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Doppler Estimation of Portal Blood Flow After Percutaneous Transhepatic Portal Vein Embolization

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Objective
To elucidate changes in portal blood flow (PBF) after percutaneous transhepatic portal vein embolization and their possible association with hypertrophy of the nonembolized hepatic segments.

Summary Background Data
The increase in PBF of the nonembolized hepatic segments after embolization is presumed to trigger hypertrophy of these segments. However, changes in PBF after embolization have not been investigated, and their extent remains unknown.

Methods
The authors prospectively measured PBF velocity, using color Doppler ultrasound, in 21 patients without cirrhosis who underwent embolization of the right portal vein or the right portal vein plus the left medial portal branch. Liver hypertrophy was assessed with a volumetric study using computed tomography.

Results
The PBF velocity significantly increased, from 11.1 ± 3.6 cm/sec before embolization to 20.1 ± 7 cm/sec 1 day after embolization. Subsequently, the velocity gradually decreased, but it remained significantly elevated until postembolization day 14. The volume of the nonembolized segments significantly increased from 370 ± 141 cm^3 to 488 ± 145 cm^3. The hypertrophy rate (cm^3/day) of the nonembolized segments after embolization correlated closely with the extent of increase in the PBF velocity, expressed as the velocity on day 1 divided by the velocity before embolization. The hypertrophy rate had a significant correlation with the absolute value of the PBF velocity on day 1, but its correlation coefficient was low. No significant correlations were observed between the hypertrophy rate and other clinical variables.

Conclusions
The hypertrophy rate of nonembolized hepatic segments after embolization is predictable from the extent of the increase in the PBF velocity. This can be estimated easily and noninvasively with Doppler ultrasound 1 day after embolization.

Percutaneous transhepatic portal vein embolization (PTPE) is a clinical application of the experimental observation that portal branch ligation causes atrophy of the corresponding hepatic lobe, with contralateral hypertrophy.[1] This radiologic intervention has become important in preparation for extensive liver resection[2–6]: it has the potential to prevent posthepatectomy liver failure[7] and, in turn, to extend the surgical indications for hepatobiliary malignancy and to increase the safety of extensive liver resections.[8] The increase in the portal blood flow (PBF) of the nonembolized hepatic segments after PTPE is presumed to trigger hypertrophy of these segments. However, changes in PBF after PTPE have not been investigated, and their extent remains unknown.

Recent advances in pulsed Doppler technology have made it possible to estimate the PBF noninvasively in humans, and the accuracy and reproducibility of Doppler blood flow measurements have been confirmed.[9–11] Dopp-

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ler ultrasonography (US) plays an increasingly important role in the diagnosis of portal vein thrombosis,[12,13] in understanding the pathophysiology of various liver diseases,[14–16] and in monitoring after a major hepatectomy or liver transplantation.[17–19]

In the current study, we prospectively measured PBF velocity after PTPE using color Doppler US and analyzed the relation between changes in PBF and the compensatory hypertrophy of the nonembolized hepatic segments after PTPE.

MATERIALS AND METHODS

This study involved 21 patients who underwent PTPE as part of their presurgical management for a planned extensive liver resection at Nagoya University Hospital. The subjects were 10 men and 11 women, with an average age of 64.8 ± 9.6 years (range 44 to 78 years). There were 10 hilar cholangiocarcinomas, 9 advanced gallbladder carcinomas, 1 hepatocellular carcinoma, and 1 metastatic liver cancer. None of the patients was cirrhotic. Thirteen patients had jaundice on admission, but neither jaundice nor cholangitis was observed at the time of PTPE because the patients had undergone percutaneous transhepatic biliary drainage.[20–23] Written informed consent for participation was obtained from each patient before enrollment in the study, which was approved by the human research review committee of the Nagoya University Hospital.

PTPE was performed 2 or 3 weeks before the expected liver resection, according to a previously reported method.[5,6] Briefly, under fluoroscopic control, a 5.5F triple-lumen balloon catheter was advanced into the target portal vein through a 6F catheter sheath introduced by US-guided puncture of the anterior branch of the right portal vein. We used fibrin glue (Beriplast P, Hoechst Japan, Tokyo, or Bolheal, Fujisawa Pharmaceutical, Tokyo) mixed with iodized oil (Lipiodol, Kodama Pharmaceutical, Tokyo) as the embolic material. The right portal vein was embolized in 16 patients, and the right portal vein plus the left medial portal branch in 5.

PBF was measured before and 1, 3, 7, and 14 days after PTPE, using a linear-array color Doppler US instrument (QAD 1, Quantum Medical Systems, Issaquah, WA) with a 3- or 5-MHz transducer and a digital video recorder. All measurements were taken with patients fasting, at rest, and during expiration in the supine position. We measured the maximal blood velocity in the portal vein at the midpoint of its umbilical portion. The velocity was obtained from the average Doppler spectrum during a 3-second period in the cardiac cycle. The portal vein was imaged using an upper abdominal sagittal scan, and the angle of the probe to the vein was kept within 60° to minimize intrinsic errors. All data were calculated from the digital video recorder after angle correction.

Computed tomography (CT) of the liver was used for volume determination before and 15.4 ± 5 days after PTPE. The liver was scanned at 1-cm intervals from the dome to the most inferior part, with postcontrast CT. The volumetric measurement was performed according to the previously reported method.[6,24] The hypertrophy rate (cm^3/day) of the nonembolized segments was defined as (postembolization volume minus preembolization volume)/days between PTPE and CT after PTPE.

Liver function parameters, such as the serum total bilirubin, aspartate transaminase, and alanine transaminase concentrations, were examined regularly before and after PTPE, using a standard laboratory method. An indocyanine green test was carried out 1 to 3 days before PTPE, according to the method described elsewhere.[25]

Results are expressed as means ± SD. Statistical analysis was performed with the Wilcoxon test. A level of $p < 0.05$ was considered statistically significant.

RESULTS

PTPE was successful in all patients, with no complications. Serum aspartate transaminase and alanine transaminase concentrations were slightly elevated after embolization but returned to baseline levels within 1 week. Serum total bilirubin concentrations remained near preembolization levels in all patients. Doppler US revealed no recanalization of the embolized portal veins during the period studied, indicating that complete embolization was achieved in all patients.

The blood flow velocity in the umbilical portion of the portal vein was satisfactorily measured in all examinations. The velocity markedly increased, from 11.1 ± 3.6 cm/sec before PTPE to 20.1 ± 7.0 cm/sec 1 day after PTPE ($p < 0.0001$). This increase was followed by a gradual decrease, but the level remained significantly elevated until postembolization day 14 (Fig. 1).

The calculated mean volume of the embolized hepatic

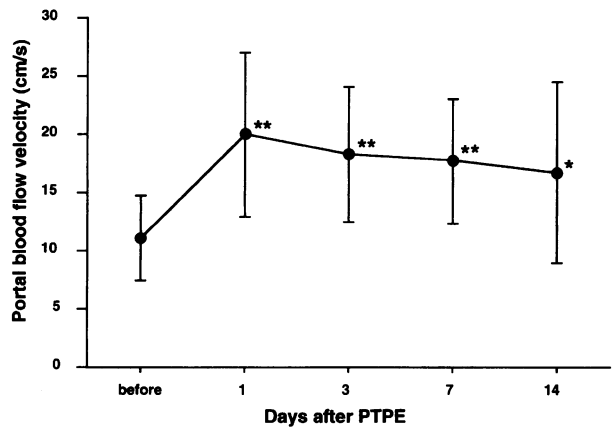

Figure 1. Changes in PBF velocity after PTPE. The velocity approximately doubled on day 1 after embolization, and it remained significantly elevated until day 14. Values are expressed as the mean with SD (vertical bars). * $p < 0.01$ and ** $p < 0.0001$ *vs.* the original value (by the Wilcoxon test).

segments significantly decreased ($p < 0.001$), from 682 ± 125 cm^3 before PTPE to 604 ± 130 cm^3 after PTPE. In contrast, the mean volume of the nonembolized segments significantly increased ($p < 0.001$), from 370 ± 141 cm^3 to 488 ± 145 cm^3. The mean volume of the whole liver exhibited no significant changes; it was 1052 ± 183 cm^3 before PTPE and 1092 ± 168 cm^3 afterward.

Correlation analyses were performed using several clinical variables to elucidate the influences on the hypertrophy rate of the nonembolized segments. The hypertrophy rate correlated closely with the increase in the portal flow velocity, expressed as the velocity on day 1 divided by the velocity before PTPE ($r = 0.775$, $p < 0.0001$; Fig. 2). A significant correlation was also found between the hypertrophy rate and the PBF velocity on day 1 after PTPE, but the correlation coefficient was low ($r = 0.494$, $p = 0.0216$). The hypertrophy rate exhibited significant correlations with neither the PBF velocity on days 3, 7, and 14 nor the other clinical variables examined (Table 1).

Table 1. CORRELATION COEFFICIENT BETWEEN HYPERTROPHY RATE OF NONEMBOLIZED SEGMENTS (CM^3/DAY) AND OTHER CLINICAL VARIABLES

Variable	Correlation Coefficient	p Value
Portal flow velocity (cm/s)		
Before embolization	−0.174	0.4560
On day 1	0.494	0.0216
On day 3	0.297	0.1943
On day 7	0.302	0.1860
On day 14	0.226	0.3904
Increase rate of portal flow velocity*	0.775	<0.0001
Volume of embolized segments (%)†	0.133	0.5698
KICG‡	0.173	0.4703
Hepaplastin test (%)‡	0.055	0.8148
Serum albumin level (mg/dl)‡	−0.107	0.6491
Serum ALT level (IU/l)‡	−0.057	0.8100
Serum AST level (IU/l)‡	−0.136	0.5612
Age (years)	−0.130	0.5799

* Velocity on day 1 divided by velocity before embolization.
† Percent volume of embolized segments to whole liver volume.
‡ Values before embolization.
KICG = plasma disappearance rate of indocyanine green; ALT = alanine transaminase; AST = aspartate transaminase.

DISCUSSION

The development of the pulsed Doppler US has prompted noninvasive and physiologic studies of portal hemodynamics. An excellent correlation between Doppler blood flow measurements and the values obtained with electromagnetic flowmetry indicates the accuracy and clinical utility of Doppler estimation.[9] We measured the blood velocity in the umbilical portion of the portal vein, where sampling error is minimal because of the small angle of the US probe to the blood flow vector. Unlike the main portal trunk, the vessel was well visualized in all patients by upper abdominal sagittal scanning. In addition, a skilled ultrasonographer measured the flow velocity with a single instrument, minimizing interobserver and interequipment variability.[26] We did not measure blood flow volumes because determination of an accurate cross-sectional area was difficult and the findings varied with each examination.

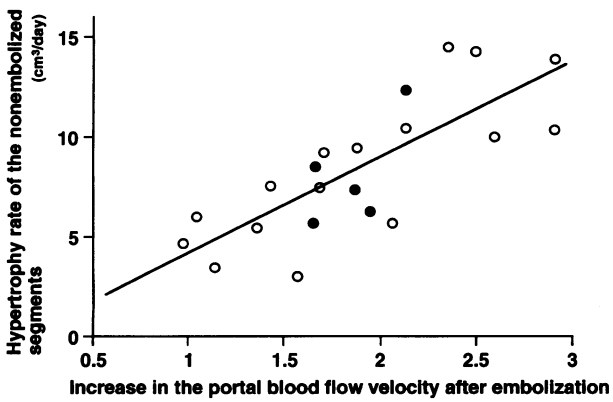

Figure 2. Correlation between the hypertrophy rate and the increase in the PBF velocity after embolization, expressed as the velocity on day 1 divided by the velocity before embolization. $Y = 4.753 - 0.603$ ($r = 0.775$, $p < 0.0001$). ○, patients with embolization of the right portal vein; ●, patients with embolization of the right portal vein plus the left medial portal branch.

The PBF velocity approximately doubled on day 1 after PTPE and, despite a subsequent gradual decrease, remained significantly elevated until day 14. This flow pattern after PTPE is similar to that after a major hepatectomy,[18] although the extent of increase after PTPE is less dramatic. The continuation of the increased PBF velocity suggests that liver regeneration induced by PTPE lasts for 2 weeks or more. The remnant liver after major hepatectomy is restored to the original volume within 1 month in humans with a noninjured liver,[27] which implies that liver regeneration after major hepatectomy proceeds rapidly. In contrast, liver hypertrophy after PTPE is thought to be mild.[24] In rats, however, liver hypertrophy after portal branch ligation is almost equal to that after liver resection.[28] This difference in liver hypertrophy between humans and rats can be explained by differences in PBF: the human liver receives 70% to 80% of its blood supply from the portal vein, whereas the rat liver receives 90% or more from the portal vein.[29]

Since Rous and Larimore first reported the relation of the portal blood to liver maintenance in 1920,[1] many studies[30–33] have demonstrated that interruption of the portal blood supply results in atrophy of the hepatic segments involved, with compensatory hypertrophy of the hepatic segments not deprived of their blood supply. A close link between the portal blood and liver hypertrophy after hepatectomy has also been well documented.[34,35] From these observations, portal blood is thought to be a particularly

important determinant of liver hypertrophy. However, only a few reports have described the relation between PBF and liver hypertrophy in humans. Kawasaki et al.[17] demonstrated decreased PBF volume in patients with a poor clinical outcome after hepatectomy, but they did not assess liver hypertrophy. Kin et al.[18] first demonstrated a significant correlation between the PBF velocity and the hepatic growth rate in patients after a major hepatectomy. The present study clearly revealed that liver hypertrophy of the nonembolized segments after PTPE is influenced mainly by PBF.

Interestingly, the liver hypertrophy rate correlated closely with the extent of the increase in the PBF velocity, whereas there were no correlations with the absolute values of the velocity, except for the velocity on day 1 after PTPE. The determinants of PBF velocity are difficult to explain; the velocity appears to reflect hepatic vascular resistance to some extent, but it may be affected by several intrinsic factors, such as the cardiac output and blood pressure.[17] It is likely that the extent of the increase in the velocity better reflects the vascular resistance of the liver, because the other factors offset each other. It has been reported that the vascular resistance of the liver increases in proportion to the degree of liver dysfunction.[18,36] Kin et al.[18] observed a high resistive index in the hepatic arteries of patients with posthepatectomy liver failure, and Nishihara et al.[36] found "reversed" PBF in 10 patients who died of liver failure after surgery. Collectively, the extent of the increase in the PBF velocity after PTPE is thought to be a good indicator of hepatic vascular resistance and, in turn, to be a good indicator of hepatic functional reserve.

In conclusion, the hypertrophy rate of nonembolized hepatic segments after PTPE is predictable from the extent of increase in the PBF velocity. This extent can be estimated easily and noninvasively by Doppler US 1 day after PTPE, indicating that Doppler US analysis of PBF has clinical utility for monitoring patients after PTPE. In patients with a small increase in velocity after PTPE, surgery should be scheduled for 3 weeks or more after PTPE to allow for satisfactory liver hypertrophy with enough functional capacity of nonembolized hepatic segments.

References

1. Rous P, Larimore LD. Relation of the portal blood to liver maintenance: a demonstration of liver atrophy conditional on compensation. J Exp Med 1920; 31:609–632.
2. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990; 107:521–527.
3. Lee KC, Kinoshita H, Hirohashi K, et al. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. World J Surg 1993; 17:109–115.
4. Baere T, Roche A, Elias D, et al. Preoperative portal vein embolization for extension of hepatectomy indications. Hepatology 1996; 24:1386–1391.
5. Nagino M, Nimura Y, Kamiya J, et al. Selective percutaneous transhepatic embolization of the portal vein in preparation for extensive liver resection: the ipsilateral approach. Radiology 1996; 200:559–563.
6. Nagino M, Nimura Y, Kamiya J, et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. Surgery 1995; 117:677–681.
7. Nagino M, Nimura Y, Hayakawa N, et al. Logistic regression and discriminant analyses of hepatic failure after liver resection for carcinoma of the biliary tract. World J Surg 1993; 17:250–255.
8. Kato T, Tanaka M, Nimura Y, et al. Enhancement of rat liver mitochondrial function by portal branch ligation secures subsequent extended hepatectomy. Biochem Int 1991; 24:107–116.
9. Moriyasu F, Ban N, Nishida O, et al. Clinical application of an ultrasonic duplex system in the quantitative measurement of portal blood flow. J Clin Ultrasound 1986; 14:579–588.
10. Bombelli L, Genitoni V, Biasi S, et al. Liver hemodynamic flow balance by image-directed Doppler ultrasound evaluation in normal subjects. J Clin Ultrasound 1991; 19:257–262.
11. Horn JR, Zierler B, Bauer LA, et al. Estimation of hepatic blood flow in branches of hepatic vessels utilizing a noninvasive duplex Doppler method. J Clin Pharmacol 1990; 30:922–929.
12. Koslin DB, Mulligan SA, Berland LL. Duplex assessment of the portal venous system. Semin Ultrasound CT MR 1992; 13:22–23.
13. Platt JF, Rubin JM, Ellis JH. Hepatic artery resistance changes in portal vein thrombosis. Radiology 1995; 196:95–98.
14. Gaiani S, Bolondi L, Bassi SL, et al. Prevalence of spontaneous hepatofugal portal flow in liver cirrhosis. Gastroenterology 1991; 100:160–167.
15. Nelson RC, Lovett KE, Chezmar JL, et al. Comparison of pulsed Doppler sonography and angiography in patients with portal hypertension. AJR 1987; 149:77–81.
16. Kanda H, Nimura Y, Yasui A, et al. Recovery of portal blood flow after percutaneous transhepatic biliary drainage in patients with obstructive jaundice. Surg Today 1997; 27:120–123.
17. Kawasaki T, Moriyasu F, Kimura T, et al. Changes in portal blood flow consequent to partial hepatectomy: Doppler estimation. Radiology 1991; 180:373–377.
18. Kin Y, Nimura Y, Hayakawa N, et al. Doppler analysis of hepatic blood flow predicts liver dysfunction after major hepatectomy. World J Surg 1994; 18:143–149.
19. Longley DG, Skolnick ML, Zajko AB, Bron KM. Duplex Doppler sonography in the evaluation of adult patients before and after liver transplantation. AJR 1988; 151:687–696.
20. Nagino M, Hayakawa N, Nimura Y, et al. Percutaneous transhepatic biliary drainage in patients with malignant biliary obstruction of the hepatic confluence. Hepato-Gastroenterology 1992; 39:296–300.
21. Nimura Y, Kamiya J, Kondo S, et al. Technique of inserting multiple biliary drains and management. Hepato-Gastroenterology 1995; 42: 323–331.
22. Nagino M, Nimura Y, Kamiya J, et al. Preoperative management of hilar cholangiocarcinoma. J Hep Bil Pancr Surg 1995; 2:215–223.
23. Kanai M, Nimura Y, Kamiya J, et al. Preoperative intrahepatic segmental cholangitis in patients with advanced carcinoma involving the hepatic hilus. Surgery 1996; 119:498–504.
24. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995; 21:434–439.
25. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal vein embolization: an appraisal by biliary indocyanine green excretion. Ann Surg 1996; 223:77–83.
26. Sabbà C, Merkel C, Zoli M, et al. Interobserver and interequipment variability of echo-Doppler examination of the portal vein: effect of a cooperative training program. Hepatology 1995; 21:428–433.
27. Yamanaka N, Okamoto E, Kawamura E, et al. Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on

the basis of computed tomography and liver function. Hepatology 1993; 18:79–85.
28. Takeuchi E, Nimura Y, Mizuno S, et al. Ligation of portal vein branch induces DNA polymerases α, δ, and ε in nonligated lobes. J Surg Res 1996; 65:15–24.
29. Lee SS, Hadengue A, Girod C, et al. Reduction of intrahepatic vascular space in the pathogenesis of portal hypertension: *in vitro* and *in vivo* studies in the rat. Gastroenterology 1987; 93:157–161.
30. Schalm L, Bax HR, Mansens BJ. Atrophy of the liver after occlusion of the bile ducts or portal vein and compensatory hypertrophy of the unoccluded portion and its clinical importance. Gastroenterology 1956; 31:131–155.
31. Ozawa K, Takasan H, Kitamura O, et al. Effect of ligation of portal vein on liver mitochondrial metabolism. J Biochem 1971; 70:755–764.
32. Rozga J, Jeppsson B, Bengmark S. Hepatotrophic effect of portal blood during hepatic arterial recirculation. Eur Surg Res 1986; 18: 302–311.
33. Takayasu K, Muramatsu Y, Shima Y, et al. Hepatic lobar atrophy following obstruction of the ipsilateral portal vein from hilar cholangiocarcinoma. Radiology 1986; 160:389–393.
34. Grindlay JH, Bollman JL. Regeneration of the liver in the dog after partial hepatectomy: role of the venous circulation. Surg Gynecol Obstet 1952; 94:491–496.
35. Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 1973; 137:179–199.
36. Nishihara K, Yagyu T, Sakata K, et al. Echo-Doppler evaluation of reverse flow sign in the intrahepatic portal branches after surgery. Ann Surg 1996; 223:370–376.