

## Liver function impairment in liver transplantation and after extended hepatectomy

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### Abstract

Extended hepatectomy, or liver transplantation of reduced-size graft, can lead to a pattern of clinical manifestations, namely "post-hepatectomy liver failure" and "small-for-size syndrome" respectively, that can range from mild cholestasis to irreversible organ non-function and death of the patient. Many mechanisms are involved in their occurrence but in the recent past, high portal blood flow through a relatively small liver vascular bed has taken a central role. Therefore, several techniques of inflow modulation have been attempted in cases of portal hyperperfusion first in liver transplantation, such as portocaval shunt, mesocaval shunt, splenorenal shunt, splenectomy or ligation of the splenic artery. However, high portal flow is not the only factor responsible, and before major liver resections, preoperative assessment of the residual liver function is necessary. Techniques such as portal vein embolization or portal vein ligation can be adopted to increase the future liver volume, preventing post-hepatectomy liver failure. More recently, a new surgical procedure, that combines *in situ* splitting of the liver

and portal vein ligation, has gradually come to light, inducing remarkable hypertrophy of the healthy liver in just a few days. Further studies are needed to confirm this hypothesis and overcome one of the biggest issues in the field of liver surgery.

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**Key words:** Small-for-size syndrome; Liver transplantation; Extended hepatectomy; Liver failure; Cirrhosis

**Core tip:** In this review we focus on the small-for-size syndrome and post-hepatectomy liver failure, the most feared complications of liver surgery, fundamentally similar in pathogenesis and clinical manifestations, occurring when the residual liver is not large enough to accommodate the markedly increased portal vein blood flow. Our aim is to simplify a concept, which has been a major concern in hepatic surgery for some time. Many efforts have been and are being made to overcome such an important problem in this field.

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### INTRODUCTION

The liver is a unique organ, capable of regeneration and functional recovery after parenchymal injury. When the volume is too small to satisfy the metabolic demand, the liver loses this peculiar ability, resulting in delayed synthetic dysfunction with poor bile production, coagulopathy, prolonged cholestasis and intractable ascites, which can lead to septic complications and high mortality. The

term “small-for-size syndrome” (SFSS) was first<sup>[1]</sup> coined in liver transplantation as a consequence of size mismatch between graft and recipient, an event occurring especially in the setting of living donor liver transplantation (LDLT) or split liver transplantation<sup>[2]</sup>, where the use of partial grafts has gained worldwide acceptance to overcome the shortage of cadaveric organs. However, the same concept can also be applied to the field of liver resection, where patients with marginally resectable tumors are at high risk of developing post-hepatectomy liver failure (PHLF)<sup>[3]</sup>, a clinical manifestation comparable to the SFSS.

## DEFINITION

There is not full consensus about the definition of SFSS. It was introduced in 1996 by Emond *et al*<sup>[1]</sup> and regarded the clinical manifestation following transplantation of small grafts in LDLT. The term SFSS on the basis of personal working experience, and no threshold values of liver function tests, was suggested. In 2005, Dahm *et al*<sup>[4]</sup> proposed a more precise definition. These authors described SFSS after liver transplantation as the presence of two of the following criteria recorded on three consecutive postoperative days: serum bilirubin > 100  $\mu\text{mol/L}$  (6 mg/dL), international normalized ratio (INR) > 2 and presence of encephalopathy grade III or IV. The small-for-size syndrome usually occurs during the first postoperative week and is diagnosed after the exclusion of other causes such as technical complications (*e.g.*, arterial or portal occlusion, outflow congestion, bile leak) and/or rejection or infections (*e.g.*, cholangitis, sepsis).

The same concept is applicable to the field of hepatic surgery, where extended resections can lead to the development of PHLF. Many different definitions of PHLF have been proposed in the literature<sup>[5-7]</sup>. In trying to propose a more standardized definition, in 2011, Rahbari *et al*<sup>[7]</sup> suggested a simple and easily applicable definition of PHLF as a “postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5”. They differentiated severity in three grades (A, B, C), according to whether changes in clinical management of the patient or invasive treatments are required. It is of interest that even if SFSS and PHLF can be viewed as the same manifestation of liver function impairment, the two terms and their relative definitions are currently separated. It would probably be of interest to join the two definitions into a single one, but at present no suggestions, regarding this topic, are present in the literature.

## PATHOPHYSIOLOGY

The magnitude of the effect of increased portal flow after hepatectomy on the development of PHLF, though recognized, is currently not yet well established and most

of the studies regarding this topic come from the transplantation experience.

High portal blood venous flow (PVF) has gained a central role in the pathogenesis of SFSS. Under normal physiological conditions, portal vein blood flow accounts for 75% of total hepatic inflow, or 90 mL/min per 100 g of liver tissue, while the hepatic artery contributes for 20%-25%<sup>[8]</sup>. The portal vein lacks intrinsic auto-regulation. Hence, after extended hepatectomy or transplantation of small grafts, the remnant liver is subjected to the portal flow destined to a whole liver, through a reduced micro-vascular bed<sup>[9]</sup>. Such a substantial increase of PVF and shear-stress on sinusoidal lining cells is inversely related to graft size. In > 75% partial hepatectomy, PVF increases by more than twice the baseline values, resulting in PHLF, with high morbidity and mortality<sup>[10]</sup>. Although shear-stress is considered to be a necessary stimulus for hepatic regeneration<sup>[11]</sup>, excessive forces can be detrimental to both the function and survival of the reduced-size organ: the result is damage of sinusoidal spaces with release of inflammatory cytokines, responsible for progressive hepatocyte necrosis<sup>[12]</sup>. Pathological findings include hepatocyte ballooning, tremendous mitochondrial swelling, irregular large gaps between sinusoidal lining cells, and collapse of the space of Disse<sup>[13]</sup>.

Although portal vein pressure (PVP) is considered a reliable predictor of graft failure<sup>[14]</sup>, the latter and PVF do not run parallel to each other; furthermore, the lack of correlation between graft weight/recipient body weight ratio (GRWR) and PVP has been investigated<sup>[15]</sup>.

Blood flow regulation, which allows a steady rate of hepatic perfusion, depends not only on the classical arterial intrinsic regulation but also on an inverse relationship between portal and hepatic arterial flow, also known as hepatic arterial buffer response (HABR)<sup>[16]</sup>. When the portal blood flow increases, this leads to an elevated wash-out of adenosine levels in the space of Mall, contracting the hepatic artery<sup>[17]</sup>. Adenosine is unlikely to be the sole vascular regulator and other vaso-active compounds may contribute to HABR<sup>[18]</sup>. The consequences of such a diminished arterial blood flow manifest in the peripheral circulation as a centrilobular microvesicular steatosis or infarcts, or, in severely affected cases, as ischemic cholangitis in the hilum<sup>[19]</sup>. Hence, the clinical manifestations can range from mild cholestasis to liver failure. However, the optimal rate needed to sustain liver regeneration and function, without damage to the liver, is still not known and further experimental studies on animal models are needed.

## PREOPERATIVE PREDICTION

Hepatectomy remains the first curative option for neoplasms of the liver. The mortality rate after major liver resections, *i.e.*, the removal of three or more Couinaud segments, ranges from 3% to 7% in non-injured liver parenchyma and increases up to 32% in patients with cirrhosis<sup>[20]</sup>. Thus, the extent of parenchymal resection

**Table 1 Predictive factors of small-for-size syndrome and post-hepatectomy liver failure**

Liver volume	Liver function	Patient-related	Other
FLR/TLV	CHILD-PUGH	CALI	Cholestasis
GRWR or GV/SLV	HVPG	Age > 65 yr <sup>[37]</sup>	Liver stiffness <sup>[31]</sup>
	ICG	Male sex <sup>[37]</sup>	Donor factors <sup>[44]</sup>
	MEGX <sup>[30]</sup>	Diabetes mellitus <sup>[37]</sup>	

FLR: Future liver remnant; TLV: Total liver volume; GRWR: Graft weight-recipient body weight ratio; GV: Graft volume; SLV: Standard liver volume; HVPG: Hepatic vein pressure gradient; ICG: Indocyanine green clearance; MEGX: Monoethylglycinexylidide; CALI: Chemotherapy-induced liver injury.

is an essential parameter in establishing both the operability of each patient and the risk of PHLF and this, to date, is still a subject of debate, probably due to different methods of measurement, variability in the segment volumetric distribution and degree of underlying disease.

The 3D volumetric computed tomography reconstruction allows preoperative calculation of the liver volume, even of the single segments, and, more important, of the future liver remnant (FLR). With a normal function, FLR should range between 20% and 30% of total liver volume, whereas smaller volumes are correlated with increase of liver failure and infections<sup>[21,22]</sup>. Care must be taken when an underlying liver disease pre-exists. In “injured” livers, (steatosis, cholestasis, fibrosis, cirrhosis or chemotherapy) the FLR should be greater than 30%-40%<sup>[23]</sup>. Therefore, an accurate preoperative assessment of liver function is needed.

In patients with cirrhosis, the Child-Pugh score and the hepatic vein pressure gradient are the two most important restrictive criteria in selecting candidates for surgery<sup>[24,25]</sup> even if they do not provide precise assessment of liver resectability<sup>[26]</sup>. Metabolic tests based on the detoxifying properties of the liver have the advantage of providing a more reliable estimation of the hepatic function, and they are based on quantitative measures. Indocyanine green clearance is the most popular test<sup>[27]</sup>, especially in Eastern countries, where it constitutes the pillar of preoperative algorithms for liver resection<sup>[28,29]</sup>. Other quantitative tests, such as the monoethylglycinexylidide<sup>[30]</sup> test, have led to good prediction of PHLF, but they have gained less popularity and are not routinely used. A simple and non-invasive method of measurement of liver stiffness (Fibroscan<sup>®</sup>) has recently been gaining broad consensus for predicting PHLF in selected patients<sup>[31]</sup>, but further studies are needed to establish its potential role in patient selection for surgery.

Chemotherapy-induced liver injury is common in patients that received chemotherapy for colorectal liver metastases, and the two typical patterns are sinusoidal injury (sinusoidal obstruction syndrome) in oxaliplatin-based regimens, and steatohepatitis (CASH), associated with irinotecan treatment<sup>[32]</sup>. More than 6 cycles of oxaliplatin need a longer time interval before major hepatectomy, even though accountability for PHLF still remains a matter of debate<sup>[33]</sup>, whereas irinotecan is associated with

an increased risk of peri-operative mortality after hepatectomy<sup>[34]</sup>. Biopsy of the liver before surgery might be helpful to assess the grade of steatosis or the histological features of CASH, thus defining more precise windows between drug administration and surgery.

Cholestasis impairs liver regeneration, and levels of bilirubin above 2.9 mg/dL are related to a higher rate of liver failure after major hepatectomy<sup>[35]</sup>. Nevertheless, the use of preoperative biliary drainage is still controversial, except for acute cholangitis or small FLR that are candidates for portal vein embolization<sup>[36]</sup>, in which case biliary drainage is highly recommended. Besides such patient-related factors, others, like age > 65 years, male sex and diabetes mellitus, are related to a high risk of PHLF<sup>[37]</sup>. Obesity is not per se a major predictor of liver failure<sup>[38]</sup>.

In the setting of transplantation, liver volume assessment is represented by the GRWR or graft volume/standard liver volume ratio (GV/SLV): in LDLT safe thresholds are at least 0.8% of GRWR or 30%-40% of GV/SLV<sup>[2,39,40]</sup>, with greater values in patients affected by portal hypertension or advanced chronic liver disease. There are reports on the successful use of smaller grafts<sup>[41]</sup>, but in association with some intraoperative inflow modulations: a case report of a left lobe LDLT as low as 0.34% of GRWR underwent splenectomy and did not develop post-operative SFSS<sup>[42]</sup>. In liver transplantation, size is not always the sole factor responsible for graft post-transplant liver function<sup>[43]</sup>, because graft quality is likewise important in order to avoid liver dysfunction or other complications. Aside from basic requirements for donor livers, the following donor factors have a negative impact on graft prognosis: age > 50 years, prolonged intensive care unit stay > 5 d, hypernatremia, prolonged cardiac/respiratory arrest and long ischemia times, administration of high dosage of vasopressors, severe systemic sepsis, steatosis > 30%, anatomic variations in vascular structure and, obviously, abnormal liver function, particularly with elevated serum bilirubin and gamma glutamyltransferase<sup>[44]</sup>.

Prediction of SFSS and PHLF is feasible and is based on the calculation of liver volume up to the assessment of liver function. Evaluation of patient status can help to find the best candidate for surgery. In the field of liver transplantation, donor characteristics also have to be taken into account, defining which grafts are at higher risk of developing SFSS than others. A list of the above mentioned factors is shown in Table 1.

## ATTENUATING SFSS IN LIVER TRANSPLANTATION

In the presence of high portal blood flow and/or small grafts (GRWR < 0.8%), several different technical flow manipulations can be performed to overcome graft hyperperfusion and reduce PVF, although there is no full consensus about their indications: portocaval shunt, mesocaval shunt, splenorenal shunt, splenectomy or ligation of the splenic artery. Boillot *et al*<sup>[45]</sup> reported the first

successful mesocaval shunt with downstream ligation of the superior mesenteric vein in a left lobe transplantation (GRWR of 0.61%), based on previous experimental studies on pigs.

Hemi-portocaval shunt, *i.e.*, anastomosis between the left or the right portal branch and the inferior vena cava in a permanent fashion, is advocated by Troisi *et al.*<sup>[10]</sup> whenever the PVF at reperfusion exceeds three-four times the one recorded in the donor. None of the patients undergoing such a graft inflow modulation developed SFSS, with significant decrease of portal vein flow.

The effects of splenic flow diversion have been investigated in the presence of portal hypertension (PVP > 20 mmHg)<sup>[15]</sup> and/or of portal hyperperfusion (PVF > 250 mL/min per gram)<sup>[46]</sup>. However, when PVF exceeds 500 mL/min per gram, portosystemic shunt cannot be avoided.

Both splenic artery ligation (SAL) and splenectomy can be performed and are comparable in terms of outcome and overall survival<sup>[47]</sup>, although for the latter, septic complications must always be taken into account. Splenectomy is considered superior to SAL for the purpose of increasing white balance and platelet count after LDLT, which is not achieved by SAL alone.

Splenic artery embolization represents a valid alternative to achieve portal decompression<sup>[48]</sup>. Furthermore, a linear correlation between PVF and graft-to-recipient spleen size ratio has been found, thus including the spleen size as a likely predictor of post-transplant portal hyperperfusion and SFSS<sup>[49]</sup>.

Techniques of graft inflow modulation account for a certain risk of steal phenomenon<sup>[50]</sup>: portal vein thrombosis, encephalopathy, septic complications or hampered liver regeneration are described as principal side effects. It remains an open question whether and when portosystemic shunts should be removed<sup>[51]</sup>, since hypoperfusion, as well as hyperperfusion, can also be detrimental for liver function.

According to the definition of Dahm *et al.*<sup>[4]</sup>, who stated that SFSS should be considered as a distinct entity, outflow obstruction per se should be excluded as a possible trigger, as it may reduce the hepatic function. However, one of the most discussed topics concerns the reconstruction of the middle hepatic vein (MHV) in right lobe grafts, since congestion of anterior segments (V-VIII) may lead to graft dysfunction<sup>[52]</sup>. A graft with inclusion of the MHV has been demonstrated to be technically and physiologically superior, but the use of this technique should be limited to selected cases in LDLT due to an increased risk for donor safety<sup>[53]</sup>. For MHV reconstruction, several transplant centers use various types of vascular grafts, with a predilection for large caliber autologous vessels (*i.e.*, the superficial femoral vein), or also cryopreserved venous or arterial grafts<sup>[54]</sup>.

future metabolic demand, a number of strategies can be adopted to increase the liver volume, preventing post-hepatectomy liver failure. Portal vein embolization (PVE) has become the most standardized procedure due to its safety and feasibility: it consists in the occlusion of portal flow ipsilateral to the lesion, inducing hypertrophy in the contralateral lobe. Makuuchi *et al.*<sup>[55]</sup> first used this technique in 1982 to extend the limits of hepatic resection, thus increasing the number of cases suitable for curative surgery: in this early report, 14 patients underwent pre-operative PVE followed by major liver resection 6-41 d after embolization, with no occurrence of postoperative liver failure. After almost 30 years, the indications of PVE are still very poorly standardized: many authors indicate a residual liver volume less than 30% of total liver volume or up to 40% in injured livers as the critical threshold<sup>[56,57]</sup>. Surgery is usually performed 2-8 wk after PVE, with future liver remnant volume increased by 10%-46%. From 70% to 100% of patients who underwent PVE, hemi-hepatectomy or extended hepatectomy could be performed. Following resection, the perioperative morbidity and mortality was less than 15% and 0%-7%, respectively<sup>[58-60]</sup>.

Portal vein ligation (PVL) represents a good alternative, although there are no controlled studies clearly showing the superiority of PVE *vs* PVL. Portal vein ligation requires laparotomy and, furthermore, the volume gain is often limited due to formation of collaterals between the two different lobes<sup>[20]</sup>. PVL is not considered such a standardized and safe procedure as PVE, but patients who are candidates for 2-stage hepatectomy can benefit from this technique<sup>[61,62]</sup>, recently adopted in a new surgical approach aimed at enhancing and accelerating the regeneration of the remnant liver<sup>[63]</sup>. In 2009, Schnitzbauer *et al.*<sup>[63]</sup> reported on a case series of 25 marginally resectable patients with massive involvement of the right lobe by neoplastic nodules, on which an innovative 2-step technique was carried out. In the first step, right portal vein ligation and *in situ* splitting of the liver on the right side of the falciform ligament was performed; in the second step, after a median time interval of 9 d, extended hepatectomy (right trisectionectomy) was completed. The observed median increase in volume of the left lobe was 74%, but morbidity and mortality were significant (68% and 12%, respectively). Thereafter, the so-called advanced liver partition and PVL for staged hepatectomy, also known by the acronym ALPPS<sup>[64]</sup>, has spread to many centers worldwide: the obtained median increase in volume ranges from 74% up to 87%, with surgery usually performed 5-30 d after the first step. However, mortality rates of 13%-22% are still reported<sup>[65-68]</sup>. Although the procedure is innovative and attractive, these latter figures make it imperative to increase the number of patients treated with this strategy to better define its feasibility and limits<sup>[69]</sup>.

In addition to the above, more studies are needed to understand the exact mechanisms of hepatic regeneration, also through biopsy of the remnant liver before and after hepatectomy, and measurements of portal flow

## ATTENUATING PHLF IN EXTENDED HEPATECTOMY

If the remnant liver volume is not sufficient to meet the

and pressure should be provided. In fact, although the preserved functional capacity of the hypertrophied remnant liver could be established with functional tests (*e.g.*, indocyanine green clearance) and through the uptake of  $^{99m}\text{Tc}$  dimethyl iminodiacetic acid<sup>[64]</sup>, excessive portal flow represents one of the main problems, determining a possible discrepancy between the relevant increase in volume and the amount of actually functioning parenchyma. de Santibañes *et al*<sup>[70]</sup>, in 2012, claimed that the diseased right hemi-liver, left in place, acts as an auxiliary liver to assist the future liver remnant for the first and critical week after resection, but in true auxiliary transplantation, both the portal and arterial flows to two hemi-livers are maintained. Thus, contrary to auxiliary transplantation, in which the growth and functional recovery may progress harmonically with a real portal flow modulation, this phenomenon is not certain after extended hepatectomy with a small residual parenchyma. In other words, how can this “beneficial” re-direction of the entire portal flow to a “small-for-size” remnant liver comply with established principles of portal flow modulation in small-for-size transplantation? Research in animal models clearly shows that a portocaval shunt has a positive effect in attenuating liver injury after extensive hepatectomy, suggesting that a slower regeneration following reduction of portal flow may be more advisable than faster regeneration associated with temporary portal hyperflow<sup>[71,72]</sup>. In this view, more insights on the mechanisms and features of liver regeneration are needed to better understand the potential benefit of portal flow modulation to prevent postoperative liver failure<sup>[64]</sup>.

## PHARMACOLOGICAL INTERVENTIONS

Many drugs have been demonstrated to be effective in attenuating SFSS after living donor liver transplantation of small grafts, but most of them have been tested only in animal models<sup>[73,74]</sup>, whereas clinical trials on human beings are still lacking. Furthermore, pharmacological portal flow modulation has been investigated: shear-stress attenuation has been achieved by somatostatin<sup>[75]</sup>, through down-regulation of the endothelin-1 (sinusoidal vasoconstrictor) and up-regulation of heme-oxygenase-1 (vasodilator and antioxidant). Nitric oxide pathway activation seems to be protective against ischemia-reperfusion injury both in liver resection and liver transplantation<sup>[76]</sup>. Therapeutic agents promoting liver regeneration, such as serotonin, are still a matter of debate for their controversial role<sup>[77]</sup>. Recently, autologous bone marrow stem cells have been used to increase liver regeneration prior to major liver resection. In particular, an enhanced parenchymal growth after portal vein embolization through the portal injection of CD133<sup>+</sup> cells (in the non-embolized hepatic lobe) has been demonstrated, with a subsequent improvement of outcome after surgery<sup>[78]</sup>. Even though the specific effect of CD133<sup>+</sup> cells is not completely understood<sup>[79]</sup>, this approach is intriguing due to the possibility of combination with other techniques

favoring post-transplant or post-hepatectomy liver function recovery, such as procedures of portal flow modulation.

## CONCLUSION

Post-hepatectomy liver failure and small-for-size liver syndrome can be viewed as two sides of the same coin, since both of them can lead to an identical pattern of clinical manifestations, that is cholestasis, impairment of coagulation and development of ascites, and that can range up to irreversible organ non-function and death of the patient. Safe thresholds of remnant liver volume differ between liver transplantation and after extended hepatectomy, probably due to graft denervation, immunosuppressive therapy and severity of ischemia-reperfusion injury. However, preoperative assessment of liver function and size is crucial, while intraoperative recording of hemodynamic changes, before and after hepatectomy or liver transplantation, should be mandatory in order to perform inflow modulation, if necessary. Other strategies, which include pharmacological perioperative protection of the liver and stem cell injection, are being explored, but further studies are needed before they can be applied in the clinical field.

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