“Small-for-flow” liver failure after extended hepatectomy: a call for update

Abstract

Emond et al.¹ first described, in 1996, a new syndrome occurring in small grafts in transplantation field, named small for Size Syndrome. After surgery, patients with a small grafts were affected by unpredictable elevation of bilirubin (not linked with surgical procedures), coagulopathy, prolonged cholestasis, portal hypertension and, if severe, ascites. The continuing liver dysfunction predisposes to further complications, including sepsis and gastrointestinal bleedings, leading to a clear liver failure. In the meantime, in liver resection field, the same syndrome was noticed after major hepatectomy (>3 segments resected), and it was named Post-Hepatectomy Liver Failure. With improvement of knowledge, nowadays we know that SFSS and PHLF are two side of the same coin. Different strategies, more in transplantation context, have been described to prevent and to treat the syndrome, but lack of data regarding the resection context is still a matter. In fact, where in transplant, pathophysiological studies and randomized clinical trial have been published to evaluate the etiology and the efficacy of procedures proposed, in resection field we are just translate transplantation experience, without a whole consensus between physician on how to predict, to diagnose, and to treat this post-hepatectomy liver failure. Diagnostic criteria, treatments, and pathophysiology are still unclear, with different opinion between physicians, and also disaccording if small for size and post-hepatectomy liver failures are really the same. Our opinion a part, we think it's time to start to analyze in deep this syndrome that account for more than 60% of death after major liver resections.

Keywords: small for size, liver failure, liver surgery, major hepatectomy, small for flow, splenectomy, somatostatin-analogue, transplant, pathophysiological, randomized clinical, coagulopathy, prolonged cholestasis, criteria, treatments; unclear

Volume 3 Issue 2 - 2017

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Received: April 18, 2017 | **Published:** May 02, 2017

Abbreviations: SAE, splenic artery embolization; SFFLF, small for flow liver failure; SFSS, small for size syndrome; TLV, total liver volume; FLR, future liver remnant; PVP, portal vein pressure; HVP, hepatic venous portal gradient

Introduction

Emond et al.¹ first described, in 1996,¹ a new syndrome occurring in small grafts in transplantation field, named Small for Size Syndrome. After surgery, patients with a small grafts were affected by unpredictable elevation of bilirubin (not linked with surgical procedures), coagulopathy, prolonged cholestasis, portal hypertension and, if severe, ascites. The continuing liver dysfunction predisposes to further complications, including sepsis and gastrointestinal bleedings, leading to a clear liver failure. In the meantime, in liver resection field, the same syndrome was noticed after major hepatectomy (>3 segments resected), and it was named Post-Hepatectomy Liver Failure. With improvement of knowledge, nowadays we know that SFSS and PHLF are two side of the same coin. Different strategies, more in transplantation context, have been described to prevent and to treat the syndrome, but lack of data regarding the resection context is still a matter. In fact, where in transplant, pathophysiological studies and randomized clinical trial have been published to evaluate the etiology and the efficacy of procedures proposed, in resection field we are just translate transplantation experience, without a whole consensus between physician on how to predict, to diagnose, and to treat this post-hepatectomy liver failure. Diagnostic criteria, treatments, and pathophysiology are still unclear, with different opinion between physicians, and also disaccording if small for size

and post-hepatectomy liver failures are really the same. Our opinion a part, we think it's time to start to analyze in deep this syndrome that account for more than 60% of death after major liver resections.²

Different opinions, lack of agreement

Even if imaging shows complete restoration of liver volume after few weeks from surgery, there is no evidence of complete restoration of liver's parenchymal micro architecture when looking at the liver biopsy of same patients taken soon after extended resection or transplantation.^{3,4} In the field of oncological surgery, liver regeneration is a very complex problem when it's approaching a malignancy. In fact, liver volume regeneration is not always accompanied by a quick and complete restoration of liver function.² Often, it has been noticed a distortion in micro and macro architecture of liver cells,⁵ with hyperproliferation of hepatocytes, and lack of proper interaction with other types of hepatic cells. Over portal flow and pressure are pointed as the “primum movens” in the pathophysiology of the syndrome. This phenomenon has been studied by Asencio et al.⁶ proposing a new approach to post-hepatectomy liver failure, leading to a predominant role of flow and pressure in the etiopathogenesis, and, consequently, a new management approach for liver surgery and related safe limits.

Because of its small size, liver remnant after major hepatectomy is suddenly submitted to a hyperperfusion induced by the whole-maintained portal vein flow. This seems to cause an adenosine wash-out in Space of Mall, who leads to hepatic artery vasoconstriction (a phenomenon named Hepatic Arterial Buffer Response, HABR). This acute and relative portal hypertension leads to endothelial damage, ischemic and reperfusion's injuries that explains liver dysfunction.⁷

sThis hypothesis came out from living donor liver transplantation's experience, where it has been noticed the good outcome of portal flow and pressure modulation strategies to avoid small-for-size syndrome. In fact, in transplantation context, reducing portal vein pressure (PVP) by portocaval shunt,⁸ or by splenic artery embolization,⁹ or by splenectomy¹⁰ had been showed to be very effective as prevention treatments. Ogura et al.¹¹ strongly showed that LDLT using small-grafts was feasible provided that Portal Vein Pressure was maintained below 15mmHg. In an oncological context, some experimental studies have showed how low PVP after surgery is a protective factor against histological damage, leading to a better functional regeneration of liver.^{12–14} Recently, Allard MA and colleagues¹⁵ observed a significantly higher post-hepatectomy PVP in patients who develop post-hepatectomy liver failure (all definitions considered) compared to those who did not. He suggested an intra-operative PVP cut off of 22mmHg, that is associated with 18.4%-21.1% (depending on definitions considered) of likelihood to develop a Small for flow liver failure, and a 90-days mortality of 12.7%. Several other studies indicate that portal pressure higher than 20mmHg show a decrease from 85% to 38% in their 6-months survival.⁸ Despite this, other authors, recently, have suggested that portal hyperperfusion after extended hepatectomy doesn't induce a hepatic arterial buffer response, but reduces mitochondrial redox state and hepatocellular oxygenation in rat's model. This wouldn't due to a deterioration of microvascular perfusion, but rather due to a relative hyper metabolism of the remnant liver after major resection.¹⁶

Criteria to diagnose SFFLF are another theme of debate. In 2005, Balzan et al.² have proposed the so-called "50-50 criteria", where an elevation of PT over 50% of baseline, or INR>1.7, and a raise of bilirubin more than 3mg/dl on or after 5th post-operative day, are related to SFFLF development, and to 59% of mortality after surgery.² The International Study Group of Liver Surgery (ISGLS) has proposed a three-grade classification (Table 1). Another criteria accepted in literature, is the peak of bilirubin>120μmol/l after day 5th. These authors have founded their classifications on their pathophysiological point of view. Thus, this lack of agreement is reflected even in SFFLF definition: according to ISGLS, post-hepatectomy liver failure is "a postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which is characterized by an increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5".¹⁷ According to Asencio et al.⁶ who have proposed the new concept of "small-for-flow", SFFLF is "the proportion between the mass of the liver remnant and the blood flow that receives, reflected by the values of portal blood flow and pressure. A disproportionate increase of portal blood flow and portal pressure would lead to sinusoidal injury, ischemic injury due to a compensatory reduction of blood flow in the hepatic artery, and to impairment of liver regeneration".⁶

Table 1 ISGLS grading system

ISGLS grading system	
Grade A	Post-hepatectomy liver failure resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient
Grade B	Post-hepatectomy liver failure resulting in a deviation from the regular clinical management but manageable without invasive treatment
Grade C	Post-hepatectomy liver failure resulting in a deviation from the regular clinical management and requiring invasive treatment

Time to clarify

All these evidences show how we're far away to an objective and whole-accepted model to understand, predict, manage and treat this liver failure in liver resection's field. Even if, in clinical practice, different authors have described different approach to reduce portal flow preventing the syndrome (porto-caval shunt;¹⁸ splenectomy; splenic artery embolization;¹⁹ somatostatin-analogue's infusion²⁰) lack of evidence and correlation permit to have a clear and evidence-based model. Nowadays, size is the center of liver surgery's planning, but, as Asencio have proposed, if portal flow would be definitely demonstrated as the key point, this paradigm could be totally changed.

It would be time to make an effort, and clarify the etiology of this syndrome, to change permanently our approach to liver surgery. In fact, if the evidences related to the portal pressure and flow as "primum movens" would be assessed, our point of view may shift from how much liver's parenchyma we are leaving in patients, to how modulate intra-operatively or post-operatively portal pressure and flow to guarantee the best liver's regeneration after surgery.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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