



## Postreperfusion syndrome during liver transplantation

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As surgical and graft preservation techniques have improved and immunosuppressive drugs have advanced, liver transplantation (LT) is now considered the gold standard for treating patients with end-stage liver disease worldwide. However, despite the improved survival following LT, severe hemodynamic disturbances during LT remain a serious issue for the anesthesiologist. The greatest hemodynamic disturbance is postreperfusion syndrome (PRS), which occurs at reperfusion of the donated liver after unclamping of the portal vein. PRS is characterized by marked decreases in mean arterial pressure and systemic vascular resistance, and moderate increases in pulmonary arterial pressure and central venous pressure. The underlying pathophysiological mechanisms of PRS are complex. Moreover, risk factors associated with PRS are not fully understood. Rapid and appropriate treatment with vasopressors, volume replacement, or venesection must be provided depending on the cause of the hemodynamic disturbance when hemodynamic instability becomes profound after reperfusion. The negative effects of PRS on postoperative early morbidity and mortality are clear, but the effect of PRS on postoperative long-term mortality remains a matter of debate.

**Key Words:** Hemodynamic disturbance, Liver transplantation, Reperfusion.

### Introduction

The first liver transplantation (LT) was attempted in 1963 [1], and the first successful LT was performed in 1967 by Dr. Starzl at the University of Pittsburgh [2,3]. However, 1-year survival following LT remained below 20% during the 1970s, until immunosuppression with cyclosporine was introduced in the early 1980s [3,4]. Improved surgical and graft preservation techniques

and advances in immunosuppression have significantly increased survival following LT and have led to the gradual adoption of LT worldwide [5]. LT is now the gold standard treatment for patients with end-stage liver disease worldwide [6]. Although contemporary survival following LT exceeds 85% at 1 year and 70% at 5 years, severe hemodynamic disturbances during LT remain a serious issue for the anesthesiologist and seem to be related to poor outcomes [5]. The greatest hemodynamic event during LT occurs at the graft reperfusion of the donated liver. This hemodynamic change has been called postreperfusion syndrome (PRS). This paper focuses on recent advances in the management of PRS during LT.

### Definition and Incidence

PRS was first explained by Aggarwal et al. [7] in 1987 as transient, profound cardiovascular collapse that occur following reperfusion of the grafted liver during LT. They reported that this severe cardiovascular disturbance was associated with progressive bradycardia and dysarrhythmia, decreased mean arterial pressure (MAP) and systemic vascular resistance (SVR)

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and increased pulmonary arterial pressure (PAP), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP). Although the etiology was unknown, it was attributed to acute acidosis, hyperkalemia, and hypothermia. PRS occurred 1–5 min after reperfusion of the grafted liver, and incidence was about 30% [7]. Therefore, PRS is considered to have occurred when profound hemodynamic instability, such as persistent hypotension, asystole, or severe dysarrhythmia, happen after reperfusion of the grafted liver during LT. In general, PRS during LT is defined when 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 of the grafted liver [8–10].

The incidence of PRS has not decreased despite improvements in operative techniques and anesthetic management. Results of early studies showed that the incidence of PRS during LT was 8–30% [11–14]. Studies published later showed a wide ranging incidence of PRS (12–50%) [9,10,15–19]. Among recent studies, some have reported PRS incidence of as high as 50% [10,19]. This diversity in PRS prevalence among studies is believed to be caused by differences in the definition of PRS, treatment strategy, or surgical technique. For example, the definition of PRS differs across some studies: absolute MAP < 60 mmHg together with classical hemodynamic disturbance within 5 min after reperfusion [14] or a relative decrease in MAP > 30% below the baseline and a tendency to continue decreasing [19]. Although the severity of PRS tends to be much greater during cadaveric donor LT than during living donor LT, the incidence of PRS between these two groups does not differ [19]. In a Korean LT center study, the incidence of PRS during living donor LT was about 35% [20], which is not much different than the aforementioned incidence of PRS.

## Pathophysiology

The underlying pathophysiological mechanisms of PRS are complex and not fully understood, but arise from a variety of factors, such as metabolic acidosis, hyperkalemia, hypocalcemia, hypothermia, air embolism, and vasoactive substances released at the time of reperfusion [1,13,21–25]. Although the exact mechanisms are unknown, the severe hemodynamic disturbance that occurs during PRS has been attributed to the response of the cardiovascular system to the release of vasoactive substances from the grafted liver and the immune system of the patient after reperfusion [8,26]. Thus, common contributors to PRS are bradycardia, reduced cardiac contractility, and decreased SVR [8].

When the portal vein is unclamped to reperfuse the graft during LT, many proinflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL)-1, IL-2, and

IL-8 are released from the grafted liver into systemic circulation [27]. Other proinflammatory cytokines, such as kallikrein and bradykinin, chemokines, and activated complement are also produced by the LT recipient in response to reperfusion of the grafted liver [8]. Release of TNF- $\alpha$  from the donor graft is predictive of PRS as well as postoperative complications [28]. However, many other proinflammatory cytokines, including IL-1b, IL-2, and IL-8, which increase in the flush blood from the donor graft, are not correlated with the quantity of catecholamines used to treat the hemodynamic instability after reperfusion [27]. In addition, a variety of other mediators, including activated circulating monocytes, arginase, endotoxin, monocyte chemoattractant protein-1, and thromboxane are present during PRS but there is a lack of evidence for a causal relationship between these mediators and PRS during LT [24,29–32].

The role of ischemia-reperfusion injury in PRS remains controversial. Ischemia-reperfusion injury has been reported to be an important factor in graft loss and organ dysfunction after transplantation [33,34], but it is unclear whether ischemia-reperfusion injury is the cause of the immediate hemodynamic deterioration seen in a patient with PRS [26]. The mechanisms of ischemia-reperfusion injury involve the cellular responses to the ischemic injury caused by interrupting the oxygen supply, which results in cell death unless the oxygen supply resumes and the following reperfusion injury, which leads to further tissue injury [33]. Reperfusion injury involves biochemical and cellular changes that produce proinflammatory cytokines and oxygen free radicals, as well as activate the complement system, which lead to an inflammatory response, mediated by neutrophil and platelet interactions associated with swelling of the endothelium, vasoconstriction, leukocyte sedimentation, and hemoconcentration [33,35]. The production of inflammatory mediators may contribute to PRS and cause a profound local inflammatory response, which eventually leads to a systemic inflammatory response syndrome [8]. However, the severity of ischemia-reperfusion injury, which occurs during all LT procedures, is not correlated with that of the immediate hemodynamic disturbances found in patients with PRS [26]. Therefore, further studies are needed to more precisely determine the correlation between ischemia-reperfusion injury and PRS during LT.

## Risk Factors

Understanding the risk factors that are significantly associated with PRS is particularly useful because effective treatment strategies can be determined for patients in imminent danger of profound cardiovascular collapse. However, the variety of risk factors presented in several studies suggests that PRS occurs in an unpredictable manner [9,10,13,14,17–19,36]. Many clinical risk factors associated with PRS have been reported, such as hy-

perkalemia and hypothermia immediately after reperfusion [14], advanced age of donors [13], increased calcium requirement during surgery [19], volume of transfused blood components [10], prolonged cold ischemic time and surgery without a temporary portocaval shunt [9], severity of liver disease and renal failure [36], surgery using a classical technique and longer surgery duration [18], and left ventricular diastolic dysfunction, as determined by echocardiography [17]. In addition, some intraoperative hemodynamic variables may explain the occurrence of PRS, such as the integrity of the vasoconstrictive response immediately after clamping the inferior vena cava [12].

Among the various risk factors, the impact of prolonged cold ischemia time on the occurrence of PRS has been identified in several studies [9,14,17,18]. Several mechanisms of cold ischemia-induced liver injury have been suggested in animal studies using the rat liver [37-39]. Cold ischemia-induced liver injury begins with early necrosis of sinusoidal endothelial cells followed by delayed apoptosis of hepatocytes [37]. Prolonged cold ischemia time enhances nuclear factor-kappa B activation, which is harmful to the inflammatory response, and could contribute to infiltration of neutrophils into the grafted liver after reperfusion [38]. Furthermore, prolonged cold ischemia time impairs the regenerative ability of the grafted liver [39]. Prolonged cold ischemia time is reportedly related to poor outcomes for the patient and the grafted liver after LT [40-42]. Therefore, the use of criteria for extended donor graft, which have become common to reduce mortality while waiting for LT, should be considered more carefully, including older donor age, a high percentage of macrosteatotic graft liver on biopsy, a graft with a small donor liver, prolonged donor hospital stay, and prolonged cold/warm ischemia time [10,40,41].

## Surgical Techniques

Many surgical interventions have been attempted to minimize severity of the cardiovascular disturbance after reperfusion of the grafted liver [43-48]. The portal vein flushing reperfusion technique without venting the vena cava results in a lower incidence of PRS and earlier graft functional recovery than the use of vena cava venting without portal vein flushing [43,46]. Adjusting the reperfusion sequence shows that initial portal revascularization offers a more favorable hemodynamic and metabolic profile after reperfusion, although initial hepatic arterial revascularization of a grafted liver increases PAP less markedly [44]. The piggy-back technique with retrograde reperfusion via the caval vein diminishes the incidence of PRS compared to that of anterograde reperfusion via the portal vein [45]. Use of venovenous bypass in hemodynamically unstable patients whose MAP decreases by > 30% and/or cardiac output (CO) decreases by > 50% in a vena cava clamping trial does not affect

the occurrence of PRS compared with hemodynamically stable LT recipients who does not receive venovenous bypass [47]. In a comparison with the piggy-back technique, which maintains hemodynamic stability without the need for venovenous bypass, the classic operation using venovenous bypass is associated with the occurrence of PRS [18,48].

It is essential to understand that the surgical technique can influence the hemodynamic status of the patient during LT. Venovenous bypass is performed during total vena cava clamping in the majority of LT procedures using cadaveric donation, dual living donors, and donation after cardiac death [49]. As venovenous bypass has several advantages in stabilizing CO by maintaining venous inflow to the heart, maintained renal perfusion pressure, decreased bowel congestion and bleeding, and greater operative comfort [50,51], this technique has been generally adopted as the practical standard for LT [49,52]. Outflow cannulas from the lower body are placed in the iliofemoral and portal veins for venovenous bypass, and inflow to the heart is provided through a cannula placed in the axillary or jugular vein [52]. When the portal vein is unclamped after anastomoses of the vena cava and portal vein, the first 500-1,000 ml of portal blood that goes through the grafted liver is drained through the vena cava vent just before reperfusion to remove the preservation solution and vasoactive substances within the grafted liver. It is important to remember that this procedure may cause transient severe hypovolemia after reperfusion, if a proper supplement is not provided. As venovenous bypass can cause additional complications, including hypothermia, air and thrombotic pulmonary embolisms, increased warm-ischemia time, and vascular access-related complications [49,51], many LT centers have been moving to more selective use of venovenous bypass, with less than 50% of cases using it routinely [49]. In addition, exposure to extracorporeal circulation can activate proinflammatory cytokines and other vasoactive substances leading to vasodilation and hypotension [53,54]. Thus, it is not surprising that use of venovenous bypass has been associated with a higher incidence of PRS [18].

In contrast, the piggy-back technique, in which hepatic venous outflow is reconstructed without total vena cava clamping [55,56], is used for living donor, split, and pediatric LT [57,58]. This is an alternative technique that leaves the recipient's vena cava in place and avoids the need for venovenous bypass during the anhepatic phase [55]. Thus, venous return from the lower body is maintained to a certain extent without bypass flow. However, the piggy-back technique may cause congestion of the intestines during portal vein clamping and abrupt central hypervolemia after portal revascularization. In addition, complex surgical procedures related to reconstruction of hepatic venous outflow can cause sudden massive bleeding at any time [57].

Venovenous bypass is now considered when a vena cava

clamping trial leads to persistent profound hypotension refractory to vasopressors and volume loading [49,59]. Use of venovenous bypass may not be permitted in thrombotic patients, such as those with Budd–Chiari syndrome, as the venovenous bypass extracorporeal circulation is associated with a high risk of pulmonary thromboembolism [49]. Therefore, total clamping of the inferior vena cava without venovenous bypass may be used in some cases involving hemodynamically stable or thrombotic LT recipients, particularly when conducted by experienced transplant surgeons and anesthesiologists [51]. However, this procedure demands special care because it involves the following risks: reduction of CO due to unstable venous return to the heart, renal hypoperfusion, congestion of the intestines and inferior vena cava, massive bleeding during the anhepatic phase, and severe hemodynamic changes after reperfusion [49].

## Anesthetic Preparation

The anesthetic preparations for PRS begin with the preoperative assessment of the LT recipient. Co-morbid liver disease should be evaluated, including the presence of hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, ascites and esophageal varices, and hepatic synthetic function of coagulation profiles [59]. The preoperative cardiac evaluation is very important because severe coronary artery disease, heart failure, and severe pulmonary hypertension are contraindications to LT. In addition, cardiovascular disease is responsible for the majority of nongraft-related deaths in patients who initially survive LT [60]. Thus, a preoperative evaluation for coronary artery disease using dobutamine stress echocardiography and/or cardiac catheterization is recommended for LT recipients, particularly for chronic smokers, patients > 50 years of age, and those with a clinical or family history of heart disease or diabetes [61].

Standard resuscitation drugs, including epinephrine, atropine, phenylephrine, amiodarone, calcium, sodium bicarbonate ( $\text{NaHCO}_3$ ), and insulin, as well as infusions of vasopressors, such as norepinephrine, dopamine, dobutamine, and vasopressin, should be prepared before the operation [8]. Irradiated, filtered, and cross-matched blood components should be immediately available if needed. Additionally, it is occasionally necessary to equip a rapid infusion system for rapid administration of warmed blood components, such as the Fluid Management System (FMS 2000, Belmont Instrument Corp., Billerica, MA, USA) or the Level 1 Rapid Infusion system (SIMS Level 1, Inc., Rockland, MA, USA). Transfusions of packed red blood cells (RBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate during LT are based on clinical decisions, guided by standard laboratory tests, or by a transfusion algorithm using thromboelastography (TEG<sup>®</sup>) or rotational thromboelastometry (ROTEM<sup>®</sup>)

point-of-care devices [62,63]. For example, blood components are transfused to maintain prothrombin time < 2.0 INR, fibrinogen concentration > 100 mg/dl, and platelet count >  $30 \times 10^3$  / $\mu\text{l}$ . According to the ROTEM guidelines, the indications for substituting fibrinogen and transfusing platelets are dependent on the EXTEM amplitude of maximum clot firmness (MCF) < 45 mm, MCF of EXTEM < 35 mm, and MCF of FIBTEM < 8 mm with or without diffuse clinical bleeding [63]. In a recent ROTEM<sup>®</sup> study, the earliest 5 min (A5) clot amplitude parameter was an effective and reliable indicator for early detection of a critically low platelet count and/or a low fibrinogen concentration during LT [64].

As a contributing factor developing PRS [10], however, transfusion guidelines during LT should be more restricted. Although restricted clinical RBC transfusion practice guidelines (hemoglobin level < 7 g/dl) cannot be applied to patients undergoing LT due to possible massive bleeding and hemodynamic instability [65], strong evidence indicates that intraoperative RBC transfusions are associated with survival and postoperative complications after LT [66–68]. Similar adverse effects on survival after LT, which were thought to be related to acute lung injury [69], have also been found after intraoperative FFP and platelet transfusions [69,70]. Therefore, intraoperative transfusions of blood components need to be reduced to a minimum.

Intraoperative monitoring differs among LT centers according to institutional practice. In general, five-lead electrocardiography (ECG) and arterial catheterization using the radial and/or femoral artery are essential to monitor cardiac rhythm and arterial blood pressure. Large-bore peripheral and/or central access is necessary to administer medications and fluids to maintain hemodynamic stability. Although use of a pulmonary artery catheter and/or transesophageal echocardiography (TEE) varies depending on the patient's condition and institution, MAP, CVP, PAP, TEE, and continuous CO devices are usually used for hemodynamic monitoring [71]. Intraoperative TEE is recommended, particularly in a patient with an abnormal preoperative cardiac evaluation, such as significant coronary artery disease, hypertrophic cardiomyopathy with a left ventricular outflow obstruction, valvular heart disease, or the inability to perform a preoperative cardiac stress test [8].

## Hemodynamic Monitoring

The major goal of hemodynamic monitoring during revascularization of a grafted liver is to maintain the proper plasma volume. Severe hypovolemia, which may decrease CO and tissue perfusion, should be avoided before reperfusion but severe hypervolemia, which may cause right heart failure, pulmonary edema, and liver congestion, should be avoided immediately after revascularization. Therefore, circulatory status of the

LT recipient should be monitored carefully using MAP, CVP, PAP, mixed venous oxygen saturation (SvO<sub>2</sub>), near-infrared spectroscopy-based cerebral oximetry, and end-tidal carbon dioxide simultaneously. Central volume status after reperfusion should be determined carefully because sudden increases in venous return lead to a transient increase in CVP and PAP. The rapid temperature changes that occur after reperfusion make continuous CO monitoring using the thermodilution method unsatisfactory [72]; therefore, SvO<sub>2</sub> monitoring should be used as a good indicator of overall tissue perfusion. Pulmonary artery catheter-derived SvO<sub>2</sub> is an important hemodynamic parameter for intraoperative monitoring, as it integrates information about oxygen consumption, CO, and hemoglobin concentration [73]. Continuous SvO<sub>2</sub> monitoring is particularly useful in hemodynamically unstable patients after reperfusion when devices for continuous monitoring of CO are unavailable. Thus, a reduction in SvO<sub>2</sub> should be treated as an indication of low CO and/or a mismatch between oxygen demand and delivery [74]. Finally, TEE can be used to search for the cause of the hemodynamic disturbance after reperfusion. TEE helps with the immediate diagnosis, such as right heart failure, in a patient with pulmonary hypertension, pulmonary thromboembolism, and anastomotic stricture of the suprahepatic vena cava during emergent hemodynamic instability after reperfusion because it provides a quick assessment of cardiac and vena cava structure and function [75].

Measuring hemodynamic parameters to understand volume status, cardiac contractility, and systemic and pulmonary vascular resistances of the LT recipient is important for the differential diagnosis of refractory hypotension after reperfusion. As static preload measurements using CVP and PAWP are reportedly poor predictors of ventricular filling volume and fluid responsiveness during various conditions [76,77], assessing volume status and fluid responsiveness in a vasodilated patient with cirrhosis remains challenging during LT [73]. Thus, CO monitoring using a pulmonary artery catheter is the standard in many LT centers [71]. However, the risks of ventricular arrhythmia and perforation during the procedure and the delayed response of continuous CO using the thermodilution method limit its clinical application during an acute hemodynamically unstable situation [72,78]. In addition, other self-calibrating arterial waveform analyzing continuous CO monitoring systems, such as the Flowtrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA), and those that use intermittent CO bolus calibration pulse contour waveform analysis, such as the PiCCO system (Pulsion Medical System, Munich, Germany) and the LiDCO system (LiDCO Cardiac Sensor System, London, UK) show considerable variability during hemodynamic instability in LT recipients [79-81]. Therefore, these hemodynamic monitoring devices have not been universally validated for LT surgery [73].

Although measuring CO using arterial waveform analysis

has failed to prove reliability during LT, continuous measurements of stroke volume variation (SVV) and pulse pressure variation (PPV) by arterial waveform analysis are utilized as dynamic fluid responsiveness indices [81]. As SVV and PPV magnitudes are proportional to preload [82], an analysis of these variations predicts fluid responsiveness during positive pressure ventilation [83]. A systemic review of the literature showed that dynamic changes in SVV < 12% and of PPV < 13% predict fluid responsiveness with higher accuracy than do static fluid responsiveness indices in critically ill patients [84]. Several LT studies have shown that SVV is a good indicator of preload and that a SVV value of 9-10% can discriminate fluid responsiveness [85-87]. However, the accuracy of SVV and PPV as dynamic indices for fluid responsiveness varies depending on the situation. Although vasopressor therapy does not affect SVV or PPV, volume challenge and vasodilator therapy alter these variables [88]. PPV is less reliable for predicting fluid responsiveness during spontaneous breathing and at tidal volumes < 8 ml/kg [89,90], whereas SVV is linearly related to tidal volume depth, indicating that higher tidal volume leads to higher SVV [91]. PPV is less accurate at predicting fluid responsiveness regardless of tidal volume when respiratory system compliance is < 30 ml cmH<sub>2</sub>O [92]. In the presence of cardiac arrhythmia, SVV is more closely related to the irregularity of diastole than to heart-lung interactions [93]. Therefore, SVV and PPV as determined by waveform analysis can be used as minimally invasive dynamic indices to monitor preload and fluid responsiveness after consideration of some of the clinical limitations mentioned above.

Although continuous CO measurements using the thermodilution method are not very accurate or precise during the early anhepatic phase and after reperfusion [94], the use of a pulmonary artery catheter during LT can be very helpful in a patient with portopulmonary hypertension [81]. Patients with high PAP are contraindicated for LT because of a very high mortality rate [95,96]. However, mild to moderate pulmonary hypertension is not a strict contraindication for LT [97]. Although a patient with mild to moderate pulmonary hypertension has an increased mortality rate [95,96], the risk of perioperative mortality can be decreased if PAP is responsive to treatment [98-100]. Treatments for elevated PAP during LT include prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, or a combination of therapies [100,101]. As a pulmonary artery catheter is the only method for directly measuring PAP, it remains one of the most accurate devices for measuring CO and is an essential monitoring tool in patients with elevated PAP.

Use of intraoperative TEE has increased recently in high-volume LT centers worldwide because esophagogastric varices are not absolute contraindications to TEE if it has more expected benefits than potential risks [102]. As intraoperative TEE is relatively safe with a low incidence of variceal hemorrhage in

patients with coagulopathy and documented esophagogastric varices undergoing LT in retrospective studies [103,104], the use of TEE during LT is routine in 40% of programs, with the preponderance seen at large-volume centers [105], and is commonly used by 86% of anesthesiologists at large-volume LT centers in the USA [106]. However, proficient TEE management requires skilled training and expertise [81]. Therefore, applying TEE during LT should be decided after considering the expected benefits of real-time hemodynamic monitoring and the potential risks of an esophageal perforation and variceal bleeding.

## Prevention

Most patients with liver cirrhosis who are scheduled for LT demonstrate high CO, low SVR, and impaired systolic and diastolic response to stress due to volume overload, known as cirrhotic cardiomyopathy [107-109]. Thus, a patient with cirrhotic cardiomyopathy has impaired ability to compensate for decreases in contractility and SVR and often develops bradyarrhythmia after reperfusion. The hemodynamic and metabolic status of the LT recipient during the revascularization of the grafted liver must be optimized to alleviate the severe PRS cardiovascular disturbance. Successive arterial blood gas analyses are performed for early detection and treatment of serum electrolyte and acid-base balance as well as oxygenation and ventilation during the anhepatic phase. For example, serum potassium < 3.5 mEq/L, ionized calcium > 1.0 mmol/L, hemoglobin > 9 g/dl, blood glucose < 150 mg/dl, and normal acid-base status should be maintained before reperfusion because these parameters are correlated with the occurrence of PRS [11,14].

Of note, hyperkalemia remains a common and potentially life-threatening complication during LT. Intraoperative hyperkalemia is associated with postoperative mortality following LT [110]. A study of predictors associated with hyperkalemia showed that independent hyperkalemic predictors before reperfusion include higher baseline serum potassium and RBC transfusion, whereas independent hyperkalemic predictors after reperfusion are higher baseline serum potassium, prolonged warm ischemia time, lower intraoperative urine output, and venovenous bypass technique [111]. Thus, treating higher baseline serum potassium is important to prevent hyperkalemia during LT. Insulin therapy with regularly divided insulin doses, compared to the conventional large bolus regimen, significantly lowers serum potassium and glucose levels during LT [112]. In addition, severe intraoperative hyperglycemia (>200 mg/dl) is related to graft rejection, surgical site infection, and increased 1-year mortality following LT [113-115]. However, tight glucose control with a target blood glucose level of 80–120 mg/dl is not routinely recommended because intensive glucose control increases mortality in critically ill patients [116]. Therefore,

controlling glucose < 150 mg/dl is recommended for patients undergoing LT [71].

Treating hyponatremia, which is a common preoperative electrolyte abnormality, is a serious issue during LT because hyponatremia is associated with adverse outcomes even if resolved during the preoperative period [117]. Central pontine myelinolysis can occur in a patient with severe hyponatremia when the serum sodium level increases rapidly due to a rapid correction of hyponatremia or a large amount of NaHCO<sub>3</sub> is administered to correct metabolic acidosis, [118]. Therefore, large changes in sodium imbalance should be avoided during LT, particularly in a patient with severe hyponatremia [119].

As bradycardia is common and occurs rapidly after reperfusion, early treatment with atropine or epinephrine is recommended. Early treatment of bradycardia produces a faster and better outcome than delaying the treatment [8]. Vasopressors, such as epinephrine and phenylephrine, are useful for severe hypotension after reperfusion. If CVP increases > 15 mmHg after reperfusion, active venesection of 200–300 ml should be considered. NaHCO<sub>3</sub> is used to correct metabolic acidosis because acidic blood goes through the grafted liver, but administering other pH adjusting agents, such as tris-hydroxymethyl aminomethane, rather than NaHCO<sub>3</sub> may be preferable in a patient with severe hyponatremia [120]. Isosorbide dinitrate and prostaglandin E1 (PGE1) should be prepared for patients with pulmonary hypertension because PAP and PAWP increase initially after reperfusion. If PAP > 30 mmHg and CVP > 15 mmHg are persistent, isosorbide dinitrate and PGE1 should be administered immediately along with active venesection. If ischemic changes in the ST segment are detected on ECG, the causes of the decreased coronary blood perfusion should be identified and treated; active venesection for volume overload, vasopressors for decreased SVR-induced circulatory hypovolemia, or fluid challenge for hypovolemic shock. Coronary spasms can occasionally be the cause of ST segment elevation, because the cold blood flowing into the heart after reperfusion and/or the placement of a cold grafted liver beneath the diaphragm can cause vasospasms in the right coronary artery [121]. In such situations, intraoperative TEE is very useful for making a differential diagnosis among hypovolemia, decreased contractility, and decreased SVR.

## Treatment

There is no fixed rule for treating PRS. The hemodynamic disturbance during PRS is usually weak and temporary but can be serious enough to precipitate intraoperative cardiac arrest [122]. As PRS is often accompanied by decreased contractility, bradycardia, and decreased SVR, the administration of epinephrine is preferred. In general, a bolus of 10–20 µg epinephrine

is sufficient but a repeated bolus of a higher dose (50–100 µg) is sometimes necessary. Use of phenylephrine alone, which increases SVR without acceleration of cardiac function, requires careful consideration. If other vasopressors are needed to treat persistent PRS hypotension, a continuous norepinephrine infusion may be a good choice. However, high doses of vasopressors may cause serious ischemic complications, such as graft dysfunction, postoperative renal failure, and death [123]. Therefore, alternative medications are of interest for treating of refractory PRS hypotension that does not respond to the usual vasopressors.

Decreased SVR in a patient with end-stage liver disease may be associated with a relative vasopressin deficiency, similar to a case of septic shock [124]. A prospective study demonstrated that administering vasopressin (3 U vasopressin bolus and continuous infusion of vasopressin 3 U/h for 20 min) increases SVR and MAP, as patients with liver disease have lower vasopressin levels than those of controls, [125]. Thus, vasopressin is an option for treating catecholamine-refractory vasoplegia during LT, particularly if it is associated with severe refractory PRS [126]. Anesthesiologists and transplant surgeons have taken special interest in perioperative therapy with the vasopressin analogue terlipressin [127,128] because perioperative use of terlipressin during LT improves early postoperative renal function without any detrimental effects on hepatosplanchnic function [129].

Methylene blue is recommended for patients with vasoplegia refractory to vasopressin and catecholamine therapy [130]; thus, it has been used for refractory PRS hypotension [131–134]. Although methylene blue is a heterocyclic aromatic chemical compound that was originally used to treat methemoglobinemia and as a marking dye, methylene blue is useful for treating refractory PRS hypotension during LT [131,132,135]. A 1.5 mg/kg bolus of methylene blue administered prophylactically prior to reperfusion of the grafted liver attenuates the hemodynamic changes after reperfusion, suggesting positive effects on cardiac contractility (unchanged SVR and increased MAP and CO) [135]. These positive effects of methylene blue on myocardial function have been demonstrated in patients with septic shock [136]. A 2 mg/kg loading dose of methylene blue over 30 min and a 0.5 mg/kg/h infusion of methylene blue over 6 h after reperfusion increases MAP in patients with vasopressor-resistant vasoplegic shock, which is correlated with an increase in SVR [131]. In addition, severe hypotension after reperfusion in LT recipients responds to a 100 mg or 2 mg/kg bolus of methylene blue, even if the patient does not meet the criteria for vasoplegia [132]. In contrast, prophylactic exposure to a 1–1.5 mg/kg bolus of methylene blue has no significant effects on the occurrence of PRS, vasopressor or transfusion requirements after reperfusion, or postoperative graft function [134]. Thus, further studies are needed to evaluate the outcomes from administering methylene blue in LT recipients.

Methylene blue directly inhibits nitric oxide (NO) synthase, which decreases NO production during inflammatory process [137]. As NO may play an important role in the development of vasoplegia during LT, use of methylene blue can restore systemic vascular tone by inhibiting inducible NO synthase [131,133]. Furthermore, methylene blue may support blood pressure even if NO production is not augmented because methylene blue also directly inhibits guanylate cyclase, which transforms guanosine triphosphate into cyclic guanosine monophosphate and thereby contributes to decreasing vascular tone [25,138]. As production of NO and the activity of the guanylate cyclase system are augmented in patients with decompensated liver cirrhosis and fulminant liver failure [25,139,140], methylene blue may be a clinically useful rescue agent for refractory PRS that does not respond to catecholamine or vasopressin therapy. This hemodynamic rescue is clinically important because intraoperative hemodynamic aberrations of PRS are associated with postoperative graft dysfunction [5,10,13].

## Outcomes

The clinical consequences of PRS have not been fully explained. Intraoperative hemodynamic aberrations of PRS are associated with adverse outcomes of early graft dysfunction, primary graft nonfunction, and death attributable to hemodynamic causes [5]. Patients with cirrhosis who exhibit PRS suffer more severe acute renal failure postoperatively and a higher first 15-day mortality rate after LT [9]. In a study at an Australian LT center, PRS did not severely affect postoperative complications or patient survival, whereas PRS was associated with higher graft dysfunction and renal dysfunction [13]. PRS is associated with higher rates of in-hospital mortality and postoperative renal dysfunction in patients with fulminant hepatic failure [36]. Developing PRS intraoperatively results in longer intensive care unit and hospital stays and higher graft loss and retransplantation rates [10]. PRS is related to more frequent renal dysfunction and more hospital deaths after LT in Chinese patients [17]; however, long-term mortality does not increase significantly. In contrast, a Polish LT center study showed that PRS is associated with a higher 1-year mortality rate and more early postoperative complications [18]. The limited number of samples examined and confounding factors associated with PRS and/or postoperative management may have led to the discrepancy between early and long-term mortality rates.

There are several possible reasons why PRS has a negative impact on early postoperative outcomes. First, persistent severe PRS hypotension causes postoperative renal dysfunction [9,13,17,36]. Postoperative acute renal failure, which is a common complication of LT, greatly decreases 30-day and 1-year patient survival following LT [141,142]. Second, the adverse

outcomes from developing PRS appear to be related to effects of intraoperative blood component transfusions, which represent an independent risk factor for PRS [10]. Intraoperative transfusions of RBCs, FFP, and platelets are independent risk factors for mortality after LT [66,67,69,70]. In addition to lower survival after LT, patients receiving massive intraoperative blood transfusions are expected to have a higher incidence of other postoperative complications, such as graft dysfunction, infections, and gastrointestinal and intra-abdominal complications [68]. Third, additional hypotheses may apply, depending on the severity of PRS. Poor perfusion of the grafted liver due to refractory PRS hypotension is related to postoperative graft dysfunction, renal impairment, and death [123]. In addition, ischemia-reperfusion injury as a possible cause of PRS should be considered [26] because it can lead to a systemic inflammatory response, which may culminate in multiple organ failure and death [33].

## Conclusion

The underlying mechanisms and clinical factors of PRS are complex and not fully understood, but severe hemodynamic disturbance during LT remains a serious issue for the anesthesiologist. The hemodynamic and metabolic status of the LT recipient during revascularization of the grafted liver should be optimized to alleviate the severe cardiovascular disturbance of PRS. Importantly, rapid and appropriate treatments using vasopressor, volume replacement, or active venesection depending on the cause of the hemodynamic disturbance should be provided if hemodynamic instability becomes profound after reperfusion. Therefore, it is essential to carefully monitor the status of LT recipients with proper anesthetic preparation. In addition, it is important to understand the surgical techniques and to communicate closely with the transplant surgeons. Finally, the adverse effects of PRS on postoperative early morbidity and mortality are clear but the effects of PRS on postoperative long-term mortality remain controversial.

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