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Postreperfusion Syndrome Presenting as Posttransplant Portal Hypertension due to Prolonged Elevation of Pulmonary Vascular Resistance and the Role of Nitroglycerin in Diagnosis and Treatment: A Case Report of Budd-Chiari Syndrome

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Postreperfusion syndrome is one of the responsible mechanisms of portal hypertension in patients undergoing liver transplantation. And post-transplant portal hypertension causes graft dysfunction. Postreperfusion syndrome is characterized by a decrease in arterial pressure and cardiac output, and an increase in central venous pressure, pulmonary artery pressure, and pulmonary vascular resistance that occurs after the release of the portal vein clamp. Although early recovery from postreperfusion syndrome is desired, there is a little medication therapy such as the administration of calcium chloride, sodium bicarbonate, and beta-agonist for postreperfusion syndrome. We present a case of postreperfusion syndrome manifested as post-transplant portal hypertension and reversed after nitroglycerin administration. A 49-year-old Asian woman was scheduled for liver transplantation because of Budd-Chiari syndrome. After portal vein reperfusion, she experienced severe postreperfusion syndrome. Administration of ephedrine and calcium restored arterial pressure; however, pulmonary artery pressure, pulmonary vascular resistance, and central venous pressure elevations were sustained, causing right ventricular overload. This condition did not improve after hepatic artery reperfusion, and caused post-transplant portal hypertension. After nitroglycerin administration, pulmonary vascular resistance and central venous pressure decreased, mean arterial pressure increased, right heart contractility recovered, and portal hypertension disappeared. Hemodynamic improvement by nitroglycerin administration helped in diagnosing postreperfusion syndrome and avoiding unnecessary splenectomy. If portal vein pressure increases after liver transplantation, the change in hemodynamic parameters by nitroglycerin administration should be assessed, which will lead to accurate diagnosis and appropriate treatment. Furthermore, postreperfusion syndrome should be listed as a differential diagnosis of post-transplant portal hypertension.

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Introduction

Portal hypertension after living-donor liver transplantation can cause graft dysfunction (Smyrniotis et al. 2002; Yagi et al. 2005). Some studies recommend reducing portal venous flow via splenectomy or splenic artery ligation to prevent liver graft injury in patients with a significantly high portal venous pressure (PVP) after reperfusion (Ito et al. 2003; Yagi et al. 2006; Ogura et al. 2010). However, fluid shift due to reperfusion, bleeding, and postreperfusion syndrome (PRS) often result in severe hemodynamic instability during liver transplantation (Siniscalchi et al. 2016;

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Manning et al. 2020). Given that PVP is affected by various factors, it is important to determine the cause of post-transplant PVP elevation. The present report discusses a case of PRS manifested as post-transplant portal hypertension, which was induced by sustained elevation of pulmonary vascular resistance (PVR) and right ventricular afterload. Improvements in hemodynamic parameters following nitroglycerin administration also aided in the diagnosis and treatment of PRS.

Case Presentation

Preoperative course

A 49-year-old Asian woman (height 163 cm; weight 59 kg) was admitted to our institution because of severe ascites. She was diagnosed with Budd-Chiari syndrome. Because her condition was difficult to treat with interventional radiology, she was scheduled for transplantation of the right hepatic lobe of her son. Electrocardiography and echocardiography revealed no right ventricular overload. Coronal-view reconstructive contrast-enhanced abdominal computed tomography revealed hepatic vein occlusion and inferior vena cava narrowing (Fig. 1).

Liver transplantation

The patient underwent intraoperative electrocardiography and peripheral oxygen saturation and invasive arterial pressure monitoring. General anesthesia was induced with 80 mg of propofol, 0.3 μg/kg/min of remifentanil, and 50 mg of rocuronium using a rapid induction and intubation technique. Next, a transesophageal echocardiography (TEE) probe was inserted. A quad-lumen central venous catheter for drug administration, a pulmonary artery catheter for hemodynamic monitoring, and a sheath introducer for massive bleeding were placed via the right internal jugular vein. Additionally, another sheath introducer was placed via the left internal jugular vein in case a veno-venous bypass was necessitated. General anesthesia was maintained with 2% of sevoflurane, 0.1 μg/kg/min of remifentanil, and intermittent administration of rocuronium. Circulation was supported with 0.2-1.5 mg/h of phenylephrine, 0.017-0.033 μg/kg/min of noradrenaline, 2 mg/h of nicorandil, and 0.01-0.02 μg/kg/min of carperitide. At the beginning of the surgery, the mean pulmonary artery pressure (mPAP) was 18 mmHg. During dissection, a large amount of ascites was drained, and it took several hours to break the adhesion. Ten hours after the surgery began, the entire liver was removed. Subsequently, inferior vena cava (IVC) and the hepatic veins of the liver allograft were reconstructed using autologous superficial femoral vein (Fig. 2A). Next, the hepatic veins were anastomosed with the IVC (Fig. 2B), followed by portal anastomosis. Intraoperatively, a veno-venous bypass was not required. Just prior to portal vein reperfusion, the patient's mean arterial pressure (mAP) was 80 mmHg, mPAP was 19 mmHg, and central venous pressure (CVP) was 8 mmHg with infusion of norepinephrine (0.02 μg/kg/min). Immediately after portal vein reperfusion, the mAP decreased to 48 mmHg, mPAP increased to 37 mmHg, and CVP increased to 22 mmHg. Ephedrine (8 mg) and calcium chloride (0.4 g) were injected to treat the PRS, following which the mAP rapidly recovered, but the mPAP and CVP remained elevated. We immediately corrected hypercarbia and hypoxia. However, the elevation of mPAP and CVP was sustained. We then explored the causes of pulmonary hypertension such as left heart failure, or air embolism. TEE revealed the hyperkinetic left ventricle, distended right ventricle without wall motion abnormality, and no air bubbles or embolus in the cardiac chambers and the pulmonary artery. The hemodynamic parameters before and after portal vein reperfusion are shown in Fig. 3A. After hepatic artery reperfusion, a portal vein catheter was inserted via the superior mesenteric vein, and the PVP was measured to rule out hepatic vein and/or IVC stenosis and portal hypertension. If portal hypertension had been observed at this point, we would have performed splenectomy or reconstruction of the veins. The PVP was greater than 20 mmHg, and the mPAP and CVP remained elevated. Additionally, TEE also indicated that the sustained right ventricular distension without wall motion abnormality. We considered that the PVP elevation was due to a right ventricular failure following a residual increase in PVR induced by PRS. Therefore, we intravenously injected nitroglycerin (0.2 mg) to decrease the PVR and right ventricular afterload. Shortly thereafter, the mPAP, PVR, CVP, and right ventricular diameter decreased, and the mAP increased. Subsequently, the PVP dropped from 20 mmHg to 12 mmHg. The hemodynamic parameters were stabilized with continuous infusion of nitroglycerin (0.4 μg/kg/min), and the PVP did not increase

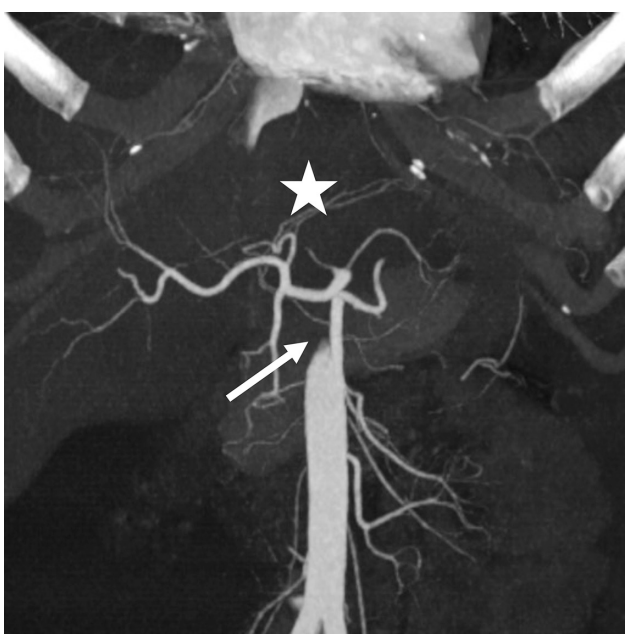

Fig. 1. Coronal-view reconstructive contrast-enhanced abdominal computed tomography image.
(☆): Hepatic vein occlusion, (→): Inferior vena cava narrowing.

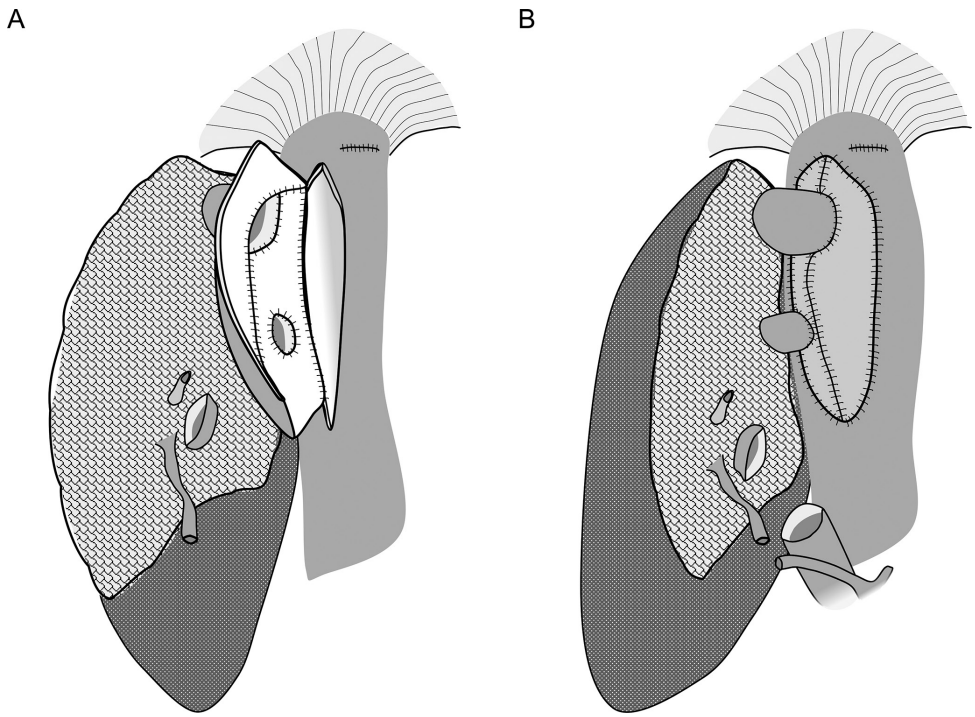

Fig. 2. Schematic diagrams demonstrating the reconstruction of the inferior vena cava (IVC) and hepatic veins. (A) The narrowing section of the IVC was incised vertically and the patch with the hepatic veins was made from the superficial femoral vein grafts. (B) Then the patch was interposed to the vertical incision of the IVC.

thereafter. Therefore, splenectomy was not performed. The hemodynamic parameters before and after the administration of nitroglycerin are illustrated in Fig. 3B and summarized in Table 1. Next, Roux-en-Y choledochojejunostomy for biliary reconstruction was performed. The patient's abdomen was then closed and the surgery completed. The duration of surgery and anesthesia were 1,058 and 1,200 min, respectively. Blood loss and urine output were 9,437 g and 813 mL, respectively. The patient was administered 7,424 mL of crystalloid, 3,754 mL of 5% albumin, 3,080 mL of packed red blood cells, 4,320 mL of fresh frozen plasma, 180 mL of cryoprecipitate, and 400 mL of platelet concentrate.

Postoperative course

The patient was transferred to the intensive care unit while intubated and sedated with 4 mg/kg/h of propofol. On the 1st postoperative day (POD), nitroglycerin infusion was discontinued, while the mPAP remained unchanged. On the 2nd POD, the patient was weaned from the ventilator. The transplanted liver showed good function, and the patient was moved to the general ward on the 6th POD. Eventually, the patient was discharged on foot on the 31st POD.

Written informed consent on the publication of the case report was obtained from the patient.

Discussion

We identified two important clinical lessons in this study: (1) PRS after liver transplantation can manifest as a prolonged increase in PVR and right ventricular afterload, and cause post-transplant portal hypertension. (2) Improvement in hemodynamic parameters after nitroglycerin administration is useful for diagnosing and correcting this condition.

PRS can lead to portal hypertension in patients undergoing liver transplantation. PRS is characterized by severe hemodynamic disturbance that typically occurs after the release of the portal vein clamp; however, the underlying pathophysiological mechanism remains unclear (Sahmeddini et al. 2022). Patients with PRS usually experience a transient decrease in mAP, heart rate, systemic vascular resistance, and cardiac index, and an increase in CVP, mPAP, and PVR (Molenaar et al. 2001; Siniscalchi et al. 2013). In general, PRS during liver transplantation is defined when mean arterial pressure (mAP) decreases by more than 30% relative to the value at the end of the anhepatic phase and lasts for at least 1 min within the first 5 min after reperfusion (Aggarwal et al. 1987). Fukazawa et al. (2014) reported that patients with PRS initially experience sudden hypotension after portal vein reperfusion, which is followed by a period of gradual blood pressure decline until hepatic artery reperfusion and sustained hemodynamic recovery occurs. In addition, Xu et al. (2012) evaluated right ventricular function during liver transplantation and found that the right ventricular ejection fraction significantly reduced from the start of the surgery to inferior vena cava clamping and 5 min after portal vein reperfusion. Although early recovery from postreperfusion syndrome is desired, there is a little medication therapy such as the

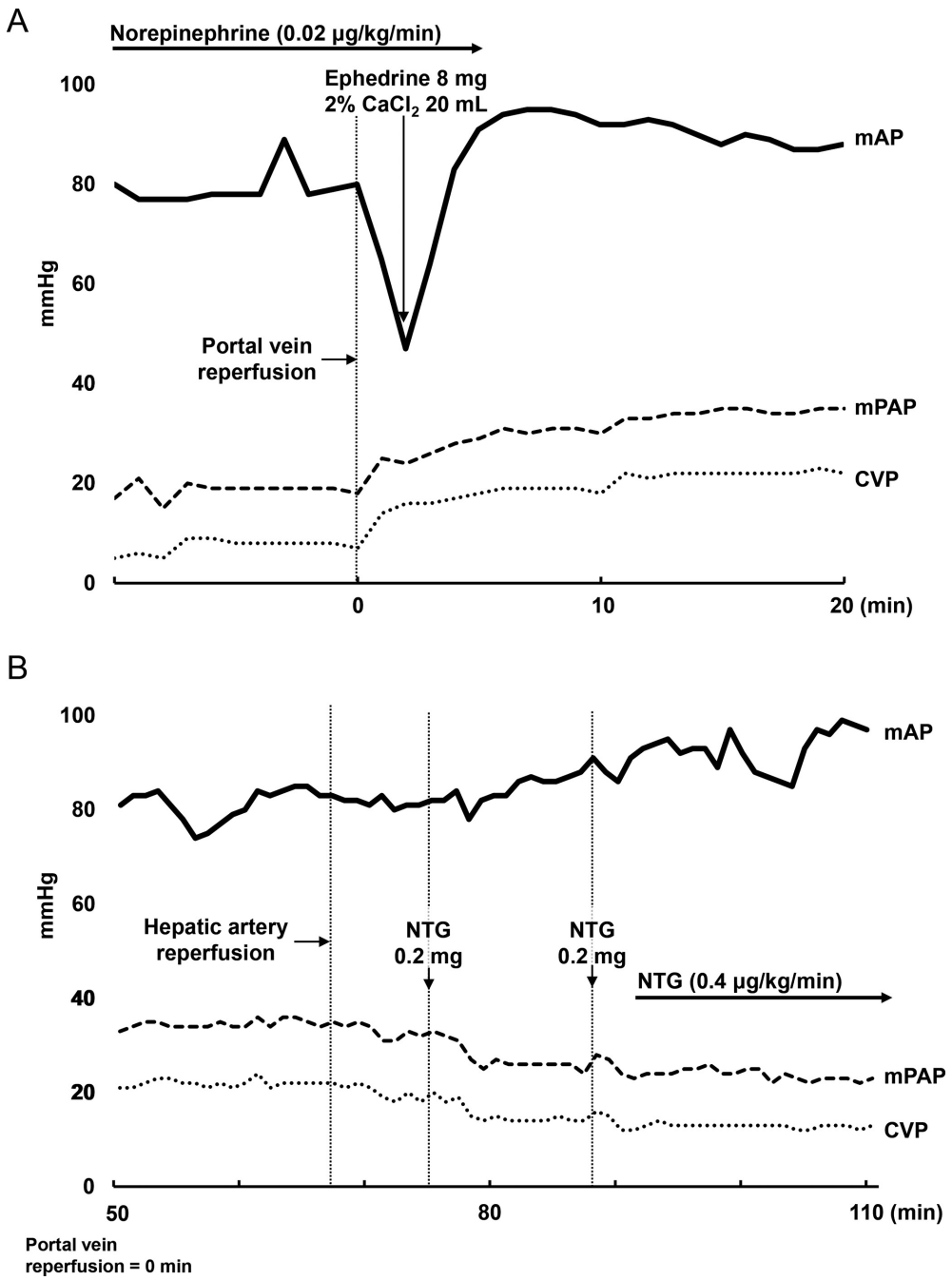

Fig. 3. Time course of hemodynamic parameters before and after portal vein reperfusion (A) and before and after nitroglycerin administration (B).
$CaCl_2$, calcium chloride; CVP, central venous pressure; mAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; NTG, nitroglycerin.

administration of calcium chloride, sodium bicarbonate, and beta-agonist for postreperfusion syndrome (Wray et al. 2020). Our patient exhibited the typical hemodynamic changes of PRS, such as a rapid decrease in mAP and an increase in mPAP, PVR, and CVP. We diagnosed the hemodynamic instability as PRS because it met the diagnostic criteria (Aggarwal et al. 1987). Administration of ephedrine and calcium led to the recovery of mAP; however, the PVR remained elevated, which induced elevation of right ventricular afterload. Unlike in patients in previous reports, this condition did not improve after hepatic artery reperfusion, causing post-transplant portal hypertension.

Nitroglycerin administration was useful for differential diagnosis and improving hemodynamics. Portal hypertension after liver transplantation causes graft damage. Therefore, it is important to control the PVP during the perioperative period. Splenectomy can be used to reduce portal vein blood flow and avoid small-for-size syndrome,

Table 1. Hemodynamic parameters at 10 minutes before and 10 minutes after nitroglycerin administration of this case, and hemodynamic conditions, and expected responses of mean arterial pressure and portal vein pressure to nitroglycerin administration in disorders causing posttransplant portal vein pressure elevation.

	CI	mPAP	CVP	PVRI	SVRI	mAP	PVP
Reference ranges	2.5-4.0	10-20	3-8	< 255-285	1,970-2,390	70-105	5-10
Units	($L•min^{-1}•m^{-2}$)	(mmHg)	(mmHg)	(dyne•sec $•cm^{-5}•m^2$)	(dyne•sec $•cm^{-5}•m^2$)	(mmHg)	(mmHg)
This case							
Before NTG	4.2	32	20	531	1,217	82	20
After NTG	4.1	22	13	300	1,506	92	12
Disorders causing posttransplant PVP elevation						Expected responses to NTG	
Residual PVR elevation for PRS	→~↓	↑	↑	↑	↓	↑	↓
Small-for-size syndrome*	→~↓	→	→	→	→	↓	→
Excessive infusion	↑	↑	↑	→~↓	↓	→~↓	→~↓
Hyperdynamic state with cirrhosis	↑	↑	↑	↓	↓	→~↓	→

*Small-for-size syndrome occurs when the implanted graft is small compared to the recipient's needs. The excessive portal venous flow may be a potential mechanism.
CI, cardiac index; CVP, central venous pressure; mAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; NTG, nitroglycerin; PRS, postreperfusion syndrome; PVP, portal vein pressure; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

but it may result in immunosuppression. Therefore, the decision to perform splenectomy should be made with caution. Elevation of post-transplant PVP is seen in small-for-size syndrome, excessive infusion and blood transfusion, stenosis of the reconstructed vein, hepatopulmonary syndrome, hyperdynamic state associated with liver cirrhosis, and right coronary artery ischemia. We believe that a residual increase in PAP and PVR due to PRS, as was seen in our case, should be differentiated from other causes of post-transplant portal hypertension. Table 1 summarizes the characteristics of the hemodynamic parameters and expected response to nitroglycerin administration for various conditions considered during the differential diagnosis of post-transplant PVP elevation. In our patient, PAP, PVR, and CVP decreased, mAP increased, and PVP improved rapidly from 20 to 12 mmHg. Changes in hemodynamic parameters after nitroglycerin administration can guide the diagnosis and treatment of elevated PVR in PRS and can help avoid unnecessary splenectomy. Future studies should be needed to investigate the generalizability of nitroglycerin administration for diagnosis and treatment of PRS. Additionally, intravenous milrinone and epoprostenol, and inhalational nitric oxide might be alternative options for the patients suffered with severe systemic hypotension and elevated PVR due to PRS. However, the differential diagnosis of post-transplant portal hypertension can be difficult owing to the complexity and coexistence of several underlying mechanisms. Anesthesiologists should base their diagnosis on a combination of nitroglycerin-induced hemodynamic parameter changes and TEE findings.

In conclusion, PRS during liver transplantation should be considered during the differential diagnosis of post-transplant portal hypertension. If PVP increases after transplantation, the change in hemodynamic parameters after nitroglycerin administration should be assessed, which will result in accurate diagnosis and appropriate treatment. Clinicians should be aware that PRS can manifest as a prolonged increase in PVR and right ventricular afterload, and induce post-transplant PVP elevation. Future studies should investigate the pathophysiology of PRS and causes of increased PVR during liver transplantation.

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Conflict of Interest

The authors declare no conflict of interest.

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