American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 137-144
DOI: 10.12659/AJCR.907178

Received: 2017.09.18
Accepted: 2017.11.01
Published: 2018.02.07

Intentional Modulation of Portal Venous Pressure by Splenectomy Saves the Patient with Liver Failure and Portal Hypertension After Major Hepatectomy: Is Delayed Splenectomy an Acceptable Therapeutic Option for Secondary Portal Hypertension?

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 56
Final Diagnosis: Secondary portal hypertension
Symptoms: Intractable ascites
Medication: —
Clinical Procedure: Splenectomy
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Major or aggressively-extended hepatectomy (MAEH) may cause secondary portal hypertension (PH), and post-operative liver failure (POLF) and is often fatal. Challenges to prevent secondary PH and subsequent POLF, such as shunt creation and splenic arterial ligation, have been reported. However, these procedures have been performed simultaneously only during the initial MAEH.

Case Report: A 58-year-old female with chronic hepatitis C developed a solitary hepatic cellular carcinoma with portal tumor thrombosis. Blood examination and imaging revealed a decreased platelet count and splenomegaly. Her liver viability was preserved, and collaterals did not develop, and her tumor thrombosis forced us to perform a right hepatectomy from an oncological standpoint. The estimated volume of her liver remnant was 51.8%. A large volume of ascites and pleural effusion were observed on post-operative day (POD) 3, and ascetic infection occurred on POD 14. Hepatic encephalopathy was observed on POD 16. According to the post-operative development of collaterals due to secondary PH, submucosal bleeding in the stomach occurred on POD 37. Though it is unclear whether delayed portal venous pressure (PVP) modulation after MAEH is effective, a therapeutic strategy for recovery from POLF may involve PVP modulation to resolve intractable PH. We performed a splenectomy on POD 41 to reduce PVP. The initial PVP value was 32 mm Hg, and splenectomy decreased PVP to 23 mm Hg. Thereafter, she had a complete recovery from POLF.

Conclusions: Our thought-provoking case is the first successfully-treated case of secondary PH and POLF after MAEH, achieved by delayed splenectomy for PVP modulation.

MeSH Keywords: Hepatectomy • Hypertension, Portal • Indocyanine Green • Portal Pressure • Portal Vein • Shear Strength

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/907178

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Background

Major or aggressively-extended hepatectomy (MAEH) for liver malignancies increases the risk of postoperative liver failure (POLF), which is associated with extended hospital stays and a high frequency of fatal complications [1]. MAEH results in a high mortality rate despite recent advances in surgical devices [2]. An optimal balance between oncological benefit and retention of remnant liver volume is the priority [3], and two-stage hepatectomy and preoperative treatments have attempted to overcome the issue of insufficient liver remnant volume in the field of hepatectomy [4,5].

MAEH often leads to portal hypertension (PH) [6,7], though secondary PH and temporal changes in shear stress in the early postoperative period trigger both liver regeneration and POLF [8–11]. Mechanisms of splenic hypertrophy following MAEH have been investigated [7,11–13]. Redistribution of the total reticuloendothelial system, reduction of the portal bed or hepatic outflow, and changes in shear stress with secondary PH may be related to POLF after MAEH [7,11–13].

Intentional modulation of portal venous pressure (PVP) has been developed as a surgical strategy to address insufficient liver volume, and has been applied mainly in the field of living-donor liver transplantation (LDLT) [14-18]. This is because a harvested graft for LDLT is functionally normal liver, even though the graft size involves inevitable insufficiency [14,17–19]. Optimal portal venous flow (PVF) and PVP will guarantee liver regeneration [14–20], though an easily measurable variable of the portal vein during surgery is PVP and not PVF. Reliable markers for PVF, such as the elimination rate of indocyanine green (ICG), have accuracy but also limitations for intraoperative use [14,19,21]. Although intentional PVP modulation has been clinically developed in the LDLT field [14–18], its actual usefulness to control PVP during MAEH, including ligation of the splenic artery, creation of systemic shunts, and extended bowel resection, have been investigated only in experimental animal models [20,22–30]. Although experimental studies began in the 1950s [20,22–30], the therapeutic significance of intentional modulation of PVP during MAEH continues to be investigated mainly in experimental animal models and not in human surgeries. Moreover, the clinical effects of intentional PVP modulation on POLF have been evaluated only during MAEH [31,32] and not in the post-operative period after MAEH.

No reports have been published of intentional modulation of PVP after MAEH to improve secondary PH and subsequent POLF. Here we report a case of POLF after MAEH, and discuss the therapeutic potential of intentional modulation of PVP by delayed splenectomy. To our knowledge, this patient is the first successfully-treated patient with POLF who recovered from intractable PH via delayed surgery for PVP modulation.

Case Report

A 56-year-old female was followed regularly at our hospital due to her diagnoses of hypertension, diabetes mellitus, and chronic hepatitis C. She had no alcohol drinking history. She received trans-arterial chemoembolization for hepatocellular carcinoma (HCC) of segment 7 of her liver at 56 years of age (4 cm in size, T2 N0 M0 Stage II according to the TNM classification), and underwent radiofrequency ablation for HCC of segment 8 when she was 57 years old (3 cm in size, T1 N0 M0 Stage I according to the TNM classification). When she was 58 years old, HCC occurred in segments 7 and 8 of her liver (Figure 1A), and was accompanied by a tumor thrombosis in the intrahepatic portal vein. A conventional blood examination showed normal ranges of all variables except for a low platelet count of $5.9\times10^4/\mu L$. The serum level of protein induced by vitamin K absence or antagonist-II was increased. On ICG kinetics, the elimination values of R15 and k were 16.3 and 0.121, respectively. The uptake ratio of the liver to the heart plus the liver at 15 minutes was 0.85 on technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin liver scintigraphy. The Child-Pugh score was 5 points. Hence, liver viability seemed to be preserved for MAEH. Dynamic computed tomography revealed splenomegaly without any development of collateral circulation. Splenomegaly could explain the decreased platelet count, though imaging did not reveal the typical findings of liver cirrhosis and associated PH. HCC invaded the intrahepatic portal vein, and tumor thrombosis was detected (Figure 1B). Because the tumor thrombosis in the intrahepatic portal vein reached nearly the portal branch of the posterior segment, the HCC forced us to pursue a right hepatectomy for its oncological benefit. The estimated volume of the liver remnant after right hepatectomy was 51.8% based on volumetric analysis (Synapse Vincent, Fujifilm, Tokyo, Japan), and the oncological margin for the tumor thrombosis was guaranteed based on three-dimensional analysis (Figure 1C). A right hepatectomy was performed with macroscopic resection. The operative time and blood loss were 348 minutes and 1,000 mL, respectively. A platelet transfusion (250 mL) was required during surgery. The main HCC had a diameter of 4 cm, and the resected specimen involved tumor thrombosis (Figure 1D). Histopathological findings clearly revealed portal venous invasion, and her HCC was categorized as T3b N0 M0 Stage IIIB according to the TNM classification [33]. The liver parenchyma was assessed as F4 according to the scoring system for liver fibrosis [34].

The post-operative course is summarized in Figure 2. A pleural effusion was drained on postoperative day (POD) 3. A large amount of ascites and pleural effusion were observed, and ascetic infection by methicillin-resistant staphylococcus aureus was detected on POD 14. Hepatic encephalopathy was observed on POD 16. Likely due to the post-operative development of

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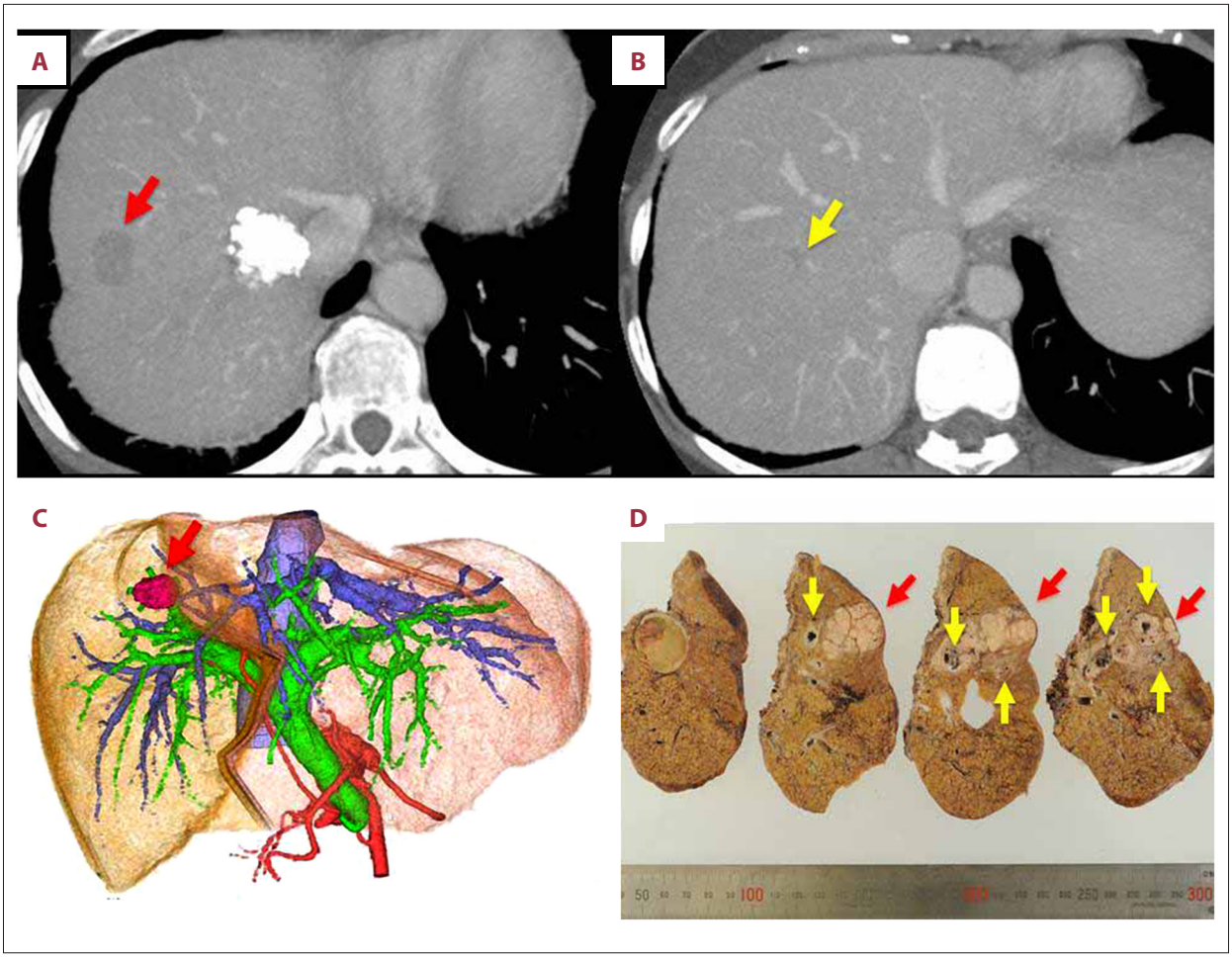

Figure 1. (**A, B**) Findings of dynamic computed tomography are shown. The main tumor (red arrow) was accompanied by a tumor thrombosis in the intrahepatic portal vein (yellow arrow). (**C**) The main tumor (red arrow) and liver remnant volume were evaluated based on three-dimensional images. (**D**) The main tumor (red arrow) and tumor thrombosis (yellow arrow) were observed in the resected specimen.

collateral vessels from secondary PH, submucosal bleeding in the stomach was endoscopically treated on POD 37.

Symptoms due to POLF were refractory, and the patient's secondary PH became intractable. Time passed after the MAEH, and it was unclear whether delayed PVP modulation after MAEH would be effective. However, the therapeutic strategy for recovery from POLF should involve PVP modulation to resolve secondary PH (Figure 3A). We believed that a better post-operative recovery without secondary PH was required for liver regeneration, which was important for recovery from POLF (Figure 2A). Finally, we performed a splenectomy on POD 41 to reduce PVP, as we had no other way to resolve POLF and secondary PH. With careful consideration of the possibility of hyperammonemia, the creation of a systemic shunt, such as a portocaval shunt or splenorenal shunt, was eliminated as a therapeutic option to decrease PVP. The operative time was four hours and the blood loss was 1,450 mL. Transfusions of red blood cells (1,400 mL), plasma (2,160 mL), and platelets (250 mL) were required during surgery. A catheter for PVP measurement was inserted from the jejunal vein, and the catheter tip was placed in the trunk of the portal vein (Figure 3B). The initial value of PVP was 32 mmHg, and splenectomy led to a decrease in PVP to 23 mmHg. A tube for enteral nutrition was placed to stimulate postoperative liver regeneration.

Plasma exchanges were repeated for two days after the splenectomy, and continuous hemodiafiltration was required for six days starting on POD 42. As shown in Figure 2, the ascites decreased after splenectomy, and two intraperitoneal drains were removed on PODs 77 and 87, respectively. Enteral nutrition was used post-operatively as soon as possible after splenectomy. The patient achieved a complete recovery from POLF and secondary PH, and was discharged on POD 140 after MAEH. She is in good health.

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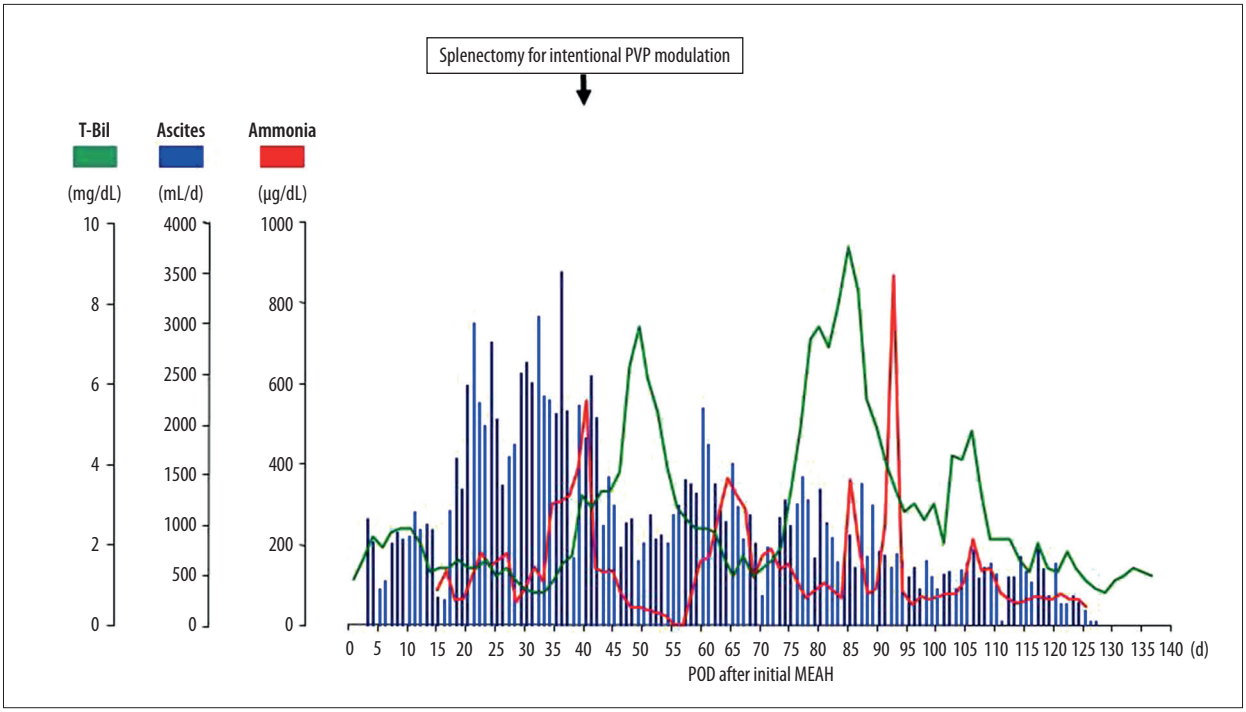

Figure 2. Clinical course after initial MAEH. MAEH – major or aggressively-extended hepatectomy; POD – post-operative day; PVP – portal venous pressure; T-Bil – total bilirubin.

Discussion

Shear stress is affected by certain diseases and conditions [6,7,35,36]; it slowly decreases in liver cirrhosis and primary PH [35,36], and rapidly increases after MAEH and during cold ischemia/warm reperfusion injury after LDLT [6,7]. Because flow to the portal bed is drastically reduced during MAEH, shear stress increases immediately after MAEH. Thus, secondary PH occurs starting in the early postoperative period after MAEH [6,7], and liver regeneration and POLF are also triggered in the early period following surgery [21]. In this case, we planned MAEH at the advanced stage of HCC in this patient. As a treatment plan for advanced HCC, the role of traditional treatment option, such as sorafenib, is currently challenged [37]. Treatment plan should be carefully considered in such patients.

The portal system is complex, particularly in cirrhotic patients [38,39]. Unpredictable systemic hemodynamics and splanchnic flow are also observed in some situations with PH, such as in the post-operative state after MAEH. Once secondary PH develops after MAEH or liver cirrhosis, post-operative persistence of a characteristic systemic hemodynamic state (i.e., hyperdynamic state) is crucial to maintain optimal PVF and subsequent liver regeneration [38,39]. A subtle disorder of the systemic hemodynamic state results in decreased PVF and subsequent POLF [38,40–43]. The small intestine is one of targets of PH [44], and therefore MAEH may cause a large amount of ascites post-operatively [45]. Intractable ascites may involve not only albumin but also coagulation factors, and severe edema and refractory hemorrhage may occur. Moreover, conditions with PH will disturb liver regeneration [46]. Increased intraperitoneal pressure due to intractable ascites reduces PVF, leading to ischemia and portal venous congestion [46]. Overall, post-operative maintenance of an optimal systemic hyperdynamic state that allows for sufficient PVF may be difficult in the setting of secondary PH [14,19,38–43].

Outflow blockage causes secondary PH after MAEH [47]. Though outflow blockage due to hepatic venous reconstruction may occur in LDLT, hepatic venous outflow is guaranteed in MAEH. However, relatively rapid hypertrophy of the asymmetric liver remnant may have led to twisting or external compression of the hepatic vein by the hypertrophic at two weeks after MAEH. The signs and symptoms of hepatic venous outflow blockage frequently present with varied clinical scenarios, including new-onset ascites, variceal bleeding, splenomegaly, abnormal liver function tests, or renal insufficiency. A simple question arose: if the outflow blockage occurred, did we miss the diagnosis and possible proper treatment? In this case, we evaluated the patency of hepatic veins, by three-dimensional image (Synapse Vincent, Fujifilm) and Doppler ultrasound. Three-dimensional image did not reveal hepatic venous stenosis, and Doppler ultrasound showed three-phase wave with an enough velocity, not flat flow. Hence, image studies did not reveal the congestion of remnant liver which might cause secondary PH in our case (Figure 4). When the patient is suspected

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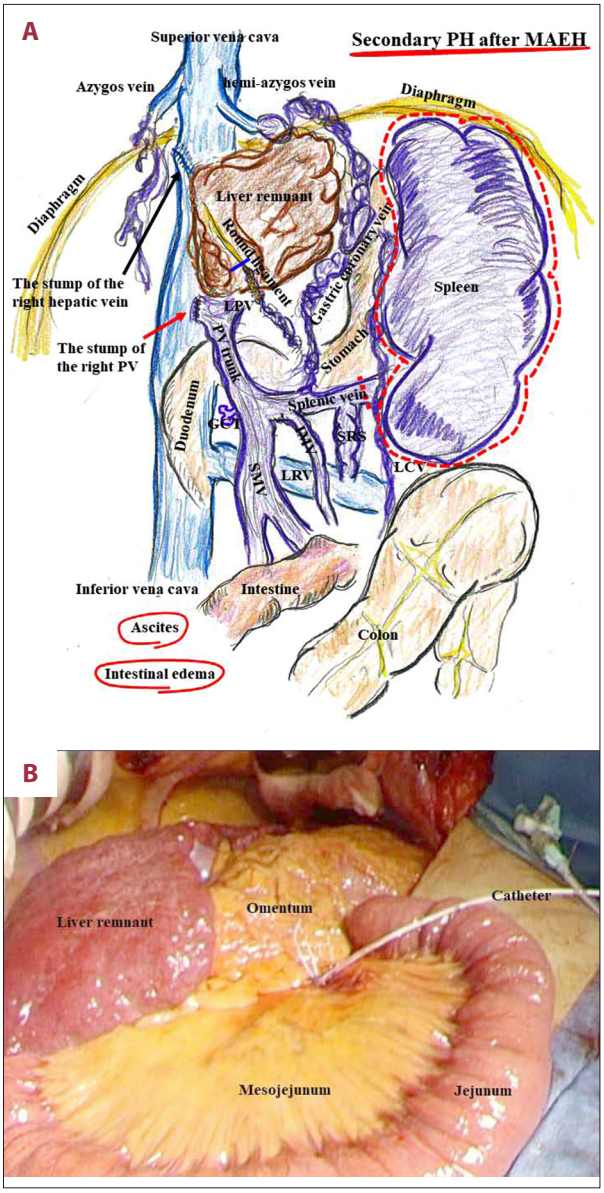

Figure 3. (**A**) Schema of intentional PVP modulation by splenectomy for secondary PH after MAEH. The round ligament (blue line) was ligated during initial MAEH. Secondary PH after MAEH caused massive ascites and intestinal edema. Splenectomy (dotted line) decreased PVP. (**B**) PVP was measured via catheter. GCT – gastrocolic trunk; IMV – inferior mesenteric vein; LCV – left colic vein; LPV – left portal vein; LRV – left renal vein; MAEH – major or aggressively-extended hepatectomy; PH – portal hypertension; PV – portal vein; SMV – superior mesenteric vein; SRS – splenorenal shunt; PVP – portal venous pressure.

of having hepatic outflow obstruction based on clinical findings and image studies, cavography with hepatic venography must be performed to consider adequate treatments, such as a balloon dilatation and a metallic stent placement.

Hepatic viability should be considered in MAEH [3], though liver function is restored by a normal liver graft in LDLT [21]. Some conditions, including advanced age, obesity, and PH, will disturb liver regeneration after MAEH [2,48]. As previously described, optimal PVF guarantees liver regeneration after MAEH [49], and even a subtle disorder of the systemic hemodynamic state can result in POLF [38,40–43]. An attempt should be made to maintain an optimal patient condition post-operatively to promote successful recovery after MAEH.

Methods to prevent POLF after MAEH, such as the creation of a splenorenal shunt, selective ligation of the splenic artery, and an ingenious reconstruction of the hepatic vein have been reported [31,32,46,50]. However, all of these procedures have been performed only during the initial MAEH procedure and not in the post-operative period following MAEH. Prior to our study, it was unclear whether post-operative PVP modulation (i.e., not a simultaneous modulation during initial MAEH) would be effective. To our knowledge, our patient is the first successfully-treated case of POLF who recovered from secondary PH after MAEH, via delayed additional surgery for PVP modulation.

PVF is an ordinary wave and not a pulse wave [17,18,20,21,51], and therefore, an adequate cross-sectional area of the monitoring catheter is required to reflect PVP accurately [17,18,20,21,51]. To continuously monitor PVP during surgery, a single-lumen central venous catheter (Argyle; Medtronic, Minneapolis, MN, USA) was employed [17,18,20,21,51], and the catheter diameter was either 16 or 18 gauge [17,18,20,21,51]. We used a pediatric central venous catheter with a smaller cross-sectional area in this case, and PVP value seemed to be higher than the estimated PVP value based on intraoperative findings and impressions.

A simple question arose from our findings: what is the cutoff level for optimal PVP during surgery? A cutoff level of 15.5 mm Hg has been documented in the normal liver during LDLT [14,15]. A final PVP value of ≤15 mm Hg during surgery may be a key for successful MAEH, but further studies are required to determine the optimal cutoff level of PVP for healthy recovery following MAEH. Unfortunately, we did not perform continuous monitoring and intentional modulation of PVP in our patient's initial MAEH procedure, which may have been able to prevent or predict POLF.

The behavior of ICG during surgery is interesting and clearly has potential to be beneficial during surgery [14,19]. Currently, ICG kinetics can be non-invasively estimated during surgery [19,52]. ICG elimination rate (i.e., *k*ICG) is typically proportional to PVF [14,19]. However, we have encountered patients with smaller liver volumes who had improved *k*ICG values despite decreased PVF during surgery [14,19]. Therefore, we believe that ICG kinetics, such as the *k*ICG value, can accurately

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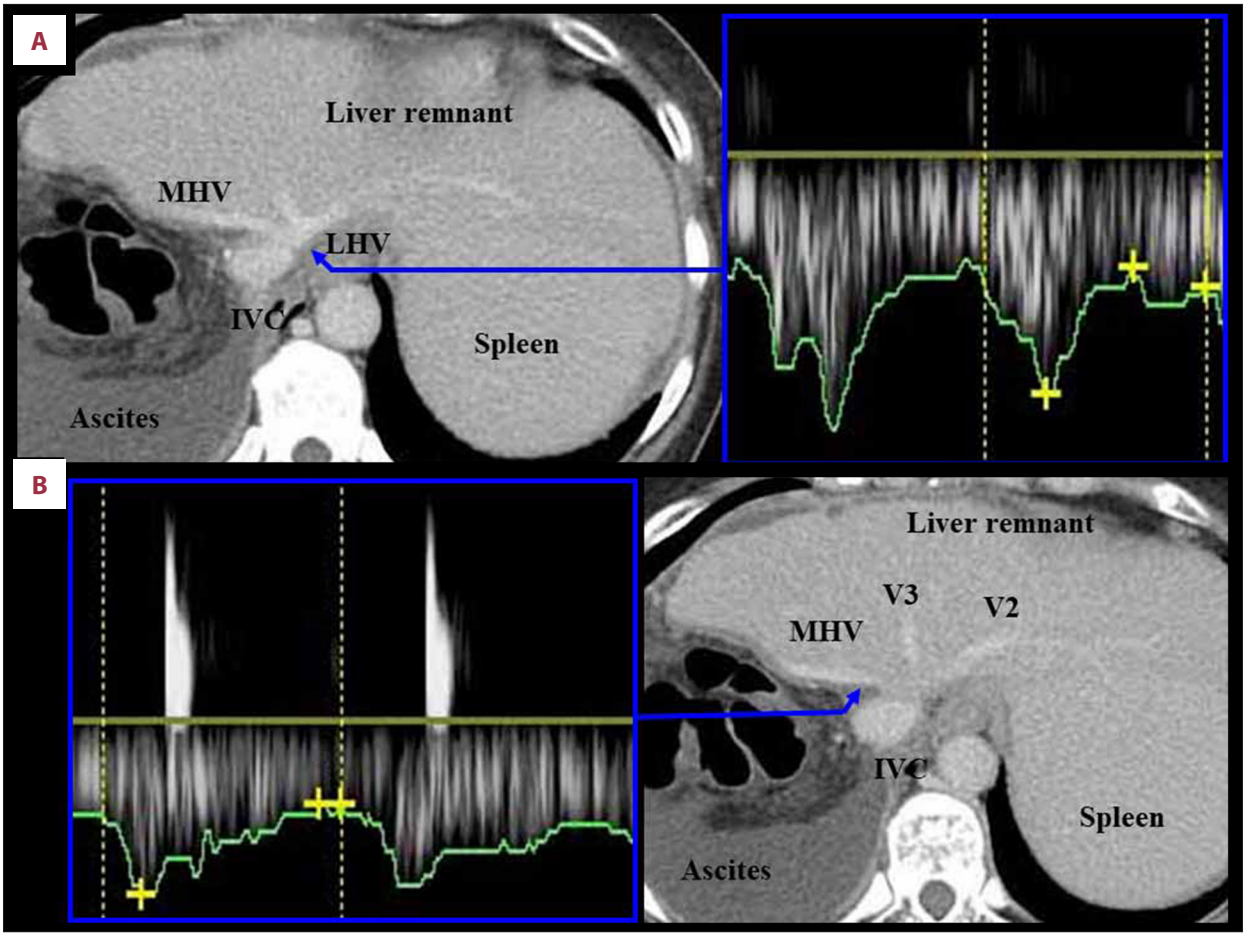

Figure 4. (**A**) CT image did not reveal hepatic venous stenosis in the LHV, and Doppler ultrasound showed a good wave form with an enough velocity (blue arrow). (**B**) CT image did not reveal hepatic venous stenosis in the MHV, and Doppler ultrasound showed a good wave form with an enough velocity (blue arrow). CT – computed tomography; IVC – inferior vena cava; LHV – left hepatic vein; MHV – middle hepatic vein; V2 – the hepatic vein for segment 2; V3 – the hepatic vein for segment 3.

indicate an optimal setup of PVF during surgery and can predict POLF [14,19]. It is likely that optimal PVF can be evaluated by using the *k*ICG value during MAEH. ICG kinetics accurately reflect PVF, and intentional PVP modulation during MAEH should be performed until intraoperative confirmation of an appropriate *k*ICG value based on the preoperative estimated volume of remnant liver. From the viewpoint of optimal PVF after MAEH, unfortunately we did not check the final value of *k*ICG during the initial MAEH procedure. This may have prevented or predicted POLF, as the cutoff level of *k*ICG in the normal liver has been demonstrated to be $3.12–4.00\times10^{-4}$/liver weight (g) [14,19]

In PH, surgical treatment using an extrahepatic systemic shunt, such as a portocaval or splenorenal shunt, may result in better post-operative quality of life if it is performed in carefully selected PH patients [53–55]. To prevent POLF, surgical approaches such as the creation of a splenorenal shunt, selective ligation of the splenic artery, and reconstruction of the hepatic vein had been attempted during initial MAEH, but not in post-operative period after MAEH [31,32,46,50]. Splenectomy can lead to decreased PVP [14,15,17–19] even after MAEH (Figure 3A). It remains unclear whether post-operative PVP modulation is effective, as liver regeneration begins in the early post-operative period [21]. However, we have shown that a delayed surgical approach for intentional PVP modulation may have the therapeutic potential to prevent or treat progressive POLF with secondary PH after MAEH.

Conclusions

To our knowledge, this is the first case of successful treatment for secondary PH and POLF after MAEH, achieved by delayed splenectomy for PVP modulation. We hope our thought-provoking case will be informative and provide inspiration for further developments in the field of hepatobiliary surgery.

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Acknowledgements

The report was approved by the Institutional Review Board of Tenriyorozusoudanjyo Hospital. The patient involved in this report provided her written informed consent authorizing the use and disclosure of her protected health information. None of the authors received financial support for this report. The authors have no conflicts of interest. Y. Takamatsu and T. Hori contributed equally to this work. Schema was written by T. Hori.

Conflict of interest

None.

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