Small-for-flow liver failure after extended hepatectomy: hot questions and an update

Simone Famularo,[1] Luca Gianotti,[1] Oliviero Riggio[2]

[1]School of Medicine and Surgery, Milano-Bicocca University; Department of Medicine and Surgery, San Gerardo Hospital, HPB Unit, Monza; [2]Department of Clinical Medicine, Center for the Diagnosis and Treatment of Portal Hypertension "Sapienza" University of Rome, Italy

Abstract

Small-for-size liver syndrome and post-hepatectomy liver failure remain a major challenge for surgeons. Recently, updates in literature points to describe this two syndrome as two face of the same coin. These syndromes are characterized by hyperbilirubinemia, coagulopathy, hyper-GGT, high portal pressure and flow in liver remnant, occurring within the first postoperative week. It can lead to post-operative sepsis and bleeding, increasing mortality and morbidity. Despite the large experience in the field of transplantation, few studies are focused on small-for-size syndrome after major hepatectomy. For years, scientists were focused on the size of liver remnant, supposing a small liver remnant, in relation with the primary liver size, was the cause of the syndrome. The strategies used to prevent it after transplantation, have however shown a predominant role of high portal pressure and flow, leading to an alteration in functional regeneration of liver parenchyma, as the prevalent mechanism. According to these evidences, we suggest adopting another nomenclature for the two syndromes: small-for-flow-liver failure. In this article, we analyze and summarize different experiences, proposing our inward algorithm, including the role of portal flow and pressure measurements. This review seeks to be an operative instrument for surgeons and hepatologists in an effort to find a common point of view regarding small for flow liver failure and its management strategies.

Introduction

This manuscript would like to be an operative instrument for surgeons and hepatologists. While a lot of opinions, articles, experimental data and suggestive procedures exist on the small-for-size syndrome in the field of living donor transplants, few specific papers are available on small-for-size syndrome (SFFS) after extended hepatectomy. Nowadays, most of physicians consider SFSS and post-hepatectomy liver failure (PHLF) two face of the same coin. Through eight questions, we attempt to roll out every situation in managing oncological patients who underwent extended hepatectomy, trying to translate the transplantation experience in liver oncological surgery's field.

What is the etiopathogenesis?

Although all clinical guidelines are focused on liver remnant size to prevent SFFLF, histopathological findings in patients who received a small graft, as well patients undergoing hepatic resections (comprising more than 70% of the parenchyma), point to a predominant role of overflow and high pressure through the portal system in the mechanism underlying the development of the syndrome and, consequently, the hepatic damage.[1] A review of literature, and our experience, support the hypothesis that post-hepatectomy liver failure is due to an excessive portal blood flow for the remnant liver parenchyma, causing over-pressure, and sinusoidal endothelial denudation and hemorrhage. Few minutes after hepatectomy, perisinusoidal and periportal hemorrhage occurs. Later, arterial vasoconstriction, and ischemic cholangitis are observed.[2] According to several experimental and clinical studies, it has been shown that when there is a portal overflow in liver remnant, it is possible to observe a fall of arterial flow to the liver, in a sort of inverse relationship, called *arterial portal buffer*.[3,4] This phenomenon is characterized by decreasing concentration of Adenosine in the Space of Mall after a portal-over-flow, that leads to arterial vasoconstriction and decrease of arterial blood flow, which is responsible for the late damage.[5] The portal vein lacks an intrinsic autoregulation system, so when the liver volume is reduced due to major hepatectomy, it reaches the same portal flow first destined to the whole liver parenchyma. This portal over-flow causes the arterio-portal buffer response. After a period of ischemia, the complement cascade is triggered, leading to the activation of Kuppfer's cells, appearance of reactive oxygen species (ROS), and endothelial cell lesion. During reperfusion a release of cytokines, cell adhesion, activation and recruitment of T-cells and polymorphon-

clear cell occurs, resulting in microvascular lesion, inflammation and cell death.[6] In addition, the number of Kupffer's cells after hepatic resections decreased and the liver's ability to react to infection also decreased, explaining the high risk of infections (above 50%). A relative increase in the production of endotoxins in the remnant liver is beneficial, once it activates the Kupffer's cells, triggering the liver regeneration; but if this state is prolonged, it may cause Kupffer's cellular dysfunction, resulting in difficulty of regeneration and even liver necrosis.[6]

As already discussed, our knowledge is mainly based on transplant experimental studies.[7] Jiang *et al.* had established that portal blood flow of 300 mL/min/100 g is the threshold above which the incidence of SFFLF increases significantly.[8] In pigs models, Fondevila *et al.* have indicated that an increased portal blood flow is both an early stimulus for regeneration and a pathogenetic factor of the sinusoidal damage,[5] and they have proposed a porto-caval anastomosis to avoid SFFLF development by preventing a portal blood flow over double of its baseline.[9] Other studies have also confirmed the role of portal pressure. Yagi *et al.*

showed that a portal pressure above 20 mmHg was associated with the development of ascites, coagulopathy, and hyperbilirubinemia as well as with an early hypertrophy of the graft, higher values of hepatocyte growth factor (HGF) and diminished levels of vascular epithelial growth factor (VEGF), suggesting that an increased portal pressure also influences liver regeneration.[10]

What is the epidemiology and what is the short term and long term course, once the SFFLF has developed?

Due to difference in the nomenclature used (Post-Hepatectomy-Liver-Failure in case of oncological surgery, and Small for size liver syndrome in liver transplantation) and difference in the underlying parenchymal function and extension of resections, the incidence of SFFLF has been ranged between 8 and 32%.[11-17] A prospective study conducted by eLISTER has shown an incidence of 30% in patients undergoing extended hepatectomy.[18] Patients with SFFLF and a portal pressure above 20 mmHg, have a 6-months-survival decreased from 85% to 38%.[19] In these patients, postoperative mortality has been estimated at around 2%,[2] but morbidity is high, approximately between 15-32%.[19-21] SFFLF accounts for 60-100% of deaths after liver surgery,[22-24] while in liver-donor-transplantation is around 5% in Western Countries.[26] In Schindl's case series,[18] severe post hepatectomy liver failure has been reported in 29.6% of patients undergoing extended hepatectomy (>5 liver segments), while moderate post hepatectomy liver failure was reported in 25.9% of cases and mild post hepatectomy liver failure was recorded in 40.7% of cases. Conversely, severe liver failure after surgery has been shown in 8.8% of cases after standard hepatectomy (3-4 liver segments), moderate in 26.3%, and mild in 49.1%.

How could we define this liver failure?

Currently, there is no agreement on the diagnostic criteria and definition.

O. N. Tucker and N. Heaton defined small-for-size syndrome as *a recognizable clinical syndrome, which occurs in the presence of a reduced mass of liver, insufficient to maintain normal liver function, characterized by postoperative liver dysfunction with prolonged cholestasis, coagulopathy, portal hypertension, and, if severe, ascites*.[25]

J. M. Asencio described the syndrome as *the disproportion between the mass and the portal blood flow of the liver remnant, reflected by the high values of portal blood flow and pressure* and he introduces the concept of *small-for-flow syndrome*, as a *relative portal hyperperfusion of liver remnant that leads to liver dysfunction*.[26]

According to the International Study Group of Liver Surgery (ISGLS),[27] 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.*

Balzan *et al.*[28] proposed a set of criteria to diagnose the post-hepatectomy liver failure, the so-called 50-50 criteria: *a serum bilirubin concentration above 50 μmol/L and a prothrombin time (PT) which is increased by more than 50% of baseline (or INR>1.7) on postoperative day five associated with a mortality of 59% as opposed to 1.2% if these criteria are not met (sensitivity 69.6%, specificity 98.5%).*

Dahm *et al.*[29] proposed to split small-for-size syndrome after liver transplantation in two sub-categories, called *Small-for-size dysfunction* (SFSD) and *Small-for-size nonfunction* (SFSNF). SFSD is *a dysfunction of a small partial liver graft (GRWR<0.8%) during the first postoperative week after the exclusion of other causes* and SFSNF is *a failure of a small partial liver graft (GRWR<0.8%) during the first postoperative week after the exclusion of other causes*. According to ISGLS, and new etiopathological evidence, we suggest defining this syndrome Small-for-Flow-Liver-Failure (SFFLF): a postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which is characterized by serum bilirubin concentration above 50 μmol/L, HVPG>10mmHg, Doppler evidences of portal overflow, on or after postoperative day five. This condition, if it's not correctly treated, could lead to liver failure and exitus.

How can SFFLF be diagnosed?

The diagnosis is based on the evidence of liver failure after an extended hepatectomy. Any other factor that could lead to liver failure such as anesthesia, iatrogenic damages or biliary structures injuries should be excluded. Thus, high bilirubin levels should be associated to a reduced liver synthetic capacity. INR (if plasma transfusion during or after surgery doesn't occur) is probably the most suitable parameter, but the serum levels of other proteins synthesized by the liver such as albumin or pseudocholinesterase can be useful. Extrahepatic cholestasis should be excluded and, according to small-for-flow theory, portal hypertension should be demonstrated by evaluating portal vein dimension and flow velocity by Doppler ultrasound. If this condition is seen, then it became important to measure pressure to plan next therapies. Summing up, SFFLF is a post-hepatectomy liver failure not explained by other causes: to assess it, we need to evaluate Bilirubin and INR levels, and perform a Liver UltraSound Doppler Scan to check portal vein condition. When the condition is diagnosed, we should proceed to perform pressure measurement (HVPG) to decide the best treatment to avoid the latest stage of disease. An algorithm, applied currently in our clinical practice, is proposed below in Figure 1.

How can you estimate the risk to develop SFFLF before surgery?

To evaluate the future liver functional remnant, it is good clinical practice to estimate the Total Liver Volume (TLV) and the Future Liver Remnant Volume (FLR-V) with a 3D CT Volume Reconstruction on the basis of Body Surface Area (BSA) and weight,[30] calculating the FLR/TLV ratio (%FLR) as a predictor to develop the SFFLF.

Several formulae are described to calculate liver volumes. Total liver volume (TLV) and Future Liver Remnant Volume (FLR) are easily estimated by CT scan, based on BSA and body weight.[31,32] These measurements correlate very well with the etiology and severity of chronic liver disease, so they are good parameters to predict patients' survival.[33] However, formulae based on BSA and body weight underestimate TLV in Western compared with Japanese patients, because of TLV in an average Western adult can be 15% greater than a Japanese adult with the same BSA.[30]

Despite this, extended resection of 80% of functional parenchyma can be performed in a healthy liver. Right now, all over the world, recommended minimal functional remnant LV is >25% in a normal liver, >30% in a steatotic liver or after chemotherapy, and >40% in case of cirrhosis.

According to new flow-theory, volume

measurements alone are unsatisfactory as predictors. In fact, alterations in hepatic hemodynamic parameters would explain the development of liver failure in patients with thresholds of liver parenchyma considered to be *safe* as well as the absence of liver failure in some patients with thresholds of liver parenchyma considered to be *unsafe*. In fact, liver with a safe remnant size after surgery showed by CT had developed SFFLF as well because of microarchitecture alterations of liver parenchyma.[34] Because of flow and pressure injuries happen after resection is performed, there are no predictor parameters that could be assessed prior to surgery in addition to liver volumes in otherwise healthy-liver. In cirrhotic patients, Child-Pugh score is mandatory to stratify patients suitable for surgery. In addition, metabolic tests based on the detoxifying properties of the liver have the advantage to estimate properly the liver residual functionality: Indocyanine-green Clearance test is the most popular instrument in Eastern countries, where it constitutes the pillar of preoperative algorithms for liver resection.[35,36]

Other test, as the monoethylglycinexylidide (MEG-X) test,[37] has not gained popularity, and it's not routinely applied in clinical context. However, the role of intraoperative measurements of portal blood flow and pressure is emerging, in addition to monitoring hepatic artery flow.[26] This measurements could lead to a better evaluation not only of the remnant, but also a better evaluation of the relationship between future remnant volume and portal blood volume destined to the remnant. According to this, pre-surgery volume measurements, plus intraoperative flow and pressure monitoring, could permit to planning the optimal strategy to prevent SFFLF in patients undergoing extended liver resections.

Recently, Allard MA and colleagues reported that intraoperative post hepatectomy portal vein pressure >21 mmHg is an independent predictor of SFFLF and 90-day post-operative mortality after major hepatectomy in non-cirrhotic liver.[26,38] In literature, patients who meet WHVP>20 mmHg, and HVPG>10 mmHg (suggested cut-off), meet a decrease in 6-months survival from 85% to 38%, indicating a portal hypertension condition.[20] To save size measurements practice, some authors use also Spleen Volume/FRLV ratio, that has showed to be related with increased SFFLF incidence.[39]

Which therapeutic strategies are adoptable to prevent SFFLF before surgery?

Several methods have been described to manipulate volume in patients with unsafe FLRV. The most important is Portal Vein Embolization (PVE), a percutaneous technique that, in few cases, could be performed by surgical ligation, or alcohol injection, to avoid vein recanalization. PVE allows increasing the future remnant volume up to 20% in the contralateral lobe, with a peak of

growth estimated in 2-4 weeks.[39,40] Patients who don't respond to this approach are considered not suitable for liver surgery.

Patients with more than one lesion bilaterally should be treated with surgical resections or ablation (radiofrequency, microwave, NanoKnife),[41,42] before PVE, in order to avoid malignancy proliferation in contralateral lobe.[42,43] Instead of this, bilateral tumors not feasible for surgical resection in one-time may be treated with two-stage hepatectomy. Nevertheless, PVE and two-stage hepatectomy are affected by
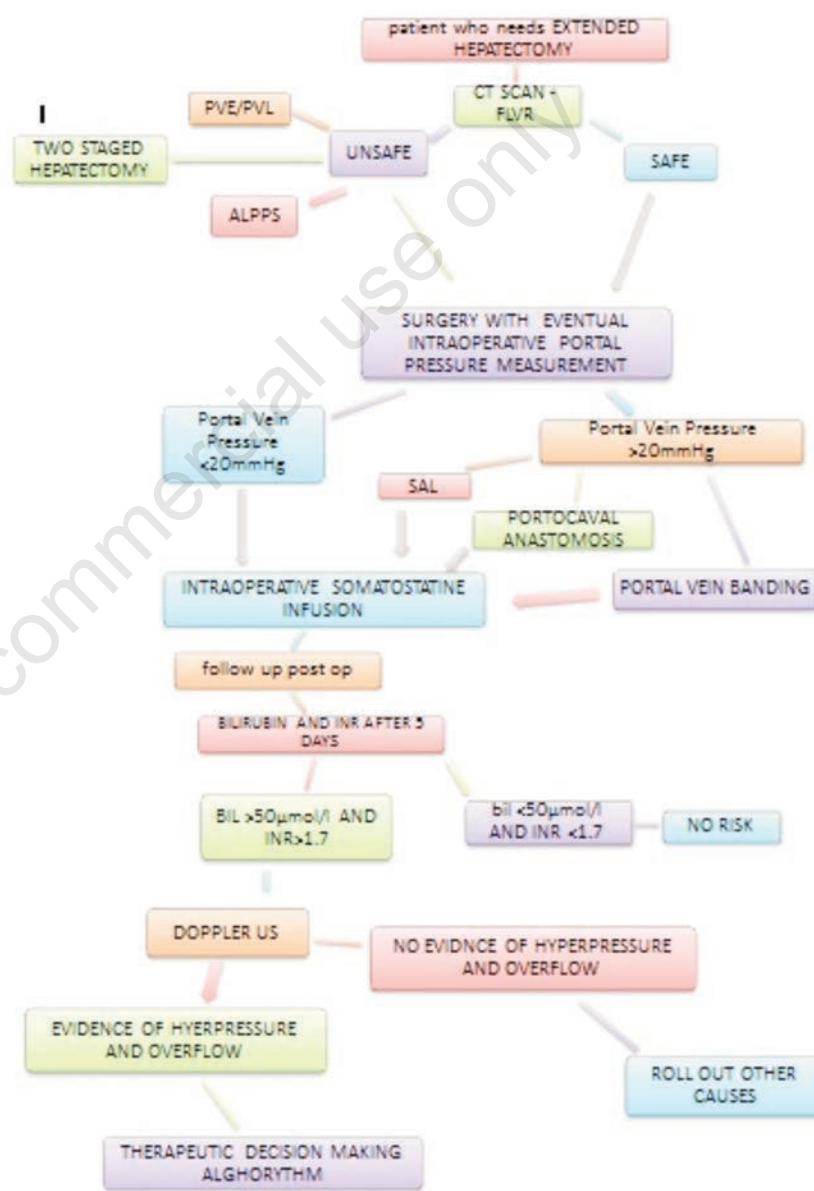

Figure 1. Alghorythm to diagnose SFFLF applied in our clinical experience. BIL: bilirubine; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; INR: international standardized ratio; PVE: portal vein embolization; PVL: portal vein ligation; SAE: splenic artery embolization; FLVR: future liver volume remnant %.

the risk of patient dropout for tumor stage progression, because of the time to wait to achieve a safe size of the future remnant.

Which surgical strategies are adoptable to prevent SFFLF?

This question lies at the heart of SFFLF prevention management. According to new evidence regarding the etiology of this syndrome, before surgery we can manage just the size of the future remnant: but SFFLF not only presents a problem of size, but also of over flow and overpressure in a small liver remnant. Flow and pressure modulations are the key strategies derived from transplant experience. Several approaches are possible.

Intermittent Pringle maneuver

Lamping the portal triad for no more than 15 min has showed a good impact on regeneration of liver. Currently, a technique consisting in 15 min of clamping on and 5 min releasing is used.[44,45] Total vascular exclusion is not recommended, but is used when we have no choice: when it happens, the clamping with preservation of caval flow should be preferred.[46]

Surgical modulation of portal blood flow

Different techniques were described and applied. Splenic Artery ligation,[47] performance of porto-caval anastomosis,[48] banding of portal vein.[49] These strategies are justified after performing intraoperative portal pressure measurement (by direct puncture of portal vein), that has shown to be a reliable predictor of remnant failure.[50-53]

Pharmacological modulation of portal blood flow

Infusion of somatostatin (or octeotride),[54] pentoxifylline,[55] adenosine,[56] or endotheline-1.[57] In case of octeotride, there is lack of evidence of a predominant role in portal pressure modulation and its

benefit.[57,58] Moreover, for all this drugs the role of infusions are still undefined, with an important lack of prospective studies.

Associating liver partition and portal vein ligation for staged hepatectomy

Described for the first time in 2010,[59] this is a newer technique with big expectation. When a portal vein ligation/embolization is performed, a partial revascularization of the lobe due to contralateral portal vessels occurs. This procedure consists in the partition of the liver along the falciform ligament line, followed by portal vein ligation. This reduces regenerative waiting time before the tumor's surgery (regenerative rates in a week of 40% to 80%, *versus* 8-27% with PVL/PVE), but is affected by high morbidity (16-64% of patients) and mortality rates (12-23% of patients).[59-61] The procedure is comforted by Nagano's theorem,[62] regarding liver regeneration, which explains how a precondition of liver cells in S-phase of cell's cycle improve functional regeneration after hepatectomy.

Which parameters should be monitored to show SFFLF development after surgery?

After surgery, it is very important to perform a strict control of operated patients. In 48-72 hours after hepatectomy, a raise of bilirubin and INR it's very common due to liver injuries caused by surgery.[15,62,63] Currently, a raise of bilirubin >50 µmol/L (3 mg/dL) and INR>1.7 after 5th day post-op is commonly accepted as early markers of liver dysfunction. These criteria are called *50-50 criteria*, as we have described before. Despite this, INR is not a very suitable parameter, because of blood and platelet infusion that are often administered during or immediately after extended hepatectomy.

According to flow-theory, if a raise of bilirubin is recognized after day 5, different

strategies can be adopted. Even if there are lack of evidence tested in SFFLF context, portal hyper pressure is usually diagnosed by Doppler US, through biliary system ectasia (according to AISF's guidelines,[64] a diameter threshold >13mm has a sensibility of 50% and specificity of 95%). Doppler US scan could be used to assess portal overflow, and a threshold of 250 mL/min/100 g of liver parenchyma has been indicated as risk factor for SFFLF development.[7,48] When bilirubin raises, a simply Doppler US could develop the suspect of disease, leading to invasive diagnostic strategies (HVPG measurement) and therapeutic choices, as well as avoiding any other iatrogenic causes. After this indication, portal pressure with HVPG could be measured to develop therapies. Indeed, as previously stated a HVPG>10 mmHg is associated with functional liver regeneration impairment (in Table 1 cut-offs are summarized). As different authors suggest, if a raise in bilirubin>50 µmol/L and HVPG>10 mmHg is recognized, then we should refer the patient to an interventional radiologist to perform a Splenic Artery Embolization (SAE), to reduce flow and pressure in portal system.[65,66] In case this strategy is not suitable, we could consider a TIPS, even if this last procedure is affected by higher morbidity than SAE. One of the authors of this article has suggested, in parallel with SAE, daily infusion of Terlipressine or Octeotride (50 mcg/hour) until bilirubin falls,[67] but this strategy is not confirmed by prospective randomized clinical trials. In Figure 2 we

Table 1. Sum-Up of parameters and their respective cut-off, to be monitored during management of affected patients.

Bilirubin	50 µmol/L - 3 mg/dL
PT	Above 50% of baseline
INR	>1.7
Portal Flow	250 mL/min/100g of liver parenchima
HVPG	>10 mmHg

PT: protombrine Time; INR: International Standardised Ratio; HVPG: hepatic venous pressure gradient.

Table 2. Sum-Up about small for size syndrome.

| Definition	Portal overflow and over pressure compared to liver remnant volume leading to liver impairment
Predictive factors	*Pre-operatively:* Preoperative volumetry and future liver remnant volume estimation. *Intra-operatively:* Portal vein flow and pressure measurements *Post-operatively:* Bilirubin>50 µmol/L after day 5th; Ultrasound evidence of portal hypertension; Doppler UltraSound to estimate portal flow; Hepatic Venous Pressure Gradient measurement
Therapeutic strategies	Portal flow and pressure modulation with surgical and/or pharmacological strategies; Liver regeneration preconditioning. *If established:* TIPS; Splenic Artery Embolization; Anti-portal hyperpressure drugs
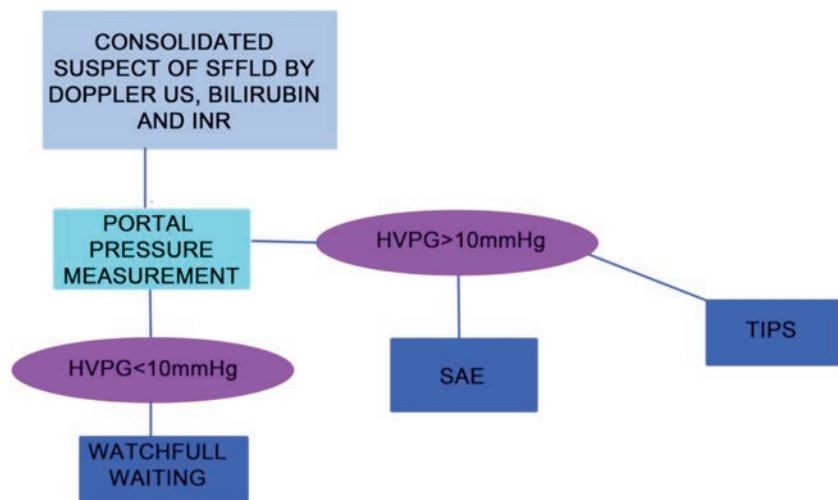
Figure 2. Therapeutic decision-making Alghorythm applied in our clinical experience. After an ultrasound evidence of portal hypertension, portal pressure measurement and estimation of Hepatic Vein Pressure Gradient are useful to address the therapy. SFFLF: small for flow liver failure; SAE: Splenic Artery Embolization; TIPS: tran-jugular porto-caval shunt; HVPG: hepatic venous pressure gradient.

show our algorithm to manage and treat patients who underwent SFFLF applied in our clinical practice.

Conclusions

SFFLF is still a challenge for oncological surgeons. In fact, in the field of oncological surgery there is a lack of data regarding outcomes after treatments, or data on how to diagnose this syndrome with increased certainty. International recognizable criteria are lacking, which leads to increased confusion. With this review, we would suggest a management protocol applied in our clinical practice to prevent and correctly diagnose this syndrome (main points are summarized in Table 2), extrapolated from the few studies published in literature. In order to validate this algorithm, it should be necessary to set up a randomized trial that can evaluate the effectiveness of it. By the way, with more data coming from literature, the role of flow and hyper-pressure is becoming clearer, conditioning therapies and surgical approach. Most of this knowledge came from transplantation experience, and it would be problematic to translate that kind of research in a similar but different context, as the liver resection is. An effort should be made, because of small-for-size syndrome after transplant and the so-called post-hepatectomy liver failure seem to be two face of the same coin. From this point of view, even if prospective data are required, it could be possible to manage this kind of surgical liver failure in both condi-

tion applying the same concepts, obviously in an empirical way.

But not only management is lacking of evidences: an HABR is never been demonstrated after human hepatic resections, and how the liver regeneration become impaired is still unclear. Clarifying this important pathological mechanism would be fundamental to discuss the role of different surgical strategies right now adopted in transplantation context, but unnecessary in resection field. Would it be, ethically and surgically, correct to manipulate portal and inferior cava veins when they are disease-free? This consideration leads until now surgeons to do not apply transplantation technique in resection context. But the emerging role of flow in liver regeneration could change, in a not so far future, our approach radically, permitting us to manipulate and drive liver regeneration through portal-flow regulation, avoiding the most important risk of this kind of surgery: liver failure.

References

1. Demetris AJ, Kelly DM, Eghtesad B, et al. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J Surg Pathol 2006;30:986-93.

2. Kelly DM, Jake Demetris A, Fung JJ, et al. Porcine partial liver transplantation: a novel model of the small-for-size liver graft. Liver Transpl 2004;10:253-63.

3. Lautt WW. The 1995 Ciba-Geigy Award Lecture. Intrinsic regulation of hepatic blood flow. Can J Physiol Pharmacol 1996;74:223-33.

4. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World J Gastroenterol 2010;16:6046-57.

5. Fondevila C, Hessheimer AJ, Taurá P, et al. Portal hyperperfusion: mechanism of injury and stimulus for regeneration in porcine small-for-size transplantation. Liver Transpl 2010;16:364-74.

6. Eshkenazy R, Dreznik Y, Lahat E, et al. Small for size liver remnant following resection: prevention and management. Hepatobiliary Surg Nutr 2014;3:303-12.

7. 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.

8. Jiang SM, Zhou GW, Zhang R, et al. Role of splanchnic hemodynamics in liver regeneration after living donor liver transplantation. Liver Transpl 2009;15:1043-9.

9. Hessheimer AJ, Fondevila C, Taurá P, 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.

10. Yagi S, Iida T, Hori T, et al. Optimal portal venous circulation for liver graft function after living-donor liver transplantation. Transplantation 2006;81:373-8.

11. Figueras J, Valls C, Rafecas A, et al. Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. Br J Surg 2001;88:980-5.

12. Karanjia ND, Lordan JT, Fawcett WJ, et al. Survival and recurrence after neo-adjuvant chemotherapy and liver resection for colorectal metastases: a ten year study. Eur J Surg Oncol 2009;35:838-43.

13. Gold JS, Are C, Kornprat P, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247:109-17.

14. Tamandl D, Gruenberger B, Herberger B, et al. Selective resection of colorectal liver metastases. Eur J Surg Oncol 2007;33:174-82.

15. Mehta NN, Ravikumar R, Coldham CA,

OPEN ACCESS

et al. Effect of preoperative chemotherapy on liver resection for colorectal liver metastases. Eur J Surg Oncol 2008;34:782-6.

16. Konopke R, Kersting S, Bunk A, et al. Colorectal liver metastasis surgery: analysis of risk factors predicting postoperative complications in relation to the extent of resection. Int J Colorectal Dis 2009;24:687-97.

17. Welsh FKS, Tekkis PP, O'Rourke T, et al. Quantification of risk of a positive (R1) resection margin following hepatic resection for metastatic colorectal cancer: an aid to clinical decision-making. Surg Oncol 2008;17:3-13.

18. Schindl MJ, Redhead DN, Fearon KCH, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289-96.

19. Boillot O, Delafosse B, Méchet I, et al. Small-for-size partial liver graft in an adult recipient; a new transplant technique. Lancet 2002;359:406-7.

20. Parikh AA, Gentner B, Wu TT, et al. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. J Gastrointest Surg 2003;7:1082-8.

21. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.

22. Sun HC, Qin LX, Wang L, et al. Risk factors for postoperative complications after liver resection. Hepatobiliary Pancreat Dis Int 2005;4:370-4.

23. Virani S, Michaelson JS, Hutter MM, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg 2007;204:1284-92.

24. House MG, Ito H, Gönen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1600 patients during two decades at a single institution. J Am Coll Surg 2010;210:744-55.

25. Tucker ON, Heaton N. The small for size liver syndrome. Curr Opin Crit Care 2005;11:150-5.

26. Asencio JM, Vaquero J, Olmedilla L, García Sabrido JL. "Small-for-flow" syndrome: shifting the size paradigm. Med Hypotheses 2013;80:573-7.

27. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS).

Surgery 2011;149:71-24.

28. Balzan S, Belghiti J, Farges O, et al. The 50-50 criteria on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-9.

29. 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.

30. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl 2002;8:233-40.

31. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-9.

32. Abdalla EK, Denys A, Chevalier P, et al. Total and segmental liver volume variations: implications for liver surgery. Surgery 2004;135:404-10.

33. Lin XZ, Sun YN, Liu YH, et al. Liver volume in patients with or without chronic liver diseases. Hepatogastroenterology 1998;45:1069-74.

34. Li C, Mi K, Wen TF, et al. Safety of patients with a graft to body weight ratio less than 0.8% in living donor liver transplantation using right hepatic lobe without middle hepatic vein. Hepatogastroenterology 2012;59:469-72.

35. Fan ST. Liver functional reserve estimation: state of the art and relevance for local treatments: the Eastern perspective. J Hepatobiliary Pancreat Sci 2010;17:380-4.

36. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298-304.

37. Ercolani G, Grazi GL, Callivà R, et al. The lidocaine (MEGX) test as an index of hepatic function: its clinical usefulness in liver surgery. Surgery 2000;127:464-71.

38. Allard MA, Adam R, Bucur PO, et al. Posthepatectomy portal vein pressure predicts liver failure and mortality after major liver resection on non-cirrhotic liver. Ann Surg 2013;258:822-30.

39. Gruttadauria S, Pagano D, Liotta R, et al. Liver volume restoration and hepatic microarchitecture in small-for-size syndrome. Ann Transplant 2015;20:381-9.

40. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy. Ann Surg 2003;237:208-17.

41. Elias D, Santoro R, Ouellet JF, et al.

Simultaneous percutaneous right portal vein embolization and left liver tumor radiofrequency ablation prior to a major right hepatic resection for bilateral colorectal metastases. Hepatogastroenterology 2004;51:1788-91.

42. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database Syst Rev 2013;CD010163.

43. Hoekstra LT, van Lienden KP, Doets A, et al. Tumor progression after preoperative portal vein embolization. Ann Surg 2012;256:812-8.

44. Belghiti J, Noun R, Malafosse R, et al. Continuous versus intermittent portal triad clamping for liver resection: a controlled study. Ann Surg 1999;229:369-75.

45. Brooks AJ, Hammond JS, Girling K, Beckingham IJ. The effect of hepatic vascular inflow occlusion on liver tissue pH, carbon dioxide, and oxygen partial pressures: defining the optimal clamp/release regime for intermittent portal clamping. J Surg Res 2007;141:247-51.

46. Cherqui D, Malassagne B, Colau PI, et al. Hepatic vascular exclusion with preservation of the caval flow for liver resections. Ann Surg 1999;230:24-30.

47. Luca A, Miraglia R, Caruso S, et al. Effects of splenic artery occlusion on portal pressure in patients with cirrhosis and portal hypertension. Liver Transpl 2006;12:1237-43.

48. Troisi R, Ricciardi S, Smeets P, 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.

49. Reyal J, Uemoto S. Percutaneously adjustable portal vein banding device could prevent post-operative liver failure—artificial control of portal venous flow is the key to a new therapeutic world. Med Hypotheses 2009;73:640-50.

50. Selzner M, Kashfi A, Cattral MS, et al. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. Liver Transpl 2009;15:1776-82.

51. Truant S, Oberlin O, Sergent G, et al. Remnant liver volume to body weight ratio > or = 0.5%: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg 2007;204:22-33.

52. Guglielmi A, Ruzzenente A, Conci S, et al. How much remnant is enough in liver resection? Dig Surg 2012;29:6-17.

53. Ito T, Kiuchi T, Yamamoto H, 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.

54. Matrella E, Valatas V, Notas G, et al. Bolus somatostatin but not octreotide reduces hepatic sinusoidal pressure by a NO-independent mechanism in chronic liver disease. Aliment Pharmacol Ther 2001;15:857-64.

55. Tian Y, Jochum W, Georgiev P, et al. Kupffer cell-dependent TNF- signaling mediates injury in the arterialized small-for-size liver transplantation in the mouse. Proc Natl Acad Sci 2006;103:4598-603.

56. Kelly DM, Zhu X, Shiba H, 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.

57. Kawachi S, Shimazu M, Wakabayashi G, et al. Efficacy of intraportal infusion of prostaglandin E1 to improve the hepatic blood flow and graft viability in porcine liver transplantation. Transplantation 1997;64:205-9.

58. Baik SK, Jeong PH, Ji SW, et al. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. Am J Gastroenterol 2005;100:631-5.

59. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.

60. de Santibañes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure. Ann Surg 2012;255:415-7.

61. Shindoh J, Vauthey JN, Zimmitti G, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg 2013;217:126-33.

62. Nagano Y, Nagahori K, Kamiyama M, et al. Improved functional reserve of hypertrophied contra lateral liver after portal vein ligation in rats. J Hepatol 2002;37:72-7.

63. Hammond JS, Guha IN, Beckingham IJ, Lobo DN. Prediction, prevention and management of postresection liver failure. Br J Surg 2011;98:1188-200.

64. AISF. Linee guida AISF per l'ipertensione portale. 2006. Available from: http://www. webaisf.org/media/7968/ipertensione_portale.pdf

65. Kaido T, Mori A, Ogura Y, 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.

66. Ikegami T, Shirabe K, Soejima Y, et al. Strategies for successful left-lobe living donor liver transplantation in 250 consecutive adult cases in a single center. J Am Coll Surg 2013;216: 353-62.

67. Famularo S, Nefotyou K, Fotiadis N, et al. Small-for-size liver syndrome: a case series with a proposal for management based on portal flow modulation. J Gastrointest Cancer 2015;46:185-9.