Original Paper

Clinical Significance of Portal Vein Embolization before Right Hepatectomy

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SUMMARY

Background/Aims: To identify clinical significances of portal vein embolization (PVE) prior to major hepatectomy, we examined clinical parameters and outcome after right hepatectomy in patients who underwent PVE.

Methodology: The subjects were 30 patients who underwent PVE (PVE group), and 52 patients (non-PVE), in whom PVE was considered unnecessary, followed by right hepatectomy for hepatobiliary cancer.

Results: Total hepatic volume after PVE (1068±268 ml) tended to increase compared with before PVE (p=0.059). After PVE, the change in hemi-liver volume was 8.9±6.0%. Increases in hepatic volume of non-embolized left liver before and at 4 weeks after hepatectomy between PVE and non-PVE groups were similar. Changes in hepatic volumes before and after PVE were not significantly influenced by background liver disease. After PVE, the functional liver volume (419±185 cm^3) was significantly lower than morphological volume (564±165 cm^3) in the embolized liver ($p<0.05$). Although preoperative liver function was worse in PVE group compared with non-PVE, serious hepatic complications were rarely observed in PVE group.

Conclusions: Marked changes in hepatic volume were noted after PVE in patients with impaired liver function and those who need large-volume right hepatectomy, especially in functional volume, suggesting that PVE is a useful procedure to prevent post-operative liver failure.

KEYWORDS: Right hepatectomy; Portal vein embolization; Liver regeneration; Hepatic failure

ABBEREVIATIONS: Portal vein embolization (PVE); technetium-99m galactosyl serum albumin (99mTc-GSA); Liver activity at 15 minutes (LHL15); Computed tomography (CT)

INTRODUCTION

The incidence of posthepatectomy liver failure has markedly decreased in recent years following the introduction of adequate preoperative evaluation of hepatic function and estimation of resected liver volume, in addition to improvements in perioperative management (1,2). However, the risk of posthepatectomy hepatic failure after extensive hepatic resection for hilar bile duct carcinoma or hepatocellular carcinoma (HCC) with preexisting impaired liver function is still a serious problem (3-5). In patients who undergo right hepatectomy or a larger volume of liver resection, the preoperative portal vein embolization (PVE) technique, which allows reduction of the size of resected liver volume and induces hypertrophy of the remnant liver volume, is a useful option to improve outcome after hepatectomy (6-8). By applying PVE, right hepatectomy may be possible in some population of patients with liver dysfunction. Interestingly, relative hypertrophy of the remnant volume may be obtained even in patients with impaired liver function including liver cirrhosis or jaundice in addition to normal liver (9, 10).

In a previous pilot study, we examined the dynamic changes in morphological and functional hepatic volume following PVE by using computed tomography (CT) and technetium-99m galactosyl serum albumin (99mTc-GSA) liver scintigraphy (11). The purpose of the present study was to clarify the clinical significance of PVE. For this purpose, we compared the outcome of patients who underwent preoperative PVE for right hepatectomy and those who underwent right hepatectomy without PVE.

METHODOLOGY

Patients

The subjects were 30 patients who underwent preoperative PVE prior to right hepatectomy (PVE group) in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between 1998 and 2006. They included 23 males and 7 females with a mean age of 63.4±10.1 years (±SD, range, 39-78 years). Liver diseases included hepatocellular carcinoma (n=16), intrahepatic cholangiocarcinoma (n=1), metastatic liver carcinoma (n=2), gallbladder carcinoma (n=5) and hilar bile duct carcinoma (n=6). The background liver diseases included normal liver function (n=8), chronic viral liver diseases (n=16; caused by hepatitis B virus [n=9] or hepatitis C virus [n=7], including 4 with cirrhosis) and obstructive jaundice (n=6). The control group consisted of 52 patients who underwent right hepatectomy without PVE during the same period (non-PVE group), in whom the latter procedure was not necessary for the reason described below. They included 41 males and 11 females with a mean age of 59.7±8.4 years (±SD, range, 35-77 years). Liver diseases included hepatocellular carcinoma (n=8), intrahepatic cholangiocarcinoma (n=11), metastatic liver carcinoma (n=25), and hilar bile duct carcinoma (n=8). The background liver diseases included normal liver function (n=26), chronic viral liver diseases (n=20; caused by hepatitis B virus [n=16] or HCV [n=4], but no cirrhosis) and obstructive jaundice (n=6).

Indications of PVE and Hepatectomy

In patients with obstructive jaundice, the biliary drainage was conducted. And the hepatic function and operative indication were evaluated at the serum bilirubin level

under 2mg/dl. In our hospital, the permitted resected liver volume is determined pre-operatively by results of indocyanine green retention rate at 15 minutes (ICGR15) using Takasaki's formula (12). The estimated resected liver volume, excluding tumor volume (cm^3), is measured by CT volumetry (13). Essentially, the planned hepatectomy is performed when the permitted resected volume of the liver is greater than the estimated resected volume of the liver. In cases where the permitted resected volume is less than the estimated volume, or the estimated volume is more than 65% in patients with normal liver and 50% in those with cirrhosis, pre-operative PVE is selected (11, 14). Liver activity at 15 minutes (LHL15) of 99mTc-GSA scintigraphy or serum hyaluronic acid level was used as a reference when evaluating operative indication (15). Functional liver volume calculated by 99mTc-GSA scintigraphy before and after PVE was also examined (11,16). Hepatectomy was abandoned after laparotomy in 3 patients because of far advanced stage of tumors, and these three cases were excluded from further analysis. The parameters used for comparisons of the two groups (with and without PVE) were changes in hepatic volumes at 14 days after PVE, changes in hepatic volumes at 28 days after hepatectomy, and postoperative complications. The study design was approved by the Ethics Review Board of our institution and a signed consent for PVE was obtained from each subject. The present analysis was a retrospective study. Data were retrieved from both anesthetic and patient charts plus the NUGSBS database, for the duration of the initial hospitalization following hepatectomy.

Techniques of PVE

Technique of portal vein embolization and evaluation was described as follows. The two approaches to the right portal vein were direct catheterization of the ileocolic vein (n=15) and percutaneous transhepatic puncture (n=15) (6-8). Substances used for

embolization in our series included 1 g of absorbable gelatin sponge powder (Gelfoam®; Upjohn, Kalamazoo, MI) and 5,000 units (5 ml) of liquid thrombin (Sankyou Co., Tokyo) mixed in the contrast media. These substances were used in PVE conducted between 1998 and 2004 and, however, could not be used because of off-sale and severe thrombosis at our institute since 2005. Between 2005 and 2006, therefore, a mixture of 0.6 g of gelatin pieces (Spongel; Astellas Pharma Inc., Tokyo) and 5 ml of lipiodol Ultra-fluid (Shering, Berlin) was used to produce PVE. Permanent embolization materials were not used in the present series. Embolization was complete when the entire right portal vein was completely occluded. At 14 days after PVE, the hepatic volumes of the non-embolized hemi-liver and embolized hemi-liver (liver to be resected) were reassessed by CT volumetry (8, 13). Surgical resection of the liver was performed at 21 -28 days after PVE. Postoperative complications occurred in 12 of 30 patients in PVE group (40%) patients, and included uncontrolled ascites (defined as massive ascites unresponsive to diuretics for more than 2 weeks) in 5 patients; hepatic failure (defined by total bilirubin of >3 mg/dl on postoperative day 14) in one.

Statistical Analysis

All continuous data were expressed as mean ± SD. Data for different groups were compared using one-way analysis of variance. Chi-square test was used for comparison of categorical variables. Differences between groups were analyzed by Fisher's exact test or Scheffé's multiple comparison test. A two-tailed P value of less than 0.05 was considered significant. StatView Software for Windows, version 5.0 (SAS Institute, Inc., Cary, NC) was used in all statistical analyses.

RESULTS

Changes of Hepatic Volumes after PVE

No serious morbidity or mortality was recorded during the 3-week period after PVE. For the 30 patients of the PVE group, total hepatic volume, volumes of the right and left hemi-livers estimated before PVE were 1027±245 ml, 631±177 ml and 395±147 ml, respectively. The ratio of the left liver to total liver was 38.1±8.8%. Total hepatic volume after PVE (1068±268 ml) tended to be higher than that before PVE but the difference was not significant (p=0.059). After PVE, the volumes of embolized and non-embolized livers were 557±185 ml (a decrease of 8.9±6.0%) and 511±150 ml (an increase of 8.9±6.0%), respectively. **Figure 1** shows changes in hepatic volumes in non-embolized liver after PVE and after hepatectomy. The volumes of non-embolized left liver were significantly increased during these periods ($p<0.05$). Increases in hepatic volume before and at 4 weeks after hepatectomy between the PVE group and the non-PVE group were not significantly different (p=0.89).

Figure 2 shows changes in hepatic volumes before and after PVE, and after hepatectomy in the PVE group. The background liver disease did not significantly influence the changes in hepatic volumes during these periods.

Figure 3 shows changes in hepatic volume calculated by CT volumetry (morphological volume) and liver scintigraphy volumetry (functional volume) before and after PVE in 11 patients of the PVE group. Morphological (609±185 cm^3) and functional (628±155 cm^3) hepatic volumes of the embolized liver before PVE were not significantly different (right liver, open bars, **Figure 3**). Morphological (354±123 cm^3) and functional (357±164 cm^3) hepatic volumes of the non-embolized liver before PVE were not significantly different (left liver, open bars, Figure 3). After PVE, the functional liver

volume (419±185 cm^3) was significantly lower than morphological volume (564±165 cm^3) in the embolized liver. On the other hand, the functional (477±118 cm^3) and morphological (481±105 cm^3) hepatic volumes in the non-embolized liver were not significantly different after PVE.

Patient Outcomes

In patients undergoing right hepatectomy, none of the patients of the non-PVE group had liver cirrhosis and proportion of patients with normal liver in the non-PVE group was higher than that of the PVE group **(Table 1)**. The distribution of background liver diseases was significantly different between groups ($p<0.05$). Similarly, the preoperative value of ICGR15 in the PVE group was significantly worse than that of the non-PVE group ($p<0.01$). The incidence of postoperative complications was similar between the two groups. Serious postoperative complications such as sepsis, disseminated intravascular coagulation and hepatic failure were observed in the non-PVE group, but rare in the PVE group. In both groups, none of the patients died during hospitalization.

DISCUSSION

PVE is an established strategy for major hepatectomy in patients with injured liver function or patients with bile duct carcinomas in the hepatic hilum (3, 6-10). However, to our knowledge, comparison of clinical results between patients undergoing right hepatectomy after PVE and patients without PVE has not been reported. In patients who underwent PVE, right hepatectomy was risky for postoperative hepatic failure under the balance between resected or remnant hepatic volume and functional liver reserve such as the parameter of ICGR15 by our criteria (11). By applying PVE, right or extended right

hepatectomy could be performed in patients with impaired liver function. We considered that clinical results of patients who undergo PVE, compared to patients who undergo right hepatectomy without PVE, are important to clarify the clinical significance of PVE.

We have previously analyzed various issues related to the efficacy and safety of preoperative PVE such as relationship with serum hyaluronic acid level, predictive parameters for changes in hepatic volumes and evaluation of functional liver volume (10,11). The present results and those of other investigators indicate marked changes within a short period, in morphological volumes of embolized and non-embolized liver after PVE (6-11, 17-19). Before PVE, surgeons may consider the extent of changes in the right and left lobes induced by PVE. Our study showed approximately 9% change in hepatic volumes between embolized and non-embolized liver. There is concern on whether the remnant liver could still regenerate after PVE followed by hepatic resection. The present results showed that the volume of remnant liver favorably increased after hepatectomy and, therefore, the capacity of regeneration should remain after PVE. Although the hepatic volume significantly increased at 2 weeks after PVE, that of the non-embolized (remnant) lobe still increased at 4 weeks after hepatectomy in the present study. Eventually, the hepatic volume attained after hepatectomy in the PVE group was similar to that after hepatectomy of the control non-PVE group. Therefore, the potential of regeneration in the non-embolized liver is well preserved regardless of post-PVE status.

Atrophy of the embolized lobe and hypertrophy of non-embolized lobe were also observed even in the impaired liver (9, 10, 19). The present results showed that changes in hepatic volumes were not significantly different between normal and impaired livers. Therefore, PVE can be applied for patients with liver cirrhosis as well. Based on our

results and those of others, 9-30% increase in the volume of the non-embolized lobe (estimated remnant liver) can be expected in any background liver (7, 11, 18, 20, 21). However, the indication for PVE in cirrhotic patients may be based on functional liver reserve. Dual embolization of portal vein and hepatic artery at the interval of a few weeks is a useful option in such cases (20). We have examined the predictors of changes in hepatic volume in patients undergoing PVE and found that alkaline phosphatase level and platelet count were associated with changes in hepatic volume (22).

Recently, measurement of functional hepatic volume in each segment or lobe of the liver by ^{99m}Tc-GSA scintigraphy has become available and correlation between the morphological volume using CT-volumetry and functional volume using RI-volumetry has been reported (23-25). In a preliminary study, we examined previously the correlation between morphological and functional hepatic volumes after PVE in 5 cases (11). Similar to this finding, the decrease in functional hepatic volume in the embolized liver after PVE in 11 patients was more than that of morphological volume. Similar to our previous study, these changes were not related to background liver disease. Sugai *et al.* (25) also reported no significant increase in functional volume of the non-embolized liver, but they noticed marked increase in liver uptake density. Asialoglycoprotein binds specifically to hepatocytes via a receptor (26). Decreased counts on scintigraphy might be observed specifically in damaged livers. Atrophy of the embolized liver is thought to be due to apoptosis and hypertrophy of non-embolized liver may be limited morphologically (27). If the ^{99m}Tc-GSA scintigraphy results were more reliable as a functional change, the safety of major hepatectomy following PVE might be confirmed (6-9, 18-21). This finding in the present study might represent a functional shift from embolized liver to

non-embolized liver after PVE, which should support the effectiveness and usefulness of PVE.

Postoperative hepatic complications have significantly decreased following the wide use of PVE technique in the last decade (6-8, 11, 19-21). However, such complications or risk of hepatic failure cannot be completely avoided at this stage (20, 21, 28-31). In the present study, hepatic complications were also observed in the PVE group and, however, serious hepatic complications including hepatic failure were observed in only one patient in the PVE group. Basically, hepatic impairment was more frequent in the PVE group compared to the non-PVE group and PVE may help to carry out right hepatectomy in patients with impaired liver function. As the purpose of PVE is to avoid hepatic failure after major hepatectomy, our results strongly support the clinical usefulness by PVE.

In conclusion, we have reported changes in hepatic volume, functional hepatic volume and outcomes after portal vein embolization in patients scheduled for extensive right hepatectomy. The effect of PVE was not different in patients with normal liver and impaired liver and further regeneration in the non-embolized liver after hepatectomy was noticed. The decrease in functional volume was apparently larger in the embolized right liver following PVE compared with morphological volume. Severe hepatic complications were avoided in patients with impaired liver who underwent right or extended right hepatectomy. Our results highlighted the clinical usefulness of PVE for patients undergoing major hepatectomy.

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FIGURE LEGENDS

Figure 1 Measurement of hepatic volume in the non-embolized lobe at 2 weeks after PVE and at 4 weeks after hepatectomy in the PVE group and control group.

Figure 2 Changes in hepatic volume in the non-embolized lobe at 2 weeks after PVE and at 4 weeks after hepatectomy in the PVE group.

Figure 3 Changes in morphological and functional hepatic volumes in the embolized and non-embolized liver before and after PVE in 11 patients. Data are mean ± SD of 11 patients.

TABLE 1 Comparison of Clinical Status and Outcome after Right Hepatectomy in the PVE group and non-PVE control group.

	PVE group	**Non-PVE group**	**p value**
Background liver			
Normal/Chronic hepatitis/Cirrhosis/Obstructive jaundice	8/12/4/6	26/20/0/6	0.016
Preoperative liver functions			
Total bilirubin (mg/dl)*	1.3±1.8	1.0±0.3	0.68
Prothrombin activity (%)*	97±15	93±11	0.57
Alanine aminotransferase (IU/L)*	65±51	45±49	0.08
ICGR15 (%)*	16.7±8.6	9.2±6.0	<0.01
99mTc-GSA (LHL15)*	0.93±0.03	0.93±0.04	0.90
Postoperative complications	11 (36.7%)	17 (32.7%)	0.76
Uncontrolled ascites	5	6	0.74
Bile leakage	2	2	
Intra-abdominal infection	2	3	
Pneumonia	1	1	
Wound infection	1	0	
Sepsis	0	1	
Disseminated intravascular coagulation	0	1	
Hepatic failure(Total bilirubin level>3 mg/dl,>14 days)	1	3	

*Data are mean±SD

Fig. 1

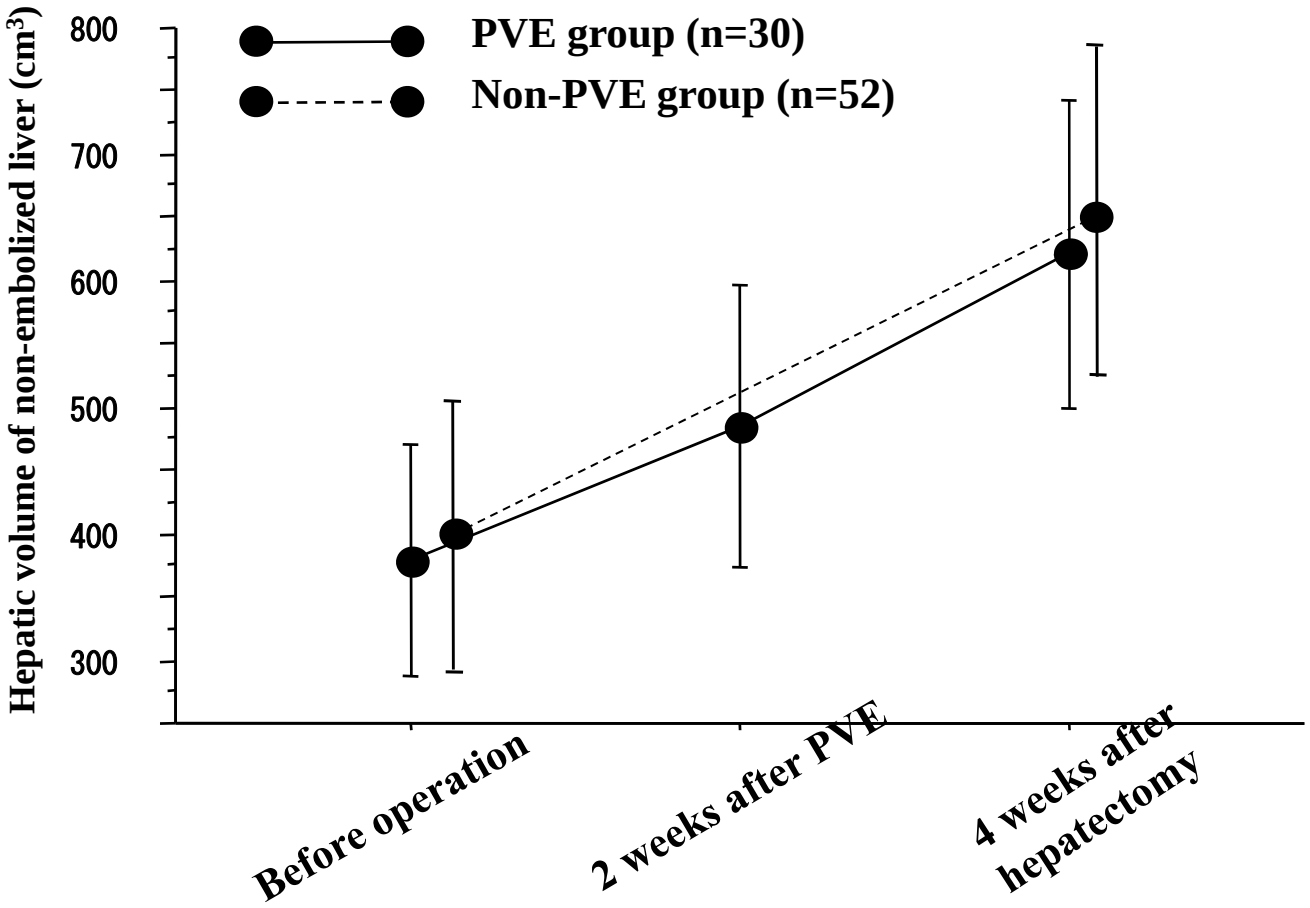

PVE group (n=30)
Non-PVE group (n=52)
Hepatic volume of non-embolized liver (cm3)
800
700
600
500
400
300
Before operation
2 weeks after PVE
4 weeks after hepatectomy

Fig. 2

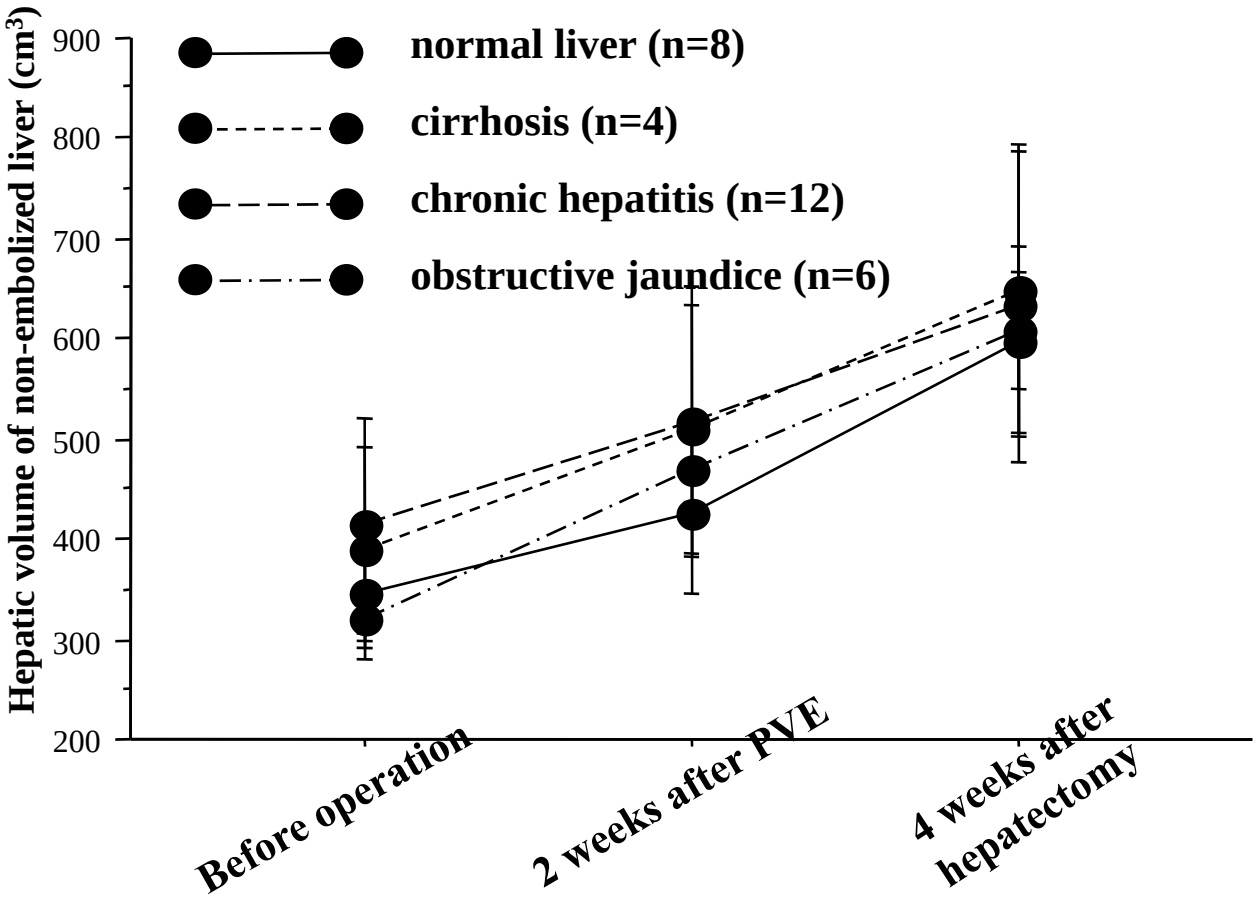
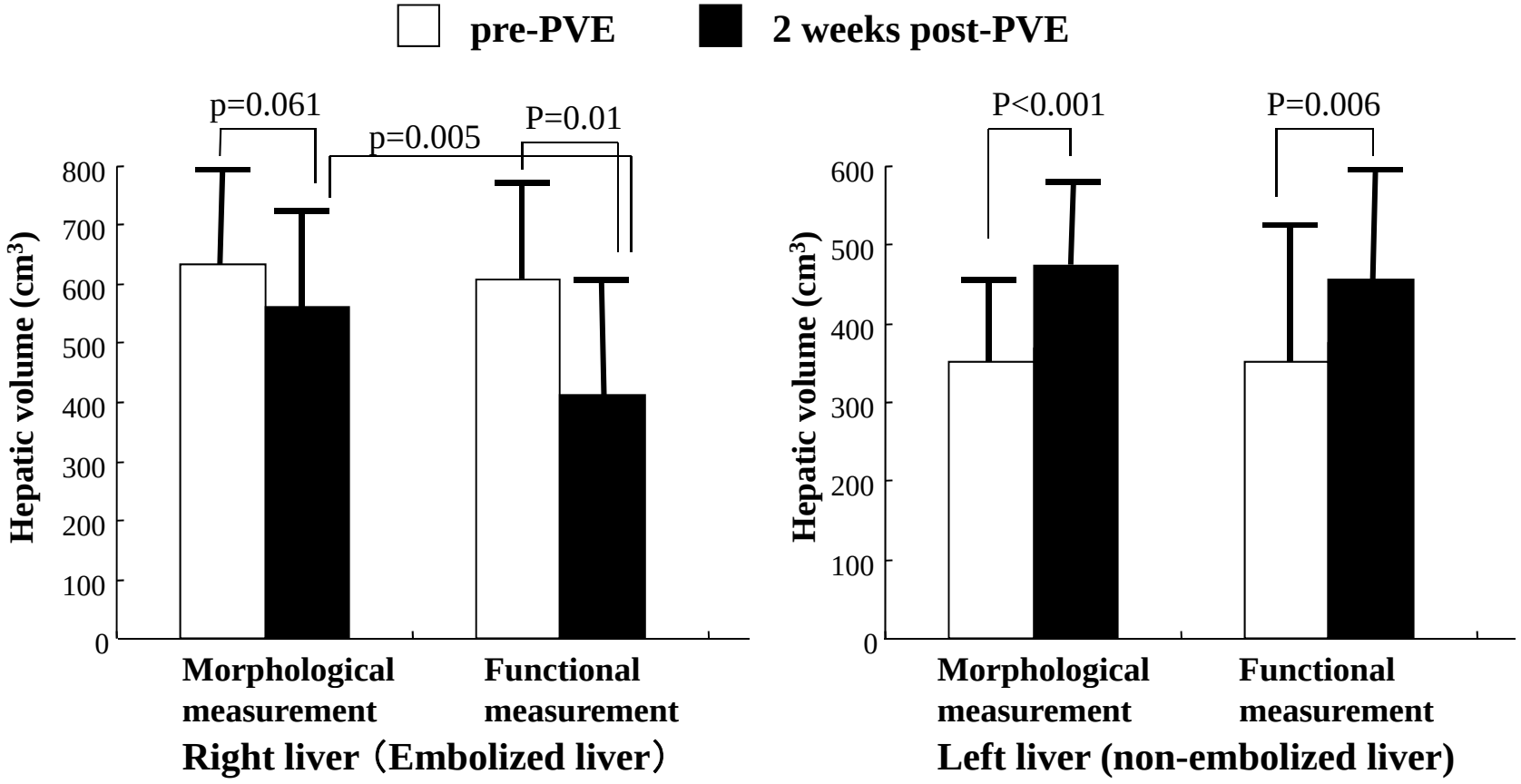

normal liver (n=8)
cirrhosis (n=4)
chronic hepatitis (n=12)
obstructive jaundice (n=6)
Hepatic volume of non-embolized liver (cm3)
900
800
700
600
500
400
300
200
Before operation
2 weeks after PVE
4 weeks after hepatectomy

Fig. 3


pre-PVE
2 weeks post-PVE
p=0.061
p=0.005
P=0.01
Hepatic volume (cm3)
800
700
600
500
400
300
200
100
0
Morphological measurement
Functional measurement
Right liver（Embolized liver）
P<0.001
P=0.006
Hepatic volume (cm3)
600
500
400
300
200
100
0
Morphological measurement
Functional measurement
Left liver (non-embolized liver)