Portal Hemodynamics in Liver Resection and Transplantation

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Abstract: The hepatic blood supply and its several homeostatic and pathologic processes have always been a matter of great interest. Many views commonly held today are derived from an earlier era, but major reorientations have occurred recently in almost all aspects of knowledge of the role and regulation of hepatic blood flow. Moreover, with the advent of liver transplantation (LT), especially living donor LT, there has been a resurgence of interest in attempting to comprehend this deceptively simple topic. It is nonetheless important to concede that even though our knowledge of the practical modulation of hepatic hemodynamics has expanded enormously, there still remains the need to explore the depths of our remaining ignorance to further improve outcomes in living donor LT. This review focuses on the current view, controversies, and gaps in knowledge of the hepatic vascular bed, with an emphasis on the importance of portal hemodynamics in liver disease and its impact on liver regeneration and LT.

Key Words: living donor liver transplantation, portal hemodynamics, pathophysiology, small-for-size syndrome

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The interrelationship between the liver's blood supply and its various homeostatic and pathologic processes has been a matter of great interest. The drive to comprehend this deceptively simple topic has seen a resurgence after the advent of liver transplantation (LT), especially living donor liver transplantation (LDLT) for end stage liver disease.[1–3] The importance of portal inflow for liver regeneration and the adverse effect of portal hypertension (PHT) after major hepatectomy is also well recognized.[4–7] Furthermore, every known form of liver disease results in altered hepatic hemodynamics, which in turn has a major impact on the cardiovascular, intermediary metabolic, and endocrine functions. Many views commonly held today are derived from an earlier era. However, major reorientations have occurred recently in almost all aspects of knowledge of the role and regulation of hepatic blood flow.

The emphasis of this review is to focus on the current view, controversies, and gaps in knowledge of the hepatic vascular bed, with an emphasis on the importance of portal hemodynamics in liver disease and its impact on liver regeneration and LT.

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HEPATIC VASCULAR BED

Macrocirculation

Even though the liver constitutes only 2.5% of body weight, it receives 25% of cardiac output.[8–11] Of a total blood flow of 100 to 130 mL/min/100 gm liver or 30 mL/min/kg body weight, about 20% to 33% is supplied by the hepatic artery (HA), and the remaining is accounted for by portal venous flow. The liver is a major reservoir of blood, and 30% of the hepatic volume is made up of blood (12% of total body blood volume). Only 40% of the hepatic blood volume is present in the major blood vessels, the remaining 60% is accounted for by the sinusoids. Interestingly, more than half of this volume can be expelled within 90 seconds under the effect of adrenergic and angiotensin stimuli without compromising liver function.[8–12]

In a normal physiological state, the mesenteric component of the blood through the superior mesenteric vein contributes to about 60% of the portal blood fraction.[8–12] The splenic component of the blood through the splenic vein makes up the remaining 40%. This can drastically change or even reverse in patients with PHT and large splenomegaly.[9,10,12]

Microcirculation

Hepatic acinus is the basic parenchymal unit of the liver and is formed by ~100,000 cells.[13–15] It is ~2 mm in diameter and the cells are located around the terminal branches of the portal triad. The unidirectional flow into the acini is from the periportal regions (zone 1) towards the hepatic venule (zone 3). Thus, there is a dramatic difference in oxygen and substrate concentration as the blood flows from zones 1 to 3 in the acinus. While zone 1 has the highest concentration of oxygen and consequently the highest activity of respiratory enzymes, zone 3 is relatively hypoxic and is rich in microsomal enzymes. This periacinar microenvironment regulates hepatocyte function.[11,13,14,16]

As evidenced by the uniform distribution of microspheres injected into either the HA or portal vein (PV), blood flow within the liver is uniformly distributed. Substances reaching the liver through either of the 2 vascular channels are equally extracted. Changes in portal flow, venous pressure, and stimulation of hepatic nerves do not disturb this homogeneity of liver perfusion and are likely a function of the hepatic artery buffer response (HABR).[8,9,17–19]

REGULATION OF VASCULAR FLOW

Although the liver does not regulate portal flow, it does regulate portal pressure (PP). Intrahepatic pressure is virtually equal to portal venous pressure in the normal basal state and is regulated by hepatic venous sphincters (HVSs) which are distensible. Even at low flows, the intrahepatic pressure allows all sinusoids to be uniformly perfused. The high-pressure, well-oxygenated arterial blood mixes completely

with the low-pressure, less well-oxygenated, but nutrient-rich, portal venous blood within the hepatic sinusoids. Thus, the only control of blood flow within the liver is through the HA.[8,9,19,20]

Hepatic Arterial Flow Regulation

The metabolic requirements of the hepatocytes or the myogenic stimulus (to reduce portal flow or arterial smooth muscle contraction) have no role in the regulation of hepatic arterial flow. Hepatic arterial flow is intrahepatically controlled through 2 mechanisms, both of which involve adenosine.[8,9,11,19,20] The first is the arterial auto-regulation wherein the HA constricts in response to a rise in arterial pressure, and the second is the HABR. The HABR is essentially a vasodilatation of the HA in response to a reduction in portal venous flow; similarly, an arterial vasoconstriction occurs when the portal venous flow increases. It is noteworthy that there is no reciprocity in the responses (changes in the hepatic arterial perfusion do not alter portal vascular flow or resistance).

Adenosine is released at a constant rate into a fluid in the space of Mall (located within the limiting plate).[10,19,20] This fluid surrounds the hepatic arterial resistance vessels and portal venules, and hence adenosine levels are controlled by its washing-out by these vascular structures. When the portal venous flow is low, there is an accumulation of adenosine resulting in hepatic arterial dilatation. Similarly, a portal venous washout of adenosine causes a reduction in hepatic arterial flow. The arterial buffer thus plays a role in the maintenance as steady state as possible of intrahepatic pressures and liver volume.

Portal Venous Pressure Regulation

PP is a direct derivative of portal flow volume and the resistance to portal venous flow. It is mathematically represented by the Ohm formula. In the basal state, wedged hepatic venous pressure is virtually equal to portal venous pressure.[13,14,18,21] It is thus clear that the raised PP must be due to vascular resistance distal to the sinusoids, that is, postsinusoidal resistance. This resistance is largely in the terminal sinusoids and terminal hepatic venules regulated by HVSs.[22–25] In the normal liver, the portal and sinusoidal vascular resistances to blood flow are insignificant, and portal venous pressure equals sinusoidal pressure.

The existence of the HVS partly protects the liver against changes in central venous pressure (CVP). HVS are distensible and during a passive rise in CVP, the resistance becomes diminished. Thus, the direct transmission of CVP is minimal when the pressure is low, but with rising CVP, its influence on PP increases.[14,21–26] At low pressures (below 5 mm Hg) the impact of CVP on the PP is negligible. However, with rising CVP due to the incompetence of the HVS, there is a curvilinear influence of CVP on PP (Fig. 1). This phenomenon is not well understood and applied clinically as there is a lot of importance given to CVP readings while interpreting PP during partial hepatectomy and LT. Most surgeons prefer a low CVP during partial hepatectomy, and at that level, PP readings are not influenced by CVP. Hence, although it is important to take into account CVP readings while measuring PP, it is equally important to understand that the 2 are not additive values.

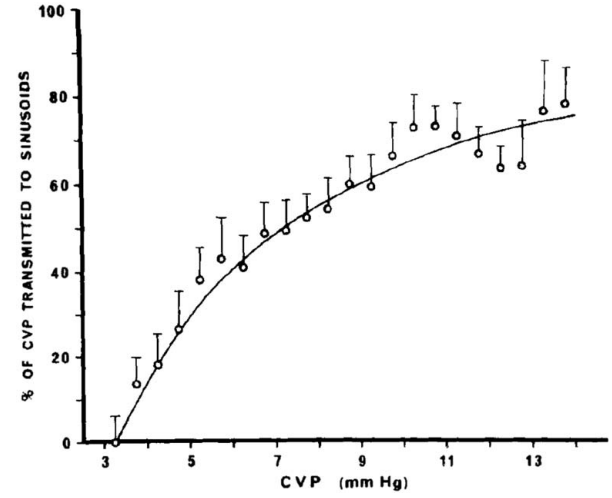

FIGURE 1. Proportion of increase in CVP transmitted to sinusoidal pressure, calculated from 16 original curves. A data point at 5.75 mm Hg CVP represents the percentage of pressure rise from 5.5 to 6.0 mm Hg CVP that was transferred to the sinusoids. Note that even very small elevations in CVP are partially transmitted upstream to the sinusoids. The percentage transmission for small elevations in CVP is low, but rises as the distending pressure of the CVP leads to distention of the hepatic sphincter and a resultant decrease in sphincter resistance. Active vasoconstriction affects this relationship by reducing the percent transmission at each point (reprinted with permission from Microvascular Research. Vol. 33, No. 1, p. 57. Copyright @ 1987 by Elsevier).[26] All permission requests for this image should be made to the copyright holder.

PORTAL HEMODYNAMICS AND LIVER REGENERATION

After major liver resections, there is an absolute decrease in hepatic mass and total sinusoidal cross-sectional area resulting in an increased portal flow relative to a smaller liver mass and as a consequence increase in PP. This state of relative portal hyperperfusion has been shown to increase with the extent of the liver resection. A 50% hepatectomy results in a two-fold increase in portal flow per centimeter.[2,27,28] Increased portal flow is a stimulus for liver regeneration and interestingly, larger the hepatectomy, the more rapid the liver regeneration.[29,30] It has been shown that up to 75% hepatectomy can be safely performed in a normal liver before damage due to hyperperfusion can be anticipated. Thus, a 2 or 3-fold increase in portal flow aids liver regeneration, and any further increase can be detrimental to the remnant liver.

Liver regeneration is a complex process in which portal hemodynamics, several growth factors, cytokines, and transcription factors play a crucial role. As the portal circulation to the remnant liver increases, a number of signal changes in the hepatocyte nuclei occur in an orderly manner within 15 minutes to 1 hour of the resection.[28,31,32] These include signaling cascades urokinase plasminogen activator activity, hepatocyte growth factor, B-catenin, and Notch 1 intracellular domain (NCID) migration to the hepatocyte nuclei. Further extrahepatic factors in the portal blood such as pancreas-derived insulin and Brenner gland-derived epidermal growth factor act as intense hepatocyte mitogens.[27–29,31,32] Animal studies suggest that hepatocyte

growth factor, a potent hepatocyte mitogen, is triggered by portal hyperperfusion and is paramount in the initiation process of liver regeneration.[27–32]

A thorough understanding of the factors which affect liver regeneration is vital in ensuring good outcomes after major liver resections including advanced procedures such as Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS), and the Resection and Partial liver segment 2 to 3 transplantation with Delayed total hepatectomy (RAPID) technique.[33–35] While the basic microphysiology of liver regeneration remains the same, some techniques such as liver venous deprivation and ALPPS result in a much more remarkable and quicker increase in liver volume (1.7–1.8 times) than other techniques such as portal vein ligation or portal vein embolization.[33,36,37]

In LDLT, donor and recipient outcomes center around the regeneration of the liver remnant and allograft respectively, and interestingly, the liver regeneration after performing ALPPS is histologically similar to that occurring after LT using a small-for-size graft (SFSG).[33] Moreover, the high hypertrophy ratio in ALPPS is attained within such a short interval is nearly equal to that after LT using SFSG. In both operations, the liver shows similar ultrastructural and microarchitectural features such as immaturity of regenerative hepatocytes and poor regeneration of the bile canalicular-ductular networks.[33,36] The RAPID procedure is a transplant variant of ALPPS wherein the principle is to transplant the patient with a small auxiliary left liver graft and ligate the right PV, followed by residual hepatectomy at a second stage when the transplanted graft has regenerated to a sufficient size.[35] First, the small liver volume transplanted mandates that the recipient needs to have a well-functioning liver remnant acting as a safeguard until the transplanted graft has regenerated to sufficient size and functional capacity to take over total liver function. Second, a very small graft is more susceptible to the small-for-size syndrome (SFSS; discussed further), and measures such portal-caval shunt may need to be performed to avoid such an eventuality. Herein lies the importance of an implicit understanding of liver regeneration to ensure an uneventful recovery of the patient.

PORTAL HEMODYNAMICS IN CHRONIC LIVER DISEASE

PHT is a pathologic state wherein there are hemodynamic alterations within the liver and in the systemic and splanchnic circulations all of which result in complications associated with chronic liver disease like ascites, hepatic encephalopathy, gastrointestinal bleeding (GIB), and hepatorenal syndrome. PHT is defined as an increase in PP above the normal range of 6 to 10 mm Hg or, the gradient between portal and hepatic veins above 5 mm Hg. However, the clinical manifestations of PHT are usually observed when the PP is above 12 mm Hg.[38–40]

The main sites of resistance to portal blood flow are the sinusoids and the hepatic venules. Cirrhosis results in a deposition of collagen within the acini and sinusoids. This fibrotic degeneration of the liver distorts the hepatic architecture and increases its resistance to blood flow.[14,41] The nodular regeneration which follows this deposition of collagen causes further resistance to portal flow, and decreases the diffusion of substrates by increasing the distance between the sinusoids and the hepatocytes.[14,41]

Further to an anatomic causation of PHT, a vasoactive and functional mechanism is involved in aggravating the state of raised PP. Myofibroblasts are present in increased numbers in a cirrhotic liver. These cells are derived from the stellate cells that are present around the sinusoids and hepatic venules.[38,42,43] Various vasoactive substances like endothelin, norepinephrine, and angiotensin II which are ineffectively metabolized in the pathologic state exert their influence and increase resistance by causing vasoconstriction. An increase in resistance to portal flow acts as a stimulus to increase splanchnic inflow, which in turn worsens PHT.[14,38,42,43]

This increase in resistance to outflow from the portal system, with the subsequent increase in PP, causes the opening of portal-systemic collaterals or shunts (PSS). Approximately 40% of patients with cirrhosis develop compensatory PSS, the frequency increasing with the severity of cirrhosis. The most common sites for these PSS include the splenic bed, retroperitoneum, and coronary veins. Varices are a manifestation of PSS and can result in GIB. These shunts also allow various vasoactive, neurogenic, and biochemical substances to bypass being metabolized in the liver. A factor that plays an important role in the pathogenesis of hyperdynamic circulation, ascites, and hepatic encephalopathy. PSS has a pathogenetic pivotal role in hyperdynamic circulatory syndrome (defined as an increase in cardiac index and a decrease in systemic vascular resistance).[39–41] Although there is an overall decrease in systemic vascular resistance, this is not reflected in all vascular beds. The splanchnic blood flow is markedly increased, but the renal flow is reduced in the kidney, brain, and muscles. Splenic blood flow is increased in patients with PHT, and studies have shown that the splenic volume correlated with the PV diameter and splenic blood flow. Therefore, in PHT, splenic enlargement is not just the result of passive congestion. Instead, splenic hemodynamics play an active part in congesting the portal circulation and exacerbating the state of PHT. This factor has often been overlooked. As mentioned earlier, while in a normal state, the splenic component represents only about 40% of portal venous flow, in PHT, in addition to the overall increase in portal flow, the splenic contribution to portal inflow also markedly increases to over 60%.[9,10,39–41] The importance of this augmented splenic component of portal flow in PHT was well understood even before the era of surgical shunt surgeries. There are reports from over 50 years ago, wherein surgical splenic artery ligation (SAL) was used as a technique to successfully arrest upper GIB in patients with PHT.[44–46] More recently, imaging evidence of reduced liver-to-spleen ratio has been used as a surrogate marker of PHT.[47–49]

CLINICAL SIGNIFICANCE OF PORTOSYSTEMIC SHUNTS DURING LIVER TRANSPLANTATION

Large PSS especially the ones in the splenic hilum divert blood away from the liver and such patients have relatively lower PP than expected when measured at operation.[50,51] Their pretransplant clinical manifestations are more commonly due to encephalopathy rather than portal hypertensive bleeding. The presence of PSS can sometimes facilitate certain steps of the LT operation like the recipient hepatectomy. Here the adverse effects of PHT like bleed can be significantly reduced.[50,52] Further, PV clamping at the completion of hepatectomy and during

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implantation of the graft is better tolerated with less mesenteric congestion. PSS, however, large, still requires higher pressure than normal PP to remain open, and post-deceased donor liver transplantation (DDLT) when the low-pressure hepato-petal portal flow is restored, these PSS involute rapidly.[50–52]

In contrast, in partial LT, the reduction in PP is not as effective as in whole liver transplant and the PSS fails to involute as rapidly. The persistence of PSS has been implicated in portal steal (PS), graft hypoperfusion and allograft dysfunction, and several authors recommend routine ligation of large collaterals to avoid this risk.[53–57] Interestingly, the presence of large PSS has not been recognized as an issue in DDLT. This is notwithstanding the premise that a whole liver is more prone to suffer from portal hypoperfusion than a smaller partial liver graft.[50,52,58] Various reasons have this postulated for this incongruence. The first is that of a perception bias. When compared with DDLT, portal hemodynamics have been extensively analyzed in the LDLT setting. This makes comparisons and a realization of outcomes difficult. Furthermore, there may be an actual difference in the hepatic hemodynamics between the two types of LT.

Whole liver grafts have a much higher graft-to-recipient weight ratio (GRWR) than partial liver grafts in LDLT. These partial grafts with their lower capacitance cannot decompress the portal system as effectively as the larger capacitance whole liver grafts. Studies have reported that there is a slower and lesser reduction in post-LT splenic and variceal sizes in LDLT as compared with DDLT.[50,52,57–59] PS is, therefore, of greater risk in LDLT due to this lower capacitance, especially during states of graft dysfunction or rejection, wherein the grafts become stiffer. Rapid regeneration seen in partial grafts can also lead to an increased resistance to portal venous blood flow. The lobular structure alters during rapid liver regeneration. The hepatic lobules with single-cell thick hepatocytes flanked by venous sinusoids and biliary canaliculi become crowded during liver regeneration when hepatocyte plates become 2-cell or 3-cell thick. This can result in compression of both hepatic venous sinusoids, as well as the biliary canaliculi, causing transient PHT and cholestasis.[50,51,60,61] The relative lag in the regeneration and canalization of biliary canaliculi may also contribute to this transient cholestasis. This phenomenon is also observed in major liver resections where transient PHT and cholestasis are observed even in the absence of sepsis.[7,14,27]

Hepatic venous reconstruction in LDLT, especially for the right lobe can be complex and challenging and remains an important consideration. Apart from the right hepatic vein, reconstructions of the inferior right hepatic vein(s), and multiple anterior sector veins may be warranted to ensure optimal outflow of the graft. Hepatic venous outflow obstruction (HVOO) can worsen PS in SFSGs by causing increased PP and persistence of these collateral channels.[50,52,56] Similarly, stenosis at the PV anastomosis can also worsen PS. These 2 complications compound and confuse the issues associated with PS due to PSS and every effort should be made to avoid these complications. Measurement of PP proximal and distal to the anastomosis can help identify the problem. The optimal management of PSS in LDLT remains unclear and Korean centres with a large experience in LDLT recommend the routine use of intraoperative portography to demonstrate steal and ligate these shunts.[53–57] Since these natural shunts are uncontrolled and have the capacity to increase in size, hemodynamically significant PSS should be ligated in LDLT to avoid PS. Small collaterals have a less hemodynamic effect and may involute after LT. They may even offer protection to the graft during states of hyperperfusion of graft.

Selective ligation of PSS is another approach that has been proposed as an alternative to routine ligation of PSS. An objective guide to this strategy is to intraoperatively measure the PP/flow at different time points.[50,59,62] The aim is to ensure adequate hepatic portal inflow preventing both portal hyper- and hypoperfusion. Intraoperatively during an LDLT, PSS ligation should be considered when large collaterals shunt blood away from the graft liver immediately after reperfusion. A combination of low PP and low portal flow is an indication of PS and clearly requires collateral ligation. A second more complex indication is when PPs are acceptable or even higher than ideal, but are associated with poor portal flow. There remains the risk of uncontrolled PS in the postoperative period. A combination of collateral ligation and portal inflow modulation (PIM) may be necessary in this setting.[1,50,53,55] Ligation of significant collaterals ensures that most portal blood is directed to the liver, and if the resulting PP and flow are high, PIM may be indicated to avoid sinusoidal hypertension.

Although the impact of PSS in DDLT is less, its role remains relevant in special scenarios such as split-LT and transplantation of pediatric grafts into adults. Studies in this regard have shown a poorer outcome when the portal flows were <1 L/min. Graft portal flows between 100 mL/100 g/minute and 250 mL/100 g/minute are considered optimal. The indication should however be conservative and restricted to patients with a combination of low portal venous flows and large collaterals, particularly in a setting of portal vein thrombosis (PVT) needing thrombectomy.[50,58,63]

Children with biliary atresia with a hypoplastic PV (diameter of <4 mm) and associated PSS are particularly susceptible to PS and PVT.[63,64] Technical factors such as HVOO, graft rotation, portal stenosis, or portal stretch along with preexisting PSS may worsen PS. The first step is therefore to rectify these technical factors. Ligation of significant PSS is recommended if portal flow remains low (<10 mL/kg body weight/minute) despite these corrective measures.[50]

Intraoperative Assessment of Significant Portal-systemic Shunt

A preexplant PP is measured either by a direct puncture of the PV or a recording in the omental vein. After which, the PV is temporarily occluded, and the PP is measured proximal to the clamp (Fig. 2). A big rise (>8 mm Hg) in PP indicates the absence of hemodynamically significant PSS. In contrast, if the rise in clamped PP is minimal, the existence of significant PSS should be strongly suspected. This should be correlated with pre-operative scans, wherein these PSS can usually be demonstrated. After ligation of PSS, a repeat PP is assessed to ensure closure of these PSS. Postreperfusion PP measurements help guide the need for PIM post-PSS ligation (described previously).

SMALL-FOR-SIZE SYNDROME

Definitions

SFSS is a term given to early liver allograft dysfunction due to a relatively small graft struggling to cope with the

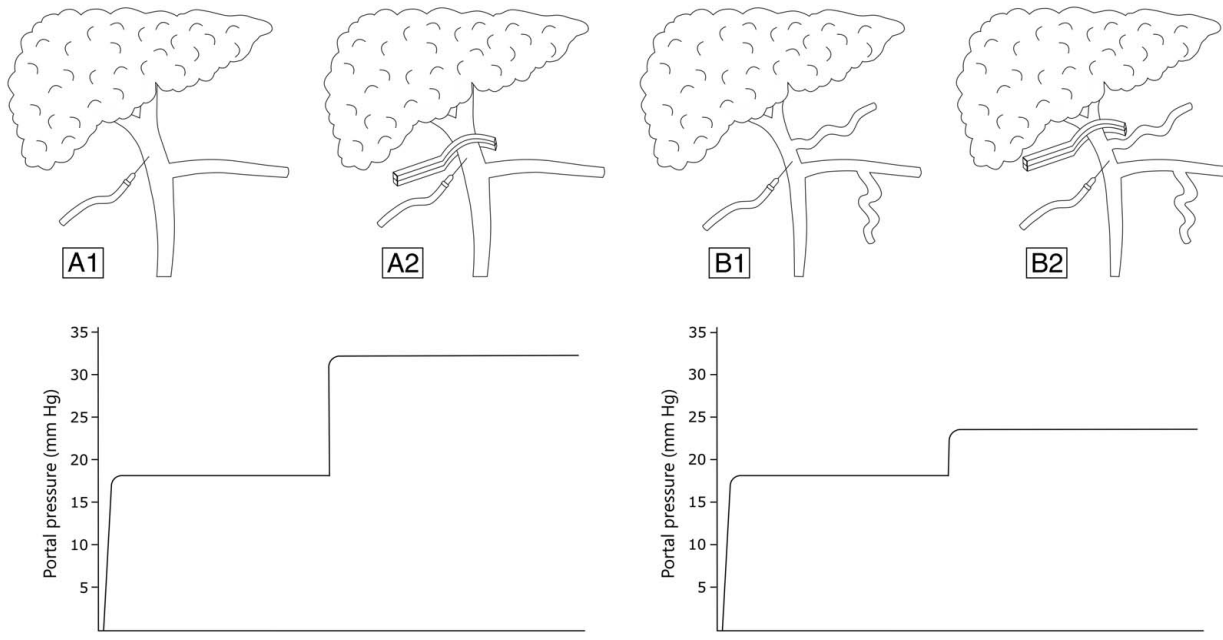

FIGURE 2. In patients without major portosystemic collaterals (A1 and A2), occlusion of the main PV increases PP significantly as there is near total interruption to the portal flow. In patients with large portosystemic shunts (B1 and B2), occlusion of the main PV does not increase the PP significantly as the portal flow is diverted through the collateral circulation. This method helps in assessing the size and flow through the collateral circulation in the LDLT setting without the need for cineportography which is traditionally used in some centres. The decision to ligate large portosystemic shunts can be based on this simple on-table test.

metabolic demands of the patient.[65,66] Even though the term is commonly employed in LDLT, the basic pathophysiology of SFSS is applicable to partial livers like split-LT, auxiliary-LT, and major hepatectomy. SFSS classically presents as prolonged cholestasis, coagulopathy, and excessive ascites after LT. However, it is important to note that this clinical presentation is no different from early allograft dysfunction due to any other reason.[65,67] Moreover, there is no single investigation to identify SFSS, and it remains a diagnosis of exclusion.

Emond et al[68] first reported the adverse impact of small grafts on the outcomes of LDLT. The authors introduced the term "small for size" and suggested that grafts smaller than 50% of the expected liver size were associated with significant functional impairment. Kiuchi et al[69] investigated the impact of GRWR on transplant outcomes and reported significantly higher morbidity in recipients receiving grafts with a GRWR of <0.8. Surgeons from Kyushu University presented the first objective definition of SFSS as total bilirubin >5 mg/dL and daily ascites output of more than 1 L on day 14 after LDLT.[70]

There is still a significant difference of opinion regarding the criteria for diagnosing SFSS. This is evident from the way the most commonly cited definition of SFSS was developed. Dahm et al[71] contacted 20 experts in the field of partial LT (12 from Europe and 2 each from North and South America, Near East and Asia) with a questionnaire, and their responses were used to define SFSS. Based on their responses SFSS was defined as posttransplant graft dysfunction/loss within the first week with at least 2 of 3 criteria (cholestasis, coagulopathy, or encephalopathy) in a patient who receives a partial graft with GRWR <0.8 after other causes have been ruled out. This definition excluded prolonged ascitic drainage as criteria, and restricted the term to grafts with GRWR <0.8. The A2ALL definition of early allograft dysfunction (EAD) in LDLT included the presence of jaundice with bilirubin >10 mg/dL or coagulopathy with an International Normalized Ratio >1.6 on day 7 without

TABLE 1. Selection of Definitions of SFSS

Author	Definition*
Kow et al[65]	Grade A: postoperative day 7 serum bilirubin >5 mg/dL Grade B: postoperative day 7 serum bilirubin >10 mg/dL 0r INR >1.6 Grade C: postoperative day 7 serum bilirubin >10 mg/dL and INR >1.6
Soejima et al[70]	Prolonged functional cholestasis (serum bilirubin >5 mg/dL on day 14) and intractable ascites (total drain output >1000 mL on day 14 or >500 mL on day 28)
Dahm et al[71]	Posttransplant graft dysfunction within the first week as defined by at least 2 of 3 criteria (cholestasis, coagulopathy, or encephalopathy) in a patient who receives a partial graft with GRWR <0.8
Hill et al[72]	Significant cholestasis (serum bilirubin >10 mg/dL and continuing to rise) after postoperative day 7, coagulopathy (INR >1.5), ascites (drain output >2 L/day)
Pomposelli et al[73]	Defined primarily for early allograft dysfunction. (postoperative day 7 serum bilirubin >10 mg/dL or INR >1.6)

*Other causes of graft dysfunction (technical, immunologic, infectious causes) should be ruled out.
INR indicates International Normalized Ratio.

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technical complications.[1] The graft survival was significantly worse if both the criteria were fulfilled. A list of published definitions of SFSS is presented in Table 1.

The publications from the ILTS-iLDLT-LTSI Consensus conference on SFSS present a modified definition of SFSS and have attempted to predict the development and prognosticate the outcomes of SFSS.[65–67,74] However, as there is no definitive test to diagnose it accurately, dogmatically defining SFSS based on graft volume may be fraught with problems. Thus, the precise definition of SFSS and objective methods of predicting it remains a work in progress.

Pathophysiology (Small-For-Flow Syndrome)

Current evidence suggests that relative portal hyperperfusion of the liver remnant/graft is the central inciting factor in the development of SFSS.[2,75,76] Partial LT results in an increased portal flow relative to a smaller hepatic vascular bed of the graft. Increased portal flow into the liver can usually be accommodated without a significant increase in PP due to the capacitance of the splanchnic circulation, hepatic sinusoids, and the compliance of the liver capsule. However, as the portal flow continues to increase beyond a certain limit, these factors do not prevent significant increases in PP. While increased portal blood flow consistently has been shown to stimulate liver regeneration, the damaging effects of portal hyperperfusion commence when the flow exceeds four times the portal flow in the donor PV (>360 mL/min/100 g graft weight).[1,3,75,77] Ideally, the postreperfusion portal venous flow should be maintained below 250 mL/min/100 g. PP is often used as a surrogate marker for the flow, and pressure below 15 mm Hg is most favorable, and <20 mm Hg is mandatory to avoid SFSS.[1,75,78]

The key variable here is the ability of the reduced graft to accommodate the increased portal flow without causing sinusoidal shear stress and injury. Graft injury by portal hyperperfusion is driven by the activation of numerous and redundant inflammatory pathways. The mechanical stress caused by the increased portal flow causes sinusoidal injury, which activates multiple inflammatory pathways. Increased endothelin and decrease in nitric oxide (NO) worsen ischemia and sinusoidal injury.[1,2,75,78,79] Expression of cytoprotective genes, such as haem-oxygenase and heat shock proteins, is also reduced. A reciprocal decrease in HA flow due to HABR compounds liver injury in the setting of portal hyperperfusion.[7,51,80] The oxygen-rich hepatic arterial flow may be reduced to $<10\%$ of total blood flow in these states, causing a state of relative hypoxia and graft ischemia, adversely impacting both liver function and liver regeneration.

Hence, it is not always a GRWR <0.8 which results in SFSS. It is, more importantly, a state of relative portal hyperperfusion (portal hyperperfusion syndrome or small-for-flow syndrome) resulting in a cascade of microcirculatory changes (endothelial activation, sinusoidal shear stress, arterial vasoconstriction, and hepatocyte overregeneration).[1,75,76,81]

Predictive Factors

A plethora of other factors apart from graft volume can lead to a relative insufficiency of graft size.[1,65,74] These include recipient-related factors (disease clinical status, Model for End Stage Liver Disease scores, and PHT), graft-related factors (donor age, steatosis, ischemia times, ischemia/reperfusion injury, and immunologic factors), and technical factors (vascular reconstruction and adequate outflow, vascular inflow, and pressure gradients; Table 2) Once the patient satisfies the criteria of SFSS, significant graft damage has already occurred and measures to correct it have limited impact. Predicting the risk of developing SFSS before it actually occurs is hence important.

Prevention and Management

In an effort to stem the deleterious effect of portal hyperperfusion, various surgical and pharmacological methods of PIM have been attempted with varying degrees of success. The more commonly used pharmacological PIM measures include the use of terlipressin and octreotide.[1,67,74]

TABLE 2. Summary of Factors that Predict the Development of SFSS

Time Period		Risk Factors or Predictors for SFSS
Preoperative factors	Graft	• Small graft size (GRWR <0.8)
		• No anterior sector drainage (for right lobe grafts)
		• Graft steatosis
	Donor	• Increased age
	Recipient	• Severe of portal hypertension (large spleen, low ratio of graft vs spleen volumes)
		• Condition of recipient (Child-Pugh and MELD scores)
		• Predicted surgical difficulty (retransplant, previous upper abdominal surgery, multiple episodes of spontaneous bacterial peritonitis)
Intraoperative factors	Graft	• Low graft weight (GRWR <0.8)
		• Graft steatosis
	Recipient	• Intraoperative blood loss
		• High prehepatectomy and postimplantation PPs, portal flow rates
		• Low arterial flow rate and high RI on Doppler study
		• Stiff liver
Postoperative factors		• Slow to normalize blood lactate levels
		• Slow correction of INR
		• High drain output, GIB
		• Doppler USG showing high portal flow and high resistance arterial wave pattern
		• Elevated HVPG

HVPG indicates hepatic venous pressure gradient; INR, International Normalized Ratio; MELD, Model for End Stage Liver Disease; RI, Resistive Index; USG, ultrasound.

All of these agents have shown benefits in improving renal function in the immediate post-LT setting. Nonetheless, it is quite uncommon for LT units to use either of these drugs in routine LDLT practice.

A systemic review showed that various surgical PIM measures were beneficial in reducing PPs and flow and hence had a tumble-down effect of enhancing recovery, especially for SFSG in LDLT.[1] Surgical techniques, such as splenectomy, SAL, and various portosystemic shunts including the more commonly performed hemiportocaval shunt demonstrated improved outcomes in SFSG.

Splenectomy results in the most precipitous drop in PP and was an often-performed procedure before the advent of antivirals for hepatitis C. Apart from its direct effect on portal flow, splenectomy has also been shown to promote liver generation by the modulation of cytokines.[1,82,83] However, splenectomy comes at the expense of higher morbidity including venous thrombosis, bleeding, and pancreatic leaks. The principle of hemiportocaval shunt is similar to that of a PSS, and causes a partial diversion of the flow away from the liver.[1,62] Again, this procedure comes with the risk of PS. SAL has the least morbidity of the PIM techniques, and apart from reducing the portal flow, it also aids in increasing hepatic arterial pressures. The reduction in portal flow is, however, the least compared with other methods, and some authors have noted this response to be short-lived.

Treatment of SFSS includes exclusion of other causes of graft dysfunction, which could have treatment options.[67] Vascular and biliary complications can cause graft dysfunction in the perioperative period. Imaging will help identify issues such as HA thrombosis, PVT or stenosis, and HVOO. Imaging may also identify infective foci and biliary issues such as bile leaks, cholangitis, etc, all of which may increase the metabolic demand and worsen the existing state of SFSS. Graft stiffness can increase due to inflammation resulting from ischemia-reperfusion injury or acute cellular rejection. Supportive care remains the mainstay of treatment for SFSS, and definitive management of SFSS includes PIM or retransplantation in refractory cases. SFSS is thus an imbalance between the metabolic demand of the recipient and the functional capacity of the graft. The endpoint of this is the disparity between the portal blood flow to the graft and the capacity of the graft to handle it leading to sinusoidal injury and graft dysfunction. Graft size is the most important among several factors, which predict the development of SFSS.[65,66] There is currently no universally accepted definition for this phenomenon and the key is to identify conditions where SFSS can develop so that measures can be taken to avoid or minimize graft damage.

CONCLUSION

Although there has been progress in our knowledge of the hepatic vasculature, many facets of the interplay between the liver and its blood supply remain undefined. Very few models to test concepts in humans exist, and none of them are comprehensive. It is important to concede that even though our knowledge of the practical modulation of hepatic hemodynamics has expanded enormously, there still remains the need to explore the depths of our remaining ignorance to further improve outcomes.

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