver disease but also ameliorates portal hypertension. It has already been reported that bleeding esophagogastric varices caused by portal hypertension improve after liver transplantation [1–3]. However, compared with full-size liver transplantation, a higher risk of re-bleeding has been observed after partial liver transplantation such as living donor liver transplantation (LDLT) [4, 5]. Many issues related to esophagogastric varices after LDLT remain unresolved, and there is little information on whether LDLT results in reduction of blood

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supply to esophagogastric varices. The aim of the present retrospective study was to assess the effects of left lobe LDLT on esophagogastric varices using both endoscopy and transendoscopic microvascular Doppler sonography (EMDS), which can measure blood flow velocity under direct vision without any obstruction such as water, and provide excellent resolution of esophagogastric varices, especially in the mucosa and submucosa [6–8].

Patients and Methods

Between September 2003 and January 2013, 64 consecutive LDLTs were performed at Juntendo University Hospital after obtaining approval from the Ethics and Indications Committee of Juntendo University. The recipients comprised 50 adults (aged ≥18 years) and 14 children (aged <18 years). All 50 consecutive adult patients underwent LDLT using a left lobe graft without the caudate lobe. 16 of the 50 patients who underwent assessment of esophagogastric varices by endoscopy before and after LDLT were the subjects of the present study.

Graft Selection Criteria

We used only left lobe grafts for adult recipients, and did not perform right lobe LDLT, as it is now accepted that this places a serious burden on the donor [9, 10]. Standard liver volume (SLV) of the recipients was calculated according to the formula of Urata et al. [11]. Graft volume (GV) was calculated by computed tomography (CT) volumetric analysis, and actual GV was measured on the back table. Our general selection criteria for grafts in adult-to-adult LDLT included a preoperatively estimated GV/SLV ratio ≥30%.

Surgical Technique

Donor hepatectomy (whole left lobectomy including the middle hepatic vein) and the recipient's operation were performed as described previously [10]. Briefly, the left hepatic vein and middle hepatic vein in the recipient were used for venoplasty. If necessary, hepatic graft venoplasty was also carried out using the left and middle hepatic veins. In all recipients, end-to-end anastomosis of the hepatic veins was performed, the donor left portal vein was anastomosed to the recipient left portal vein, and the graft was reperfused. The donor left hepatic artery was anastomosed to either the recipient right hepatic artery or the left hepatic artery, depending on the size match, under direct observation with an operating microscope. All LDLTs were carried out without modification of the graft portal inflow using techniques such as splenectomy and portosystemic shunt. Bile duct reconstruction was performed in a Roux-en-Y manner. A jejunostomy tube was placed in the afferent limb for intrabowel decompression.

Endoscopic Examination for Assessment of Esophagogastric Varices

Endoscopic examination was performed by two experienced operators before and after LDLT using a model GIF XW240 endoscope (Olympus Optical Corp., Tokyo, Japan). The endoscopic features of esophageal and gastric varices were evaluated according to the grading system outlined in 'The General Rules for Recording Endoscopic Findings of Esophageal Varices' prepared by the Japanese Research Committee on Portal Hypertension [12]. The form (F) of the varices was classified as either small, straight (F1), enlarged and tortuous (F2), large and coil-shaped (F3), or no varices (F0) after treatment. Red color sign (RC) referred to dilated, small vessels or telangiectasia on the variceal surface, the grading being categorized as RC0, RC1, RC2, or RC3.

EMDS Examination for Evaluation of Esophagogastric Varices

EMDS was performed by a single operator with the patient in the left lateral decubitus position breathing gently. If respiratory motion prevented adequate measurement, the vein was examined during breath-holding. The equipment used was the display unit of the Pioneer Multi-Channel Transcranial Doppler Monitor System (Pioneer TC2020; EME Co. Ltd., Germany) [6]. An ultrasonic microprobe (20 MHz) with a diameter of 1 mm was connected to the system and passed down through the accessory channel of the endoscope. The location of varices was recorded clearly in order to compare the velocity at exactly the same place before and after LDLT. The microprobe was placed directly on esophagogastric varices. Color Doppler ultrasonography provides a color display of blood flow, and displays blood flowing towards the probe appears hues of red and orange, whereas that flowing away from the probe appears shades of green, with the brightness increasing and decreasing with flow velocity.

Measurement of Portal Vein Pressure

In 10 of the 16 patients, we measured the portal vein pressure of the native diseased liver before hepatectomy, and also after graft implantation, by direct puncture with a 25-gauge needle and pressure tubing attached to a normal central venous pressure-monitoring transducer [13].

Statistical Analysis

Continuous variables were expressed as mean ± SD or the median with range, and statistical analysis of hemodynamic data was performed using paired samples t test. Calculations were performed using the JMP 8.0 software package (SAS Institute, Inc., Cary, N.C., USA). Differences at $p < 0.05$ were considered to be statistically significant.

Results

Recipient Characteristics

Detailed demographic data for the enrolled patients are presented in table 1. The median age of the recipients was 54.5 years (range 22–66), and 5 of them were men. All of the patients had a cirrhotic liver and 4 had associated hepatocellular carcinoma. The etiology of liver cirrhosis was hepatitis C in 8 patients, primary biliary cirrhosis in 4, alcoholic liver disease in 2, Alagille syndrome in 1, and biliary atresia with hepatitis C in 1. The

Table 1. Characteristics of the patients enrolled

Patient No.	Age, years	Sex	Etiology	HCC	MELD score	Child-Pugh	GV/SLV ratio	Posttransplant complications
1	57	F	LC (HCV)	no	17	C	34.3%	hepatitis C recurrence
2	65	F	LC (HCV)	no	26	C	41.1%	acute renal failure
3	66	F	LC (HCV)	yes	15	C	36.0%	hepatitis C recurrence
4	22	M	Alagille syndrome	no	20	B	36.3%	none
5	62	M	LC (alcoholic)	yes	7	A	46.5%	none
6	60	M	LC (HCV)	yes	10	B	44.6%	outflow block
7	54	F	PBC	no	26	C	39.2%	CMV
8	56	F	LC (HCV)	yes	17	C	37.9%	none
9	50	F	PBC	no	15	C	36.1%	none
10	55	F	PBC	no	16	B	45.1%	none
11	54	F	LC (HCV)	no	18	C	36.9%	none
12	63	M	LC (HCV)	no	14	C	35.2%	none
13	36	F	LC (HCV)	no	10	B	41.3%	hepatitis C recurrence
14	50	M	LC (alcoholic)	no	15	C	54.0%	none
15	34	F	biliary atresia, HCV	no	21	C	52.3%	none
16	43	F	PBC	no	18	C	42.7%	none

LC = Liver cirrhosis; HCV = hepatitis C virus; PBC = primary biliary cirrhosis; HCC = hepatocellular carcinoma.

median model for end-stage liver disease (MELD) score calculated for the liver recipients before LDLT was 17 (range 7–26). Among the 16 recipients, 11 had Child-Pugh class C disease, 4 had class B disease, and 1 had class A disease. Overall mean actual GV was 456 ± 89 g (median 425, range 350–690), which was equivalent to 41.2 ± 6.0% (median 40.1, range, 34.3–54.0) of the recipient SLV. The GV/SLV ratio was <40% in 8 of the 16 cases.

Endoscopic Findings (table 2)

The median interval between LDLT and posttransplant endoscopic examination was 129 days (range 20–624). Esophagogastric varices were observed in all 16 patients, and RC sign was recognized in 6 of them. Esophagogastric varices were graded as F2RC1 in 4 patients, F2RC0 in 4, F1RC1 in 2, and F1RC0 in 6. After LDLT, esophagogastric varices improved from F2 to F0 in 4 patients, from F2 to F1 in 4, and from F1 to F0 in 7. Esophagogastric varices remained unchanged in only 1 patient. The F factor improved after LDLT in 15 of 16 patients (94%). With regard to the RC sign, it improved from RC1 to RC0 in all 6 patients in whom it was evident by endoscopic examination before LDLT (100%). Gastric varices were identified in 5 of the 16 patients. The gastric varices were graded as F2RC0 in 2 patients and as F1RC0 in 3. After LDLT, these improved from F2 to F1 in 2 patients and from F1 to F0 in 2. In the remaining patient whose gastric varices remained unchanged, the RC sign deteriorated from RC0 to RC1.

EMDS Findings

EMDS was carried out in 12 of the 16 patients with esophagogastric varices before and after LDLT. The median interval between LDLT and posttransplant EMDS examination was 112 days (range 64–624). The changes in blood flow velocity in esophagogastric varices are shown in figure 1a. The mean variceal blood flow velocity after LDLT was significantly lower than that before LDLT (8.8 ± 3.6 vs. 0.9 ± 1.2 cm/s, $p < 0.001$). Figure 1b shows a representative example of improvement of esophagogastric varices; here, there was an improvement from F2 to F1, and blood flow velocity decreased from 14 to 1 cm/s. EMDS was performed in 4 of 5 patients with gastric varices before and after LDLT. Figure 2a shows the change in blood flow velocity in the gastric varices. Although the change did not reach a statistically significant level, blood flow velocity in the gastric varices showed a tendency to decrease after LDLT (from 6 to 4, from 25 to 6, from 2 to 0, and from 20 to 0 cm/s, respectively). Figure 2b shows a representative example of improvement of gastric varices; here, there was an improvement from F2 to F1, and blood flow velocity decreased from 25 to 6 cm/s.

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Table 2. Endoscopic assessment of esophageal varices and gastric varices before and after LDLT

Patient No.	Esophageal varices		Judge	Gastric varices		Judge	Time from LDLT, days
	before LDLT	after LDLT		before LDLT	after LDLT		
1	LmF2RC1	LiF1RC0	I	F0	F0	NC	99
2	LmF2RC0	LiF1RC0	I	F0	F0	NC	92
3	LiF1RC0	LiF0RC0	I	F0	F0	NC	106
4	LmF2RC1	LmF1RC0	I	Lg-cF1RC0	Lg-cF1RC1	D	64
5	LiF1RC0	F0	I	F0	F0	NC	572
6	LiF2RC0	F0	I	Lg-fF2RC0	Lg-fF1RC0	I	342
7	LiF1RC0	F0	I	F0	F0	NC	237
8	LmF1RC0	LmF1RC0	NC	F0	F0	NC	413
9	LiF2RC0	F0	I	F0	F0	NC	20
10	LmF2RC0	LiF1RC0	I	F0	F0	NC	139
11	LmF1RC0	F0	I	F0	F0	NC	624
12	LiF1RC0	F0	I	Lg-cF2RC0	Lg-cF1RC0	I	876
13	LiF1RC1	F0	I	Lg-cF1RC0	F0	I	118
14	LmF2RC1	F0	I	F0	F0	NC	106
15	LmF2RC1	F0	I	Lg-cF1RC0	F0	I	279
16	LiF1RC1	F0	I	F0	F0	NC	435

I = Improvement; NC = no change; D = deterioration.

Change in Portal Vein Pressure

The mean portal vein pressure before transplantation was 25.2 ± 5.2 mm Hg (median 24.0, range 16–35), and that after graft implantation was 23.1 ± 3.6 mm Hg (median 24, range 17–27); the changes in these values were not statistically significant (fig. 3).

Discussion

Although the decision to proceed to transplantation evaluation for patients who have suffered variceal hemorrhage should be driven by the degree of hepatic decompensation and not simply by the history of gastrointestinal bleeding, liver transplantation can be regarded as the ultimate treatment for portal hypertension. Without the option of liver transplantation, the 5-year survival of patients with Child C cirrhosis and variceal bleeding is approximately 25%, whereas that after liver transplantation it is 70–75% [14]. It has already been reported that bleeding esophagogastric varices and portal hypertension improve after liver transplantation. The present study clearly showed that LDLT ameliorated esophagogastric varices, as demonstrated endoscopically by improvement in the F factor (94%) and the RC factor (100%). The beneficial effects of LDLT on esophagogastric varices were also reflected in reduced variceal blood flow velocity after surgery.

A high risk of re-bleeding has been observed after split-liver transplantation in comparison with whole-liver transplantation [4, 5]. The reduction in liver vasculature induces an increase of portal venous pressure [13, 15, 16]. Our data showed that portal vein pressure did not decrease immediately after LDLT. This may delay the disappearance of collateral circulation and thus esophagogastric varices. Jiang et al. [17] reported an improvement of esophagogastric varices on postoperative day 14 after surgery in patients who underwent whole-liver transplantation, whereas no change was observed in those who underwent LDLT. Gastrointestinal bleeding commonly occurs within 1 month after LDLT, and the small liver graft regenerates almost to SLV within that time. The rapid regeneration of hepatocytes compresses the hepatic sinusoids, and this compression may be another cause of portal hypertension [18, 19].

Changes in portosystemic collaterals and splenic volume after LDLT have been investigated [20, 21]. Although approximately 2 months after LDLT, varices and splenic volume became stable, the rate of volume reduction of the varices and spleen was significantly correlated with the weight of the transplanted liver. Patients who received large liver grafts showed a greater decrease in collaterals and spleen volume than patients with small liver grafts [20]. We have been performing

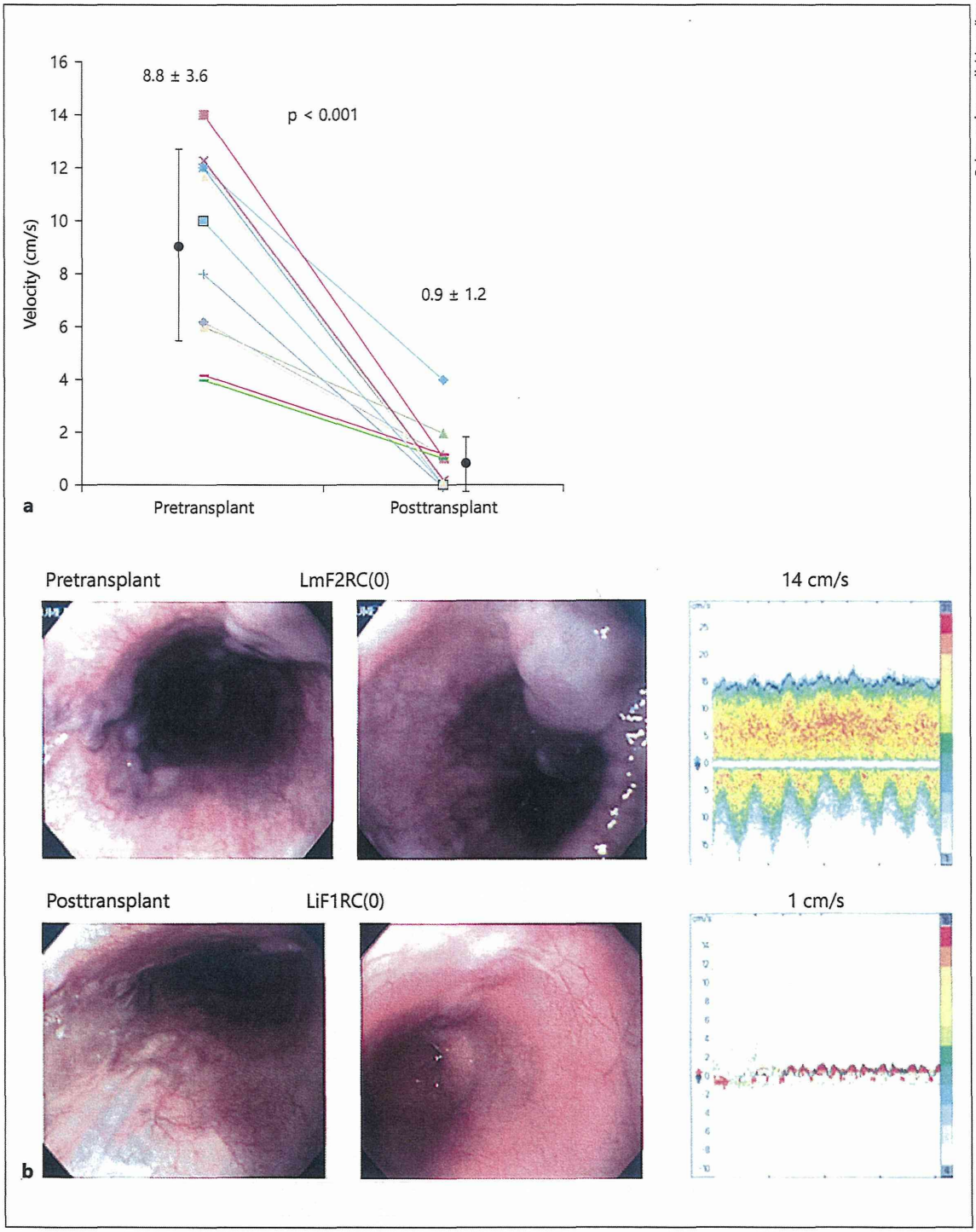
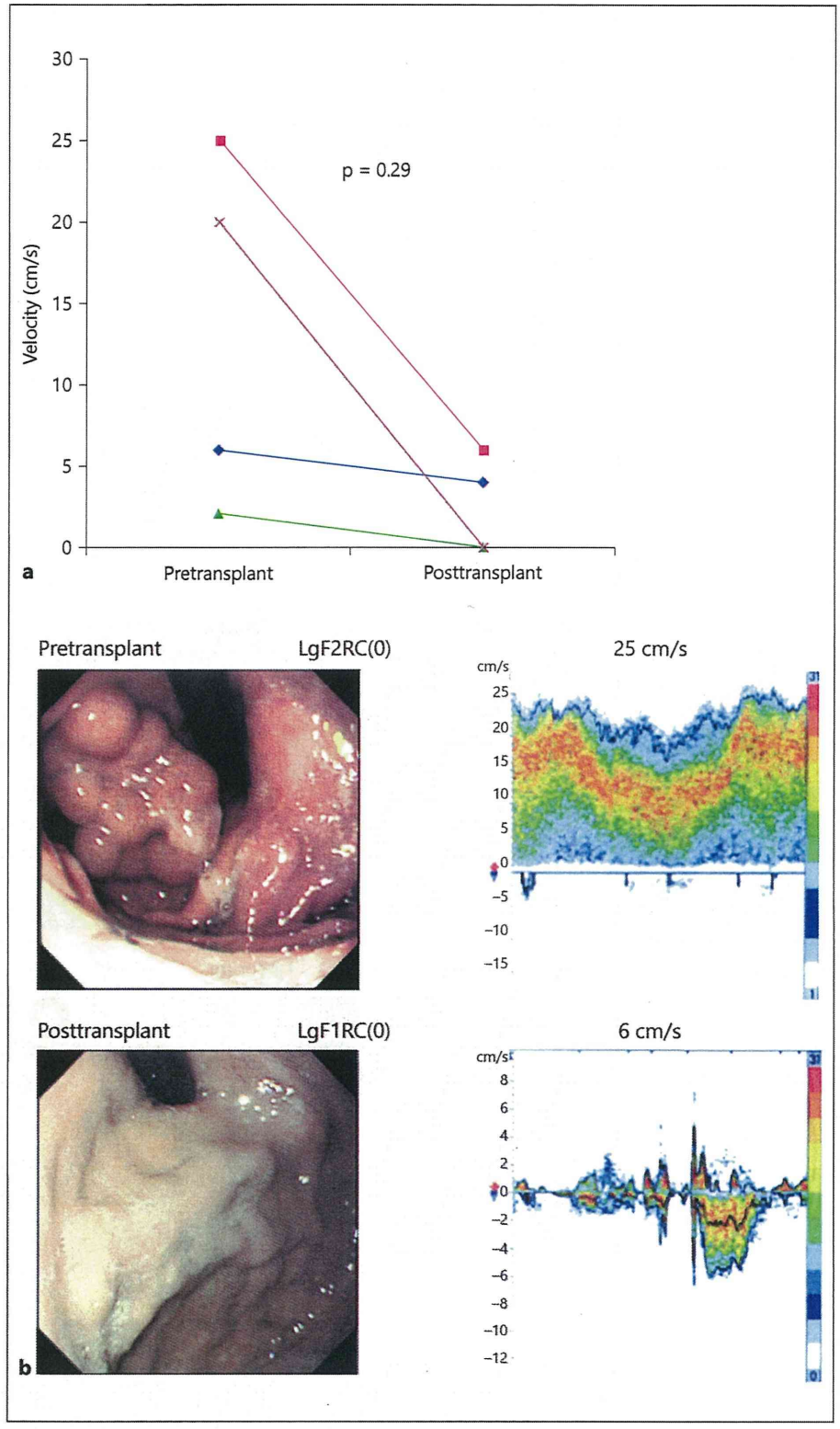


Fig. 1. a Mean blood flow velocity after LDLT was significantly lower than that before LDLT (8.8 ± 3.6 vs. 0.9 ± 1.2 cm/s, $p < 0.001$). **b** A representative patient who demonstrated improvement of esophagogastric varices. F2 varices improved to F1 varices and variceal blood flow velocity decreased from 14 to 1 cm/s.



Color version available online

Fig. 2. a Although the change was not statistically significant, blood flow velocity in gastric varices showed a tendency to decrease after LDLT (from 6 to 4, from 25 to 6, from 2 to 0, and from 20 to 0 cm/s, respectively). **b** A representative patient who showed improvement of gastric varices. F2 varices improved to F1 varices, and blood flow velocity decreased from 25 to 6 cm/s.

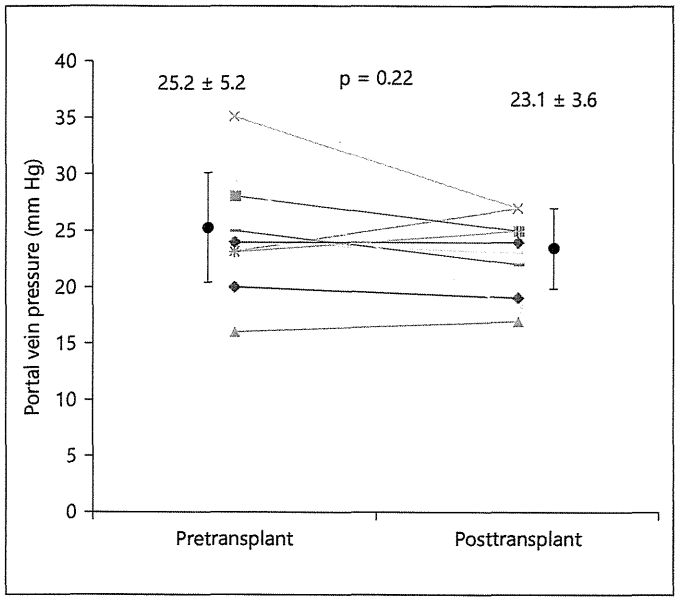


Fig. 3. Mean portal vein pressures before and after left lobe LDLT were not significantly different (25.2 ± 5.2 vs. 23.1 ± 3.6 mm Hg, p = 0.22).

adult-to-adult LDLT using a left lobe graft with a preoperatively estimated GV/SLV ratio of ≥30%, without either splenectomy or portocaval shunt in any of the patients [10]. LDLT using a left lobe graft requires more time for recovery of stable hepatic hemodynamics than the use of a right lobe graft. In the present series, the median interval between LDLT and posttransplant endoscopic examination was 129 days. At least a few months after LDLT, some improvement of portal hypertension may be observed even in patients who receive a left lobe graft. In order to evaluate the correlation between the decrease in variceal flow and the time after LDLT, a long-term observation by endoscopic examination is necessary.

Direct measurement of blood flow in esophagogastric varices after LDLT has rarely been reported. EMDS is useful for analyzing the velocity of blood flow under direct vision [7]. High-frequency probes for EMDS provide excellent resolution of varices located in the superficial layer of the esophagus [7]. A recent study has reported that high-resolution endoluminal sonography using a 20-MHz probe was more sensitive for measuring variceal blood flow velocity than conventional endoscopic ultrasonography because it could be used without any obstructions such as water, with which the esophagus must be filled when endoscopic ultrasonography is performed [6].

In conclusion, although portal vein pressure does not decrease immediately after left lobe LDLT, esophagogastric varices are ameliorated a few months after the procedure, and the variceal blood flow velocity becomes reduced in almost all patients.

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8. 生体肝移植における左葉グラフト vs 右葉グラフト
a) 左葉グラフト*

石崎陽一　川崎誠治**

〔要旨〕左葉グラフトによる成人生体肝移植は，右葉グラフト移植に比べてレシピエントにとって不利であることに相違ないが，左葉グラフト移植の最大のメリットは，ドナーの残肝容積が大きくドナーの安全性が高い点である．初期の成績が不良であったため右葉グラフトの使用が一般的となっていたが，最近は左葉グラフトを見直す傾向が認められる．左葉グラフトの選択基準として，グラフト容積標準肝容積比30％以上，あるいはグラフトレシピエント体重比0.6％以上が提唱され，門脈血流量調節として脾摘，門脈下大静脈シャントを併施した，あるいは併施しない左葉グラフトの良好な成績が報告されている．

はじめに

成人生体肝移植で用いられる主たるグラフトは左葉グラフトと右葉グラフトであり，日本肝移植研究会の2011年までの集計では成人生体肝移植4,137例中，左葉グラフト1,747例（42％），右葉グラフト2,267例（55％）となっている．いずれのグラフトにも一長一短があるが，当科ではドナーの安全性を重視し一貫して左葉グラフトを使用している．本稿では現在の左葉グラフトの動向につき概説する．

Ⅰ．生体肝移植における部分肝グラフトの推移

生体肝移植は当初左葉グラフトで始まったが，1998年ごろより右葉グラフトが登場し，2000年には右葉グラフトが左葉グラフトを超え，2005年には右葉グラフトは295例まで増加したが，その後は減少に転じ2009年以降は左葉グラフトの移植が多くなっている（図1）．米国では初期の左葉グラフトの成績が不良であったことから，生体肝移植のほとんどが右葉グラフトである．しかし右葉グラフトドナーの死亡が報告され，その数は激減している．こうしたことを反映して左葉グラフトを見直す動きがあり，数は右葉に比べてはるかに少ないが，2004年ごろから左葉グラフトが増加する傾向が認められる．

Ⅱ．左葉グラフトドナーの安全性

左葉グラフト移植の最大のメリットは，ドナーの残肝容積が右葉グラフト移植に比べて大きく，ドナーの安全性が高い点である．アジア主要5施設の生体ドナーの周術期合併症の集計では，右葉切除の術後合併症率が28％と左葉切除の術後合併症率7.3％に比べて高く，術後ビリルビン値の

キーワード：生体肝移植，左葉グラフト，右葉グラフト，門脈血流調節

* Left lobe graft versus right lobe graft in living donor liver transplantation；left lobe graft

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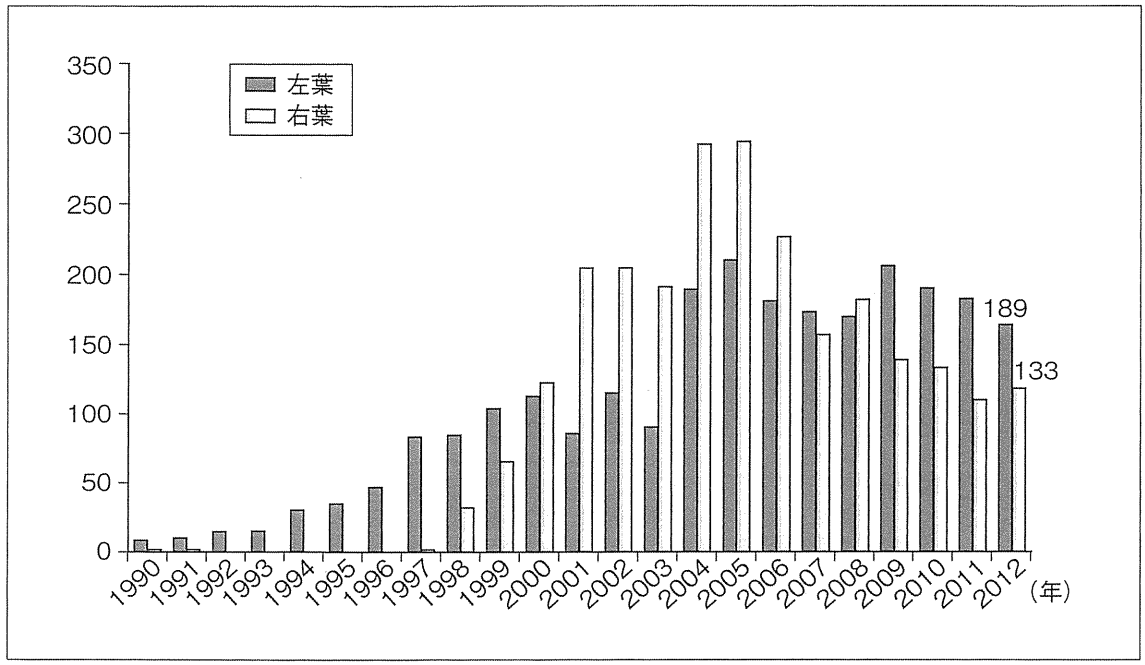

図1．わが国における生体肝移植での左葉，右葉グラフト数の推移

ピークが5 mg/dl以上の症例が7.3％であった[1]．京都大学の右葉グラフトドナーで，残肝容積が40％未満の症例の術後ビリルビンのピークは3.4 mg/dlと高値を示していたが，残肝容積が40％以上あってもピークは2.7 mg/dlと高かった[2]．九州大学の右葉グラフトと左葉グラフトのドナーの術後合併症の比較では，術後のビリルビン値のピークは右葉グラフトドナーで3.6 mg/dlと有意に高く，総合併症数，胆道系合併症いずれも右葉グラフトドナーで多く認められた[3]．

Ⅲ．左葉グラフトの移植成績

これまではグラフト選択基準として，グラフト容積標準肝容積比（GV/SV比）40％以上，あるいはグラフトレシピエント体重比（GRWR）0.8％以上が安全域とされ，これを満たさないグラフトは，過小グラフト症候群をきたしてグラフト不全になる可能性が高いとされてきた．初期の報告では，東京大学の80例の生体肝移植で，GV/SV比40％未満の24例中入院死亡が5例（20％）[4]，サムソン医科大学の成人生体肝移植79例では，GRWR 0.8％未満11例の1年生存率は55％[5]，京都大学の成人例では，GRWR 0.8％未満の11例の3ヵ月生存率は54.5％[6]と不良であった．このように小さなグラフトの成績が不良である原因の一つに，過剰な門脈血流負荷が推測されており[7]，各施設から門脈血流量の調節を付加した左葉グラフトの成績が報告されている．

京都大学は，移植操作終了後の門脈圧が15 mmHg以上の症例では1年生存率が73％，2年生存率が66％と不良であり，15 mmHg以上の症例で脾摘による門脈血流調節が必要としている[8]．Bothaらは，左葉グラフトで門脈下大静脈シャント作成による門脈血流量調節を行い，門脈下大静脈圧較差は18 mmHgから5 mmHgまで低下し，GRWRの中央値は0.67％であったのにもかかわらず，過小グラフト症候群を呈したのは1例だけで，グラフト1年生存率は81％と報告した[9]．また生体肝移植後の門脈血流量調節の指標として，Shimamuraらは，全肝移植後の100 gグラフト重量あたりの門脈血流量が約130 ml/分であったことから，この2倍である260 ml/分以下[10]，Troisiらも，自験例から100 gグラフト重量あたり250 ml以下[11]を目標にして門脈血流調節が必要としている．

しかしながら，門脈下大静脈シャントでは門脈血流スティール，肝再生の障害，肝性脳症，脾摘では手術時間の延長，出血量の増加，門脈血栓，overwhelming postsplenectomy infection（OPSI）などの問題点も報告されている．

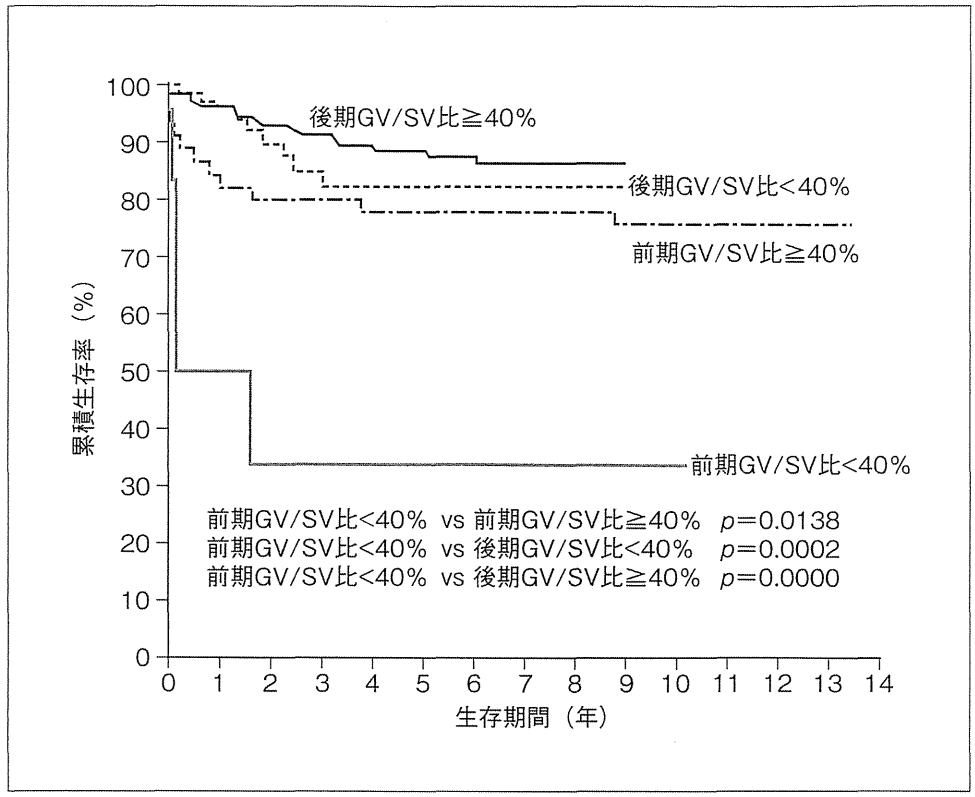

図2. 前期と後期における移植成績の比較（文献12より引用改変）

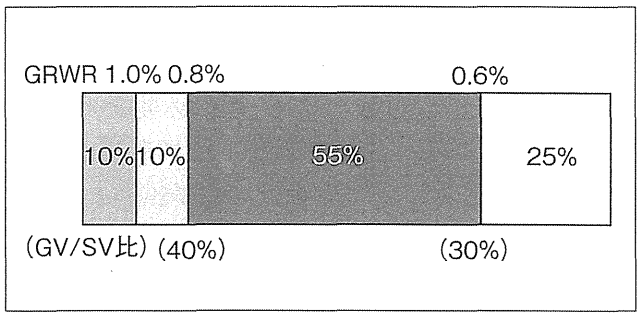

図3. 左葉容積とGRWR，GV/SV比（文献14より引用改変）

Ⅳ．生体肝移植のラーニングカーブ

九州大学は左葉グラフトによる生体肝移植を前期群，後期群に分けて検討し，後期群で有意に成績が良好であったと報告した[12]．これは多くの経験の蓄積と，手技の向上，術後管理の進歩によるものとしている．香港大学は右葉グラフトで，GV/SV比40％未満の症例の移植成績を前期群，後期群に分けて検討し，前期群の入院死亡率50％から後期群では1.9％まで減少し，成績が著明に改善したと報告した（図2）[13]．このように血流調節を行わない生体肝移植のデータからも，ラーニングカーブにより成績が改善しているのは明らかであり，門脈血流調節によって成績が改善しているのかは依然として不明である．

Ⅴ．左葉グラフトの適応基準

Yamadaらは，右葉グラフトドナーのボリューメトリーによる左葉容積の後ろ向き解析を行い，左葉ではGRWRが1％以上となる症例が10％，0.8％以上1％未満が10％，0.6％以上0.8％未満が55％，0.6％未満が25％であり，GRWRが0.8％以上の左葉グラフトが得られる症例は全体の20％にしかならず，逆に0.6％以上を適応とすれば75％は左葉グラフトの適応になるとしている（図3）[14]．

このように，左葉グラフトの大半はこのGRWR 0.6～0.8％，GV/SV比30～40％の範囲に集中しており，わずかに適応基準をかえることで左葉グラフトの適応がかなり増加することになる．

一方，GRWR 0.6％未満あるいはGV/SV比30％未満の症例は左葉グラフトの適応とならないが，もし体の大きさが同等のレシピエントで，左葉容積がGRWR 0.6％未満，GV/SV比30％未満の症例で右葉グラフトを考慮した場合，残肝容

表1. 過小グラフト症候群（自験例，$n = 53$）

	GV/SV＜40％ ($n = 30$)	GV/SV≧40％ ($n = 23$)	計	p値
遷延する胆汁うっ滞	1（3％）	1（4％）	2（4％）	0.82
難治性腹水	14（47％）	13（57％）	27（51％）	0.39
凝固障害	0（0％）	0（0％）	0（0％）	—
過小グラフト症候群（九大基準またはClavien分類）	0（0％）	0（0％）	0（0％）	—

積が少なくドナーの安全性の観点からも右葉グラフトの適応にもならない．

Ⅵ．自験例の成績

当科の移植適応基準はGV/SV比30％以上の左葉グラフトで，2003年9月～2013年7月に成人生体肝移植53例を施行した．グラフトは全例尾状葉を含まない左葉グラフトでportal inflow modulationとしての脾摘，シャント作成は施行していない．移植したグラフト重量の中央値は420（280～690）g，GV/SV比の中央値は38.6（26.1～54）％，GRWRの中央値は0.81（0.48～1.12）％であった．移植後に門脈圧を測定した40例中，門脈圧が15 mmHg以下は1例だけで，39例で門脈圧は15 mmHg以上であった．

移植後に遷延する黄疸が2例に認められたが，1例はC型肝炎，1例は結核の発症に起因したもので，原疾患治療によりすみやかに改善した．術後2週間の平均1日腹水量が1 l以上の症例は27例であったが，GV/SV比40％未満の群と以上の群で発生率に差はなく，全例でドレーン抜去可能であった．九大基準，Clavien基準いずれかを満たした過小グラフト症候群は1例も認められず（表1），1，2年生存率は100％であった[15]．

おわりに

右葉グラフトに比べ，左葉グラフトは生体肝移植では肝容積の点でドナーの安全性が高い．レシピエントでは右葉グラフトに比べ左葉グラフトは不利であるが，自験例からは，門脈血流調節をしない左葉グラフトでも良好な成績であり，術前評価でGV/SV比30％を適応基準とすれば，左葉グラフトでの移植がかなり増加することが予想される．

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胆管癌におけるNF-κB活性亢進と腫瘍増殖の関連性

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猪股雅史* 北野正剛**

索引用語：胆管癌，NF-κB，protease-activated receptor-2（PAR-2），cyclooxygenase-2（COX-2）

1 はじめに

胆道癌は消化器癌の中でも予後不良であり，本邦でもその死亡率は上昇傾向にある．2007年に，胆道癌は癌死亡の第6位であり1万7千人近くが胆道癌で死亡していた[1]．胆道発癌の背景には慢性炎症や胆管閉塞に関連した胆汁うっ滞による慢性・持続的な胆管上皮の障害が存在し，胆管上皮の修復機転の異常，癌関連遺伝子の異常が生じる結果，発癌に至ると推測されている[2]．nuclear factor-kappa B（NF-κB）は，当初は炎症・免疫応答に関わる転写因子として同定されたが[3,4]，増殖・浸潤・転移など癌細胞の特性に関与することが報告されている[5]．

当科では，胆・膵領域悪性腫瘍におけるprotease-activated receptor-2（PAR-2）と呼ばれる炎症・腫瘍増殖関連受容体の役割について検討を行ってきた[6-9]．

本稿では，胆管癌のPAR-2腫瘍増殖経路の調節におけるNF-κBの関与について主に述べることとする．

2 Protease-activated receptor-2とCyclooxygenase-2

Protease-activated receptors（PARs）は特異的セリンプロテアーゼにより活性化される7回膜貫通型受容体であり，PARファミリーとして4つの受容体がクローニングされている[10]．PAR-1, 3, 4がトロンビンにより活性化されるのに対し，PAR-2は主にトリプシンにより活性化される．当科の検討では，PAR-2が胆嚢癌[6]・胆管癌[9]，および通常型膵癌・膵管内乳頭粘液性腺癌[7]など多くの胆・膵領域悪性腫瘍において高発現を認めていた．特に胆嚢癌においては分化型（乳頭型）においてより発現の増強を示した[6]．また膵癌の増殖進展にPAR-2経路が関与することを*in vitro*, *in vivo*にて明らかにした[7,8]．

また，PAR-2はヒト臍帯静脈内皮細胞（HUVEC）や線維芽細胞においてcyclooxygenase-2（COX-2）の発現を亢進させ

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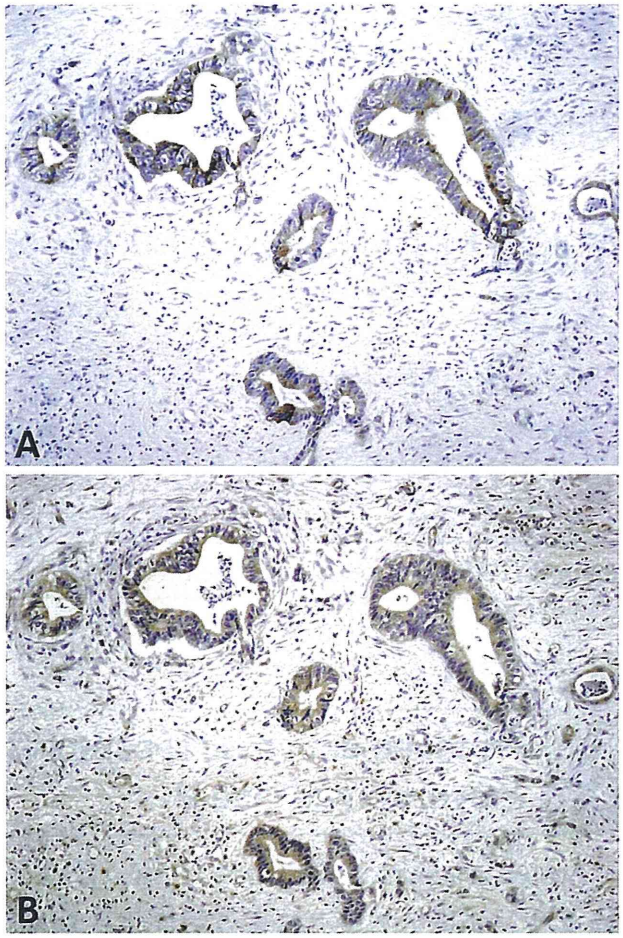

図1　胆管癌におけるPAR-2（A）およびCOX-2（B）の発現（×100）
細胞質・細胞膜への染色をほぼ同じ部位に認める．

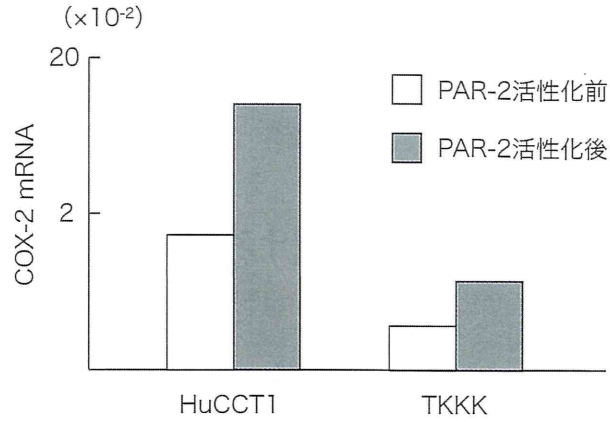

図2　PAR-2発現胆管癌細胞株（HuCCT1・TKKK）におけるCOX-2 mRNAの発現（文献9より引用改変）
PAR-2活性化ペプチドにより，COX-2 mRNAの発現亢進が認められた．

る[11,12]ことが示されており，腫瘍細胞におけるPAR-2・COX-2経路についても検討されてきている．そのCOX-2はさまざまな消化器癌[13~15]や肺癌[16]において腫瘍増殖に関与しており，胆管癌においても高発現を示す．当科の胆管癌に対する免疫組織学的検討では，PAR-2ならびにCOX-2は腫瘍細胞の細胞質・細胞膜に発現を認め，その発現部位はほぼ一致していた[9]（図1）．胆管癌の63％がPAR-2陽性，58％がCOX-2陽性であり，両者の発現には有意な相関関係を認めた．さらにわれわれはPAR-2発現陽性を示す胆管癌細胞株（HuCCT1・TKKK）を用いて*in vitro*の実験を行った．PAR-2の活性化ペプチド（SLIGKV）の投与により両細胞株を刺激するとCOX-2 mRNA・蛋白発現が亢進し（図2），細胞増殖が認められた[9]．正常細胞のみならず，腫瘍細胞増殖においてもPAR-2・COX-2経路が関与することが明らかとなった．

3　COX-2発現亢進におけるNF-κBの役割

HUVEC[17]，ヒト肺癌[18]，ヒト大腸癌[19]，ヒト胆管癌[20]において，PAR-2・COX-2経路活性化の際のmitogen-activated protein kinase（MAPK）やNF-κBの関与が報告されている．特に，Yoonらはヒト胆管癌細胞株においてepidermal growth factor receptor（EGFR）がCOX-2を発現亢進させる際にp44/42 MAPKやp38 MAPKのリン酸化が関与することを示した[20]．同様にわれわれも，胆管癌細胞株を用いてPAR-2・COX-2経路の活性化にMAPKやNF-κBが関与するか検討を行った．PAR-2発現陽性胆管癌細胞株（HuCCT1・TKKK）において，p44/42 MAPK阻害薬またはp38 MAPK阻害薬，NF-κB阻害薬（MG132）を投与することにより，PAR-2