Anesth Pain Med 2016; 11: 117-129
http://dx.doi.org/10.17085/apm.2016.11.2.117

■ Review ■
pISSN 1975-5171 • eISSN 2383-7977

Effects of portal hyperperfusion on partial liver grafts in the presence of hyperdynamic splanchnic circulation: hepatic regeneration versus portal hyperperfusion injury

Department of Anesthesiology and Pain Medicine, School of Medicine, Catholic University of Daegu, Daegu, Korea

Jong Hae Kim

In cirrhotic patients undergoing liver transplantation, reperfusion of a liver graft typically increases portal venous blood flow (PVF) because of a decrease in resistance in the liver graft to the PVF and underlying hyperdynamic splanchnic circulation, which develops due to liver cirrhosis complicated by portal hypertension and persists even after successful liver transplantation. If the liver graft has enough capacity to accommodate the increased PVF, the shear stress inflicted on the sinusoidal endothelial cells of the graft promotes hepatic regeneration; otherwise, small-for-size syndrome (SFSS) develops, leading to poor graft function and graft failure. In particular, a partial graft transplanted to patients undergoing living donor liver transplantation has less capacity to accommodate the enhanced PVF than a whole liver graft. Thus, the clinical conditions that the partial graft encounters determine either hepatic regeneration or development of SFSS. Consistent with this, this review will discuss the two conflicting effects of portal hyperperfusion (hepatic regeneration vs. portal hyperperfusion injury) on the partial grafts in cirrhotic patients suffering from hyperdynamic splanchnic circulation, in addition to normal physiology and pathophysiology of hepatic hemodynamics. **(Anesth Pain Med 2016; 11: 117-129)**

Key Words: Liver cirrhosis, Liver regeneration, Liver transplantation, Portal hypertension, Splanchnic circulation.

INTRODUCTION

Hyperdynamic splanchnic circulation is commonly known as a complication of liver cirrhosis. However, strictly, it is a complication of portal hypertension, which develops due to liver cirrhosis. The hyperdynamic splanchnic circulation persists for more than 28 days even after the replacement of a cirrhotic native liver with a new liver graft [1], due to a decrease in the resistance of the vascular bed in the liver graft, pre-existing portal hypertension, and splanchnic vasodilatation [2]. The persistent hyperdynamic splanchnic circulation leads to an increase in portal venous blood flow (PVF) to the liver graft, which is termed "portal hyperperfusion," and the resulting intrahepatic shear stress stimulates and regulates hepatic regeneration [3,4]. However, in living donor liver transplantation (LDLT) using a partial liver graft, the vascular bed does not always have enough capacity to accommodate the increased PVF. Although the increased PVF plays a crucial role in regeneration of the partial liver graft [1], an excessive increase in the PVF could cause failure of the liver graft to control directly the PVF, eventually threatening the viability of the graft [5] with the development of small-for-size syndrome (SFSS). This review will deal with the two conflicting results caused by the shear stress secondary to portal hyperperfusion, which is inflicted on the sinusoidal bed of a partial graft (hepatic regeneration vs. portal hyperperfusion injury) as well as the underlying physiology and pathophysiology of hepatic hemodynamics, knowledge of which contributes to a better understanding of the effects of portal hyperperfusion in a partial graft.

Received: February 1, 2016.
Revised: March 7, 2016.
Accepted: March 8, 2016.

Corresponding author: Jong Hae Kim, M.D., Department of Anesthesiology and Pain Medicine, School of Medicine, Catholic University of Daegu, 33, Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea. Tel: 82-53-650-4979, Fax: 82-53-650-4517, E-mail: usmed@cu.ac.kr

PHYSIOLOGY OF HEPATIC HEMODYNAMICS

Serving as a major blood volume reservoir in the human body, the liver receives blood at 800-1,200 ml/min, which is equivalent to 100-130 ml/min per 100 g of liver weight [6] and constitutes approximately 25% of cardiac output (1-2

L/min) [7]. The liver contains blood at 25–30 ml/100 g of liver weight – accounting for 10–15% of the total blood volume [8] – although it constitutes only 2.5% or 33 g/kg of total body weight [9,10]. Large capacitance vessels, such as the portal and hepatic veins and hepatic artery, hold 40% of the blood that the liver receives; the sinusoids hold the remaining 60% [6]. The hepatic blood volume can compensate for up to 25% of blood loss [11].

The liver has a unique dual blood supply system consisting of the hepatic artery, which carries approximately 25% of the total hepatic blood flow (30 ml/min per 100 g of liver weight; with well-oxygenated blood [oxygen saturation of 95%] providing 30–50% of the liver oxygen requirement); and the portal vein, which receives all the blood from the spleen, stomach, small and large intestines, gall bladder, and pancreas [12], and provides partially deoxygenated blood (oxygen saturation of up to 85% during the fasting state) responsible for 75–80% of the total blood flow to the liver (90 ml/min per 100 g of liver weight) and 50–70% of the liver oxygen requirement. The two vessels form the portal triad together with the bile duct. In the resting state, the liver consumes approximately 20% of the total oxygen used in the body [13]. With increased oxygen demand, such as isovolemic hemodilution or upregulation of hepatic enzymes, more oxygen is simply extracted from the blood, but the hepatic artery does not dilate [14]. The saturation of hepatic venous blood, which is normally two-thirds saturated with oxygen, would be reduced upon low delivery of oxygen to the liver, leading to an increase in oxygen extraction from the hepatocytes. The portal venous system is protected from hepatic arterial pressure by a reduction in the hepatic arterial pressure towards portal venous pressure (PVP), due to hepatic arteriolar resistance in combination with the intermittent closure of the presinusoidal arterioles in the peribiliary plexus [15].

Mesenteric and splanchnic arteriolar vascular tone, as well as intrahepatic vascular resistance, regulate the valveless portal vein system, maintaining low pressure and resistance. The normal range of PVP is between 5 and 10 mmHg [16]. Due to the large capacity of the sinusoidal structure and intrahepatic vasculature, which easily accommodates additional PVF by releasing nitric oxide (NO) that dilates intrahepatic vessels [17], an increase in PVF does not influence the PVP [18]. The mean hepatic arterial pressure is similar to that of the aorta [19]. The high pressure and resistance hepatic artery system [6] is regulated by classical arterial autoregulation and interacts with the portal vein system via the hepatic arterial buffer response (HABR), which maintains overall hepatic blood flow and an adequate oxygen supply to the liver by compensating for diminished or increased PVF with a reciprocal increase or decrease in hepatic arterial blood flow (HAF) [20]. The compensatory interaction between the hepatic artery and portal vein systems will be discussed in the following section. The both afferent vessels enter the hepatic lobule and merge at the sinusoidal bed, which is drained by the hepatic venous system into the inferior vena cava. Sinusoid pressure or hepatic venous wedge pressure, which may be an indicator of PVP, ranging from 3 to 10 mmHg is between PVP (5–10 mmHg) and inferior vena cava pressure (1–2 mmHg) [19].

REGULATION OF HEPATIC BLOOD FLOW BY THE HEPATIC ARTERIAL BUFFER RESPONSE

In addition to classical arterial autoregulation, in which the HAF is intrinsically regulated via the myogenic response of the hepatic artery to arterial pressure, there is another mechanism for the intrinsic regulation of the HAF, namely HABR. Although an increase in HAF in response to reduced PVF was first reported in 1911, the relationship between the two vascular systems was termed HABR for the first time in 1981 [19]. The hepatic artery dilates or constricts secondarily to a decrease or increase in the PVF, respectively [20]. Temporary occlusion of the portal vein induced a sharp and significant increase in the HAF, by approximately 30% in anesthetized patients with carcinoma of the splanchnic area [20]. The increase in the HAF compensates for 25–60% of the decreased PVF [21]. The hepatic arterial response alleviates the effects of changes in the PVF on hepatic clearance and maintains oxygen supply to the liver [22]. However, HABR is not reciprocal; that is, PVF or portal venous resistance does not change in response to changes in hepatic arterial perfusion [20] because the PVF passively depends on the outflow of the extrahepatic splanchnic organs. Under physiological conditions, HABR operates at all ages [19], even prenatally [23].

The adenosine washout hypothesis well explains the HABR. Adenosine, which is a potent hepatic arterial vasodilator [21], is released at a constant rate into the fluid in the space of Mall, which is a space between the periportal hepatocytes and portal connective tissue surrounding the hepatic arterioles and the portal venules. The concentration of adenosine is dependent on the rate of washout into the portal vein. A reduction in washout of adenosine from the space of Mall secondary to the

decreased PVF results in dilation of the hepatic artery, thereby leading to an increase in the HAF [14]. The mediation of adenosine in HABR is supported by several lines of evidence, which show the potentiation of HABR by adenosine uptake inhibitors [21], competitive blockade of HABR by adenosine antagonists [24-27], and a lower effect of adenosine infused into the portal vein compared with that infused into the hepatic artery (thus indicating communication between the two vascular systems) [14]. However, adenosine dose not diffuse from the portal venous vasculature to the hepatic arterial vasculature [28]. The substance that diffuses from the portal venous to the hepatic arterial bed in response to hypoxia [29], caused by a reduction in the PVF [30], is adenosine-5'-triphosphate (ATP), rather than adenosine itself [28]. Only the adenosine produced from ATP catabolism in the hepatic arterial vasculature contributes to hepatic arterial dilation [27], whereas the adenosine created in the portal venous vasculature is rapidly taken up by the endothelium and vascular smooth muscle immediately after its production [31].

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION AND SUBSEQUENT HYPERDYNAMIC SPLANCHNIC CIRCULATION IN LIVER CIRRHOSIS

Portal hypertension is defined as a sustained increase, by more than 5 mmHg, in the hepatic venous pressure gradient (HVPG) [32]. The HVPG represents the difference between hepatic venous wedge pressure reflecting sinusoidal pressure, which provides an accurate estimate of PVP due to loss of normal intersinusoidal communications in cirrhotic patients, and free hepatic venous pressure [33]. However, an HVPG between 5 and 10 mmHg presents with no clinical manifestations and is considered to be subclinical portal hypertension. A diagnosis of clinically significant portal hypertension is made when the HVPG reaches more than 10 mmHg, which predicts the development of complications of liver cirrhosis, including ascites, portosystemic collaterals, varices, circulatory dysfunction, and even death [34]. The threshold of the HVPG for variceal hemorrhage is 12 mmHg [35]. In addition, liver cirrhosis patients with HVPG greater than 20 mmHg following variceal bleeding have a five-fold increase in the risk of death [36].

In portal hypertension, intrahepatic vascular resistance increases not only upon mechanical obstruction caused by architectural changes in the liver (fibrosis and capillarization of the sinusoids, development of microthrombi in the intrahepatic vasculature, and regenerative nodule formation) [37], but also upon the dynamic obstruction that results from impaired sinusoidal relaxation due to overproduction of inflammatory mediators. The overproduction in turn results in oxidative stress, which causes sinusoidal endothelial cell dysfunction thus leading to overproduction of, and enhanced sensitivity to, vasoconstrictors such as endothelin-1, angiotensin II, leukotrienes, and norepinephrine, coupled with underproduction of vasodilators such as NO, carbon monoxide, and prostaglandin E2 [18]. Activated hepatic stellate cells differentiating into contractile fibrogenic myofibroblasts also increase intrahepatic vascular resistance by producing an excessive amount of extracellular matrix, inflammatory cytokines, and endothelin-1. Vasoconstrictive substances, such as endothelin-1, reduce the sinusoidal space and increase intrahepatic vascular resistance by inducing hepatic stellate cell contraction [37].

In contrast to vasoconstriction, which occurs in the intrahepatic vasculature, the splanchnic vasculature experiences progressive vasodilatation during the progression of liver cirrhosis. However, in the early stage of cirrhosis, when portal hypertension develops due to an increase in intrahepatic vascular resistance in the absence of extensive collateral circulation, the splanchnic circulation is normodynamic or hypodynamic, rather than hyperdynamic [38]. Consequently, a reduction in the PVF with a reactive increase in the PVP ensues [39]. This physiological alteration constitutes the main postulation of the "backward flow" theory. As liver cirrhosis progresses to an advanced stage, the consequent physiological alteration would be explained by the "forward flow" theory, in which the splanchnic circulation becomes hyperdynamic due to portal hypertension-induced splanchnic vasodilatation with subsequent development of extensive collaterals [40]. Under this physiological milieu, the decreased PVF during the early stage of liver cirrhosis increases again [41].

NO, which causes vasodilatation by the activation of soluble guanylyl cyclase, in turn leading to the generation of cyclic guanosine monophosphate in the vascular smooth muscle [42], is the most important vasodilator associated with portal hypertension and subsequent hyperdynamic splanchnic circulation. There are three isoforms of NO synthase (NOS) that synthesize vascular NO: endothelial NOS (eNOS) [43], inducible NOS (iNOS) [44], and neuronal NOS (nNOS) [45]. Among these isoforms, eNOS, which produces NO in the endothelial cell in response to mechanical forces caused by sheer stress, endothelial growth factor, or inflammatory cytokines [46], plays a major role in the overproduction of

vascular NO in the splanchnic arterial circulation [47]. In addition, an increase in intestinal absorption of lipopolysaccharides, due to changes in intestinal permeability, activates iNOS by releasing inflammatory cytokines, such as tumor necrosis factor-α, from macrophages [48], which contributes to hyperdynamic splanchnic circulation. nNOS, which is synthesized in neuronal and vascular smooth muscle cells, was also found to be upregulated in the mesenteric artery [49] and in the aorta [50], resulting in the development and maintenance of hyperdynamic splanchnic circulation in liver cirrhosis [50]. In contrast, intrahepatic NO decreases because of reduced activity of eNOS in portal hypertension [37].

In response to splanchnic and peripheral vasodilatation, retention of sodium and water occurs, resulting in the expansion of the plasma volume, a large part of which accounts for the portosystemic collateral circulation [51]. The resulting increase in venous return to the heart leads to an increase in cardiac output [51]. Despite the essential role of vasodilatation, the systemic hyperdynamic circulation cannot be maintained in the absence of the portosystemic shunt, which contributes to the expansion of plasma volume [52]. A cardiac index higher than normal ($>$ 4 L/min/m^2) often does not sufficiently compensate for the decreased arterial pressure caused by progressive vasodilatation. The splanchnic and systemic hemodynamic derangement in cirrhotic patients is reversible by liver transplantation [53].

HEPATIC REGENERATION INDUCED BY PORTAL HYPERPERFUSION

Upon replacement of the native cirrhotic liver with a new liver graft from a living donor, the partial liver graft should receive a large amount of PVF from the hyperdynamic splanchnic circulation such that liver cells, including Kupffer cells and sinusoidal endothelial cells, are exposed to excessive hemodynamic forces caused by PVF against the vessel walls. An increase in sinusoidal blood flow to the partial liver graft inflicts shear stress on the endothelial surface, which stimulates hepatic regeneration [54]. Shear stress is defined as a viscous drag at the surface of the sinusoidal endothelial cells, which is created by adjacent blood flow [55]; its amount is proportional to the volume of the blood flow and the inverse of the cube of the vessel radius [55]. However, excessive shear stress may induce liver failure [54].

Because the sinusoidal domain of the hepatocyte faces the perisinusoidal space of Disse, which is the space between the hepatocytes and endothelial sinusoidal-lining cells (with fenestrae into the sinusoidal lumen forming the sieve plate structure), the hepatocyte may be exposed directly to the PVP through the fenestrae. Thus, not only the sinusoidal endothelial cells, but also the hepatocytes, respond to PVP-induced shear stress [56]. The shear stress arising from alteration of the hemodynamic pattern of hepatic blood flow initiates signal cascades that trigger hepatic regeneration. The existence of shear stress-responsive cell surface modulators on the hepatocytes and sinusoidal endothelial cells, such as the calcium ionic channel, sodium ionic channel [57], and gap junctions [58], has been suggested. Electron microscopic observations showed widening of sinusoidal endothelial fenestrations and spaces of Disse, contributing to an increase in sinusoidal endothelial permeability to circulating hepatotrophic substances and enlargement of the intercellular spaces. This in turn leads to extracellular matrix degradation, with subsequent induction of responsiveness of hepatocytes in the periportal area to circulating and liver-borne growth factors [59]. In addition, ATP, which enhances cell cycle progression and hepatocyte proliferation [60], is released from isolated rat hepatocytes and hepatectomized livers of rats and human living donors by mechanical stress [61,62]. The rapid loss of adenine nucleotides after partial hepatectomy also generates early stress signals to the remnant liver, contributing to the onset of hepatic regeneration [63].

Interestingly, portal hypertension does not induce hepatic regeneration in liver cirrhosis. As liver cirrhosis progresses, the sinusoidal endothelial cells become capillarized [64], thereby leading to disappearance of the sieve plate structure. The absence of the sieve plate structure hinders any direct influence of portal hypertension-induced shear stress on the hepatocytes, thereby preventing the initiation of hepatic regeneration. However, hepatocytes isolated from cirrhotic livers have the potential to proliferate [56].

Within the normal liver, sinusoidal endothelial cells express eNOS that produces NO, the amount of which is dependent on flow [65]. An increase in endothelial shear stress modulates the release of endothelial NO and prostaglandins [66,67] and increased PVP immediately after partial hepatectomy activates eNOS and upregulates iNOS [3]. In contrast to adenosine, which is dependent on hepatic blood flow, NO acts in response to vasoconstriction-induced shear stress [11]. Accordingly, NO produced in response to an increase in shear stress affects vascular accommodation following a partial hepatectomy [68] and provides the residual liver with permeability to growth

factors, contributing to triggering of the hepatic regeneration cascade [3,66,67]. In addition, NO downregulates the level of S-adenosylmethionine – the synthesis of which is essential for methionine metabolism – causing hepatocytes to respond to hepatocyte growth factor [69].

If the graft-to-recipient weight ratio (GRWR) is > 0.8, which is known to be the minimum size of a liver graft to fulfill the metabolic demand of a recipient [70], in the absence of any occlusion of hepatic venous outflow, SFSS rarely develops. For liver grafts uncomplicated by SFSS, portal venous hemodynamics have a major impact on hepatic regeneration. The portal venous velocity and PVF increased considerably after the reperfusion of a liver graft and then returned to the baseline value, which was measured before hepatic parenchymal transection in donors, at 3 months after LDLT [71]. The size of the liver graft is restored to the standard liver volume of recipients in 2 weeks after LDLT [1]. Many previous studies have found correlations between PVP or PVF and the degree of graft regeneration, which were measured at different postoperative time points [1,72-74] (Table 1). However, there is still no consensus about which portal venous hemodynamic parameter is of paramount importance in predicting the degree of graft regeneration.

PORTAL HYPERPERFUSION INJURY AND SMALL-FOR-SIZE SYNDROME

SFSS has emerged as a new challenge with the increasing practice of LDLT [75]. It is manifested as graft function impairment, characterized by portal hypertension, refractory ascites, encephalopathy, prolonged cholestasis with hyperbilirubinemia, and coagulopathy during the 1st postoperative week in the absence of technical problems such as hepatic venous outflow obstruction [76,77]. In severe cases, the syndrome progresses to acidosis, hypoglycemia, renal failure, and septic shock unless prompt retransplantation is performed [78]. The histopathological examination of grafts complicated by SFSS in a porcine model showed evidence of hepatic artery vasospasm and resulting cholestasis, centrilobular necrosis, and biliary ischemia [79]. In the early era of LDLT, SFSS was known to develop in liver grafts with a GRWR < 0.8%, or a graft weight to standard liver volume < 35% [80], which might indicate a relative shortage of hepatic parenchymal volume for life maintenance. However, several definitions of SFSS have been proposed without a single accepted definition [76,81-83] (Table 2) and the size of the liver graft is no longer an absolute determinant of the development of SFSS. Hepatic hemodynamic derangement, particularly portal hyperperfusion producing high intravascular shear stress, might also have an influence on its development [84]. Recently, it was suggested that high portal blood inflow to a partial graft, transplanted in a recipient with a persistent hyperdynamic splanchnic circulation, caused hepatic dysfunction and impairment of hepatic regeneration [85-87]. The generated shear stress also leads to an imbalance in endothelin-1 and NO, which contributes to graft injury [88]. Accordingly, improvements in surgical techniques for modulating PVF led to a reduction in the lower limit of GRWR to 0.6 [89].

Portal hyperperfusion activates HABR, which causes hepatic arterial hypoperfusion in the partial liver graft. In patients undergoing LDLT, an increase in PVF to the grafts is by more than two-fold [19]. In the absence of HABR, the HAF would increase in line with the increase in the PVF. However, a considerable decrease in the HAF was observed in patients receiving right-lobe grafts [90], indicating that HABR operates in response to an increase in the PVF to maintain the total hepatic blood flow within a physiological range [91]. The mean PVF of recipients transplanted with small-sized liver grafts (GRWR < 0.8) was at least three times higher than that of donors [92]. In contrast, the hepatic arterial contribution to total hepatic blood flow was decreased from 30% in donors to 6% in recipients, due to a substantial reduction in the HAF [92]. SFSS developed in 3 of 11 (27%) patients who did not undergo graft inflow modulation and a PVF of 250 ml/min per 100 g of liver weight predicted the development of SFSS [92]. In a porcine model transplanted with a small-for-size graft, the portal-to-hepatic flow ratio, which was poorly tolerated by the liver graft, remained increased until the 5th postoperative day [93].

Graft inflow modulation

Because a recipient transplanted with a liver graft, the GRWR of which was 0.61%, survived following a mesocaval shunt that reduced PVP [94], several techniques to divert the PVF to the systemic circulation – or to decrease the portal inflow by modifying the splenic blood flow – have been developed, such as hemiportocaval shunt [95,96], mesorenal shunt [97,98], delayed ligation of spontaneous portosystemic shunts [99], splenectomy [100], splenic artery ligation and embolization [101,102].

A hemiportocaval shunt between the right portal vein and inferior vena cava reduced the HVPG from 18 to 5 mmHg in

Table 1. Correlations between Portal Venous Hemodynamic Parameters and the Degree of Hepatic Regeneration after Living Donor Liver Transplantation

Reference	Number of patients	Etiology of liver disease	Portal venous hemodynamic parameters	Parameters representing the degree of hepatic regeneration	Statistical method	Correlation coefficient (r) or coefficient of determination (r^2)	P
Eguchi et al. (2003) [1]	15	Fulminant hepatic failure (n = 4), liver cirrhosis (n = 9)	Mean portal venous velocities measured on the 7th postoperative day (cm/s)	The proportion of the liver graft to standard liver volume at postoperative month 1 (liver volume ratio) (%)	Simple linear regression	r = 0.666*	0.0181
			Mean portal venous velocities measured on the 1st and 28th postoperative days (cm/s)	Liver volume ratio at postoperative month 1 (%)		UA	< 0.05
			Mean portal venous velocities measured on the 1st and 7th postoperative days (cm/s)	Liver volume ratio at postoperative month 3 (%)		UA	< 0.05
			Mean portal venous velocities measured on the 7th postoperative day (cm/s)	Liver volume ratio at postoperative week 1 or 2 (%)		UA	< 0.05
García-Valdecasas et al. (2003) [72]	22	Liver cirrhosis	Difference in portal venous blood flow per 100 g of liver weight between recipient and donor (ml/min/100 g)	Percent change in liver graft weight between time of graft harvest and postoperative month 2 (%)	Spearman rank correlation	r^2 = 0.2343†	< 0.05
Park et al. (2008) [73]	31	Fulminant hepatic failure (n = 3), liver cirrhosis (n = 28)	Portal venous velocity per 100 g of liver graft at postoperative day 1 (cm/s)	Ratio of liver graft volume at postoperative day 7 to graft weight measured immediately after graft retrieval (%)	Simple linear regression	r^2 = 0.273	0.009
			Portal venous blood flow per 100 g of liver graft at postoperative day 1 (ml/min/100 g)			r^2 = 0.275	0.009
			Portal venous blood flow per 100 g of liver graft at postoperative day 5 or 6 (ml/min/100 g)			r^2 = 0.237	0.012
Jiang et al. (2009) [74]	18	Liver cirrhosis	Mean maximal velocity of the portal vein multiplied by a coefficient of 0.57 (PBV) at postoperative day 1 (cm/s)	Percent change in the liver graft volume between the preoperative period and postoperative day 30 (%)	Simple linear regression	r = 0.67492*	0.0001
					Multiple regression	UA	0.0011
			Portal venous blood flow at postoperative day 1 (ml/min)		Simple linear regression	UA	< 0.05
					Multiple regression	UA	0.0003
			PBV (cm/s) and portal venous blood flow (ml/min) at postoperative day 3		Simple linear regression	UA	< 0.05

UA: unavailable. *Although the statistical analysis was performed using simple linear regression that generally shows a coefficient of determination (r^2), the correlation coefficient (r) was presented. †Although Spearman rank correlation generally shows Spearman's rho (ρ), the coefficient of determination was presented.

Table 2. Various Definitions of Small-for-size Syndrome

Reference	Definition
Dahm et al. [76]	Small-for-size dysfunction Dysfunction* of a 'small' partial liver graft (graft-versus-recipient weight ratio < 0.8%) during the 1st postoperative week after the exclusion of other causes† Small-for-size non-function Failure‡ of a 'small' partial liver graft (graft-versus-recipient weight ratio < 0.8%) during the 1st postoperative week after the exclusion of other causes
Soejima et al. [81]	Small-for-size syndrome Prolonged cholestasis (total serum bilirubin > 10 mg/dl on the 14th postoperative day without any other definitive causes of cholestasis) and intractable ascites (daily production of ascites of > 1 L on the 14th postoperative day or > 500 ml on the 28th postoperative day
Hill et al. [82]	Small-for-size syndrome The presence of significant cholestasis with serum bilirubin > 10 mg/dl (and continuing to increase) after the 7th postoperative day, coagulopathy with an international normalized ratio > 1.5, and ascites with drain out > 2 L/day in the absence of an obvious technical problem such as biliary leak, vascular thrombosis, or stenosis.
Ikegami et al. [83]	Delayed functional hyperbilirubinemia (yields the highest area under the receiver operating characteristic curve (0.977), representing a sensitivity of 100% and specificity of 95.4% for detecting early graft loss compared with the three definitions above.) Total serum bilirubin > 20 mg/dl for > 7 consecutive days occurring after the 7th postoperative day, excluding technical, immunological, and hepatitis factors.

*The presence of two of the following on 3 consecutive days: serum bilirubin > 100 μmol/L, international normalized ratio > 2, and encephalopathy grade 3 or 4. †Technical (e.g., arterial or portal occlusion, outflow congestion, biliary leak), immunological (e.g., rejection), and infection (e.g., cholangitis, sepsis) problems. ‡Clinical conditions that necessitate retransplantation, or are otherwise followed by death of a recipient.

16 patients with a median GRWR of 0.67, among whom only one patient required retransplantation due to the development of SFSS [96]. Given the complications associated with the procedure (e.g., encephalopathy due to systemic shunting of the PVF with subsequent hyperammonemia [96], and graft atrophy due to insufficient portal inflow caused by the systemic shunting), the shunt was closed postoperatively to restore the PVF back to the liver by deploying an aortic covered endograft [103] or by tightening of the endo-loop left around the shunt at the time of transplantation [104]. As an alternative, a mesorenal shunt between the inferior mesenteric vein to the left renal vein is easy to perform and prevents excessive portosystemic shunting while also decreasing the PVP [97,98].

Occlusion of the splenic circulation (splenectomy, splenic artery ligation or embolization), which contributes considerably to the portal inflow, not only decreases the PVF [92] and PVP [85,87], but also increases the HAF [92] with a subsequent increase in oxygen supply [105] via HABR [106]. Although splenectomy, which abolishes both arterial and venous blood flow to the portal vein, is more effective in decreasing the PVF than splenic artery ligation or embolization, it increases the length of the operation [107] and the risks of bleeding, infection [107], and portal vein thrombosis [108] in cirrhotic patients exhibiting a hyperdynamic state with collateral circulation around the splenic artery (such as a gastric coronary vein and spleno-renal shunt) [109]. However, despite the absence of complications associated with splenectomy, a splenic abscess resulting from a splenic infarction may occur following splenic artery ligation in patients with an enlarged spleen due to portal hypertension [110]. The effect of splenic artery embolization is comparable to that of splenic artery ligation [101].

The criteria of the hepatic hemodynamic parameters for graft inflow modulation are still debated. An elevated mean PVP of more than 20 mmHg early in the first week after LDLT was found to be associated with an increased incidence of bacteremia in the first 3 months and worse graft survival at the 6th postoperative month [87]. Patients with a final PVP less than 15 mmHg had better 2-year survival and recovery from hyperbilirubinemia and coagulopathy after LDLT than those with a PVP more than 15 mmHg [100]. Thereafter, a PVP less than 15 mmHg was suggested as a surgical strategy for small-for-size grafts in the subsequent study in which intentional PVP modulation was performed to achieve a target PVP of less than 20 mmHg [111].

The PVF is another hepatic hemodynamic parameter used to determine whether to perform graft inflow modulation. In full-size liver transplantation, four times the PVF of healthy donors (360 ml/min per 100 g of liver weight) was shown to be a risk factor for graft failure; a flow rate below 180 ml/min per 100 g of liver weight was also associated with lower survival rates [112]. These results were confirmed in an experimental study that used small-for-size grafts [113]. In addition, the results of other studies showed a PVF less than 260 ml/min 100 g of liver weight for preventing allograft dysfunction [114]. Similarly, a PVF of 250 ml/min per 100 g of liver weight predicted the development of SFSS [92]. By incorporating several criteria, including PVF, PVP, or HVPG, many flowcharts for graft inflow modulation have been proposed [84,112,115]. However, a detailed discussion of these flowcharts is beyond the scope of this review.

Pharmacological intervention

Adenovirally overexpressed redox factor-1 in a partial liver graft [116], an endothelin A receptor antagonist that maintains a balance between endothelin-1 and NO [88], low-dose somatostatin (which attenuates acute-phase shear stress due to transient portal hypertension) [117], a preservation solution containing activated protein C (which has cytoprotective properties due to its anti-inflammatory and anti-apoptotic effects) [118], venous systemic oxygen persufflation with NO gas [119], and a newly developed low-viscosity preservation solution (POLYSOL) [120] reduced graft injury after reduced-size rat liver transplantation. Subcutaneous injection of granulocyte colony-stimulating factor [121] and hyperbaric oxygen treatment [122] also reduced liver damage in rats undergoing massive partial hepatectomy. Intraportal infusion of nafamostat mesilate (protease inhibitor), prostaglandin E1, and thromboxane A2 synthetase inhibitor for 7 days prevented SFSS in patients undergoing LDLT [123].

Anesthetic considerations for portal hyperperfusion

The role of anesthesiologists in liver transplantation is to maintain multiple systemic hemodynamic parameters (e.g., radial, femoral, and pulmonary arterial pressure, central venous pressure [measured from the internal jugular or subclavian vein, and femoral vein], cardiac index, stroke volume index, stroke volume variation, and systemic vascular resistance index) within normal ranges for patient protection against the physiological derangements caused by the surgical procedure. Among these parameters, central venous pressure measured from the internal or subclavian vein (into which a catheter is inserted with its tip located within the lower third of the superior vena cava close to the junction of the superior vena cava and right atrium) [124] is comparable to hepatic vein pressure [125] which might influence the portal hemodynamic parameters. Accordingly, PVP has been reported to be modulated by central venous pressure [112,126,127]. An increase in central venous pressure by 58% was found to be transmitted to the PVP in patients receiving liver transplantation [112] and 60% [126] and 90% [127] of inferior vena cava pressure contributed to PVP in experimental studies. Recently, maintenance of central venous pressure between 5 and 10 mmHg during the neohepatic phase was recommended to prevent portal hyperperfusion of a liver graft. This recommendation was derived from a predictive model built with percent change in peak portal vein flow velocity (which was measured by spectral Doppler ultrasonography after reconstruction of the hepatic artery and bile duct as well as on the 1st postoperative day), and the central venous pressure measured from the right internal jugular vein (which was averaged for 5 min after the measurement using spectral Doppler ultrasonography during the neohepatic phase) [128].

CONCLUSIONS

In accordance with the clinical conditions that liver grafts encounters, the graft either regenerates or fails to accommodate portal hyperperfusion. Although GRWR $<$ 0.8, standard liver volume $<$ 35%, or excessive portal blood inflow to a partial graft in the presence of hyperdynamic splanchnic circulation were found to contribute to hyperperfusion injury, they are not yet used as absolute determinants of hyperperfusion injury and still have to be confirmed in further investigations. Furthermore, clinical strategies and modalities to maintain the viability of grafts showing reduced direct control of enhanced PVF have not been standardized. It is hoped that anesthesiologists will contribute to the prevention of hyperperfusion injury of liver grafts by maintaining optimal systemic hemodynamic stability, and by conducting systemic pharmacological interventions in collaboration with transplantation surgeons based on a comprehensive understanding of the clinical implications of portal hyperperfusion caused by the underlying hyperdynamic splanchnic circulation resulting from portal hypertension.

REFERENCES

1. Eguchi S, Yanaga K, Sugiyama N, Okudaira S, Furui J, Kanematsu T. Relationship between portal venous flow and liver regeneration in patients after living donor right-lobe liver transplantation. Liver Transpl 2003; 9: 547-51.
2. Hadengue A, Lebrec D, Moreau R, Sogni P, Durand F, Gaudin C, et al. Persistence of systemic and splanchnic hyperkinetic circulation in liver transplant patients. Hepatology 1993; 17: 175-8.
3. Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide 2001; 5: 453-64.
4. Abshagen K, Eipel C, Kalff JC, Menger MD, Vollmar B. Kupffer cells are mandatory for adequate liver regeneration by mediating hyperperfusion via modulation of vasoactive proteins. Microcirculation 2008; 15: 37-47.
5. Troisi R, Ricciardi S, Smeets P, Petrovic M, Van Maele G, Colle I, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. Am J Transplant 2005; 5: 1397-404.
6. Greenway CV, Stark RD. Hepatic vascular bed. Physiol Rev 1971; 51: 23-65.
7. Bradley SE. Variations in hepatic blood flow in man during health and disease. N Engl J Med 1949; 240: 456-61.
8. Atkinson M, Sherlock S. Intrasplenic pressure as index of portal venous pressure. Lancet 1954; 266: 1325-7.
9. Wakim KG. Physiology of the liver. Am J Med 1954; 16: 256-71.
10. Wakim KG. Basic and clinical physiology of the liver: normal and abnormal. Anesth Analg 1965; 44 Suppl: 632-710.
11. Lautt WW. Regulatory processes interacting to maintain hepatic blood flow constancy: Vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. Hepatol Res 2007; 37: 891-903.
12. Vollmar B, Menger MD. The hepatic microcirculation: mechanistic contributions and therapeutic targets in liver injury and repair. Physiol Rev 2009; 89: 1269-339.
13. Pirola RC, Lieber CS. Hypothesis: energy wastage in alcoholism and drug abuse: possible role of hepatic microsomal enzymes. Am J Clin Nutr 1976; 29: 90-3.
14. Lautt WW, Greenway CV. Conceptual review of the hepatic vascular bed. Hepatology 1987; 7: 952-63.
15. Rappaport AM. The microcirculatory hepatic unit. Microvasc Res 1973; 6: 212-28.
16. Davis WD Jr, Batson HM Jr, Reichman S, Gorlin R, Storaasli JP. Clinical applications of intrasplenic technique of portal pressure and hepatic blood flow determinations. Gastroenterology 1958; 34: 52-64.
17. Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. Gastroenterology 2008; 134: 1715-28.
18. Buob S, Johnston AN, Webster CR. Portal hypertension: pathophysiology, diagnosis, and treatment. J Vet Intern Med 2011; 25: 169-86.
19. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World J Gastroenterol 2010; 16: 6046-57.
20. Jakab F, Ráth Z, Schmal F, Nagy P, Faller J. The interaction between hepatic arterial and portal venous blood flows; simultaneous measurement by transit time ultrasonic volume flowmetry. Hepatogastroenterology 1995; 42: 18-21.
21. Lautt WW, Legare DJ, d'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). Am J Physiol 1985; 248: H331-8.
22. Lautt WW. The hepatic artery: subservient to hepatic metabolism or guardian of normal hepatic clearance rates of humoral substances. Gen Pharmacol 1977; 8: 73-8.
23. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Hepatic artery hemodynamics suggest operation of a buffer response in the human fetus. Reprod Sci 2008; 15: 166-78.
24. Ezzat WR, Lautt WW. Hepatic arterial pressure-flow autoregulation is adenosine mediated. Am J Physiol 1987; 252: H836-45.
25. Lautt WW, Legare DJ. The use of 8-phenyltheophylline as a competitive antagonist of adenosine and an inhibitor of the intrinsic regulatory mechanism of the hepatic artery. Can J Physiol Pharmacol 1985; 63: 717-22.
26. Richter S, Vollmar B, Mücke I, Post S, Menger MD. Hepatic arteriolo-portal venular shunting guarantees maintenance of nutritional microvascular supply in hepatic arterial buffer response of rat livers. J Physiol 2001; 531: 193-201.
27. Browse DJ, Mathie RT, Benjamin IS, Alexander B. The role of ATP and adenosine in the control of hepatic blood flow in the rabbit liver in vivo. Comp Hepatol 2003; 2: 9.
28. Browse DJ, Mathie RT, Benjamin IS, Alexander B. The action of ATP on the hepatic arterial and portal venous vascular networks of the rabbit liver: the role of adenosine. Eur J Pharmacol 1997; 320: 139-44.
29. Belloni FL, Elkin PL, Giannotto B. The mechanism of adenosine release from hypoxic rat liver cells. Br J Pharmacol 1985; 85: 441-6.
30. Ralevic V, Milner P, Kirkpatrick KA, Burnstock G. Flow-induced release of adenosine 5'-triphosphate from endothelial cells of the rat mesenteric arterial bed. Experientia 1992; 48: 31-4.
31. Pearson JD, Carleton JS, Gordon JL. Metabolism of adenine nucleotides by ectoenzymes of vascular endothelial and smooth-muscle cells in culture. Biochem J 1980; 190: 421-9.
32. Bloom S, Kemp W, Lubel J. Portal hypertension: pathophysiology, diagnosis and management. Intern Med J 2015; 45: 16-26.
33. Kumar A, Sharma P, Sarin SK. Hepatic venous pressure gradient measurement: time to learn! Indian J Gastroenterol 2008; 27: 74-80.
34. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis-a histological classification of the severity of cirrhosis. J Hepatol 2006; 44: 111-7.

35. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005; 353: 2254-61.
36. Procopeţ B, Tantau M, Bureau C. Are there any alternative methods to hepatic venous pressure gradient in portal hypertension assessment? J Gastrointestin Liver Dis 2013; 22: 73-8.
37. Bosch J, Abraldes JG, Fernández M, García-Pagán JC. Hepatic endothelial dysfunction and abnormal angiogenesis: new targets in the treatment of portal hypertension. J Hepatol 2010; 53: 558-67.
38. Moreno AH, Burchell AR, Rousselot LM, Panke WF, Slafsky F, Burke JH. Portal blood flow in cirrhosis of the liver. J Clin Invest 1967; 46: 436-45.
39. Vollmar B, Siegmund S, Richter S, Menger MD. Microvascular consequences of Kupffer cell modulation in rat liver fibrogenesis. J Pathol 1999; 189: 85-91.
40. Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. Gastroenterology 1984; 87: 1120-6.
41. Colle I, Geerts AM, Van Steenkiste C, Van Vlierberghe H. Hemodynamic changes in splanchnic blood vessels in portal hypertension. Anat Rec (Hoboken) 2008; 291: 699-713.
42. Ignarro LJ, Byrns RE, Wood KS. Endothelium-dependent modulation of cGMP levels and intrinsic smooth muscle tone in isolated bovine intrapulmonary artery and vein. Circ Res 1987; 60: 82-92.
43. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 288: 373-6.
44. Xie QW, Cho HJ, Calaycay J, Mumford RA, Swiderek KM, Lee TD, et al. Cloning and characterization of inducible nitric oxide synthase from mouse macrophages. Science 1992; 256: 225-8.
45. Bredt DS, Hwang PM, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 1990; 347: 768-70.
46. Tazi KA, Moreau R, Hervé P, Dauvergne A, Cazals-Hatem D, Bert F, et al. Norfloxacin reduces aortic NO synthases and proinflammatory cytokine up-regulation in cirrhotic rats: role of Akt signaling. Gastroenterology 2005; 129: 303-14.
47. Tsai MH, Iwakiri Y, Cadelina G, Sessa WC, Groszmann RJ. Mesenteric vasoconstriction triggers nitric oxide overproduction in the superior mesenteric artery of portal hypertensive rats. Gastroenterology 2003; 125: 1452-61.
48. Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. J Hepatol 2009; 50: 604-20.
49. Jurzik L, Froh M, Straub RH, Schölmerich J, Wiest R. Up-regulation of nNOS and associated increase in nitrergic vasodilation in superior mesenteric arteries in pre-hepatic portal hypertension. J Hepatol 2005; 43: 258-65.
50. Xu L, Carter EP, Ohara M, Martin PY, Rogachev B, Morris K, et al. Neuronal nitric oxide synthase and systemic vasodilation in rats with cirrhosis. Am J Physiol Renal Physiol 2000; 279: F1110-5.
51. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology 2006; 43(2 Suppl 1): S121-31.
52. Genecin P, Polio J, Groszmann RJ. Na restriction blunts expansion of plasma volume and ameliorates hyperdynamic circulation in portal hypertension. Am J Physiol 1990; 259: G498-503.
53. Vaughan RB, Angus PW, Chin-Dusting JP. Evidence for altered vascular responses to exogenous endothelin-1 in patients with advanced cirrhosis with restoration of the normal vasoconstrictor response following successful liver transplantation. Gut 2003; 52: 1505-10.
54. Sato Y, Koyama S, Tsukada K, Hatakeyama K. Acute portal hypertension reflecting shear stress as a trigger of liver regeneration following partial hepatectomy. Surg Today 1997; 27: 518-26.
55. Busse R, Fleming I. Pulsatile stretch and shear stress: physical stimuli determining the production of endothelium-derived relaxing factors. J Vasc Res 1998; 35: 73-84.
56. Sato Y, Tsukada K, Hatakeyama K. Role of shear stress and immune responses in liver regeneration after a partial hepatectomy. Surg Today 1999; 29: 1-9.
57. Koch KS, Leffert HL. Increased sodium ion influx is necessary to initiate rat hepatocyte proliferation. Cell 1979; 18: 153-63.
58. Yee AG, Revel JP. Loss and reappearance of gap junctions in regenerating liver. J Cell Biol 1978; 78: 554-64.
59. Morsiani E, Aleotti A, Ricci D. Haemodynamic and ultrastructural observations on the rat liver after two-thirds partial hepatectomy. J Anat 1998; 192: 507-15.
60. Thevananther S, Sun H, Li D, Arjunan V, Awad SS, Wyllie S, et al. Extracellular ATP activates c-jun N-terminal kinase signaling and cell cycle progression in hepatocytes. Hepatology 2004; 39: 393-402.
61. Schlosser SF, Burgstahler AD, Nathanson MH. Isolated rat hepatocytes can signal to other hepatocytes and bile duct cells by release of nucleotides. Proc Natl Acad Sci U S A 1996; 93: 9948-53.
62. Gonzales E, Julien B, Serrière-Lanneau V, Nicou A, Doignon I, Lagoudakis L, et al. ATP release after partial hepatectomy regulates liver regeneration in the rat. J Hepatol 2010; 52: 54-62.
63. Crumm S, Cofan M, Juskeviciute E, Hoek JB. Adenine nucleotide changes in the remnant liver: An early signal for regeneration after partial hepatectomy. Hepatology 2008; 48: 898-908.
64. Schaffner F, Poper H. Capillarization of hepatic sinusoids in man. Gastroenterology 1963; 44: 239-42.
65. Shah V, Haddad FG, Garcia-Cardena G, Frangos JA, Mennone A, Groszmann RJ, et al. Liver sinusoidal endothelial cells are responsible for nitric oxide modulation of resistance in the hepatic sinusoids. J Clin Invest 1997; 100: 2923-30.
66. Wang HH, Lautt WW. Does nitric oxide (NO) trigger liver regeneration? Proc West Pharmacol Soc 1997; 40: 17-8.
67. Wang HH, Lautt WW. Evidence of nitric oxide, a

flow-dependent factor, being a trigger of liver regeneration in rats. Can J Physiol Pharmacol 1998; 76: 1072-9.
68. Hortelano S, Zeini M, Casado M, Martín-Sanz P, Boscá L. Animal models for the study of liver regeneration: role of nitric oxide and prostaglandins. Front Biosci 2007; 12: 13-21.
69. García-Trevijano ER, Martínez-Chantar ML, Latasa MU, Mato JM, Avila MA. NO sensitizes rat hepatocytes to proliferation by modifying S-adenosylmethionine levels. Gastroenterology 2002; 122: 1355-63.
70. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999; 67: 321-7.
71. Gondolesi GE, Florman S, Matsumoto C, Huang R, Fishbein TM, Sheiner PA, et al. Venous hemodynamics in living donor right lobe liver transplantation. Liver Transpl 2002; 8: 809-13.
72. García-Valdecasas JC, Fuster J, Charco R, Bombuy E, Fondevila C, Ferrer J, et al. Changes in portal vein flow after adult living-donor liver transplantation: does it influence postoperative liver function? Liver Transpl 2003; 9: 564-9.
73. Park MY, Lee YJ, Rha SE, Oh SN, Byun JY, Kim DG. Correlation of portal venous velocity and portal venous flow with short-term graft regeneration in recipients of living donor liver transplants. Transplant Proc 2008; 40: 1488-91.
74. Jiang SM, Zhou GW, Zhang R, Peng CH, Yan JQ, Wan L, et al. Role of splanchnic hemodynamics in liver regeneration after living donor liver transplantation. Liver Transpl 2009; 15: 1043-9.
75. Lo CM, Liu CL, Fan ST. Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver graft-successful treatment with splenic artery ligation. Liver Transpl 2003; 9: 626-8.
76. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am J Transplant 2005; 5: 2605-10.
77. Takeda K, Tanaka K, Kumamoto T, Nojiri K, Mori R, Taniguchi K, et al. Emergency versus elective living-donor liver transplantation: a comparison of a single center analysis. Surg Today 2012; 42: 453-9.
78. Gruttadauria S, Pagano D, Luca A, Gridelli B. Small-for-size syndrome in adult-to-adult living-related liver transplantation. World J Gastroenterol 2010; 16: 5011-5.
79. Kelly DM, Zhu X, Shiba H, Irefin S, Trenti L, Cocieru A, et al. Adenosine restores the hepatic artery buffer response and improves survival in a porcine model of small-for-size syndrome. Liver Transpl 2009; 15: 1448-57.
80. Fan ST, Lo CM, Liu CL, Yong BH, Wong J. Determinants of hospital mortality of adult recipients of right lobe live donor liver transplantation. Ann Surg 2003; 238: 864-69.
81. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, et al. Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single-center experience of 107 cases. Am J Transplant 2006; 6: 1004-11.
82. Hill MJ, Hughes M, Jie T, Cohen M, Lake J, Payne WD, et al. Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? Liver Transpl 2009; 15: 1056-62.
83. Ikegami T, Shirabe K, Yoshizumi T, Aishima S, Taketomi YA, Soejima Y, et al. Primary graft dysfunction after living donor liver transplantation is characterized by delayed functional hyperbilirubinemia. Am J Transplant 2012; 12: 1886-97.
84. Asencio JM, Vaquero J, Olmedilla L, García Sabrido JL. "Small-for-flow" syndrome: shifting the "size" paradigm. Med Hypotheses 2013; 80: 573-7.
85. Luca A, Miraglia R, Caruso S, Milazzo M, Gidelli B, Bosch J. Effects of splenic artery occlusion on portal pressure in patients with cirrhosis and portal hypertension. Liver Transpl 2006; 12: 1237-43.
86. Kiuchi T, Tanaka K, Ito T, Oike F, Ogura Y, Fujimoto Y, et al. Small-for-size graft in living donor liver transplantation: how far should we go? Liver Transpl 2003; 9: S29-35.
87. Ito T, Kiuchi T, Yamamoto H, Oike F, Ogura Y, Fujimoto Y, et al. Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. Transplantation 2003; 75: 1313-7.
88. Palmes D, Minin E, Budny T, Uhlmann D, Armann B, Stratmann U, et al. The endothelin/nitric oxide balance determines small-for-size liver injury after reduced-size rat liver transplantation. Virchows Arch 2005; 447: 731-41.
89. Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Lower limit of the graft-to-recipient weight ratio can be safely reduced to 0.6% in adult-to-adult living donor liver transplantation in combination with portal pressure control. Transplant Proc 2011; 43: 2391-3.
90. Marcos A, Olzinski AT, Ham JM, Fisher RA, Posner MP. The interrelationship between portal and arterial blood flow after adult to adult living donor liver transplantation. Transplantation 2000; 70: 1697-703.
91. Rocheleau B, Ethier C, Houle R, Huet PM, Bilodeau M. Hepatic artery buffer response following left portal vein ligation: its role in liver tissue homeostasis. Am J Physiol 1999; 277: G1000-7.
92. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. Liver Transpl 2003; 9: S36-41.
93. Fondevila C, Hessheimer AJ, Taurá P, Sánchez O, Calatayud D, de Riva N, et al. Portal hyperperfusion: mechanism of injury and stimulus for regeneration in porcine small-for-size transplantation. Liver Transpl 2010; 16: 364-74.
94. Boillot O, Delafosse B, Méchet I, Boucaud C, Pouyet M. Small-for-size partial liver graft in an adult recipient; a new transplant technique. Lancet 2002; 359: 406-7.
95. Yamada T, Tanaka K, Uryuhara K, Ito K, Takada Y, Uemoto S. Selective hemi-portocaval shunt based on portal vein pressure for small-for-size graft in adult living donor liver transplantation. Am J Transplant 2008; 8: 847-53.
96. Botha JF, Langnas AN, Campos BD, Grant WJ, Freise CE, Ascher NL, et al. Left lobe adult-to-adult living donor liver transplantation: small grafts and hemiportocaval shunts in the

prevention of small-for-size syndrome. Liver Transpl 2010; 16: 649-57.
97. Kanazawa H, Takada Y, Ogura Y, Oike F, Egawa H, Uemoto S. Mesorenal shunt using inferior mesenteric vein and left renal vein in a case of LDLT. Transpl Int 2009; 22: 1189-92.
98. Sato Y, Yamamoto S, Takeishi T, Kato T, Nakatsuka H, Kobayashi T, et al. Inferior mesenteric venous left renal vein shunting for decompression of excessive portal hypertension in adult living related liver transplantation. Transplant Proc 2004; 36: 2234-6.
99. Sato Y, Yamamoto S, Takeishi T, Hirano K, Kobayashi T, Kato T, et al. Management of major portosystemic shunting in small-for-size adult living-related donor liver transplantation with a left-sided graft liver. Surg Today 2006; 36: 354-60.
100. Ogura Y, Hori T, El Moghazy WM, Yoshizawa A, Oike F, Mori A, et al. Portal pressure <15 mm Hg is a key for successful adult living donor liver transplantation utilizing smaller grafts than before. Liver Transpl 2010; 16: 718-28.
101. Umeda Y, Yagi T, Sadamori H, Matsukawa H, Matsuda H, Shinoura S, et al. Effects of prophylactic splenic artery modulation on portal overperfusion and liver regeneration in small-for-size graft. Transplantation 2008; 86: 673-80.
102. Humar A, Beissel J, Crotteau S, Cohen M, Lake J, Payne WD. Delayed splenic artery occlusion for treatment of established small-for-size syndrome after partial liver transplantation. Liver Transpl 2009; 15: 163-8.
103. Botha JF, Campos BD, Johanning J, Mercer D, Grant W, Langnas A. Endovascular closure of a hemiportocaval shunt after small-for-size adult-to-adult left lobe living donor liver transplantation. Liver Transpl 2009; 15: 1671-5.
104. Raut V, Alikhanov R, Belghiti J, Uemoto S. Review of the surgical approach to prevent small-for-size syndrome in recipients after left lobe adult LDLT. Surg Today 2014; 44: 1189-96.
105. Eipel C, Abshagen K, Ritter J, Cantré D, Menger MD, Vollmar B. Splenectomy improves survival by increasing arterial blood supply in a rat model of reduced-size liver. Transpl Int 2010; 23: 998-1007.
106. Payen DM, Fratacci MD, Dupuy P, Gatecel C, Vigouroux C, Ozier Y, et al. Portal and hepatic arterial blood flow measurements of human transplanted liver by implanted Doppler probes: interest for early complications and nutrition. Surgery 1990; 107: 417-27.
107. Samimi F, Irish WD, Eghtesad B, Demetris AJ, Starzl TE, Fung JJ. Role of splenectomy in human liver transplantation under modern-day immunosuppression. Dig Dis Sci 1998; 43: 1931-7.
108. Pan C, Shi Y, Zhang JJ, Deng YL, Zheng H, Zhu ZJ, et al. Single-center experience of 253 portal vein thrombosis patients undergoing liver transplantation in China. Transplant Proc 2009; 41: 3761-5.
109. Piscaglia F, Zironi G, Gaiani S, Mazziotti A, Cavallari A, Gramantieri L, et al. Systemic and splanchnic hemodynamic changes after liver transplantation for cirrhosis: a long-term prospective study. Hepatology 1999; 30: 58-64.
110. Balci D, Taner B, Dayangac M, Akin B, Yaprak O, Duran C, et al. Splenic abscess after splenic artery ligation in living donor liver transplantation: a case report. Transplant Proc 2008; 40: 1786-8.
111. Hori T, Ogura Y, Ogawa K, Kaido T, Segawa H, Okajima H, et al. How transplant surgeons can overcome the inevitable insufficiency of allograft size during adult living-donor liver transplantation: strategy for donor safety with a smaller-size graft and excellent recipient results. Clin Transplant 2012; 26: E324-34.
112. Sainz-Barriga M, Scudeller L, Costa MG, de Hemptinne B, Troisi RI. Lack of a correlation between portal vein flow and pressure: toward a shared interpretation of hemodynamic stress governing inflow modulation in liver transplantation. Liver Transpl 2011; 17: 836-48.
113. Hessheimer AJ, Fondevila C, Taurá P, Muñoz J, Sánchez O, Fuster J, et al. Decompression of the portal bed and twice-baseline portal inflow are necessary for the functional recovery of a "small-for-size" graft. Ann Surg 2011; 253: 1201-10.
114. Shimamura T, Taniguchi M, Jin MB, Suzuki T, Matsushita M, Furukawa H, et al. Excessive portal venous inflow as a cause of allograft dysfunction in small-for-size living donor liver transplantation. Transplant Proc 2001; 33: 1331.
115. Feng AC, Fan HL, Chen TW, Hsieh CB. Hepatic hemodynamic changes during liver transplantation: a review. World J Gastroenterol 2014; 20: 11131-41.
116. Guo L, Haga S, Enosawa S, Naruse K, Harihara Y, Sugawara Y, et al. Improved hepatic regeneration with reduced injury by redox factor-1 in a rat small-sized liver transplant model. Am J Transplant 2004; 4: 879-87.
117. Xu X, Man K, Zheng SS, Liang TB, Lee TK, Ng KT, et al. Attenuation of acute phase shear stress by somatostatin improves small-for-size liver graft survival. Liver Transpl 2006; 12: 621-7.
118. Kuriyama N, Isaji S, Hamada T, Kishiwada M, Ohsawa I, Usui M, et al. The cytoprotective effects of addition of activated protein C into preservation solution on small-for-size grafts in rats. Liver Transpl 2010; 16: 1-11.
119. Yagi S, Nagai K, Kadaba P, Afify M, Teramukai S, Uemoto S, et al. A novel organ preservation for small partial liver transplantations in rats: venous systemic oxygen persufflation with nitric oxide gas. Am J Transplant 2013; 13: 222-8.
120. Yagi S, Doorschodt BM, Afify M, Klinge U, Kobayashi E, Uemoto S, et al. Improved preservation and microcirculation with POLYSOL after partial liver transplantation in rats. J Surg Res 2011; 167: e375-83.
121. Ji Y, Dahmen U, Madrahimov N, Madrahimova F, Xing W, Dirsch O. G-CSF administration in a small-for-size liver model. J Invest Surg 2009; 22: 167-77.
122. Ijichi H, Taketomi A, Yoshizumi T, Uchiyama H, Yonemura Y, Soejima Y, et al. Hyperbaric oxygen induces vascular endothelial growth factor and reduces liver injury in regenerating rat liver after partial hepatectomy. J Hepatol 2006; 45: 28-34.
123. Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, et al. Effect of intraportal infusion to improve small

for size graft injury in living donor adult liver transplantation. Transpl Int 2005; 18: 923-8.
124. Vesely TM. Central venous catheter tip position: a continuing controversy. J Vasc Interv Radiol 2003; 14: 527-34.
125. Sand L, Rizell M, Houltz E, Karlsen K, Wiklund J, Odenstedt Hergès H, et al. Effect of patient position and PEEP on hepatic, portal and central venous pressures during liver resection. Acta Anaesthesiol Scand 2011; 55: 1106-12.
126. Greenway CV, Lautt WW. Distensibility of hepatic venous resistance sites and consequences on portal pressure. Am J Physiol 1988; 254: H452-8.
127. Laine GA, Hall JT, Laine SH, Granger J. Transsinusoidal fluid dynamics in canine liver during venous hypertension. Circ Res 1979; 45: 317-23.
128. Ryu TH, Jung JY, Choi DL, Han YS, Kim JD, Kim JH. Optimal central venous pressure during the neohepatic phase to decrease peak portal vein flow velocity for the prevention of portal hyperperfusion in patients undergoing living donor liver transplantation. Transplant Proc 2015; 47: 1194-8.